NHC-Catalyzed Ring Expansions And Cascade Reactions

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Finally, I would like to thank my parents who are presently 10,000 miles away in China, and my girlfriend for their love!

Dedications

This thesis is dedicated to my parents

Mr. **Jie Wang (王杰)**

&

Ms. **Mi Li (李蜜)**

for their love and for their generous support of my study in Canada

This thesis is also dedicated to my “小亲亲” girlfriend

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for her patience, for her understandings and for her love

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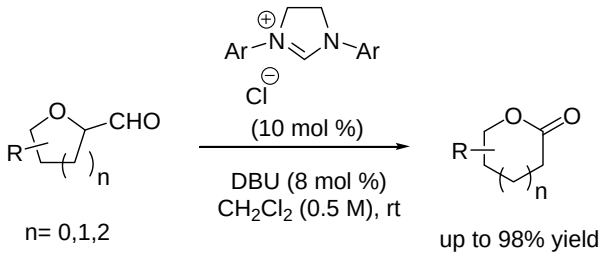
Abstract

In recent years, *N*-hetereocyclic carbenes (NHCs) have received considerable attention as organocatalysts due to their unusual ability to induce a reversal of reactivity (*Umpolung*) in aldehydes. Indeed, NHCs' unique properties have been applied to the efficient and metal-free synthesis of organic compounds that have proven elusive using traditional approaches.

My Master's research program has been focused on the use of NHCs as organocatalysts in ring expansion reactions and their applications to cascade reactions.

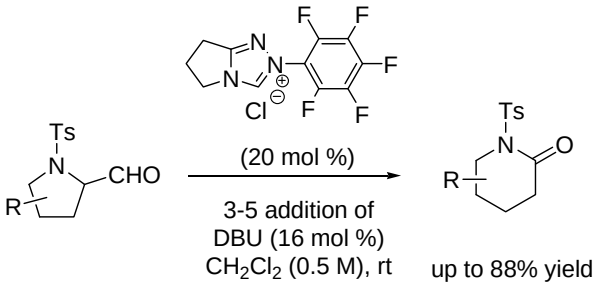
During my Masters studies, an NHC-catalyzed efficient ring expansion of 4-, 5-, and 6-membered oxacycloalkane-2-carboxaldehydes to generate the corresponding lactone derivatives was developed. This reaction provides access to a variety of lactones using readily available NHCs under mild conditions.



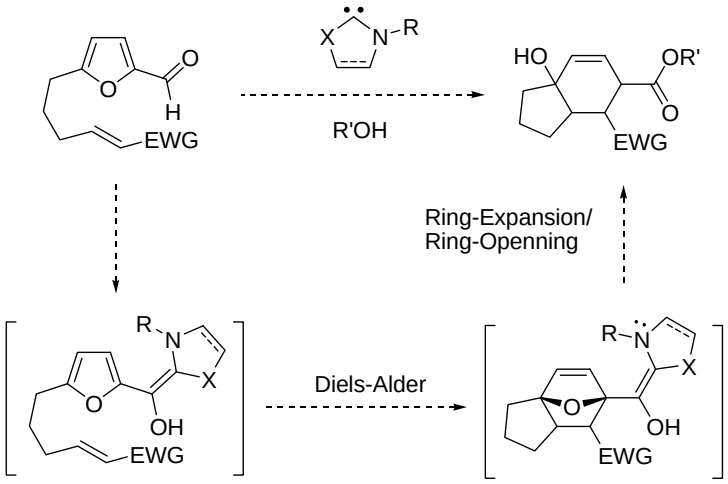
n= 0,1,2

up to 98% yield

Then, the ring-expansion lactonization has been successfully extended to an efficient lactamization using azacycloalkane-2-carboxaldehydes, which could provide functionalized lactams in moderate yields under mild conditions.



In addition, intrigued by the possibility of effecting the *Umpolung* of electron-poor dienes using NHC catalysts, the ring-expansion lactonization was applied to an attempted Diels-Alder-ring expansion cascade reaction. Though no cascade reactions were observed, some very interesting results were obtained, and those results will guide future investigations in this area.



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List of Schemes

The synthesis was completed by Karen Thai

List of Abbreviations

Ar	Aryl
aq.	aqueous
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BocNHTs	*tert*-Butyl tosylcarbamate (Weinreb's reagent)
Bu	Butyl
BuLi	Butyl Lithium
CSA	(±)-10-Camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
Decomp.	Decomposition
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N,N*-Diisopropylethylamine
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-(Dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMPA	2,2-Bis(hydroxymethyl)propionic acid
DYKAT	Dynamic Kinetic Asymmetric Transformation
EDCI	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
ee	Enantiomeric Excess
E_p	Energy of the Product
E_{SM}	Energy of the Starting Material
Et	Ethyl
EtOH	Ethanol

EWG	Electron-Withdrawing Group
FG	Functional Group
HOMO	Highest Occupied Molecular Orbital
IBX	2-Iodoxybenzoinc acid
***i*Pr**	*iso*-propyl
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital
***m*CPBA**	*meta*-Chloroperbenzoic acid (or 3-Chloroperbenzoinc acid)
Me	Methyl
Mes	Mesityl
n.d.	Not Determined
N.R.	No Reaction
NaHMDS	Sodium bis(trimethylsilyl)amide
NHC	*N*-Heterocyclic carbene
NHC*	Chiral *N*-heterocyclic carbene
NMR	Nuclear Magnetic Resonances
***n*Pr**	*n*-Propyl
Ph	Phenyl
PPh_3	Triphenylphosphine
redox	Reduction-Oxidation Reaction
r.t.	room temperature
S.M.	Starting Material
TBDPS	*tert*-Butyldiphenylsilyl
TBME	*tert*-Butyl methyl ether
TBS	Tributylsilyl
TLC	Thin-layer Chromatography

Ts	*p*-Toluenesulfonyl
TsOH	*p*-Toluenesulfonic acid

I. INTRODUCTION

In the search of efficient chemical transformations, *Umpolung* mediated carbon-carbon or carbon-heteroatom bond formations have played an outstanding role.

Umpolung or "polarity inversion" refers to the chemical modification with the aim of reversed polarity of functional groups (more commonly aldehydes). This modification provides access to certain important carbon-carbon bond formations that would otherwise be impossible.

The first example of reactivity *Umpolung* was the benzoin reaction back to 1830s. [1] However, the concept of *Umpolung* was first introduced by D. Seebach in 1970's. One of the very famous examples of *Umpolung* was Seebach and Corey's dithiane chemistry [2-3], and the scope of the reactions was expanded with the use of NHCs as organocatalysts in recent years. [4]

N-heterocyclic carbenes (NHCs) are by far most studied members of the persistent carbenes [5], which were first isolated and reported by the groups of Bertrand and Arduengo. [6] Besides, NHCs have contributed to the development of organometallic chemistry in the 20th century, due to their being excellent ligands for transition metal-based catalysts.

1.1 *N*- Heterocyclic carbenes (NHCs) in organometallics

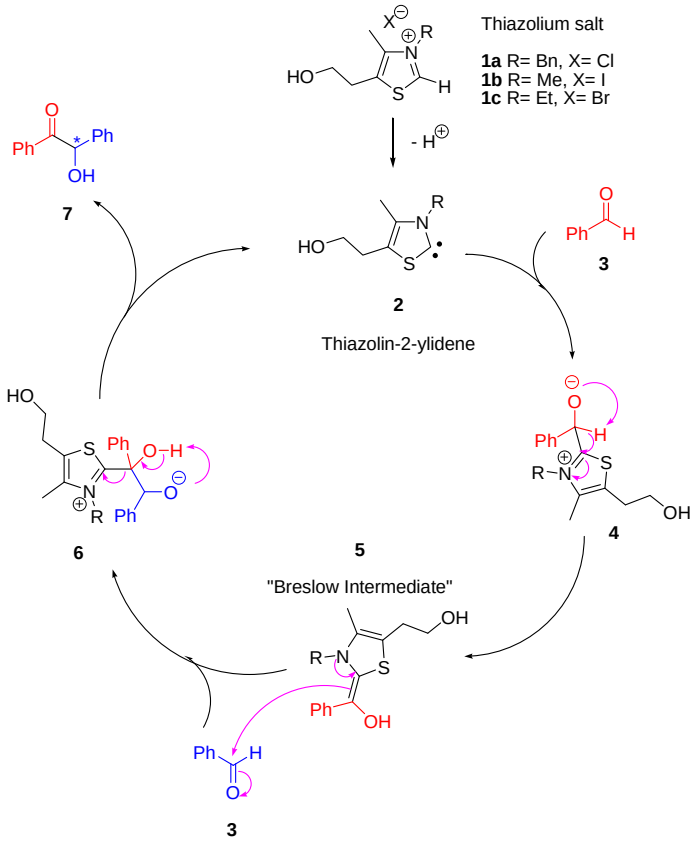
One of the most successful applications of NHCs as ligands in organometallic chemistry thus far is the cross metathesis reaction developed by Grubbs et al. [7] However, in recent years, a number of NHCs have been developed as ligands [8] for a variety of transition metal-based catalysts [9] to catalyze a wide spectrum of reactions. [10]

The success of NHCs as ligands in transition metal chemistry is attributed to their excellence as σ-electron donors. In addition, since Breslow's proposal of the mechanism of Benzoin reaction in 1958, [14] NHCs has been proven to be able to induce the *Umpolung* of aldehydes. Hence, NHCs have been used as organocatalysts to produce seminal and exciting methodologies.

1.2 *N*- Heterocyclic carbenes (NHCs) in organocatalysis

1.2.1 Reaction of d^1- nucleophiles: NHC-Catalyzed Benzoin Reaction

The earliest investigations of *Umpolung* reactions catalyzed by NHCs date back to 1943 when Ugai et al. [11] demonstrated that the use of the thiazolium salts could serve for benzoin reaction, a reaction that was first achieved catalytically by Nikolay Zinin in late 1830s. [12] In 1958, based on Lapworth's postulation of the mechanism of cyanide-catalyzed benzoin reaction [13], Breslow proposed a mechanism for thiazolium salt-catalyzed benzoin reaction (**Scheme 1**). [14]



Scheme 1 Thiazolium salt-catalyzed benzoin reaction mechanism proposed by Breslow. [14]

In this mechanism, thiazolium salt **1** is deprotonated at its most acidic position to form a thiazolin-2-ylidene carbene species **2** which starts a catalytic cycle by nucleophilic attack of the carbonyl functional group of benzaldehyde **3** to give the thiazolium salt adduct **4**. Proton transfer leads to a resonance stabilized acyl anion equivalent "Breslow intermediate" **5**, which then adds to the carbonyl group of another benzaldehyde molecule **3**. The catalytic cycle completes by the elimination of benzoin product **7** from intermediate **6** and returning thiazolin-2-ylidene **2** to the catalytic cycle.

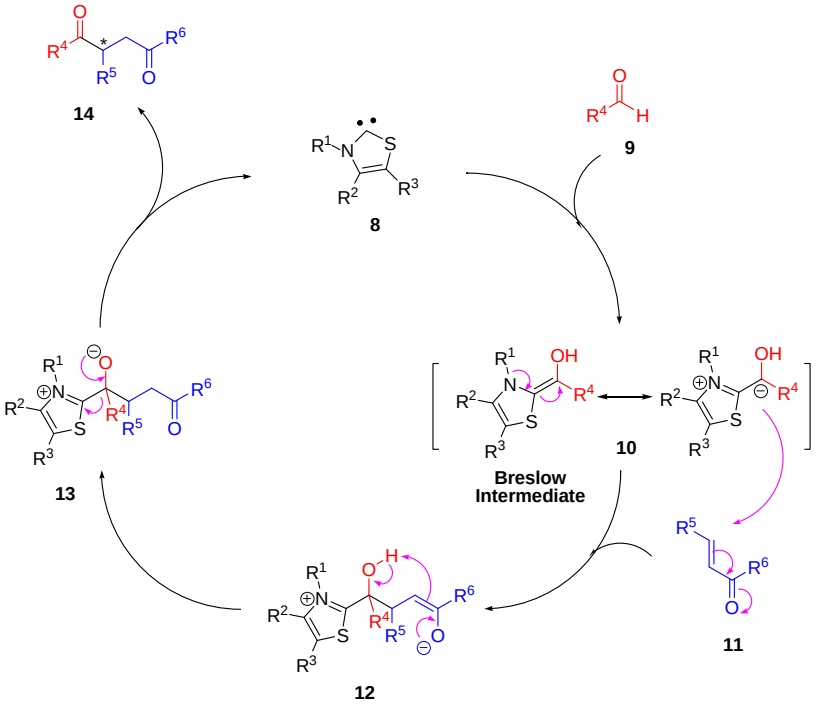
The mechanism proposed by Breslow fostered the development of chiral thiazolium catalysts for use in an asymmetric version of benzoin reaction to synthesize enantiopure benzoin products.

For this purpose, a variety of chiral NHCs was synthesized and applied to both intermolecular and intramolecular bezoin reactions. Though moderate to excellent yields were obtained, the reaction was limited as to the stereochemical outcome. The benzoin reaction catalyzed by chiral carbenes results in products with low to moderate enantiomeric excess (ee); [15] the chemoselectivity of cross benzoin reactions is always poor; [16] and because aliphatic aldehydes always give unstable Breslow intermediates, benzoin reactions of aliphatic aldehydes remain problematic. [16]

1.2.2 Reactions of d^1- nucleophiles with Michael acceptors: NHC-Catalyzed Stetter Reactions

In 1976, Stetter et al. first succeeded in applying acyl donors to Michael acceptors using NHCs as catalysts, which became known as the Stetter reaction. [17] Stetter reactions provide an alternate pathway to 1, 4-bifunctional molecules with up to two new stereogenic centers. The reaction (**Scheme 2**) started with the formation of resonance stabilized Breslow intermediate **10** from aldehydes **9** and NHCs **8**. Nucleophilic attack of such acyl anion equivalent **10** to Michael

acceptors **11** leads to intermediate **12**. After tautomerism, the Stetter adduct is released by elimination of intermediate **13** and NHC **8** is regenerated.



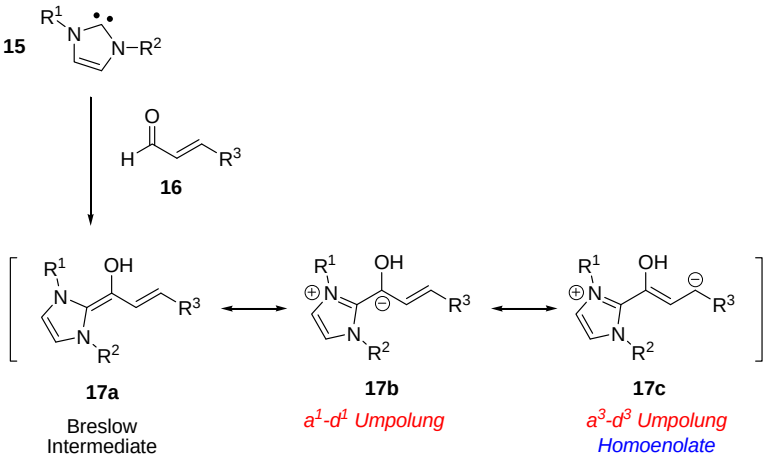
Scheme 2 Proposed mechanism for Stetter reaction. [17]

Recent advances of Stetter reaction have focused on intra- and intermolecular enantioselective versions and on natural products synthesis.

1.2.3 a^3 to d^3 *Umpolung*: Reactions of NHC-induced homoenolates

In the benzoin reaction and the Stetter reaction, the reversal of polarity happens on the

C1-position. As a result, benzoin and Stetter reactions can be regarded as a^1 to d^1 *Umpolung* (C1-position electron acceptor is converted into C1-position electron donor). However, reactivities of α,β-unsaturated aldehydes are quite different in the context of NHC-catalyzed reactions. This is due to the negative charge on the C1-position **17b** of α,β-unsaturated aldehydes **16**, generated by *Umpolung*, can be transferred to C3 position **17c** through resonance stabilization. Hence, in NHC-catalyzed reactions, α,β-unsaturated aldehydes can demonstrate both a^1-d^1 and a^3-d^3 *Umpolung* reactivity during the course of the reaction. (**Scheme 3**)

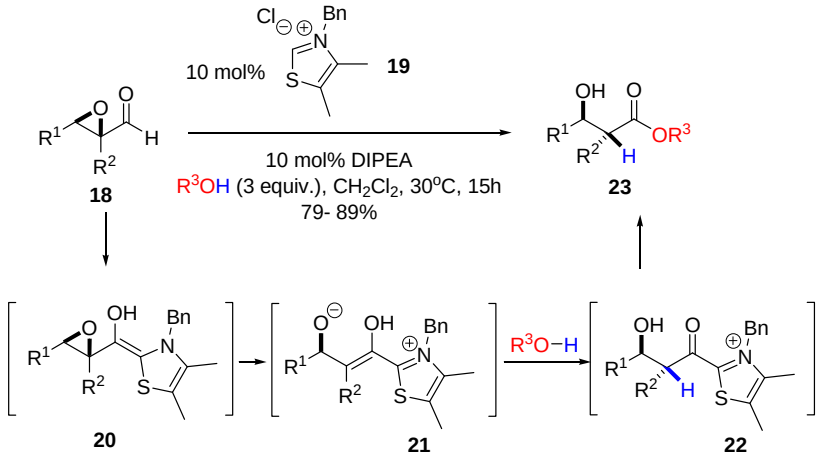


Scheme 3 a^1-d^1 and a^3-d^3 *Umpolung* (homoenolate) of α, β-unsaturated aldehydes.

The homoenolate reactivities induced by NHCs give rise to a formal redox process. In this redox process, the reduction aspect is illustrated in three fashions: 1) conversion of triple bonds to double bonds; 2) conversion of double bonds to single bonds; or 3) elimination of an α-substituent of aldehydes (including ring opening processes). The oxidation counterpart is generally the oxidation of aldehydes into esters. Some recent examples of NHC-catalyzed homoenolate formal redox processes are shown in **Schemes 4-9**.

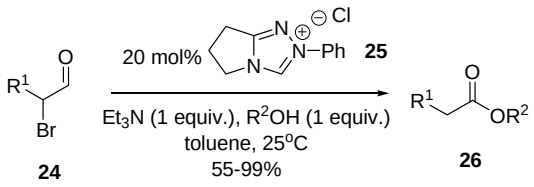
In 2004, Chow and Bode reported an NHC-catalyzed diastereoselective synthesis of *anti*-β-

hydroxyl esters. [18] In this methodology, the Breslow intermediate **20** that is formed from the epoxyaldehyde **18** and thiazolin-2-ylidene **19** eliminates an unsaturation by opening epoxide ring to fufill a reduction process. After tautomerism of intermediate **21**, an activated carboxylate **22** was formed. Nucleophilic attack of alkoxide on the activated carboxylate **22** gives an ester **23**, which completes the formal redox transformation. (**Scheme 4**)



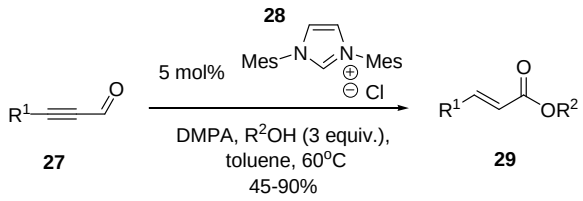
Scheme 4 NHC formal red-ox reaction of epoxyaldehydes reported by Chow and Bode. [18]

Under the same rationale, shortly after Chow and Bode's publication, Rovis and co-workers demonstrated an NHC-catalyzed formal redox reaction by converting α-bromoaldehydes **24** to saturated esters **26**. [19] (**Scheme 5**)



Scheme 5 NHC-catalyzed redox transformation of α-haloaldehydes to saturated esters reported by Rovis and co- workers. [19]

Inspired by the formal redox mechanism of homoenolates, Zeitler et al. reported an interesting NHC-catalyzed formal redox reaction of propargylic-derived aldehydes **27** to (*E*)-configured α, β- unsaturated esters **29**. (**Scheme 6**) [20]

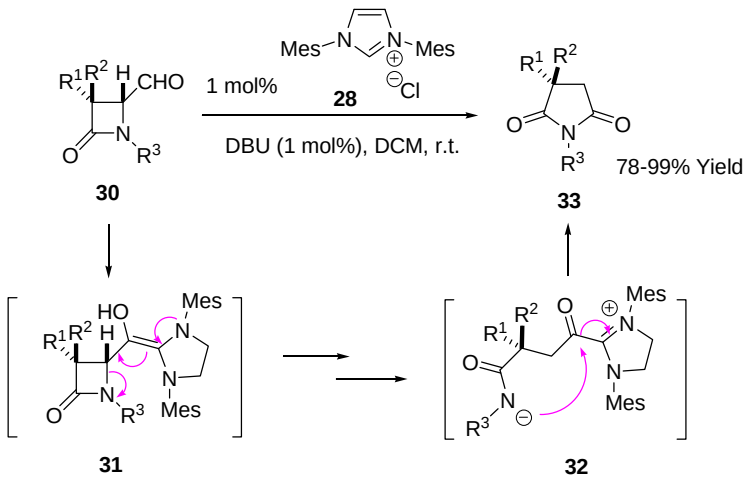


Scheme 6 NHC- catalyzed formal redox reaction of propargylic-derived aldehydes to (*E*)-configured α-, β- unsaturated esters reported by Zeitler et al. [20]

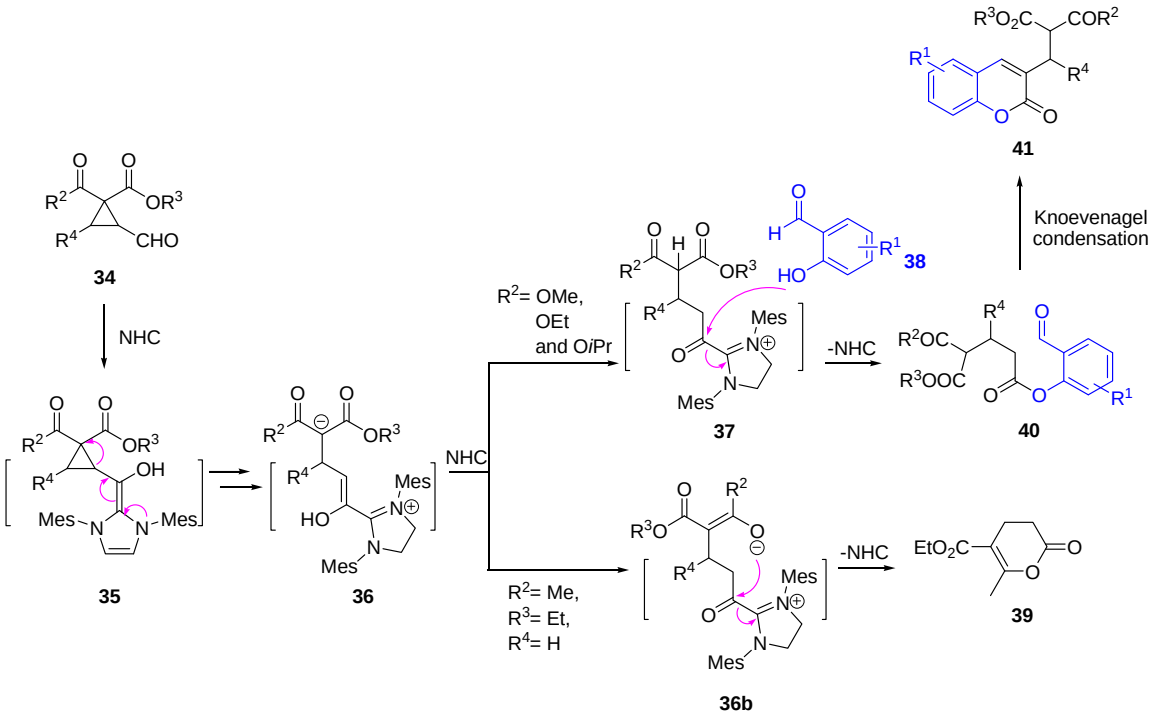
More recently, You and co-workers demonstrated that intramolecular generation of an amide nucleophile and an activated carboxylate **32** simultaneously by NHC-mediated formal redox reaction of 4-formyl-*β*-lactam **30** would result in ring closure and produced succinimide derivatives **33** (**Scheme 7**). [21] An asymmetric application of this reaction by kinetic resolution with a chiral carbene was also achieved. However, as the α-position of succinimides is highly susceptible to deprotonation, the product succinimide suffered from partial racemization and gave moderate to low ee's. [22]

Inspired by the possibility of ring closure if a nucleophile and an activated carboxylate emerge in the same molecule, Wang and Du reported a tandem synthesis of coumarins catalyzed by NHCs. [23] In this reaction, homoenolate mediated ring-opening of cyclopropane moiety **34** generates enolate **36**. Then two pathways are possible depending on the stability of enolate **36**. A stable enolate **36b** provides an excellent oxygen nucleophile that subsequently attacks the activated carboxylate and gives 3,4-dihydro-α-pyrone **39**. On the other hand, an unstable enolate will promptly be protonated to give intermediate **37** followed by esterification to produce

intermediate **40**. Finally, functionalized coumarins **41** can be obtained through a Knoevenagel condesation (**Scheme 8**).

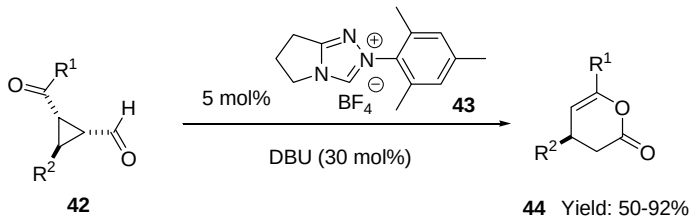


Scheme 7 Ring expansion reaction 4-formyl-*β*-lactam reported by You and co- workers. [21, 22]



Scheme 8 NHC-catalyzed tandem synthesis of coumarins reported by Wang and Du. [23]

Very recently, You et al. reported a method to synthesize 3,4- dihydro-α-pyrone derivatives **44** through an NHC-catalyzed formal redox transformation (**Scheme 9**). [24]



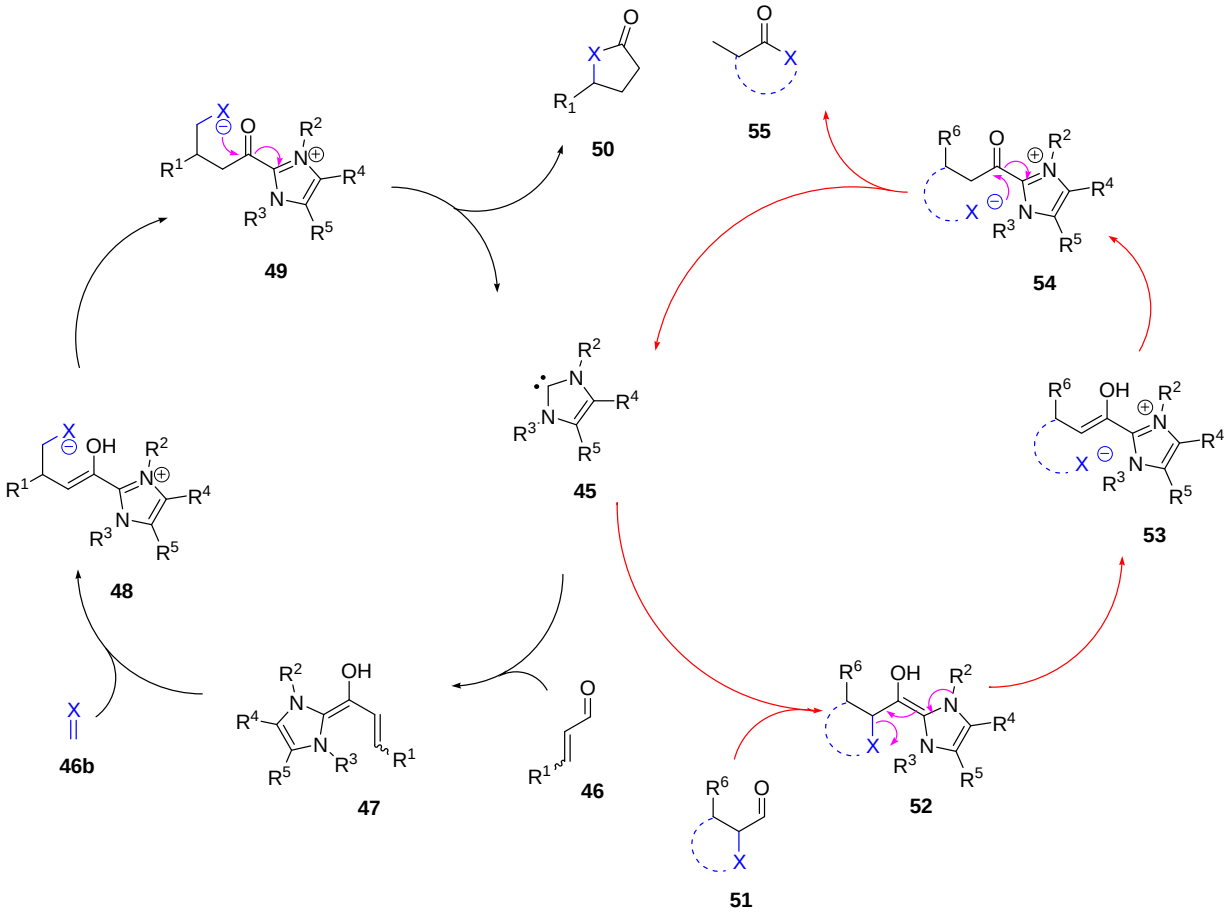
Scheme 9 NHC- catalyzed synthesis of 3,4- dihydro-α-pyrone derivatives **44** reported by You et al. [24]

II. RESULTS AND DISCUSSIONS PART I:

NHC- Catalyzed Ring-Expansion Lactonization Reactions

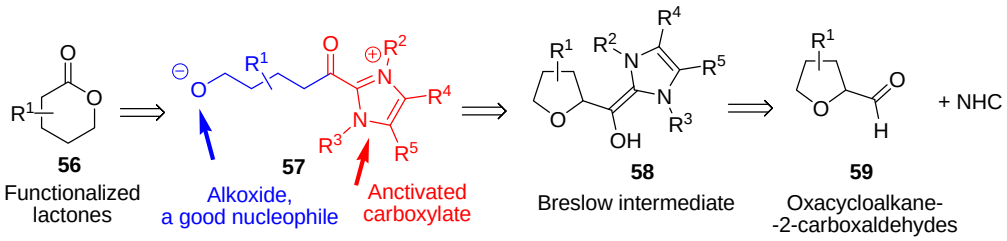
2.1 Research objectives

As demonstrated in the introductory chapter, a lot of attention has been focused on NHC-induced formal redox transformations. [18-25] Those original studies not only further introduced a novel chemical transformation, but also generated convenient and alternative methods to provide some highly functionalized and useful molecules, including amino alcohols, oxazolidinones [26], coumarins [27], azalactones [28], cyclopentane derivatives [29] and ketimines. [30-31] Though a diverse number of these formal redox reactions have been reported, an unchanged critical step is always involved: the completion of these formal redox transformations is always directed by nucleophilic attack on an activated carboxylate (**Scheme 10**). Generally, in these formal redox reactions, the formal reduction occurs intermolecularly through nucleophilic addition onto an external electrophile, or intramolecularly through a ring opening process (**51- 53**). The choice of those two different pathways is dependent on the structure of aldehydes (eg. aldehydes **46** and **51)**. Following the formal reduction, the formal oxidation reaction is initiated by the tautomerism of **48** and **53** to give activated carboxylates **49** and **54**, respectively. Attack of a nucleophile on the activated carboxylate (**49** or **54**) will result in ring closure and ejection of the catalyst **45**.



Scheme 10 Typical catalytic cycle of NHC-induced formal redox reactions.

In my first research project, we sought to develop a methodology toward the production of functionalized lactones **56** [25]. As illustrated in **Scheme 11**, an intermediate containing both nucleophile and an activated carboxylate, such as **57**, must be formed. Retrosynthetic analysis of this route indicated that Breslow intermediate **58** must be formed before the ring opening happened, and oxacycloalkane-2-carboxaldehydes **59** are the required starting materials (**Scheme 11**).



Scheme 11 Retroanalysis of NHC-catalyzed synthesis of lactones.

2.2 Formation of functionalized 5-, 6-, and 7-membered lactones through NHC-catalyzed ring expansion of oxacycloalkane-2-carboxaldehydes [25]

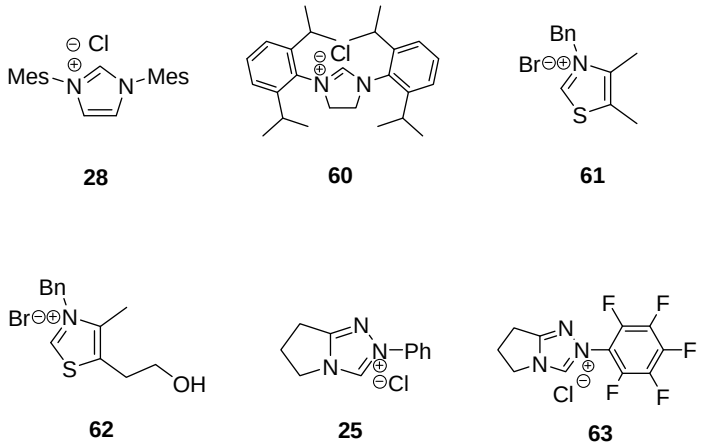
2.2.1 Reaction optimization

Although NHC-catalyzed ring-opening has been observed by Chow and Bode who described a ring-opening and redox esterification of epoxyaldehydes in their seminal research paper [18], the five-membered oxygen heterocycles **59** are significantly less strained, suggesting the ring-opening process may be difficult.

