DISSERTATION

N-HETEROCYCLIC CARBENE CATALYZED α-REDOX REACTION: CATALYTIC SYNTHESIS OF AMIDES AND CARBOXYLIC ACIDS

Submitted by

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ABSTRACT

N-HETEROCYCLIC CARBENE CATALYZED α-REDOX REACTION:

CATALYTIC SYNTHESIS OF AMIDES AND CARBOXYLIC ACIDS

N-heterocyclic carbene catalyzed α-redox reaction has been utilized towards the catalytic synthesis of amides utilizing amines and substoichiometric quantities of an acyl transfer reagent in a waste reduced acylation process. The reaction is amenable to a plethora of amines and amine hydrochloride salts as nucleophiles. The reaction is applicable towards a variety α-reducible aldehydes as α,α-dichloro aldehydes, enals, epoxy and aziridnyl aldehydes all provide the respective amides in moderate to excellent yields with the latter in high diastereoselectivity. The asymmetric amidation reaction provides chiral amides in moderate enantioselectivity.

Additionally, the N-heterocyclic carbene catalyzed α-redox reaction was also utilized for the synthesis of enantioenriched α-chloro and α-fluoro carboxylic acids. The reaction also provide for a mild installation of a deuterium from D_2O furnishing enantioenriched isotopically labeled compounds. Investigations in to the mechanism have revealed that the carbene displays behavior of a phase transfer reagent by shuttling hydroxide from the aqueous phase to the organic phase. Additionally, it has been found that the turover limiting step in this acylation process in the hydrolysis of the acyl azolium.

ACKNOWLEDGMENT

There are many people that have played an important role in my professional and personal development that need to be acknowledged and without whom this personal milestone could not have been achieved. I would like to begin with thanking my graduate advisor Tomislav Rovis. Tom has truly been an inspiration during my time at Colorado State University. The passion and excitement with which Tom pursues science is admirable and contagious. I wish that I am fortunate enough to carry on that excitement and passion for my work throughout my career. I was lucky in having the opportunity to work with him over these years. In addition, I would like to thank my committee, Professor Robert Williams, Professor John Wood, Professor Eugene Chen and Professor Michael McNeil for all of your advice and words of encouragement during my graduate career.

My passion for research began during my undergraduate years where under the guidance of Professor Paul Floreancig I was given the opportunity to conduct research. It was during this time that I fell in love with synthetic chemistry. The guidance I received from Paul played a pivotal role in my chemical career and without his supervision I would not have been able to obtain a position as a research associate at Roche and pursue my doctoral studies.

I would also like to thank my family for all the sacrifice they have made in allowing me to have the opportunity to achieve my dreams. Without them I would not be

where I am today. This work would not have been possible with out the support of my wife Heather. She has been an inspiration to me since we met and this work is dedicated to her. Without her support I would not have been able to accomplish what I have done.

Having been in this field for 12 years many have contributed to my growth and development as a synthetic chemist and scientist. I cannot thank you all enough for pushing me and making me strive for more.

This work is dedicated to Heather

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Chapter 1

N-heterocyclic Carbene Catalysis

1.1 Introduction

The generation of acyl anion equivalents has been of interest to the synthetic community since the 1960's. Interest in these intermediates stems from their atypical behavior, where an electrophilic acyl group **1** has been rendered nucleophilic **2** (Figure 1). This reversal of polarity is also known as umpolung.[1] Their generation can be readily accomplished from aldehydes via stoichiometric or catalytic methods.

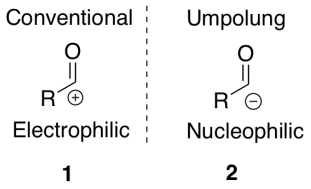


Figure 1.

The stoichiometric generation of acyl anion equivalents from aldehydes universally requires functionalization of the aldehyde followed by treatment with strong base to afford the acyl anion equivalent (Figure 2). The aldehyde is typically functionalized to provide dithianes **3**,[2] protected cyanohydrins **5**[3] and α-amino nitirles **6**[4] prior to treatment with strong base in furnishing the acyl anion equivalent **4** and **6**. An alternative approach has been treatment of an acyl silane with Lewis bases, which generates the acyl anion equivalent via Brook rearrangement.[5]

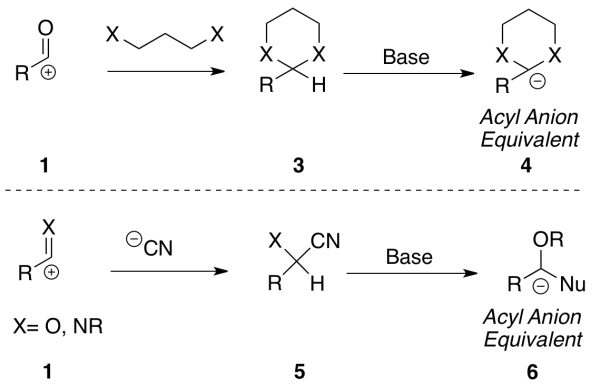


Figure 2.

The catalytic production of acyl anion equivalents from aldehydes has been through the use of cyanide and N-heterocyclic carbenes (NHC). The latter has emerged as a prominent method to catalyze the formation of acyl anion equivalents from aldehydes in an umpolung process (Figure 3) facilitating the discovery of new transformations and the development of asymmetric variants of benzoin, Stetter and α-redox reactions (Figure 3).

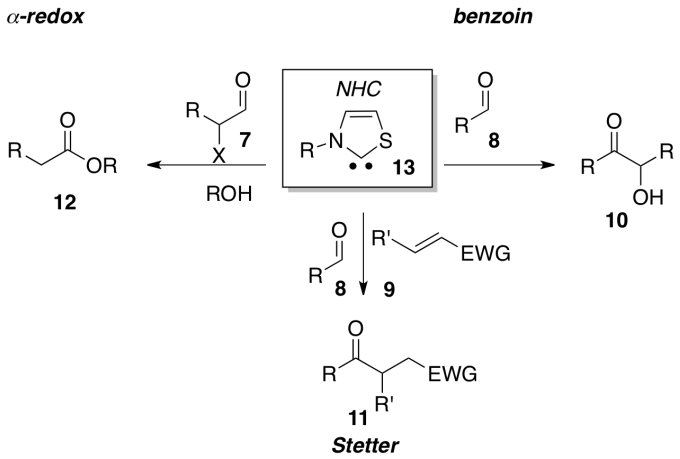


Figure 3.

1.2 Structure and Reactivity

Though carbenes have been widely studied, our understanding of their stability and reactivity has dramatically improved in recent decades.[6] They have typically been considered as highly reactive intermediates, and only recently has it been shown that their reactivity can be harnessed and controlled through appropriate manipulation of their steric and electronic parameters. This has primarily been achieved through the study of N-heterocyclic carbenes where manipulation of steric and electronic parameters can be readily achieved.

Carbenes are neutral compounds bearing a divalent carbon with six electrons in the valence shell. The two nonbonding electrons can either be spin paired **14** (Figure 4) (singlet) or unpaired (triplet). Stabilizing effects in the ground state can be broken down to the π-and σ- framework.[7] In the ground state, the nonbonding electrons of a singlet carbene occupy a σ-orbital leaving a vacant p-orbital available to accept π-donation from proximal atoms around the divalent carbon. This π-donation **15** (Figure 4) results in an overall increase of s-character, aids in stabilization, and renders the carbene more nucleophilic. An additional but more controversial stabilizing interaction involves a σ-withdrawing effect **16** (Figure 4) with a concomitant increase in s-character. The effect of π-donation and σ-withdrawing stabilizing events can be observed in crystal structures of isolable carbenes as a decrease in the N-C-N bond angle as well as an increase in the C-N bond length.[8]

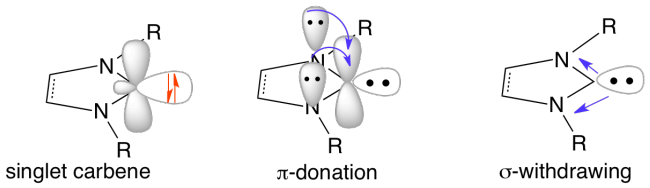


Figure 4.

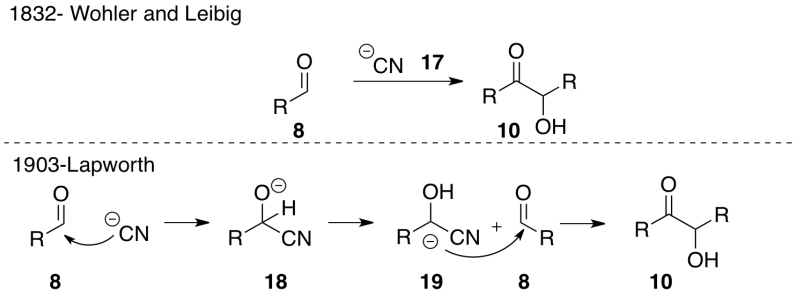
The advent of nucleophilic singlet carbenes in organic synthesis is premised on the seminal work of Wanzlick and Arduengo. In 1962, Wanzlick reported the synthesis of bis-[1,3-diphenyl-2-imidazolidinylidene], a dimeric product obtained from the reaction of two carbenes. He also noted that the dimer has a high affinity to dissociate and react with a variety of electrophiles and nucleophiles.[9]

In 1991, Arduengo[10] reported the isolation of a stable NHC and this communication renewed interest in the use of such compounds as ligands in metal catalyzed reactions and as nucleophilic catalysts in the emerging field of organocatalysis.[11] The recent applications of NHCs in Lewis base-mediated processes[12] and acyl anion chemistry have provided an additional platform to increase our understanding of these reactive intermediates.[13]

1.3 Benzoin Reaction

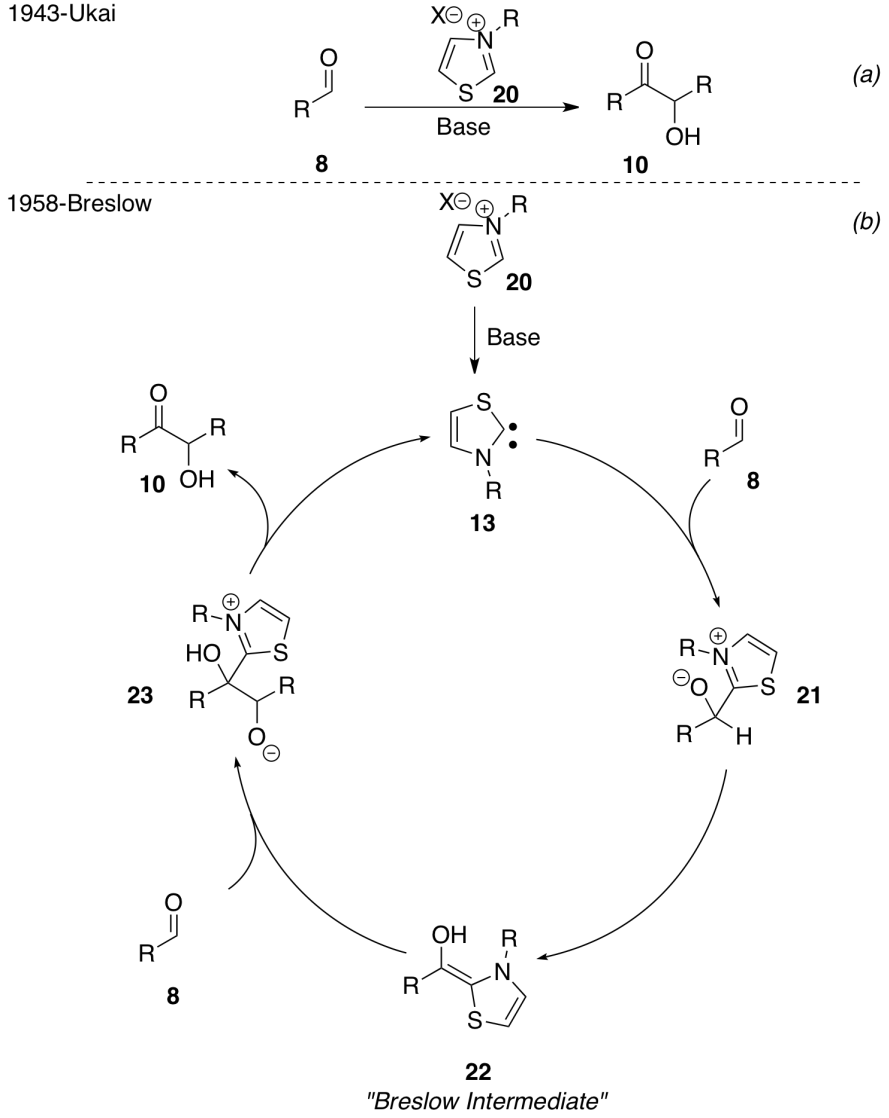
In 1832, Wöhler and Liebig reported the self condensation of benzaldehyde in the presence of cyanide **17** to provide benzoin, an α-hydroxy ketone **10**.[14] The α-hydroxy ketone **10** was proposed by Lapworth to arise from the addition of cyanide to the aldehyde to afford cyanohydrin **18**, which generates acyl anion equivalent **19** upon proton transfer (Scheme 1).[15] This is the currently accepted mechanism of the cyanide catalyzed benzoin reaction and would lay the mechanistic foundation for future work in this area.

Scheme 1.



In 1943, Ukai demonstrated that stoichiometric amounts of thiazolium salts **20** in the presence of alkaline bases were also capable of generating α-hydroxy ketones **10** from aldehydes **8** (Scheme 2, *a*).[16] The mechanistic proposal put forth by Breslow for the thiazolium catalyzed process resembles that proposed by Lapworth, suggesting both proceed via an acyl anion intermediate **22** (Scheme 2, b).[17] Breslow was able to identify that the umpolung process is initiated by an ylide or nucleophilic carbene **13**, which is generated upon deprotonation of the C2-proton of the azolium salt **20**. This mechanism for carbene formation was confirmed by observation of H/D exchange.[18] Nucleophilic addition of the carbene to the electrophilic aldehyde provides **21**, followed by an intermolecular proton transfer furnishing the acyl anion equivalent **22**, which is more commonly known as the Breslow intermediate. Addition of the Breslow intermediate **22** to another equivalent of aldehyde provides tetrahedral intermediate **10**. Proton transfer and collapse of intermediate **23** regenerates the nucleophilic carbene **13** and affords the benzoin product **10** (Scheme 2, *b*).

Scheme 2.



The benzoin reaction became the arena in which the efficiency of novel azolium carbenes was measured. Efforts to render the reaction asymmetric and substoichiometric in catalyst began in 1966 when Sheehan and Hunneman succeeded in facilitating benzoin formation in 22% optical purity with chiral thiazolidine carbene **26** (Figure 5).[19] Further development of chiral thiazolidine carbenes spanning three decades all comprised of a common structural feature, in which free rotation was feasible around the chiral center **27** and **28**, to which low enantioselectivities were attributed.[20] However, introduction of

bicyclic thiazolium salts **29** and **30** (Figure 5) only led to modest improvement in enantioselectivities over those obtained with the acyclic counterparts.[21] An additional rationale for low selectivities across the thiazolium scaffolds, albeit not explicitly stated, could be due to retro benzoin processes. The emergence of triazolylidene carbenes **31** and **34**, developed by Enders and Teles (Figure 5),[22] and bicyclic triazolylidene carbenes by Leeper[23] **32** and **33** (Figure 5) provided acceptable enantioselectivities of benzoin product.

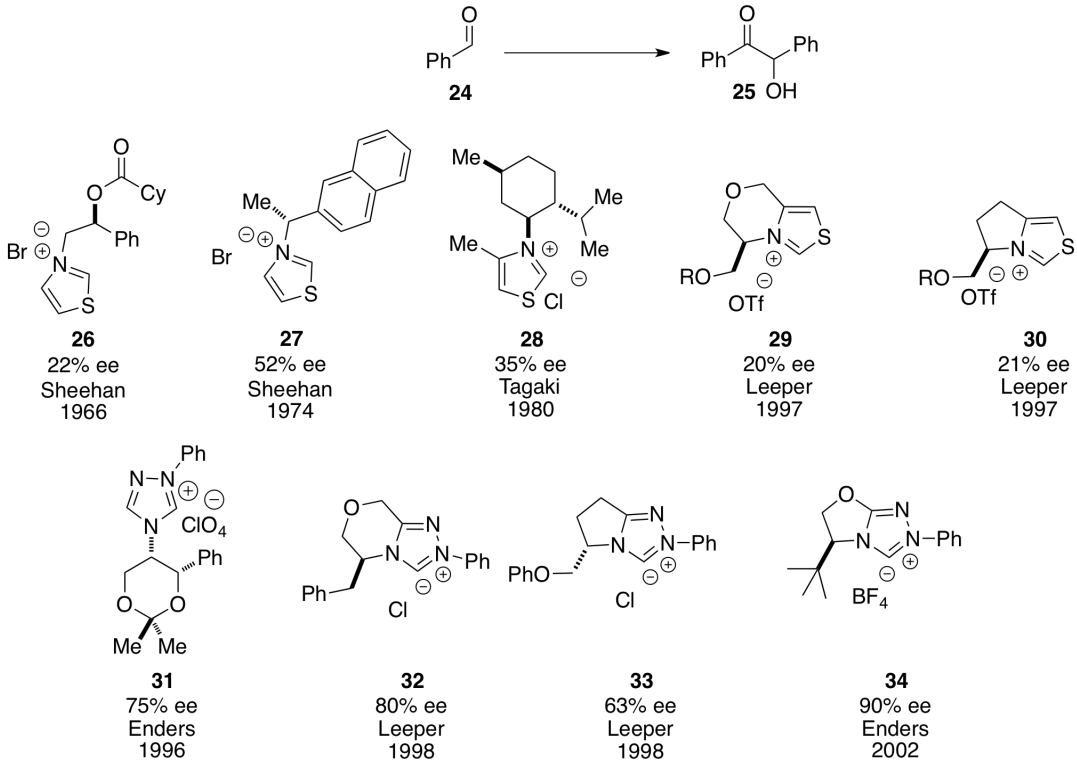


Figure 5.

