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Exploiting Acyl and Enol Azolium Intermediates via NHeterocyclic Carbene Catalyzed Reactions of Alpha-Reducible Aldehydes

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Abstract

N-heterocyclic carbenes are well known for their role in catalyzing benzoin and Stetter reactions: the generation of acyl anion equivalents from simple aldehydes to react with a variety of electrophiles. However, when an aldehyde bearing a leaving group or unsaturation adjacent to the acyl anion equivalent is subjected to an NHC, a new avenue of reactivity is unlocked, leading to a number of novel transformations which can generate highly complex products from simple starting materials, many of which are assembled through unconventional bond disconnections. The field of these new reactions - those utilizing α-reducible aldehydes to access previously unexplored catalytic intermediates – has expanded rapidly in the past eight years. This review aims to provide the reader with a historical perspective on the underlying discoveries that led to the current state of the art, a mechanistic description of these reactions, and a summary of the recent advances in this area.

Keywords

N-heterocyclic carbene; Acylation; Homoenolate; Asymmetric; Organocatalysis

1 Introduction

The catalytic generation of acyl anion equivalents from aldehydes, so-called polarity reversal or “umpolung”,[1] and the subsequent functionalization of these intermediates has become a topic of intense research in recent years. Within this field, N-heterocyclic carbenes (NHCs) have found broad use as catalysts. This rapidly emerging field of organocatalysis has been the subject of many reviews that detail the numerous efforts in this area.[2]

An emerging interest in reactions beyond the scope of traditional acyl anion equivalents (benzoin and Stetter-type reactions) has led to the discovery of an assortment of novel transformations that are the focus of this review. Specifically, substrates that bear α-reducible functionality, a leaving group or unsaturation adjacent to the carbonyl, can be diverted to unique reaction pathways via three distinct catalytic intermediates: electrophilic acyl azolium **1**, nucleophilic enol **2**, and nucleophilic homoenolate **3** (Scheme 1). This class of reactivity has been termed NHC-redox catalysis, after the concomitant reduction of α-functionality and oxidation of the aldehyde that occurs in the process.

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Each of these intermediates has been exploited in new reactions to give a variety of highly functionalized and enantioenriched products from simple starting materials. A diverse array of acylated products, heterocycles and carbocycles have been made accessible by this reaction manifold, often by bond disconnections that would not have been available previously.

The purpose of this review is to provide the reader with an overview of the progress made in this area since 2004. Section 2 will provide the reader with an historical perspective into the cyanide catalyzed redox reaction and ensuing mechanistic elucidation. Section 3 will focus on the reactivity of acyl azolium **1**, and application of the NHC-redox reaction as a mild acylation strategy for the synthesis of esters, amides, and carboxylic acids. Section 4 will highlight the reactivity of enol **2** and its use in the synthesis of oxygen and nitrogen-containing heterocycles. Section 5 will discuss the reacticity of homoenolate **3** and its use in the synthesis of both heterocycles and carbocycles. Lastly, the review will conclude with current challenges and limitations in this area of research.

2 Cyanide Catalyzed Reactions

Like the related benzoin and Stetter reactions, NHC-catalyzed reactions of reducible aldehydes are rooted in cyanide catalysis. In 1873, Wallach reported the redox neutral conversion of chloral **4** to dichloroacetic acid **5** in the presence of aqueous potassium cyanide (Scheme 2).[3]

The mechanism for this reaction was first proposed by Kötz in 1913.[4] Two distinct pathways were envisioned upon formation of cyanohydrin **6** (Scheme 3). Intermediate **7** can arise via elimination of HCl to generate nucleophilic enol, which can tautomerize to afford the acyl cyanide **8**. On the other hand, intermediate **9** can arise from cyanohydrin **6** by nucleophilic displacement of a chloride by the alcohol to form an epoxide followed by a hydride shift to result in formation of the acyl cyanide **8**. Hydrolysis of **8** affords dichloroacetic acid **5**. Subsequent studies focused on validating or dismissing the proposal put forth by Kötz.

The ensuing mechanistic investigations spanned 5 decades and included contributions by Chattaway and Irving,[5] Rosenblum,[6] Lapworth,[7] Cram and Hammond,[8] and Katritzky.[9] However, it was the work of Nowak in 1963 which led to the currently accepted mechanism for the cyanide-catalyzed transformation of chloral to dichloroacetic acid.[10]

Nowak reported the conversion of chloroacetaldehyde **10** to 2-chloro-1-cyanoethyl acetate **11** in 90 % yield catalyzed by aqueous cyanide (Scheme 4, a).

He proposed that formation of cyanohydrin **12** is followed by net loss of HCl to provide enol **13**. Tautomerization of **13** provides acyl cyanide **14**, upon which cyanohydrin **12** can condense to provide **11** (Scheme 4, b). The formation of acyl cyanide **14** as an intermediate was validated by addition of cyanoacetate to an aqueous solution of acetaldehyde **15** and sodium cyanide, which provides 1-cyanoethyl acetate **16** in 92 % yield (Scheme 4, c).

To probe the intermediacy of epoxide **9** (Scheme 3), epoxynitrile **17** was subjected to aqueous cyanide with no observation of the formation of acetic acid (Scheme 5). Therefore, epoxide **9** is an improbable intermediate in the redox process, and a mechanism via enol **7** is more likely (Scheme 4).

3 NHC Redox Acylation

Acylations represent an important class of reactions in the synthetic chemist's tool box. However, these reactions can be problematic and often require superstoichiometric quantities of activating reagents to conduct sometimes trivial condensation reactions. The conversion of chloral to dichloroacetic acid described in Section 2 represents, in principle, complementary access to the ester, amide and carboxylic acid products furnished by such reactions. Furthermore, the application of enantioenriched NHC catalysts offers the opportunity for asymmetric catalysis. Finally, the NHC catalyzed redox acylation strategy offers an alternative closer to the ideal process in terms atom economy,[11] redox neutrality[12] and efficiency.[13]

3.1 Redox Esterification

In 2004 the Rovis and Bode groups independently and concurrently reported the use of N-heterocyclic carbenes with α-reducible aldehydes and alcohols to furnish esters. α-Halo aldehydes **19** were demonstrated by Rovis as substrates with alcohols **20** as nucleophiles to provide saturated esters **21** in 55-99 % yield (Scheme 6, a).[14] Bromide was found to eliminate more readily than chloride, but both proved competent in the reaction.

Additionally, enantioenriched ethyl lactate (99 % ee) may also be used in the acylation process, which provides the respective product in 56 % yield and 94 % ee. Use of a chiral carbene **22** and racemic lactate **20a** leads to a kinetic resolution providing the ester **21a** in 71 % yield and 31 % ee suggesting that acylation occurs on the acyl azolium **23** (Scheme 6, b).

Bode and coworkers demonstrated α,β-epoxy aldehydes and α,β-aziridinyl aldehydes **24** as viable substrates in the NHC-redox acylation catalyzed by thiazolium catalyst **25** with a variety of alcohols **20** to furnish β-hydroxy esters and β-amino esters **26**, respectively (Scheme 7, a).[15] Mechanistic investigation into the redox process revealed an intramolecular hydride transfer of **27** directly to the acyl azolium **28** is not operative based on subjection of substrate **24a** to deuterated methanol and termination of the reaction at 50 % conversion. The product **26a** is obtained with 50 % deuterium incorporation at the α-position (Scheme 7, b). Inspection of the recovered starting material also shows no deuterium incorporation at the aldehydic carbon disfavoring a hydride-shift mechanism and thus favoring an E2 mechanism, where a concerted opening of the epoxide **29** occurs to give enol **30**, which can tautomerize to **28** (Scheme 7, c).

Based on the findings of Rovis and Bode, the proposed mechanism of this redox acylation starts with deprotonation of the azolium salt to generate the nucleophilic carbene **31** (Scheme 8). Addition of **31** to the α-reducible aldehyde **32** furnishes tetrahedral intermediate **33**. Intermolecular proton transfer provides the acyl anion equivalent or Breslow intermediate **34**,[16] followed by loss of the leaving group to generate enol **35**. Tautomerization of **35** furnishes the acyl azolium **36** which is intercepted by the alcohol to provide the ester **21** and regenerate carbene **31** (Scheme 8).

The Córdova[17] and Jørgensen[18] groups have recently reported that secondary amine catalysis coupled with NHC catalysis is a viable strategy for the synthesis of β-hydroxy and β-amino esters **24**, respectively, directly from α,β-unsaturated aldehydes (Scheme 9). The complete consumption of enal **37** is necessary to provide the β-epoxy or β-aziridinyl aldehyde utilizing secondary amine **38** prior to addition of carbene precursor **39** and alcohol, providing the enantioenriched β-hydroxy esters **27a** in 34-84 % yield and 92-98 % ee, and β-amino esters **27b** in 77-96 % yield and 93-96 % ee (Scheme 9). Additionally, triazolium precatalyst **39** was shown to provide higher yields in the optimized one-pot procedure than the original report by Bode using thiazolium precatalyst **25** (Scheme 7).

Bode and Scheidt have independently shown that α,β-unsaturated aldehydes can be converted to saturated esters in the presence of NHC and alcohols. Scheidt and coworkers observe that enals **37** can be used with benzimidazolium precursor **40** to acylate primary and secondary alcohols as well as phenols. Aromatic and aliphatic substitution on **37** is tolerated to give saturated esters **21** in 56-90 % yield (Scheme 10, a).[19] In this reaction, the extended Breslow intermediate **41** (homoenolate) is quenched with proton to give enol **42**, which tautomerizes to acyl azolium **43** and reacts with the alcohol **21** to give the product (Scheme 10, b).

Bode and Sohn have also demonstrated that the choice of base can have a profound effect on the reaction outcome generating lactone dimer **44** (see Section 5.1) or saturated ester **21** (Scheme 11, a).[20] With either NHC precursor **45** or **46** (Scheme 11, b), the use of a strong base such as potassium *tert*-butoxide leads to generation of the lactone dimer **44** which arises from the nucleophilic addition of the homoenolate **41** to another equivalent of aldehyde **37** (Scheme 11, b), presumably due to the absence of an efficient proton source (pKa of *t*-butanol = 29.4 in DMSO). This can tautomerize to the acyl azolium **47** and trap the alkoxide intramolecularly to give the product. However, when a base whose conjugate acid is sufficiently strong is employed, such as a tertiary amine, monomeric ester **21** is obtained (pKa of $i\text{-Pr}_2\text{EtNH}^+$ = 13 in THF) from a similar pathway as above (Scheme 10, b). Phenols, primary and secondary alcohols are tolerated in the reaction to produce the saturated esters in 63-99 % yield (Scheme 11, a).

An intramolecular variant of the redox esterification of enals **49** has been reported by Zeitler to give 3,4-dihydrocoumarins **50** with precatalyst **51** (Scheme 12).[21] Additionally, it was found that exclusion of oxygen from the solvent prevents the formation of coumarin products. Substitution at all positions is tolerated on the aromatic backbone.

The use of formyl cyclopropanes **52** in the NHC redox esterification reaction was also developed by Bode and Sohn.[22] Active catalyst is formed from triazolium **55** and DBU, which catalyzes a C–C bond cleavage reaction in the presence of electron withdrawing substituents to provide intermediate **56** (Scheme 13). Two sequential proton transfers provide the acyl azolium **57**, which is then shown to react with primary alcohols, thiols and water to provide the respective acyl derivatives **53**.

The electron withdrawing group on the cyclopropane encompasses ketones, esters, amides, and nitro groups. Mechanistic investigation into the reaction with 5 equivalents of deuterated methanol shows mono-deuterium incorporation at the β and α-carbons. Reversible formation of the acyl anion equivalent was confirmed by deuterium labeling experiments.

A divergent reaction pathway with formylcyclopropanes **52** leading to 3,4-dihydroxy-α-pyrone derivatives **59** was identified by You and coworkers with triazolium **55** (Scheme 14).[23] In the absence of an external nucleophile, enol **56** generated upon C-C bond cleavage tautomerizes to the acyl azolium **60** which *O*-acylates the enolate in an intramolecular process to provide the ring expansion product. For this transformation, the electron withdrawing group must be an aryl ketone. Aliphatic ketones give tetrahydropyrone as the major product.

Oxacycloalkyl carboxyaldehydes **61** can also be converted to lactones **62** via an NHC catalyzed intramolecular esterification reaction. Gravel and coworkers identified partially saturated imidazolium **63** as proficient in this ring expansion process, giving lactones in 48-98 % (Scheme 15). Expansion of 4- and 5-membered oxacycloalkyl carboxaldehydes to provide 5- and 6-membered lactones proceeds efficiently, while expansion of a 6-membered oxacycloalkyl carboxaldehyde to furnish the 7-membered lactone is low yielding.[24]

The synthesis of *(E)*-α,β-unsaturated esters can also be accomplished by redox esterification of propargylic aldehydes **64**. Zeitler has identified benzimidazolium salt **65** to be efficient in this process in the presence of DMAP as the base to furnish enoates with high levels of *E:Z* selectivity (typically >95:5). A variety of alcohols participate in the reaction and aromatic, heteroaromatic, and aliphatic substituents are tolerated on the propargylic aldehyde to provide *(E)*-α,β-unsaturated esters **66** in 45-90 % yield (Scheme 16).[25]

Recently, Bode and coworkers have extended the scope of the redox esterification of propargylic aldehydes **64** with enols **67**, which undergo a Coates-Claisen rearrangement upon acylation of the acyl azolium to provide lactones **68** in excellent enantioselectivities with chiral NHC **69** (Scheme 19). The reaction proceeds via interception of acyl azolium **70** by the enol **67** to give tetrahedral intermediate **71** (Scheme 19, b). This then undergoes a [3,3] sigmatropic rearrangement to enol **72**. Tautomerization to the acyl azolium followed by displacement with methanol gives the observed product in 74-95 % yield and 68-99 % ee (Scheme 17).[26]

Ynals bearing aromatic and aliphatic substituents are tolerated. Mildly acidic nucleophiles such as enols of Kojic acids, pyruvic esters and phenols are competent. It is noteworthy that the process is catalyzed without base to facilitate carbene formation from the azolium salt. It is hypothesized that the chloride anion of the azolium salt is responsible for generating trace amounts of the carbene under these conditions which catalyze the reaction.

α-Aryloxy aldehydes **73** are also competent substrates in the esterification reaction. Their enhanced stability compared to that of α-halo aldehydes makes these substrates useful in the arsenal of reducible substrates available in the redox reaction. Using triazolium precatalyst **46**, Smith and Ling observed that saturated esters **21** can be obtained from substrates **73** in 22-95 % yield. [27]

A *para*-nitro benzoyl (PNB) group was necessary to obtain optimal reactivity. Phenols, primary and secondary alcohols are viable nucleophiles with aliphatic and cinnamyl derived substrates. However, tertiary aryloxy aldehydes do not provide any product. This may be due to sterics and the necessary orbital overlap required for elimination.

The asymmetric synthesis of enantioenriched α-chloro esters was also reported by Rovis and Reynolds promoted by a chiral NHC via an asymmetric protonation of enol intermediate **74** (Scheme 19, a).[28] The use of triazolium **75** under basic conditions with phenols **76** and α,α-dichloro aldehydes **77** provides the enantioenriched ester **78** in 62-80 % yield and 76-93 % ee (Scheme 19, b). Excess phenol is necessary to insulate the newly generated stereocenter, which is highly prone to epimerization at the acyl azolium **79**. A variety of α,α-dichloro aldehydes and substituted phenols participate in the reaction to provide aryl esters; however, β-branching on the aldehyde is not tolerated.

3.2 Redox Amidation

Early on, alcohols were well established as competent nucleophiles with a variety of reducible aldehydes. However, a notable limitation of this catalytic acylation strategy was the inability of amines to participate in this mild process. Clearly, access to amides in a catalytic method would be a useful addition to the synthetic chemist's arsenal. However, the addition of an amine nucleophile directly to the acyl azolium **1** presents a greater challenge than that of oxygen nucleophiles.

In 2007, the Rovis[29] and Bode[30] groups concurrently and independently showed that the use of acyl transfer reagents in the presence of amines and NHCs with reducible aldehydes provides amide products. The method developed by Rovis and Vora uses substoichiometric

amounts of additives commonly used in peptide coupling reactions as acyl transfer reagents to give amide products from a variety of reducible aldehydes. Using α,α-dichloro aldehydes **77** a variety of aromatic and aliphatic amines **80** can be added to provide α-chloroamide products **81** in 72-89 % yields (Scheme 20, a). Epoxy and aziridinyl aldehydes were also shown to participate in the reaction to provide β-hydroxy- **82** and β-amino amides **83** with high levels of diastereoselectivity (Scheme 20, b). It was noted that non α-substituted epoxy aldehydes provide a complex mixture of products. Enals also provide saturated amides **84** in moderate yields. The reaction can be performed asymmetrically on α,α-dichloro aldehydes with chiral NHC precursor **75** and benzyl amine to provide the amide in 80 % ee. Acylation is thought to proceed via a general base catalyzed condensation on the HOAt ester **85** which is generated by HOAt intercepting the acyl azolium **86** (Scheme 20, c).

Concurrently, the Bode group identified imidazole as the acyl transfer reagent which is used in stoichiometric quantities to furnish an acyl imidazole from formylcyclopropanes **52**. Subsequent addition of the amine **77** provides the desired amide product **87** in 54-90 % yield (Scheme 21, a). Further work in this area by the Bode group has revealed that α'-hydroxy enones **88** obtained from aldehydes are also competent substrates with substoichiometric quantities of 1,2,4-triazole to provide saturated amide products **84** in 47-99 % yield (Scheme 21, b).[31] The reaction proceeds through a retro-benzoin reaction catalyzed by **55** and base to liberate acetone and give the Breslow intermediate **91** (Scheme 21, c). This then continues to the redox pathway to provide product. An example of chemoselective N-acylation over O-acylation is provided and attributed to the cocatalyst. However, one limitation to this process is that amine hydrochloride salts are not compatible.