Initial screening was performed with tetrahydrofurfural **64** as a model substrate and six different NHC precatalysts were used in varing quantities (**Scheme 12**). Precatalysts from the four most commonly used classes of NHCs were screened: imidazolium **28**, imidazolinium **60**,

thiazolium **61** and **62**, as well as triazolium **25** and **63**.

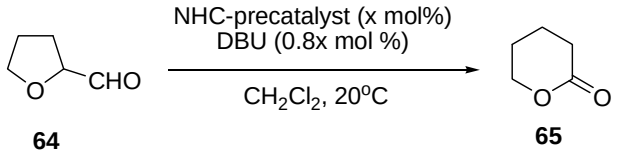
Results from catalysts screening are listed in **Table 1**. Those reactions were carried out at room temperature using 50 mol % catalytic loading. In order to minimize benzoin reaction, concentration of the aldehyde substrate was kept low (0.02M).



Scheme 12 Six different NHC precatalysts that were screened for the ring expansion reaction of tetrahydrofurfural as the model substrate.

In sharp contrast to the ring opening and redox esterification of epoxyaldehydes reported by Chow and Bode [18], thiazolium precatalysts **61** and **62** (**Table 1**, entries 1 and 2) gave a mixture of unidentifiable products. Triazolium precatalyst **25** (entry 3) gave trace amount of desired lactone **65** in a complex mixture of side products, whereas a moderate yield was obtained with an analogous catalyst bearing an electron-withdrawing group **63** (entry 4). Imidazolium precatalyst **28** (entry 5) did not catalyze the formation of lactone **66**, but promoted the slow transformation of tetrahydrofurfural to trace amounts of presumed benzoin product. However, imidazolinium precatalyst **60** (entry 6) facilitated a fast and quantitative conversion to the desired lactone **65**.

Futher experimentation with **60** (entry 7) revealed that conversion of the starting material to the lactone **65** can still be effected even in in high concentration (0.5M) with low catalytic loading (10 mol %).



64 **65**

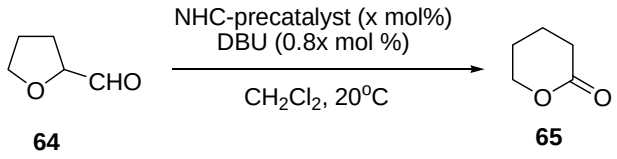
Entry [a]	NHC- Precatalyst	Catalytic loading (mol-%)	Concentration (M)	Time (h)	Yield [b] (%)
1	**61**	50	0.02	5	38
2	**62**	50	0.02	5	5
3	**25**	50	0.02	5	<5
4	**63**	50	0.02	5	42
5	**28**	50	0.02	5	<5
6	**60**	50	0.02	5	82
7	**60**	10	0.5	13	78

[a] All reactions were performed on a 0.4-0.6 mmol scale; DBU= 1, 8-diazabicyclo[5.4.0]undec-7-ene. [b] Yield of pure, isolated product.

Table 1 Evaluation of NHC catalysts and reaction conditions on conversion of tetrahydrofurfural (**64**) to δ -valerolactone (**65**).

Remarkably, precatalysts **28** and **60** of (entries 5 and 6, **Table 1**) produced dramatically different results, despite their structural similarity. This intriguing observation prompted us to further explore the catalytic nature of imidazolium- and imidazolinium-derived carbenes (**Table 2**).

Subsequently, the steric and electronic properties of imidazolium- and imidazolinium-derived NHCs (**Table 2**) were investigated. We found that the imidazolinium-derived carbenes (entries 1 and 3) both provided the desired lactone **65**, and catalyst **60** which is more sterically bulky produced a higher yield than did the less bulky catalyst **67**. In contrast, despite the structural similarity with imidazolinium precatalysts, imidazolium-derived carbenes (entries 2 and 4) did not catalyze the transformation to lactone **65**. Hence, it is obvious that the ring expansion reaction is more affected by the electronic nature than steric hindrance of NHC catalysts.



64 **65**

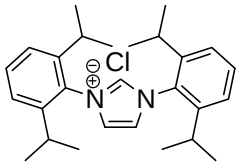
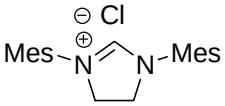
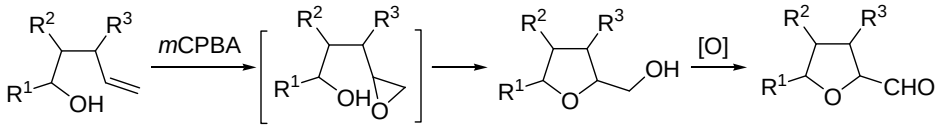
Entry	Catalyst	Catalytic loading (mol-%)	Concentration (M)	Time (h)	Yield (%)
1	**60**	50	0.02	5	82
2	 **66**	50	0.02	5	<5
3	 **67**	10	0.5	17	35
4	**28**	50	0.02	5	<5

Table 2 Influences of electronic and steric properties of imidazolium- and imidazolinium-derived NHCs on the ring expansion reaction.

2.2.2 Synthesis of substrates.

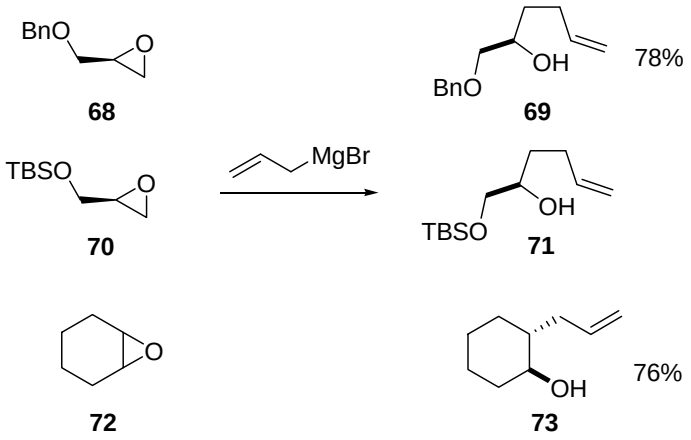
Substrates required for the ring-expansion reaction were readily prepared in two steps from functionalized pent-4-en-1-ols using a tandem epoxidation-cyclization followed by oxidation (**Scheme 13**). Pent-4-en-1-ols were achieved via four different synthetic routes (**Scheme 14-18**). The remainder substrates **64** and **93** were directly prepared through oxidation of commercially available tetrahydrofurfuryl alcohol and tetrahydropyranol. [32] Substrate **84** was prepared by photo [2+2] cycloaddition followed by oxidation (**Scheme 18**). [33]



Scheme 13 Synthesis of functionalized oxacycloalkane-2-carboxaldehydes.

Synthetic route I: ring- opening of epoxides using allylmagnesium bromide (**Scheme 14**)

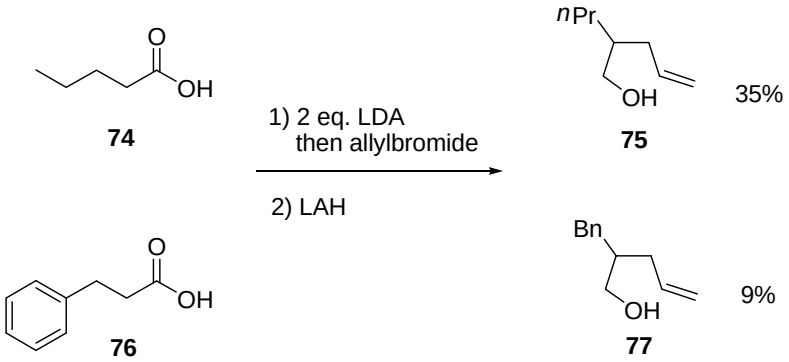
Functionalized pent-4-en-1-ols **69**, **71** and **73** were readily obtained by the Grignard reaction of allylmagnesium bromide and the cooresponding epoxides.



Scheme 14 Synthesis of **69**, **71** and **73**.

Synthetic route II: α-alkylation of carboxylic acids followed by reduction (**Scheme 15**)

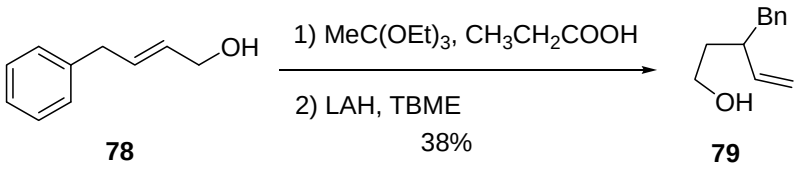
Functionalized pent-4-en-1-ols **75** and **77** were synthesized in two steps. Lithium enolates were generated *in situ* by treating pentanoic acid **74** or hydrocinnamic acid **76** with 2 equivalents of LDA. Subsequent allylation produced the corresponding allylic acids, which were readily transformed to alcohols **75** and **77** by LAH reduction.



Scheme 15 Synthesis of **75** and **77**.

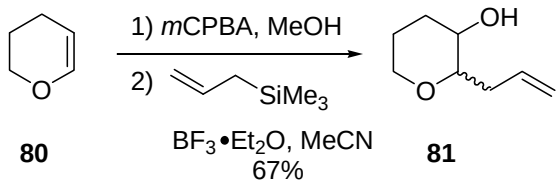
Synthetic route III: Claisen rearrangement followed by reduction (**Scheme 16**)

A mixture of (*E*)-4-phenylbut-2-en-1-ol **78**, triethyl orthoacetate and propanoic acid produces (*E*)-4-phenylbut-2-enyl acetate, which then undergoes a Claisen rearrangement. LAH reduction of the rearrangement product yields the desired pent-4-en-1-ol **79**.



Scheme 16 Synthesis of **79**.
The synthesis was completed by Karen Thai.

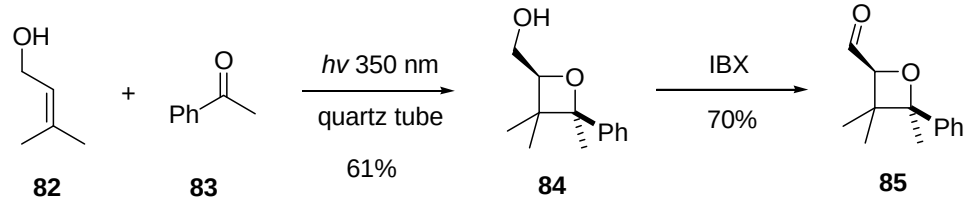
Synthetic route IV: functionalized pent-4-en-1-ol **81** was prepared as described by Rousseau *et al.* (**Scheme 17**) [34]



Scheme 17 Synthesis of **81**.
The synthesis was completed by Karen Thai.

Synthetic route V: substrate **85** was prepared through oxidation of the alcohol **84**. Alcohol **84** was obtained from photo [2+2] cycloaddition of allylic alcohol **82** and acetophenone **83** as

described by Stegmann *et al.* (**Scheme 18**). [33]



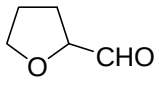
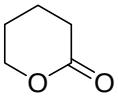
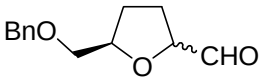
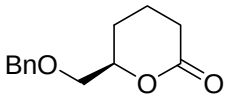
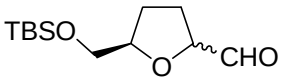
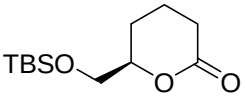
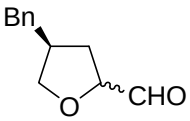
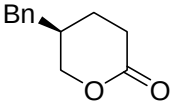
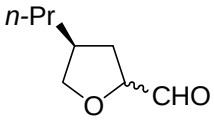
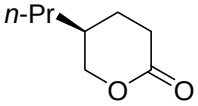
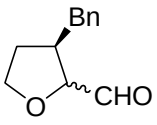
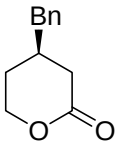
Scheme 18 Syntheses of **85**.

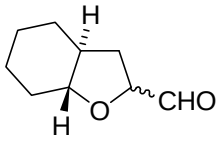
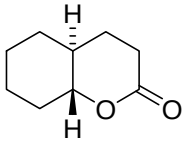
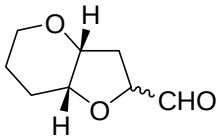
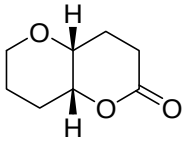
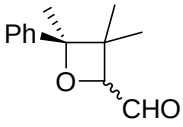
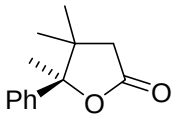
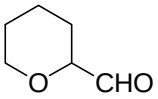
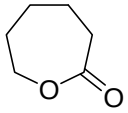
2.2.3 Scope of the reaction

We then extended the scope of our reaction to the synthesis of functionalized lactones (**Table 3**). Under the optimal conditions, a series of tetrahydrofuran derivatives with substituents at the 3, 4 and 5-positions was transformed efficiently into the corresponding lactones (entries 2-6). [35] Importantly, trialkylsilyl protecting groups were well tolerated (entry 3) during the reaction, and no 1,2-silyl transfer or other side products were detected. [35] Of interest, both *trans*- and *cis*-fused bicyclic lactones (entries 7 and 8) were obtained in moderate to high yields from corresponding bicyclic tetrahydrofuran derivatives.

This novel ring-expansion lactonization reaction was not restricted to the syntheses of six-membered lactones. Through an efficient ring-expansion of readily accessible oxetane-2-carboxaldehydes, *γ*-butyrolactone derivatives with a quaternary center were obtained in high yield (entry 9). Besides, even seven-membered lactones can be formed, though in moderate yield, using our lactonization reaction (entry 10). However, the observation of only trace amounts of impurities in the crude reaction mixture, in this case, suggested that the reduced yield in the synthesis of seven-membered lactone might be due to the formation of water soluble side products.

The efficient synthesis of a seven-membered lactone through our ring-expansion reaction under an unusually high concentration (0.5M) is noteworthy. In addition, although NHC-catalyzed reactions were routinely carried out under inert atmospheres, our lactonization reactions can also be conducted in air without any adverse effect on the yield. Furthermore and surprisingly, no benzoin-type dimmers were found in any of those reactions.

Entry	Substrate	Product	Yield [b] (%)
1	 **64**	 **65**	78
2 [c]	 **86**	 **94**	98 [d]
3 [e,f,k]	 **87**	 **95**	30 (>95) [g]
4	 **88**	 **96**	90
5	 **89**	 **97**	94
6 [f,h,k]	 **90**	 **98**	98

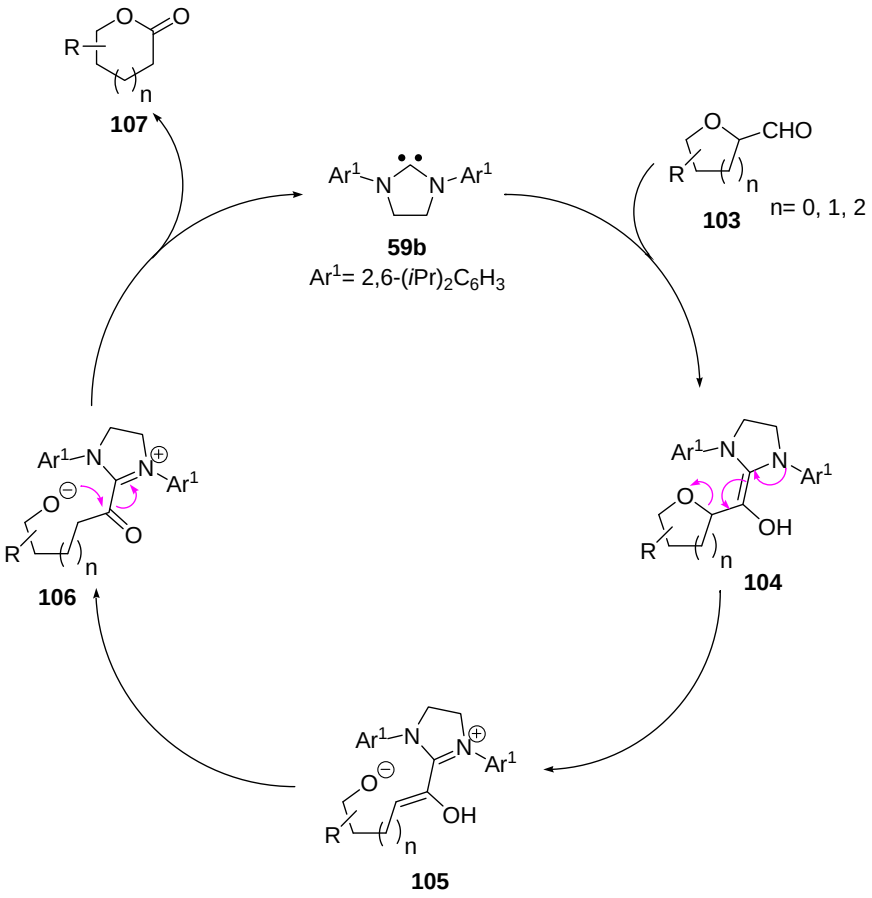
7	 **91**	 **99**	88
8 [e,f,k]	 **92**	 **100**	62 (>95) [i]
9	 **85**	 **101**	86
10 [j]	 **93**	 **102**	48

[a] Unless otherwise noted, all reactions were performed using racemic substrates at 0.5 M in CH_2Cl_2 at 20 °C for 12-24 h using 10 mol % of **60** and 8 mol % of DBU. Substrates **86-91** were used as a ~1:1 mixture of epimers. [b] Yield of pure, isolated product; conversion based on ^{1}H NMR analysis of the crude reaction mixture is shown in parentheses. [c] Enantiomerically enriched substrate (>99% ee) was used. [d] >99% ee. [e] 30 mol % of catalyst was used. [f] The presence of small amounts of Dess-Martin-derived impurities in the substrate mandated the use of a higher catalytic loading. [g] The product was found to be unstable to chromatography. [h] 20 mol % catalyst was used. [i] Isolation of the product proved problematic due to difficulty in detection by thin-layer chromatography. [j] Reaction performed at 40 °C for 10 days. [25] [k] Substrates contributed by Karen Thai.

Table 3 Scope of the NHC-catalyzed ring expansion of functionalized oxacycloalkane-2-carboxaldehydes.

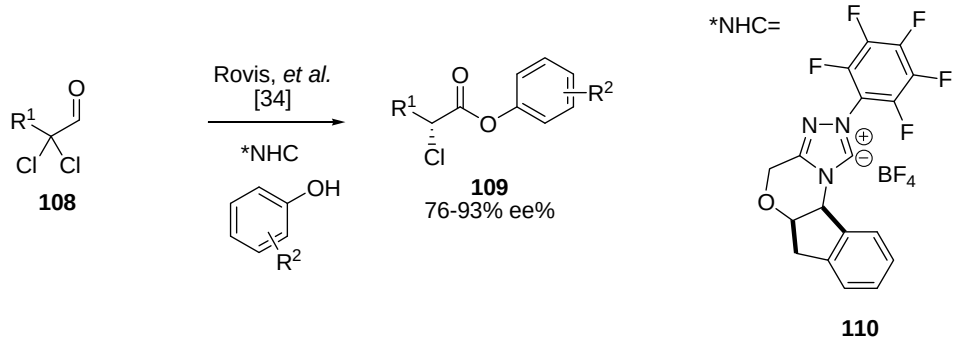
2.2.4 Reaction Mechanism

Based on the results of Chow and Bode, the mechanism outlined in **Scheme 19** was proposed. We proposed that the imidazolinylidene **60b** combines with oxacycloalkane-2-carboxaldehydes **103** to form the Breslow intermediate **104**. The ring opening of the Breslow intermediate **104** would result in the oxygen heterocycle to form intermediate **105**. After tautomerism, intermediate **106** would be formed, followed by the nucleophilic attack of the alkoxide on the activated carboxylate to provide the desired lactone **107**.

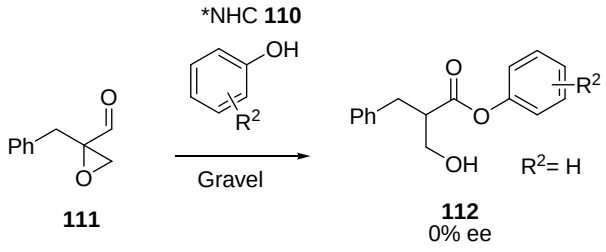


Scheme 19 Proposed mechanism for the NHC-catalyzed ring-expansion via an activated carboxylate intermediate.

Rovis et al. reported an enantioselective synthesis of α-chloroesters **109** using a chiral NHC **110** (**Scheme 20**) recently. [34] Remarkably, when Dr. Michel Gravel applied the same chiral NHC **110** for a ring-opening reaction of epoxyaldehydes **111**, a racemic mixture of **112** was obtained (**Scheme 21**). The failure to induce enantioselectivity using a chiral NHC suggested that the reaction did not proceed through a chiral activated carboxylate intermediate. Based on these results we proposed that the reaction went through an achiral ketene intermediate (**Scheme 22**).



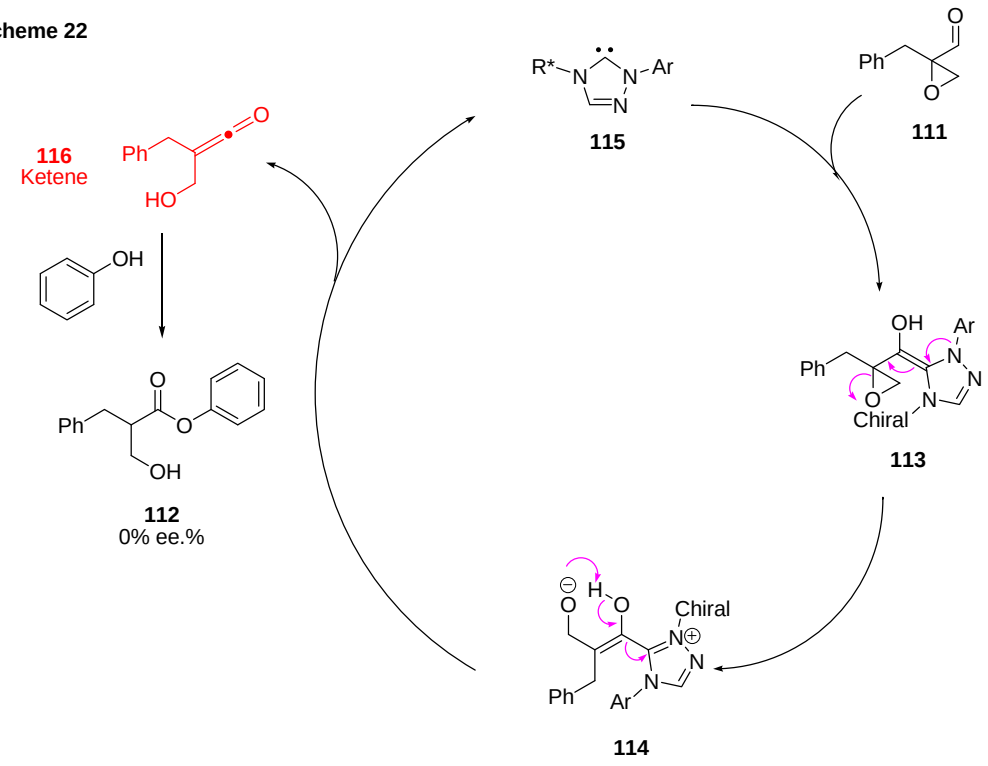
Scheme 20 Rovis' [34] enantioselective synthesis of α-chloroesters **109** using a chiral NHC **110.**



Scheme 21 Gravel's attempts on an enantioselective ring opening of **111** using Rovis' chiral NHC.

In the ketene mechanism (**Scheme 22**), epoxyaldehyde **111** would still form a Breslow intermediate **113** with chiral triazolium-derived carbene **115**. After ring-opening of the epoxide, intermediate **114** does not tautomerize, but goes through an oxyanion-initiated elimination process to form an achiral ketene intermediate **116**. As ketene **116** is achiral, nucleophilic attack of phenol resulted in racemic product **112**.

Scheme 22



Scheme 22 Proposed mechanism for the NHC-catalyzed ring-expansion via a ketene intermediate.

Compared to Rovis' enantioselective synthesis, the ketene pathway may be favored due to the basicity of the alkoxide intermediate generated after ring opening of epoxyaldehyde, which is much stronger than that of chlorides. Hence, combined with the observation of a racemic product,

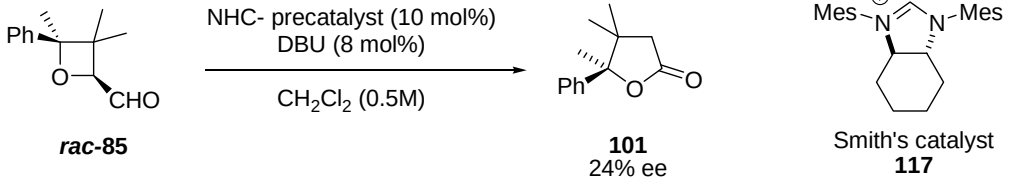
we strongly believe that a ketene intermediate from alkoxide-assisted elimination was formed.

However, this ketene mechanism might be unique to the ring opening of epoxyaldehyde, since the ring expansion of tetrahydrofurfural has not been achieved. A collaboration is being carried out with Travis Dudding at Brock University, and the mechanism of the reaction will be studied by using DFT models.

2.3 Kinetic resolution of 3,3,4-Trimethyl-4-phenyloxetane-2-carbaldehyde

The successful invention of a novel lactonization method based on NHC-catalyzed ring expansion reaction [25] prompted kinetic resolution investigations in the hopes of obtaining enatioenriched lactones.

The kinetic resolution was carried out using racemic 3,3,4-trimethyl-4-phenyloxetane-2-carbaldehyde **85**. Rovis' catalyst **110** [34] and Smith's catalyst **117** [36] were employed for the investigation (**Table 4**).



***rac*-85** → **101** 24% ee

Smith's catalyst **117**

Entry	Catalyst	T (°C)	Time (min)	Conversion (%) [a]	Product ee (%)	Selectivity factor [35]
1	**117**	20	60	N.R.	n.d. [b]	n.d.
2	**110**	20	60	86	n.d.	n.d.

3	**117**	20	80	N.R.	n.d.	n.d.
4	**110**	0	80	30	24	1.8

[a] Conversion was calculated based on the integration of ^{1}H NMR.
[b] nd: not determined.

Table 4 Kinetic resolution of racemic 3,3,4-Trimethyl-4-phenyloxetane-2-carbaldehyde **84**.

Surprisingly, although catalyst **117** belongs to imidazolinium-derived NHCs, it did not show any catalytic activity in the ring-expansion reaction (entries 1 and 3, **Table 4**). Rovis' catalyst **110** efficiently facilitated the lactonization at room temperature with some unidentified impurities (entry 2, **Table 4**). This result confirmed our observation made during initial screening that (entry 4, **Table 1**): triazolium-based NHCs with electron-withdrawing groups provide moderate yield of the desired lactone **65**.

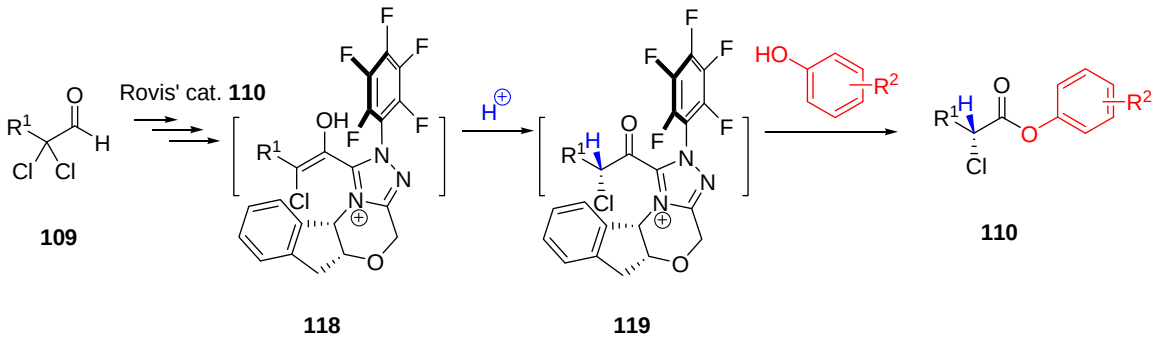
At 0°C, the reaction was catalyzed by **110** at a slower and hence more controllable rate, allowing for the reaction to be quenched at 30% conversion. Analysis of the reaction mixture by HPLC using a chiral stationary phase revealed that the lactone **101** was obtained in 24% e.e. The stereoselectivity factor for this kinetic resolution was calculated [35] (the stereoselectivity factor was calculated to be 1.8); one enantiomer of the starting material **85** reacts 1.8 times faster than the other.

2.4 NHC-catalyzed ring-expansion of oxacycloalkane-2-alkyl-2-carboxyaldehydes

Another possible stereoselective method using this novel lactonization [25] was performed through a dynamic kinetic asymmetric transformation (DYKAT) process. (See 5.2.1 for details of DYKAT.)

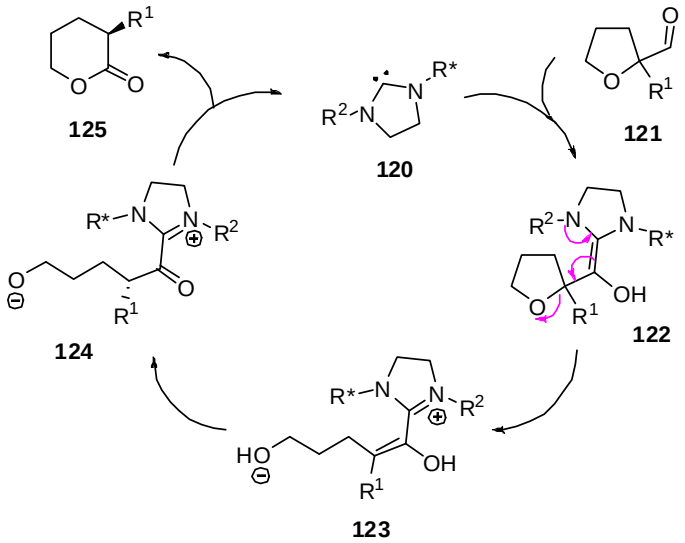
Reported by Rovis *et al.* [34], enantioselective NHC-catalyzed redox transformation of an α-reducible aldehyde was obtained at the tautomerism step by facially discriminated protonation

(**Scheme 23**).



Scheme 23 Facially discriminated protonation in Rovis' synthesis. [34]

By applying DYKAT to our ring expansion reactions, we proposed that starting from racemic α-substituted oxacycloalkane-2-carboxaldehydes **121** and using chiral NHC **120**, Breslow intermediate **122** would form followed by ring-opening to produce intermediate **123**. Enantioselectivity could be obtained at this step as the facially discriminated protonation of **123** to give enantiomerically enriched carboxylate **124**. Ring closure through nucleophilic attack of the alkoxide would produce the enantioenriched lactone **125**. (**Scheme 24**)

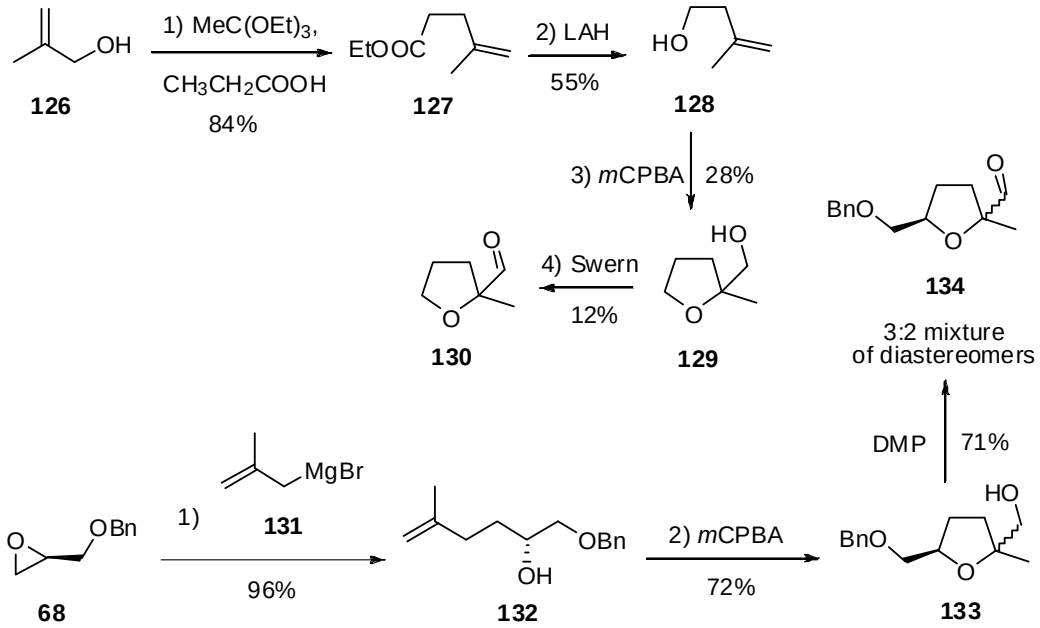


Scheme 24 Proposed mechanism for NHC-catalyzed DYKAT.