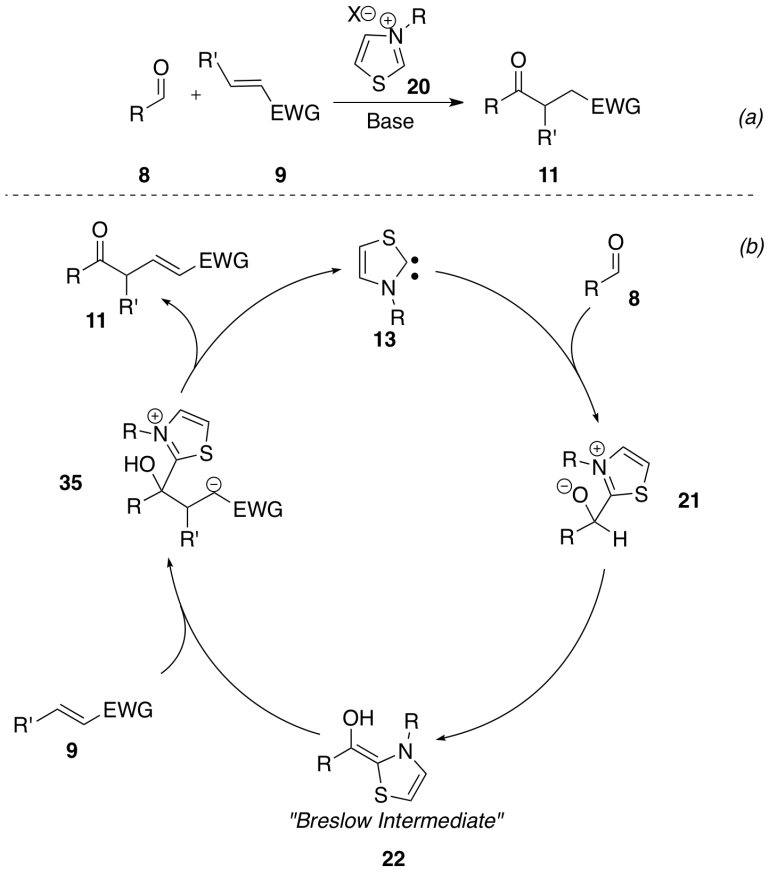
1.4 Stetter Reaction

In 1974, Stetter demonstrated that thiazolylidene carbenes could be employed to facilitate the nucleophilic addition of aldehydes via their acyl anion equivalent to activated double bonds to generate functionalized ketones. Although Stetter had

previously demonstrated that cyanide could mediate this process, thiazolylidene carbenes exhibited improved efficiency for aliphatic aldehydes (Scheme 3, a).[24]

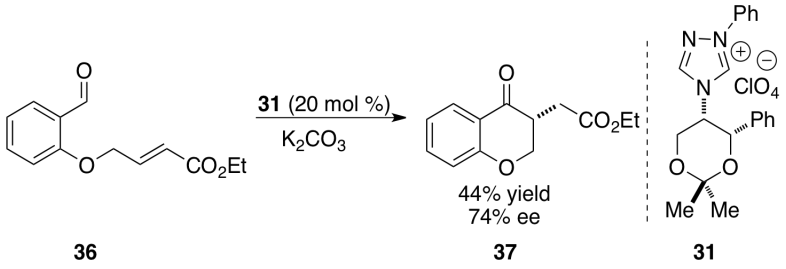
The mechanism for the Stetter reaction is similar to that of the benzoin reaction. The thiazolium salt **20** is deprotonated by base to generate the nucleophilic carbene **13**, which undergoes addition to the aldehyde to generate tetrahedral intermediate **21** (Scheme 3, b). Intermolecular proton transfer generates acyl anion equivalent or Breslow intermediate **22** which adds to a Michael acceptor **9** to generate an additional tetrahedral intermediate **35**. Proton transfer and collapse of resultant tetrahedral intermediate **35** affords the carbene **13** and product **11** (Scheme 3).

Scheme 3.



In 1995, Ciganek communicated the synthesis of chromanones **36** via an intramolecular Stetter reaction[25], and Enders would develop the first asymmetric variant of this process in 1996, which provided the chromanone **37** from **36** in 74% ee and 44% yield (Scheme 4) with chiral triazolium salt **31**.[26]

Scheme 4.



36 **37** **31**

In 2002, Rovis and coworkers introduced two novel triazolium scaffolds for the purpose of improving the intramolecular Stetter reaction. The triazolium scaffold **39** possesses several advantages over that of thiazolium **38** and imidazolium precursors (Figure 6). Namely the number of sites available for structural and electronic modification in the triazolium skeleton surpasses those in the other scaffolds (Figure 6). Additionally, the triazolium scaffold **39** occupies a greater degree of chiral space than thiazolium carbene precursors (Figure 4). That is to say that while thiazolium precursors **38** block a single quadrant the corresponding triazolium-derived catalysts **39** can affect three quadrants (Figure 6), presumably leading to improved selectivities arising from substitution on the backbone and the N-aryl substituent.

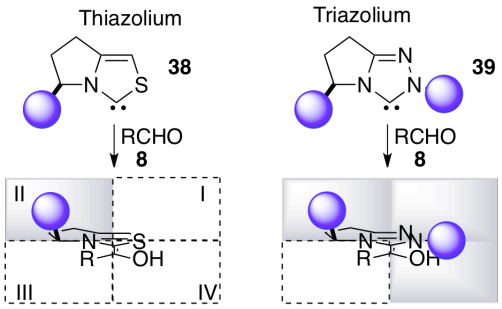


Figure 6.

In order to rapidly survey the newly developed chiral triazolium salts, Rovis and coworkers devised a method for their rapid access. They conceived that the chiral backbone of these catalysts could be assembled from amino alcohols **40** (morpholine series), or amino acids **41** (pyrrolidine series) with aryl hydrazines **44**. Modification of the aryl substituent of the hydrazine **44** would provide additional means to tune electronic and steric parameters (Figure 7). Given the proximity of the N-aryl substituent to the carbene carbon, such modifications would be expected to have a profound effect on carbene reactivity.

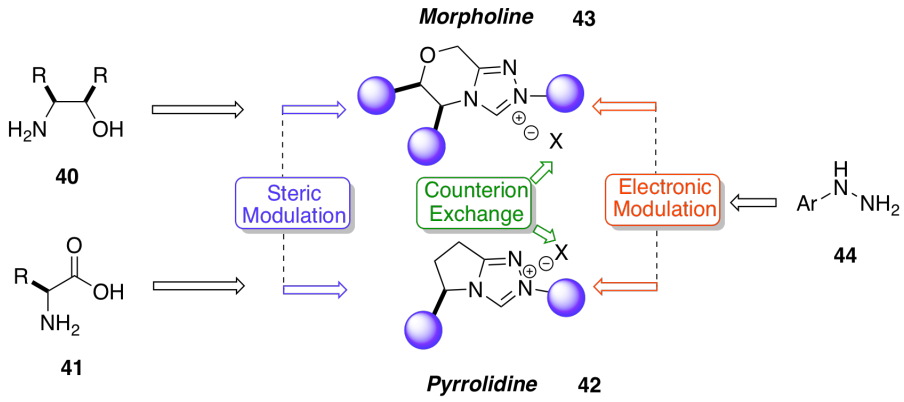
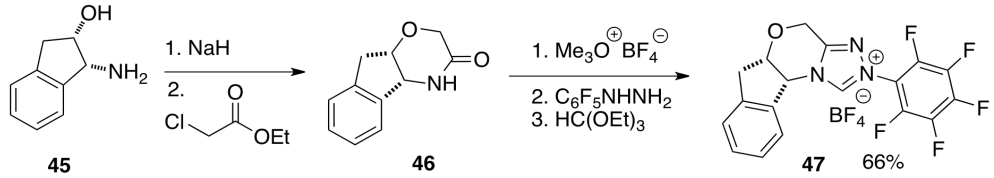


Figure 7.

Rovis and coworkers identified amino indanol **45** (Scheme 5) as the optimal chiral amino alcohol in the morpholine series **43** (Figure 7), which could be coupled with a

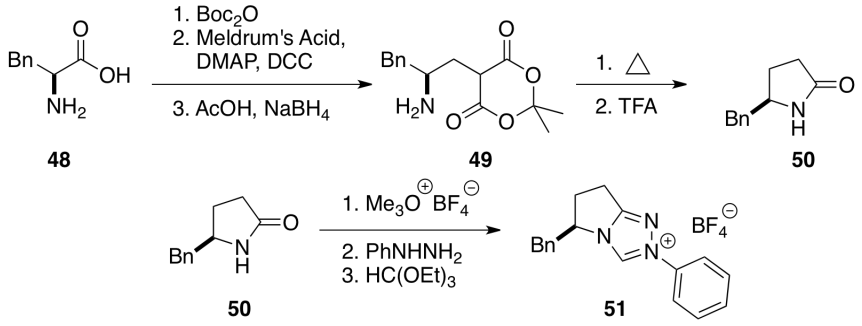
variety of structurally and electronically diverse hydrazines to furnish bench stable triazolium salts. Starting from amino indanol **45** (Scheme 5) the azolium salt **47** can be obtained in 5 steps, the last three of which are conducted in one pot.[27] Since the initial report of the syntheses of these triazolium salts, a modified procedure was developed to access N-aryl substituted triazolium salts in good yields and high purity on scale.[28]

Scheme 5.



In the pyrrolidine series **42** (Figure 7), sidechains ultimately derived from amino acids such as phenylalanine and valine were identified as efficient chiral scaffolds in the synthesis of pyrolidinone **50** (Scheme 6). From pyrolidinone **50**, a one pot three step procedure can be utilized to access the bench stable triazolium salts **51** (Scheme 6). Preparations of these catalysts can also be accomplished on scale (Appendix A).

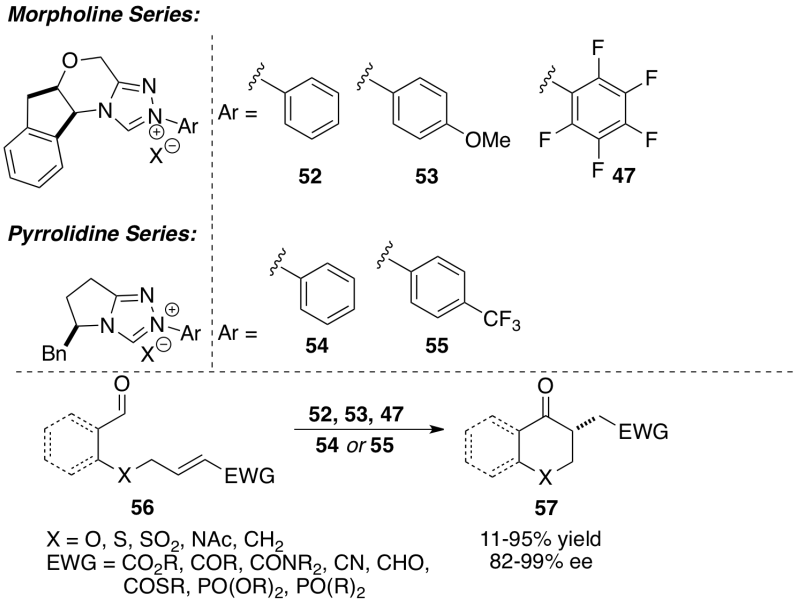
Scheme 6.



The intramolecular Stetter reaction was used as the platform wherein the effectiveness of the novel triazolium catalysts was measured. A variety of salicyl-aldehyde derived substrates and aliphatic aldehydes **56** bearing a range of linkers

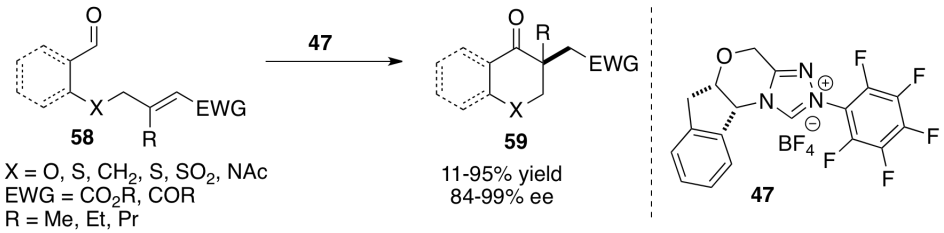
including ether, thioether, sulfone, and protected amines, effective in this process (Scheme 7). An electron-withdrawing group on the prochiral alkene **56** was a necessary requirement but encompasses esters, thioesters, amides, ketones, aldehydes, nitriles, phosphine oxides, and phosphonates (Scheme 7).[29] More recently, Stetter products arising from the addition of acyl anion equivalents to nonactivated π- systems have also been reported.[30]

Scheme 7.



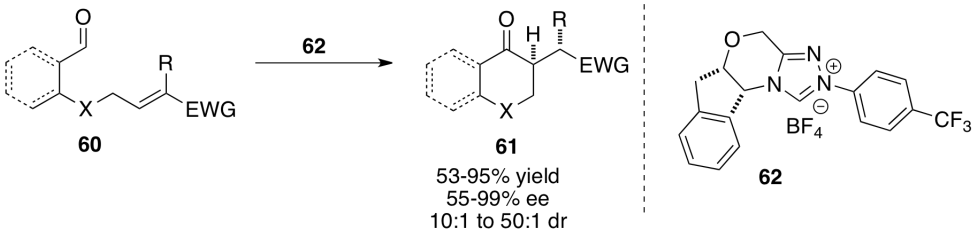
Michael acceptors bearing an additional β-substituent **58** also participate in the Stetter reaction to furnish quaternary stereocenters **59** (Scheme 8).[31]

Scheme 8.



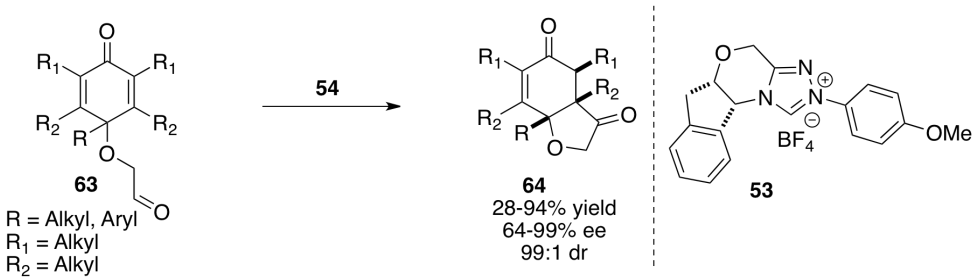
Contiguous stereocenters were generated by using precatalyst **62** with a variety of salicylaldehyde substrates **60** to provide a highly enantioselective and diastereoselective process **61** (Scheme 9). The reaction is not limited to salicylaldehyde derived substrates as aliphatic aldehydes **60** also partake in the reaction with high levels of enantio- and diastereoselectivity, where the latter is attributed to an intramolecular proton transfer event (Scheme 9).[32]

Scheme 9.



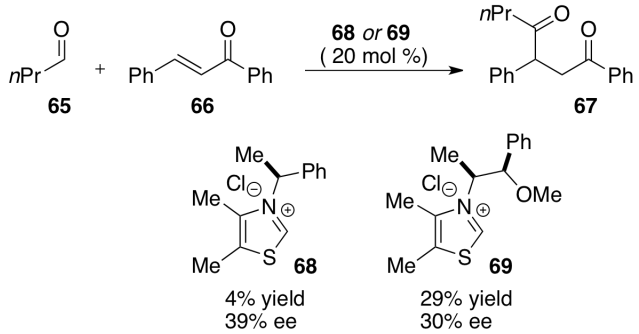
To advance the scope of the Stetter reaction, Rovis and Liu next focused on the synthesis of hydrobenzofuranones **64** arising from a Stetter reaction on cyclohexadienones (Scheme 10). These substrates **63** are readily accessible in two steps and when subjected to optimized reaction conditions with triazolium salt **53** hydrobenzofuranones **64** are obtained in excellent enantio- and diastereoselectivity (Scheme 10).[33]

Scheme 10.



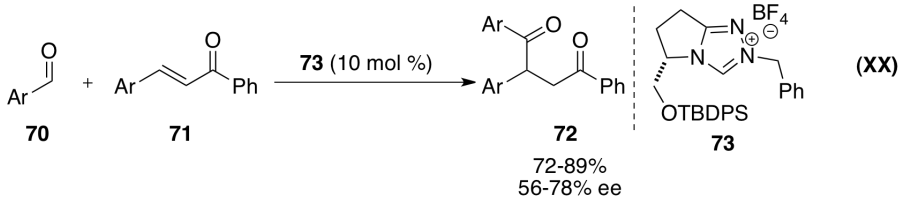
The development of the asymmetric intermolecular Stetter reaction was met with limited success in spite of the numerous examples reported by Stetter utilizing achiral thiazolium salts.[34] The few examples known have been reported by Enders with the reaction of butanal **65** and chalcone **66** in the presence of precatalysts **68** and **69** providing the 1,4-dicarbonyl product **67** in low yield and poor ee (Scheme 11).[35]

Scheme 11.