Recently, Bode has also found that a chiral acyl transfer cocatalyst can effect a kinetic resolution of secondary amines. In a similar fashion as above, α'-hydroxy enones **88** are first converted to the corresponding Breslow intermediate by a retro benzoin reaction catalyzed by achiral NHC precursor **93**; then, the redox pathway gives the corresponding acyl azolium. Chiral hydroxamic acid **94** then displaces the azolium to give a chiral acylating reagent capable of resolving secondary amines **95** with an S-value up to 74.[32]

A cocatalyst does not seem to be necessary for the amide bond forming process to take place in an intramolecular reaction, based on the findings of You and Gravel. You and coworkers identified that 4-formyl β-lactams **97** were viable substrates in the presence of NHC precursor **45** to furnish succinimide derivatives **98 (**Scheme 23). Redox reaction proceeds with elimination of the amide to form acyl azolium **99**, which traps the amide to give the observed ring expanded product. It was found that a *N*-PMP or *N*-Mes group is necessary on the β-lactam.[33]

The ring expansion product is generated without epimerization of enantioenriched substrate under the reaction conditions. Additionally, subjection of rac-4-formyl-β-lactam **97a** to the reaction catalyzed by chiral NHC precursor **100** provides the respective product **98a** in low enantioselectivites (39 % yield, 27 % ee), while providing unreacted aldehyde in 40 % yield and 99 % ee, converted to the corresponding alcohol **101a** by reductive workup (this corresponds to an S-value of 24, if one assumes that conversion is 60 %). A variety of racemic substrates were demonstrated, giving alcohol products **101** in 19-99 % ee after reductive workup (Scheme 24).[34]

Gravel and coworkers have extended the scope of the NHC catalyzed ring expansion amidation reaction to provide 6-membered lactams.[35] A variety of common protecting groups on the nitrogen of 2-formylpyrrolidines **102** are tolerated to furnish the 6-membered lactams **103** in 49-100 % yields (Scheme 25). Expansion of piperidines to seven membered lactams was found to be difficult, giving less than 5 % yield.

Recently, Yamada and co-workers have developed a one-pot NHC catalyzed amidation with saturated aldehydes and *N*-chloro succinimide (NCS).[36] The redox reaction thus takes place on the α-chloro aldehyde generated from saturated aldehyde **104** via secondary amine catalysis to provide the acyl azolium. The use of NHC precursor ent-**75** and base with substoichiometric quantitites of HOBt generates the HOBt ester which is substituted by the amine to provide the saturated amide products **84** in 71-91 % yield (Scheme 26, a). Additionally, the authors report that substitution of the HOBt ester **105** occurs selectively with the amine over water to provide the amide product **106** (Scheme 26, b).

An NHC mediated intermolecular amidation was used by Forsyth and coworkers to unite two complex fragments in an effort toward the natural product largazole (Scheme 27).[37] Under substoichiometric conditions, decomposition of **107** was observed, thus necessitating the use of stoichiometric thiazolium **25**. Despite the failure of the catalytic reaction, the complementarity of this acylation to traditional peptide coupling allowed the authors to carry an unprotected carboxylic acid on the amine fragment **108**.

3.3 Redox Azidation

Rovis and coworkers have also reported the synthesis of carbamoyl azides and oxazolidinones with epoxy aldehydes as the reducible aldehyde with NHC precursor **39** and an azide source. Judicious choice of reaction conditions dictates product selectivity.[38] A combination of azidotrimethyl silane and sodium azide in a (2.5:1) ratio provides the carbamoyl azide **110** in 20-84 % with a dr of 2.7:1 to 6.5:1. Conditions developed with azidotrimethylsilane, sodium azide and ethanol provide the oxazolidinones **111** in 20-84 % yield and 3:1 to 6.5:1 dr (Scheme 28). The low diastereoselectivites are attributed to epimerization at the acyl azolium or acyl azide.

3.4 Redox Hydration

The use of water in the NHC catalyzed redox reaction would provide carboxylic acids in a mild and atom economical manner. Previous work inspired by interest in thiamine catalysis led to the study of stoichometrically generated acyl azoliums derived from imidazolylidene and thiazolylidene carbenes and their capacity to react with nucleophiles. Contributions from Breslow,[16b] Daigo,[39] White and Ingharam,[40] Bruice,[41] Lienhard and Owen[42] revealed that water was the most proficient nucleophile followed by alcohols and amines. Additionally, work by Bode has recently confirmed this paradox of nucleophilicity versus reactivity with triazolylidene derived acyl azoliums.[43]

Rovis and Vora applied the propensity of water to react with the acyl azolium in the synthesis of enantioenriched α-chloro carboxylic acids and α-fluoro carboxylic acids.[44] The use of NHC **112** in conjuction with α,α-dichloro aldehydes **77** with 1M potassium carbonate, tetrabutyl ammonium iodide and brine provides the respective carboxylic acid **113** in 75-95 % yield and 78-95 % ee. Additionally, if 1M potassium carbonate in D_2O is used the reaction proceeds with installation of an α-deuterium in an asymmetric manner to provide isotopically labelled carboxylic acids in simlar yield and enantioselectivity.

Enantioenriched α-fluoro carboxylic acids can also be generated by subjecting α-fluoro enals **114** with NHC **112** and 1M potassium bicarbonate in brine. Aromatic and aliphatic substitution is tolerated at the β-position of the enal to provide the respective acid **115** in 65-80 % yield and 90-96 % ee (Scheme 30, a). Isotopically labeled fluoro carboxylic acids can also be obtained by subjecting α-bromo,α-fluoro carboxaldehyde **116** to the optimized conditions to obtain the deuterated product **117** in 77 % yield and 96 % ee (Scheme 30, b).

4 Enolate Equivalents

The NHC-redox catalysis pathway proceeds through a number of reactive catalytic intermediates. The acylation reactions described above are applications of the acyl azolium intermediate as an electrophile. However, in the process of generating the acyl azolium, two key nucleophilic intermediates are also generated: the acyl anion equivalent and the enol resulting from the elimination step. While limited at this point in time, electrophilic trapping of the enol intermediate has been demonstrated, most notably to allow for the rapid generation of heterocycles.

4.1 Synthesis of Oxygen Heterocycles

In 2006, Bode and coworkers reported the enantioselective NHC catalyzed Diels-Alder reaction of racemic α-chloro aldehyde with enones to provide 3,4,6-trisubstituted dihydropyran-2-ones.[45] The reaction is amenable to aromatic and aliphatic α-chloro aldehydes **19** and electron withdrawing aromatic and aliphatic enones **118**. The reaction proceeds with 0.5 mol % catalyst loadings of NHC precursor ent-**69** and provides the dihydropyran-2-ones **119** in 70-95 %, 86-99 % ee, and 3:1 to >20:1 d.r. (Scheme 31).

The *cis*-diastereoselectivity is attributed to the formation of the *(Z)*-enolate in the NHC redox reaction with the α-chloro aldehyde and a high preference for the *(Z)*-enolate to react in an endo cycloaddition with the enone. Subjection of enantioenriched α-chloro aldehyde with either antipode of chiral NHC precursor **69** provides identical ee (98 %) and d.r. (4.5:1) with an inversion of absolute stereochemistry (Scheme 32).

Due to the sensitivity of α-chloro aldehydes, a more process friendly alternative was developed by Bode.[46] Bisulfite salts of α-chloro aldehydes **120** are also viable substrates in the Diels-Alder reaction under biphasic conditions. An excess of K_2CO_3 is used to liberate the aldehyde which undergoes the redox reaction to provide the diene for the cycloaddition process.

Moreover, Bode has shown that enals can also be used to generate enolate equivalents from the reaction with NHC in the presence of weak base such as *N*-methylmorpholine (NMM, conjugate acid pKa = 7.4).[47] The enolate equivalent then undergoes a hetero-Diels-Alder reaction with a variety of α-hydroxyenone or α-Cbz-aminoenones **121** to provide dihydropyran-2-ones **122** in 63-98 % yields, 94-99 % ee and >20:1 d.r. (Scheme 34). Additionally, preliminary computational experiments suggest that the high levels of enantioselectivity are attributed to a non-conjugated complex of azolium and the enolate olefin.

Recently, Chi and co-workers have expanded on the scope of the NHC catalyzed hetero-Diels Alder reaction of enals and enones to benzylidene β-diketone derivatives **123**.[48] The scope of enals includes aromatic and hetero-aromatic which provide the products **124** in 50-88 % yield with high enantioselectivities of 97-99 % ee and dr of 12:1 to >20:1 (Scheme 35).

Scheidt and coworkers have reported the use of α-aryloxy aldehydes for the synthesis of coumarins and β-amino amides.[49] Coumarins are prepared from a tethered α-phenoxy aldehyde **125** which provides the enolate equivalent upon reaction with the NHC generated from **126**. This then adds in a conjugate fashion to the Michael acceptor to generate the acyl azolium which acylates the phenoxide to provide 3,4-dihydrocoumarins **127** in 66-91 % yield (Scheme 36).

Subsequent work by Scheidt utilized a similar intramolecular Michael-redox reaction to provide fused indanes **129** from substrates **128** with chiral NHC ent-**69**.[50] The base was found to play a key role not only in yield but also selectivity as DBU provides the product in 6 % yield. Using DIPEA as the base, product is obtained in 50 % yield with a d.r. of >20:1. Thus, products **129** are provided in 52-80 % yield, 62-99 % ee and excellent diastereoselectivity. The tether in the reaction typically contains an aromatic backbone, although two alkyl tethered substrates are also reported.

Additionally, Scheidt and coworkers have reported the synthesis of carbocycles which proceed via a fused β-lactone to undergo a spontaneous decarboxylation.[51] NHC **130** was identified as the optimal catalyst with enal **131** to give cyclopentene products **132** (Scheme 38, a). This reaction is thought to proceed through enol **133**, which is stabilized by an intramolecular hydrogen bond to the ketone (Scheme 38, b). Addition of the enol to the ketone followed by displacement of the acyl azolium **134** leads to β-lactone **135**. This can then decarboxylate to give the observed cyclopentene products, obtained in 51-80 % yield and 82-96 % ee. Moreover, two examples are provided in which the β-lactone **135** can be isolated without decarboxylation.

A divergent reaction pathway was identified by Bode toward the synthesis of fused β-lactones and γ-lactones governed by choice of carbene precursor.[52] It was found that use of triazolium NHC **69** provides the fused β-lactone **136** in 40-65 % yield and 99% ee Scheme 39, a). However, use of chiral imidazolium precatalyst **137** affords fused γ-lactones **138** and **139** in 40-65 % yield, 3:1 to 5:1 d.r. and 99 % ee of the major *cis*-diastereomer (Scheme 39, b). Selectivity is determined by whether conformer **140** closes to give the stereoisomer capable of closing to the β-lactone **136**, or if a hydrogen bond from the tertiary alcohol reinforces conformer **141**, which closes to the γ-lactone **138** (Scheme 39, c). The relative rates are rationalized by the steric and electronic differences between **69** and **137**.

4.2 Synthesis of Nitrogen Heterocycles

In addition to α-chloroaldehydes, α,β-unsaturated aldehydes were identified by Bode and coworkers as competent precursors for enolate reactivity and applied to the synthesis of nitrogen-containing heterocycles.[53] Utilizing NHC precursor **69**, protonation of the extended Breslow intermediate (or homoenolate) derived from **142** at the β-position under optimized conditions proceeds efficiently to provide the enolate equivalent (dienophile) which can participate in an inverse electron demand hetero Diels-Alder reaction with α,β-unsaturated para-methoxybenzenesulfonyl imine **143** (diene) to provide dihydropyridones **144**. The enal must bear an electron withdrawing ester or ketone at the β-position, while the diene can have aromatic and aliphatic substitution providing the dihydropyridone in 52-80 % yield, 62-99 % ee and >20:1 d.r. (Scheme 40). Selectivity for the cis isomer in the reaction is rationalized by a *Z*-selective dienophile reacting with the diene in an endo fashion. It is hypothesized that protonation of the Breslow intermediate proceeds via a fully conjugated extended system affording the *(Z)*-enol exclusively, which leads to the invariably excellent diastereoselectivity.

The synthesis of β-lactams is also feasible with enals and sulfonylimines **145** derived from chalcones. Bode and He identified NHC **69** to be optimal with the appropriate base to provide the respective β-lactams **146** in 45-94 %, 78-99 % ee, and as single diastereomers in most cases (Scheme 41).[54] A profound effect of the base on diasteroselectivity was identified wherein DMAP was found to be optimal. While a homoenolate pathway can be envisioned for this process, the authors rationalize the sterochemistry as arising from a concerted crossed- aza-benzoin/oxy-Cope reaction. The *cis*-relatioship is thought to arise from secondary orbital overlap considerations proceeding via a boat configuration **147**

(Scheme 41, b). The remaining stereocenter can then equilibrate by a reversible intramolecular Mannich reaction from enolate **148** onto the sulfonylimine, whose adjacent *C*-*C* bond has free rotation. Catalyst can only be turned over when the acyl azolium and resultant amine are *cis* and therefore capabale to react and form *β*-lactam **146.**

4.3 Intermolecular Reactions

Subsequently, Scheidt reported the synthesis of enantioenriched β-amino amides from the NHC catalyzed redox reaction of α-aryloxy aldehydes **149** and tosyl imines **150**.[55] NHC precursor **151** was identified as optimal for the reaction of *α*-4-nitrophenoxy-acetaldehyde and tosyl imines derived from aromatic aldehydes to provide the *β*-amino phenoxy ester. Once complete, the arylester is then treated with benzyl amine to provide the *β*-amino amide product **152** in 56-75 % yield and 88-95 % ee (Scheme 42).

5 Homoenolate Equivalents

Homoenolate reactivity represents a sought after umpolung reaction manifold that has been of interest to the synthetic community. Catalytic generation of homoenolate intermediates from readily available starting materials has been achieved only recently. NHC catalysis has enabled a powerful method to access diverse heterocycles and carbocycles from α,β-unsaturated aldehydes. Typically, imidazolium and electron rich sterically encumbered N-aryl triazolium catalyst precursors have been identified as optimal catalysts for this process. Additionally, their deprotonation by strong bases to generate weak acids has been found to be crucial.

5.1 Synthesis of Oxygen Heterocycles

In 2004, Bode[56] and Glorius[57] independently reported the synthesis of γ-butyrolactones from the reaction of α,β-unsaturated aldehydes with aromatic aldehydes **153**. NHC precatalyst **45** was identified as optimal with aromatic enals and ynenals. Aromatic aldehydes are typically the coupling partner to provide a mixture of cis to trans *γ*-butyrolactones (**154**/**155**) in 41-87 % yield and 3:1 to 5:1 d.r. (Scheme 43). Mechanistic insight is provided by the discovery that both cis and trans enals provide identical stereochemical outcomes. Additionally, quenching the reaction prior to completion reveals extensive isomerization of *cis*-enal to *trans*-enal. Bode has also reported that in the absence of an exogenous electrophile, homodimerization is a potential pathway.

Concurrent to the report by Bode, Glorius and coworkers developed a similar process also utilizing NHC **45**. With cinnamaldehyde **37a** as the reducible aldehyde, a variety of aromatic aldehydes were demonstrated in this process in 32-70 % yield and 4:1 d.r. favoring the cis-isomer **154a** (Scheme 44, a). Electron deficient ketones **156** gave trisubstituted lactone diastereomers **157** and **158** in 74-92 % yield and 2:1 d.r. (Scheme 44, b) Use of chiral imidazolium **159** with cinnamaldehyde **37a** provides the products **157a** and **158a** in 70 %, 3:1 d.r. and 12 and 25 % ee, respectively (Scheme 44, c).

Recently, Scheidt and Cohen have demonstrated that a chiral Lewis acid can promote this transformation enantioselectively with an achiral NHC. Using imidazolium precatalyst **45**, Taddol-based titanium complex **159** and DBU as the base, cinnamaldehyde can be dimerized to *γ*-butyrolactone **160** in 60 % yield, 20:1 dr, and 60 % ee (Scheme 45).[58]

In 2006, Nair and coworkers reported the synthesis of *γ*-butyrolactones from 1,2-dicarbonyl derivatives facilitated by NHC **57**.[59] It was identified that cyclohexane dione **161** and isatins **162** are suitable electrophiles in this process with electron rich and electron withdrawing substituents tolerated on the aromatic enals to provide the respective spiro-

cyclohexanone γ-lactones **163** in 60-74 % yield (Scheme 46a), and the spiro isatin γ-lactones **164** in 85-98% yield (Scheme 46b). In both cases, a 1:1 d.r. is obtained. The scope was later extended to incorporate diaryl 1,2-diones.[60]

An independent discovery by You demonstrated that glyoxylate derivatives **165** can also undergo reaction with homoenolate equivalents generated from cinnamaldehyde to give γ-butyrolactones.[61] A wide study of chiral NHC precursors revealed NHC **130** as the most enantioselective catalyst giving 78 % ee of the trans isomer (Scheme 47, a). However, this catalyst also gives low diastereoselectivity (60:40 *trans:cis*). Optimal diastereoselectivity was obtained with NHC **100**, providing γ-butyrolactone diastereomers **166** and **167** in 45-95 % yield and up to 82:18 selectivity for the *cis* isomer (Scheme 47, b).

Nair also discovered an [8+3] annulation of homoenolate equivalents generated by NHC **45** with tropone **168**.[62] The reaction proceeds in 39-62 % yield to generate fused δ-lactones **169** (Scheme 48).

5.2 Synthesis of Nitrogen Heterocycles

Recently, a number of reports have described additions of homoenolate equivalents into nitrogen-containing electrophiles followed by displacement of the acyl azolium to give nitrogen heterocycles. This reaction presents a challenge in terms of substrate scope as the NHC itself can react with many such electrophiles. A careful balance must be struck in regard to the reactivity of the electrophile. Regardless, a number of structurally interesting products have been obtained.

The use of imines as electrophiles in this process to form γ-lactams was reported by Bode and He.[63] To overcome inhibition of NHC **46** by the imine itself, para-methoxysulfonylimines **170** were necessary as substrates. It was observed that a balance between electrophilicity and reversibility of the carbene addition was required in the design of the imine. The scope of the reaction encompasses aromatic aldehydes and aryl and heteroaryl imines, giving γ-lactams **171** in 50-73 % yield and 1.7:1 to 10:1 d.r. (Scheme 49).