To test the proposed mechanism, two oxacycloalkane-2-methyl-2-carboxaldehydes **130** and **134** were prepared to test the enantioselectivity and the diastereoselectivity in the ring-expansion reaction.

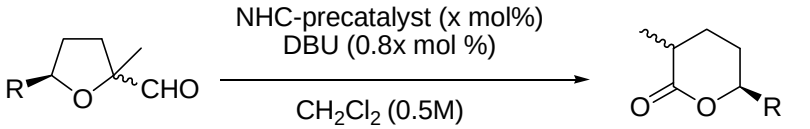
Substrate **130** was synthesized in four steps: 1) Claisen rearrangement of 2-methyl-3-propen-1-ol **126** gave ethyl 4-methyl-5-pentenate **127**; 2) reduction of the ester **127** using LAH yielded the corresponding alcohol **128**; 3) reaction of the alcohol **128** with *m*CPBA resulted in the tandem epoxidation-cyclization to produce racemic (2-methyl-tetrahydrofuran--2-yl)methanol **129**; and 4) oxidation of **129** to obtain aldehyde **130** (**Scheme 25**).

Substrate **134** was synthesized in three steps: 1) ring-opening of (*S*)-2-(benzyloxymethyl) oxirane **68** using 2-methylallylmagnesium bromide **131** to yield the corresponding enantiopure alcohol **132**; 2) cyclization of alcohol **132** to produce a 3:2 mixture of diastereomers of (*R*)-(5-(benzyloxymethyl)-2-methyl-tetrahydrofuran-2-yl)methanol **133**; and 3) oxidation of **133** yielded substrate **134** (**Scheme 25**).



Scheme 25 Synthesis of substrates **130** and **134**.

We then applied the imidazolinium-derived NHC-catalyst **60** on those two substrates under various conditions, but unfortunately we observed no reaction (entries 1, 2 and 4 **Table 5**).



130 R= H;
134 R= CH_2OBn

135 R= H;
136 R= CH_2OBn

Entry	R	NHC precatalyst	Catalytic loading (mol %)	T °C	Yield
1	H	**60**	50	25°C	N.R. [a]
2	H	**60**	50	45°C [c]	Decomp. [b]
3	H	**67**	50	25°C	N.R. [a]
4	CH_2OBn	**60**	30	25°C	N.R. [a]

[a, b] Determined by ^{1}H NMR, followed the reactions for up to 7 days. [c] reflux.

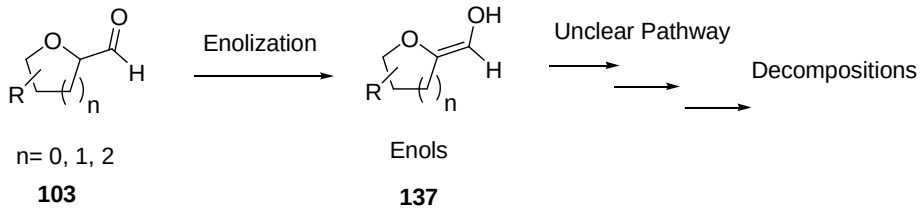
Table 5 Evaluation of reaction conditions for NHC-catalyzed ring expansion of **130** and **134**.

The unsuccessful ring expansion of **130** and **134** (entries 1, 2 and 4) is likely due to the bulkiness of catalyst **60** and the elevated level of steric hindrance of the quarternary centers in **130** and **134**, preventing NHC **60** from reacting with the aldehydes. A slightly less hindered catalyst **67** (entry 3) was screened and still no reaction was observed. Clearly, this version of NHC-catalyzed ring expansion is highly sensitive to steric hindrance. As a consequence of our results and

previous precedents in this area, this investigation was abandoned to pursue more attractive avenues of research.

2.5 Difficulties in the synthesis of oxacycloalkane-2-carboxaldehydes

The synthesis of oxacycloalkane-2-carboxaldehydes were proved to be difficult in the oxidation step of the corresponding alcohols. We reasoned that those difficulties might be due to the enolization of α-alkoxyaldehydes **103** to form enols **137**, followed by a presumed aldol reaction pathway toward decomposition (**Scheme 25**).



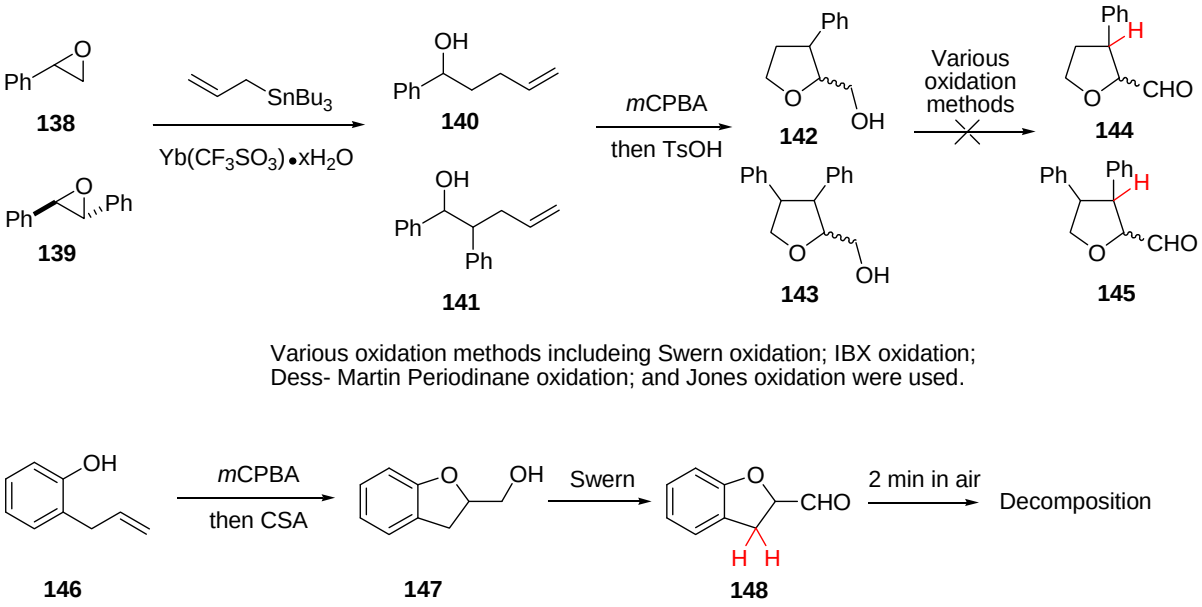
Scheme 26 A possible explanation for the instability of oxacycloalkane-2-carboxaldehydes.

Although various oxidation reactions were attempted, we failed to produce several of the desired oxacycloalkane-2-carboxaldehydes. In general, difficulties in the oxidation step occurred with two kinds of aldehyde precursors: 1) aldehydes with β- benzylic hydrogen; and 2) volatile aldehydes.

1) Aldehydes with β- benzylic hydrogen

Substrates with phenyl groups were prepared, in the hopes of obtaining phenyl-substituted or

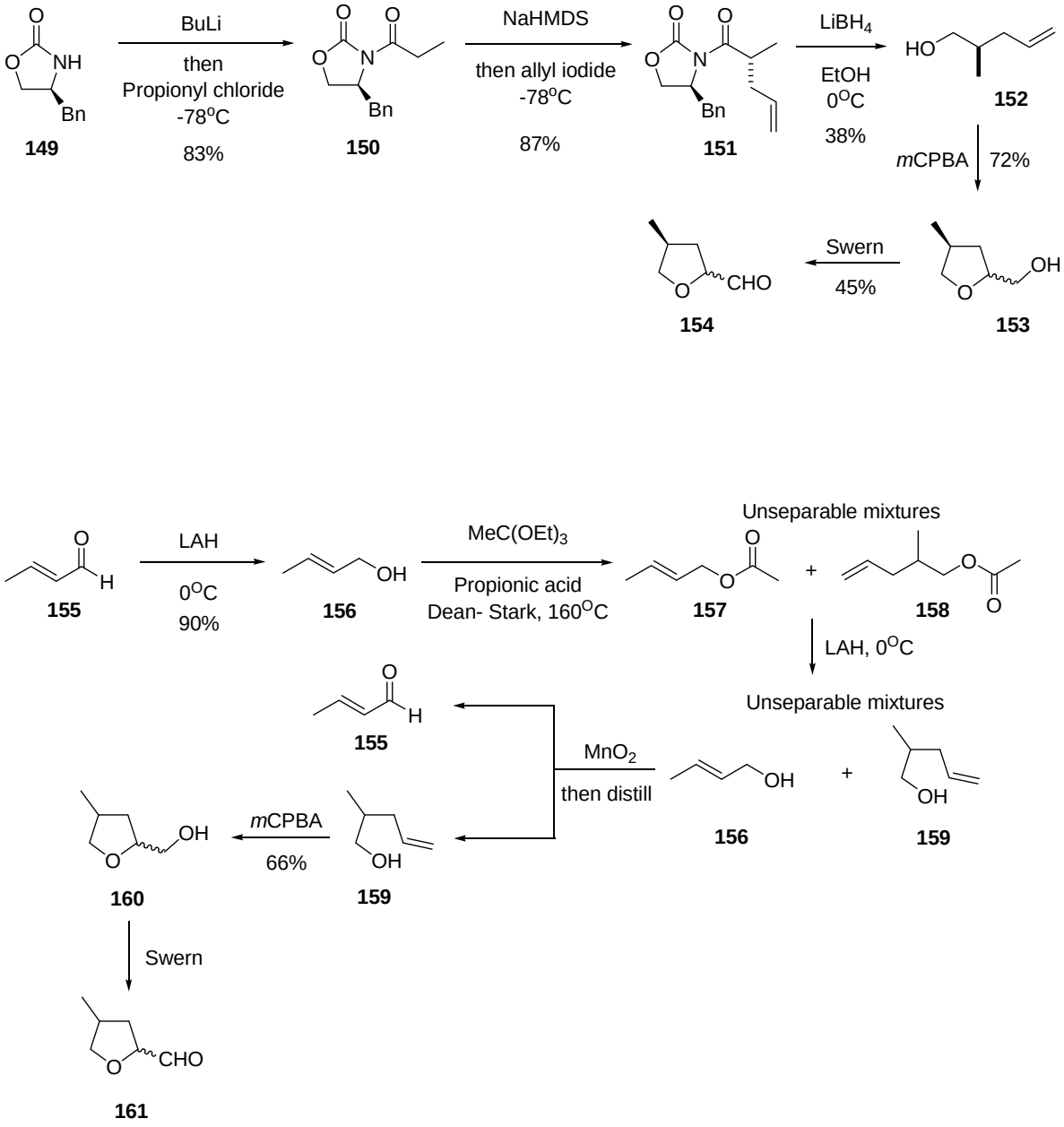
bicyclic lactones. [37] However, a variety of mild oxidation methods all resulted in the decomposition of these aldehydes (**Scheme 27**). The decomposition could be due to β- benzylic hydrogen atoms that are highly susceptible to oxidation reactions.



Scheme 27 Difficulties in oxidation of β-benzylic hydrogen bearing tetrahydrofurfural derivatives (β- benzylic hydrogen are showed in red color).

2) Volatile aldehydes

Some oxacycloalkane-2-carboxaldehydes could be obtained through oxidation reactions. However, their low molecular weights, and hence volatile nature made it difficult to obtain these aldehydes in substantial yields. (**Scheme 28**) [38]



Scheme 28 Synthesis of volatile oxacycloalkane-2-carboxaldehydes.

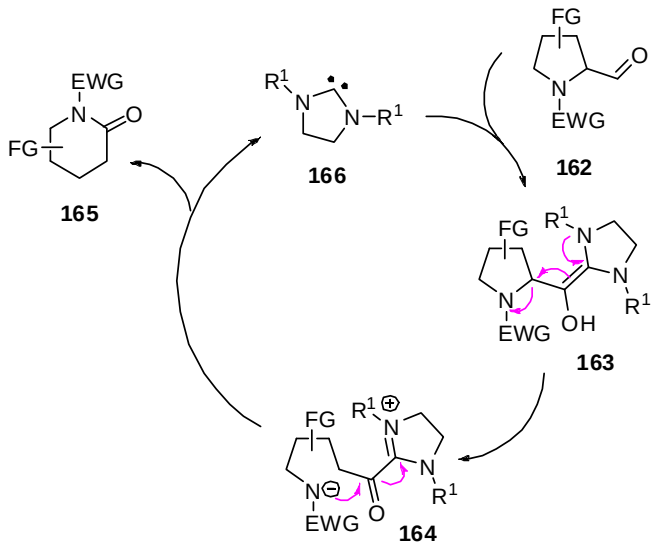
III. RESULTS AND DISCUSSIONS PART II:

NHC- Catalyzed Ring-Expansion Lactamization Reactions

3.1 Research objectives

An extension of the previously discussed ring-expansion lactonization reaction is the formation of lactams. To the best of our knowledge, NHC-catalyzed ring-expansion lactamization reactions have never been performed. Due to the importance of lactam functionality, and therefore novel methodologies for the Synthesis of functionalized lactams, we decided to look into such transformation.

According to the proposed reaction mechanism (**Scheme 29**), after the formation of Breslow intermediate **163** between NHC **166** and aldehyde **162**, an intermediate with both a stabilized amide and an activated carboxylate **164** is formed through the ring-opening process. Intramolecular nucleophilic attack of the amide onto the activated carboxylate of **164** gives functionalized lactams **165**.



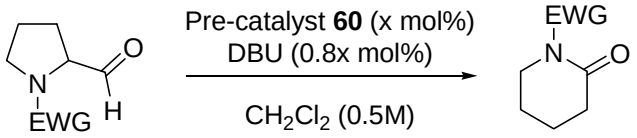
Scheme 29 a proposed mechanism for NHC-catalyzed ring-expansion lactamization.

As amides are poor leaving groups, [21-22] electron-withdrawing groups were installed on the nitrogen atom to facilitate the ring-opening process.

3.2 Formation of functionalized 6- membered lactams through NHC-catalyzed ring-expansion of azacycloalkane-2-carboxaldehydes.

3.2.1 Reaction optimization

The ideal reaction conditions for the formation of lactones encouraged us to first try the imidazolinium-derived carbene for the catalytic lactamization. [25] Although we did observe a low conversion of the aldehydes into the corresponding lactams (entries 1 and 3, **Table 6**), yields were low and the reaction appears to be sensitive to the electronic properties of the electron-withdrawing groups attached on the nitrogen atom, as we expected.



167, EWG= $COOC(CH_3)_3$
168, EWG= $COCH_3$
169, EWG= Ts

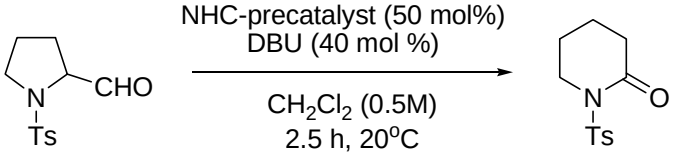
170, EWG= $COOC(CH_3)_3$
171, EWG= $COCH_3$
172, EWG= Ts

Entry	**EWG**	**Catalytic loading (%)**	**Temperature**	**Time (d)**	**Conversion(%)**[a]
1 [b]	$COOC(CH_3)_3$	10	25	7	14
2	$COCH_3$	10	25	11	30
3	$COCH_3$	10	45	3	Decomp
4	$COCH_3$	30	45	3	Decomp
5	Ts	10	25		Decomp

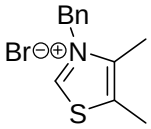
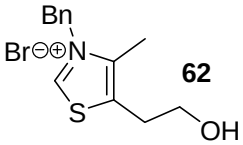
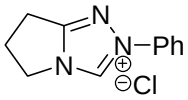
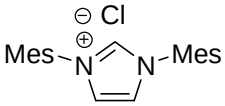
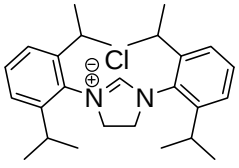
[a] Conversions were calculated based on integrations of ^{1}H NMR; [b] substrate contributed by Karen Thai.

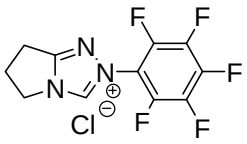
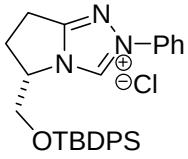
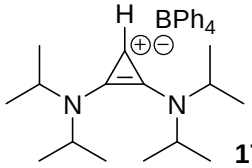
Table 6 Preliminary results for NHC- catalyzed ring expansion of azacycloalkane-2-carboxaldehydes.

Based on those encouraging results, we decided to screen different NHC catalysts with the lactamization reaction. Toluenesulfonyl (Ts) group was employed as the electron-withdrawing group. (**Table 7**) The choice of tosyl group as the electron-withdrawing group was made because we found tosyl-bearing aldehyde **169** was stable to silica gel chromatography and can be stored under air and room temperature for months.



169 **172**

Entry	NHC- precatalyst	Yield [b] (%)
1	 **61**	Decomp.
2	 **62**	Decomp.
3	 **25**	Decomp.
4	 **28**	Decomp.
5	 **60**	Decomp.

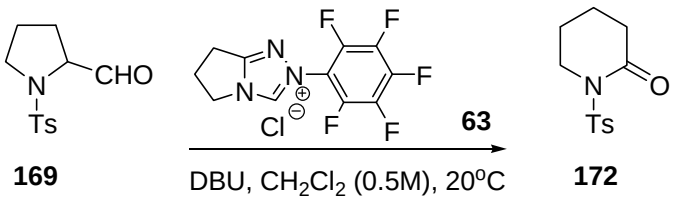
6	 **63**	88
7	 **173**	Decomp.
8	 **174**	Decomp.

[a] All reactions were performed on a 60 mg scale of aldehyde; DBU= 1, 8- diazabicyclo[5.4.0]undec-7-ene. [b] Yield of pure, isolated product.

Table 7 Optimization of the lactamization reaction with different NHC pre-catalysts.

After screening different NHC pre-catalysts, we found that the pentafluorophenyl triazolium carbene **63** was exclusively effective for the lactamization reaction (entry 6, **Table 7**). As we previously discussed in the lactonization reaction, electron-poor carbenes promoted the reaction most efficiently.

The effects of catalytic loading and equivalents of base were determined using **63**. (**Table 8**)



Entry	**Catalytic loading (mol %)**	**DBU loading (mol %)**	**Time (h)**	**Yield [b] (%)**

1	**50**	**40**	**2.5**	**88**
2	**10**	**8**	**24**	**N.R.**
3 [a]	**20**	**48**	**16**	**82**
4	**10**	**100**	**12**	**Decomp.**

[a] DBU was added in three portions with 16 mol % each portion. The reaction was followed by TLC, a second or third portion of DBU was added once no obvious progress of the reaction was occuring. [b] Yield of pure isolated product.

Table 8 Further optimization of the lactamization reaction with the pentafluorotriazolium--derived carbene **63**.

In order to reduce the catalytic loading, we first applied our optimal conditions for lactonization reaction to the lactamization, in which 10 mol % NHC precatalyst **63** and 8 mol % DBU were used (entry 2, **Table 8**). However, no reaction was observed in the first 24 hours followed by slight decomposition of the starting material **169**.

Consequently, we raised the catalytic loading to 20 mol-% and the loading of DBU to 16 mol-%, correspondingly (entry 3, **Table 8**). The desired product was observed within 5 hours by both TLC and ^{1}H NMR analysis. However, after this point, the lactamization ceased to progress. Notably, the brown color observed at the beginning of the reaction had faded. Though none have reported the relationship between the color and NHC-catalyzed reactions, dark brown or yellow colors are always associated with the generation of NHCs upon the addition of DBU to NHC precatalysts. This observation suggested that the pentafluorotriazolium carbene **63** was somehow deactivated. Then a second portion of 16 mol % DBU was added to the reaction mixture. The addition resulted in the regeneration of the dark brown color. TLC analysis of the reaction 30 minutes after the second addition indicated a dramatic progress of the lactamization. Once more the reaction ceased to progress, and a third portion of 16 mol % DBU was added. The lactamization was accomplished in additional 30 minutes with an isolated yield of 82%.

This highly intriguing result reflected the importance of DBU in this lactamization reaction.

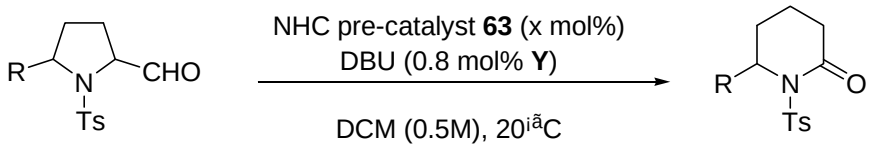
Hence, we tried the reaction with 10 mol % of catalytic loading and 100 mol % of DBU (entry 4, **Table 8**). However, this reaction ended up with decomposition in one hour.

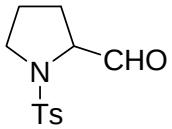
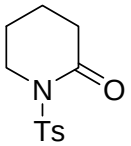
Based on all those results discussed above, we recognized the optimal conditions of the ring-expansion lactamization reaction as follows.

1) Catalytic loading: 20 mol % loading of the pentafluorotriazolium carbene pre-catalyst **63**;
2) The reaction is carried out at room temperature and 0.5 M concentration;
3) DBU should be added portion-wise with 16 mol % each portion till the completion of the reaction.

3.2.2 Scope of the reaction

We then applied our optimal conditions to the synthesis of functionalized lactams, as shown in **Table 9**. Under the catalysis of **63**, prolinal derivatives with substituents at the 5-position were transformed into the corresponding monosubstituted lactams in good yields (entry 2 and 3, **Table 9**). Ring-expansion lactamization of 2, 3 and 4-position substituted prolinal derivatives are still being investigated.



Entry	Substrate [a]	Times of DBU addition (Y) [b]	Product	Yield [c] (%)
1	 **169**	3	 **172**	82

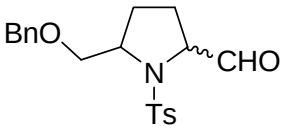
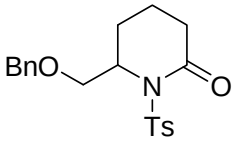
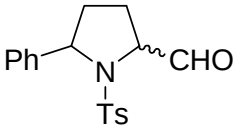
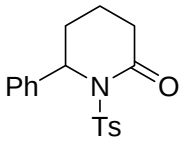
2	 **175**	3	 **177**	60
3	 **176**	5	 **178**	56
[a] Unless otherwise noted, all reactions were performed using racemic substrates at 0.5 M in CH_2Cl_2 at 20 °C for 7-12 h using 20 mol % of **63** and addition of 3 or 5 portions of 16 mol % of DBU. Substrates **175** and **176** were used as a ~1:1 mixture of epimers. [b] Reactions were followed by TLC, when there was no significant progress, another portion of DBU was added. This procedure was repeated until the completion of the reaction. [c] Yield of isolated pure product.				

Table 9 Scope of the ring-expansion lactamization reaction.

3.2.3 Conundrums in the NHC-catalyzed ring-expansion lactamization

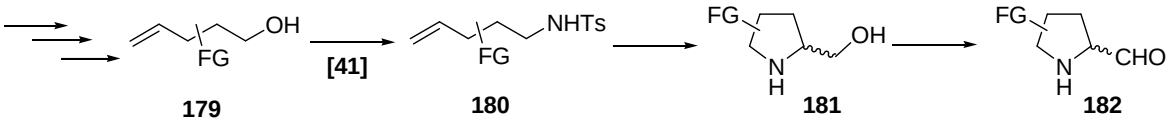
Despite the good results we have obtained, two observations are still waiting to be explained: 1) why DBU should be added portionwise; and 2) why DBU should be added in a large excess compared to the NHC-precatalyst.

To understand these unexplained observations, we have established cooperation with Travis Dudding at Brock University. Preliminary calculation results from Travis Dudding strongly suggested that after deprotonation of the carbene pre-catalyst, the protonated DBU is essential to the ring-opening step of lactonization reactions. This is because hydrogen bonding between the protonated DBU and the oxygen atom of tetrahydrofuran ring can be formed, which facilitates the ring-opening process (Gravel and Dudding Group, *unpublished results*).

3.2.4 Synthesis of substrates **175** and **176**

The few known methods for the synthesis of multi-substituted prolinal derivatives required at least 10 synthetic steps. As a result, an easy and general synthetic scheme to produce substituted prolinal derivatives was required.

A synthetic pathway similar to the method for the synthesis of tetrahydrofuran derivatives was developed (**Scheme 30)**.

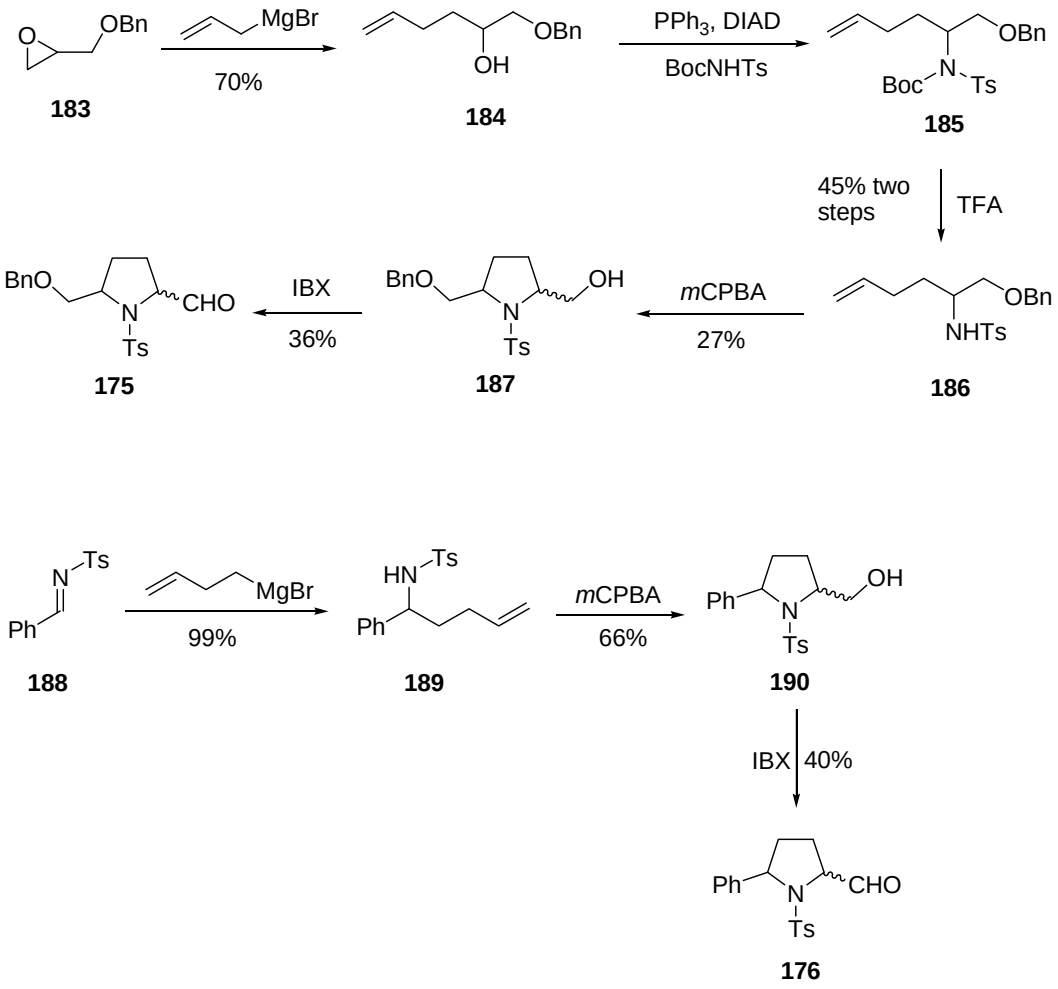


179 **180** **181** **182**

Scheme 30 Novel and general synthetic route to functionalized prolinal derivatives (FG: functional groups).

The most important step of our design is the *O*→*N* transformation (**179** to **180**, **Scheme 30**). Though there is no direct literature precedent for this step, we found several papers that described such a transformation using Weinreb's reagent (Boc-protected *p*-tolenesulfonamide) under Mitsunobu reaction conditions. [39] The tandem epoxidation-cyclization reaction (**180** to **181**) was also possible after our experimentations.

Aldehyde **175** was synthesized in 5 steps, in which intermediate **186** was obtained through *O*→*N* transformation. Mitsunobu reaction conditions using Weinreb's reagent produced **185** followed by deprotection to produce **186**. Tandem epoxidation-cyclization gave alcohol **186**, which was oxidized using IBX to yield the prolinal aldehyde **175**. Aldehyde **176** was also synthesized efficiently in 3 steps (**Scheme 31**).



183 **184** **185** **186** **187** **175** **188** **189** **190** **176**

Scheme 31 Synthesis of substrates **175** and **176**.

IV. RESULTS AND DISCUSSIONS PART III:

NHC-Catalyzed Diels-Alder Reactions and Its Applications to Cascade Reactions

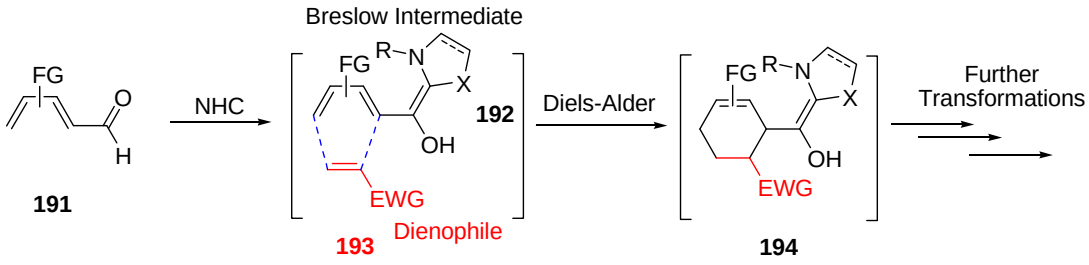
4.1 Research objectives

In Chapters II and III, two different NHC-catalyzed ring expansion reactions were discussed: lactonization and lactamization. The main feature of these reactions is NHC-induced reversal of aldehyde reactivity through the formation of a Breslow intermediate. [14] During the transformations, aldehyde is converted into an electron-donating group. Although NHC-induced reversal of aldehyde reactivity is well established, [14] this concept has never been applied to the activation of dienes in Diels-Alder reactions.

Dienals are typically inactive toward Diels-Alder reactions due to the electron-withdrawing nature of the aldehyde group, which increases the energy gap between the highest occupied molecular orbital (HOMO) of dienals and the lowest unoccupied molecular orbital (LUMO) of dienophiles. The resulting energy gap is too large to favor a Diels-Alder reaction to occur. However, under the catalysis of NHCs, the aldehyde group of dienals is converted into an electron-donating Breslow intermediate. Through this so-called "HOMO-raising" effect, the energy gap between HOMO of dienes and LUMO of dienophile gets smaller. As a result, Diels-Alder reactions would be possible.

The possibility of effecting the *Umpolung* of electron-poor dienes using NHC catalysts, which would lead to the activation of inactivated dienes toward Diels-Alder reactions, intrigued us to pursue this research project **(Scheme 32)**. We envisioned that inactivated diene **191** would form Breslow intermediate **192** under the catalysis of certain NHCs. The activated diene **192** could then serve for the Diels-Alder reaction with an activated dienophile **193** to give the Diels-Alder adduct **194**. Note that adduct **194** is actually a Breslow intermediate, which means it

could still carry out further transformations. This gave us the basis for the design of the cascade reaction.

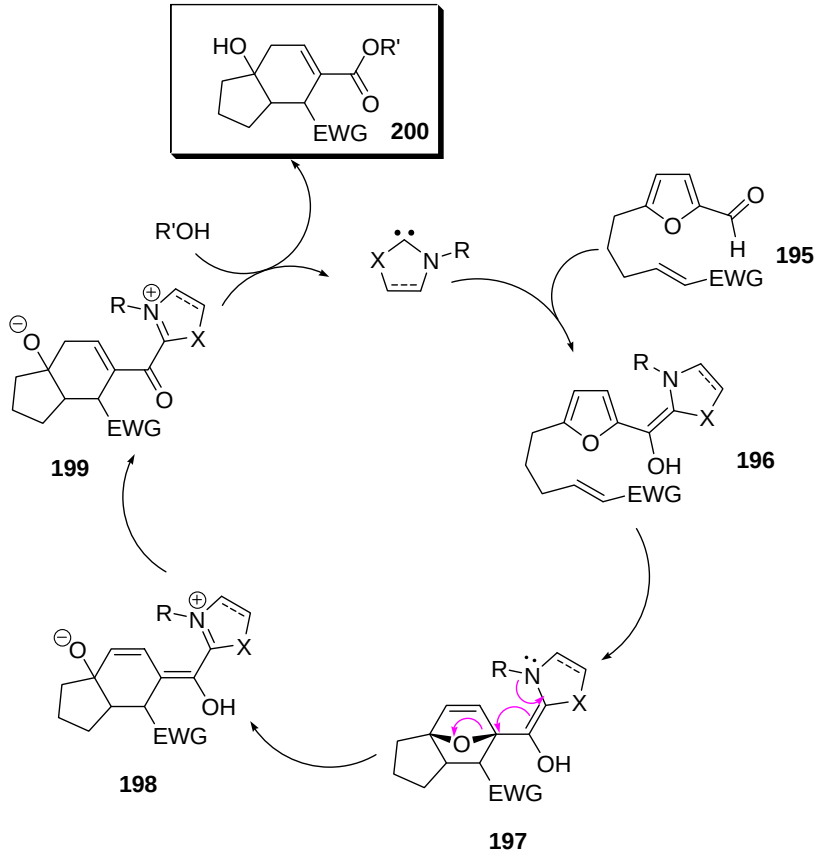


Scheme 32 The proposed Diels-Alder reaction of inactivated dienes under the catalysis of NHCs.