Enders subsequently introduced an improved triazolium catalyst **73** for the intermolecular Stetter reaction of aromatic aldehydes **70** and chalcones **71** (Scheme 12) wherein the *N*-benzyl substituent on the triazolium **73** was found to be key for providing improved yields and selectivites.[36]

Scheme 12.

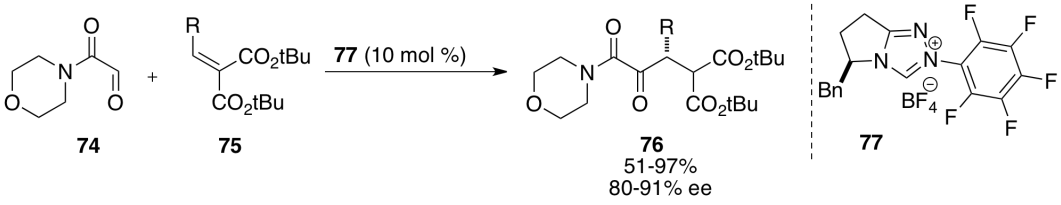


More recently, Rovis and Liu have identified glyoxamides as competent aldehyde partners and β-substituted alkylidene malonates as reactive electrophiles. During catalyst optimization it was noted that while precatalyst **77** produced the desired product in 50%

yield and 51% ee (Scheme 13), the phenyl analogue **54** (Scheme 7) did not provide any product.[37] These results again stress the significance of the *N*-aryl substituent in impacting carbene catalyzed reactions.[38]

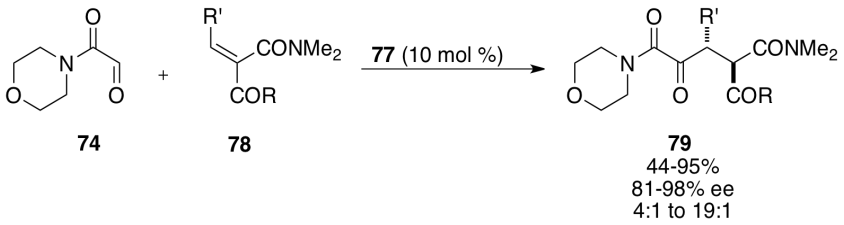
A morpholine-derived glyoxamide **74** proved to be a superior nucleophile in the reaction with alkylidene malonates **75** (Scheme 13). A variety of substituents are tolerated at the β-position of the alkylidene malonate to provide α-ketoamides (Scheme 13). Under the reaction conditions, the glyoxamide **76** is rapidly consumed to generate the benzoin product, which simply serves as the reservoir for the aldehyde via a retro-benzoin, and then participates in the desired Stetter process.

Scheme 13.



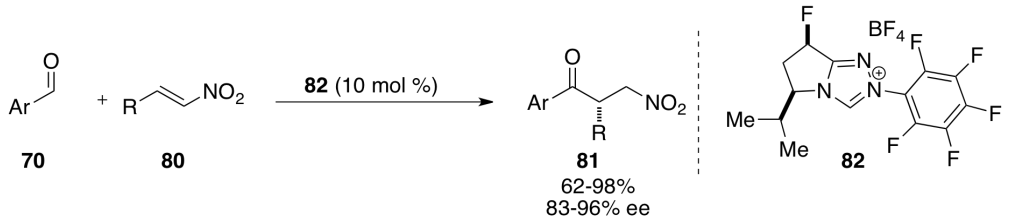
This reaction was further developed to generate contiguous stereocenters in a highly enantio- and diastereoselective manner. It was hypothesized that a highly diastereoselective protonation event would result in a second stereocenter if the two activating carbonyls are different **78** (Scheme 14). The resultant stereocenter would have been difficult to maintain under the basic reaction conditions but high diastereoselectivities were attributed to the tertiary amide which insulated the stereocenter due to $A_{1,3}$ strain. The use of alkylidene ketoamides **78** with glyoxamide **74** under the mediation of precatalyst **77** leads to the desired Stetter product **79** in 68-97% yield and 81-97% ee and high diastereoselectivity (Scheme 14).[39]

Scheme 14.



The above studies, although inherently limited to glyoxamide **74** as the sole nucleophile, provide insight that electron-deficient aldehydes and more activated Michael acceptors provide higher yields with the triazolium catalysts. Efforts were then directed at utilizing nitroalkenes **80** as electrophiles and heteroaryl aldehydes as nucleophiles **70** (Scheme15). Rovis and coworkers found that triazolium salts **83** (Scheme 15) derived from the pyrrolidine series **42** bearing the electron deficient pentafluorophenyl group are necessary to obtain reactivity. A sterically demanding substituent such as an *iso*-propyl group is also necessary to obtain moderate enantioselectivity (Scheme 15). Further modification of the pyrrolidine core **50** with a fluorine provides optimal reactivity and selectivity. Upon synthesis of both diastereomers, it was identified that the cis-diastereomer provides the β-nitro ketone in 95% yield and 95% ee while the trans only provides the product in 22% yield and 88% ee. The difference in selectivity between diastereomers is currently hypothesized to arise from a conformational pucker (exo/endo) induced via a stereoelectronic effect. The scope of the reaction is restricted to heteroaromatic aldehydes **70** while a variety of aliphatic substituents can be tolerated on the nitroalkene **80** (Scheme 15).[40]

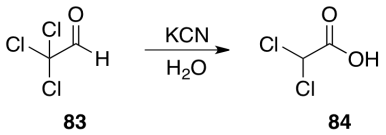
Scheme 15.



1.5 Redox Reaction

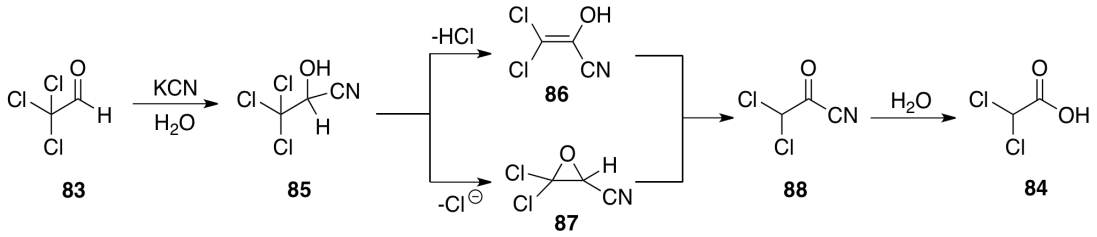
In 1873, Wallach reported the conversion of chloral **83** to dichloroacetic acid **84** in the presence of aqueous potassium cyanide (Scheme 16).[41] The net process is an internal redox reaction, wherein one functionality gets reduced while a second is oxidized.

Scheme 16.



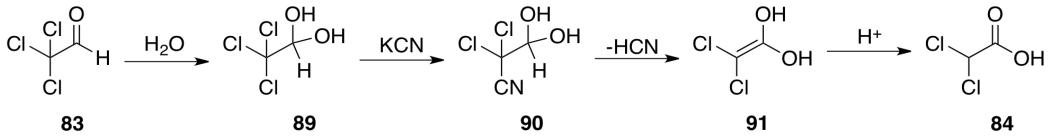
Kötz offered the first mechanistic proposal to explain this unusual transformation.[42] Upon cyanohydrin formation **85** two pathways were identified leading to intermediate **86** or **87**. Intermediate **86** can be envisioned to arise via elimination of HCl to generate nucleophilic enol **87**, which can tautomerize to afford the acyl cyanide **88**. On the other hand, intermediate **87** can arise from cyanohydrin **85** via nucleophilic displacement of a chloride followed by a hydride shift to result in formation of the acyl cyanide **88**. Hydrolysis of the acyl cyanide **88** would liberate cyanide and afford the carboxylic acid **85** (Scheme 17).

Scheme 17.



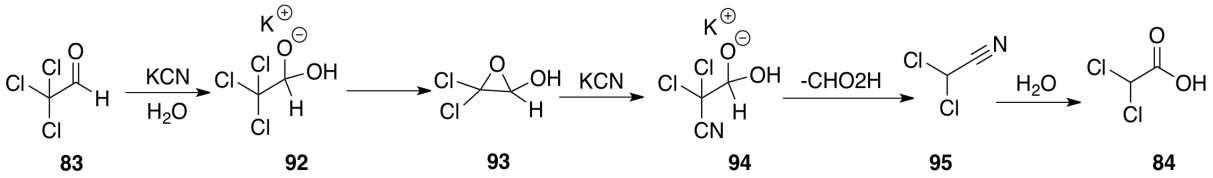
Future mechanistic work focused on validating or dismissing the proposal put forth by Kötz. In 1929, Chattaway and Irving proposed that cyanohydrin **85** was not necessary for the reaction to occur thus implicating the reaction did not proceed via an acyl anion equivalent. Their proposal relied on formation of hydrate **89**, followed by cyanide displacement of chloride to furnish intermediate **90**, which loses HCl to generate enol **91**. Enol **91** can then tautomerize to produce dichloroacetic acid (Scheme 18).[43] Lapworth who had previously demonstrated the necessity for cyanohydrin **17** formation in the benzoin reaction (Scheme 1) quickly rejected this hypothesis suggesting that the reaction should proceed via an acyl anion equivalent.[44]

Scheme 18.



In 1958, Cram and Hammond put forth a proposal suggesting formation of intermediate epoxide **93** formed via an intramolecular chloride displacement from hydrate **92** as an alternative to the initial formation of cyanohydrin **85** and acyl anion equivalent.[45] The epoxide undergoes nucleophilic opening by cyanide ion to generate **94**, which can disproportionate to produce dichloroacetonitrile **95** and formic acid, with the former undergoing hydrolysis to produce product **84**.

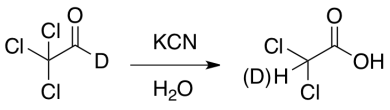
Scheme 19.



Studies conducted by Rosenblum and coworkers discounted this hypothesis by conducting studies with ^{14}C labeled cyanide where they observed insignificant isotopic effects, suggesting that the proposal put forth by Cram and Hammond is inoperative.[46]

Thus, formation of cyanohydrin **85** was identified as a requisite at the onset of the reaction. Whether epoxide **87** was generated leading to acyl cyanide **88**, via a speculative hydride shift was next addressed. In 1961, Katritzky ruled out the possibility of a 1,2-hydride shift as proposed by Kötz in the formation of intermediate **88** (Scheme 17), by subjecting deuterium labeled chloral **96** to aqueous cyanide conditions only to observe 90% proteo incorporation at the α-position of the acid **84** (Scheme 20), suggesting a hydride shift was inoperative and implicating path a (Scheme 17) as the viable process.[47] The currently accepted mechanism for the cyanide catalyzed α-redox reaction is that proposed by Nowak, which is analogous to the proposal put forth by Kötz.

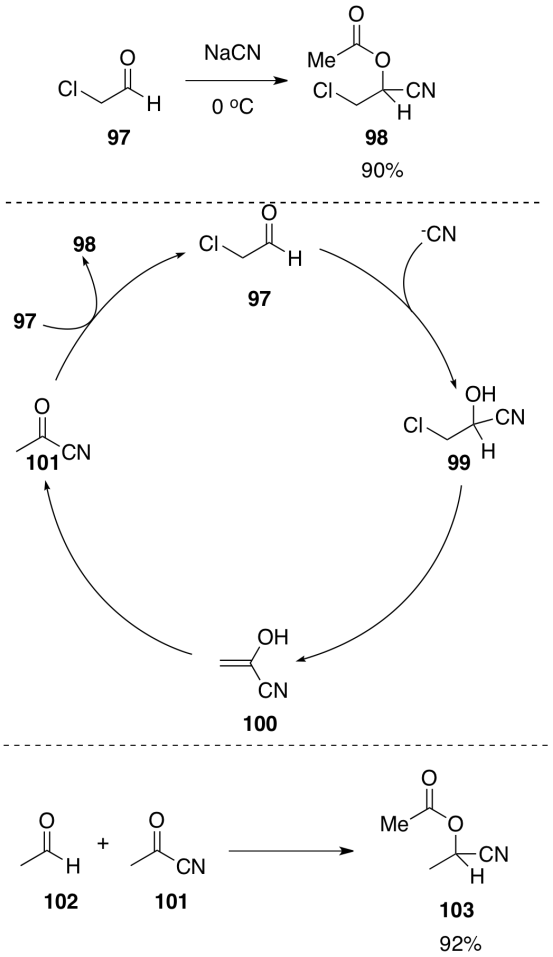
Scheme 20.



H incorporation >90%

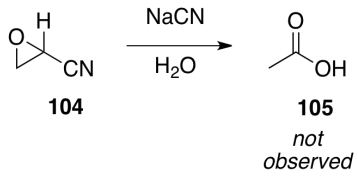
In 1963, Nowak reported the conversion of chloroacetaldehyde **97** to 2-chloro-1-cyanoethyl acetate **98** in the presence of aqueous cyanide (Scheme 3).[48] Nowak proposed the mechanism to proceed via formation of cyanohydrin **99** followed by net loss of HCl to generate enol **100** and subsequent tautomerization furnishes acyl cyanide **101**. The acyl cyanide is then hydrolyzed with **97** to produce **98**. The formation of acyl cyanide **101** as an intermediate was validated upon addition of cyanoacetate **101** to an aqueous solution of acetaldehyde **102** and sodium cyanide, which provided 1-cyanoethyl acetate **103**, implicating that the process proceeds via an acyl cyanide (Scheme 3).

Scheme 21.



Further investigation into the formation of epoxide **87** (Scheme 17), glycidonitrile **104** was subjected to aqueous cyanide with no observation for the formation of acetic acid **105** (Scheme 21), implicating epoxide **87** not to be a viable intermediate in the redox process, and that enol **86** is more likely (Scheme 17).

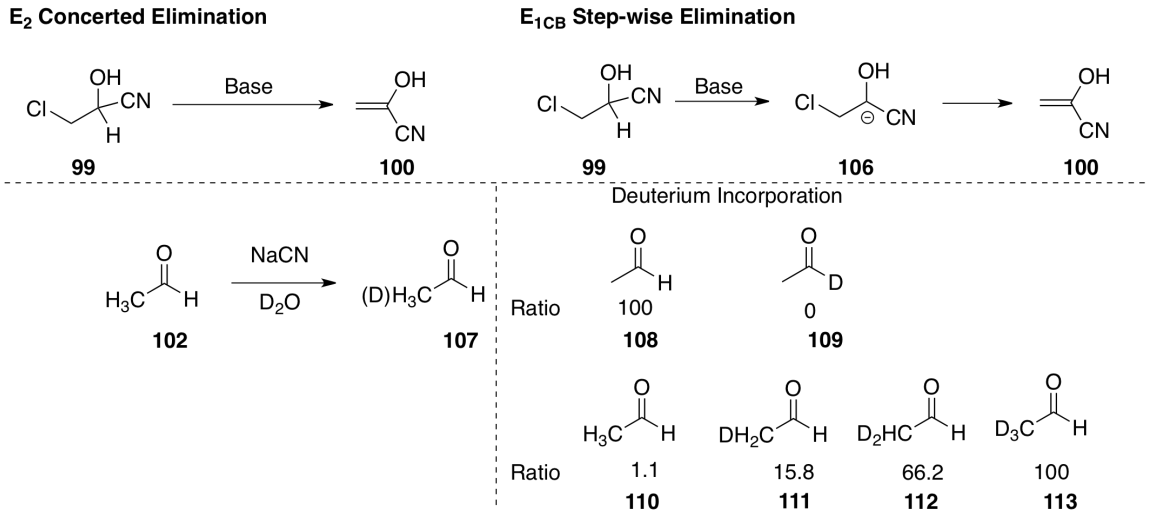
Scheme 22.



104 **105** *not observed*

Loss of HCl upon formation of cyanohydrin **85** leading to enol **86** can proceed by either an $E1_{CB}$ or an E_2 process (Scheme 23). In order to discern which process was operative, Nowak subjected acetaldehyde to sodium cyanide in D_2O (Scheme 23) only to observe a mixture of deuterium incorporation at the α-carbon but no deuterium incorporation at the aldehydic carbon, suggesting the formation of acyl anion to be rapid and non reversible.

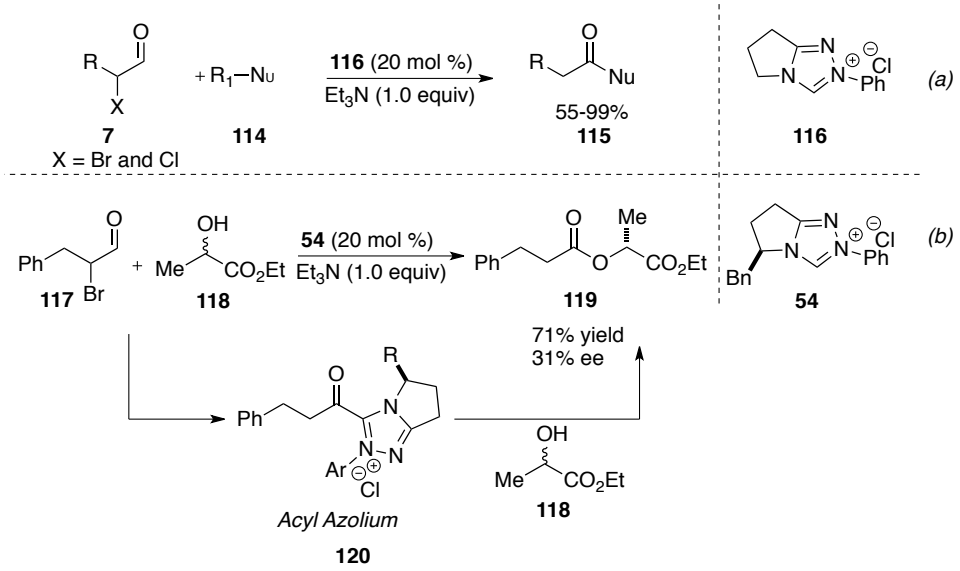
Scheme 23.