Cyclic sulfonylketimines were also identified to be superior electrophiles by Bode, in the NHC catalyzed homoenolate additions to furnish cyclic suflonyl-γ-lactams.[64] NHC precursor **46** facilitates the reaction with aliphatic and aromatic enals **37** and saccharin-derived imines **172** to give cyclic sulfonamide derivatives **173** in 55-95 % and 1:1 to >20:1 d.r. (Scheme 50, a). Cyclic sulfonyl imines undergo reversible reactions with the NHC catalyst as identified with acyclic variants. To rationalize enhanced reactivity and selectivity observed with the cyclic sulfonyl imine, the authors proposed a transition state analogous to that of the ene reaction in which a hydrogen bond to the sulfonyl oxygen in **174** facilitates proton transfer of the acyl proton to the nitrogen of the sulfonyl imine nitrogen with concomitant C-C bond formation. Tautomerization of enol **175** to the acyl azolium is followed by intramolecular trapping with the amine to give the observed product (Scheme 50, b). The asymmetric variant of this process with chiral, enantioenriched NHC precursor **176** proceeds in 91 % yield, 73 % ee and 6:1 d.r. (Scheme 50, c).

Diazines **177** have also proven suitable electrophiles for homoenolates generated by NHC precursor **126** to provide pyrazolidinones **178** in 61-84 % yield.[65] Electron-donating and electron withdrawing substitutents are tolerated on the aromatic system along with β-alkyl substituents. The diazine component is limited to electron rich aromatic substituents; electron deficient systems do not provide any product. The reaction can be rendered asymmetric with NHC **120** to provide pyrazolidinone **178a** in 61 % yield and 90 % ee.

Scheidt and coworkers have reported the Lewis acid catalyzed synthesis of γ-lactams with NHC precursor **179**, magnesium *tert*-butoxide and *N*-acyl hydrazones **180**.[66] Enals bearing both aromatic and aliphatic substituents are tolerated to provide the γ-lactams **181** in 61-85 % yield, 85-97 % ee and 5:1 to >20:1 d.r. (Scheme 52). The authors propose that Lewis acid activation of the *N*-acyl hydrazone occurs with reversible binding of the carbene to the metal.

Recently, Rovis and coworkers reported an example of NHC and Brønsted acid cooperative catalysis to give γ-lactams.[67] A catalytic amount of weak base **182** generates the NHC from **183** which forms the extended Breslow intermediate from **37b**. Meanwhile, the conjugate acid of **182** can activate the imine **184** for attack selectively over protonation of the homoenolate. In contrast to examples by Bode, Glorius and others which deliver *cis*-γ-lactones (see Section 5.1), this method furnishes *trans* γ-lactam products **185** selectively in 64-95 % yield, 85-93 % ee and 4:1 to 20:1 d.r. (Scheme 53).

Scheidt and Chan have also identified azomethine ylides **186** as viable electrophiles with enals **37** and NHC **187** to provide pyridazinones **188** with high levels of *cis*-selectivity.[68] Only enals bearing electron releasing substituents participate in this process. Additionally, dienyl and β-alkyl substituents are tolerated on the enal to provide the pyridazinones in up to 94 % yield, and >20:1 d.r. in each example. (Scheme 54, a). Electron withdrawing and electron donating groups on the imine are tolerated, while 2-substituted aryl substitutents or enolizabile imines do not provide any product. The *cis*-diastereoselectivity is attributed to a hydrogen bond between extended Breslow intermediate **189** and the azomethine ylide **186** leading to *syn*-addition (Scheme 55, b). The resultant enolate **190** can tautomerize with proton transfer to acyl azolium **191**, which closes to give the observed product.

Nitrones as useful electrophiles in the NHC catalyzed homoenolate reaction were demonstrated by Scheidt and coworkers.[69] NHC generated from **130** activates the enal as the homoenolate, which attacks nitrone **192** and tautomerizes to the acyl azolium. The nitrone then closes on the acyl azolium to give **193**. The heterocyclic lactone generated from the formal [3+3] cycloaddition then undergoes ring opening upon treatment with alcohols to provide **194** in 64-78 % yield and 89-94 % ee (Scheme 55).

5.3 Synthesis of Carbocycles

Homoenolate intermediates have also been exploited to form carbon-carbon bonds in a number of instances. Cyclopentenes, spirocycles, and densely functionalized cyclopentanes can all be accessed through this reaction manifold.

In 2006, Nair and coworkers reported an NHC catalyzed carboannulation giving cyclopentenes from cinnamaldehyde derivatives **37** and chalcones **195** in 55-88 % yield (Scheme 56, a).[70] He proposed a catalytic cycle wherein the extended Breslow intermediate adds in a conjugate fashion to the chalcone, followed by proton transfer and enolate addition to the aryl ketone to give tertiary alkoxide **196**. This alkoxide can then displace the azolium to regenerate the NHC and give β-lactone **197**. This can then eliminate CO_2 to give the observed cyclopentene product **198** (Scheme 56, b).

Following his initial report, Nair described the reaction of dienones **199** in this reaction manifold to give both cyclopentanone **200** and cyclopentene products **201** (Scheme 57, a).[71] In this case, intramolecular *C*-acylation of the acyl azolium **202** leads to the cyclopentenone (Scheme 57, b), while aldol reaction as in the original report leads to the cyclopentene (Scheme 56, b). Dibenzylidene cyclopentanones **203** can also lead to spirocycles **204** (Scheme 57, c).

Nair also demonstrated that the intermediate acyl azolium can be intercepted by an external alcohol nucleophile to give cyclopentanol products **205** and acyclic ketoester products **206** (Scheme 58).[72] Each of the products is isolated as a single diastereomer.

Bode and coworkers reported an enantioselective version of the carboannulation catalyzed by the NHC corresponding to chiral precursor **67**. Starting from enones **207** bearing an ester at the β-position, 1,3,4-trisubstituted cyclopentenes **208** can be obtained in 26-93 % yield, 4:1 to >20:1 dr and 96-99 % ee (Scheme 59, a).[73] In contrast to Nair's observation with chalcones, *cis*-cyclopentene products are formed selectively. Furthermore, mechanistic studies provided evidence that this transformation does not, in fact, proceed through a homoenolate mechanism. Rather, an asymmetric cross-benzoin reaction followed by a stereospecific oxy-Cope rearrangement can give the observed products. The divergent stereoselectivity can be explained by an *s*-cis conformer **209** being accessible to the ester substrate leading to a boat transition state in the [3,3]-rearrangement. Chalcone substrates are locked in an *s-trans* conformation **210** and must proceed through a chair transition state to give *trans* products. Tautomerization and enolate addition to acyl azolium gives the β-lactone **197** proposed by Nair, which eliminates CO_2 to the observed *cis*-cyclopentene product **208**. This mechanistic proposal is supported by the fact that α'-hydroxyenone **211** gives both Nair's observed *trans* product **198a** and the starting materials **37a** and **195a** under the reaction conditions (Scheme 59, c).[74]

Working from the proposed reversible benzoin mechanism, Bode discovered that by using α'-hydroxyenones **88** as substrates, he could expand the scope of the cyclopentene annulation. Substrates **88** can be prepared readily from aromatic aldehydes.

In 2010, Scheidt and coworkers demonstrated that by adding a Lewis acid to the NHC catalyzed carboannulation reaction of chalcones, high selectivity for the *cis* stereoisomer is obtained rather than the *trans* selectivity reported by Bode and Nair.[75] Using chiral NHC presursor **179**, *cis*-cyclopentene products **212** are furnished in 50-82 % yield, 20:1 dr, and 98-99 % ee (Scheme 61).

Scheidt also reported the cooperative NHC/Lewis acid catalyzed enantioselective addition of homoenolates derived from cinnamaldehydes **37** to α,β-unsaturated α'-ketoesters **213**. NHC presursor **179** with DBU in isopropanol delivers cyclopentane products **214** in 52-85 % yield, 91-99 % ee and 5:1 to 20:1 d.r. (Scheme 62).[76]

6 Conclusion

The field of NHC-catalyzed redox reactions has experienced tremendous growth in the eight years since work was first published in this area. This has led to the development of waste minimized acylation processes which provide acess to a valuable array of acyl derivatives. In some very recent and complementary work, Studer has demonstrated that access to acyl azoliums is also possible through oxidation of the Breslow intermediate, allowing similar reactivity without the restrictive need for an a-reducible aldehyde.[77] Additionally, enolate and homoenolate equivalents generated catalytically can lead to the formation of complex heterocycles and carbocycles under mild conditions with high diastereo- and enantioselectivities.

However, as with any method, limitations exist and have been highlighted during the previous studies. Most notably, many of these methods suffer from limited scope. In the case of acylation reactions utilizing acyl azolium intermediates **1**, oxygen, sulfur, and nitrogen nucleophiles have been demonstrated as well as intramolecular addition of enolates. On the other hand, reactions of enolate equivalents **2** and homoenolate equivalents **3** are largely

limited to a narrow range of substrates owing to the complexity of the catalytic cycles that can lead down many unproductive pathways. Further exploration of catalyst scaffolds is a promising avenue to overcome these limitations. Moreover, the advent of Lewis and Brønsted acid activation in the NHC-mediated redox reaction will no doubt provide reactivity with less specialized substrates and expand the current scope of products available from this promising reaction manifold.

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Biography

Harit U. Vora was born in Calcutta, India and raised in Tobyhanna, PA. He received his undergraduate education at the University of Pittsburgh, where he carried out research under the guidance of Professor Paul E. Floreancig. He then joined the Medicinal Chemistry Division of Roche USA in Palo Alto, CA. He earned his doctoral degree in 2011 at Colorado State University under the guidance of Professor Tomislav Rovis and is currently a postdoctoral research associate at the Scripps Research Institute with Professor Jin-Quan Yu.

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Tomislav Rovis was born in Zagreb in the former Yugoslavia, but was largely raised in Southern Ontario, Canada. Following his undergraduate studies at the University of Toronto, he earned his Ph.D. degree at the same institution in 1998 under the direction of Professor Mark Lautens. From 1998 to 2000, he was a NSERC postdoctoral fellow at Harvard University with Professor David A. Evans. In 2000, he began his independent career at Colorado State University, and was promoted to Associate Professor in 2005 and Professor in 2008. He currently holds the John K. Stille Chair in Chemistry.

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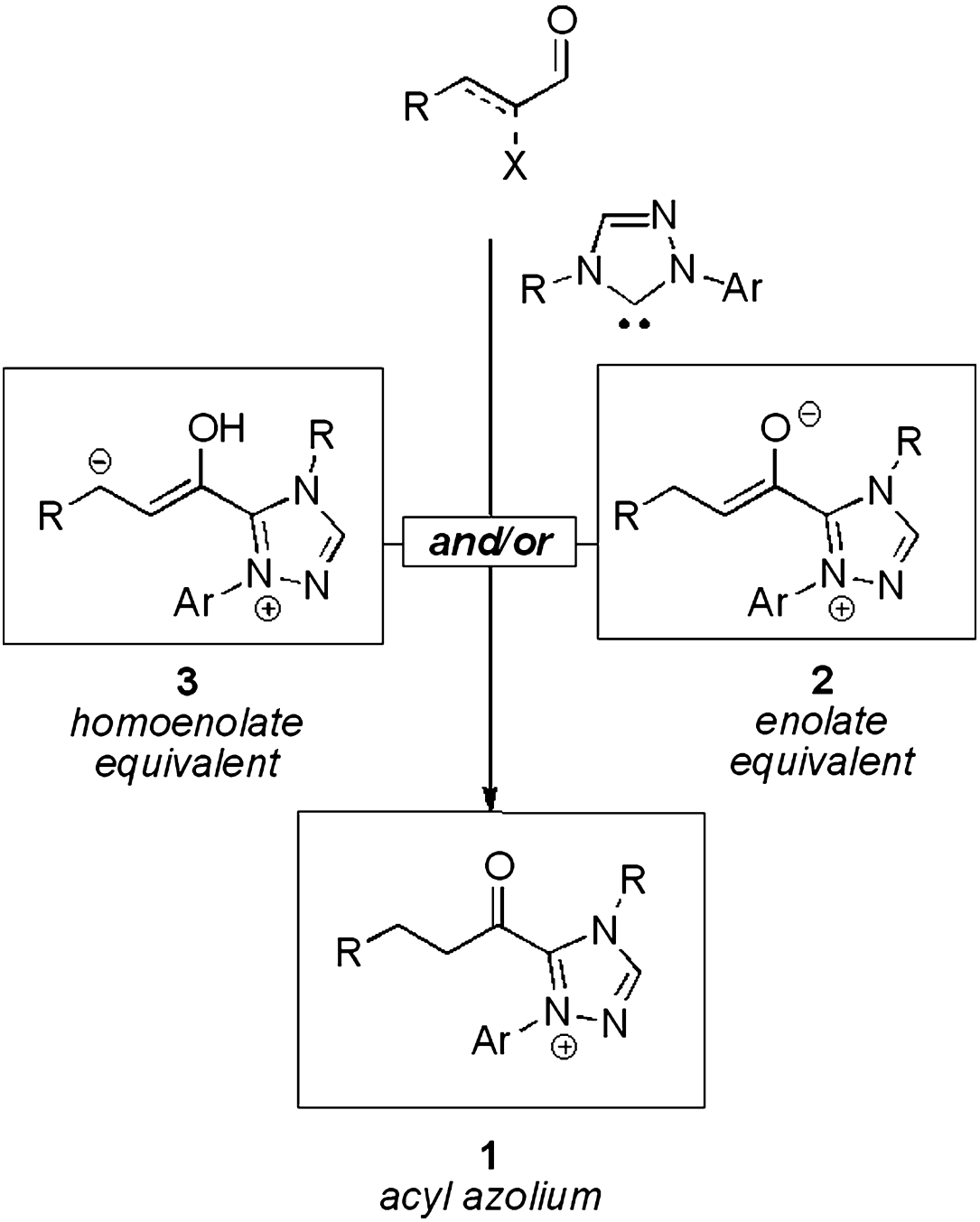
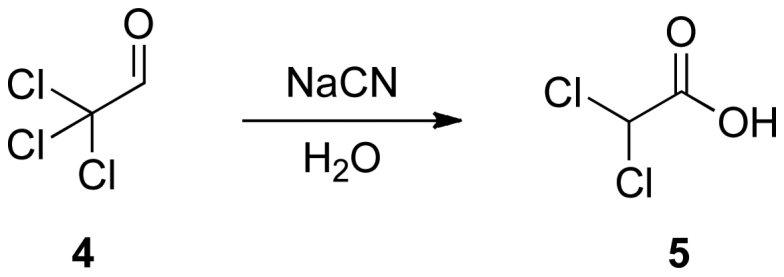
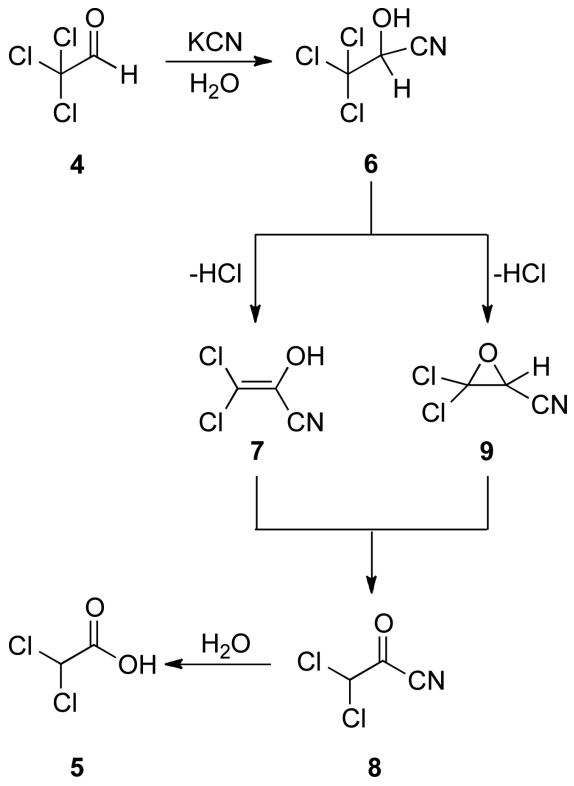


Scheme 1.
Catalytic intermediates exploited in NHC-redox reactions.

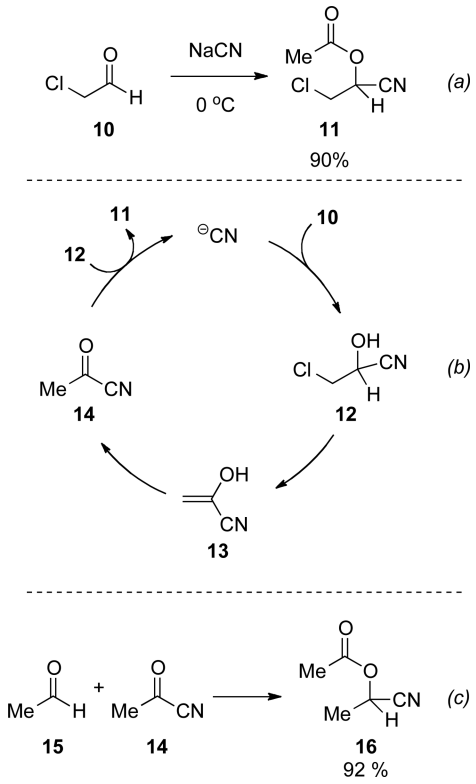


4 **5**

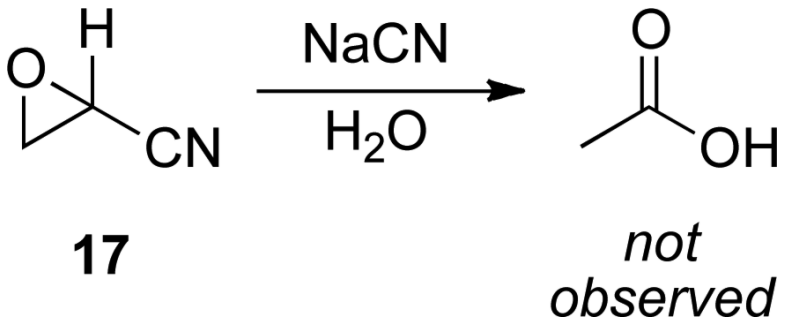
Scheme 2.
Cyanide-catalyzed redox.



Scheme 3.
Kötz mechanistic proposal.