4.2 NHC-catalyzed cascade reactions and a proposed mechanism

The Diels-Alder reactions of inactivated dienes, as we illustrated in **Scheme 32**, is based on NHCs' ability in effecting the a^1-d^1 *Umpolung* of dienals. Most importantly, as mentioned earlier, Breslow intermediate **194** is still able to carry on further transformations. We decided to apply our newly developed ring-expansion to the Diels-Alder reaction and try to demonstrate a fascinating cascade reaction.

Under NHC catalysis, starting with functionalized 2-furaldehydes **195** as the inactivated diene, Breslow intermediate **196** would be formed, which would transform the inactivated diene into an electron-rich diene. As a result, another Breslow intermediate in the form of Diels-Alder adduct **197** would be formed. Intermediate **197** could then go through a ring-opening reaction to give intermediate **198** as we described in Chapter II. After tautomersim of **198**, activated carboxylate **199** could be attacked by alcohols in a nucleophilic addition pathway to give the desired cascade product **200** (**Scheme 33**). A ring-expansion product resulting from an intramolecular alkoxide attack in **199** would not be possible due to the endocyclic double bond.

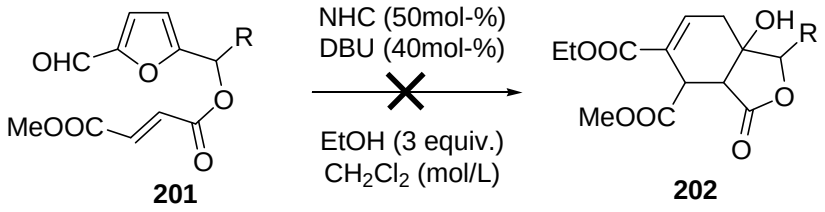


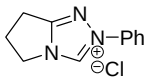
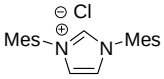
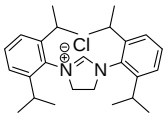
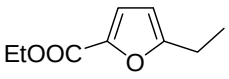
Scheme 33 Our design: NHC-catalyzed Diels-Alder-ring opening cascade reactions.

4.3 Preliminary results

4.3.1 Efforts toward NHC-catalyzed intramolecular cascade reactions:

Our first attempts at NHC-catalyzed intramolecular cascade reactions were carried during my undergraduate summer research (between April and August, 2007), two substrates were synthesized and screened for the cascade reaction using different NHCs. (**Table 10**)



Entry	R=	NHC pre-catalyst	Results
1	H	 **25**	Decomposition
2	H	 **28**	Decomposition
3	H	 **60**	Decomposition
4	CH_3	**25**	Decomposition
5	CH_3	**28**	 **203** [a]
6	CH_3	**60**	Decomposition

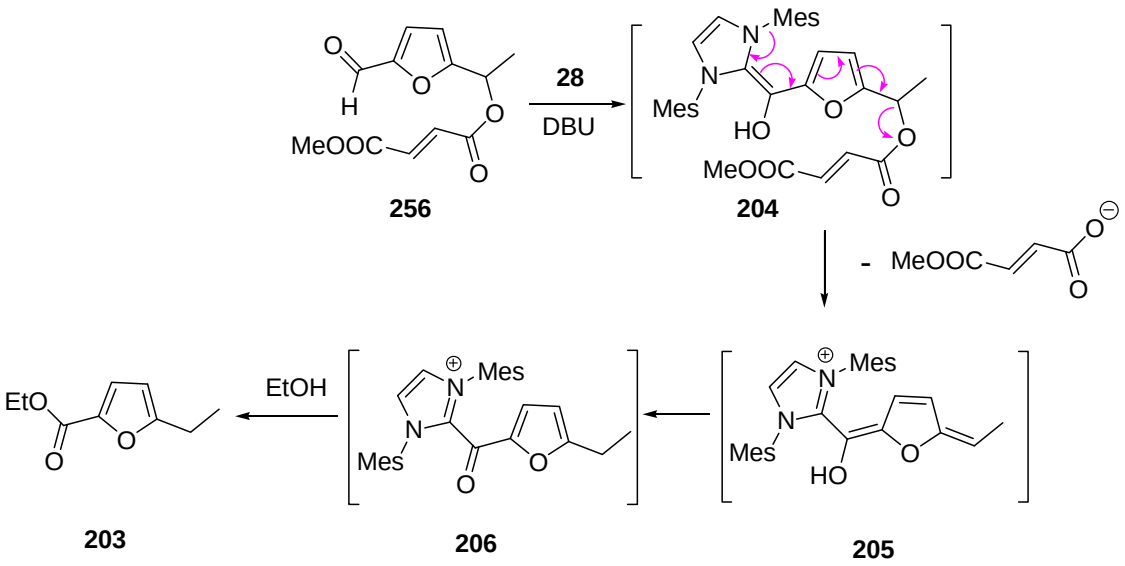
[a] The structure of **203** was tentatively assigned based on its ^{1}H NMR spectra.

Table 10 First attempts at NHC-catalyzed intramolecular cascade reaction during my summer research in 2007.

The substrates for the first attempt were investigated because the analogues lacking the aldehyde substitutent were able to go through Diels-Alder reactions, as demonstrated independently by Jung [40] and Sauer [41]. However, except for the observation of an unexpected

eliminated side product **203**, all other substrates (entries 1-4 and 6) using different NHCs resulted in decomposition.

Although we failed to observe any cascade reaction, the structure of **203** offered us new directions. After further consideration, a proposed mechanism could explain the source of **203**, as shown in **Scheme 34**. In the proposed mechanism, we reasoned that after the formation of the formation of Breslow intermediate **204** could initiate the elimination to give **205**. After tautomerism of **205**, activated carboxylate **206** was attacked by ethanol, giving rise to the observed side product **203**.

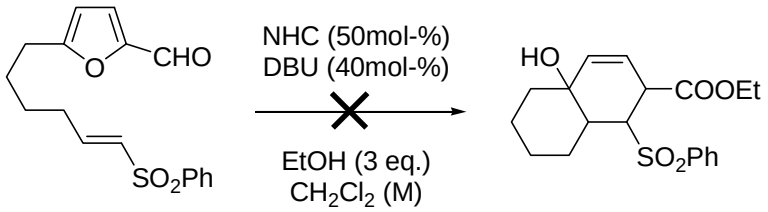


Scheme 34 A possible mechanism for the source of side product **203**.

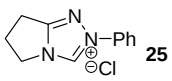
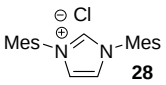
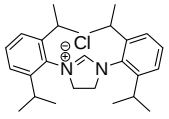
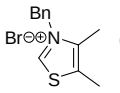
The mechanism we proposed (**Scheme 34**) suggested that it was possible to raise the electron density of inactivated dienes through NHC catalysis (see arrows in **204**). Hence, it encouraged us to further look into the cascade reaction. In addition, the mechanism also showed us that a

carboxylate moiety should not be installed in our substrates, as the carboxylate moiety could be eliminated (**204** to **205**).

Based on the observations made in **Table 8**, we then synthesized substrate **207**, which has no possible eliminating fragment on the C5-position of the furan ring (**Table 9**). In the substrate **207**, the dienophile is activated through a sulfone group, and we viewed this substrate as a good candidate for the NHC-catalyzed cascade reaction (**Table 11**). We screened six different NHCs with substrate **207**. However, instead of a Diels-Alder reaction, an uncommon and efficient oxidation was observed (entry 6) using pentafluorophenyltriazolium **63** as pre-catalyst. Though NHC-catalyzed oxidation of aldehydes using a variety of oxidants has been reported by Scheidt et al [42], the oxidation reaction directly utilized air as the oxidant as we observed has not been reported.



207 **208**

Entry	NHC precatalyst	Results
1	 **25**	N.R.
2	 **28**	N.R.
3	 **60**	N.R.
4	 **61**	N.R.

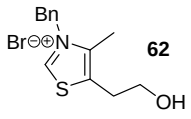
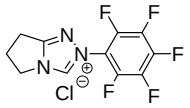
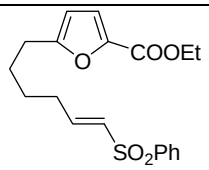
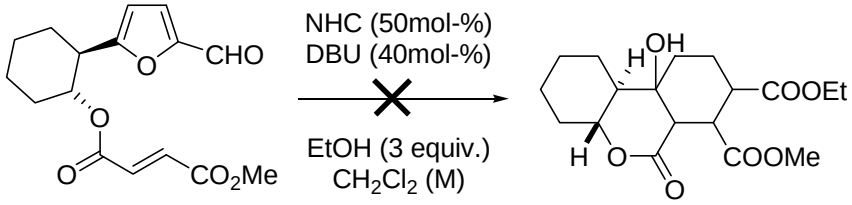
5	 **62**	N.R.
6	 **63**	 **209**

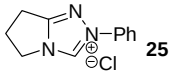
Table 11 Results of NHC-catalyzed intramolecular cascade reactions using substrate **207**.

Reasoning that the saturated carbon linear chain in **207** may not adopt a conformation that favors the desired Diels-Alder reaction, we decided to restrict the flexibility of the substrate.

With this conformational constraint in mind, we installed both the inactivated diene and activated dienophile on a cyclohexyl ring (substrate **210**) in the hope that the molecule will adopt a suitable conformation to undergo Diels-Alder reaction. Unfortunately, only the oxidation product **213** was observed under the catalysis of pentafluorotriazolium carbene precursor (Entry 3, **Table 12**). Noticeably, this oxidation reaction is very efficient under the reaction conditions. As shown in **Table 12**, NHC **63** catalyzes the oxidation reaction in 3 hours with a yield of 85%.



210 **211**

Entry	NHC precatalyst	Results
1	 **25**	N.R.

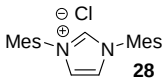
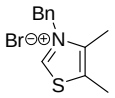
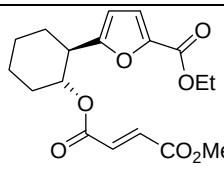
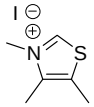
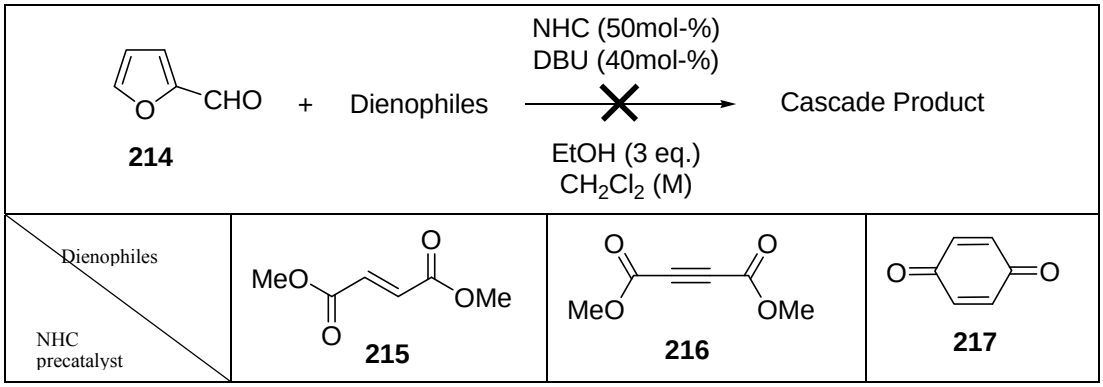
2	 **28**	N.R.
3	 **61**	 **212** 85% yield
4	 **212**	N.R.

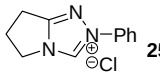
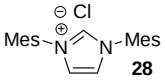
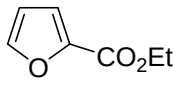
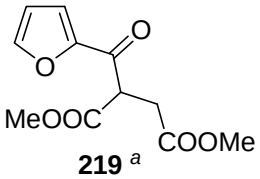
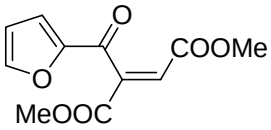
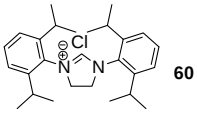
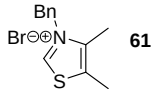
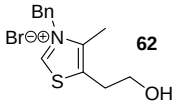
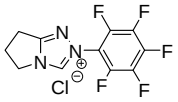
Table 12 Results of NHC-catalyzed intramolecular cascade reactions using substrate **210**.

Concurrently to the screening of various substrates with NHCs to pursue the cascade reaction, the intermolecular version of the reaction was also investigated.

4.3.2 Efforts toward NHC-catalyzed intermolecular cascade reactions:

The initial investigation was performed with 2-furaldehyde **214** as our inactivated diene, and dimethyl fumarate **215**, dimethyl acetylenedicarboxylate (DMAD) **216**, as well as *p*-benzoquinone **217** as activated dienophiles (**Table 13**).



 **25**	N.R.	Decomposition	Decomposition
 **28**	 **218**  **219** [a]	 **220** [a]	Decomposition
 **60**	n.d. [b]	Decomposition	n.d.
 **61**	n.d.	Decomposition	n.d.
 **62**	n.d.	Decomposition	n.d.
 **63**	n.d.	Decomposition	n.d.

[a] The structure of **219** and **220** were tentatively assigned based on its ^{1}H NMR spectra of the crude reaction mixture..

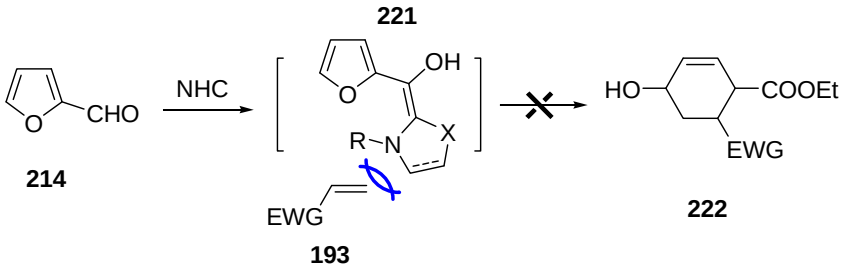
[b] n.d.: not determined.

Table 13 Results of NHC-catalyzed intermolecular cascade reactions using 2-furaldehyde as the inactivated diene.

To our disappointment, no intermolecular cascade reactions were observed. Under the catalysis of imidazolium carbene precursor **28**, 2-furaldehyde was oxidized to the corresponding ethyl ester **218** and the Stetter addition product **219** was also obtained. Interestingly, Stetter adduct **220** between 2-furaldehyde and DMAD was also obtained under the catalysis of **28**. To the best of our knowledge, Stetter reaction between aldehydes and alkyne has not been reported.

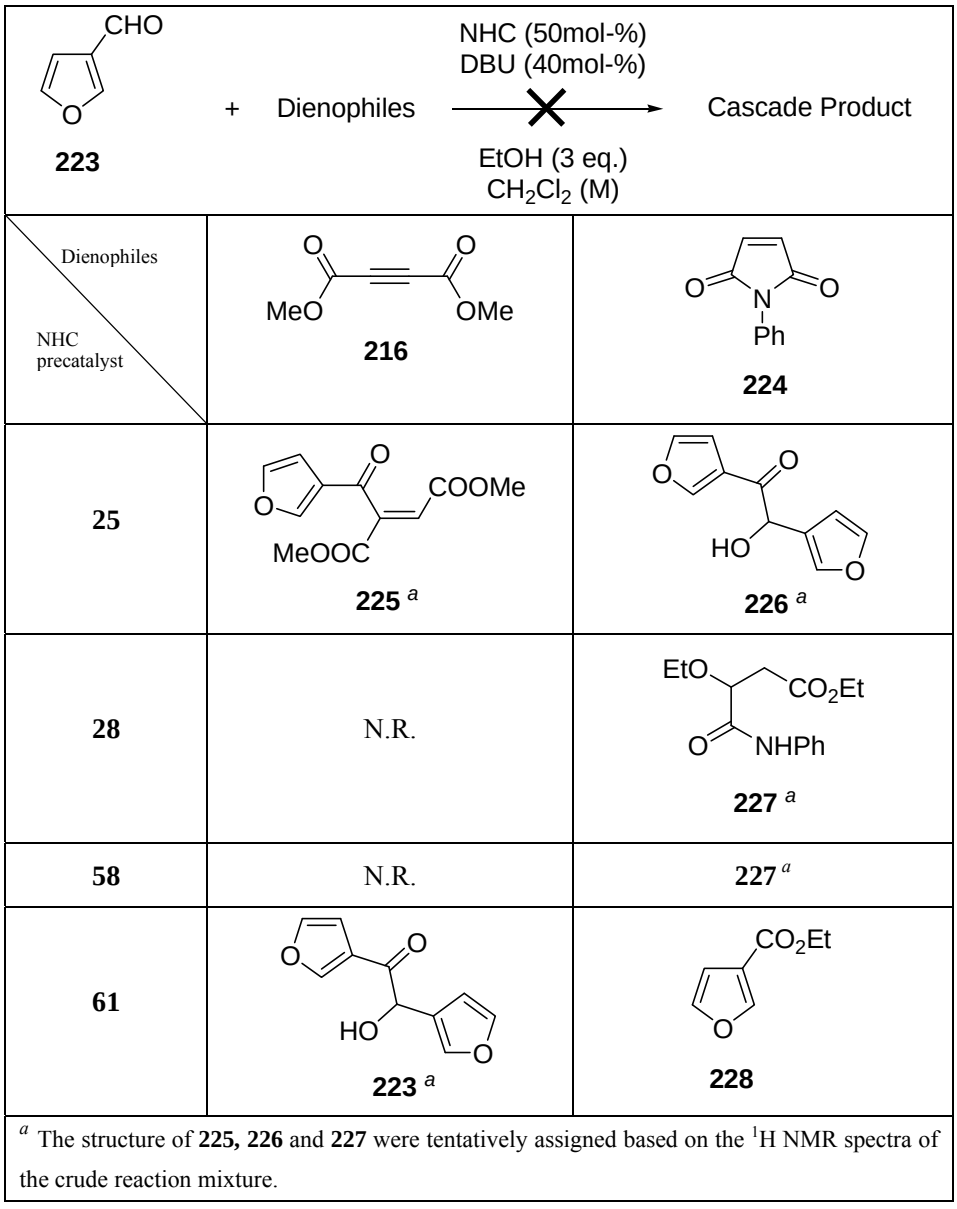
Encouragingly, we observed the first example of this type of Stetter reaction, even though the initial goal to perform the cascade reactions was not achieved.

From the experimental results gathered, we realized that the the bulkiness of the NHC after the formation of the Breslow intermediate may hinder the approach of the dienophile required for the intramolecular or intermolecular Diels-Alder reaction, and hence the cascade reaction cannot occur. (**Scheme 35**)



Scheme 35 Steric hindrance of **219** and the failure of the cascade reaction.

As a result, we screened another series of intermolecular cascade reactions by using 3-furaldehyde **223** as the inactivated diene (**Table 14**). Unfortunately, no cascade reactions were observed. However, the Stetter adduct **225** between 3-furaldehyde **221** and DMAD under the catalysis of phenyltriazolium carbene precursor **25** was observed. The catalytic screening of other carbenes resulted in the formation of benzoin reaction product **226** and oxidation product **228**. The tandem ring-opening Michael addition product **227** can be obtained using only DBU after further experimentations.



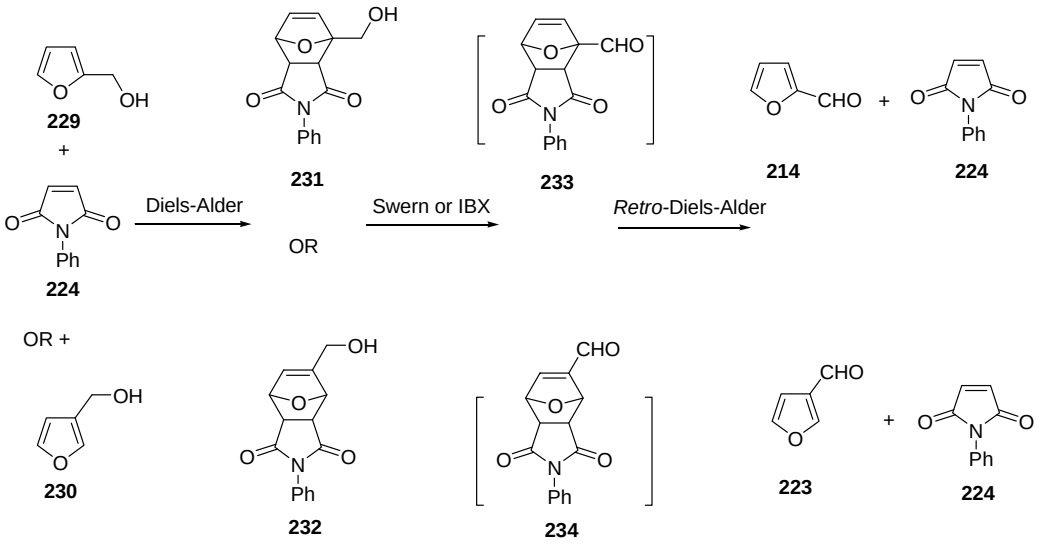
[a] The structure of **225, 226** and **227** were tentatively assigned based on the ^{1}H NMR spectra of the crude reaction mixture.

Table 14 Results of NHC-catalyzed intermolecular cascade reactions using 3-furaldehyde as the inactivated diene.

As seen in Chapter II, the ring-opening reaction or ring-expansion is possible under the catalysis of NHCs. [25] Therefore, to gain more insights of this proposed cascade reaction, the separate steps of the proposed reaction were investigated individually: 1) Diels-Alder reaction; and 2) ring-opening or ring-expansion reaction.

Our plan was to first carry out a Diels-Alder reaction between furan derivatives without the aldehyde group, then install an aldehyde group on the Diels-Alder adduct ring; followed by inducing ring-opening or ring-expansion using NHCs.

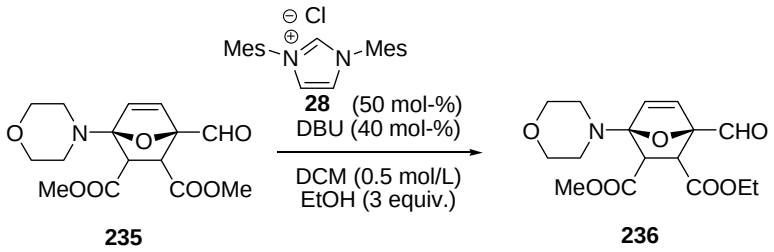
Both activated dienes **229** and **230** gave Diels-Alder adduct **231** and **232**, respectively, with dienophile **224** in high yields. These adducts were then oxidized with the goal of subjecting the corresponding aldehydes to NHC-catalyzed ring opening. However, *retro*-Diels-Alder reactions occurred upon oxidation, as evidenced by the formation of aldehydes **214** and **223** (**Scheme 36**).



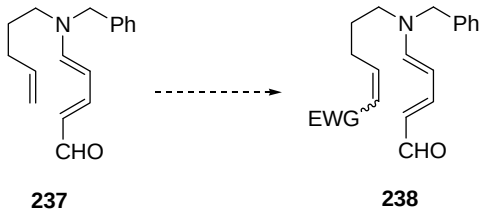
Scheme 36 Attempted formation of ring opening substrates.

Then we looked for a stable Diels-Alder adduct with an aldehyde group. We then synthesized Diels-Alder adduct **235** as reported by Zarrouk et al. [43] However, after subjecting aldehyde **235** to NHC catalysis, we still did not observe a ring opening product. Instead, trans-esterification product **236** was obtained (**Scheme 37**). This result finally told us that the furan system is a poor

one for the proposed cascade reaction. We then turned our attention to non-furan diene systems. Presently, our efforts are focused on the synthesis of substrate **238** (**Scheme 38**).



Scheme 37 Trans-esterification reaction of the stable Diels-Alder adduct **235**.



Scheme 38 The non-furan diene system.

V. CONCLUSIONS AND SUGGESTIONS FOR FUTURE WORK

In summary, two NHC-mediated novel transformations, which provided new ways to synthesize functionalized lactones and lactams, have been developed.

In the catalytic lactonization, imidazolinium-derived carbene was used as the catalyst. Ten lactones with substituents on different positions were synthesized using our method. Preliminary results of kinetic resolution using chiral Rovis' catalyst provided low selectivity. We also found that the ring expansion reaction is sensitive to the steric effect of both the substrates and the carbene, since α-substituted aldehyde precursors provided no reactivity. More importantly, based on our observations of a racemic ring-opening product under the catalysis of chiral NHC, we proposed a different reaction mechanism, which includes a ketene intermediate.

In the catalytic lactamization, pentafluorotriazolium-derived carbene was exclusively served for the reaction. We are still working on the scope of the reaction and three examples of lactam formation have been achieved. During our research, we found an intriguing yet unclear relationship between the progress of the reaction and the amount of DBU added. For the synthesis of substrates, we have developed a convenient and new sequence to produce multi-substituted tetrahydropyrrol derivatives.

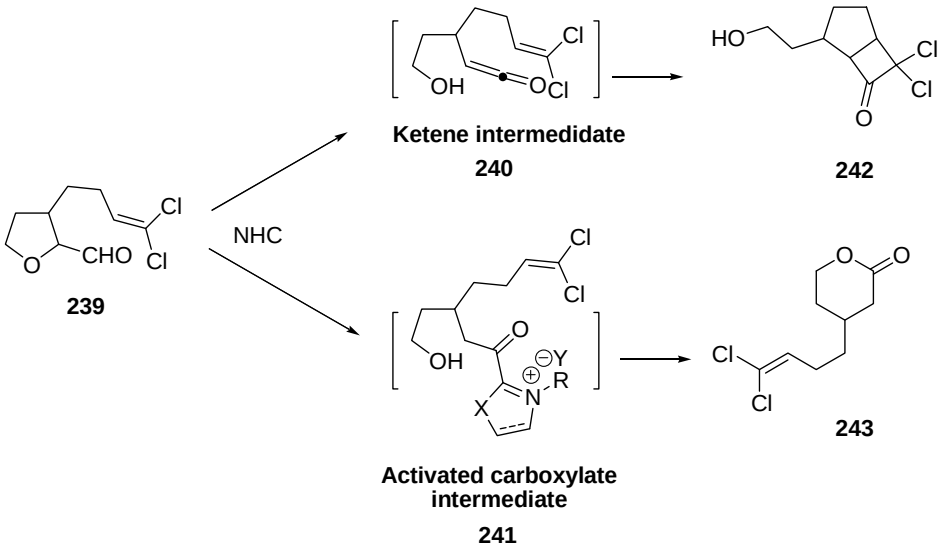
The NHC-catalyzed Diels-Alder reaction and its applications to cascade reactions is still under investigation. We have tried both intramolecular and intermolecular reactions under the catalysis of NHC, but none has shown any reactivity toward the Diels-Alder or cascade reactions. However, we observed the first example of the Stetter reaction between furaldehyde and alkyne (in our case, Stetter reaction between 2- or 3-furaldehyde and DMAD was observed); and an efficient NHC-catalyzed oxidation of aldehydes using air as the oxidant.

5.1 Future work for the NHC-catalyzed ring-expansion lactonization reaction.

Future work for the NHC-catalyzed ring-expansion lactonization will be focused on two aspects: 1) the mechanism of the reaction, namely, if the lactonization was achieved through a commonly accepted "activated carboxylate intermediate" or through a "ketene intermediate"; and 2) extension of the NHC-catalyzed ring expansion lactonization reaction.

5.1.1 Studies on the mechanism

As discussed in chapter 2, a racemic ring-opening product was obtained when a chiral NHC catalyst was used. This result suggests that the reaction proceeds through an achiral ketene intermediate. To verify this postulation, a method to trap the ketene is being developed (**Scheme 39**).

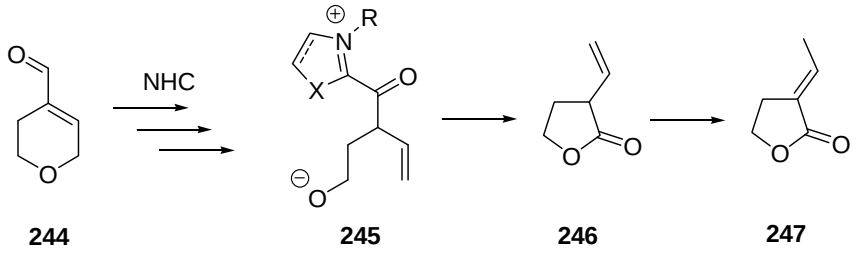


Scheme 39 The method to trap the ketene intermediate.

Subjection of **239** to NHC catalysis could yield two possible products. If the ring expansion goes through a ketene intermediate **240**, the dicholoroalkene moiety would trap such intermedidate to form a compound **242** that bears 4- and 5-membered bicyclic rings; if the reaction proceeds via an activated carboxylate intermediate **241**, only the formation of lactone **243** will be observed. However, even if the ketene intermediate **240** is formed, the formation of lactone might be much faster than the formation of cyclobutane moiety. Hence, failure to observe the formation of cyclobutane moiety may not indicate that the ring-expansion reaction goes through the "activated carboxylate mechanism". A series of the ketene trappers will be synthesized to investigate the reaction.

5.1.2 Extensions of the NHC-catalyzed ring-expansion lactonization reaction.

Based on the promising results from the ring-expansion lactonization reaction, another type of ring-expansion reaction has been proposed: synthesis of α,β-unsaturated lactones **247** (**Scheme 40**).

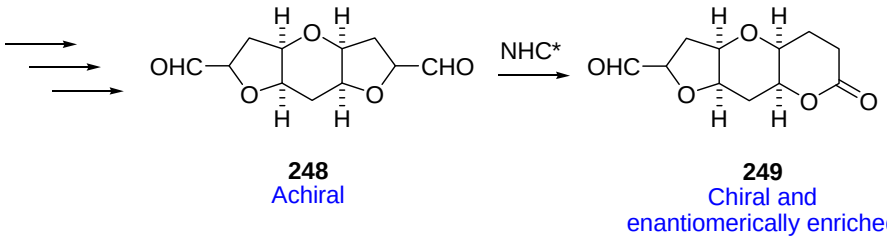


Scheme 40 proposed synthesis of α,β-unsaturated lactones **247**.

Starting from aldehyde **244** with the catalysis of NHCs, after formation of Breslow intermediate and ring-opening process, activated carboxylate **245** undergoes intramolecular nucleophilic attack of the alkoxide to give lactone **246** followed by base-induced isomerization of the olefin to give α,β-unsaturated lactone **247**.

Another possible application of the ring-expansion lactonization is the desymmtrization of dialdehyde **248**, which would give enantiomerically enriched lactone **249** (**Scheme 41**).

In the synthetic plan, chiral NHCs will be used to catalyze ring-expansion reaction of dialdehyde **248**. Ideally, only one aldehyde group of **248** will react with chiral NHC to proceed the ring-expansion. As a result, by stopping the reaction after the first ring expansion, the product **249** obtained will be chiral, and would be enantiomerically enriched.



248
Achiral

249
Chiral and
enantiomerically enriched

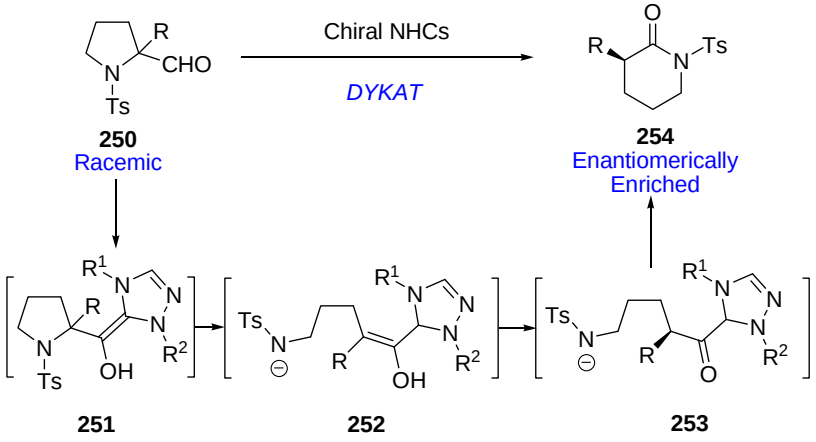
Scheme 41 Desymmetrization and synthesis of enantiomerically enriched lactone **249**.

5.2 Future work for the NHC-catalyzed ring-expansion lactamization reaction.

Future work for the NHC-catalyzed ring-expansion lactamization reaction will focus on two aspects: 1) enantioselective synthesis of lactams; and 2) synthesis of β-lactams.

5.2.1 Enantioselective synthesis of lactams

Chiral lactams are important pharmaceutical reagents [44], and hence synthesis of enantiopure functionalized lactams are of importance. An enantioselective version of ring-expansion lactamization under the concept of dynamic kinetic asymmetric transformation (DYKAT) has been proposed (**Scheme 42**).



Scheme 42 Enantioselective synthesis of lactams.

In a typical DYKAT, both enantiomers of a racemic starting material are transformed into a common enantiomerically pure product.