131 years after the publication by Wallach, interest in the redox reaction was renewed by the advent of *N*-heterocyclic carbenes in catalyzing such processes, where acylation using these intermediates would constitute an example of redox economy.[49]

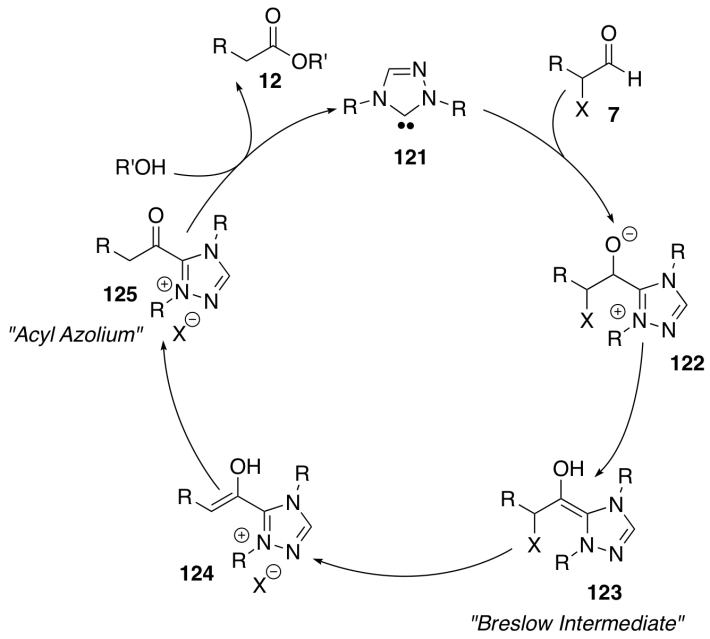
In 2004 Rovis[50] and Bode[51] independently and concurrently reported the use of *N*-heterocyclic carbenes with α-reducible aldehydes and alcohols to furnish esters. Resurgence in the development of α-halogenation of aldehydes **7** led to their use as substrates with alcohols **114** as nucleophiles by Rovis and coworkers (Scheme 24, a). Investigation of the leaving group reveals that bromide is more facile to eliminate than chloride with a variety of alcohols participating in the acylation process. Enantioenriched ethyl lactate may also be used in the acylation process, which proceeds with minor epimerization; while the use of racemic lactate **118** with chiral carbene **54** occurs with enantioenrichment suggesting acylation occurs on the acyl azolium **120** (Scheme 24, b).

Scheme 24.



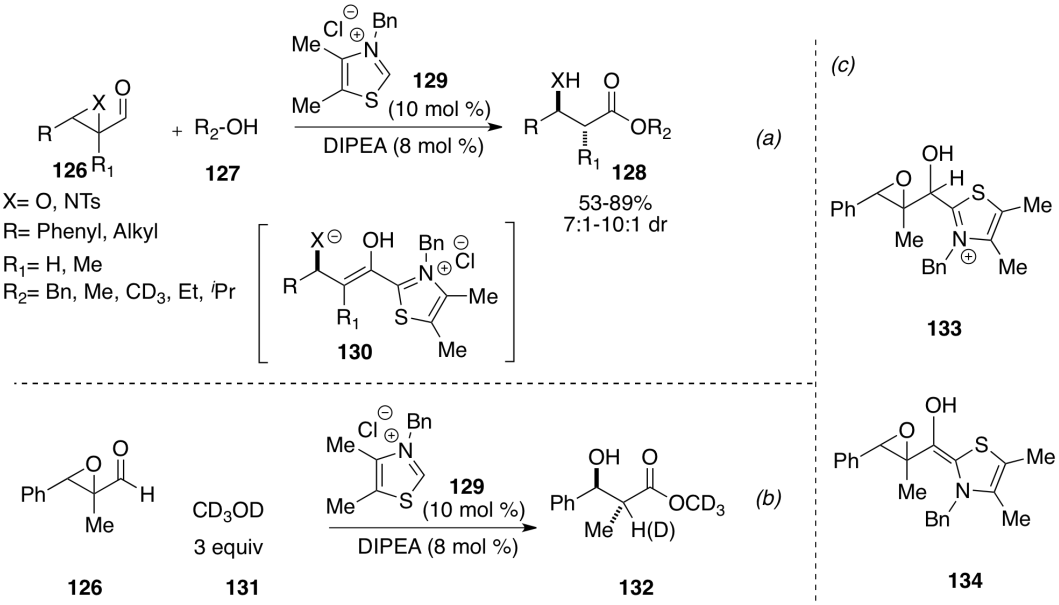
The mechanism is thought to proceed via deprotonation of the azolium salt to generate the nucleophilic carbene **121.** Addition of the nucleophilic carbene to the aldehyde **7** furnishes tetrahedral intermediate **122**. Intermolecular proton transfer provides the acyl anion equivalent or Breslow intermediate **123**, followed by loss of the leaving group to generate nucleophilic enol **124**. Tautomerization of enol **124** furnishes the acyl azolium **125** which is intercepted by alcohol to provide the ester **12** and regenerate carbene **121** (Scheme 25).

Scheme 25.



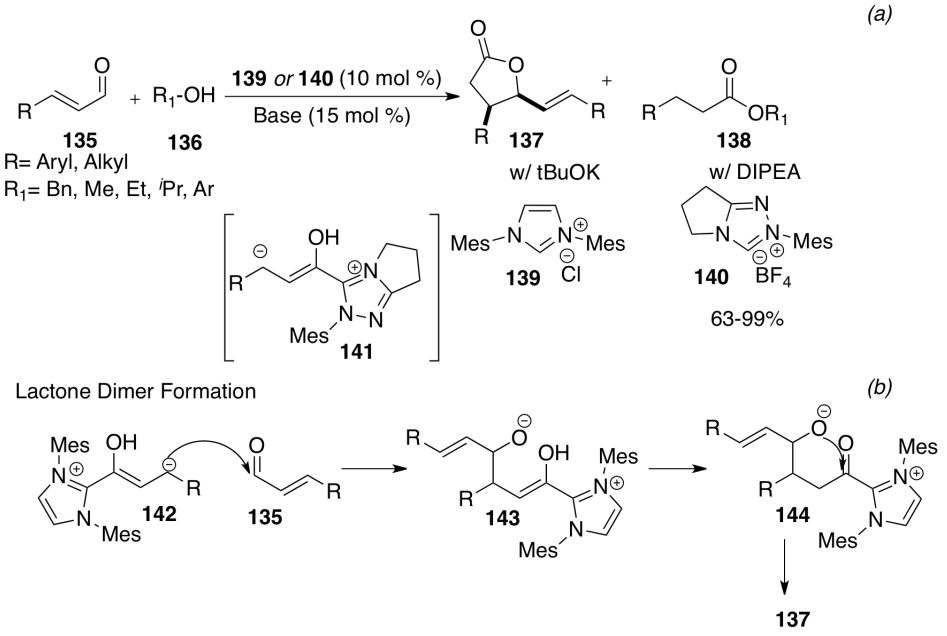
Bode and coworkers have shown that epoxy aldehydes **126** are viable substrates in the NHC redox reaction with a variety of alcohols **127** indentified as competent nucleophiles to furnish β-hydroxy esters **128** (Scheme 25, a). Mechanistic investigation into the redox process revealed a hydride mechanism is not operative based on subjection of substrate **126** to deuterated methanol **131** and termination of the reaction at 50% conversion furnishing the product with 50% deuterium incorporation **132** (Scheme 25, b). Inspection of the recovered starting material shows no deuterium at the aldehydic carbon suggesting an E_2 mechanism may be operative (Scheme 25, C). Since the two initial reports by Rovis and Bode, the carbene catalyzed redox process has been developed to include other α-reducible aldehydes such as enals, ynals, and cyclopropyl carboxaldehydes which participate in the esterification process.

Scheme 26.



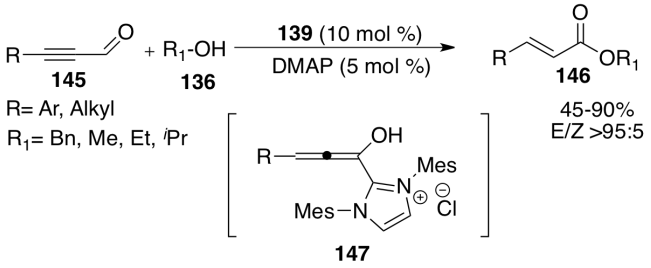
Bode[52] and Scheidt[53] have independently shown that enals in the presence of imidazolium salt **139** or triazolium salt **140** can either generate a lactone dimer **137** or saturated ester **138** upon choice of reaction conditions (Scheme 27, a). The use of a strong base such as *tert*-butoxide leads to generation of the lactone dimer **137** which arises from the nucleophilic addition of the homoenolate **142** to another equivalent of aldehyde **135** (Scheme 27, b), presumably due to an inefficient proton source (pKa of *t*-butanol = 29.4 in DMSO); however, when a base whose conjugate acid is sufficiently acidic is employed, one obtains the protio-acylation product **138** (pKa of $^{i}Pr_2EtNH^{+}$= 13 in THF). A variety of alcohols **136** are tolerated in the reaction to produce the saturated esters in 63-99% yield (Scheme 27, a).

Scheme 27.



The synthesis of (E)-α,β-unsaturated esters **146** can also be accomplished via redox esterification of propargylic aldehydes **145**. Zeitler has identified imidazolium salt **139** to be efficient in this process in the presence of DMAP as the base to furnish high levels of *E:Z* selectivity (typically >95:5) (Scheme 28).[54] A variety of alcohols **136** participate in the reaction and aromatic, heteroaromatic, and aliphatic substituents are tolerated on the propargylic aldehyde to provide the ester in suitable yields 45-90% (Scheme 28).

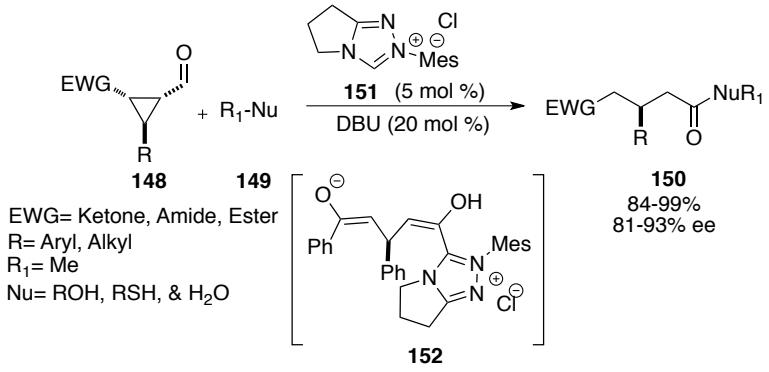
Scheme 28.



Recently, Bode and coworkers have been able to observe the acyl azolium generated in this process and study its intrinsic reactivity with nucleophiles other than alcohol, and they observe that nitrogen centered nucleophiles are less competent in the acylation process.[55]

Bode has also found that formylcyclopropanes **148** are competent in the *N*-heterocyclic redox esterification with a variety of nucleophiles including alcohols, thiols, and water (Scheme 29). Subjection of the chiral substrates under optimized reaction conditions with precatalyst **151** proceeds with minor epimerization to furnish the 1,5 dicarbonyl adducts **150** in good yields of 84-93% (Scheme 29).[56]

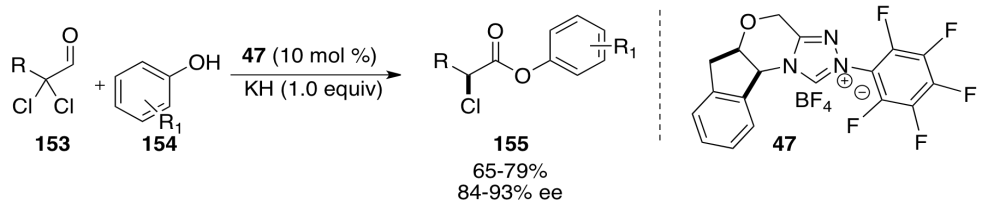
Scheme 29.



Rovis and Reynolds also reported the synthesis of enantioenriched α-chloro aryl esters by the treatment of α,α-dichloro aldehydes **153** with phenols **154** in the presence of chiral NHC precursor **47** via an asymmetric protonation.[57] Generating the potassium phenoxide with KH and 18-crown-6 provides the desired product in 75% yield and 81% ee. The additional use of 2,6-dibromo-4-methyl phenol provides a reservoir for the base, minimizing epimerization, leading to the product in 79% yield and 92% ee. A variety of α,α-dichloro aldehydes participate in the reaction to provide the respective esters in 65-

79% yield and 84-93% ee (Scheme 30), with the current limitation being β-branching on the aldehyde.[58] A variety of substituted phenols work in the reaction which provides distinct advantages and complementarity to other methods generating enantioenriched α-chloro aryl esters.[59]

Scheme 30.



The aforementioned examples primarily relate to the electrophilic trapping of a proton in the redox reaction. The extent of work conducted in this area has primarily identified alcohols as the most competent nucleophiles with fewer reports of amines, thiols, and water participating in this process.

1.6 Conclusion

The advent of NHC catalysis and its application to umpolung processes has allowed for the development of asymmetric transformations in the benzoin and Stetter and α-redox reactions. In turn the use of NHCs in the development of the aforementioned reactions has led to the development of novel carbene precursors which in turn have provided insight into the stability and reactivity associated with nucleophilic carbenes.

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Chapter 2

N-heterocyclic Carbene Catalyzed Synthesis of Amides

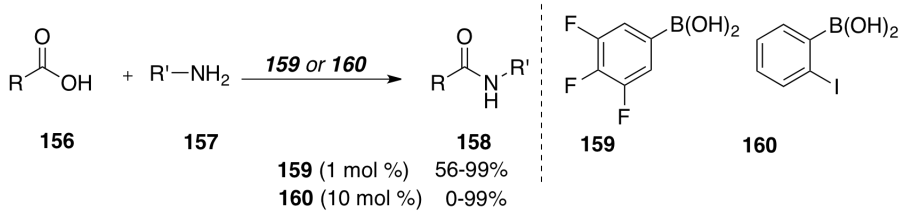
2.1 Introduction

Amides are an ubiquitous functional group found in important medicinal and biological molecules. A survey conducted in 2007 by the ACS Green Chemistry Institute among leading pharmaceutical companies identified "amide formation avoiding poor atom economy reagents" as a pivotal challenge facing the synthetic community.[1] Additionally, a recent survey described that one out of twelve reactions conducted towards the synthesis of pharmaceutical agents is formation of an amide bond.[2] Despite this need, direct amide bond formation still relies on the dehydrative activation of a carboxylic acid to generate an activated acyl intermediate, which reacts with an amine to furnish an amide.[3] This type of activation typically requires stoichiometric reagents and can generate substantial quantities of waste considering that it only facilitates the elimination of water. Moreover, the significance and limitation associated with catalytic amide bond formation has been recently reviewed.[4] Thus the synthetic community has strived to provide waste reduced solutions and identification of novel methods to generate amide bonds from different functional groups.

2.2 Catalytic Synthesis of Amides

Catalytic amide bond formations from carboxylic acids and amines have been realized though the use of catalytic electron deficient boronic acids. Yamamoto's[5] seminal report (Scheme 1) followed by the work of Hall[6] (Scheme 1), have provided a catalytic solution to amide bond formation where the only byproduct is water. Yamamoto identified boronic acid **159** as a capable catalyst in the coupling of aromatic and aliphatic carboxylic acids **156** with primary and secondary amines **157** to afford amides **158** in 56-99% yield. The major limitation with his process is the requirement for Dean-Stark conditions in facilitating the removal of water. Alternatively, Hall identified *ortho*-iodophenylboronic acid **160** to facilitate the same process with 4 Å molecular sieves providing milder reaction conditions with longer reaction times.

Scheme 1.

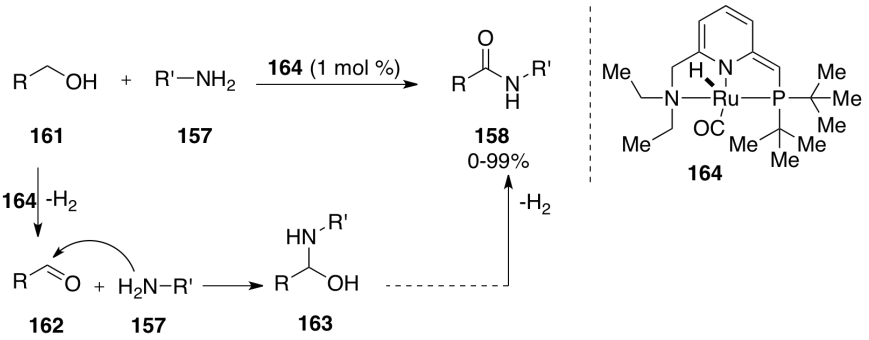


Recently, a computational study conduct by Marcelli has concluded that the catalytic activity of ortho-halophenylboronic acids was attributed to the Lewis basicity of the halogen in engaging in an O-H···X hydrogen bond, which aids in stabilizing the transition state.