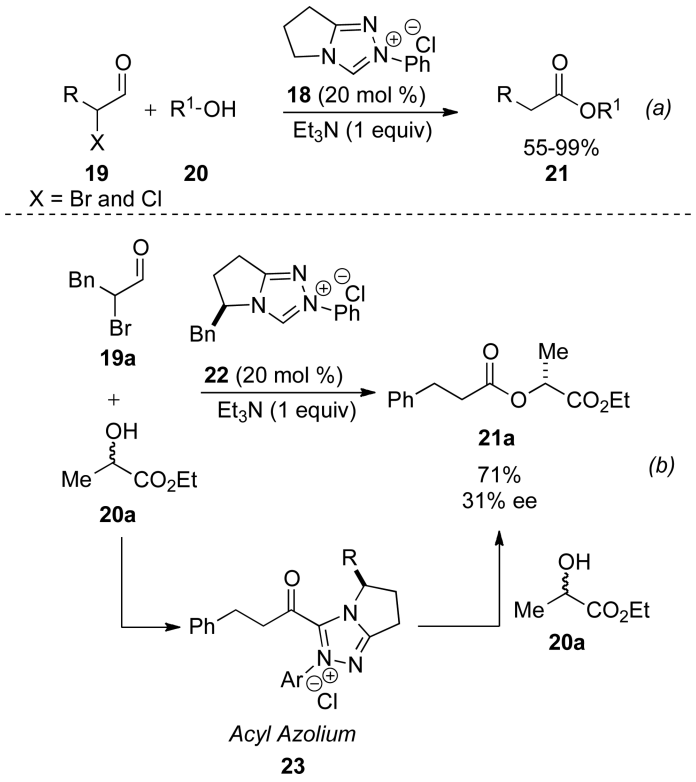
Scheme 4.
Nowak's mechanistic proposal.



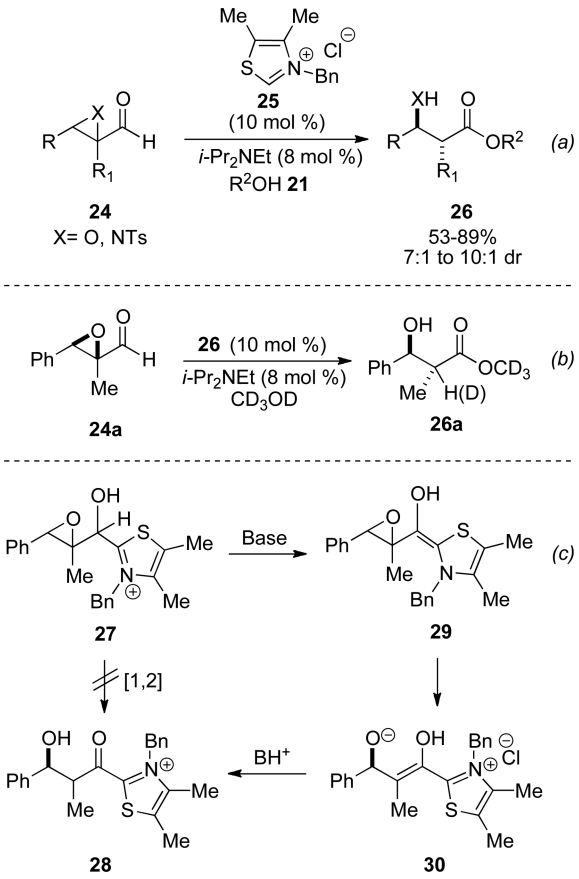
17

not observed

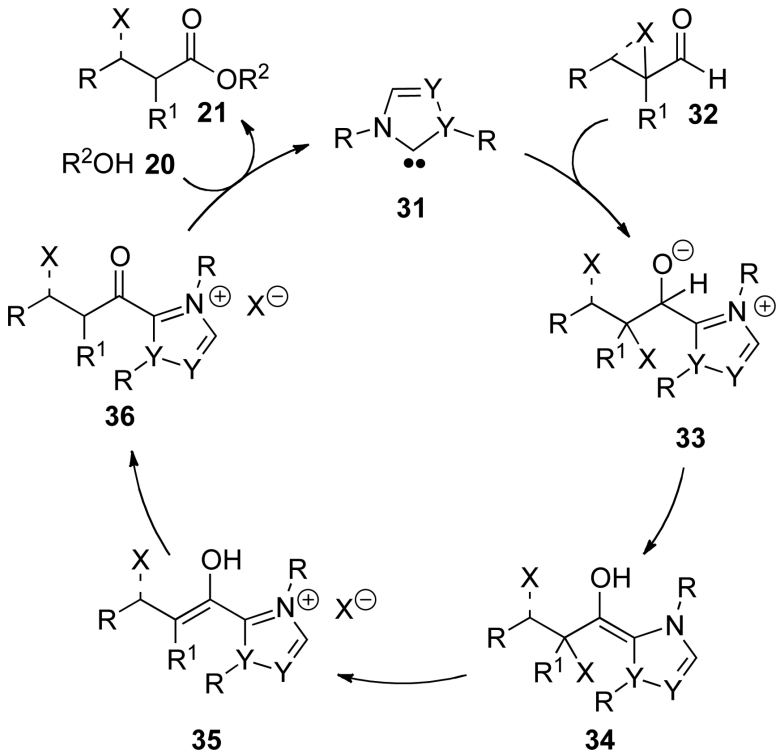
Scheme 5.
Possible epoxide intermediate.



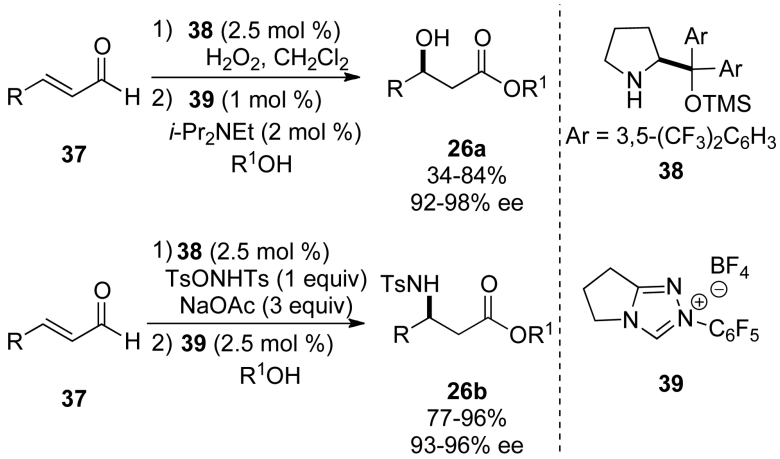
Scheme 6.
Redox esterification of α-halo aldehydes.



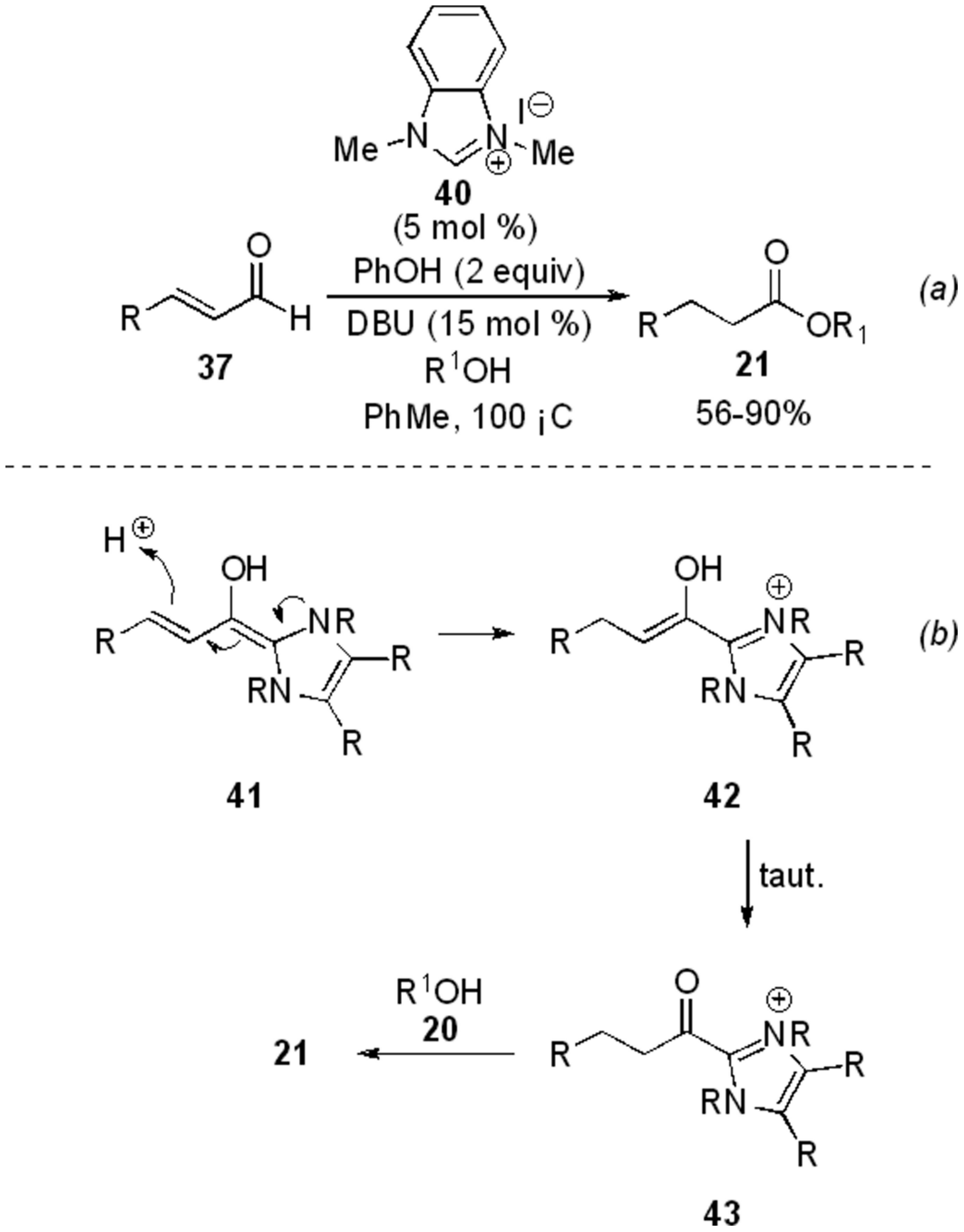
Scheme 7.
Redox esterification of α,β-epoxy aldehydes.



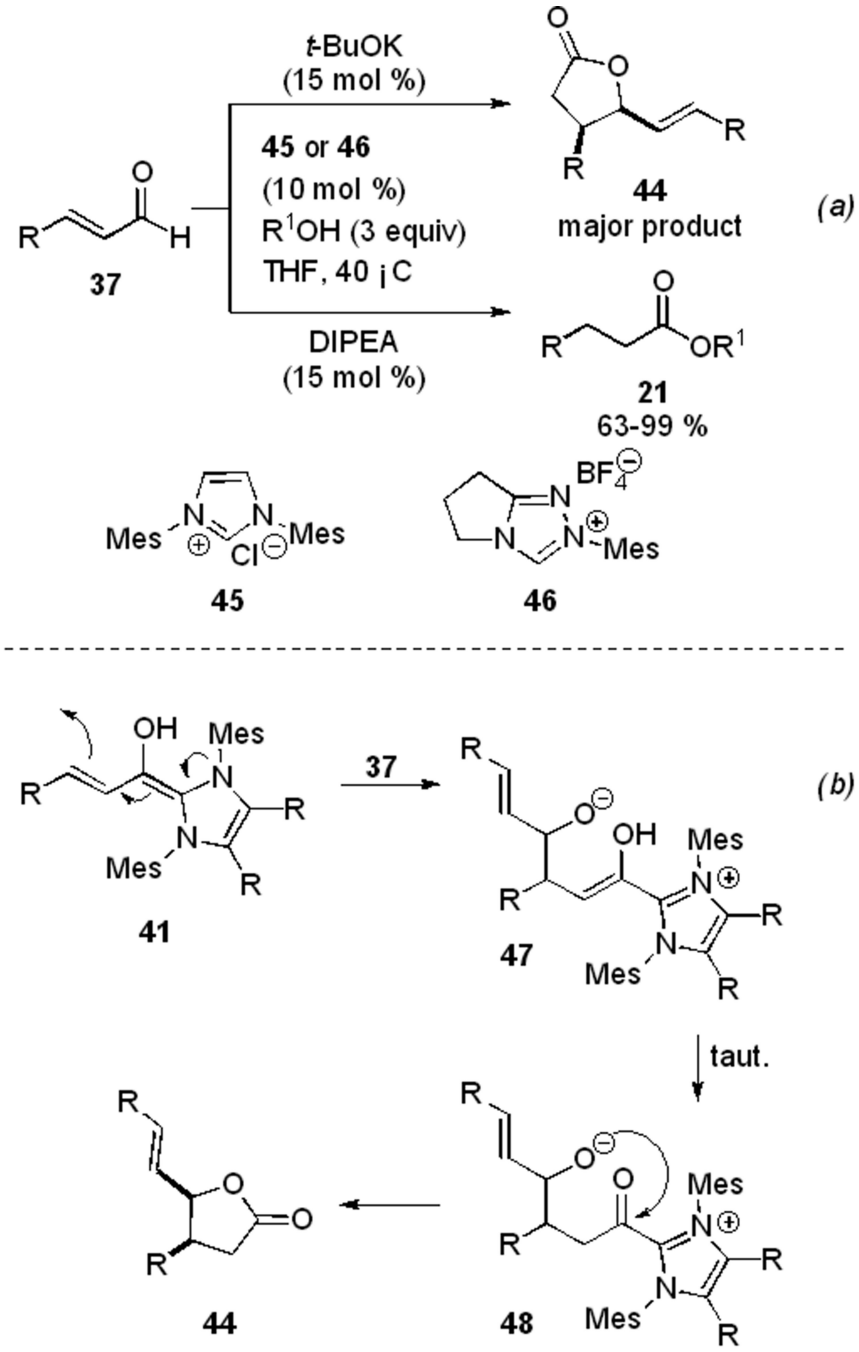
Scheme 8.
Mechanism of redox esterification of α-reducible aldehydes.



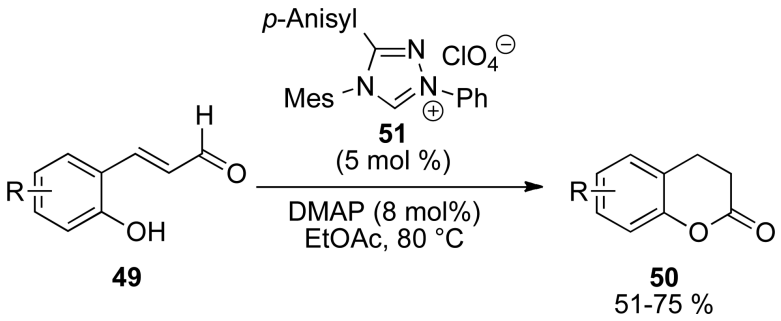
Scheme 9.
Secondary amine and NHC catalysis.



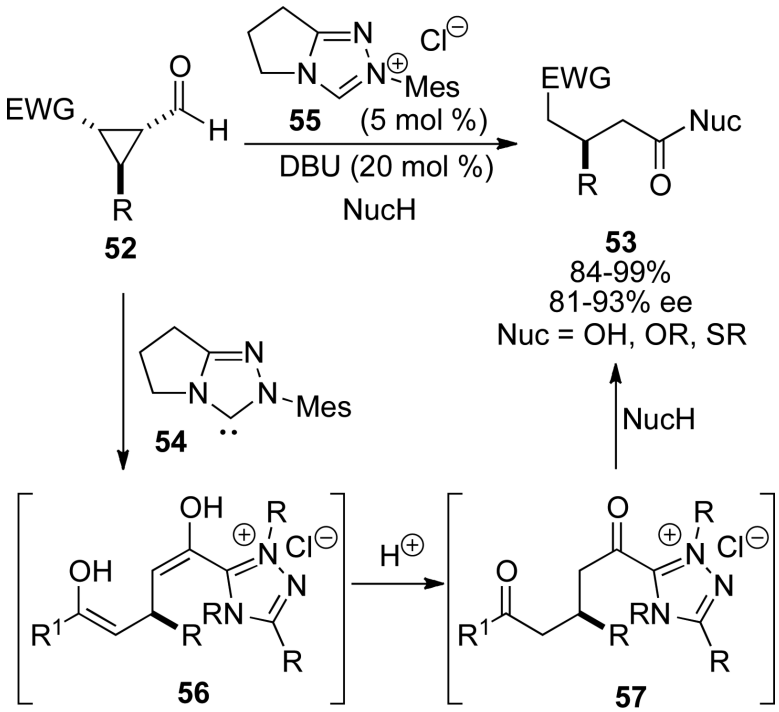
Scheme 10.
Acylation of alcohols by enals.



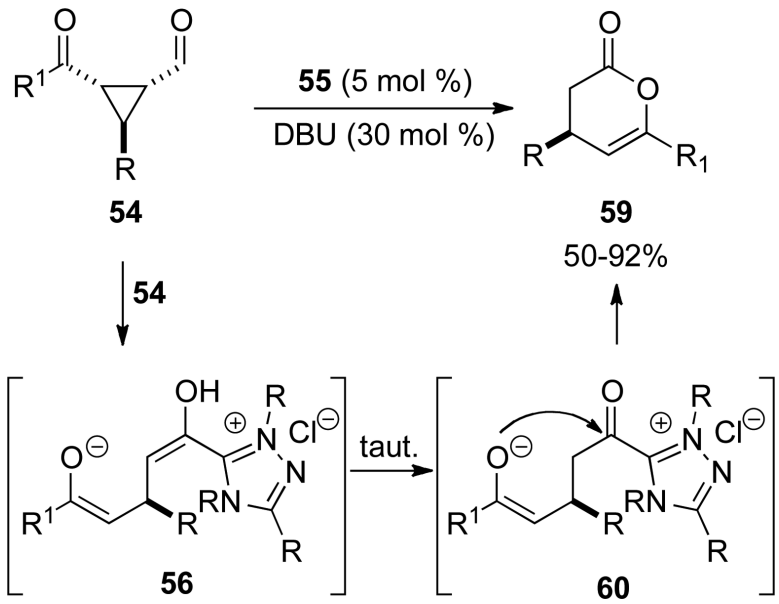
Scheme 11.
Divergent pathways leading to saturated esters and lactone dimers.