Our goal is to develop a method using the concept of DYKAT to fully transform a racemic mixture of azacycloalkane-2-carboxaldehydes **250** into enantiomerically enriched lactam **254** (**Scheme 42**). In our plan, a racemic mixture of azacycloalkane-2-carboxaldehydes containing an alkyl substituent (R) at the α-position of the aldehyde **250** will be used. As proposed in **Scheme 42**, both enantiomers of aldehyde **250** will be converted to the intermediate **252**. As chiral NHCs will be used, diastereoselective tautomerization of the intermediate **252** will give enantiomerically enriched intermediate **253**. After the ring-closure, optically pure lactams **254** would be obtained.

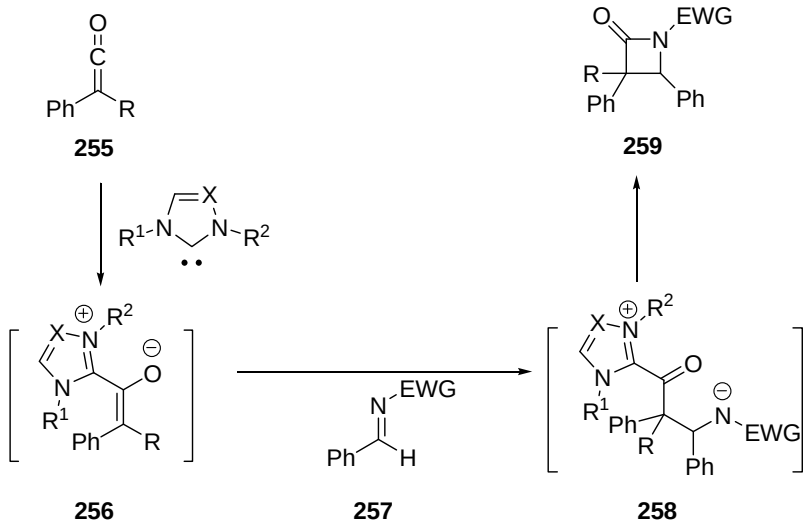
Previous research on the ring-expansion lactonization (**Table 5**) suggests that NHCs with

bulky substituents should not be used for the reaction of substrates with a quaternary center at the α-position due to steric hindrance. Hence, a series of pentafluorophenyltriazolium-derived carbenes with substituents of different size will be screened for this reaction.

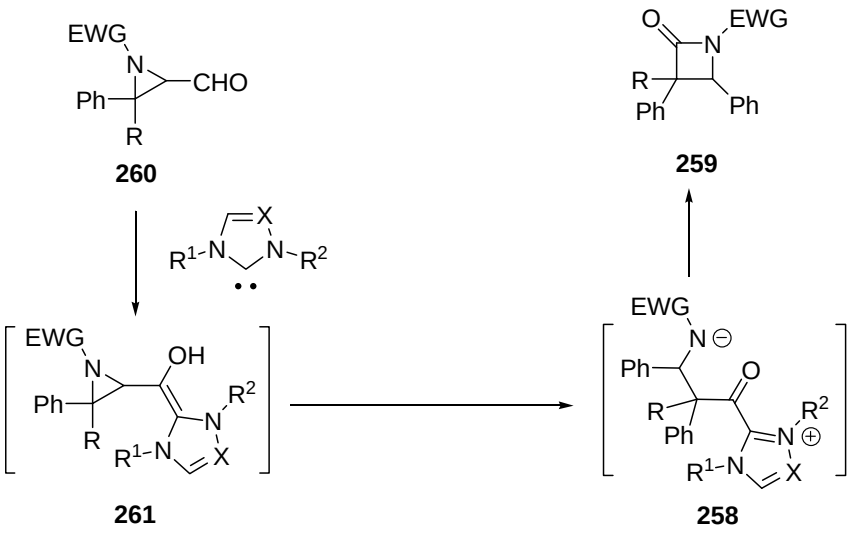
5.2.2 Synthesis of β-lactams

In 2008, Ye et al. reported a seminal synthesis of β-lactams **259** using triazolium carbenes starting from ketene **255** (**Scheme 43**). [45] According to our proposed mechanism for ring-expansion lactamization, aziridine-2-carbaldehydes **260** will have the same intermediate **258** as did Ye et al; and intermediate **258** would result in ring-closure and give β-lactams **259** (**Scheme 44**).

After treating aldehyde **260** with NHC catalyst, Breslow intermediate **261** will be formed. Ring-opening and tautomerism of **261** produces Ye's proposed intermediate **258**. Closure of the expanded ring yields β-lactams **258** (**Scheme 44**).



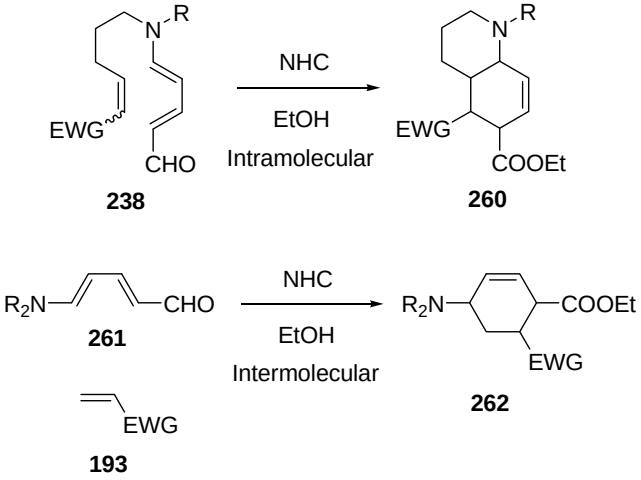
Scheme 43 Synthesis of β-lactams carried out by Ye et al. [45]



Scheme 44 Our design of the synthesis of β-lactams.

5.3 Future work for the NHC-catalyzed cascade reactions.

Our future work for the NHC-catalyzed cascade reactions will focus on the synthesis of Zincke's aldehyde **238** and subsequently, its behavior in intramolecular and intermolecular cascade reactions. (**Scheme 45**)



Scheme 45 Zincke's aldehydes and their applications in both intramolecular and intermolecular cascade reactions.

EXPERIMENTAL

General Methods.

Anhydrous solvents were dried using a Braun Solvent Purification System and stored under nitrogen over 3 Å molecular sieves. Commercially available aldehydes were purified by bulb-to-bulb distillation prior to use. 2-Iodoxybenzoic acid (IBX) and Dess-Martin periodinane (DMP) were synthesized according to literature. [49,50] Unless otherwise noted, all other reagents used were commercially available.

Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} and was visualized with UV light and 5 % phosphomolybdic acid (PMA) and/or $KMnO_4$. Silica gel 60 (40-63 nm) used for column chromatography was purchased from Silicycle Chemical Division. NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^1H and 125 MHz for ^{13}C. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards for chemical shifts. Relative configurations were determined when necessary by NOE experiments. High-resolution mass spectra (HRMS) were obtained on a VG 70E double focusing high resolution spectrometer. EI ionization was accomplished at 7 eV and CI at 50 eV with ammonia as the reagent gas. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise stated, all samples were prepared as a film on a KBr pellet for IR analysis. Optical rotations were determined from an average of 5 measurements at ambient temperature using a 1 mL, 1 dm cell; the units are 10^{-1}deg cm^2 g^{-1}, the concentrations are reported in units of g/100 mL. The enantiomeric excess was determined, when necessary, using an HP 1200 HPLC system. CHIRALPAK® IC column was purchased from Daicel Chemical Industries, Ltd.

I. General Procedures for NHC-Catalyzed Ring Expansion of Oxacycloalkane-2-Carboxaldehydes

Epoxidation-Ring Closing Reactions.

Method A.

A solution of pent-4-en-1-ol in CH_2Cl_2 (0.2 M) was cooled to 0 °C. *m*CPBA (1.2 equiv.) was added in one portion and the reaction was allowed to warm up to room temperature. The reaction was monitored by thin layer chromatography. Upon complete consumption of the alcohol, camphorsulfonic acid (0.25 equiv.) was added and stirred for an additional 24 hours. The reaction was quenched with saturated $NaHCO_3$ (aq) and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over $MgSO_4$ or Na_2SO_4, then concentrated under reduced pressure. The resulting residue was purified by column chromatography.

Method B.

A solution of pent-4-en-1-ol in CH_2Cl_2 (0.2 M) was cooled to 0 °C. *m*CPBA (1.2 equiv) was added in one portion and the reaction was allowed to warm up to room temperature, then stirred for 48 hours. The reaction was quenched with saturated $NaHCO_3$ (aq) and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over $MgSO_4$ or Na_2SO_4, then concentrated under reduced pressure. The resulting residue was purified by column chromatography.

Oxidation reactions.

IBX oxidation.

A suspension of alcohol and IBX (synthesized in one step [46])(1.4 equiv.) in CH_3CN (0.2 M) was refluxed until complete consumption of the alcohol. The mixture was cooled to room temperature, then filtered through a pad of basic alumina or celite, washing with ethyl acetate. The filtrate was collected and concentrated under reduced pressure.

Swern oxidation.

A solution of oxalyl chloride (1.1 equiv.) in dry CH_2Cl_2 (0.2 M) was cooled to –78 ^oC, under inert atmosphere. DMSO (2.2 equiv.) was added to the reaction mixture, followed by the alcohol (1 equiv.) and the reaction was stirred for 30 minutes at –78^oC. Et_3N (5 equiv.) was added dropwise and the reaction was allowed to warm up to room temperature. After complete consumption of the alcohol, the reaction was quenched with saturated NH_4Cl (aq), stirred for 5 minutes and the reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, then concentrated under reduced pressure.

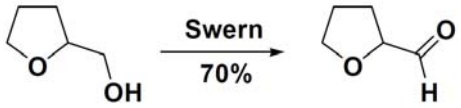
Dess-Martin Periodinane oxidation.

DMP (synthesized from IBX [47]) was added to a solution of the appropriate alcohol in CH_2Cl_2 (0.2 M) at 0 °C. The reaction was allowed to warm up to room temperature. Upon consumption of the alcohol, the mixture was diluted with CH_2Cl_2 and washed several times with a 1:1 mixture of saturated $NaHCO_3$ (aq) and saturated $Na_2S_2O_3$ (aq). The resulting organic extract was dried over $MgSO_4$ or Na_2SO_4, then concentrated under reduced pressure.

NHC-catalyzed ring expansion reaction.

To a 0.5 M solution of oxacycloalkane-2-carboxaldehyde (1.0 equiv.) in anhydrous CH_2Cl_2 was added 1,3-bis-(2,6-diisopropylphenyl)imidazolinium chloride (0.1 equiv.), followed by DBU (0.08 equiv.) under nitrogen at room temperature. The reaction was monitored by thin layer chromatography, and quenched using 10 % NH_4Cl (aq.). The mixture was then extracted using CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography to afford the lactone.

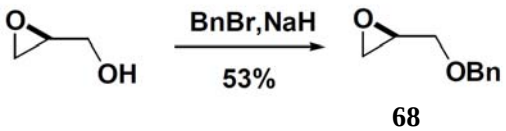
Synthesis and Characterization Data



64

Tetrahydrofuran-2-carbaldehyde. 64

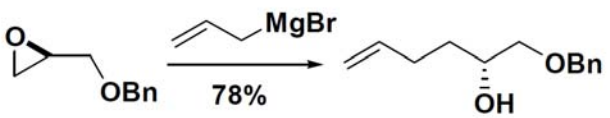
Tetrahydrofuran-2-carbaldehyde **64** was prepared from commercially available racemic tetrahydrofurfuryl alcohol as reported. [32] **^{1}H NMR** (500 MHz, CDCl3) δ 9.65 (d, *J* = 1.4Hz, 1H), 4.26 (dd, *J* = 13.1, 6.6 Hz, 1H), 3.95-3.90 (m, 2H), 2.13-1.87 (m, 4H).



68

(*R*)-2-(Benzyloxymethyl)oxirane. 68

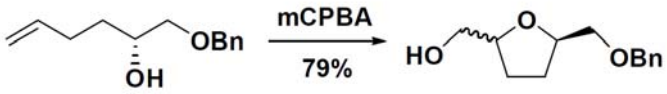
(*R*)-2-(Benzyloxymethyl)oxirane **68** was prepared from commercially available (*S*)-glycidol as reported. [48] **^{1}H NMR** (500 MHz, CDCl3) δ 7.45-7.19 (m, 5H), 4.59 (dd, *J* = 27.7, 11.9 Hz, 2H), 3.77 (dd, *J* = 11.4, 2.8 Hz, 1H), 3.45 (d, *J* = 11.4, 5.7 Hz, 1H), 3.20-3.18 (m, 1H), 2.80 (dd, *J* = 4.8, 4.8 Hz, 1H), 2.62 (dd, *J* = 2.6, 1.8 Hz, 1H).



68 **69**

(*R*)-1-(Benzyloxy)hex-5-en-2-ol. 69

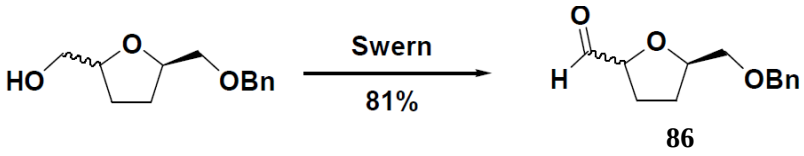
Allylmagnesium bromide (2.44 mL of a 1.0 M solution in Et_2O, 2.44 mmol) was added dropwise to a solution of (*R*)-2-(benzyloxymethyl)oxirane **68** (100 mg, 0.61 mmol) and copper (I) iodide (11.6 mg, 0.061 mmol) in THF (6 mL) at 0°C. After 30 min, the reaction was quenched with aqueous saturated NH_4Cl (5 mL) and extracted with Et_2O (3×5 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography (10 % EtOAc/ Hexanes) to afford the title compound **69** (97 mg, 78% yield) as a colorless oil. [α]D –11 (*c* 1.00, CHCl3); **IR** ν max: 3442, 2976, 2919, 1640, 1496 cm-1 ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 5.86-5.80 (m, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 4.98 (d, *J* = 10.1 Hz, 1H), 4.56 (s, 2H), 3.86-3.81 (m, 1H), 3.51 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.35 (dd, *J* = 7.9, 7.9 Hz, 1H), 2.49 (br s, 1H), 2.25-2.20 (m, 1H), 2.17-2.11 (m, 1H), 1.62-1.50 (m, 2H); **^{13}C NMR** (125 MHz, CDCl3) δ 138.4, 138.2, 128.6, 127.9, 127.88, 115.0, 74.7, 73.5, 70.0, 32.5, 29.9; **HRMS** (EI^+) *m/z* calcd for $C_{13}H_{18}O_2$ $[M]^+$: 206.1306, found: 206.1305.



(5(*R*)-(Benzyloxymethyl)tetrahydrofuran-2-yl)methanol.

Reaction of (*R*)-1-(benzyloxy)hex-5-en-2-ol (90 mg, 0.44 mmol) with *m*CPBA (182 mg, 0.53 mmol) following the general procedure A afforded 76 mg (79% yield) of the title alcohol as a colorless oil (1.3:1 mixture of epimers). **IR** ν max: 3441, 2867, 1496, 1364 cm^{-1} ; **^{1}H NMR** (500 MHz, CDCl3) δ 7.42-7.27 (m, 10H, both epimers), 4.61-4.53 (m, 4H, both epimers), 4.22-4.09 (m, 4H, both epimers), 3.77 (dd, *J* = 11.6, 2.9 Hz, 1H, major epimer), 3.69 (dd, *J* = 11.6, 3.2 Hz, 1H, minor epimer), 3.61 (dd, *J* = 10.0, 3.6 Hz, 1H, major epimer), 3,62-3.49 (m, 1H, minor epimer), 3.50-3.45 (m, 4H), 2.04-1.87 (m, 8H, both epimers), 1.79-1.65 (m, 2H, both epimers); **^{13}C NMR** (125 MHz, CDCl3) δ : 138.4, 138.1, 128.5, 128.4, 127.84, 127.81, 127.8, 127.7, 80.2,

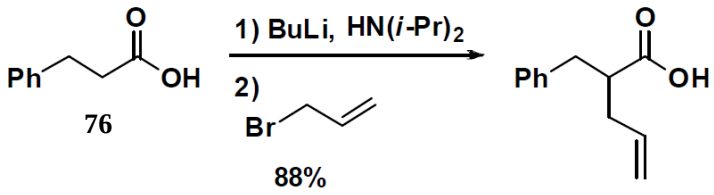
79.9, 78.7, 78.4, 73.5, 73.47, 73.0, 72.6, 65.3, 65.26, 64.6, 29.0, 28.5, 27.6; **HRMS** (EI^+) *m/z* calcd for $C_{13}H_{18}O_3$ $[M]^+$: 222.1256, found: 222.1251.



86

(5*R*)-5-(Benzyloxymethyl)tetrahydrofuran-2-carbaldehyde. 86

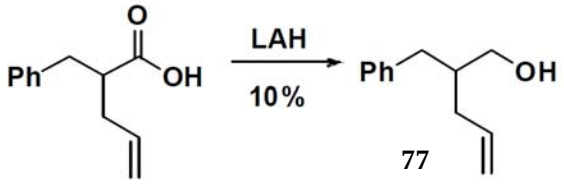
Swern oxidation of (5(*R*)-(benzyloxymethyl)tetrahydrofuran-2-yl)methanol (76 mg, 0.34 mmol) following the general procedure afforded 40 mg (81 % yield) of the title aldehyde **86** as a colorless oil (1.3:1 mixture of epimers). **IR** ν max: 2865, 1731, 1496, 1453, 1365 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl3) δ 9.684 (s, 1H, major epimer), 9.681 (s, 1H, minor epimer), 7.36-7.27 (m, 10H, both epimers), 4.59-4.57 (m, 4H, both epimers), 4.36-4.27 (m, 4H, both epimers), 3.57-3.51 (m, 4H, both epimers), 2.13-1.72 (m, 8H, both epimers); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.4, 202.8, 138.2, 128.5, 127.8, 83.6, 83.3, 80.1, 79.9, 73.6, 72.7, 72.4, 28.0, 27.9, 27.3; **HRMS** (EI^+) *m/z* calcd for $C_{13}H_{16}O_3$ $[M]^+$: 220.1099, found: 220.1098.



2-Benzylpent-4-enoic acid.

2-Benzylpent-4-enoic acid was prepared from commercially available hydrocinnamic acid **76** as reported. [50] **IR** ν max: 2925 (br), 2676, 1706, 1642, 1584, 1496, 1283 cm^{-1}; **^{1}H NMR** (500

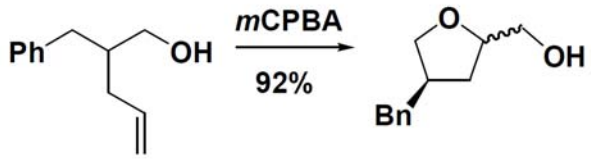
MHz, CDCl3) δ 11.67 (br s, 1H), 7.32-7.20 (m, 5H), 5.81-5.78 (m, 1H), 5.13 (d, *J* = 15.1 Hz, 1H), 5.08 (d, *J* = 15.1 Hz, 1H), 3.02-2.99 (m, 1H), 2.82 (dd, *J* = 14.3, 6.7 Hz, 2H), 2.45-2.11 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 181.6, 139.0, 134.9, 129.1, 128.6, 126.7, 117.7, 47.2, 37.5, 35.8; **HRMS** (CI^+) *m/z* calcd for $C_{12}H_{18}NO_2$ $[M+NH_4]^+$: 208.1337, found: 208.1333.



77

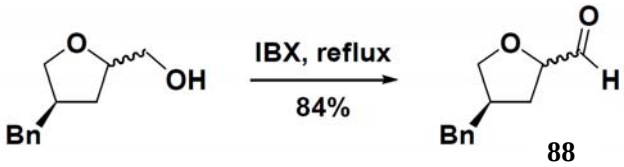
2-Benzylpent-4-en-1-ol. 77

Lithium aluminum hydride (0.43 g, 11.3 mmol) was added to a solution of racemic 2-benzylpent-4-enoic acid (2.50 g, 13.2 mmol) in dry Et_2O (45 mL) slowly at 0 ^oC. The reaction was allowed to warm up to ambient temperature. After 1.5 hour, the reaction was refluxed at 50◦ C for another 5 hours. The reaction was cooled to room temperature, and was poured into a mixture of 50 mL of 1M NaOH (aq) and ice with vigorous stirring. After the formation of a white precipitate, the suspension was filtered, then extracted with Et_2O (3×50 mL). The combined organic layers were washed using 1M HCl (aq) (3×40 mL) then brine (1×40 mL), dried over Na_2SO_4, concentrated, and purified by column chromatography (20 % EtOAc/ Hexanes) to afford the title compound **77** (340 mg, 10 % yield) as a colorless oil. **IR** *ν* max: 3346, 3026, 2922, 1636, 1603, 1495, 1453 cm^{-1}; **^{1}HNMR** (500 MHz, CDCl3) δ 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 5.86-5.80 (m, 1H),5.09 (d, *J* = 16.7 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 3.58-3.52 (m, 2H), 2.67-2.61 (m,2H), 2.14 (dd, *J* = 7.0, 7.0 Hz, 2H), 1.97-1.89(m, 1H), 1.26 (br s, 1H); **^{13}C NMR** (125 MHz, CDCl3) δ 140.6, 136.8, 129.3, 128.4, 126.0, 116.6, 64.5, 42.4, 37.2, 35.4; **HRMS** (CI^+) *m/z* calcd for $C_{12}H_{20}NO$ $[M+NH_4]^+$: 194.1544, found: 194.1553.



(4-Benzyltetrahydrofuran-2-yl)methanol.

Reaction of racemic 2-benzylpent-4-en-1-ol (310 mg, 1.76 mmol) with *m*CPBA (0.85 g, 2.46 mmol) following the general procedure B afforded 294 mg (92% yield) of the title alcohol as a colorless oil (1.2:1 mixture of epimers). **IR** ν max: 3423, 3026, 2924, 1603, 1496, 1453 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (Major epimer) 7.29-7.15 (m, 5H), 4.16-4.13 (m, 1H), 3.92 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.60 (d, *J* = 11.3 Hz, 1H), 3.52 (dd, *J* = 16.1, 8.1 Hz, 2H), 3.03 (br s, 1H), 2.75-2.70 (m, 2H), 2.61-2.49 (m, 1H), 1.83-1.77 (m, 1H), 1.72-1.67 (m, 1H); (Minor epimer) 7.29-7.15 (m, 5H), 4.04-3.99 (m, 1H), 3.87 (dd, *J* = 7.7, 7.7 Hz, 1H), 3.68 (d, *J* = 11.4 Hz, 1H), 3.47 (dd, *J* = 10.2, 4.3 Hz, 2H), 3.09 (br s, 1H), 2.68-2.64 (m, 2H), 2.60-2.49 (m, 1H), 2.04-1.96 (m, 1H), 1.43-1.37 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.6, 140.5, 128.6, 128.5, 128.4, 128.1, 126.11, 126.10, 80.3, 79.1, 73.2, 72.9, 65.0, 64.7, 41.6, 40.9, 39.1, 39.0, 33.9, 33.3; **HRMS** (EI^+) *m/z* calcd for $C_{12}H_{16}O_2$ $[M]^+$: 192.1150, found: 192.1148.

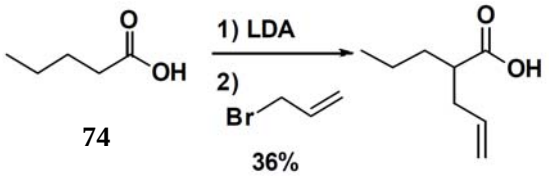


88

4-Benzyltetrahydrofuran-2-carbaldehyde. 88

Oxidation of (4-benzyltetrahydrofuran-2-yl)methanol (100 mg, 0.52 mmol) using IBX following the general procedure afforded the title aldehyde **88** (82 mg, 84 % yield) as a colorless oil (1.2:1

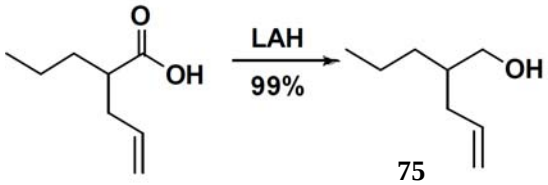
mixture of two epimers). **IR** ν max: 3061, 3026, 2924, 2856, 2713, 1732, 1602, 1496, 1453 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (major epimer) 9.65 (s, 1H), 7.31-7.14 (m, 5H), 4.37 (dd, J = 8.8, 5.2 Hz, 1H), 4.04-3.98 (m, 1H), 3.66-3.61 (m, 1H), 2.73-2.64 (m, 2H), 2.52-2.48 (m, 1H), 2.15-2.10 (m, 1H), 1.93-1.88 (m, 1H); (minor epimer) 9.70 (d, J = 1.6 Hz, 1H), 7.31-7.14 (m, 5H), 4.27 (dd, J = 7.7, 7.7 Hz, 1H), 4.04- 3.98 (m, 1H), 3.66-3.61 (m, 1H), 2.73-2.64 (m, 2H), 2.62-2.58 (m, 1H), 2.29-2.38 (m, 1H), 1.71-1.66 (m, 1H); **^{13}C NMR** (125 MHz, CDCl3) δ 202.8, 202.6, 140.2, 140.0, 128.73, 128.72, 128.71, 128.70, 128.68, 126.4, 83.0, 82.7, 74.3, 74.2, 41.3, 40.6, 38.7, 38.6, 33.7, 33.4; **HRMS** (EI^+) *m/z* calcd for C12H14O2 $[M]^+$: 190.0994, found: 190.0989.



2-Propylpent-4-enoic acid.

Valeric acid **74** (2.16 mL, 19.9 mmol) was added dropwise to a solution of LDA [prepared from ^{n}BuLi (42.0 mmol) and (iPr)$_2$NH (42.0 mmol)] in dry THF (50 mL) at 0^{o}C. After 30 min; allylbromide (1.81 mL, 21.0 mmol) was added slowly. The reaction was then allowed to warm to ambient temperature. After 30 hours, the reaction was quenched using 1M HCl (aq) (20 mL). The mixture was washed using saturated $NaHCO_3$ (aq.) (3×30 mL), then brine (1×30 mL). The combined aqueous layers were extracted using CH_2Cl_2 (2×20 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and distilled (150^{o}C at 50 torr) to afford 1.0 g (36% yield) of 2-propylpent-4-enoic acid as a colorless oil. **IR** ν max: 3080 (br), 2960, 1707, 1466, 1280 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.12 (br s, 1H), 5.80-5.72 (m, 1H), 5.08 (d, J = 17.0 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 2.45-2.44 (m, 1H), 2.44-2.36 (m, 1H), 2.26-2.23 (m, 1H), 1.63-1.61 (m,

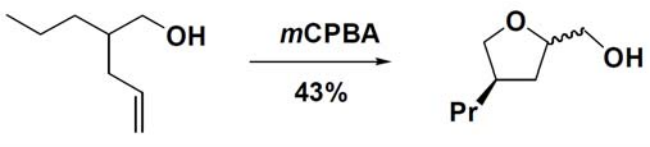
1H), 1.48-1.47 (m, 1H), 1.39-1.32 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 182.7, 135.4, 117.1, 45.2, 36.3, 33.9, 20.6, 14.1; HRMS (EI^+) m/z calcd for $C_8H_{14}O_2$ $[M]^+$: 142.0993, found: 142.0989.



75

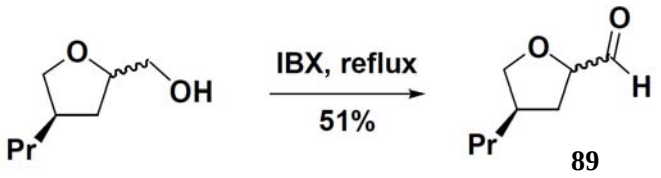
2-Propylpent-4-en-1-ol. 75

Lithium aluminum hydride (0.5g, 13.1 mmol) was added slowly to a solution of racemic 2-propylpent-4-enoic acid (930 mg, 6.55 mmol) in dry Et_2O (33 mL) at 0 ^oC. After 20 minutes, the reaction was quenched by adding 1M HCl (aq) (100 mL) slowly. The combined aqueous layers were extracted using CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated to afford the title compound **75** (830 mg, 99%) as a colorless oil without further purification. **IR** ν max: 3334, 2958, 2873, 1640, 1466, 1043 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.86-5.78 (m, 1H), 5.06 (d, *J* = 17.1 Hz, 1H), 4.99 (d, *J* = 15.8 Hz, 1H), 3.58-3.52 (m, 2H), 2.12 (dd, *J* = 6.9, 6.9 Hz, 2H), 1.65-1.57 (m, 1H), 1.40-1.20 (br m, 1H), 1.37-1.25 (m, 4H), 0.90 (t, *J* = 6.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.3, 116.2, 65.5, 40.3, 35.8, 33.0, 20.2, 14.5. **HRMS** (CI^+) *m/z* calcd for $C_8H_{20}NO$ $[M+NH_4]^+$: 146.1545, found: 146.1551.



(4-Propyltetrahydrofuran-2-yl)methanol.

Reaction of racemic 2-propylpent-4-en-1-ol (830 mg, 6.48 mmol) with *m*CPBA (3.14g, 9.10 mmol) following the general procedure afforded 360 mg (43%) of the title alcohol as a colorless oil (1:1 mixture of epimers). **IR** ν max: 3428, 2957, 2926, 2872, 1456, 1379, 1047 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.03-3.99 (m, 1H, one epimer), 3.98-3.96 (m, 1H, one epimer), 3.94 (dd, J = 8.3, 7.0 Hz, 1H, one epimer), 3.87 (dd, J = 7.8, 7.8 Hz, 1H, one epimer), 3.61(dd, J = 11.7, 3.1 Hz, 1H, one epimer), 3.54 (dd, J = 11.6, 3.5 Hz, 1H, one epimer), 3.43 (ddd, J = 17.8, 11.7, 6.1 Hz, 2H, both epimers), 3.31 (ddd, J = 16.7, 8.4, 8.4 Hz, 2H, both epimers), 2.96 (br s, 2H, both epimers), 2.25-2.10 (m, 2H, both epimers), 1.98 (ddd, J = 12.3, 6.7, 6.7 Hz, 1H, one epimer), 1.77 (ddd, J = 14.1, 8.3, 5.9 Hz, 1H, one epimer), 1.51 (ddd, J = 15.0, 7.6, 7.6 Hz, 1H, one epimer), 1.34- 1.13 (m, 9H, both epimers), 0.88-0.83 (m, 6H, both epimers).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 80.4, 79.3, 73.9, 73.4, 65.3, 64.9, 39.9, 39.2, 35.4, 35.3, 34.3, 33.9, 21.7, 21.6, 14.2, 14.2; **HRMS** (CI^+) *m/z* calcd for $C_8H_{20}NO_2$ $[M+NH_4]^+$: 162.1494, found: 162.1489.

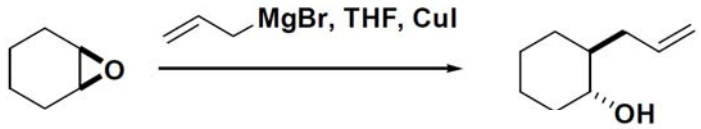


89

4-Propyltetrahydrofuran-2-carbaldehyde. 89

Oxidation of (4-propyltetrahydrofuran-2-yl)methanol (200 mg, 1.39 mmol) using IBX following the general procedure afforded the title aldehyde **89** 100 mg (51% yield) as a colorless oil (1:1 mixture of epimers). **IR** ν max: 2959, 2873, 1734, 1466, 1380 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$)

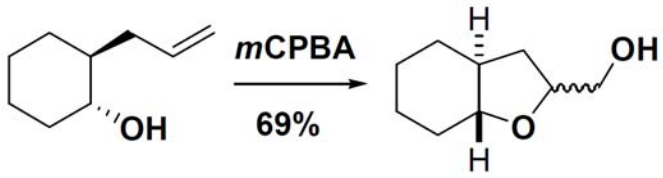
δ 9.64-9.62 (m, 1H, one epimer), 9.62-9.59 (m, 1H, one epimer), 4.29-4.24 (m, 1H, one epimer), 4.24-4.18 (m, 1H, one epimer), 3.47-3.41 (m, 2H, both epimers), 2.29-2.19 (m, 1H, one epimer), 2.15-2.08 (m, 1H, one epimer), 1.75-1.68 (m, 1H, one epimer), 1.53-1.46 (m, 1H, one epimer), 1.37-1.19 (m, 4H, both epimers), 0.89-0.84 (m, 3H, both epimers); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.2, 202.8, 83.1, 82.9, 74.78, 74.75 39.5, 38.8, 34.9, 34.7, 34.2, 34.0, 21.7, 21.6, 14.2, 14.2; **HRMS** (CI^+) *m/z* calcd for $C_8H_{18}NO_2$ $[M+NH_4]^+$: 160.1324, found: 160.1331.