In 2007, Milstein and coworkers identified a Ru- pincer complex **164,** which promotes the coupling of alcohols and amines to furnish amides with the extrusion of hydrogen (Scheme 2).[7] The reaction proceeds via dehydrogenation of the alcohol mediated by the Ru hydride **164** to afford the corresponding aldehyde **162** followed by

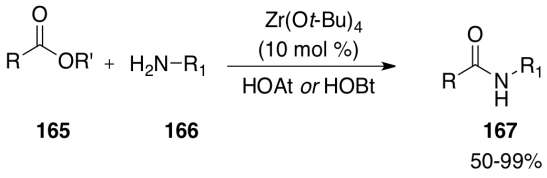
hemiaminal formation **163** with the amine **157**. **163** reacts with complex **164** leading to an intermediate which undergoes β-hydride elimination to afford the amide **158** and generates the *trans*-Ru dihydride complex. Elimination of dihydrogen regenerates catalyst **164**. The reaction is sensitive to sterics around the amine as α-branched amines provide the amide in low yields.

Scheme 2.



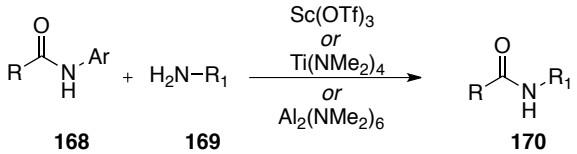
Additionally, amides can be obtained catalytically from esters using group IV metal complexes. Porco and coworkers identified that a range of esters and amines can be coupled in the presence of HOAt or HOBt as an additive and Zr(O*t*-Bu)$_4$ in catalytic amounts to furnish the amide in excellent yields.[8]

Scheme 3.



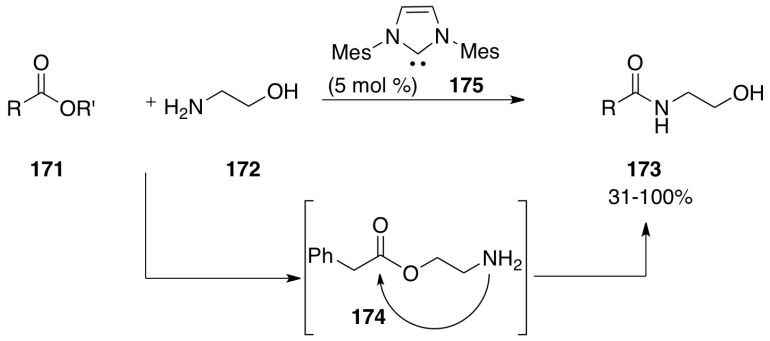
Moreover, Stahl and coworkers have reported a trans-amidation process catalyzed by Lewis acids such as Sc(OTf)$_3$, Ti(NMe$_2$)$_4$, and Al$_2$(NMe$_2$)$_6$. They identified that aryl amides **168** are susceptible to exchange with aliphatic and aromatic amines **169** in the presence of these Lewis acids providing the amide **170** in good yields (Scheme 4).[9]

Scheme 4.



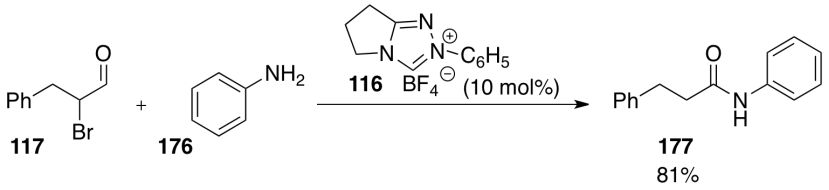
Amino alcohols **172** also participate to furnish amides **173** from esters **171** in the presence of catalytic NHC **175** as described by Movassaghi and co-workers. Trans-esterification of the aminoaclohol with the ester provides **174,** which provides the amide via an O-N acyl transfer with the NHC acting as a Lewis base.[10]

Scheme 5.



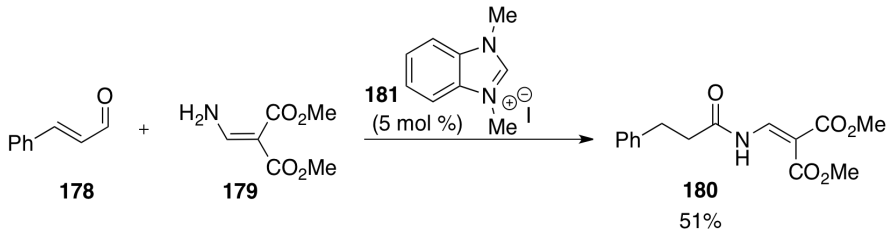
The development of catalytic amidations from aldehydes has been limited compared to the synthesis of amides from carboxylic acids and esters. The oxidative coupling of aldehydes and primary amines to yield amides is reported to be catalyzed by an assortment of metals including, Cu,[11] Pd,[12] Rh,[13] Ru,[14] and lanthanide[15] complexes. Reports of non-metal catalyzed amidation processes with aldehydes are few and far between. The use of amines as nucleophiles in the NHC catalyzed α-redox processes have been met with disappointment. Rovis and Scheidt have independently reported amide bond formation with NHCs and α-reducible aldehydes. In 2004, Rovis and coworkers identified that in the presence of 10 mol % of NHC **116**, α-bromo aldehydes and aniline provide the amide in 81% yield (Scheme 6).[16]

Scheme 6.



Scheidt and coworkers identified NHC **181** in the presence of *trans*-cinnamyl aldehyde **178** and β-amino alkylidene malonate **179** to afford the amide in 51% yield.[17] Outside these two examples the NHC catalyzed α-redox amidation has met with little success.

Scheme 7.



2.3 Plan of Investigation

It was speculated that the inherent lack of amines to participate in the amidation reaction was their inability in the breakdown of the acyl azolium **125**. The decomposition of acyl azoliums derived from thiazolylidene **181**, imidazolylidene **182**, and triazolylidene carbenes **183** are more susceptible to hydrolysis by alcohols, thiols and water than with amines (Figure 1).[18]

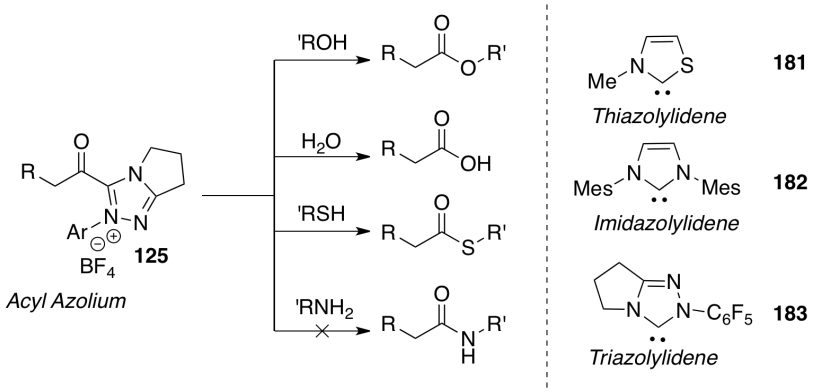
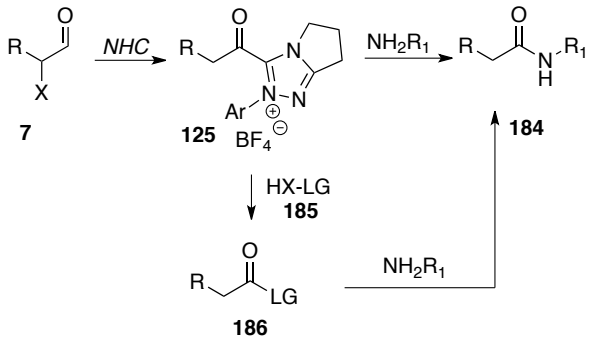


Figure 1.

As alcohols had been shown to participate in the α-redox reaction with great proficiency it was hypothesized that the addition of nucleophilic additives or cocatalyst such as O-protic or N-protic nucleophiles **185** could be introduced in the amidation reaction to facilitate acyl transfer upon generation of the acyl azolium **125** to furnish **186** (Scheme 8). Subsequent breakdown of the acyl additive intermediate **186** by the amine can provide the amide.

Scheme 8.

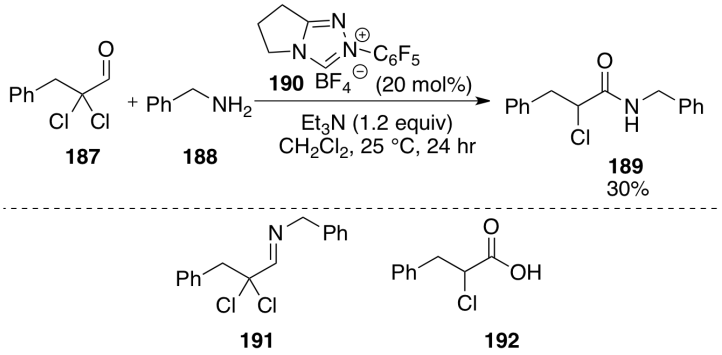


2.4 Synthesis of α-chloro amides.

Investigations into the amide bond forming process began with α,α-dichloroaldehydes as the reducible aldehyde **187**, benzyl amine as the nucleophile **188**, and NHC **190** to provide the benzyl amide **189** in 30% yield. Additional products arising

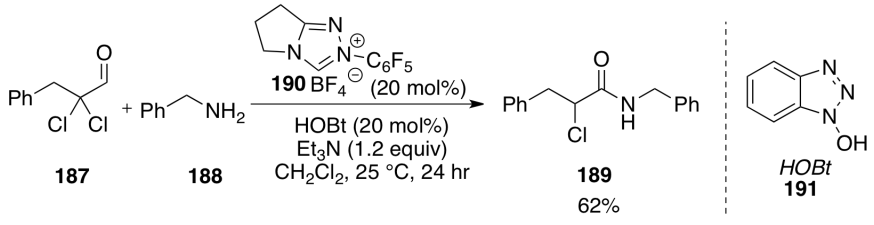
from the reaction were imine formation and hydration products, the latter occurring from the redox reaction with water participating as the nucleophile (Scheme 9).

Scheme 9.



This approach was validated with our studies involving HOBt **191** as a nucleophilic cocatalyst (Scheme 10). The reaction conducted under identical conditions with HOBt **191** provided the respective amide **189** in 62% yield, albeit still providing imine and hydration product (Scheme 10). To confirm if the hydration product was arising from the extrusion of water during imine formation, special care was taken to ensure all reagents were anhydrous prior to use. The reaction conducted under anhydrous conditions also provided the acid suggesting water generated from imine formation was responsible for the formation of carboxylic acid. It also suggested that under the reaction conditions imine formation was not reversible.

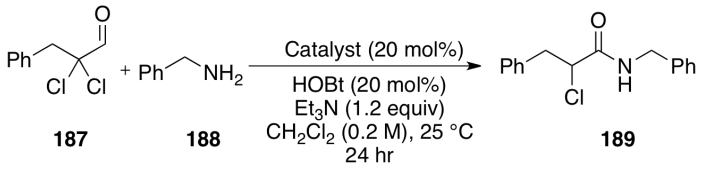
Scheme 10.



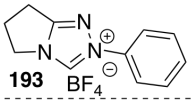
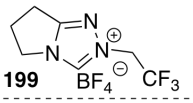
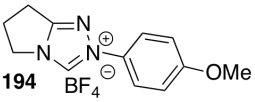
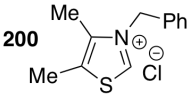
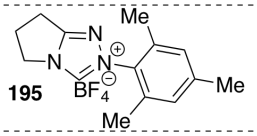
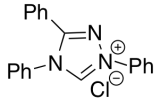
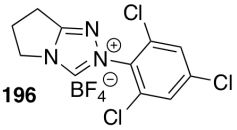
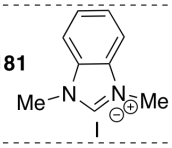
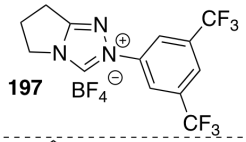
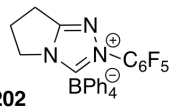
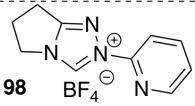
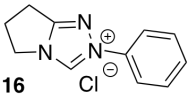
Encouraged by this initial result, the effect of different catalysts on the reaction was surveyed. It was readily identified that electron deficient triazolium salts **196** and **197** were more efficient than electron rich triazolium salts **193**, **194**, **195** and **199** in

affording the desired product (Table 1). This disparity in reactivity can be attributed to a more electrophilic acyl azolium providing a more efficient acyl transfer. However, to ensure that the lower yields of amide attributed with electron rich triazolum salts **193**, **194**, **195** and **199** did not correspond to a lack of deprotonation by triethylamine, the reaction was conducted with a stronger base such as DBU, nonetheless providing the amide in similar yields. The counterion was also modified (**202** and **116)** to test its effect on the reaction, albeit with no improvement in yield.

Table 1.



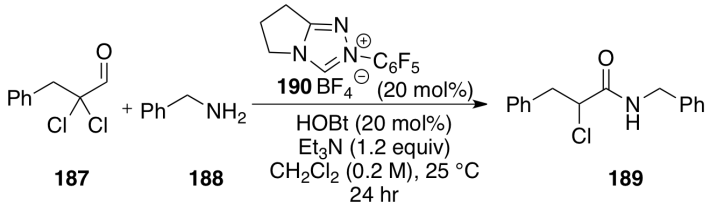
187 **188** **189**

entry	catalyst	yield (%)	entry	catalyst	yield (%)
1	 **193**	48	7	 **199**	13
2	 **194**	32	8	 **200**	47
3	 **195**	41	9	 **201**	53
4	 **196**	63	10	 **181**	40
5	 **197**	51	11	 **202**	64
6	 **198**	24	12	 **116**	52

Identifying triazolium salt **190** to be the most efficient precatalyst, the effect of concentration was next examined. The reaction relied on slow addition of the amine to

suppress imine formation. It was found that a concentration of 0.5 M was ideal and allowed for the addition of the amine over a period of 2 hours. Having identified a suitable concentration the effect of solvent was next examined.

Table 2.

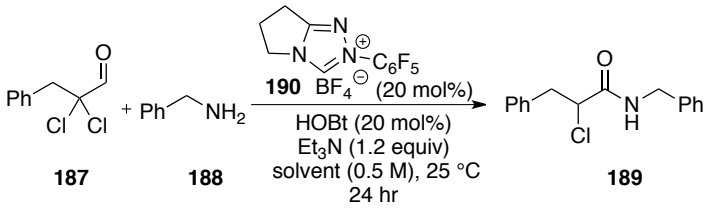


187 **188** **189**

concentration (M)	yield (%)
0.02	64
0.01	68
0.50	78
0.20	62

A survey of non-polar and polar solvents revealed that non-polar solvents typically provided the amide with higher yields while polar solvents and protic solvents provided the amide with lower yields. It should be noted that when the reaction was conducted in acetonitrile no amide, imine, or hydration products were observed.

Table 3.

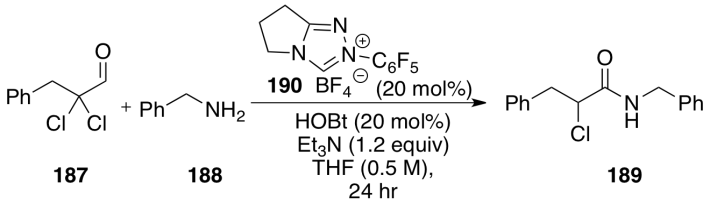


187 **188** **189**

entry	solvent	yield (%)
1	hexanes	70
2	toluene	68
3	diethlyether	40
4	methyl-t-butylether	54
5	tetrahydrofuran	92
6	dioxane	88
7	dichloroethane	74
8	dimethyl formamide	31
9	*N*-Methyl pyrrolidone	27
10	dimethylsulfoxide	NR
11	acetonitrile	NR

The effect of temperature on the reaction was studied next to reveal that at 0 °C the redox reaction was inoperative. Additionally, elevated temperatures only provided greater quantities of imine and hydration products (Table 4).

Table 4.



T (°C)	yield (%)
0	NA
40	86
60	64

The use of α,α-dihalo aldehydes in the redox process requires stoichiometric or super stoichiometric base to sequester HCl generated during the reaction. The conjugate acid generated from this process can have a profound effect in the ease with which the nucleophilic enol **203** can be protonated to furnish the acyl azolium **204**, thus expediting the catalytic process (Figure 2).

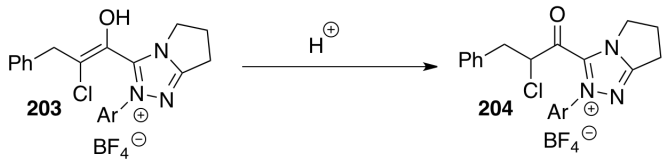
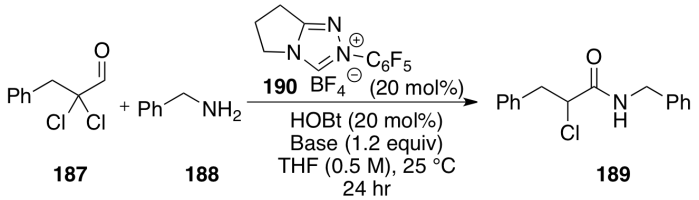


Figure 2.

The base screen revealed that reactions conducted in a basic medium producing a weak conjugate acid furnished greater percentage of imine and hydration products. When an acidic conjugate acid is generated, an equilibrium can be established between the conjugate acid and the amine favoring the thermodynamic weakly acidic proton donor. The base screen revealed that triethylamine (entry 1, Table 5) and diisopropylethyl amine (entry 2, Table 5) provide the desired product in 89-92% yield.