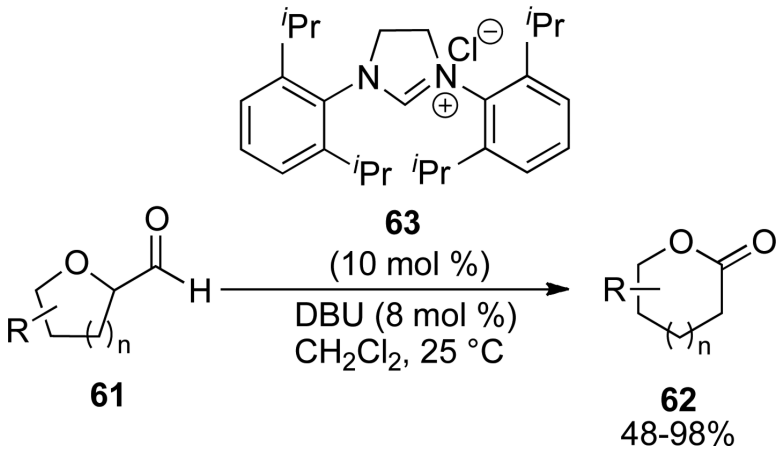
Scheme 12.
Intramolecular redox esterification to form dihydrocoumarins.



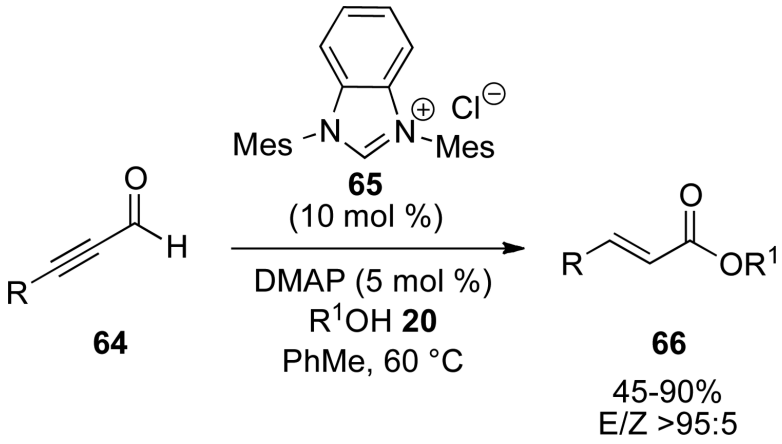
Scheme 13.
Redox esterification of formylcylopropanes.



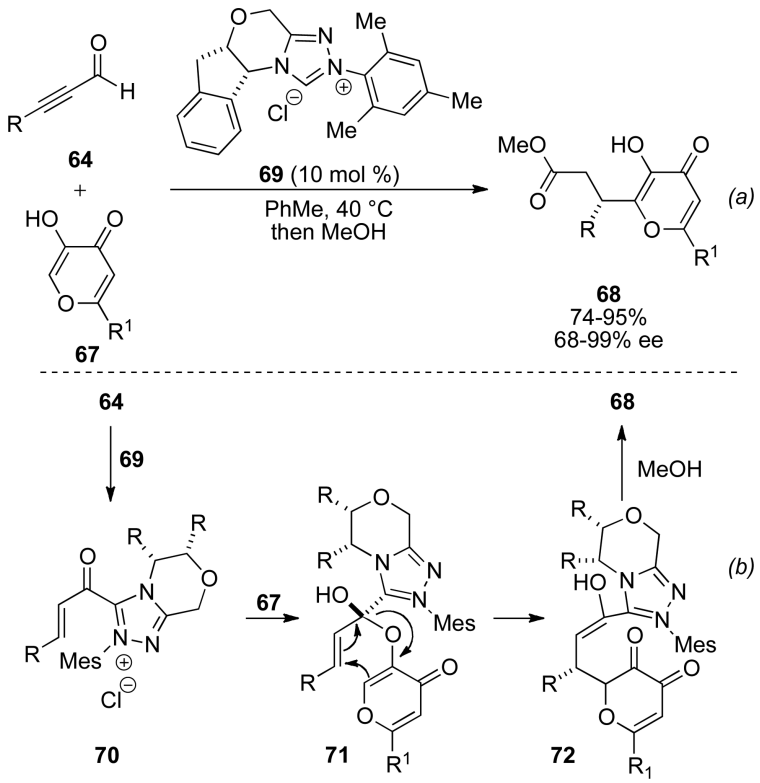
Scheme 14.
Intramolecular esterification of cyclopropyl carboxaldehydes.



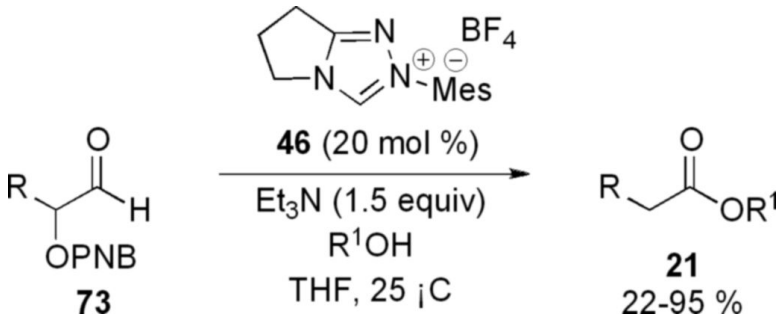
Scheme 15.
NHC catalyzed synthesis of lactones.



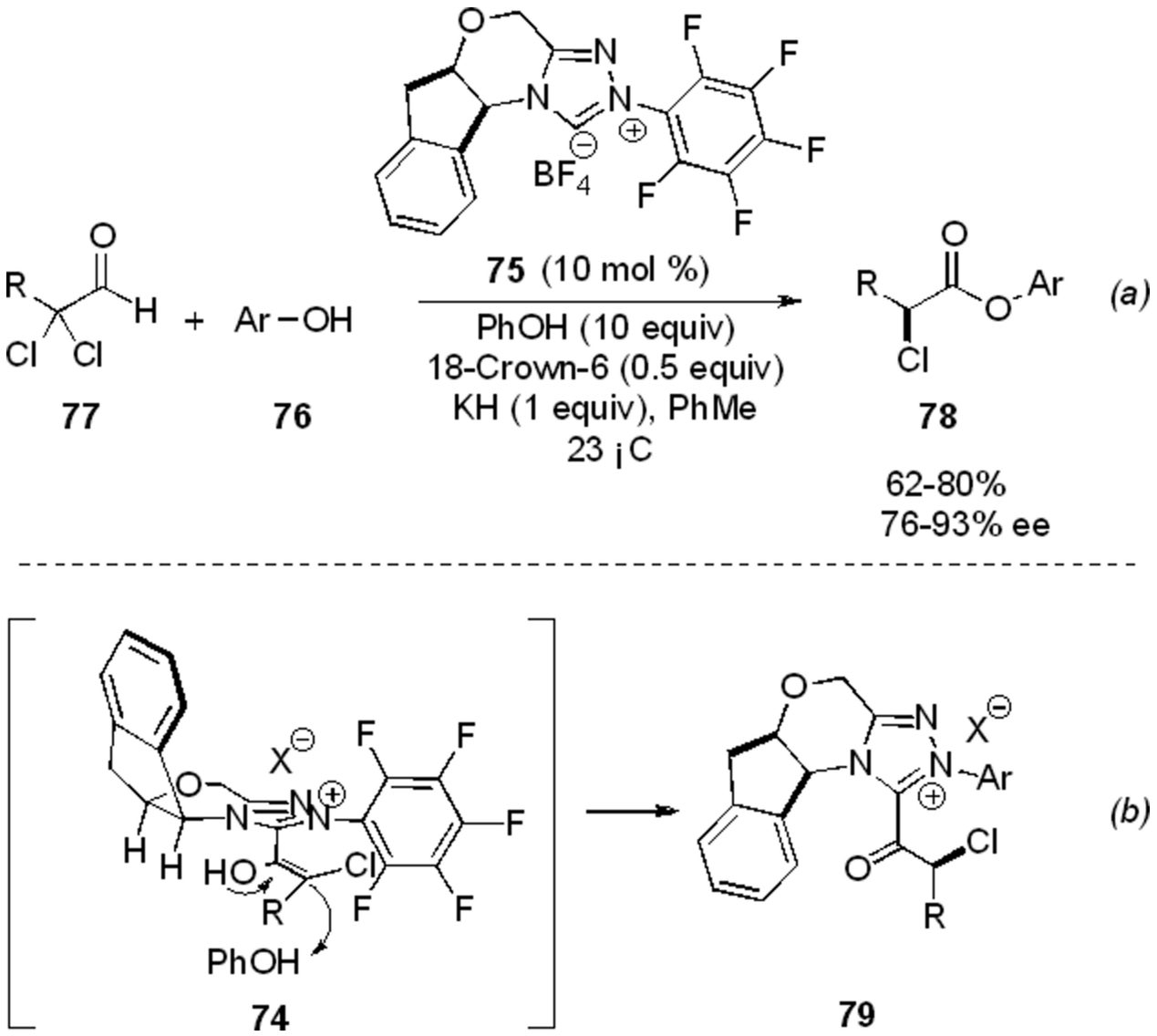
Scheme 16.
Redox esterification of ynals.



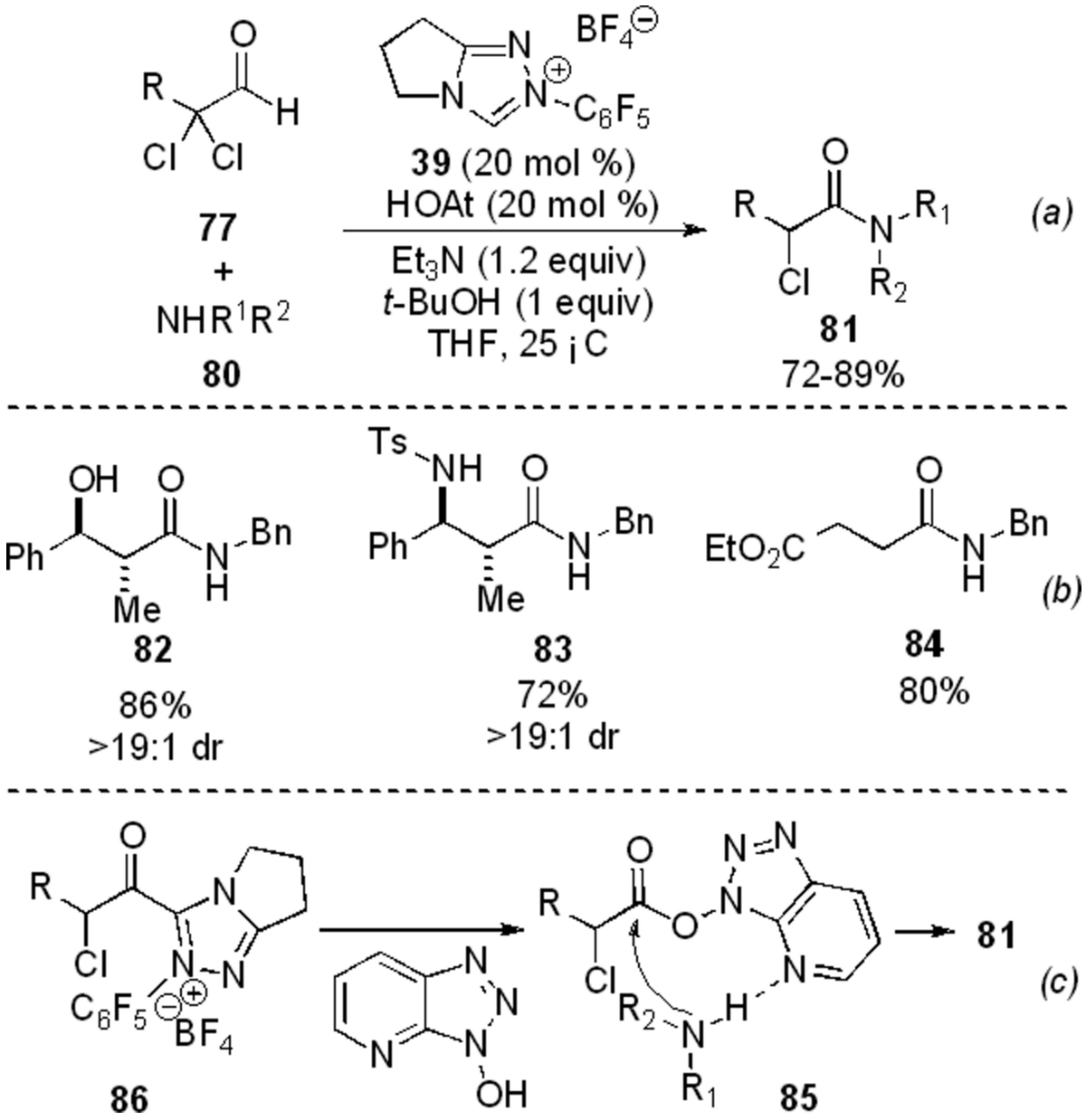
Scheme 17.
NHC Coates-Claisen rearrangement.



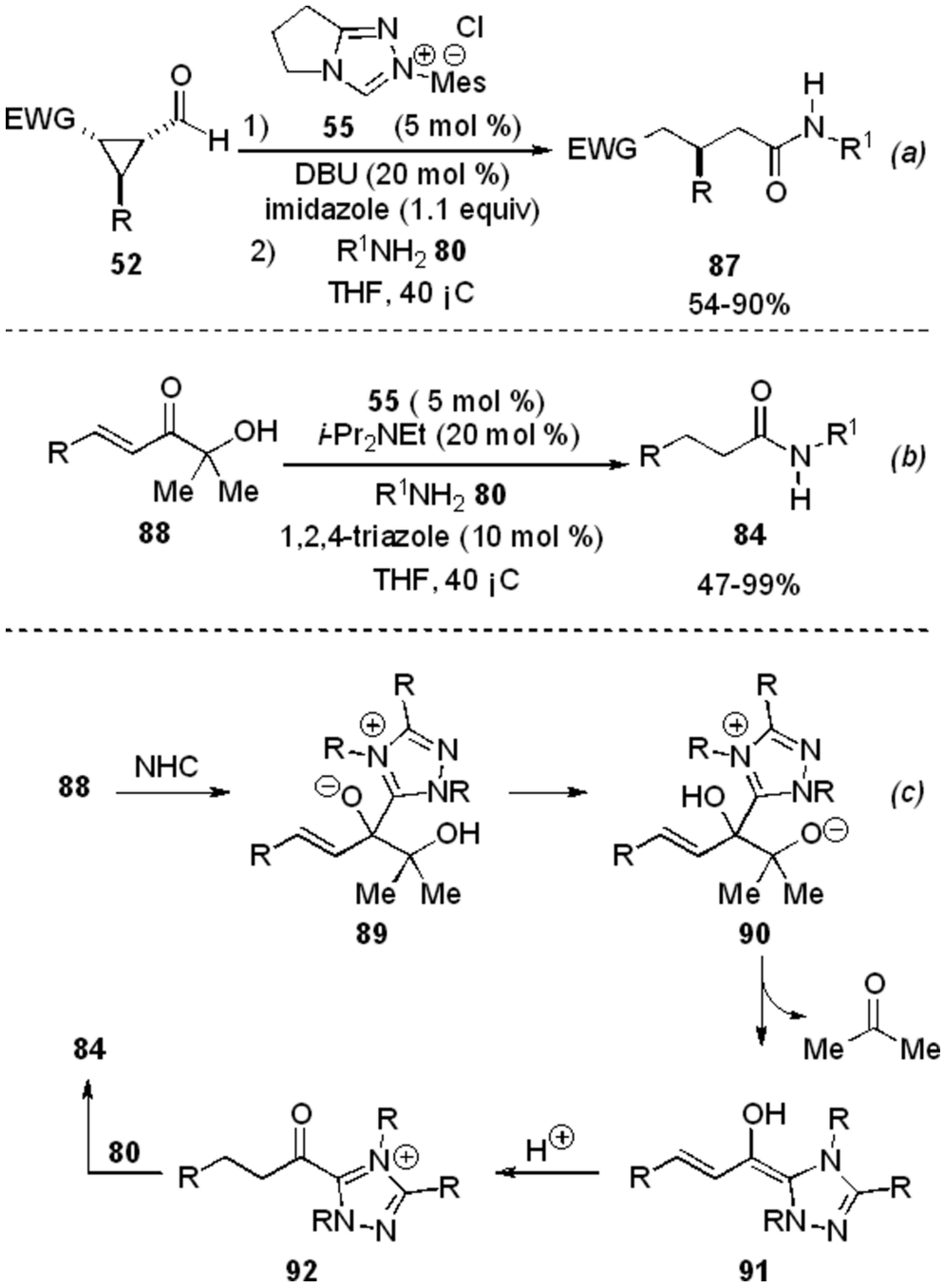
Scheme 18.
Redox esterification of α-Aryloxy aldehydes.



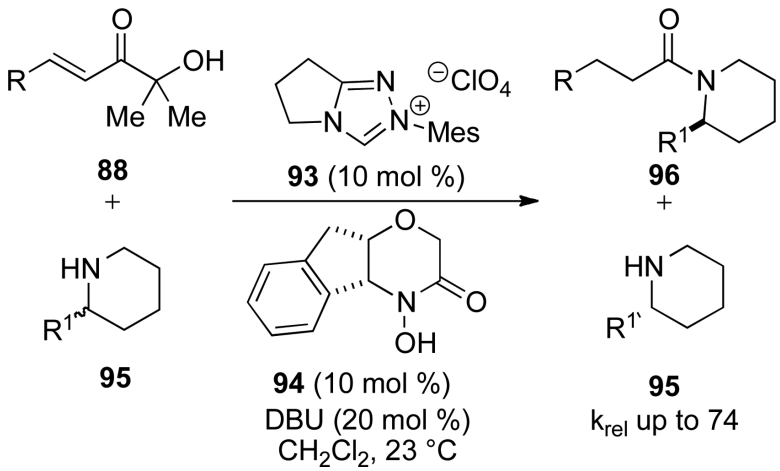
Scheme 19.
Esterification of dichloroaldehydes.