72 **73**

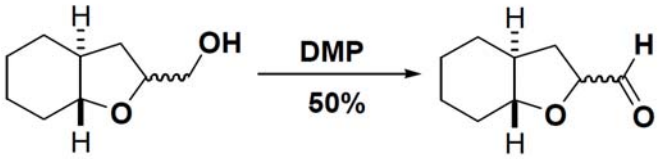
***trans*-2-Allylcyclohexanol. 73**

Allylmagnesium bromide (7.2 mL of a 1.0 M solution in Et_2O, 7.2 mmol) was added dropwise to a solution of cyclohexene oxide **72** (0.61 mL, 6.0 mmol) and copper (I) iodide (171.5 mg, 0.9 mmol) in THF (10 mL) at -20◦C. The reaction was allowed to warm up to ambient temperature. After 17 hours, the reaction was quenched with aqueous saturated NH_4Cl (20 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography (20% EtOAc/Hexanes) to afford the title alcohol **73** (635 mg, 76 % yield) as a colorless oil. **IR** ν max: 3343, 3075, 2927, 2856, 1640, 1448 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.85-5.78 (m, 1H), 5.04 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.99 (dd, *J* = 10.1, 0.9 Hz, 1H), 3.26-3.19 (m, 1H), 2.46-2.41 (m, 1H), 1.96-1.92 (m, 2H), 1.84 (br s, 1H), 1.76- 1.20 (m, 7H), 0.94-0.83 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.7, 116.1, 74.7, 45.1, 37.6, 35.8, 30.5, 25.7, 25.1; **HRMS** (CI^+) *m/z* calcd for $C_9H_{20}NO$ $[M+NH_4]^+$: 158.1545, found: 158.2168.



(Octahydrobenzofuran-2-yl)methanol.

Reaction of *trans*-2-allylcyclohexanol (495 mg, 3.5 mmol) with *m*CPBA (1.47g, 4.25 mmol) following the general procedure afforded 375 mg (69%) of the title alcohol as a colorless oil (2:1 mixture of epimers). **IR** ν max: 3421, 2932, 2857, 1652 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl3) δ (major epimer) 4.09-4.02 (m, 1H), 3.65-3.53 (m, 1H), 3.51-3.41 (m, 1H), 3.11-2.99 (m, 1H), 2.69 (br s, 1H), 2.11-2.10 (m, 1H), 1.88-1.84 (m, 1H), 1.81-1.73 (m, 2H), 1.69-63 (m, 1H), 1.60-1.52 (m, 1H), 1.33- 0.97 (m, 5H); (minor epimer) 4.15- 4.09 (m, 1H), 3.65-3.53 (m, 1H), 3.51-3.41 (m, 1H), 3.11-2.99 (m, 1H), 2.82 (br s, 1H), 2.11-2.10 (m, 1H), 2.00- 1.92 (m, 1H), 1.88-1.84 (m, 1H), 1.81-1.73 (m, 2H), 1.69-63 (m, 1H), 1.33- 0.97 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ : 84.2, 82.7, 79.2, 78.0, 66.0, 65.7, 46.0, 45.2, 33.3, 33.2, 31.47, 31.42, 29.3, 29.1, 25.9, 25.8, 24.45, 24.42; **HRMS** (CI^+) *m/z* calcd for $C_9H_{20}NO_2$ $[M+NH_4]^+$: 174.1494, found: 174.1434.

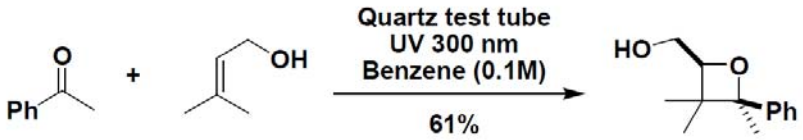


91

Octahydrobenzofuran-2-carbaldehyde. 91

Oxidation of racemic (octahydrobenzofuran-2-yl)methanol (50.3 mg, 0.320 mmol) using Dess-Martin periodinane following the general procedure afforded 22 mg (50 % yield) of the title aldehyde **91** as a colorless oil (2: 1 mixture of epimers). **IR** ν max: 2934, 2858, 1731 cm^{-1}; **^{1}H**

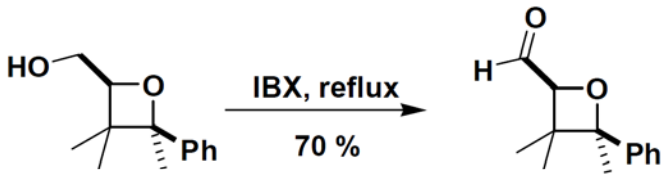
NMR (500 MHz, $CDCl_3$) δ (major epimer) 9.72 (s, 1H), 4.32 (d, *J* = 10.7 Hz, 1H), 3.21 (ddd, *J* = 10.5, 10.5, 3.7 Hz, 1H), 2.23-2.17 (m, 2H), 2.00- 1.72 (m, 4H), 1.53-1.05 (m, 5H); (minor epimer) 9.68 (s, 1H), 4.36 (d, *J* = 8.2 Hz, 1H), 3.16 (ddd, *J* = 10.4, 10.4, 3.8 Hz, 1H), 2.34-2.27 (m, 2H), 2.00- 1.72 (m, 4H), 1.53- 1.05 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.4, 203.0, 85.0, 84.8, 81.8, 81.6, 45.4, 44.8, 34.0, 33.09, 33.07, 31.4, 31.2, 29.0, 28.96, 25.7, 24.3, 24.28; **HRMS** (CI^+) *m/z* calcd for $C_9H_{18}NO_2$ $[M+NH_4]^+$: 172.1337, found: 172.1583.



82 **83** **84**

(3,3,4-trimethyl-4-phenyloxetan-2-yl)methanol. 84

(3,3,4-trimethyl-4-phenyloxetan-2-yl)methanol **84** was prepared from commercially available acetophenone **82** and 3-methyl-2-buten-1-ol **83** as reported. [33] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 7.26-7.21 (m, 3H), 4.56 (dd, *J* = 6.6, 4.8 Hz, 1H), 3.81 (dd, *J* = 11.7, 7.2 Hz, 1H), 3.69-3.66 (dd, *J* = 11.7, 4.4 Hz, 1H), 1.82 (s, 3H), 1.31 (s, 3H), 0.72 (s, 3H).

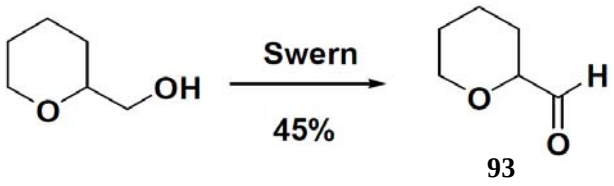


84 **85**

3,3,4-Trimethyl-4-phenyloxetane-2-carbaldehyde. 85

Oxidation of the alcohol **84** (150 mg, 0.73 mmol) using IBX following the general procedure afforded the title aldehyde **85** (101 mg, 70 % yield) as a colorless oil. **IR** ν max: 2937, 1727, 1467, 1255 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.86 (d, *J* = 1.5 Hz, 1H), 7.37-7.25 (m, 5H),

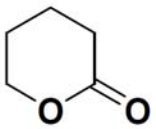
4.73 (d, J = 1.6 Hz, 1H), 1.76 (s, 3H), 1.41 (s, 3H), 0.71 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.5, 144.5, 128.2, 127.0, 124.3, 90.6, 87.4, 47.5, 25.7, 23.5, 22.0; **HRMS** (CI^+) *m/z* calcd for $C_{13}H_{20}NO_2$ $[M+NH_4^+]^+$: 222.1494, found: 222.1488.



93

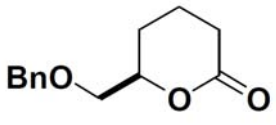
Tetrahydro-2*H*-pyran-2-carbaldehyde. 93

Swern oxidation of racemic tetrahydropyran-2-methanol (1.70 mL, 15 mmol) following the general procedure afforded **93** 1.32 g (77 % yield) of the title aldehyde as a colorless oil as reported. [48] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 4.08-4.05 (m, 1H), 3.82 (dd, J= 11.2, 2.8 Hz, 1H), 3.54 (ddd, J = 11.2, 11.2, 3.0 Hz, 1H), 1.94-1.83 (m, 2H), 1.68-1.41(m, 4H).



Tetrahydro-2*H*-pyran-2-one 65.

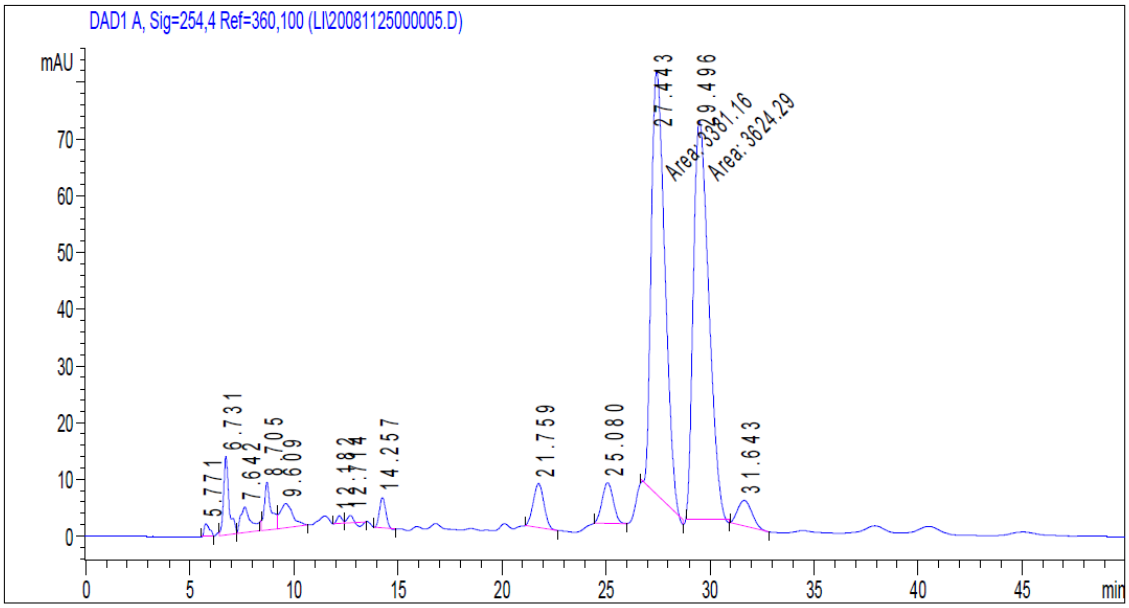
Lactone **65** was synthesized by reacting aldehyde **64** (60 mg, 0.6 mmol) with 10 mol % catalyst loading of **60** (25.6 mg, 0.06 mmol) and DBU (7.2 μL, 0.048 mmol). The reaction was performed by following the general procedure. The crude was purified by column chromatography (50 % EtOAc/Hexane) to yield a colorless oil (47 mg, 78 % yield). **^{1}HNMR** (500 MHz, $CDCl_3$) δ 4.31 (t, J = 5.8 Hz, 2H), 2.53(t, J = 6.9 Hz, 2H), 1.91-1.83 (m, 4H).



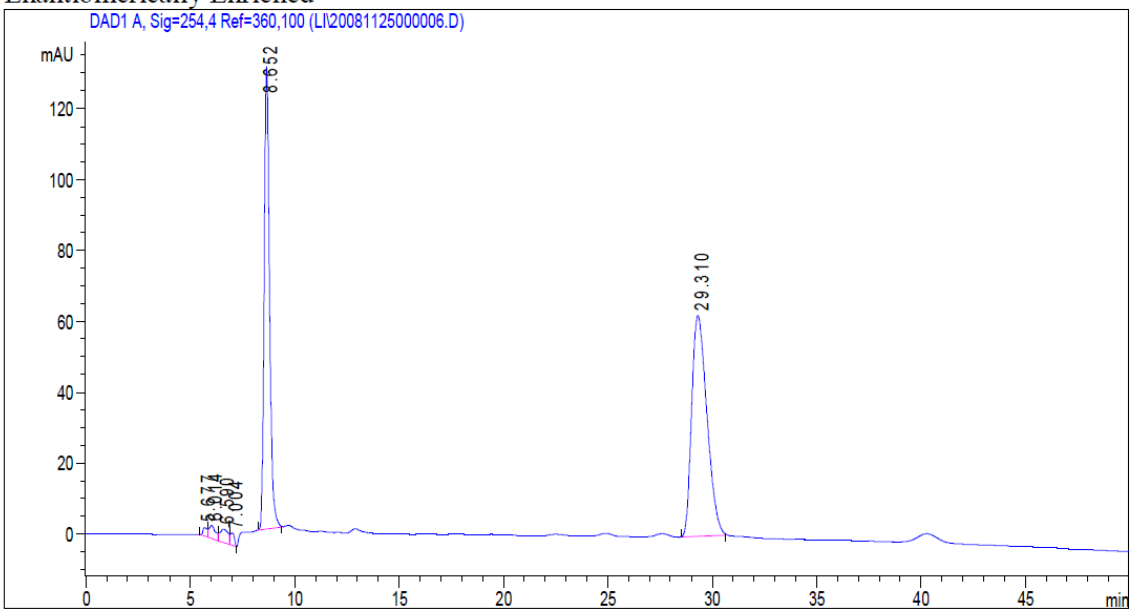
(*R*)-6-(Benzyloxymethyl)tetrahydro-2*H*-pyran-2-one 94.

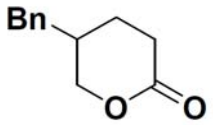
Lactone **94** was synthesized by reacting aldehyde **86** (60 mg, 0.254 mmol) with 10 mol % catalyst loading of **60** (11 mg, 0.025 mmol) and DBU (3 μL, 0.021 mmol). The reaction was performed by following the general procedure. The crude was purified by column chromatography (30 % EtOAc/Hexane) to yield a colorless oil (59 mg, 98 % yield). [α]D –16 (*c* 1.00, $CHCl_3$); **IR** ν max: 3062, 3030, 2866, 1727, 1496, 1241 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59-7.18 (m, 5H), 4.58 (s, 2H), 4.48 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.65-3.58 (m, 2H), 2.58 (ddd, *J* = 17.7, 6.0, 6.0 Hz, 1H), 2.47 (ddd, *J* = 17.6, 8.8, 6.8 Hz, 1H), 1.97-1.25 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.2, 137.9, 128.5, 127.8, 127.7, 79.2, 73.6, 72.0, 29.7, 24.6, 18.3; **HRMS** (EI^+) *m/z* calcd for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1178, found: 221.1189. HPLC (CHIRALPAK® IC column 30 % *i*PrOH/Hexanes at 0.1mL/min., UV detection at 254 nm, major peak at 29.5 min., minor peak at 27.4 min., >99% ee).

Racemic Mixture



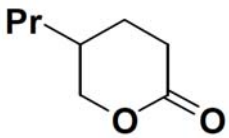
Enantiomerically Enriched





5-Benzyltetrahydro-2*H*-pyran-2-one 96.

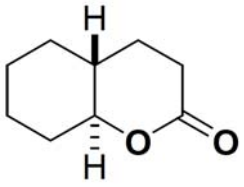
Lactone **96** was synthesized by reacting aldehyde **88** (60 mg, 0.316 mmol) with 10 mol % catalyst loading of **60** (13.5 mg, 0.0316 mmol) and DBU (3.8 μL, 0.0253 mmol). The reaction was performed by following the general procedure. The crude was purified by column chromatography (30 % EtOAc/Hexane) to yield a colorless oil (54 mg, 90 % yield). **IR** ν max: 2924, 1736, 1496, 1454, 1183 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32-7.14 (m, 5H), 4.29 (dd, J = 10.7, 3.4 Hz, 1H), 4.01 (dd, J = 10.5, 10.5 Hz, 1H), 2.66-2.58 (m, 3H), 1.58-2.50 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.4, 138.6, 129.0, 128.8, 126.8, 73.2, 38.0, 34.8, 29.1, 25.4; **HRMS** (EI^+) *m/z* calcd for $C_{12}H_{14}O_2$ $[M]^+$: 190.0994, found: 190.0993.



5-Propyltetrahydro-2*H*-pyran-2-one 97.

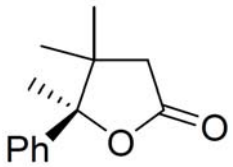
Lactone **97** was synthesized by reacting aldehyde **89** (50 mg, 0.35 mmol) with 10 mol % catalyst loading of **60** (15 mg, 0.035 mmol) and DBU (4.2 μL, 0.028 mmol). The reaction was performed by following the general procedure. The crude was purified by column chromatography (20 % EtOAc/Hexane) to yield a colorless oil (47 mg, 94 % yield). **IR** ν max: 2958, 2873, 1738, 1459, 1338, 1182, 1055 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.32 (dd, J =

11.1, 4.5 Hz, 1H), 3.94 (dd, *J* = 9.8, 9.8 Hz, 1H), 2.60-2.49 (m, 2H), 2.08-1.85 (m, 2H), 1.58-1.51 (m, 1H), 1.41-1.23 (m, 4H), 0.93 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.7, 73.8, 33.8, 32.6, 29.2, 25.6, 20.0, 14.2; **HRMS** (EI^+) *m/z* calcd for $C_8H_{14}O_2$ $[M]^+$: 142.0994, found: 142.0994.



Octahydro-2H-chromen-2-one 99. [51]

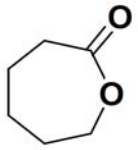
Lactone **99** was synthesized by reacting aldehyde **91** (40 mg, 0.26 mmol) with 10 mol % catalyst loading of **60** (11.1 mg, 0.026 mmol) and DBU (3.1 μL, 0.021 mmol). The reaction was performed by following the general procedure. The crude was purified by column chromatography (30 % EtOAc/Hexane) to yield a colorless oil (35 mg, 88 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.87 (ddd, *J* = 10.8, 10.8, 4.2 Hz, 1H), 2.71-2.64 (m, 1H), 2.58-2.50 (m, 1H), 2.12-2.09 (m, 1H), 1.89-1.83 (m, 3H), 1.75-1.68 (m, 1H), 1.64-1.58 (m, 1H), 1.56-1.37 (m, 2H), 1.34-1.21 (m, 2H), 1.10-1.15 (m, 1H).



4,4,5-Trimethyl-5-phenyldihydrofuran-2(3*H*)-one 101.

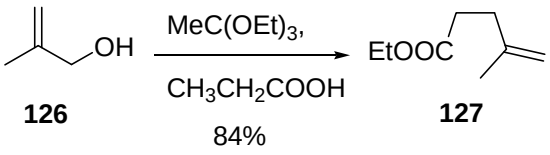
Lactone **101** was synthesized by reacting aldehyde **85** (50 mg, 0.25 mmol) with 10 mol % catalyst

loading of **60** (10.7 mg, 0.025 mmol) and DBU (2.98 μL, 0.02 mmol). The reaction was performed by following the general procedure. The crude was purified by column chromatography (30 % EtOAc/Hexane) to yield a colorless oil (43 mg, 86 % yield). **IR** ν max: 2975, 1772, 1446, 1242, 1056 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 2.66 (d, *J* = 17.1 Hz, 1H), 2.20 (d, *J* = 17.8 Hz, 1H), 1.81 (s, 3H), 1.30 (s, 3H), 0.69 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.6, 141.4, 128.4, 127.6, 124.7, 91.4, 44.4, 42.8, 26.0, 24.3, 23.1; **HRMS** (EI^+) *m/z* calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1150, found: 204.1147.



Oxepan-2-one 102. [52]

Lactone **102** was synthesized by reacting aldehyde **93** (60 mg, 0.53 mmol) with 10 mol % catalyst loading of **60** (22.6 mg, 0.053 mmol) and DBU (6.3 μL, 0.042 mmol). The reaction was performed under reflux for 10 days. The crude was purified by column chromatography (30 % EtOAc/Hexane) to yield a colorless oil (29 mg, 48 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.23 (t, *J* = 4.6 Hz, 2H), 2.63 (t, *J* = 6.5 Hz, 2H), 1.64-1.59 (m, 6H).



126 **127**

Ethyl 4-methylpent-4-enoate 127.

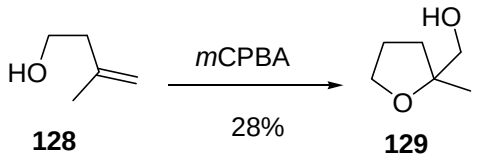
A solution of the alcohol **126** (5.0 ml, 60 mmol), triethyl orthoacetate (27.2 mL, 149 mmol), and

propanoic acid (2.66 ml, 35.7 mmol) was stirred in a flask fitted with a Dean-Stark apparatus and a reflux condenser, at 150 °C for 27 h. The reaction was allowed to cool down to room temperature before diluting with Et_2O (20 mL), followed by 1M HCl (aq) (40 mL). The two layers were separated, then the aqueous layer was extracted with Et_2O (3×20 mL), the combined organic extracts were dried over Na_2SO_4 then concentrated under reduced pressure to yield the title compound **127** as a yellow oil (7.78 g, 84 % yield) without further purifications. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.71 (d, J = 26.7 Hz, 2H), 4.13 (q, J = 7.1, 14.2 Hz, 2H), 2.45 (t, J = 6.7 Hz, 2H), 2.33 (t, J = 8.0 Hz, 2H), 1.74 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H).

127 **128**

3-Methylbut-3-en-1-ol 128.

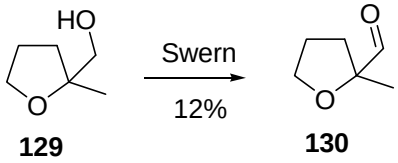
Lithium aluminum hydride (1.80 g, 47.5 mmol) was added to a solution of ethyl ester **127** (9.78 g, 68.9 mmol) in dry Et_2O (70 mL) slowly at 0 ^oC. The reaction was allowed to warm up to ambient temperature. After 2 hour, the reaction was refluxed at 35 ^oC for another 2 hours. The reaction was cooled to room temperature, and was poured into a mixture of 50 mL of 1M NaOH (aq) and ice with vigorous stirring. After the formation of a white precipitate, the suspension was filtered, then extracted with Et_2O (3×50 mL). The combined organic layers were washed using 1M HCl (aq) (3×40 mL) then brine (1×40 mL), dried over Na_2SO_4, concentrated, and purified by distillation (100°C, 2 mmHg) to afford the title compound **128** (3.26 g, 55 % yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.72 (d, J = 6.2 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 2.10 (t, J = 7.4 Hz, 2H), 1.74 (s, 3H), 1.41 (br, 1H).



128 **129**

(2-Methyl-tetrahydrofuran-2-yl)methanol 129.

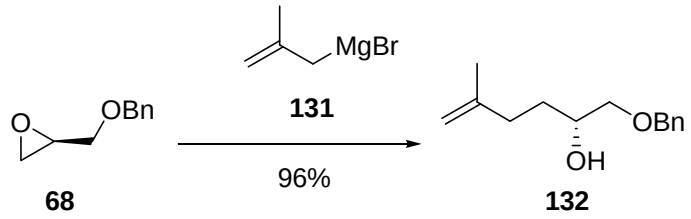
Reaction of the alcohol **128** (3.26 g, 32.6 mmol) with *m*CPBA (13.4 g, 39.1 mmol) following the general procedure afforded 0.99 g (28%) of the title alcohol **129** as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.87-3.79 (m, 2H), 3.42 (dd, *J* = 11.3, 16.3 Hz, 2H), 2.37 (br, 1H), 1.95-1.87 (m, 3H), 1.61-1.58 (m, 1H), 1.16 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 83.1, 68.6, 68.2, 33.7, 26.6, 23.4.



129 **130**

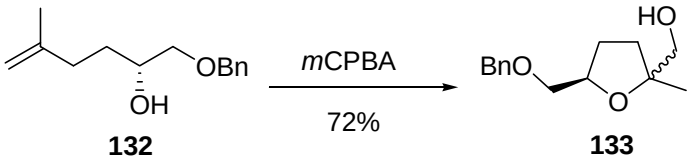
2-Methyl-tetrahydrofuran-2-carbaldehyde 130.

Oxidation of the alcohol **129** (200 mg, 1.72 mmol) using Swern oxidation following the general procedure afforded 23 mg (12 % yield) of the title aldehyde **130** as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 4.01 (dd, *J* = 7.3, 14.3 Hz, 1H), 3.87 (dd, *J* = 7.3, 14.2 Hz, 1H), 2.21-2.14 (m, 1H), 2.03-1.84 (m, 2H), 1.68 (ddd, *J* = 6.7, 8.3, 12.8 Hz, 1H), 1.29 (s, 3H).



(*R*)-1-(Benzyloxy)-5-methylhex-5-en-2-ol 132.

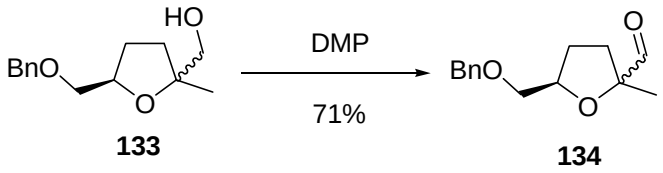
Methallylmagnesium bromide (freshly prepared with 0.24 g magnesium and 1.34 ml methallyl bromide, 2 mmol) was added dropwise to a solution of (*R*)-2-(benzyloxymethyl)oxirane **68** (0.32 g, 0.5 mmol) in Et_2O (4 mL) at 0°C. After 30 min, the reaction was quenched with aqueous saturated NH_4Cl (5 mL) and extracted with Et_2O (3×5 mL). The combined organic layers were dried over Na_2SO_4, concentrated to afford the title compound **132** (103 mg, 96% yield) as a colorless oil without purifications. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 4.72 (d, *J* = 12.4 Hz, 2H), 4.56 (s, 2H), 3.83-3.81 (m, 1H), 3.52 (dd, *J* = 3.1, 7.5 Hz, 1H), 3.36 (dd, *J* = 7.7, 9.3 Hz, 1H), 2.53 (br, 1H), 2.29-1.99 (m, 2H), 1.74 (s, 3H), 1.63-1.57 (m, 2H).



(*R*)-(5-(Benzyloxymethyl)-2-methyl-tetrahydrofuran-2-yl)methanol 133.

Reaction of the alcohol **132** (103 mg, 0.47 mmol) with *m*CPBA (196 mg, 0.57 mmol) following the general procedure afforded 80 mg (72%) of the title alcohol **133** as a colorless oil (3:2 mixture of epimers). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 10H, both epimers), 4.60 (dd, *J* = 8.4, 12.3 Hz, 2H, minor epimer), 4.54 (dd, *J* = 7.2, 12.1 Hz, 2H, major epimer), 4.27-4.22 (m, 1H,

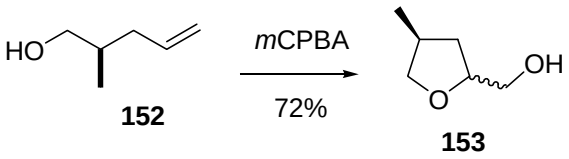
major epimer), 4.20-4.15 (m, 1H, minor epimer), 3.65-3.36 (m, 8H, both epimers), 2.91 (br, 2H, both epimers), 2.15-1.62 (m, 8H, both epimers), 1.20 (s, 3H, minor epimer), 1.18 (s, 3H, major epimer).



133 **134**

(*R*)-5-(Benzyloxymethyl)-2-methyl-tetrahydrofuran-2-carbaldehyde 134.

Oxidation of the alcohol **133** (50 mg, 0.21 mmol) using Dess-Martin Periodinane (135 mg, 0.32 mmol) following the general procedure afforded 35 mg (71 % yield) of the title aldehyde **134** as a colorless oil (5:4 mixture of epimers). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.60 (s, 1H, minor epimer), 9.59 (s, 1H, major epimer), 7.35-7.27 (m, 10H, both epimers), 4.64-4.53 (m, 4H, both epimers), 4.41-4.35 (m, 2H, both epimers), 3.56-3.49 (m, 4H, both epimers), 2.31-1.52 (m, 8H, both epimers), 1.32 (s, 3H, minor epimer), 1.30 (3H, major epimer).



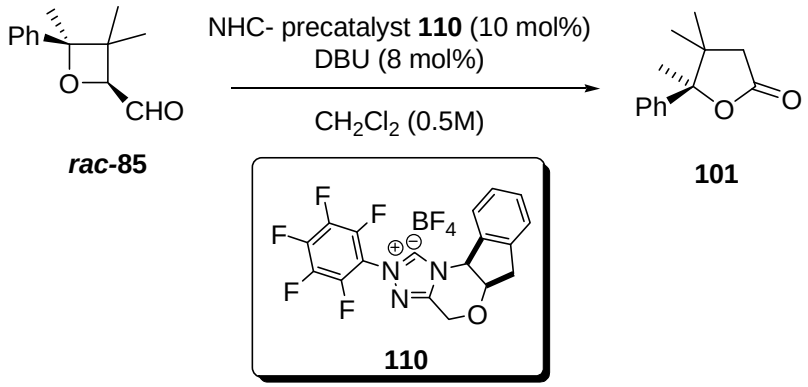
152 **153**

(*S*)-(4-Methyl-tetrahydrofuran-2-yl)methanol 153.

Compound **152** was synthesized as described by Hansen et al. [38] Reaction of the alcohol **152** (200 mg, 2 mmol) with *m*CPBA (818 mg, 2.4 mmol) following the general procedure afforded 167 mg (72%) of the title alcohol **152** as a colorless oil (5:4 mixture of epimers). **^{1}H NMR** (500

MHz, $CDCl_3$) δ 4.15-4.10 (m, 1H, major epimer), 4.08-4.03 (m, 1H, minor epimer), 3.98 (dd, *J* = 7.6, 7.6 Hz, 1H, major epimer), 3.92 (dd, *J* = 7.8, 7.8 Hz, 1H, minor epimer), 3.69 (dd, *J* = 2.2, 11.3 Hz, 1H, minor epimer), 3.65 (dd, *J* = 2.7, 11.3 Hz, 1H, major epimer), 3.52 (dd, *J* = 6.0, 11.4 Hz, 1H, minor epimer), 3.48 (dd, *J* = 6.2, 11.5 Hz, 1H, major epimer), 3.33 (dd, *J* = 8.4 Hz, 2H, both epimer), 2.41-2.29 (m, 2H, both epimers), 2.07 (ddd, *J* = 7.0, 7.0, 13.1 Hz, 1H, major epimer), 1.85 (ddd, *J* = 6.8, 6.8, 13.1 Hz, 1H, minor epimer), 1.61-1.59 (br, 2H, both epimers), 1.59-1.53 (m, 1H, minor epimer), 1.30-1.21 (m, 1H, major epimer), 1.05 (d, *J* = 3.3 Hz, 3H, minor epimer), 1.04 (d, *J* = 3.7 Hz, 3H, major epimer).

Results for the Kinetic Resolution



T (°C)	Time (min)	Conversion (C) (%)	ee of product (%)	Selectivity factor [35]
0	80	30	24	1.8

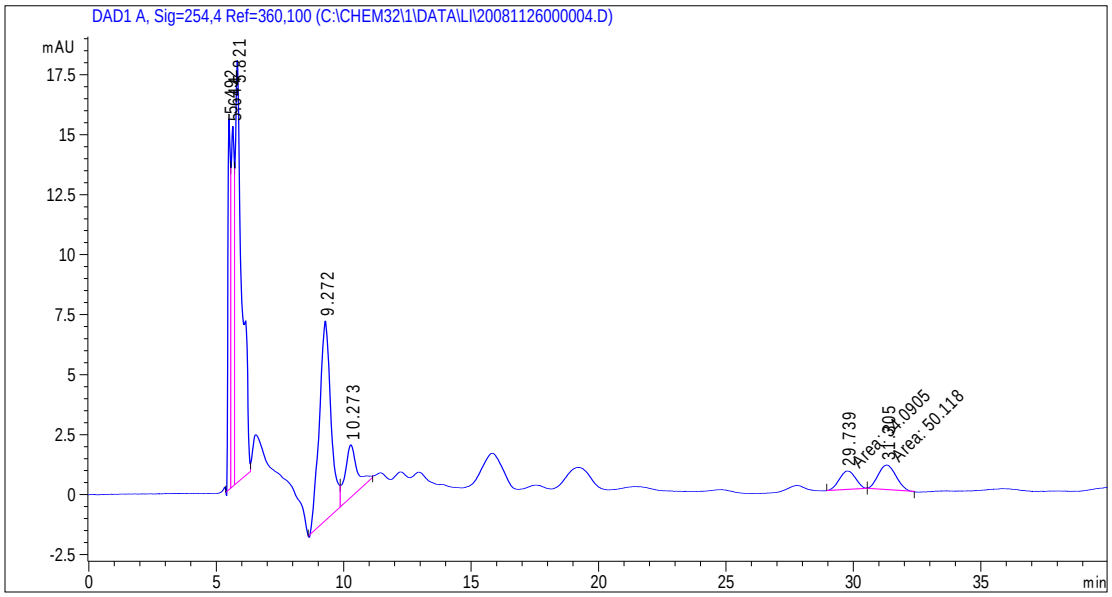
HPLC (CHIRALPAK® IC column 5% *i*PrOH/Hexanes at 0.1 mL/min., UV detection at 254 nm, major peak at 31.3 min., minor peak at 29.7 min., 24% ee).