Table 5.

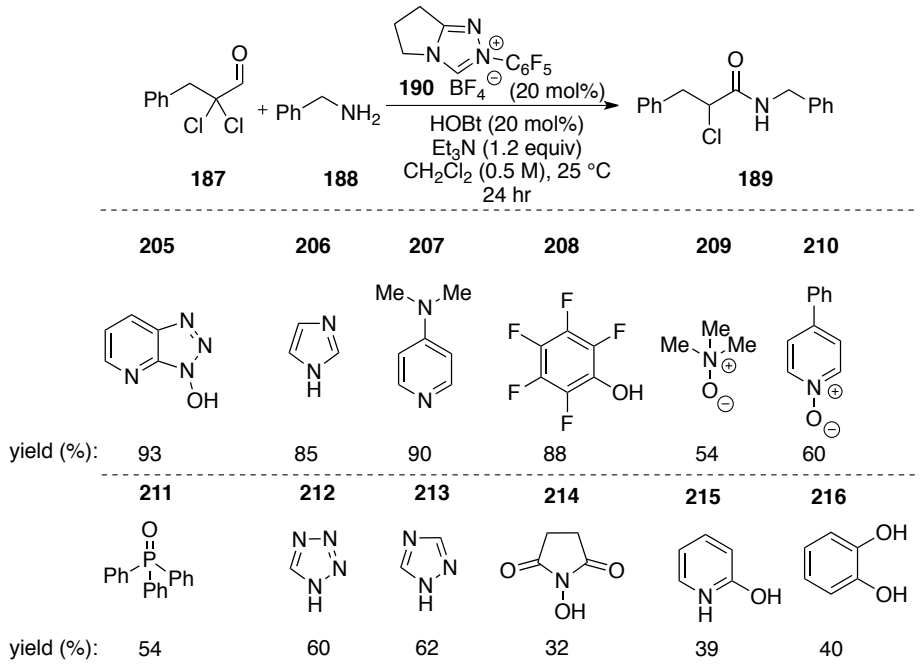


187 188 189

entry	Base	yield (%)
1	Et_3N	92
2	DIPEA	89
3	Pyridine	74
4	Proton Sponge	61
5	DABCO	78
6	Quinuclidine	67
7	DBU	54

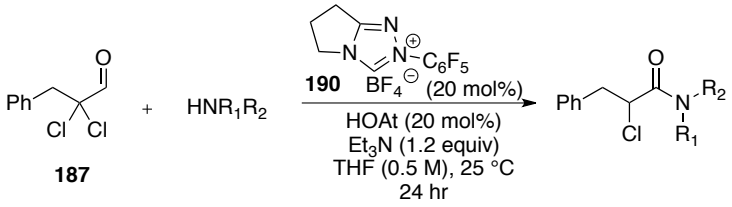
Having identified optimized conditions, cocatalysts commonly used in C-N amide bond formations were examined. It was clear that a variety of cocatalyst were apt at facilitating C-N bond formation providing the amide in good yields. However, O-protic additives **205** and **208** generally provided the amide in higher yields than *N*-protic additives **206**, **212**, and **213**. Additionally, *N*-oxides **209** and **210** and phosphine oxide **211** was also identified as a less competent acyl transfer reagent. Thus, HOAt and HOBt were identified as the most competent acylation transfer reagents for α,α-dichloro aldehydes, as the amide product were obtained in 93 and 92% yield respectively (Scheme 11).

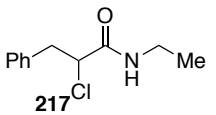
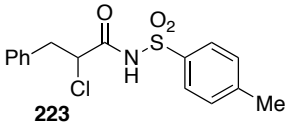
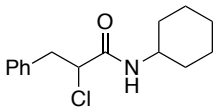
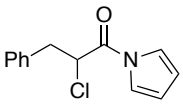
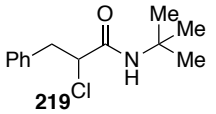
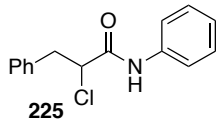
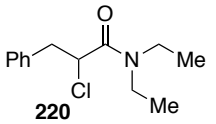
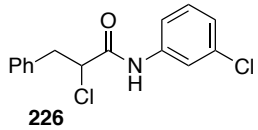
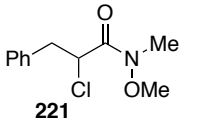
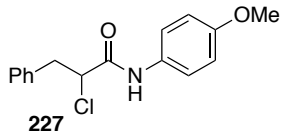
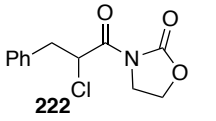
Scheme 11.



Amines were examined next with α,α-dichloro aldehydes under the optimized reaction conditions. A plethora of amines are competent in the acylation process with aliphatic primary and secondary amines providing amides in good to excellent yields 73-89% (entry 1-4, Table 6). Aryl amines also work well as electron withdrawing and releasing groups are tolerated (82-87%, entries 9-11, Table 6). However, pyrrole **224**, oxazolidinone **222**, and sulfonamide **223** do not work under the reaction conditions to afford amide products.

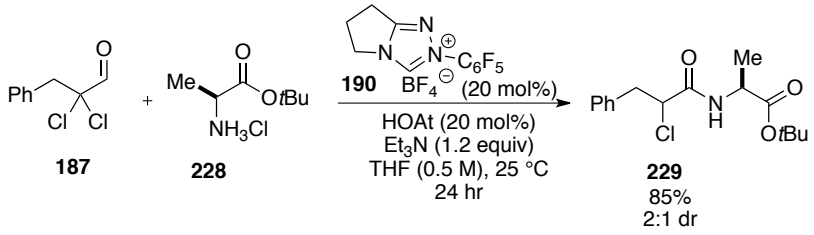
Table 6.



entry		yield (%)	entry		yield (%)
1	 **217**	89	7	 **223**	NR
2	 **218**	85	8	 **224**	NR
3	 **219**	73	9	 **225**	87
4	 **220**	89	10	 **226**	82
5	 **221**	72	11	 **227**	83
6	 **222**	NR			

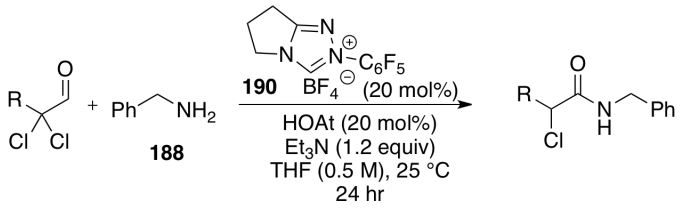
As an extension to the scope of amines, we hypothesized that amine hydrochloride salts should participate as competent nucleophiles in the amidation reaction. When a chiral amino acid ester hydrochloride salt **228** is used, one obtains the amide product with 85% yield and a 2:1 diastereoselectivity. The 2:1 diastereoselectivity is attributed to protonation by the chiral amine.

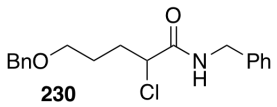
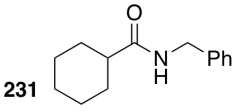
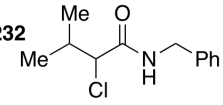
Scheme 12.



The scope of α,α-dichloro aldehydes was investigated with benzylamine as the nucleophile. Benzyloxy ether **230** is tolerated on the backbone 83% yield, along with α,α-dialkyl substitution **231** to afford the product in 80% yield. More interestingly, β,β-disubstitution **232** is tolerated as the amide is obtained in 72% yield.

Table 7.

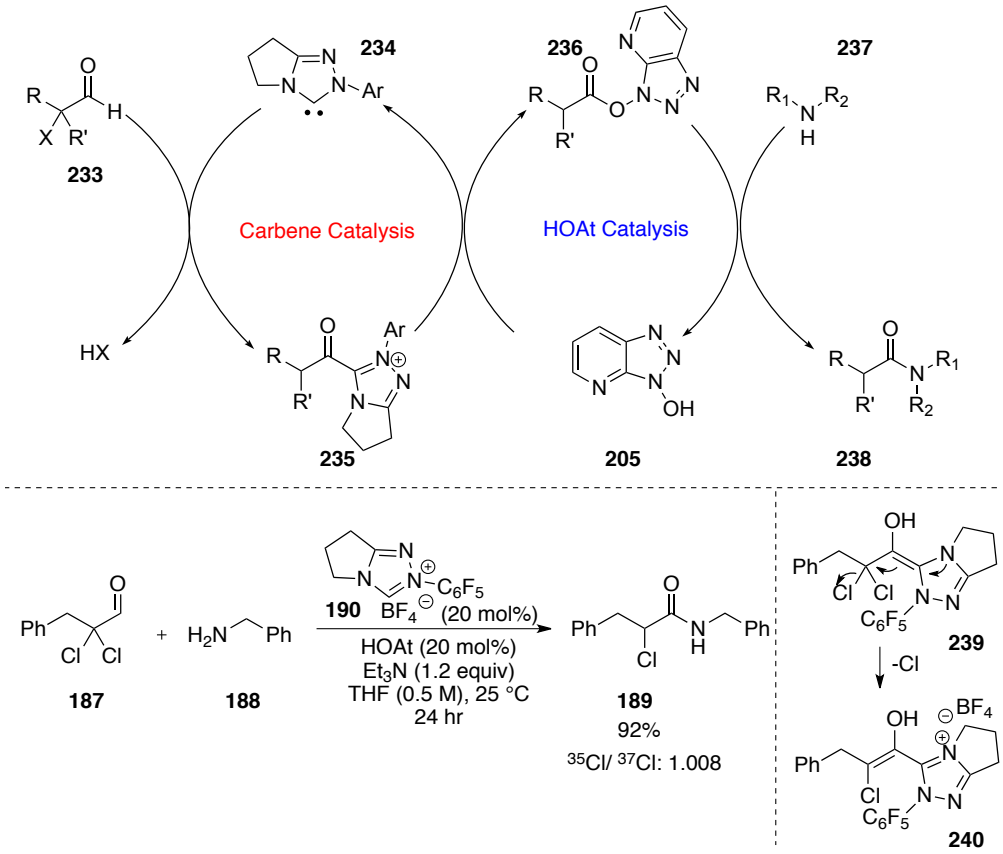


entry	product	yield (%)
1	 **230**	83
2	 **231**	80
3	 **232**	72

Having shown the scope of the α-redox amidation reaction with α,α-dichloro aldehydes, effort was placed on confirming the mechanism of the concurrent tandem catalytic process (Scheme 13). The mechanism of this process proceeds upon addition of

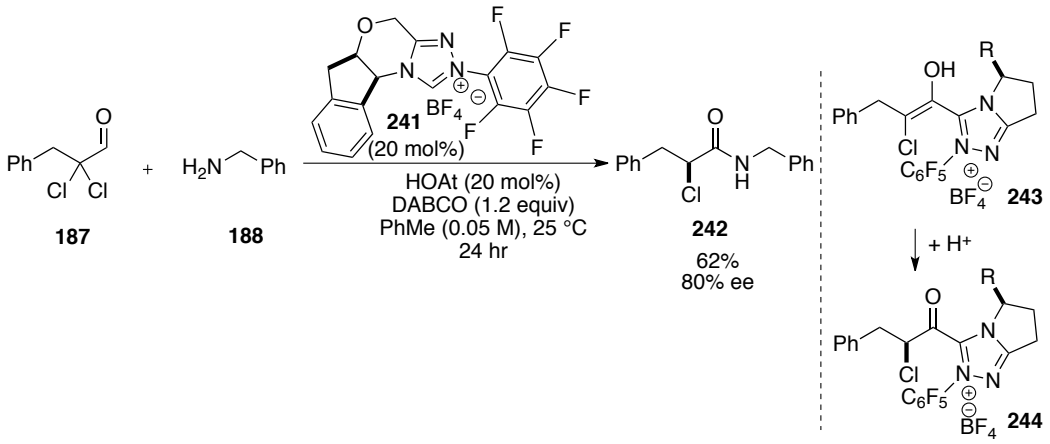
the nucleophilic carbene **234** to the α-reducible aldehyde **233** to provide acyl azolium **235**. The acyl azolium is then trapped with HOAt **205** to provide the imidoyl ester **236**. The HOAt ester is then hydrolyzed by the amine **237** to furnish the amide **238**. Studies into whether the elimination process to furnish enol **240** from the acyl anion equivalent **239** occurs via a concerted E_2 or stepwise $E1_{CB}$ pathway were determined by a chlorine Cl^{35}/Cl^{37} isotope effect. Analysis of the α-chloro amide reveals a primary isotope effect of 1.008 supporting a concerted mechanism. Previous studies utilizing chlorine isotope effects to study concerted elimination pathways implicate primary chlorine isotope effects as responsible for concerted elimination pathways, however, they are not conclusive.

Scheme 13.



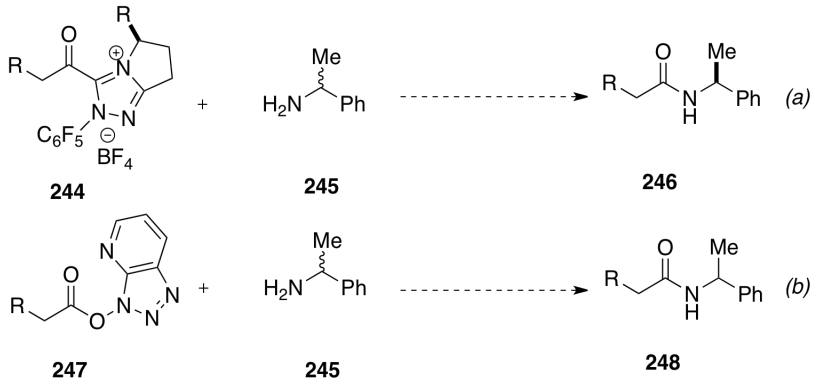
Having shown that the enol **239** (Scheme 13) is presumably generated via a concerted mechanism, confirmation of the carbene on the nucleophilc enol was investigated next. Subjection of chiral carbene **241** in the reaction provides the desired amide **242** in 62% and 80% ee (Scheme 14) implicating the carbene is involved in the enantiodetermining step in protonation of enol **243**.

Scheme 14.



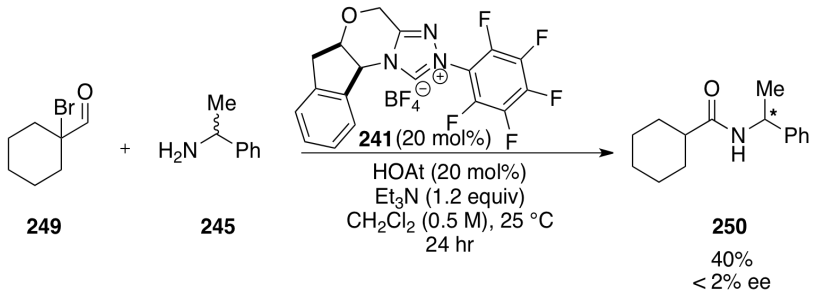
Attempts to identify catalytically generated intermediates **235** and **236** (Scheme 14) by spectroscopic methods were futile. The extent with which N-acylation occurs on the acyl azolium was investigated next. A chiral NHC in conjunction with a racemic amine should provide chiral amide via a kinetic resolution if acylation should occur on the acyl azolium (Scheme 15, a). Alternatively, if acylation should occur on the imidoyl ester **247** the product would be racemic (Scheme 15, b).

Scheme 15.



Chiral NHC **241** in combination with α-bromo cyclohexylcarboxyaldehyde **249** and racemic α-methyl benzyl amine **245** affords the amide product **250** in negligible enantioselectivities. This suggests that acylation takes place on the HOAt ester in preference over the acyl azolium **244**. N-acylation occuring on the HOAt ester was confirmed upon generating the HOAt ester stoichiometrically in 64% yield under the optimized reaction conditions in the absence of amine. Subsequent treatment of the imidoyl ester with benzyl amine provides the desired product in quantitative yield confirming that the HOAt ester is capable of participating in the amide bond forming event.

Scheme 16.



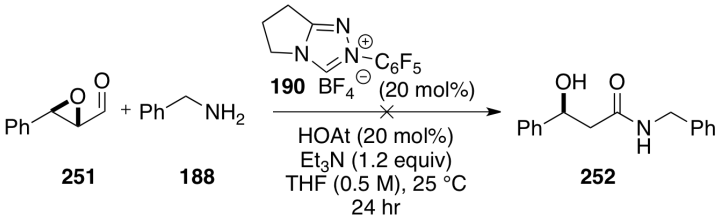
Imine formation still represented a major hurdle, as it consumes both aldehyde and amine and reduces the yield of the desired product. The electrophilicity of the aldehyde and nucleophilicity of the amine has a profound impact on how rapidly the

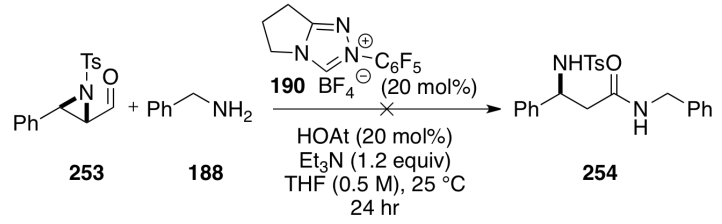
imine is formed. It was hypothesized that the addition of water would allow for the interconversion of imine to aldehyde with the aldehyde subsequently participating in the redox reaction. Addition of water to the reaction to assist in imine hydrolysis only results in formation of hydration product. As imine formation is also facilitated by acid, buffering the reaction was met with little success. To prevent further consumption of aldehyde in the formation of acid we investigated how to suppress water by addition of $MgSO_4$, $MgCl_2$, and 4 A mol sieves. The addition of the dehydrating reagents also did not provide any product and only facilitated imine formation.