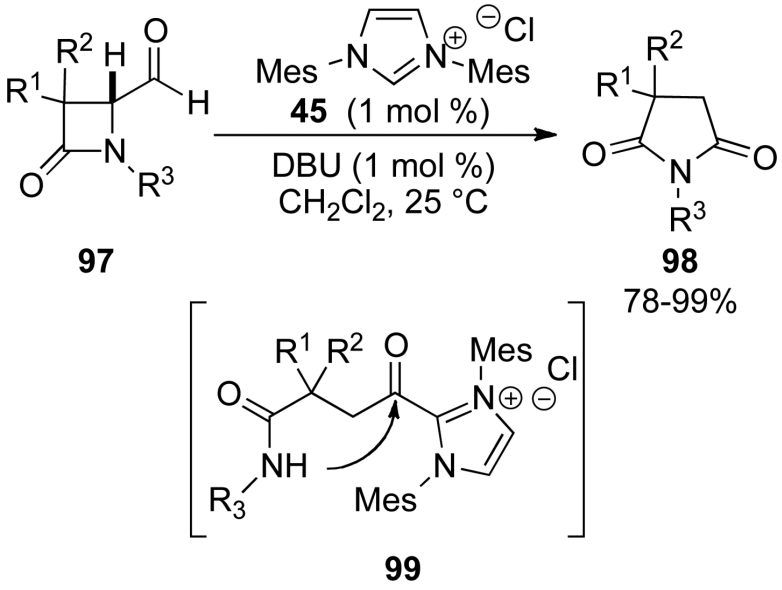
Scheme 20.
Redox amidation using HOAt as the acyl transfer reagent.



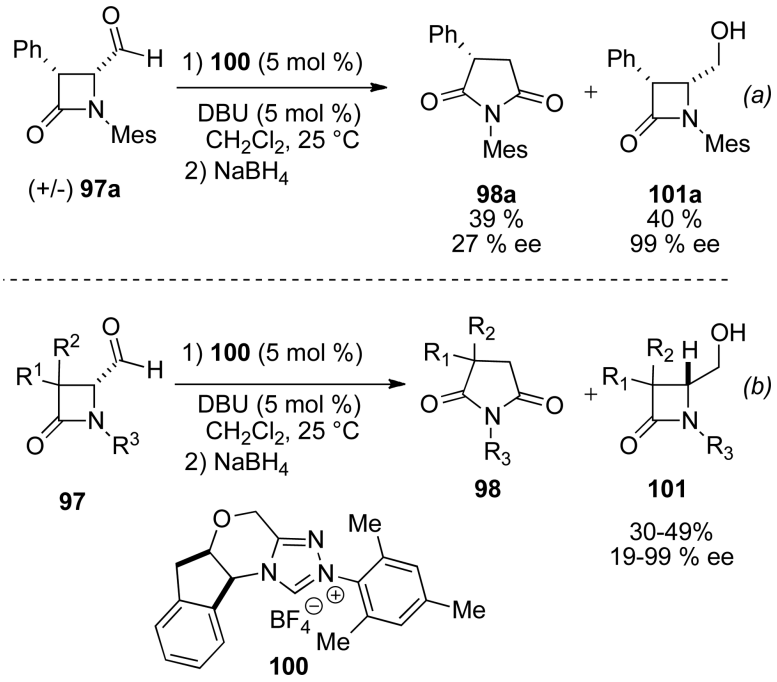
Scheme 21.
Redox amidation using imidazole or triazole as the acyl transfer reagent.



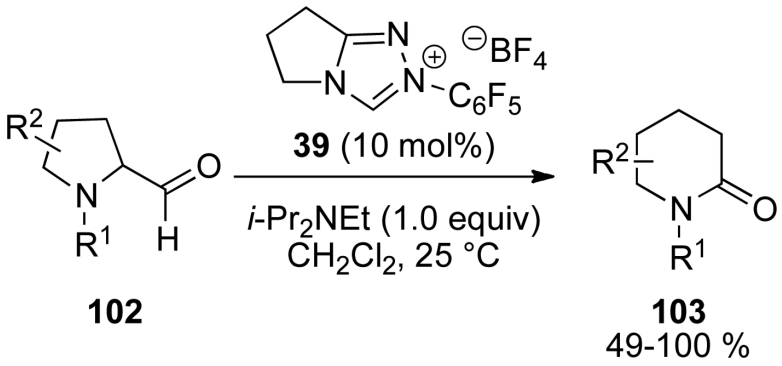
Scheme 22.
Kinetic resolution of secondary amines.



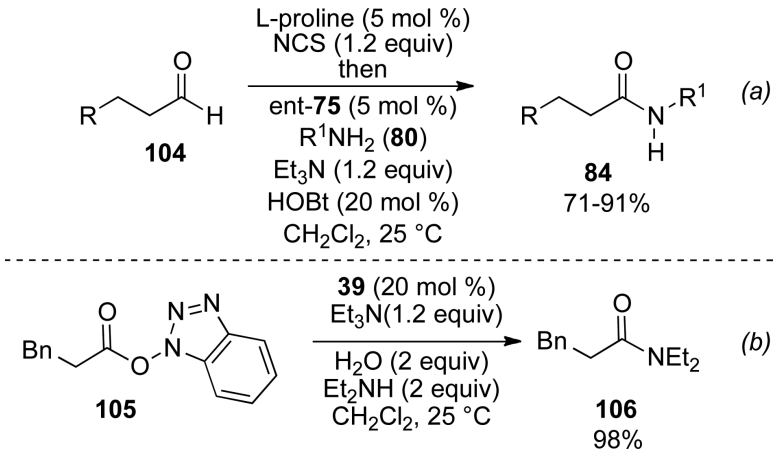
Scheme 23.
NHC catalyzed ring expansion of β-lactams.



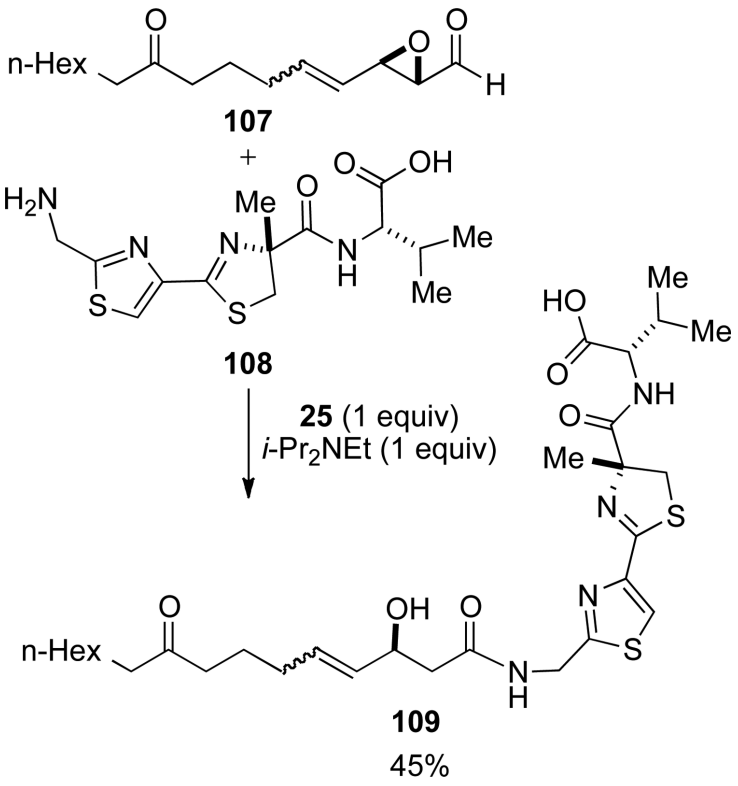
Scheme 24.
Kinetic resolution of racemic β-lactam.



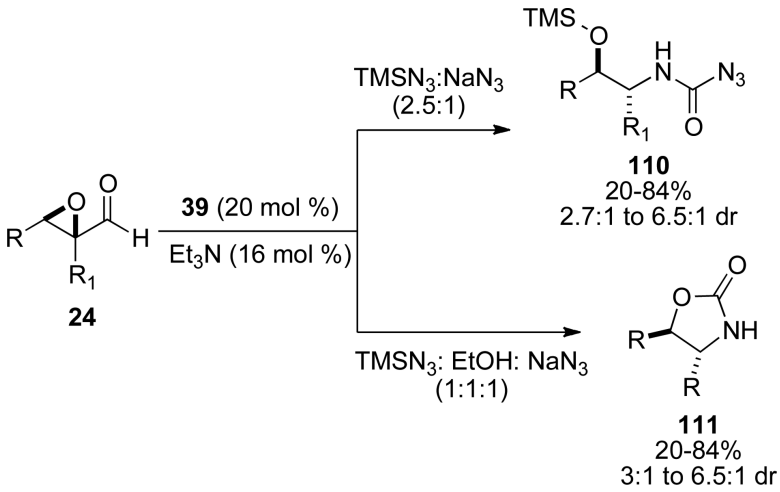
Scheme 25.
Ring expansions of 2-formyl pyrrolidines to lactams.



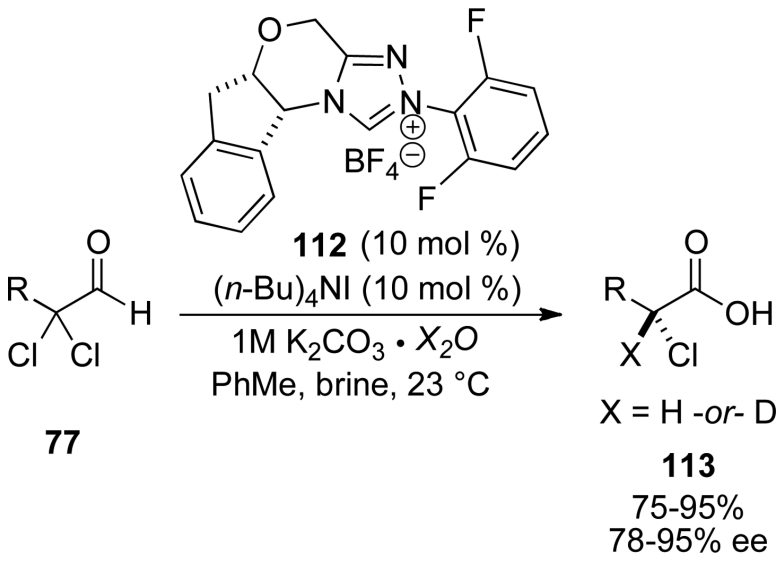
Scheme 26.
One-pot chlorination/amidation.



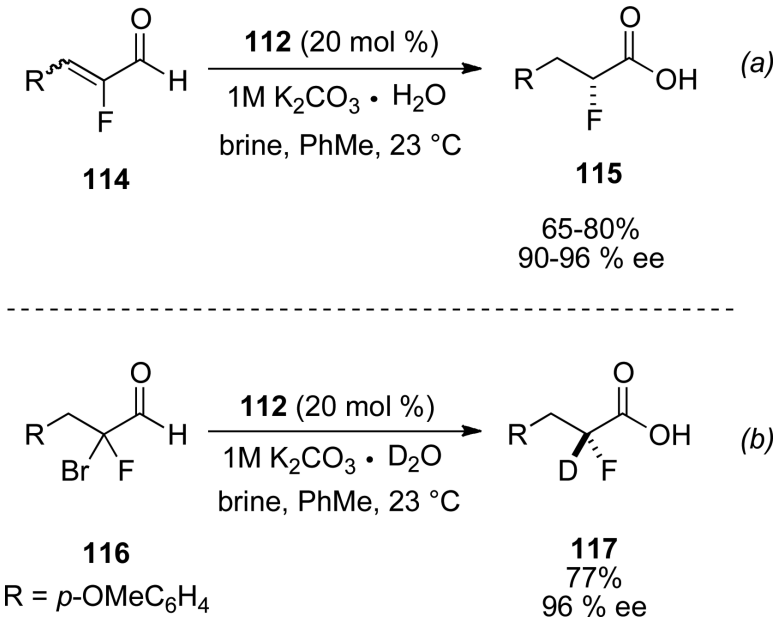
Scheme 27.
Application of NHC mediated redox acylation to the synthesis of largazole.



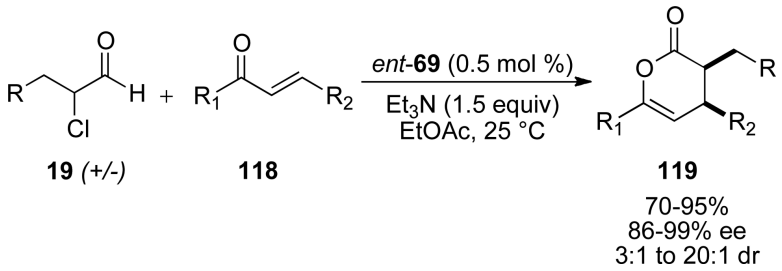
Scheme 28.
Azidation of epoxyaldehydes.



Scheme 29.
Hydration of dichloroaldehydes.



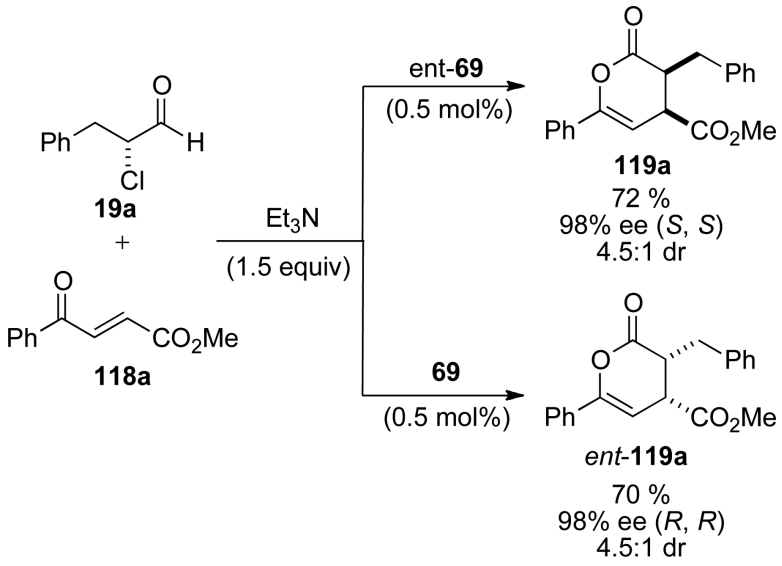
Scheme 30.
Hydration of fluoroenals.



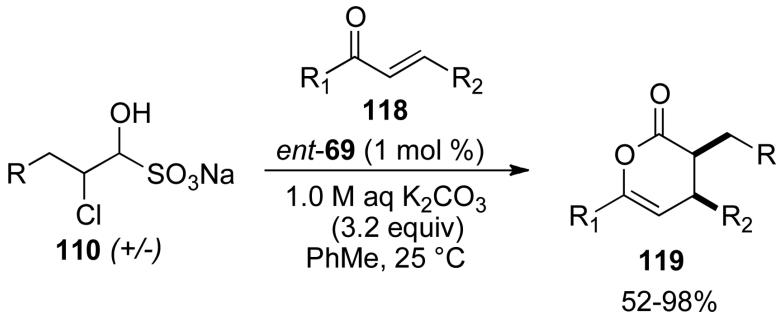
19 *(+/-)* **118** **119**

70-95%
86-99% ee
3:1 to 20:1 dr

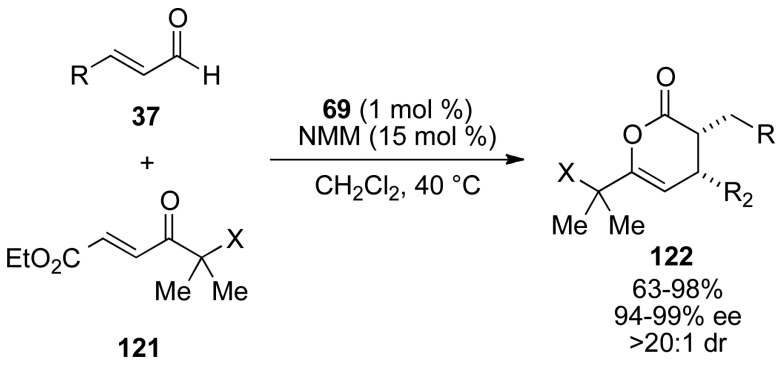
Scheme 31.
Hetero Diels-Alder reaction on the catalytically generated nucleophilic enol.



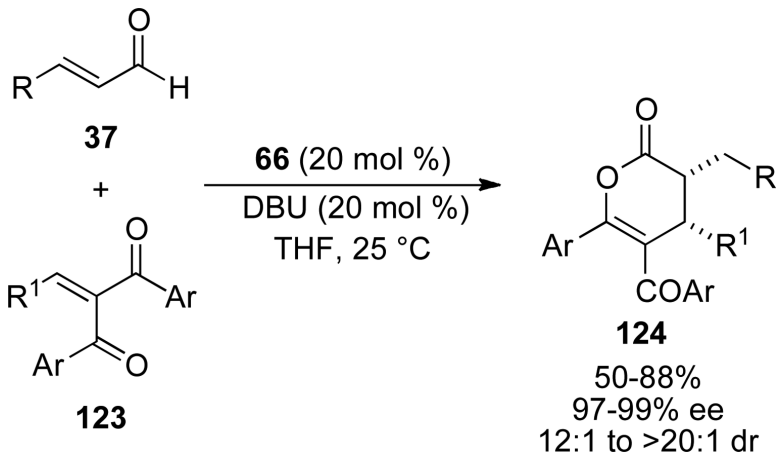
Scheme 32.
Catalyst control of enantioselectivity.



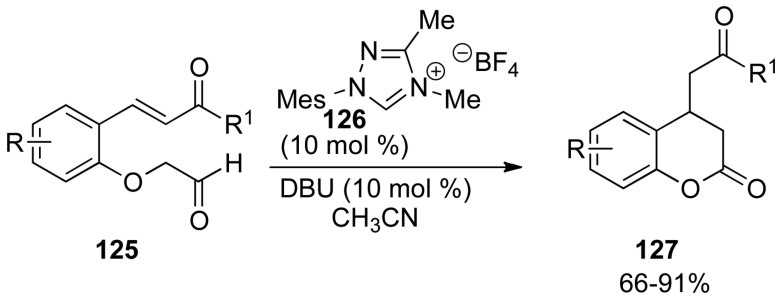
Scheme 33.
Bisulfites as an alternative to chloroaldehydes.