Equation for the calculation of enantiomeric excess (ee):

$ee = [(R-S)/(R+S)] \times 100\%$

Equation for the calculation of selectivity factor (S): [35]

$S = \ln [1- C (1 + ee)] / \ln [1- C (1 - ee)]$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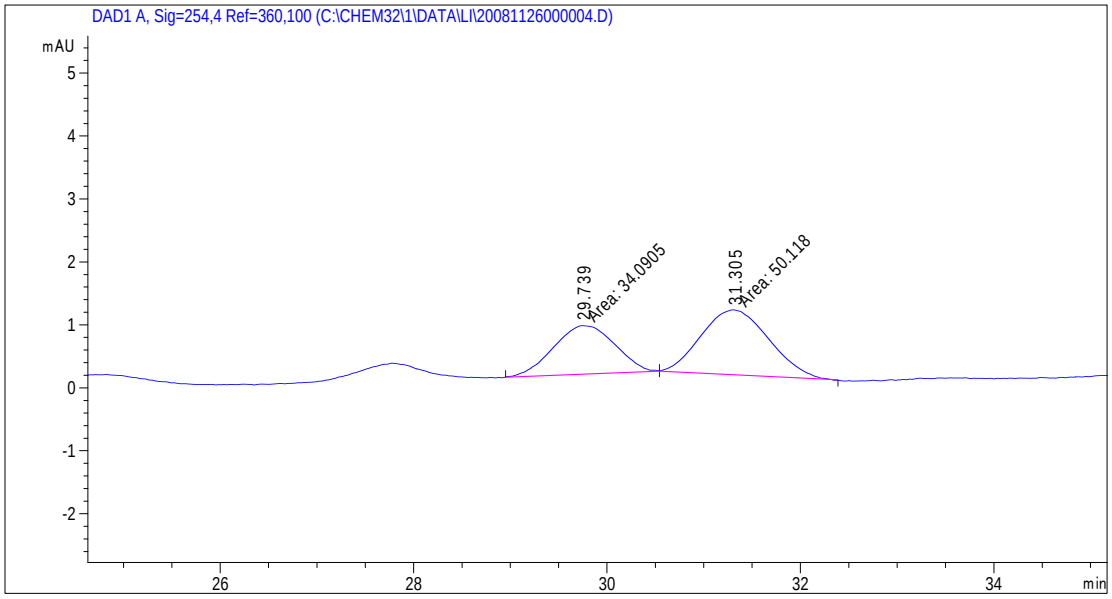
15
12.5
10
7.5
5
2.5
0
-2.5
5.492
5.644
6.021
9.272
10.273
29.739
Area: 34.0905
31.305
Area: 50.118
0
5
10
15
20
25
30
35
min


DAD1 A, Sig=254,4 Ref=360,100 (C:\CHEM32\1\DATA\LI\20081126000004.D)
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4
3
2
1
0
-1
-2
29.739
Area: 34.0905
31.305
Area: 50.118
26
28
30
32
34
min

II. General Procedures for NHC-Catalyzed Ring Expansion of Azacycloalkane-2-Carboxaldehydes

Epoxidation-Ring Closing Reactions.

A solution of the alcohol in CH_2Cl_2 (0.2 M) was cooled to 0 °C. *m*CPBA (1.2 equiv) was added in one portion and the reaction was allowed to warm up to room temperature, then stirred for 48 hours. The reaction was quenched with saturated $NaHCO_3$ (aq) and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over $MgSO_4$ or Na_2SO_4, then concentrated under reduced pressure. The resulting residue was purified by column chromatography.

Oxidation reactions.

IBX oxidation.

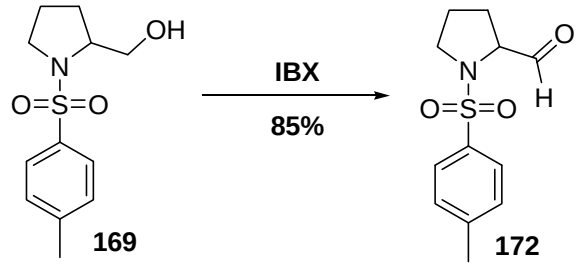
A suspension of alcohol and IBX (1.4 equiv.) in CH_3CN (0.2 M) was refluxed until complete consumption of the alcohol. The mixture was cooled to room temperature, then filtered through a pad of celite, washing with ethyl acetate. The filtrate was collected and concentrated under reduced pressure

NHC-catalyzed ring expansion reaction.

To a 0.5 M solution of azacycloalkane-2-carboxaldehyde (1.0 equiv.) in anhydrous CH_2Cl_2 was added 1,3-bis-(2,6-diisopropylphenyl)imidazolinium chloride (0.2 equiv.), followed by DBU

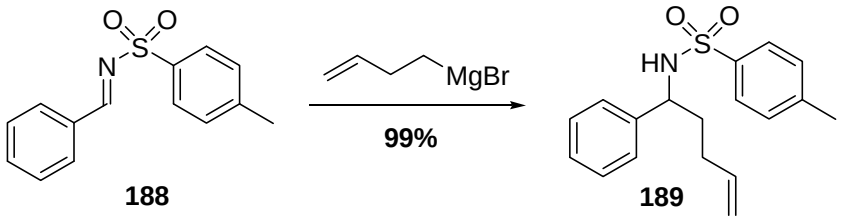
(0.16 equiv.) under nitrogen at room temperature. The reaction was monitored by thin layer chromatography, when there was no progress of the reaction, DBU (0.16 equiv.) was added again until the completion of the reaction. Then the reaction was quenched using saturated NH_4Cl (aq.). The mixture was then extracted using CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography to afford the lactame.

Synthesis and Characterization Data



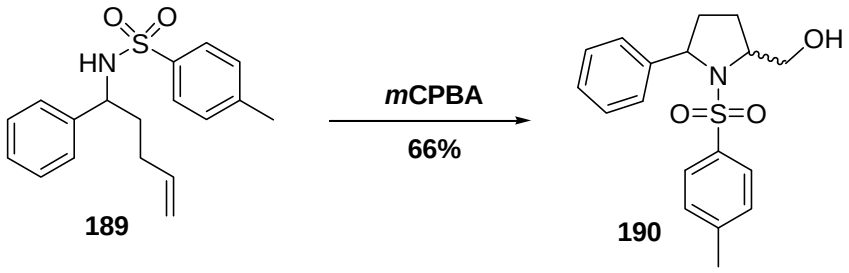
1-Tosylpyrrolidine-2-carbaldehyde 172.

Oxidation of the alcohol **169** (50 mg, 0.196 mmol) using IBX following the general procedure afforded the title aldehyde **172** (47 mg, 94% yield) as a yellow crystal. **IR** ν max: 3091, 2988, 2867, 1732, 1596, 1339 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.68 (d, J = 2.1 Hz, 1H), 7.72 (d, J = 8.1 Hz ,2H), 7.34 (d, J = 8.0 Hz, 2H), 3.84-3.81 (m, 1H), 3.55 (ddd, J = 6.4, 11.5, 16.0 Hz, 1H), 3.18 (ddd, J = 7.32, 14.9, 17.0 Hz, 1H), 2.44 (s, 3H), 2.07-2.02 (m, 1H), 1.83-1.77 (m, 2H), 1.67-1.62 (m, 1H) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.3, 144.9, 130.1, 127.9, 100.2, 66.7, 49.3, 27.8, 24.9, 21.7; **HRMS** (CI^+) *m/z* calcd for $C_{12}H_{19}N_2O_3S$ $[M+NH_4^+]^+$: 271.1116, found: 271.1120.



4-Methyl-N-(1-phenylpent-4-enyl)benzenesulfonamide 189.

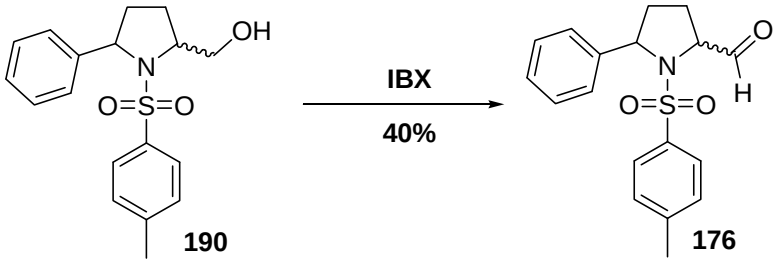
(*E*)-*N*-Benzylidene-4-methylbenzenesulfonamide **188** (synthesized in one step from benzaldehyde and *p*-toluenesulfonamide[53])(75.1 mg, 0.29 mmol) was added slowly to a solution of but-3-enylmagnesium bromide (0.98 mmol) (freshly prepared from 5-bromo-1-butene and magnesium) in diethyl ether (1.96 ml) at 0°C. After 30 min, the reaction was quenched with aqueous saturated NH_4Cl (5 mL) and extracted with Et_2O (3×5 mL). The combined organic layers were dried over Na_2SO_4, and concentrated to afford the title compound **189** (90 mg, 98% yield) as a colorless oil. **IR** ν max: 3064, 2924, 1640, 1456, 1323, 1184 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 2H), 7.19-7.12 (m, 3H), 7.09 (d, J = 7.9 Hz, 2H), 7.05-6.98 (m, 2H), 5.73-5.64 (m, 1H), 5.33 (d, J = 7.2 Hz, 1H), 4.95-4.90 (m, 2H), 4.29 (dd, J = 7.4, 14.6 Hz, 1H), 2.34 (s, 3H), 2.0-1.74 (m, 4H) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.1, 140.9, 137.9, 137.4, 129.5, 128.6, 127.5, 127.2, 126.7, 115.7, 58.0, 36.8, 30.2, 21.6; **HRMS** (CI^+) *m/z* calcd for $C_{18}H_{25}N_2O_2S$ $[M+NH_4^+]^+$: 333.1636, found: 33.1627.



(5-Phenyl-1-tosylpyrrolidin-2-yl)methanol 190.

A solution of the tosyl amide **189** (90 mg) in CH_2Cl_2 (2.9 ml) was cooled to 0 °C. *m*CPBA (138 mg) was added in one portion and the reaction was allowed to warm up to room temperature, then stirred for overnight. The reaction was quenched with 10% $Na_2S_2O_3$ in saturated $NaHCO_3$ (aq) and extracted with CH_2Cl_2 (3×5 ml). The combined organic extracts were dried over Na_2SO_4, then concentrated under reduced pressure. The resulting residue was purified by column chromatography (30% ethyl acetate in hexanes) to afford the alcohol **190** (43 mg, 46%) as a yellow oil. **IR** ν max: 3275, 3030, 2924, 2864, 1599, 1495, 1456, 1325, 1148 cm^{-1}; **^{1}H NMR**

(500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 6.71 Hz, 2H, one epimer), 7.52 (d, *J* = 8.2 Hz, 2H, one epimer), 7.16-7.11 (m, 6H, both epimers), 7.11-7.06 (m, 4H, both epimers), 7.04-6.97 (m, 4H, both epmers), 5.53 (br, 2H, both epimers), 4.35-4.27 (m, 2H, both epimers), 2.85-2.82 (m, 2H, both epimers), 2.69 (dd, *J* = 4.3, 8.9 Hz, 2H, both epimers), 2.38 (dd, *J* = 2.6, 4.7 Hz, 2H, both epimers), 2.33 (s, 6H, both epimers), 1.96-1.26 (m, 8H, both epimers) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.17, 143.15, 140.75, 140.72, 140.62, 140.61, 137.9, 137.8, 129.4, 128.67, 128.65, 127.62, 127.60, 127.59, 127.2, 126.6, 58.3, 58.1, 51.9, 51.8, 47.3, 47.2, 34.0, 33.8, 28.93, 28.93 21.61, 21.61; **HRMS** (CI^+) *m/z* calcd for $C_{18}H_{22}NO_3S$ $[M+NH_4^+]^+$: 332.1320, found: 271.1308.

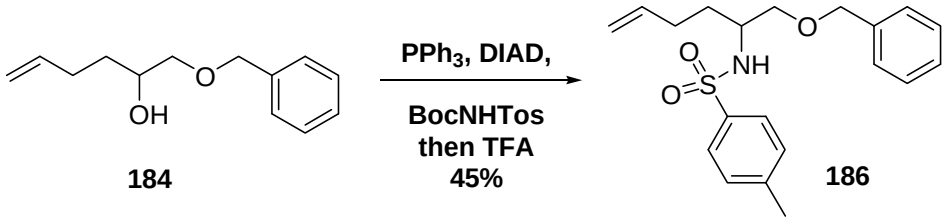


190 **176**

5-Phenyl-1-tosylpyrrolidine-2-carbaldehyde 176.

Oxidation of the alcohol **190** (238 mg) using IBX following the general procedure afforded the title aldehyde **176** (95 mg, 39% yield) as a yellow oil (5:4 mixture of epimers). **IR** ν max: 3064, 2816, 1733, 1494, 1345, 1216 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.85 (d, *J* = 1.9 Hz, 1H, major epimer), 9.82 (d, *J* = 3.3 Hz, 1H, minor epimer), 7.67 (d, *J* = 8.2 Hz, 2H, major epimer), 7.36 (d, *J* = 7.5 Hz, 2H, major epimer), 7.32-7.29 (m, 5H, both epimers), 7.26-7.22 (m, 1H, minor epimer), 7.20-7.19 (m, 3H, both epimers), 7.16-7.13 (m, 1H, major epimer), 7.07 (t, *J* = 7.7 Hz, 2H, minor epimer), 7.00 (d, *J* = 8.0 Hz, 2H, minor epimer), 6.87 (d, *J* = 7.3 Hz, 2H, minor epimer), 5.22 (dd, *J* = 1.9, 7.8 Hz, 1H, minor epimer), 4.77 (dd, *J* = 5.1, 7.3 Hz, 1H, major epimer), 4.32 (ddd, *J* = 2.9, 2.9, 8.5 Hz, 1H, minor epimer), 4.15 (ddd, *J* = 1.7, 1.7, 7.5 Hz, 1H, major epimer),

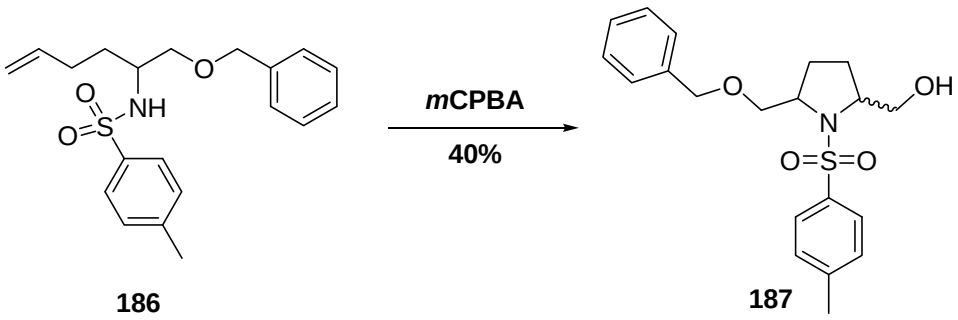
2.46-2.43 (m, 1H, minor epimer), 2.42 (s, 3H, major epimer), 2.42-2.38 (m, 1H, major epimer), 2.32 (s, 3H, minor epimer) 2.2-1.8 (m, 4H, both epimers); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.2, 199.8, 144.4, 143.3, 141.5, 140.6, 137.4, 134.3, 130.0, 129.3, 128.7, 128.4, 127.9, 127.7, 127.5, 127.3, 126.9, 126.5, 68.4, 67.6, 64.8, 64.6, 35.1, 34.2, 27.2, 25.9, 21.7, 21.6; **HRMS** (CI^+) *m/z* calcd for $C_{18}H_{23}N_2O_3S$ $[M+NH_4^+]^+$: 347.1429, found: 347.1438.



***N*-(1-(Benzyloxy)hex-5-en-2-yl)-4-methylbenzenesulfonamide 186.**

Triphenylphosphine (254 mg, 0.97 mmol), Weinreb reagent (BocNHTos, 171 mg, 0.63 mmol) and diisopropyl azadicarboxylate (DIAD, 0.14 ml, 0.63 mmol) was added slowly to a solution of **184** (100 mg, 0.48 mmol) in dry THF (1.6 ml) at room temperature. The reaction flask was protected using aluminum foil and stirred overnight. Then the reaction was concentrated, CH_2Cl_2 (2 ml) and trifluoroacetic acid (TFA, 1 ml) were added. After 5 hours, the reaction was quenched by adding saturated $NaHCO_3$ (aq) slowly, extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by chromatography (20% ethyl acetate in hexanes) to afford the title compound **186** (158 mg, 72% yield) as a colorless oil. **IR** ν max: 3064, 2924, 2826, 1640, 1453, 1208, 1161 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.35-7.20 (m, 7H), 5.71-5.66 (m, 1H), 4.92 (ddd, *J* = 1.5, 1.5, 4.2 Hz, 2H), 4.90-4.80 (m, 1H), 4.34 (s, 2H), 3.37-3.33 (m, 1H), 3.31 (dd, *J* = 3.5, 9.4 Hz, 1H), 3.20 (dd, *J* = 4.1, 9.3 Hz, 1H), 2.42 (s, 3H), 2.04-1.94 (m, 2H), 1.60 (q, *J* = 7.3, 14.7 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.4, 138.4, 137.9, 137.8, 129.8, 128.6, 128.0, 127.8, 127.3, 115.4, 73.4, 71.2,

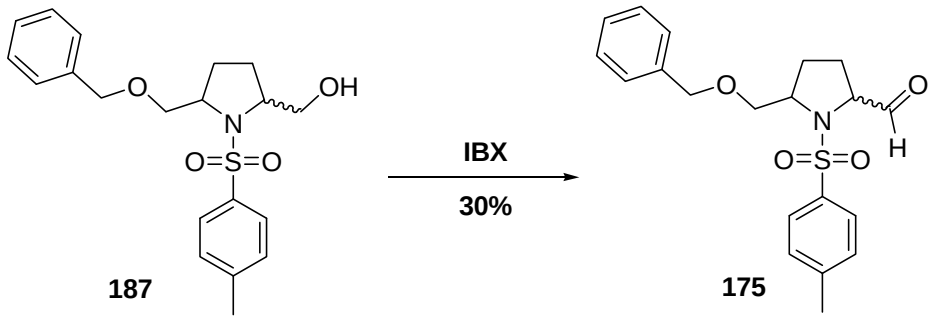
53.3, 32.0, 29.9, 21.7; **HRMS** (CI^+) *m/z* calcd for $C_{20}H_{29}N_2O_3S$ $[M+NH_4^+]^+$: 377.1898, found: 377.1909.



186 **187**

(5-(Benzyloxymethyl)-1-tosylpyrrolidin-2-yl)methanol 187.

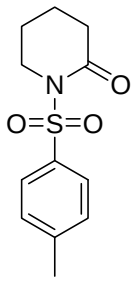
A solution of the alcohol **186** (528 mg, 1.47 mmol) in CH_2Cl_2 (15 ml) was cooled to 0 °C. *m*CPBA (711 mg, 2.06 mmol) was added in one portion and the reaction was allowed to warm up to room temperature, then stirred for overnight. The reaction was quenched with 10% $Na_2S_2O_3$ in saturated $NaHCO_3$ (aq) and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over Na_2SO_4, then concentrated under reduced pressure. The resulting residue was purified by column chromatography (30% ethyl acetate in hexanes) to afford the alcohol **187** (359 mg, 27% yield) as a yellow oil (single diastereomer). **IR** ν max: 3031, 2923, 1598, 1495, 1327, 1206, 1092, 918, 739, 550 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2H), 7.34-7.27 (m, 3H), 7.23 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 6.8 Hz, 2H), 5.02 (d, J = 8.4 Hz, 1H), 4.31 (dd, J = 12.7, 12.7 Hz, 2H), 3.42-3.36 (m, 1H), 3.29 (dd, J = 3.6, 9.4 Hz, 1H), 3.16 (dd, J = 4.4, 9.4 Hz, 1H), 2.85 (ddd, J = 3.7, 3.7, 6.6 Hz, 1H), 2.70 (dd, J = 4.5 Hz, 1H), 2.41 (br, 1H), 2.39 (s, 3H), 1.71-1.57 (m, 3H), 1.43-1.37 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.4, 138.2, 137.8, 129.7, 128.6, 127.9, 127.8, 127.1, 73.3, 71.2, 53.2, 51.9, 47.3, 29.0, 28.5, 21.7; **HRMS** (CI^+) *m/z* calcd for $C_{20}H_{26}NO_4S$ $[M+H]^+$: 376.1582, found: 376.1595.



187 175

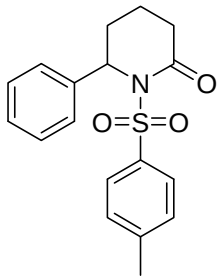
5-(benzyloxymethyl)-1-tosylpyrrolidine-2-carbaldehyde 175.

Oxidation of the alcohol **187** (153 mg, 0.41 mmol) using IBX following the general procedure afforded the title aldehyde **175** (53 mg, 36% yield) as a yellow oil (single epimer). **IR** ν max: 3030, 2867, 2702, 1734, 1597, 1495, 1347, 1249, 1205, 1161, 1092, 911, 816, 739, 699 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.60 (d, J = 2.6 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.38-7.21 (m, 7H), 4.57 (dd, J = 11.9, 16.8 Hz, 2H), 3.89-3.83 (m, 1H), 3.82 (ddd, J = 2.4, 7.8, 15.7 Hz, 1H), 3.75 (dd, J = 3.2, 9.4 Hz, 1H), 3.62 (dd, J = 6.9, 9.3 Hz, 1H), 2.45 (s, 3H), 2.09-1.56 (m, 4H) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.3, 144.4, 138.1, 130.1, 128.6, 128.4, 127.9, 172.83, 127.82, 73.7, 73.1, 68.1, 60.8, 28.4, 26.3, 21.7; **HRMS** (CI^+) *m/z* calcd for $C_{20}H_{27}N_2O_4S$ $[M+NH_4]^+$: 391.1691, found: 391.1690.



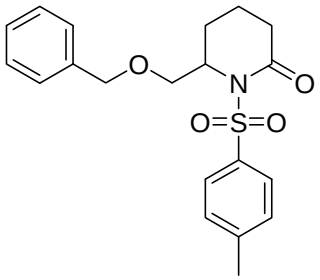
1-Tosylpiperidin-2-one 172. [54]

Lactam **172** was synthesized by reacting aldehyde **169** (25 mg, 0.099 mmol) with 20 mol % catalyst loading of **63** (6.05 mg, 0.02 mmol) and 3×DBU (16mol%, 2.36 µL, 0.016 mmol for each addition). The reaction was performed by following the general procedure. The crude was passed through a pad of silica and washed with 70% ethyl acetate in hexanes to yield a yellow oil (22mg, 88% yield).



6-Phenyl-1-tosylpiperidin-2-one 178.

Lactame **178** was synthesized by reacting aldehyde **176** (62 mg, 0.19 mmol) with 20 mol % catalyst loading of **63** (13.8 mg, 0.038 mmol) and 5×DBU (16mol%, 4.48 µL, 0.03 mmol for each addition). The reaction was performed by following the general procedure. The crude was purified by column chromatography (30% ethyl acetate in hexanes) to yield a yellow oil (35 mg, 56% yield). **IR** ν max: 2953, 1693, 1597, 1494, 1453, 1351, 1169, 1087, 814, 702 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.2 Hz, 2H), 7.32-7.28 (m, 3H), 7.16 (d, J = 8.2 Hz, 2H), 7.12-7.07 (m, 2H), 5.81 (dd, J = 4.5 Hz, 1H), 2.59-2.54 (m, 2H), 2.38 (s, 3H), 2.24-2.16 (m, 1H), 2.05-2.03 (m, 1H), 1.73-1.61 (m, 2H) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.8, 144.8, 140.6, 136.1, 129.7, 128.9, 128.7, 127.8, 126.6, 60.5, 33.8, 31.6, 21.8, 15.9; **HRMS** (CI^+) *m/z* calcd for $C_{18}H_{20}NO_3S$ $[M+H]^+$: 330.1164, found: 330.1166.



6-(Benzyloxymethyl)-1-tosylpiperidin-2-one 177.

Lactame **177** was synthesized by reacting aldehyde **175** (43 mg, 0.12 mmol) with 20 mol % catalyst loading of **63** (8.4 mg, 0.24 mmol) and 3×DBU (16mol%, 2.84 μL, 0.02 mmol for each addition). The reaction was performed by following the general procedure. The crude was purified by column chromatography (20% ethyl acetate in hexanes) to yield a yellow oil (26 mg, 60%). **IR** ν max: 2922, 1695, 1596,1453, 1349, 1260, 1163, 1088, 872, 699 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.3 Hz, 2H), 7.34-7.24 (m, 7H), 4.81-4.77 (m, 1H), 4.52 (dd, J = 11.9, 23.8 Hz, 2H), 3.74 (dd, J = 3.6, 9.7 Hz, 1H), 3.66 (dd, J = 7.8, 9.5 Hz, 1H), 2.45-2.44 (m, 1H), 2.39 (s, 3H), 2.38-2.28 (m, 1H), 2.23-2.18 (m, 1H), 1.94-1.66 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.9, 144.7, 137.9, 136.8, 129.3, 129.1, 128.6, 128.0, 127.8, 73.6, 71.0, 55.4, 33.7, 25.6, 21.8, 16.9; **HRMS** (CI^+) *m/z* calcd for $C_{20}H_{24}NO_4S$ $[M+H]^+$: 374.1426, found: 374.1437.

III. General Procedures for NHC-Catalyzed Cascade Reactions

Nucleophilic addition of lithiated furan reactions.

n-Butyl lithium was added dropwise to a solution of furan in THF (0.1 mol/L) at 0°C. After 30 min, the electrophile was added dropwise. The reaction was stirred 30 minutes and was quenched with saturated NH_4Cl (aq.) and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography

Formylation of furan derivatives.

n-Butyl lithium was added dropwise to a solution of furan derivatives in THF (0.2 mol/L) at 0°C. After 30 min, dry *N, N*-dimethylformamide was added dropwise. The reaction was stirred 30 minutes and was quenched with saturated NH_4Cl (aq.) and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography

Esterification reactions.

Esterification reaction A, Mitsunobu Reaction.

Triphenylphosphine (2.0 equiv.), and diisopropyl azadicarboxylate (2.0 equiv.) was added slowly to a solution of alcohol (1 equiv.) and carboxylic acid (1 equiv.) in dry THF (0.3 mol/L) at 0°C. The reaction flask was protected using aluminum foil and was monitored using thin layer

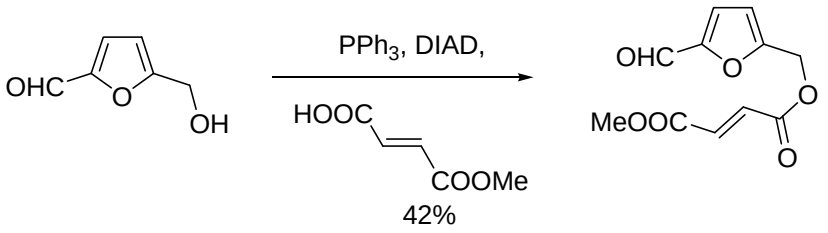
chromatography. After completion, the reaction was concentrated, and purified by chromatography to give the esters.

Esterification reaction B.

1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide (EDCI, 2.5 equiv.), 4-dimethylaminopyridine (DMAP, 0.1 equiv.) was added slowly to a solution of alcohol (1.0 equiv) and carboxylic acid (1.0 equiv.) in dry THF (0.3 mol/L) at room temperature. The reaction was monitored using thin layer chromatography. After completion, the reaction was quenched with saturated NH_4Cl (aq.), extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by chromatography to afford the esters.

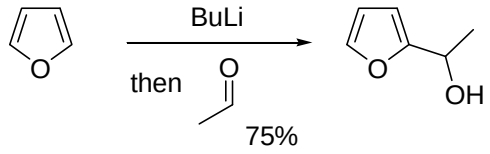
Reaction conditions for the reactions with *N*-heterocyclic carbene catalysts.

To a 0.02 M solution of furaldehyde derivatives (1.0 equiv.) in anhydrous CH_2Cl_2 was added the N-heterocyclic carbene (0.5 equiv.), followed by EtOH (3.0 equiv.) and DBU (0.4 equiv.) under nitrogen at room temperature. The reaction was monitored by thin layer chromatography, After the starting material was fully consumed, the reaction was quenched using saturated NH_4Cl (aq.). The mixture was then extracted using CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography.



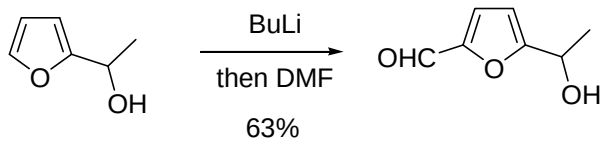
(5-Formylfuran-2-yl)methyl methyl fumarate

Esterification of the commercially available alcohol (58 mg, 0.46 mmol) with the mono-carboxylic acid (120 mg, 0.92 mmol) using PPh_3 (241 mg, 0.92 mmol) and DIAD (0.2 ml, 0.92 mmol) following the general procedure (Mitsunobu reaction) afforded the title ester (46 mg, 42% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 6.88 (d, *J* = 15.8 Hz, 1H), 6.84 (d, *J* = 16.6 Hz, 1H), 6.62 (d, *J* = 2.3 Hz, 1H), 5.23 (s, 2H), 3.78 (s, 3H).



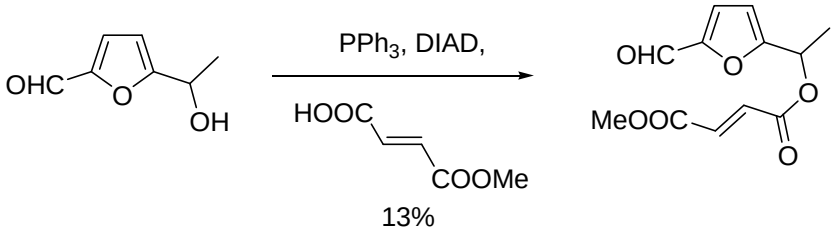
1-(furan-2-yl)ethanol. [55]

The reaction of the furan (0.79 ml, 11 mmol) with butyl lithium (1.5 mol/L in hexanes, 6.70 ml, 10 mmol) and acetaldehyde (0.67 ml, 12 mmol) following the general procedure afforded the title alcohol (0.92 g, 75% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 0.8 Hz, 1H), 6.32 (dd, *J* = 1.7, 3.1 Hz, 1H), 6.2 (d, *J* = 3.1 Hz, 1H), 4.88 (q, *J* = 6.6, 13.1 Hz, 1H), 2.12 (br, 1H), 1.54 (d, *J* = 6.6 Hz, 3H).



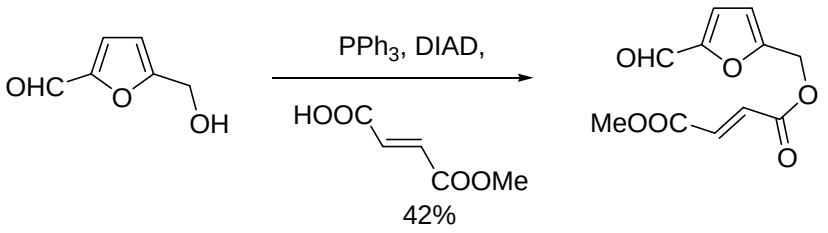
5-(1-hydroxyethyl)furan-2-carbaldehyde.

Formylation of the furfuryl alcohol derivative (58 mg, 0.52 mmol) using butyl lithium (1.5 mol/L in hexanes, 0.76 ml, 1.14 mmol) and DMF (0.1 ml, 1.3 mmol) following the general procedure afforded the title aldehyde (46 mg, 63% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.59 (d, J = 8.9 Hz, 1H), 7.20 (d, J = 3.5 Hz, 1H), 6.47 (d, J = 3.6 Hz, 1H), 4.96 (q, J = 6.6, 13.2 Hz, 1H), 2.16 (br, 1H), 1.58 (d, J = 6.6 Hz, 3H)



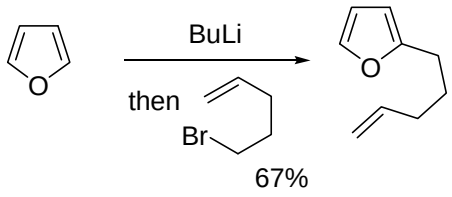
1-(5-formylfuran-2-yl)ethyl methyl fumarate.

Esterification of the alcohol (165.75 mg, 1.18 mmol) with the mono-carboxylic acid (307.8 mg, 2.37 mmol) using PPh_3 (0.62 g, 2.37 mmol) and DIAD (0.47 ml, 2.37 mmol) following the general procedure (Mitsunobu reaction) afforded the title ester (41.4 mg, 13% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.19 (d, J = 3.6 Hz, 1H), 6.89 (d, J = 16 Hz, 1H), 6.85 (d, J = 11.4 Hz, 1H), 6.5 (d, J = 3.6 Hz, 1H), 6.06 (q, J = 6.7, 13.4 Hz, 1H), 3.79 (s, 3H), 1.68 (d, J = 6.7 Hz, 3H).



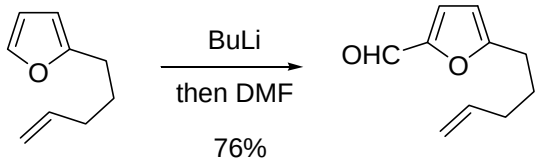
(5-Formylfuran-2-yl)methyl methyl fumarate.

Esterification of the commercially available alcohol (58 mg, 0.46 mmol) with the mono-carboxylic acid (120 mg, 0.92 mmol) using PPh_3 (241 mg, 0.92 mmol) and DIAD (0.2 ml, 0.92 mmol) following the general procedure (Mitsunobu reaction) afforded the title ester (46 mg, 42% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.20 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 15.8 Hz, 1H), 6.84 (d, J = 16.6 Hz, 1H), 6.62 (d, J = 2.3 Hz, 1H), 5.23 (s, 2H), 3.78 (s, 3H).