2.5 Synthesis of β-hydroxy and β-amino amides and saturated amides

Expanding the scope of the amidation reaction to other reducible aldehydes, the synthesis of β-hydroxy and β-amino amides **252** and **254** from epoxy and aziridinyl aldehydes was investigated. Under the previously developed conditions for the synthesis of α-chloro amides, epoxy aldehyde **251** and aziridinyl aldehyde **253** did not afford any of the respective amide products (Scheme 17). Manipulation of all reaction parameters to facilitate a substoichometirc amidation process failed to provide any product.

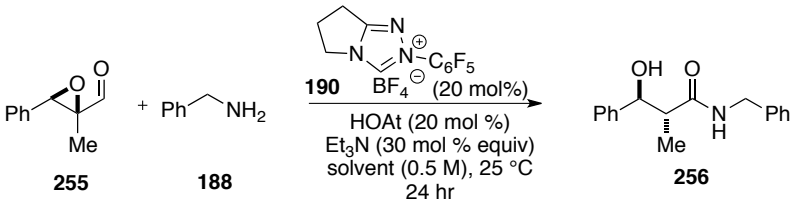
Scheme 17.





Next, a diastereoselective amidation using α-substituted epoxy aldehydes was investigated. Application of previously optimized conditions only provided minor quantities of the desired amide product in moderate diastereoselectivity. A solvent screen revealed that the majority of non-polar and polar solvents provide the product in low dr and moderate yields. However, *t*-BuOH was identified as capable of providing product in 78% yield and 5:1 dr (Table 8).

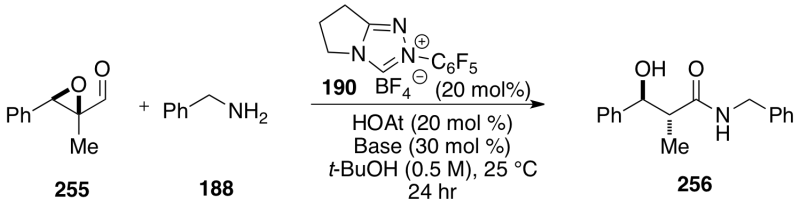
Table 8.



entry	solvent	yield (%)	dr
1	hexanes	25	1:1
2	toluene	40	3:1
3	diethly ether	10	2:1
4	methyl *tert*-butyl ether	31	2:1
5	tetrahydrofuran	44	3:1
6	dioxane	56	3:1
7	dichloroethane	61	1:1
8	dimethyl formamide	39	1:1
9	*tert*-butanol	78	5:1

The effect of the base on yield and diastereoselectivity was next examined. It was difficult to imagine that epimerization was responsible for the low diastereoselectivity. Indeed, we observe that strong bases provide the amide **256** in low diastereoselectivity (entry 6 and 7, Table 9).

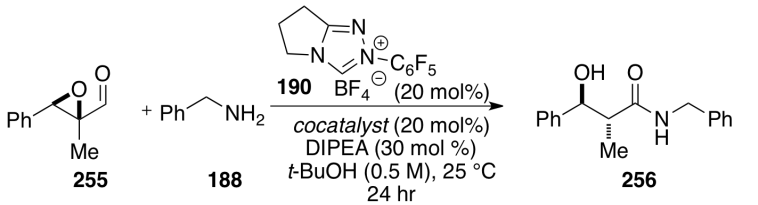
Table 9.

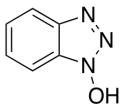
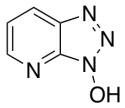
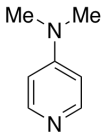


entry	Base	yield (%)	dr
1	Et_3N	78	5:1
2	DIPEA	80	6:1
3	Pyridine	67	2:1
4	Proton Sponge	41	1:1
5	DABCO	73	4:1
6	Quinuclidine	65	3:1
7	DBU	60	1:1

The effect of cocatalyst was next surveyed to see what effect it has on diastereoselectivity. In this case, O-protic cocatalysts provide the product with low diastereoselectivities (Table 10). Alternatively, the use of N-protic cocatalysts provide excellent diastereoselectivities (Table 10). At this time it is not clear why N-protic cocatalysts provide such high levels of diastereoselectivities.

Table 10.

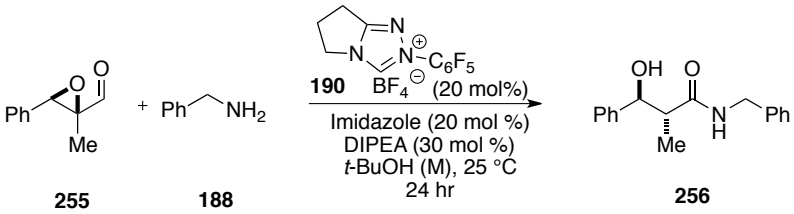


	191	205	206	207
				
yield (%)	72	80	65	55
dr (%)	4:1	6:1	>19:1	10:1

The concentration was next studied and it was found to have a positive effect on the reaction. An increase in the concentration in the reaction provided the product in good

yields and excellent diastereoselectivity. Additionally, a more dilute reaction provides the product in lower yields and diastereoselectivity. This suggests that one potential reason for the high levels of diastereoselectivity can be attributed to proton transfer.

Table 11.

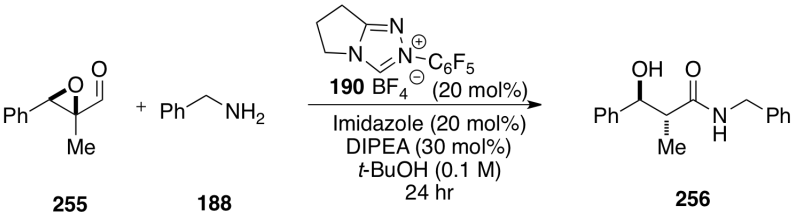


255 **188** **256**

concentration (M)	yield (%)	dr
0.10	84	>19:1
0.50	65	>19:1
0.02	60	>10:1
0.01	57	>8:1

As the solubility of reagents varied due to the solvent, the temperature was next investigated.

Table 12.

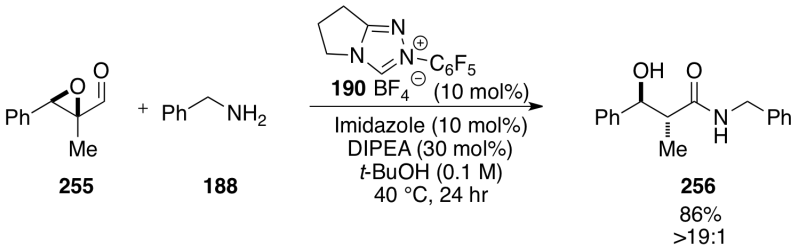


255 **188** **256**

T (°C)	yield (%)	dr
0	NR	NA
40	86	>19:1
60	76	10:1

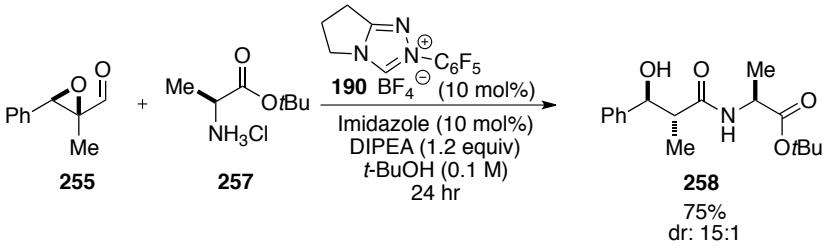
Having determined acceptable conditions we next surveyed the effect of catalyst loading and were pleased to find that the reaction was efficient at 10 mol % of catalyst without any deleterious effect on yield and diastereoselectivity.

Scheme 18.



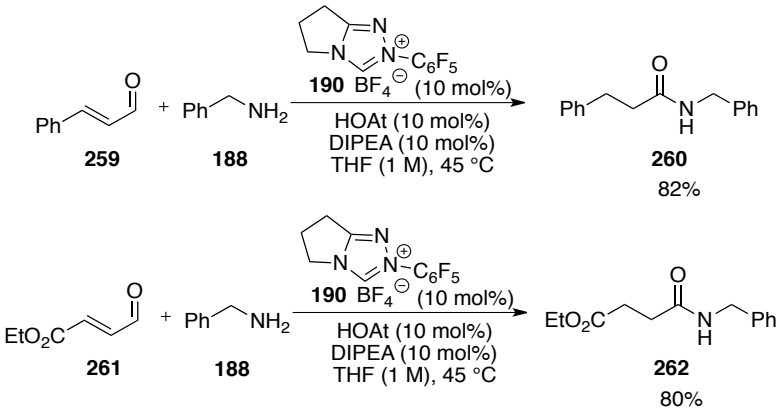
The efficiency of amine HCl salts to participate in the reaction was studied next. It was determined that alanine t-butyl ester HCl salt under the optimized reaction conditions provided the respective product in good ee and diastereoselectivity.

Scheme 19.



The scope of α-reducible aldehyde was also extended to enals, which provide saturated amides. We quickly identified that HOAt as the optimal cocatalyst and the reaction conducted at 1M concentration provided the respective amide with good yields. Trans-cinnamyl aldehyde provides the benzyl amide with 82% yield, whereas the more reactive butenoate provides the benzyl amide with 80% yield (Scheme 20).

Scheme 20.



2.6 Asymmetric Synthesis of α-substituted amides

Based on our previous example of an asymmetric amidation we sought to generate enantioenriched amides from α-reducible aldehydes and amines. Enals were chosen as the α-reducible aldehyde over α,α-dichloro aldehydes **263** and **264** (Figure 1) due to their stability and ease of handling. Enal **266** was found to be a competent substrate in the amidation reaction, whereas enal **265** did not provide any product. The lack of reactivity observed with enal **265** is in agreement with observations made by Bode in the NHC catalyzed esterification of enals.[19]

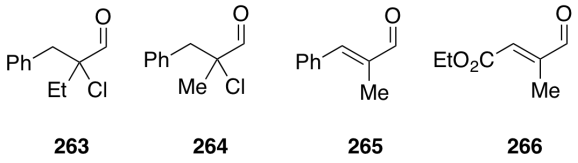
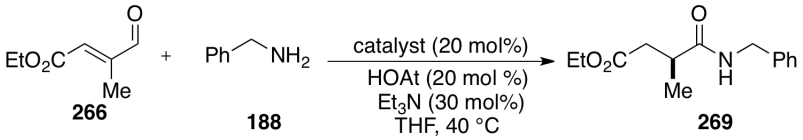
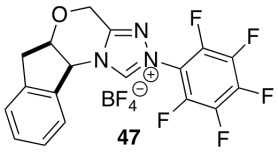
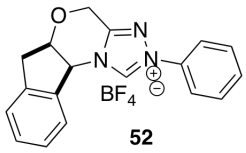
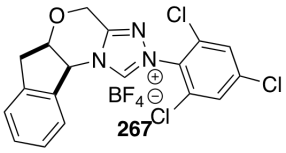
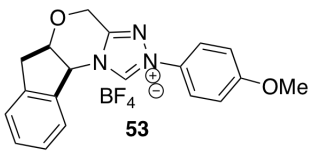
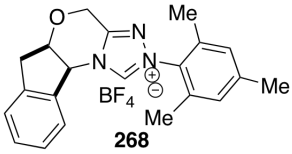
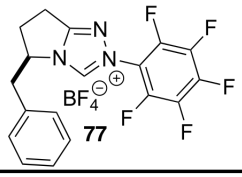


Figure 3.

Having identified a suitable α-reducible aldehyde and benzyl amine as the nucleophile with chiral NHC **47** the amide was obtained in 68% yield and 50% ee. A survey of catalyst revealed that NHC **47** and **77** provided higher enantioselectivities and yields over electron rich NHC **268**, **52**, and **53**. Chiral NHC derived from pyrolidine **77** provided the respective product with 81% yield and 24%.

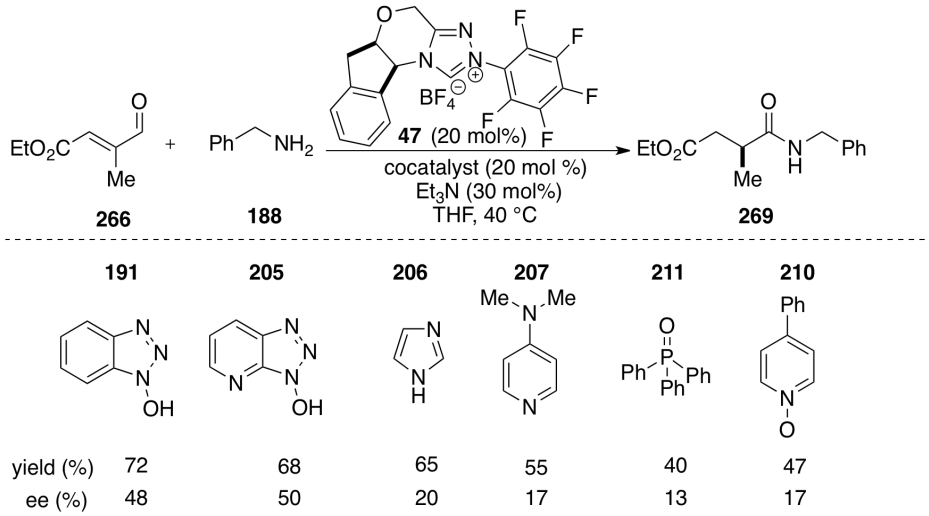
Table 13.



entry		yiled (%)	ee (%)	entry		yield (%)	ee (%)
1	 **47**	68	50	4	 **52**	40	20
2	 **267**	70	46	5	 **53**	46	18
3	 **268**	58	31	6	 **77**	81	24

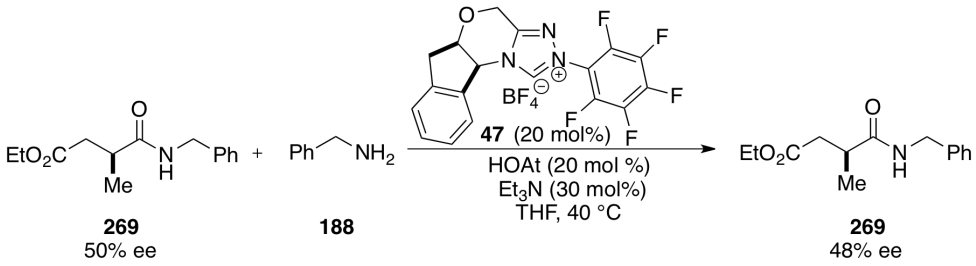
A survey of cocatalyst was next conducted only to observe that HOAt and HOBt provided optimal yields and enantioselectivities, whereas *N*-protic cocatalysts only provided the product with poor enantioselectivities.

Scheme 21.



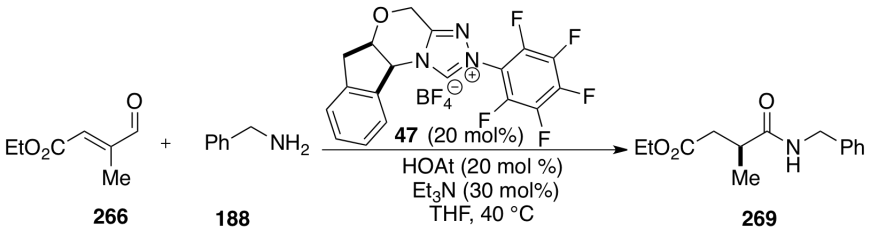
The enantioenriched product was subjected to the reaction conditions to see if any variation in ee was observed, thus identifying an epimerization pathway for the product. The reaction provided the respective product **269** with 48% ee ruling out epimerization of product.

Scheme 22.



An aliquot study was next conducted to see if epimerization was occurring during the reaction at the acyl azolium. If epimerization was taking place we should observe a decrease in enantioselectivity during the course of the reaction. The study revealed that the product is generated with an ee of 60% (entry 1, Table 14) and as the reaction continues the ee is reduced to 50% (entry 4, Table 14). This can be attributed to epimerization occurring at the acyl azolium or an indiscriminate protonation.

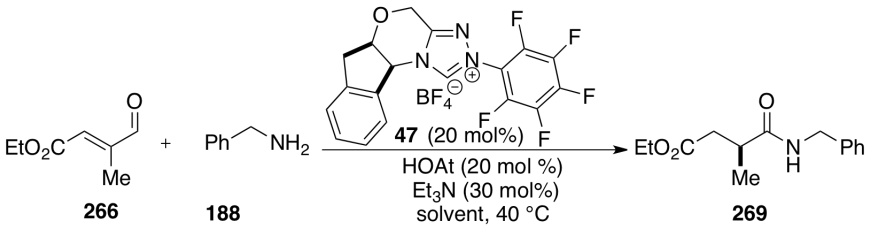
Table 14.



entry	time (min)	conv (%)	ee (%)
1	5	15	60
2	10	23	57
3	60	50	53
4	720	64	50

Next, solvent was surveyed and the product was obtained with higher enantioselectivities in non-polar solvents (entry 1, 2, and 3, Table 15) while polar solvents provide the product with diminished enantioselectivities (entry 4, Table 15). The need for nonpolar solvents may suggest that ion pairing is important in the enantiodetermining step.