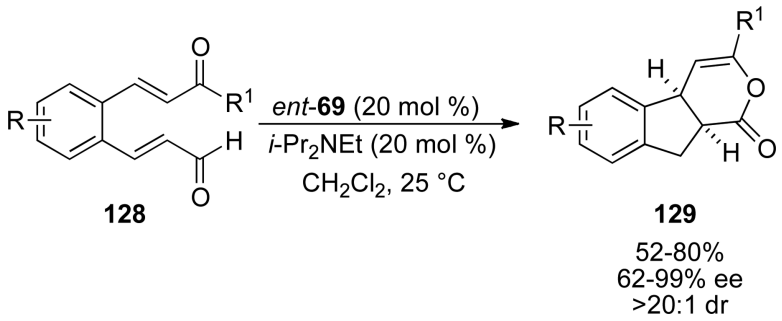
Scheme 34.
Enals as enolate precursors.



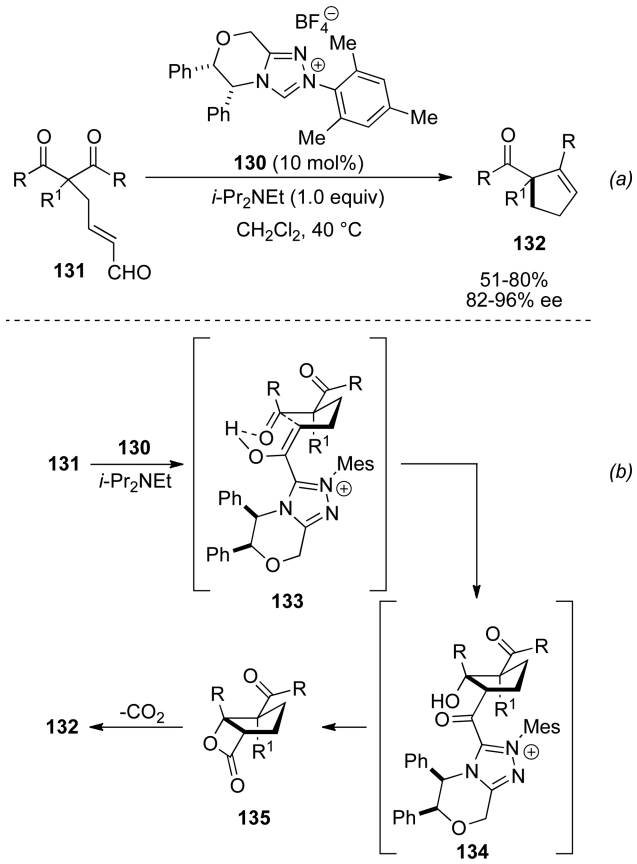
Scheme 35.
Hetero Diels-Alder reaction with chalcones.



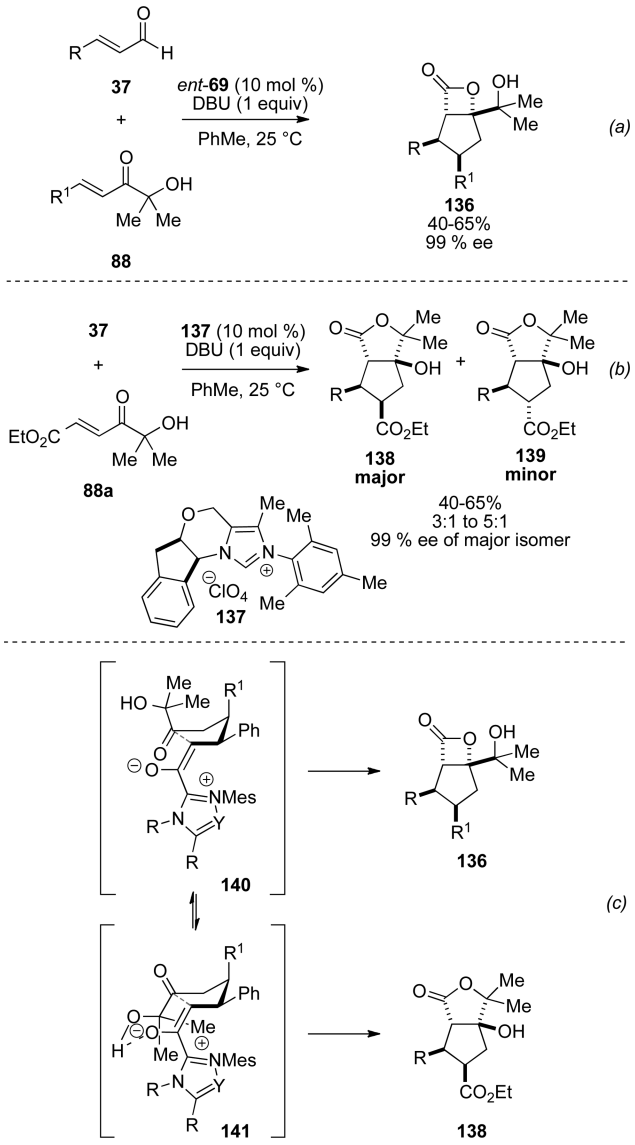
Scheme 36.
Coumarin synthesis.



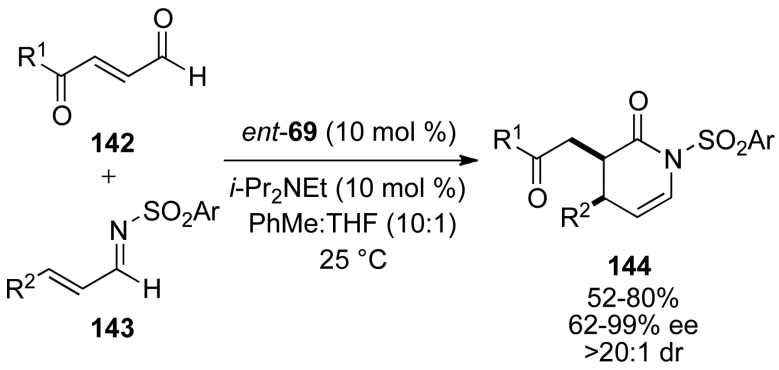
Scheme 37.
Intramolecular Michael reaction.



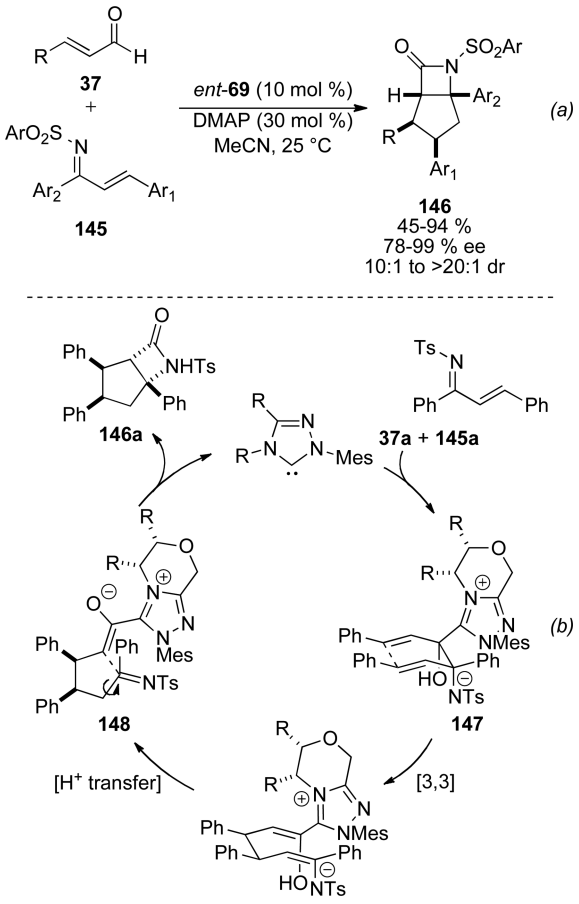
Scheme 38.
Decarboxylative cyclization to form cyclopentenes.



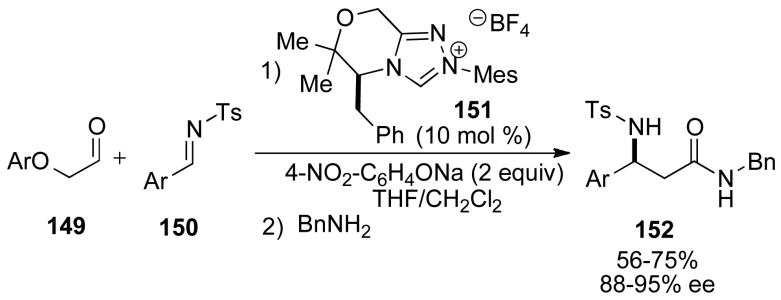
Scheme 39.
Divergent synthesis of β-lactone and γ-lactone products.



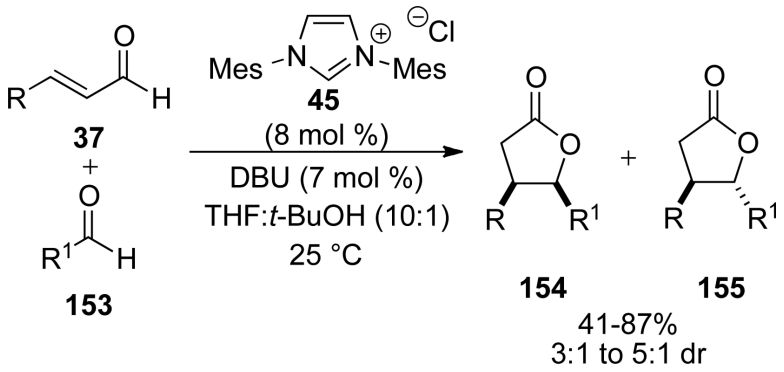
Scheme 40.
Hetero Diels-Alder reaction to give dihydropyridones.



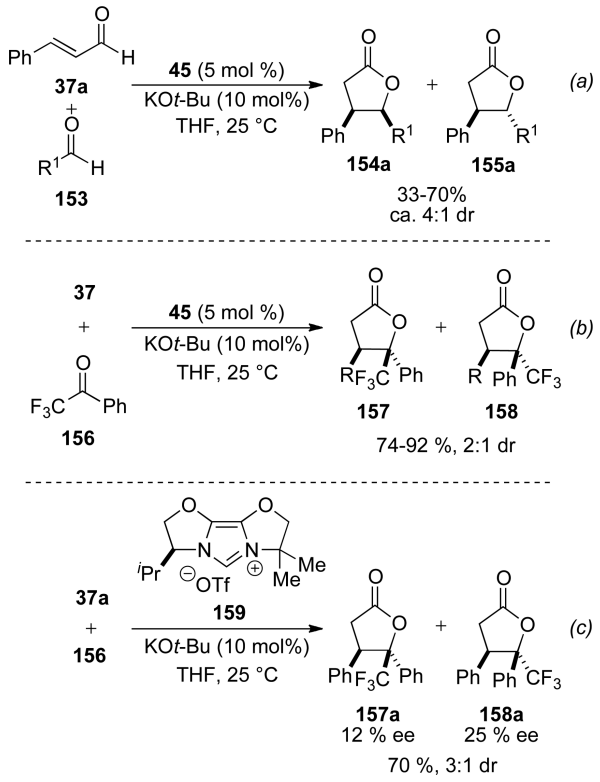
Scheme 41.
β-lactam synthesis by NHC catalysis.



Scheme 42.
Synthesis of β-amino amides.

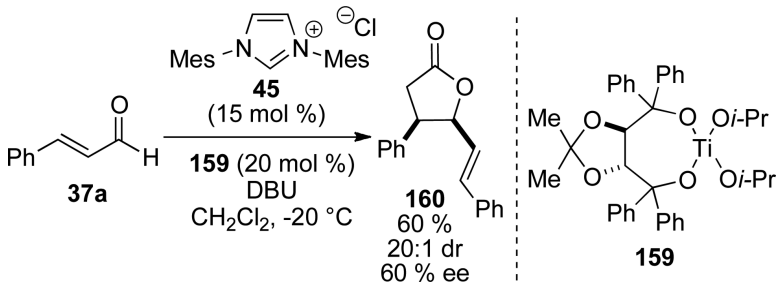


Scheme 43.
Homoenolate reactivity to form γ-butyrolactones from aryl aldehydes.

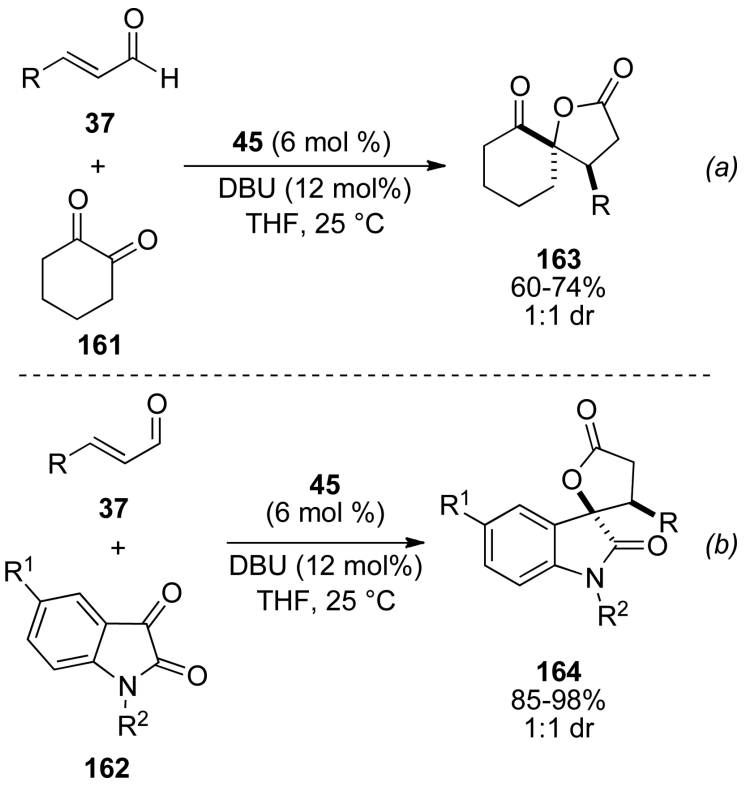


Scheme 44.

Homoenolate reactivity to form γ-butyrolactones from aryl aldehydes and trifluoromethyl ketones.

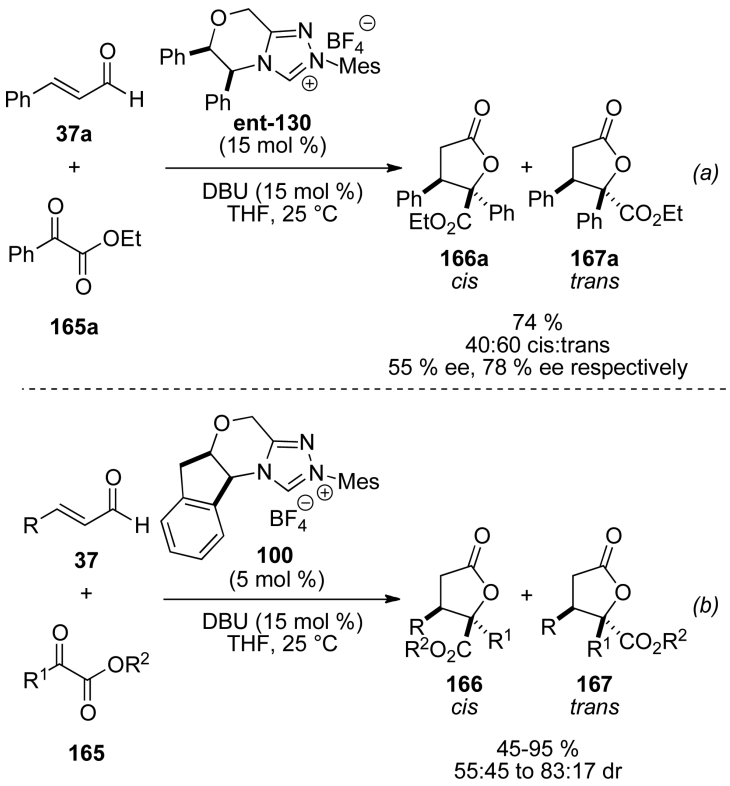


Scheme 45.
Chiral Lewis acid controlled γ-butyrolactone synthesis.

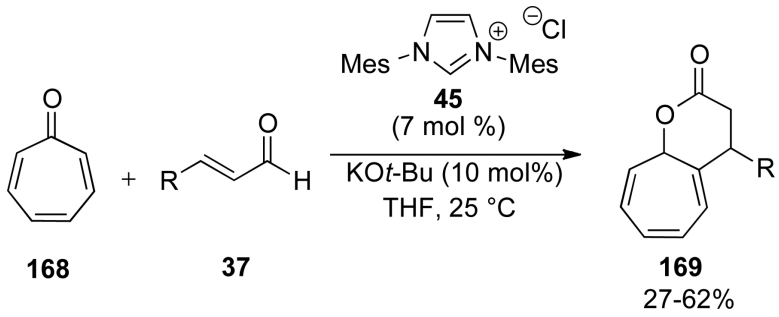


Scheme 46.

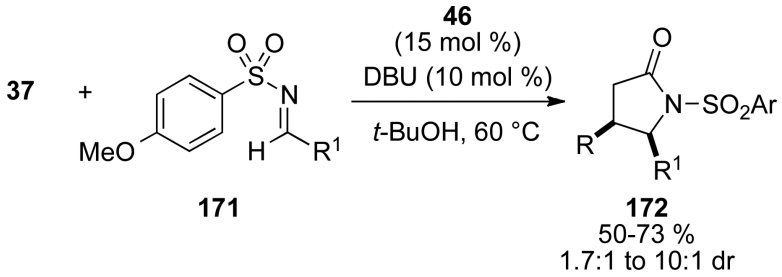
γ-butyrolactone synthesis from 1,2-dicarbonyl compounds.



Scheme 47.
Homoenolate addition to glyoxylates.