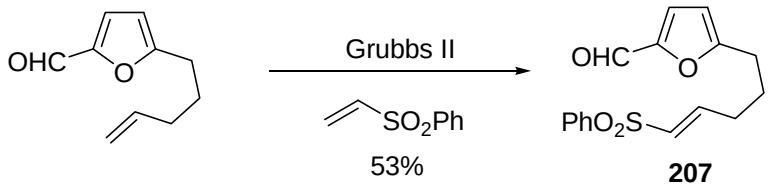
2-(pent-4-enyl)furan. [56]

The reaction of the furan (0.37 ml, 5.07 mmol) with butyl lithium (2.45 mol/L in hexanes, 1.90 ml, 4.65 mmol) and 5-bromo-1-butene (0.5 ml, 4.23 mmol) following the general procedure afforded the title furan derivative (384 mg, 67% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.28 (s, 1H), 5.98 (d, J = 2.6 Hz, 1H), 5.86-5.79 (m, 1H), 5.03 (d, J = 17 Hz, 1H), 4.98 (d, J = 9.7 Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.11 (q, J = 6.9, 14.1 Hz, 2H), 1.77-1.72 (m, 2H).



5-(Pent-4-enyl)furan-2-carbaldehyde.

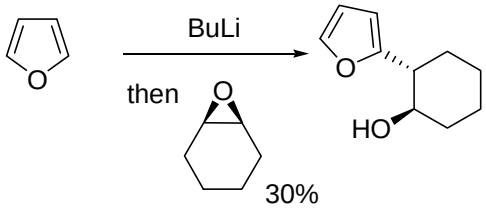
Formylation of the furan derivative (384 mg, 2.82 mmol) using butyl lithium (2.45 mol/L in hexanes, 1.27 ml, 3.11 mmol) and DMF (0.28 ml, 3.67 mmol) following the general procedure afforded the title aldehyde (350 mg, 76% yield) as a colorless oil. **IR** ν max: 3077, 2931, 2862, 2361, 2335, 1679, 1519, 1398 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.15 (d, J = 3.3 Hz, 1H), 6.22 (d, J = 3.2 Hz, 1H), 5.69-5.83 (m, 1H), 5.00 (d, J = 18.9 Hz, 1H), 4.98 (d, J = 11.3 Hz, 1H), 2.71 (t, J = 7.7 Hz, 2H), 2.09 (q, J = 7.7, 15.3 Hz, 2H), 1.79-1.76 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.1, 163.77, 163.79, 152.0, 137.7, 115.6, 108.9, 33.1, 27.8, 26.7; **HRMS** (EI^+) *m/z* calcd for $C_{10}H_{12}O_2$ $[M]^+$: 164.0837, found: 164.0834.



(*E*)-5-(5-(Phenylsulfonyl)pent-4-enyl)furan-2-carbaldehyde. 207

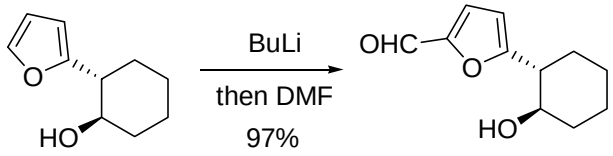
To a 0.1 M solution of the 2-furaldehyde derivatives (313 mg, 1.91 mmol) in anhydrous CH_2Cl_2 was added phenyl vinyl sulphone (482 mg, 2.81 mmol), followed by 2.5 mol% catalytic loading of Grubbs II catalyst (40 mg, 0.048 mmol) under nitrogen at room temperature. The reaction was then brought to reflux and monitored by thin layer chromatography. After the starting material was fully consumed, the reaction was concentrated under reduced pressure, and purified by

column chromatography (50% ethyl acetate in hexanes) to afford the title compound **207** (306 mg, 53% yield) as a black oil. **IR** ν max: 3118, 3057, 2936, 2826, 1673, 1583, 1479, 1399, 1306, 1192, 1022 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.89-7.51 (m, 5H), 7.14 (s, 1H), 6.97-6.91 (m, 1H), 6.34 (d, J = 15 Hz, 1H), 6.21 (s, 1H), 2.72 (t, J = 7.4 Hz, 2H), 2.29 (q, J = 7.0, 14.1 Hz, 2H), 1.90-1.84 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.1, 162.2, 152.2, 145.49, 145.47, 140.6, 133.5, 131.5, 129.5, 127.7, 109.4, 30.8, 27.7, 25.7; **HRMS** (EI^+) *m/z* calcd for $C_{16}H_{16}O_4S$ $[M]^+$: 304.0769, found: 304.0771.



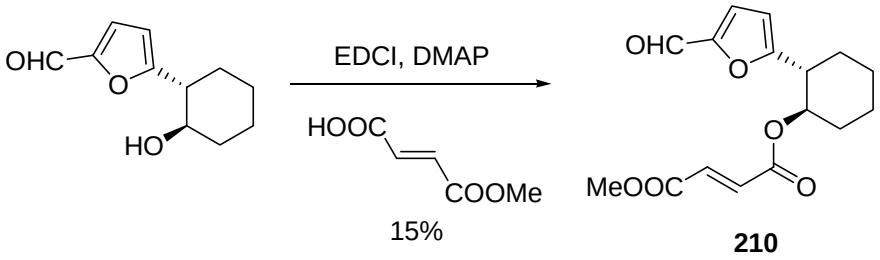
(1*R*,2*R*)-2-(furan-2-yl)cyclohexanol (and its enantiomer). [57]

The reaction of the furan (0.73 ml, 10 mmol) with butyl lithium (2.45 mol/L in hexanes, 4.1 ml, 10 mmol) and cyclohexene oxide (1.01 ml, 10 mmol) following the general procedure afforded the title alcohol (490 mg, 30% yield) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (dd, J = 0.7, 1.7 Hz, 1H), 6.32 (dd, J = 1.9, 3.1 Hz, 1H), 6.11 (d, J = 3.1 Hz), 3.62-3.59 (br, 1H), 2.56 (ddd, J = 3.7, 9.8, 12.9 Hz, 1H), 2.19-1.30 (m, 9 H).



5-((1*R*,2*R*)-2-hydroxycyclohexyl)furan-2-carbaldehyde. (and its enantiomer)

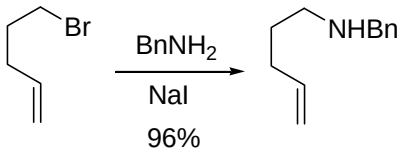
Formylation of the alcohol (490 mg, 2.95 mmol) using butyl lithium (2.45 mol/L in hexanes, 2.65 ml, 6.49 mmol) and DMF (0.6 ml, 7.67 mmol) following the general procedure afforded the title aldehyde (553 mg, 97% yield) as a colorless oil. **IR** ν max: 2932, 2857, 1672, 1578, 1499, 1396, 1281 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.19 (d, J = 3.5 Hz, 1H), 6.34 (d, J = 3.5 Hz), 3.75 (br, 1H), 2.67 (ddd, J = 3.6, 11.3, 13.1 Hz, 1H), 2.12-1.28 (m, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.2, 165.16, 165.13, 152.1, 109.2, 46.5, 35.1, 30.5, 25.3, 24.6; **HRMS** (EI^+) *m/z* calcd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found:194.0940.



210

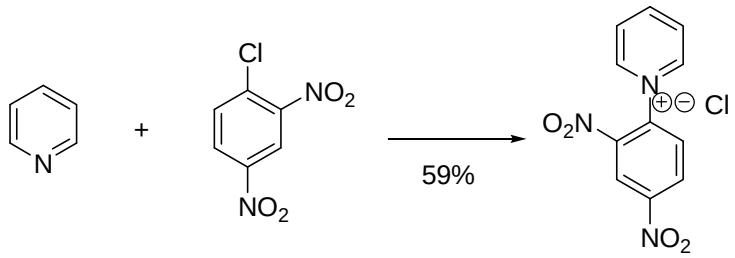
(1*R*,2*R*)-2-(5-formylfuran-2-yl)cyclohexyl methyl fumarate (and its enantiomer). 210

Esterification of the alcohol (255 mg, 1.31 mmol) with the mono-carboxylic acid (342 mg, 2.63 mmol) using EDCI (326.4 mg, 1.70 mmol) and DMAP (15.9 mg, 0.13 mmol) following the general procedure afforded the title ester **210** (60 mg, 15% yield) as a colorless oil. **IR** ν max: 2940, 2862, 1716, 1684, 1582, 1517, 1437, 1260, 1156 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.12 (d, J = 3.5 Hz, 1H), 6.76 (d, J = 15.9 Hz, 1H), 6.73 (d, J = 15.8 Hz, 1H), 6.24 (d, J = 3.5 Hz, 1H), 5.04 (br, 1H), 3.78 (s, 3H), 2.97 (ddd, J = 3.8, 12.0, 12.0 Hz, 1H), 2.16-1.45 (m, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.5, 164.2, 163.3, 152.2, 133.82, 133.78, 133.59, 133.58, 108.6, 75.2, 52.5, 43.1, 31.8, 30.5, 24.9, 24.2.



***N*-Benzylpent-4-en-1-amine.** [24]

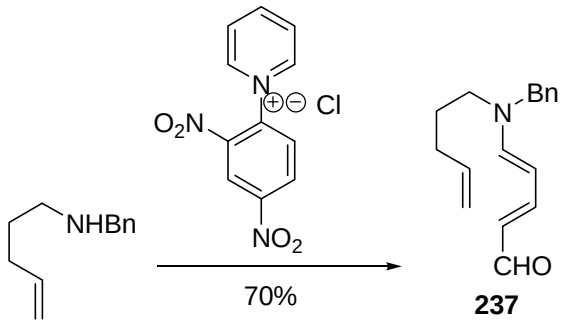
To a solution of 5-bromo-1-butene (0.59 ml, 5 mmol) and benzyl amine (2.73 ml, 25 mmol) in EtOH (12.5 ml) added NaI (37.5 mg, 0.25 mmol) in one portion. The reaction was stirred under reflux and monitored using thin layer chromatography. After completion, the reaction was concentrated. The crude oil was washed into 1 mol/L NaOH (aq. 50 ml) using CH_2Cl_2 (3×20 ml). Combined organic layers were then dried through Na_2SO_4, and concentrated on reduced pressure. Resulting brown oil was purified by distillation (110° C, 6 mmHg) to afford the title compound as a yellow oil (866 mg, 96% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79-7.28 (m, 5H), 5.86-5.77 (m, 1H), 5.0 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 9.9 Hz, 1H), 3.79 (s, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.10 (q, *J* = 7.1, 14.4 Hz, 2H), 1.64-1.58 (m, 2H), 1.33 (br, 1H).



Zincke's Salt. [58]

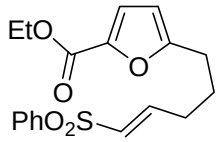
Zincke's salt was prepared from reacting pyridine (1.43 ml, 17.7 mmol) and 2,4-dinitro chlorobenzene (3.53 g, 17.5 mmol) in acetone (17 ml) under reflux following Vanderwal *et al*'s procedure [58] to afford Zincke's salt as a white crystal (2.9 g, 59% yield). **^{1}H NMR** (500 MHz, D_2O) δ 9.32 (d, *J* = 2.2 Hz, 1H), 9.13 (d, *J* = 6.0 Hz, 2H), 8.9-8.85 (m, 2H), 8.34 (t, *J* = 6.9 Hz,

2H), 8.26 (d, *J* = 8.6 Hz, 1H).



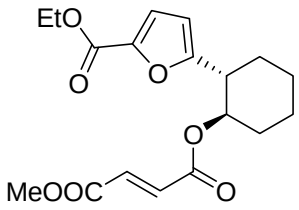
(2*E*,4*E*)-5-(Benzyl(pent-4-enyl)amino)penta-2,4-dienal. 237

Zincke's salt (129.3 mg, 0.46 mmol) was added into a solution of *N*-Benzylpent-4-en-1-amine (200 mg, 1.14 mmol) in EtOH (2.3 ml) and H_2O (51.6 mg). The reaction was stirred under reflux and monitored using thin-layer chromatography. After completion, the reaction was concentrated. The resulting black oil was added 1 mol/L NaOH (aq. 2 ml) then was extracted using CH_2Cl_2 (3×3 ml). Combined organic layers were dried through Na_2SO_4, then concentrated under reduced pressure. Crude oil was purified by chromatography (50% ethyl acetate in hexanes) to afford the title aldehyde **237** (82 mg, 70% yield) as a brown red oil. **IR** ν max: 3030, 2931, 2695, 2270, 1657, 1495, 1422, 1217 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.29 (d, *J* = 8.3 Hz, 1H), 7.37-7.29 (m, 3H), 7.19 (d, *J* = 7.2 Hz, 2H), 7.10 (dd, *J* = 11.6, 14.3 Hz, 1H), 6.91 (d, *J* = 12.7 Hz, 1H), 5.84-5.72 (m, 2H), 5.37 (t, *J* = 11.8 Hz, 1H), 5.04-5.00 (m, 2H), 4.37 (s, 2H), 3.18 (t, *J* = 7.2 Hz, 2H), 2.0 (q, *J* = 6.9, 13.9 Hz, 2H), 1.69-1.63 (m, 2H).



(*E*)-Ethyl 5-(5-(phenylsulfonyl)pent-4-enyl)furan-2-carboxylate. 209

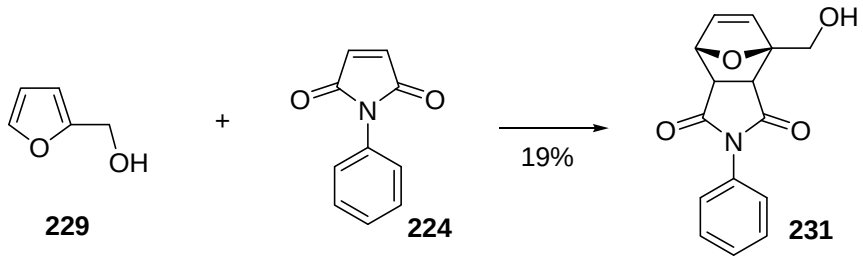
Ethyl ester **209** was synthesized by reacting aldehyde **207** (20 mg, 0.066 mmol) with 50 mol % catalyst loading of **63** (8.42 mg, 0.033 mmol), DBU (4.48 μL, 0.03 mmol) and EtOH (11.53 μL, 0.198 mmol). The reaction was performed by following the general procedure. The crude was purified by preparative thin-layer chromatography (50% ethyl acetate in hexanes) to yield the title ethyl ester **209** (<3 mg). **^{1}H NMR** (500 MHz, D_2O) δ 7.8 (d, *J* = 7.1 Hz, 2H), 7.65-7.49 (m, 3H), 7.06 (s, 1H), 7.0-6.91 (m, 1H), 6.35 (d, *J* = 15.1 Hz, 1H), 6.11 (s, 1H), 4.34 (q, *J* = 6.8, 12.7 Hz, 2H), 2.69 (t, *J* = 8.6 Hz, 2H), 2.32-2.26 (m, 2H), 1.89-1.84 (m, 2H), 1.36 (t, *J* = 6.6 Hz, 3H).



(1*R*,2*R*)-2-(5-(ethoxycarbonyl)furan-2-yl)cyclohexyl methyl fumarate. 212

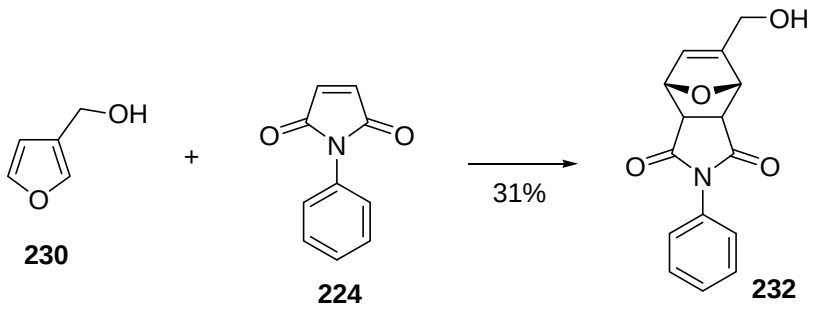
Ethyl ester **212** was synthesized by reacting aldehyde **210** (12 mg, 0.04 mmol) with 50 mol % catalyst loading of **61** (4.42 mg, 0.02 mmol), DBU (2.69 μL, 0.018 mmol) and EtOH (6.99 μL, 0.12 mmol). The reaction was performed by following the general procedure. The crude was purified by preparative thin-layer chromatography (30% ethyl acetate in hexanes) to yield title ethyl ester **212** (<3 mg). **^{1}H NMR** (500 MHz, D_2O) δ 7.0 (d, *J* = 3.4 Hz, 1H), 6.75 (s, 2H), 6.13 (d, *J* = 3.4 Hz, 1H), 5.03 (ddd, *J* = 4.4, 10.1, 10.1 Hz, 1H), 4.32 (q, *J* = 7.1, 14.1 Hz, 2H), 3.78 (s,

3H), 2.95 (ddd, *J* = 3.8, 11.8, 11.8 Hz, 1H), 2.17-1.27 (m, 8H), 1.34 (t, *J* = 7.1 Hz, 3H).



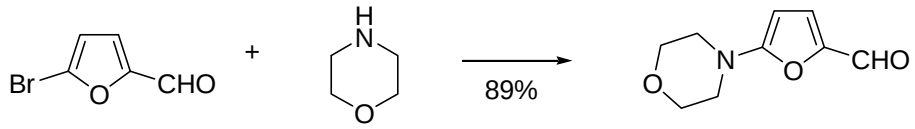
Diels-Alder adduct 221.

To a solution of 2-furfuryl alcohol **229** (1.0 ml, 11.6 mmol) in Et_2O (23 ml) added *N*-phenylsuccinimide **224** (2.0 g, 11.6 mmol) in one portion. The reaction was stirred at room temperature overnight and white precipitate was formed. Then the reaction was filtered through a fritted funnel, resulting white crystal was washed with Et_2O (3×5 ml). The *endo*- and *exo*- adducts were separated using chromatography (1% methanol in dichloromethane) to afford *endo*-adduct (370 mg, 12% yield) and *exo*-addut (205 mg, 7% yield) both as white crystal. ***Endo* adduct ^{1}H NMR** (500 MHz, D_2O) δ 7.54-7.36 (m, 3H), 7.13 (dd, *J* = 1.4, 3.4 Hz, 2H), 6.6 (dd, *J* = 1.5, 5.78 Hz, 1H), 6.52 (d, *J* = 5.8 Hz, 1H), 5.42 (dd, *J* = 1.5, 5.5 Hz, 1H), 4.35 (dd, *J* = 5.6, 12.5 Hz, 1H), 4.25 (dd, *J* = 7.1, 12.5 Hz, 1H), 1.92 (dd, *J* = 5.5, 7.8 Hz, 1H), 3.60 (d, *J* = 7.8 Hz, 1H), 2.05 (dd, *J* = 5.6, 7.1 Hz, 1H). ***Exo* adduct: ^{1}H NMR** (500 MHz, D_2O) δ 7.51-7.39 (m, 3H), 7.29-7.27 (m, 2H), 6.68 (d, *J* = 5.72 Hz, 1H), 6.61 (dd, *J* = 1.4, 5.7 Hz, 1H), 5.39 (d, *J* =1.6 Hz, 1H), 4.18 (dd, *J* = 7.9, 12.6 Hz, 1H), 4.16 (dd, *J* = 6.8, 12.7 Hz, 1H), 3.16 (dd, *J* = 6.6, 18.2 Hz, 2H), 2.73 (dd, *J* = 6.8, 7.8 Hz, 1H).



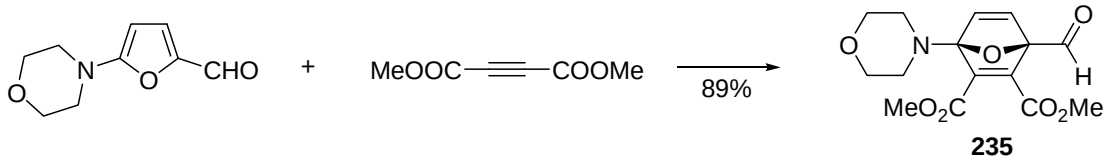
Diels-Alder adduct 232.

To a solution of 3-furfuryl alcohol **230** (0.58 g, 5.93 mmol) in Et_2O (12 ml) added *N*-phenylsuccinimide **224** (1.02 g, 5.93 mmol) in one portion. The reaction was stirred at room temperature overnight and then was concentrated on reduced pressure. Resulting light yellow oil was purified by using chromatography (1% methanol in dichloromethane) to afford one diastereomer (353 mg, 22% yield) and the other diastereomer (141 mg, 9% yield) both as white crystal. **One diastereomer ^{1}H NMR** (500 MHz, D_2O) δ 7.47-7.33 (m, 3H), 7.15-7.09 (m, 2H), 6.33 (s, 1H), 5.42 (d, *J* = 2.3 Hz, 1H), 5.33 (d, *J* = 4.2 Hz, 1H), 4.44 (d, *J* = 15.6 Hz, 1H), 4.28 (dd, *J* = 4.1, 16.0 Hz, 1H), 3.74 (ddd, *J* =7.8, 10.9, 10.9 Hz, 2H), 1.73 (dd, *J* = 5.3, 5.3 Hz, 1H). **Another diastereomer ^{1}H NMR** (500 MHz, D_2O) δ 7.49-7.38 (m, 3H), 7.30-7.27 (m, 2H), 6.35 (s, 1H), 5.41-5.31 (m, 2H), 4.44 (dd, *J* = 6.0, 15.4 Hz, 1H), 4.41 (dd, *J* = 5.1, 15.1 Hz, 1H), 3.09 (dd, *J* = 6.9, 6.9 Hz, 2H), 1.65 (dd, *J* = 5.3 Hz, 1H).



5-morpholinofuran-2-carbaldehyde.

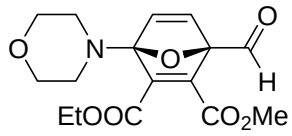
Preparation of product using 5-bromo-2-furadehyde (0.5 g, 2.86 mmol), freshly distilled morpholine (0.52 ml, 6.0 mmol) and triethylamine (1.19 ml, 8.58 mmol) in H_2O (2 mL) following literature procedure [27] afforded the title product (458 mg, 89% yield) as a brown red solid. **^{1}H NMR** (500 MHz, D_2O) δ 9.09 (br, 1H), 7.21 (s, 1H), 5.32 (d, *J* = 3.9 Hz, 1H), 3.79 (t, *J* = 4.8 Hz, 4H), 3.42 (t, *J* = 4.9 Hz, 4H).



235

(1*R*,4*S*)-dimethyl 1-formyl-4-morpholino-7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate. 235 [43]

Diels-Alder reaction of the aldehyde (200mg, 1.10 mmol) and dimethyl acetylenedicarboxylate (DMAD, 0.41 ml, 3.3 mmol) in toluene (5.5 mol) following literature procedure [26] afforded the title compound **235** (420 mg, 89% yield) as a color less oil. **^{1}H NMR** (500 MHz, D_2O) δ 10.90 (s, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.74 (t, *J* = 4.4 Hz, 4H), 2.86 (t, *J* = 4.6 Hz, 4H).



(1*S*,4*R*)-2-ethyl 3-methyl 4-formyl-1-morpholino-7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarb--oxylate. 236

Ethyl ester **236** was synthesized by reacting aldehyde **235** (6 mg, 0.014 mmol) with 50 mol % catalyst loading of **28** (3.0 mg, 0.007 mmol), DBU (0.89 μL, 0.006 mmol) and EtOH (2.45 μL, 0.042 mmol) in CH_2Cl_2 (30 μL). The reaction was performed by following the general procedure. The crude was purified by passing through a pad of silica gel to yield the title ethyl ester (< 2 mg). **^{1}H NMR** (500 MHz, D_2O) δ 11.05 (s, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 4.38 (q, *J* = 7.1, 14.3 Hz, 2H), 3.90 (s, 3H), 3.73 (t, *J* = 4.2 Hz, 4H), 2.85 (t, *J* = 3.9 Hz, 4H), 1.37 (t, *J* = 7.2 Hz, 3H).

References:

[1] Wöhler, L. *Annalen der Pharmacie*, **1832**, *3*, 249-282.

[2] Seebach, D.; Corey, E. J. *J. Org. Chem.*, **1975**, *40*, 231- 237.

[3] (a) Seebach, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 239- 258. (b) Seebach, D.; Gröbel, B. T. *Synthesis- Stuttgart*, **1977**, *6*, 357- 402.

[4] For a recent review on *N*- heterocyclic carbenes in organoctalysis: (a) Marion, N.; Díez-Gonza´lez, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (c) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857- 7870.

[5] A. Igau, H. Grutzmacher, A.Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, *110*, 6463- 6466.

[6] A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am.Chem. Soc.* **1991**, *113*, 361- 363.

[7] Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414- 7415.

[8] For a brief review on recent development of functionalized NHC ligands for metal- based catalysts: Lee, H. M.; Lee, C.; Cheng, P. *Curr. Org. Chem.* **2007**, *11*, 1491- 1524.

[9] For a brief review on recent advances of transition metal- based catalysts using NHCs as ligands: (a) for silver: Busetto, L.; Cassani, M. C.; Femoni, C.; Macchioni, A.; Mazzoni, R.; Zuccacia, D. *J. Organometallic Chem.* **2008**, *693*, 2579- 2591. (b) for gold: Wang, H. M. J.; Vasam, C. S.; Tsai, T. Y. R.; Chen, S. H.; Chang, A. H. H.; Lin, I. J. B. *Organometallics*, **2005**, *24*, 486-493. (c) for copper: Díez-Gonza´lez, S.; Nolan, S. P. *AldrichimicaACTA*, **2008**, *41*, 43- 51. (d) for nickel, palladium and platinum: Chen, C.; Qiu, H.; Chen, W.; Wang, D. *J. Organometallic Chem.* **2008**, *693*, 3273- 3280. (e) for rhenium and technetium: Braband, H.; Kückmann, T. I., Abram, U. *J. Organometallic Chem.* **2005**, *690*, 5421- 5429. (f) for rhodium: Jiménez, M. V.; Pérez- Torrente, J. J.; Bartolomé, M. I.; Gierz, V.; Lahoz, F. J.; Oro, L. A. *Organometallics*, **2008**, *27*, 224- 234. (g) for ruthenium: Dragutan, V.; Dragutan, I.; Delaude, L.; Demonceau. A. *Coord. Chem. Rev.* **2007**, *251*, 765- 794. (f) for tungsten: Wu, F.;

Dioumaev, V. K.; Szalda, D. J.; Hanson, J.; Bullock, R. M. *Organometallics*, **2007**, *26*, 5079-5090.

[10] For a brief review on recent advances of transition metal using NHC as ligands catalyzed reactions: Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290- 1390.

[11] Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296. (*Chem. Abstr.* **1951**, *45*,5148).

[12] a) Zinin, N. *Annalen der Pharmacie*, **1839**, *31*, 329-332; b) Zinin, N. *Annalen der Pharmacie,* **1840**, *34,* 186-192.

[13] Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.

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

[15] For some examples of enzymatic cross benzoin condensation: (a) Demir, A. S.; Pohl, M.; Janzen, E.; Müller, M. *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 633. (b) Demir, A. S.; Sü esü enoglu, Ö.; Eren, E.; Hosrik, B.; Pohl, M.; Janzen, E.; Kolter, D.; Feldmann, R.; Dünkelman, P.; Müller, M. *Adv. Synth. Catal.* **2002**, *344*, 96. (c) Demir, A. S.; Sü esünoglu, Ö.; Dünkelmann, P.; Müller, M. *Org. Lett.* **2003**, *5*, 2047. (d) Demir, A. S.; Dünnwald, T.; Iding, H.; Pohl, M.; Müller, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4769. (e) Iding, H.; Dünnwald, T.; Greiner, L.; Liese, A.; Müller, M.; Siegert, P.; Grötzinger, J.; Demir, A. S.; Pohl, M. *Chem. Eur. J*. **2000**, *6*, 1483. (f) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc.* **2002**, *124*, 12084.

[16] (a) Stetter, H.; Dämbkes, G. *Synthesis*, **1977**, 403. (b) Stetter, H.; Dämbkes, G. *Synthesis,* **1980**, 309.

[17] Stetter, H. *Angew. Chem.* **1976**, *88*, 695; *Angew. Chem. Int. Ed.* **1976**, *15*, 639.

[18] Chow, K. Y. –K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126.

[19] Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518.

[20] Zeitler, K. *Org. Lett.* **2006**, *8*, 637.

[21] Li, G-Q.; Li, Y.; Dai, L-X.; You, S-L. *Org. Lett.* **2007**, *9*, 3519- 3521.

[22] Li, G-Q.; Li, Y.; Dai, L-X.; You, S-L. *Adv. Synth. Catal.* **2008**, *350*, 1258- 1262.

[23] Du, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 4949- 4954.

[24] Li, G-Q.; Dai, L-X.; You, S-L. *Org. Lett.* **2009**, *11*, 1623- 1625.

[25] Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891- 893.

[26] Vora, H. U.; Moncecchi, J. R.; Epstein, O.; Rovis, T. *Org. Lett.* **2008**, *73*, 9727- 9731.

[27] Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105-108.

[28] Yang, L.; Tan, B.; Wang, F.; Zhong, G. *J. Org. Chem.* **2009**, *74*, 1744- 1746.

[29] Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677- 680.

[30] Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.*, **2008**, *130*, 17266- 17267.

[31] He, M.; Bode, J. W. *J. Am. Chem. Soc.*, **2008**, *130*, 418- 419.

[32] Bianchi, P.; Roda, G.; Riva, S.; Danieli, B.; Zabelinskaja-Mackova, A.; Griengl, H. *Tetrahedron*2001, 57, 2213-2220.

[33] Stegmann, V. R.; Adam, W. *Synthesis*, **2001**, 1203-1214.

[34] Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406.

[35] Eliel, E. L. and Wilen, S. H. *Stereochemistry of Organic Compounds*, John Wiley & Sons: NY. **1994**, pg 397 (ISBN: 0-471-01670-5).

[36] Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108-1113.

[37] Likhar, P. R.; Kumar, M. P. and Bandyopadhyay, A. K. *Tetrahedron Lett.* **2002**, *43*, 3333-3335.

[38] Hansen, D. B.; Starr, M-L.; Tolstoy, N. and Joullié, M. M. *Tetrahedron: Asymm.* **2005**, *6*, 3623-3627.

[39] a) Lu, H. –J.; and Li, C. –Z. *Org. Lett.* **2006**, *8*, 5365-5367; b) Jones, A. D.; Knight, D. W. and Hibbs, D. E. *J. Chem. Soc., Perkin Trans 1* **2001**, 1182-1203.

[40] Jung, M. and Gervay, J. *Tetrahedron Lett*. **1988**, *29*, 2429-2432.

[41] Sauer, J. and Butz, T. *Tetrahedron: Asymm.* **1997**, *8*, 703-714.

[42] a) Marki, B. E. and Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331-4334; b) Marki, B. E.; Chan, A.;

Phillips E. M. and Scheidt, K. A. *Tetrahedron*, **2009**, *65*, 3102-3109.

[43] Medimagh, R.; Marque, S.; Prim, D.; Chatti, S. and Zarrouk, H. *J. Org. Chem.* **2008**, *73*, 2191-2197.

[44] Baldwin, J. E.; Lynch, G. P. and Pitlik, J. *J. Antibiotics*, **1991**, *44*, 1-24.

[45] Zhang, Y. –R.; He, L.; Wu, X.; Shao, P. –L. and Ye, S. *Org. Lett.* **2008**, *10*, 277-280.

[46] IBX Synthesis: Frigerio, M.; Santagostino; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538.

[47] Dess-Martin periodinane synthesis: Boeckman, R. K.; Shao, P. Jr.; Mullins, J. *J. Org.Synth.* **2004**, *10*, 696-708.

[48] Heathcock, C. H.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 12836- 12843.

[49] Ichimaru, N.; Mura, M.; Kakutani, N.; Kako, J.; Ishihara, A.; Nakagawa, Y.; Nishioka, T.; Yagi, T.; Miyoshi, H. *Biochemistry* **2008**, *47*, 10816-10826.

[50] Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron* **2004**, *60*, 6533-6539.

[51] Griffiths, D. V.; Wilcox, G. *J. Chem. Soc Perkin Trans. II* **1988**, 431-436.

[52] Brodsky, B. H.; Bois, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 94305-95080.

[53] Wyne, J. H.; Price, S. E.; Rorer, J. R. and Stalick, W. M. *Syn. Comm.* **2003**, *33*, 341-352.

[54] Dake, G. R.; Fenster, M. D. B.; Hurley, P. B. and Patrick, B. D. *J. Org. Chem.* **2004**, *69*, 5668-5675.

[55] Cheng, K.; Kelly, A. R.; Kohn, R. A.; Dweck, J. F. and Walsh, P. J. *Org. Lett.* **2009**, *11*, 2703-2706.

[56] McKeown, N. B.; Chambier, I. and Cook, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, *4*, 1169.

[57] Montaña, A. M. and Grima, P. M. *Tetrahedron*, **2002**, *58*, 4769-4786.

[58] Michels, T. D.; Rhee, J. U. and Vanderwal, C. D. *Org. Lett.* **2008**, *10*, 4787-4790.