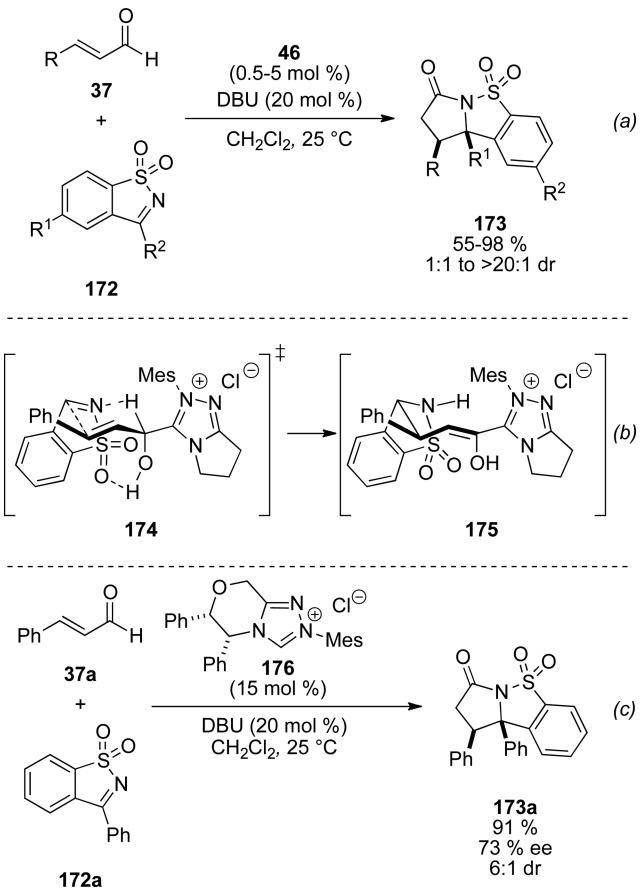


Scheme 48.
[8+3] annulation of homoenolate with tropone.

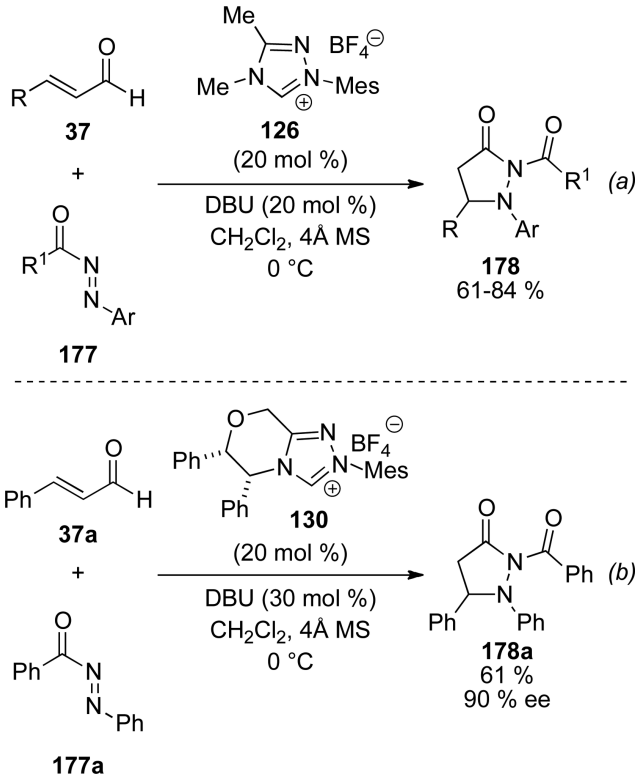


Scheme 49.

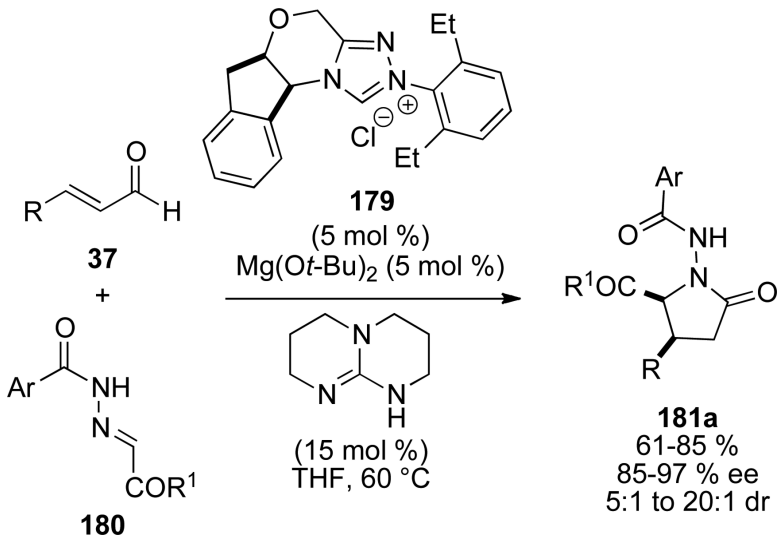
γ-lactam synthesis by homoenolate addition to sulfonylimines.



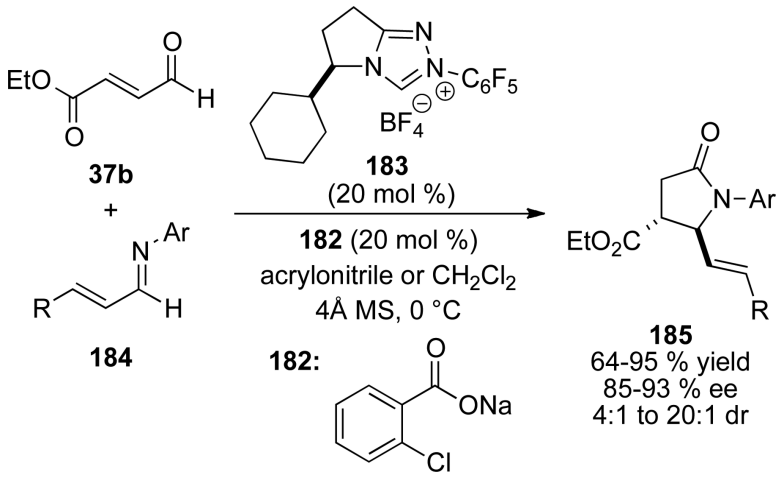
Scheme 50.
Enhanced reactivity with cyclic sulfonylketimines.



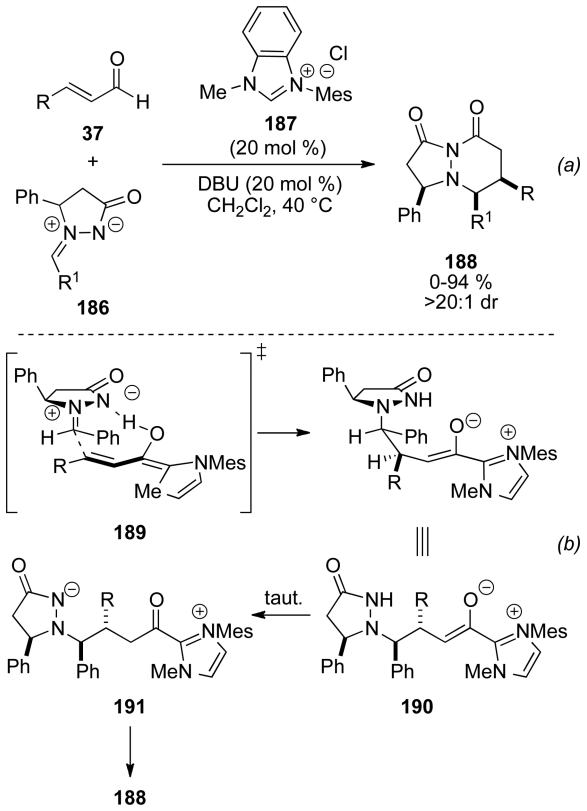
Scheme 51.
Homoenolate addition to diazines.



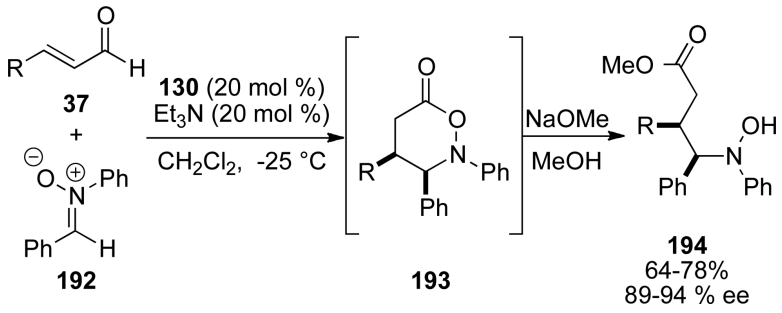
Scheme 52.
Synthesis of γ-lactams by homoenolate addition to acylhydrazones.



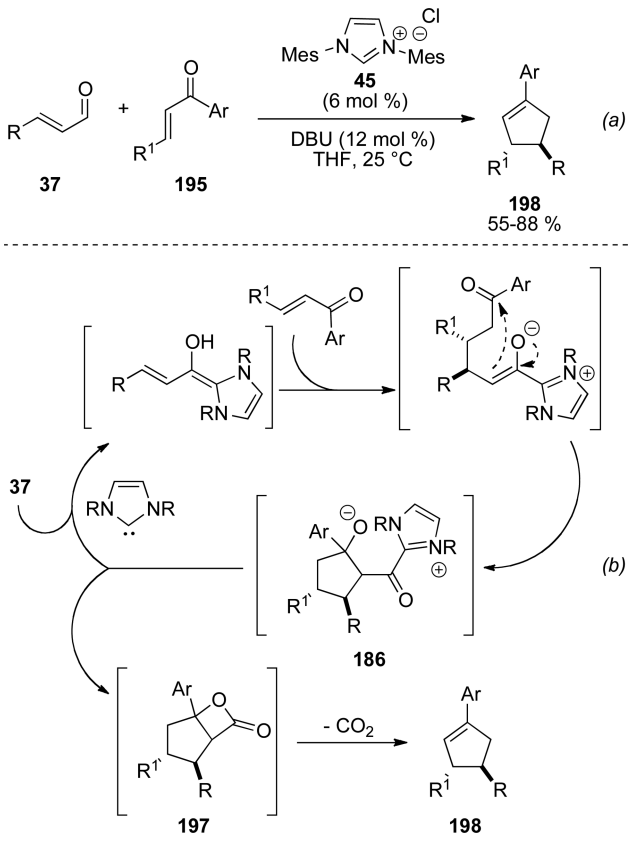
Scheme 53.
Brønsted acid catalyzed homoenolate addition to imines generating *trans*-γ-lactams.



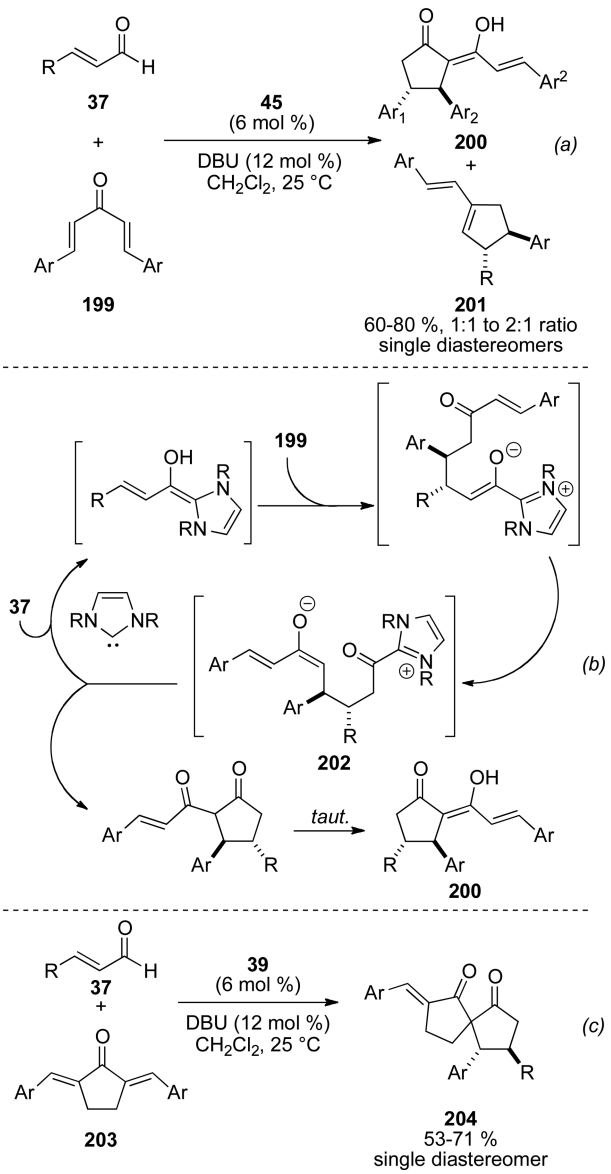
Scheme 54.
Homoenolate addition to azomethine ylides.



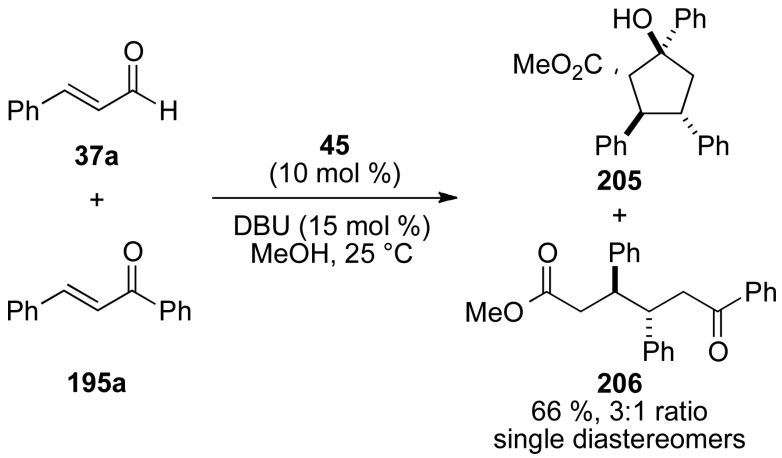
Scheme 55.
Homoenolate addition to nitrones.



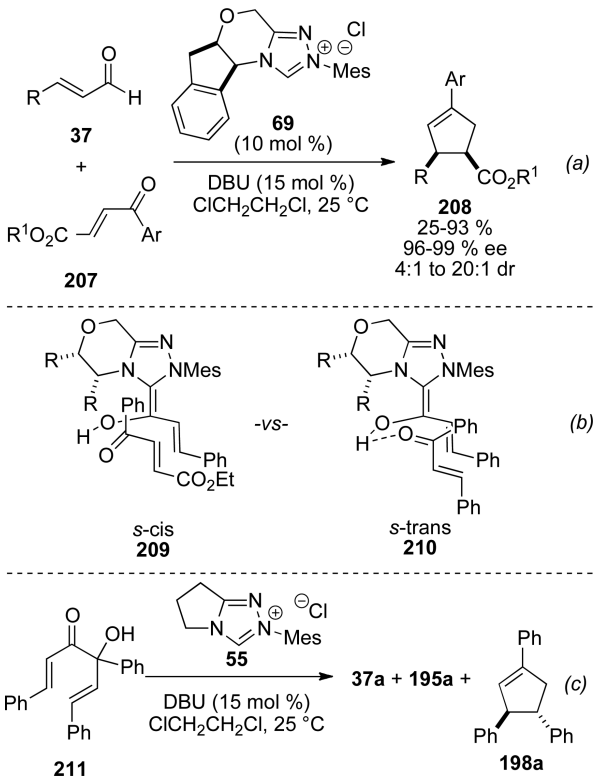
Scheme 56.
Carboannulation and proposed homoenolate mechanism.



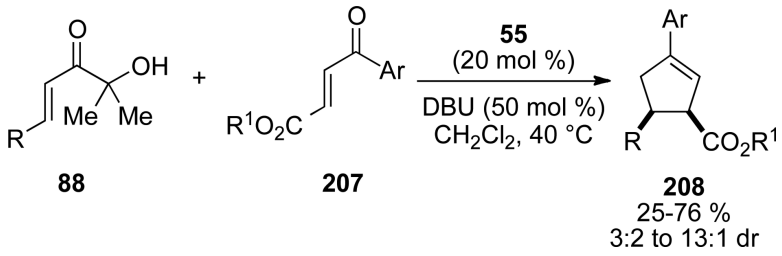
Scheme 57.
Spirocyclopentane synthesis.



Scheme 58.
Cyclopentanol and acyclic ester formation.

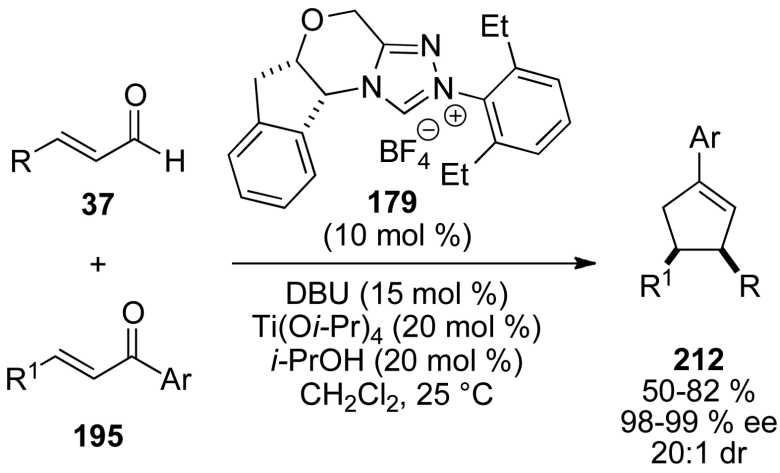


Scheme 59.
Asymmetric cyclopentene synthesis.

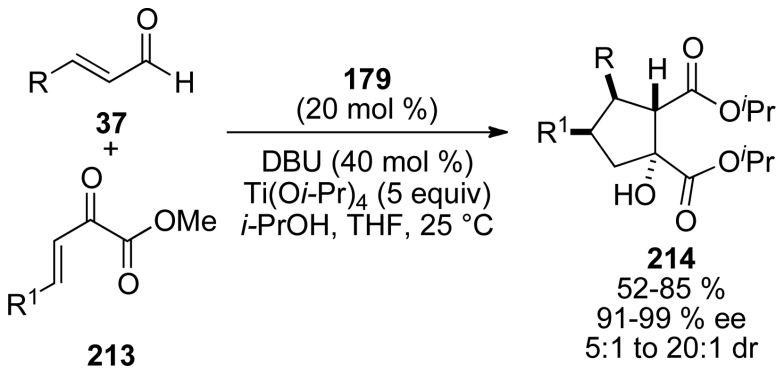


Scheme 60.

α‘-hydroxyenone as substrates for NHC catalyzed cyclopentene synthesis.



Scheme 61.
Enantioselective cyclopentene synthesis using NHC/Lewis acis cooperative catalysis.



Scheme 62.
Cooperative catalysis to give enantioenriched cyclopentane products.