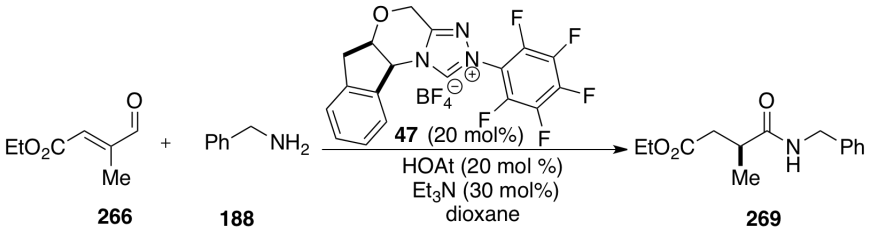
Table 15.



entry	solvent	yield (%)	ee (%)
1	dioxane	79	65
2	toluene	75	64
3	DCE	68	50
4	NMP	80	20

Additionally, a temperature study revealed that 40 °C was the optimal temperature and lowering or increasing the temperature provided product with diminished enantioselectivities.

Table 16.



entry	T (°C)	yield (%)	ee (%)
1	25	46	46
2	40	79	65
3	60	63	63

It was hypothesized that triethylammonium **270** and benzyl ammonium **272** exist in equilibrium leading to an indiscriminate protonation and the low enantioselectivites. Due to similarity in pKa of triethylammonium (10.7) and benzylammonium (10.4) both conjugate acids are viable proton shuttles in protonation of catalytically generated enol (Figure 4). Further investigation into an indiscriminate proton donor, *meta*-chloroaniline was used as the nucleophile as it would have a more acidic pKa than triethylammonium (Figure 4). It was hypothesized that the product would be obtained in lower enantioselectivity.

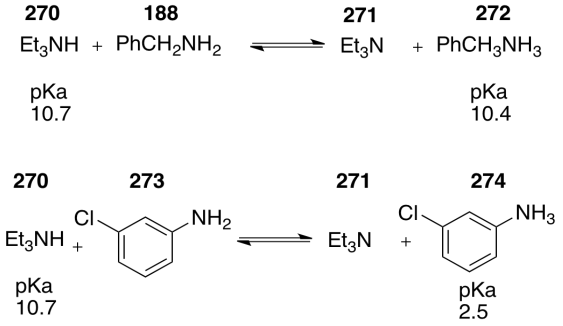
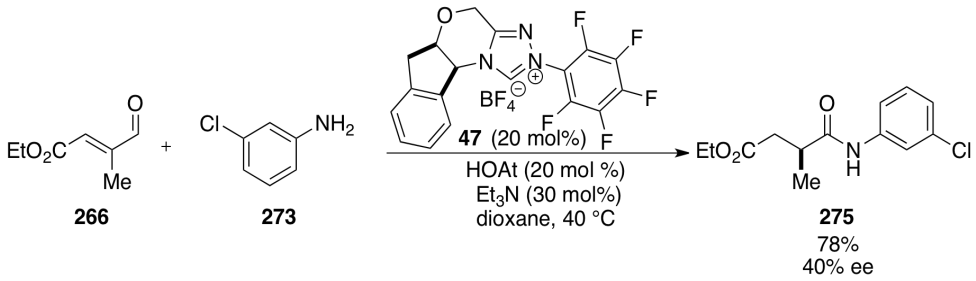


Figure 4.

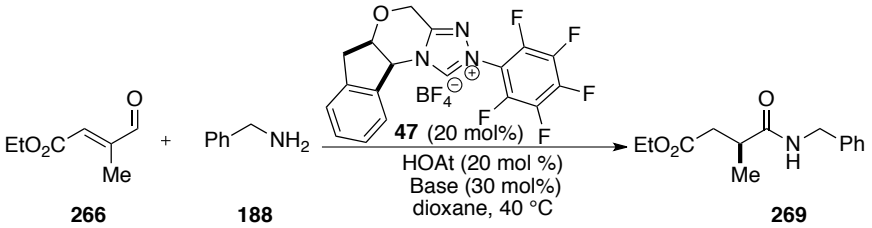
Indeed, when *meta*-chloroaniline was used in the reaction the product was obtained in 40% ee (Scheme 23). The diminished enantioselectivity is attributed to an indiscriminate protonation by both triethylammonium **274** and anilium **274** (Figure 4). Additionally, *meta*-chloroaniline is less basic than benzyl amine thus excluding epimerization at the acyl azolium contributing to the lower enantioselectivity.

Scheme 23.



To further validate this hypothesis, bases were next surveyed to see their effect on enantioselectivity. We observed that weak conjugate acids result in diminished enantioselectivities with the exception of potassium *tert*-butoxide (entry 1, Table 15). Strong conjugate acids derived from weak bases typically provided the product in moderate enantioselectivities (entry 5 and 6, Table 15). A catalyst loading study was next conducted to see what effect it has on the reaction.

Table 17.

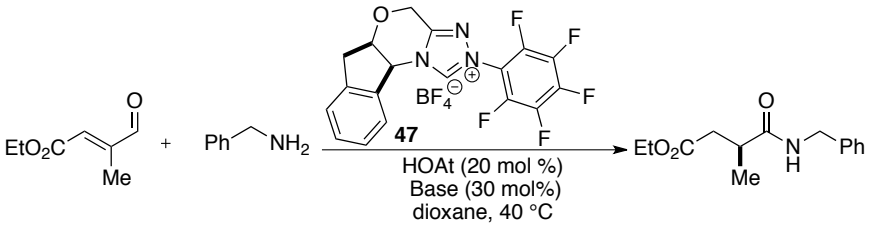


266 **188** **269**

entry	base	pKa	yield (%)	ee (%)
1	KOtBu	18	65	62
2	DBU	12	50	40
3	DBN	12	48	39
4	N-MeMorpholine	10	57	32
5	Pyridine	7	68	63
6	DABCO	8	70	65

Catalyst loading was reduced from 20 mol% to 10 mol%, which provided the respective product with lower enantioselectivity of 62% (entry 2, Table 16). Further reduction of catalyst loading to 5 mol% has an adverse effect on both yield and enantioselectivity as the product is obtained in 50% yield and 40% ee (entry 3, Table 16). If an increase in catalyst loading leads to an increase in enantioselectivity, it would suggest that multiple catalysts may be operative. Indeed, an increase of catalyst loading to 40 mol% provides the respective product in 73% ee suggesting an additional proton source (entry 1, Table 16). Presumably this proton donor can be hypothesized to arise from the nucleophilic addition of the amine into the azolium salt.

Table 18.



entry	catalyst (mol %)	yield (%)	ee (%)
1	40 mol%	70	73
2	10 mol%	65	62
3	5 mol%	50	40

The further development of the asymmetric NHC catalyzed amidation reaction was not pursued.

2.7 Conclusion

In conclusion the NHC catalyzed amidation reaction was developed where the use of catalytic acyl transfer reagents facilitate the formation of the amide bond. This waste reduced amidation allows a variety of amines and the hydrochloride salts of amines to participate in the reaction. The α-reducible aldehyde scope incorporates α,α-dichloro aldehydes, epoxy and aziridinyl aldehydes, and enals. The study of the asymmetric NHC catalyzed amidation reaction provided modest enantioselectivities of the amide product. It was shown that multiple proton sources are responsible for the moderate enantioselectivities.

2.8 References

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Chapter 3

N-heterocyclic Carbene Catalyzed Synthesis of Carboxylic Acids

3.1 Introduction

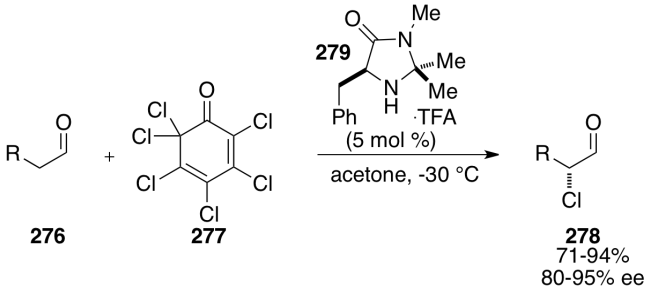
The synthesis of carboxylic acids is typically achieved through the oxidation of primary alcohols or aldehydes with stoichiometric oxidants.[1] N-heteocyclic carbene catalysis offers a catalytic approach towards the synthesis of synthetically useful carboxylic acids from α-reducible aldehydes under mild reaction conditions. The development of methods for the synthesis of enantioenriched α-chloro, α-bromo, and α-fluoro acyl derivatives has flourished in recent years due to their importance as synthetic intermediates. Current approaches to access these valuable synthons currently rely on the asymmetric generation of the α-halo aldehyde or α-halo ester followed by subsequent manipulation via oxidation or saponification to furnish the α-halo acid. To the best of our knowledge, no catalytic method exists to generate the α-halo acid and such a catalytic method warrants attention.

3.2 Background

Current methods for the synthesis of α-halo carboxylic acids has been through the oxidation of α-halo aldehydes, which can be attained by chiral secondary amine catalysis. In 2004, MacMillan[2] and Jørgensen[3] independently reported the first catalytic asymmetric synthesis of α-chloro aldehydes using secondary amine catalysis (Scheme 1). MacMillan and coworkers identified chiral imidazolidinone catalyst **279** in combination

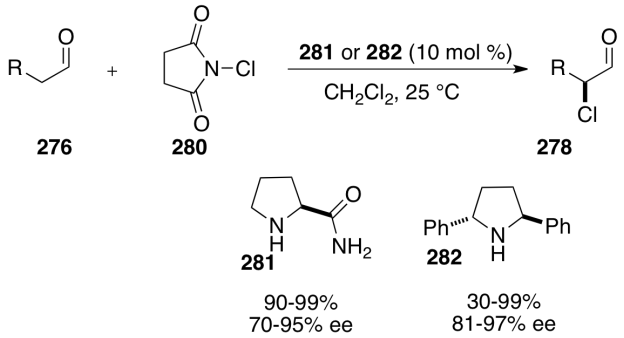
with perchlorinated quinone **277** to furnish α-chloro aldehydes in high enantiomeric excess (Scheme 1).

Scheme 1.



Jørgensen and coworkers identified two efficient secondary amines, a C_2-symmetric diphenyl pyrrolidine **282** and proline derivate **281** in the presence of NCS **280** to also furnish the chloro aldehyde **278** in high enantioselectivity (Scheme 2).

Scheme 2.

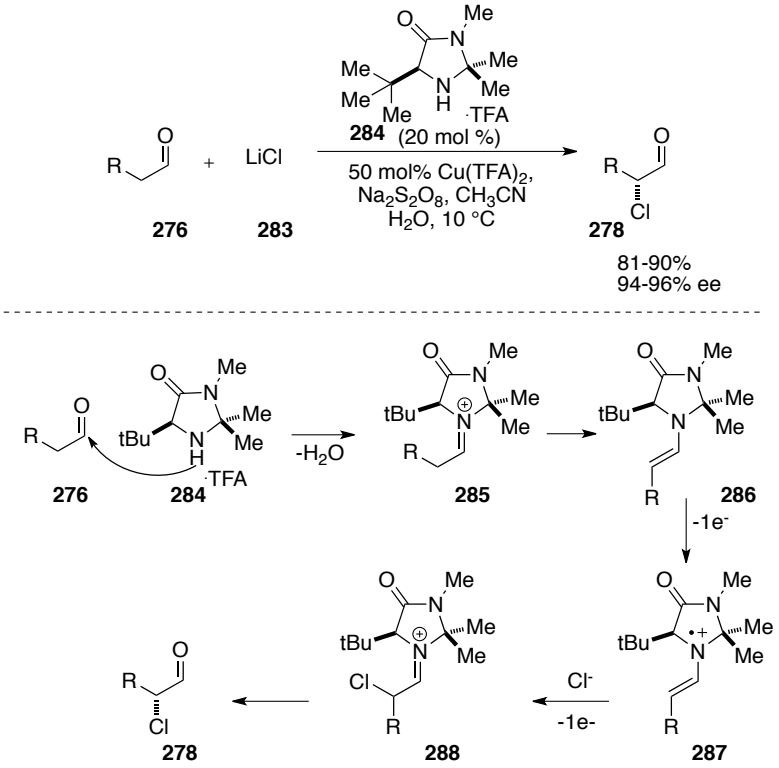


The current limitation with the generation of α-chloro aldehydes is the instability of the respective products; in fact the aldehydes are universally reduced to the halo alcohol upon workup to minimize epimerization. These can be subsequently oxidized to furnish the α-chloro carboxylic acid.

More recently, MacMillan and coworkers have introduced a strategy where SOMO catalysis is utilized to generate enantioenriched α-chloro aldehydes.[4] SOMO catalysis is

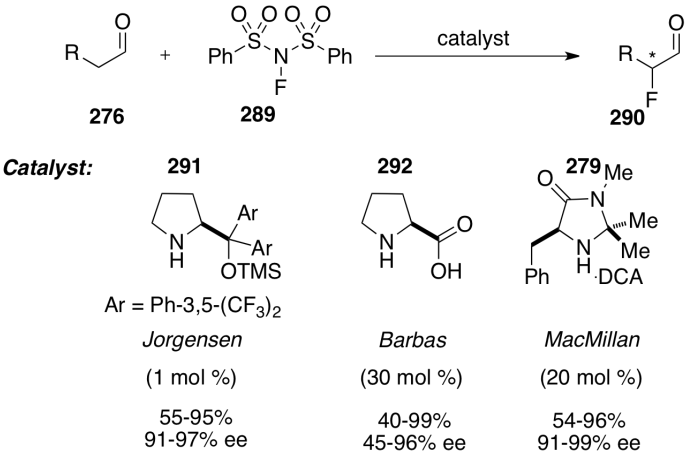
the extension of chiral amine based organocatalysis: HOMO (Highest Occupied Molecular Orbital) activation through the formation of an enamine, and LUMO (Lowest Unoccupied Molecular Orbital) activation through the formation of an imminium. SOMO (Singly Occupied Molecular Orbital) activation relies on the one electron oxidation of an enamine **286** to the radical cation **287** which can react with a somophile to provide imminium **288**. Utilizing SOMO catalysis, lithium chloride, a low molecular weight, inexpensive chlorine source is used to generate the α-chloro aldehyde (Scheme 3). The reaction is proposed to proceed upon condensation of the secondary amine **284** with the aldehyde **276** to generate imminium **285** which tautomerizes to afford the enamine **286**. Oxidation of the enamine **286** to generate the radical cation **287** is facilitated by cupric trifilate which reacts with lithium chloride **283** to afford the imminium **288. 288** is hydrolyzed to afford the α-chloro aldehyde (Scheme 3).

Scheme 3.



In 2005, Jørgensen,[5] Barbas[6] and MacMillan[7] groups independently and concurrently reported the asymmetric synthesis of α-fluoro aldehydes by secondary amine catalysis (Scheme 4). All three reports identified NFSi **289** as the optimal electrophilic fluorinating reagent with secondary amines derived from proline **291**, **292** and imidiazolidinone **279** identified as being able to catalyze the reaction. Similar to α-chloro aldehydes the α-fluoro aldehydes were also reduced upon workup due to product instability. However, Barbas reports the isolation of the α-fluoro aldehyde without loss in enantioselectivity and in good yields.

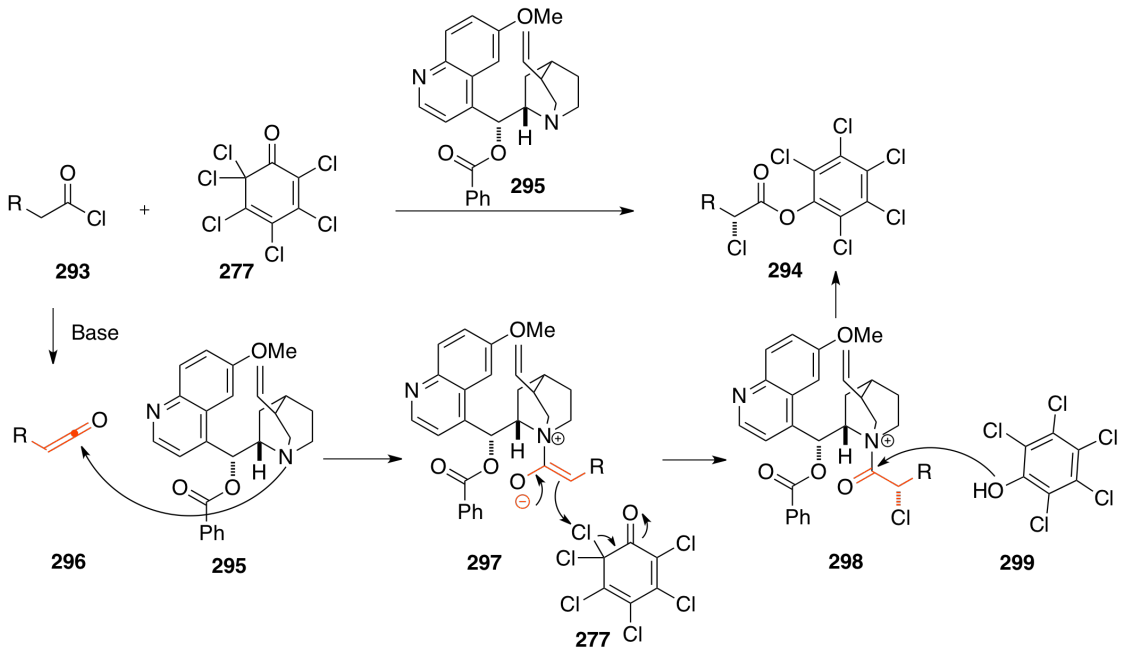
Scheme 4.



An additional method to access enantioenriched α-chloro carboxylic acids is via saponification of the α-chloro ester which proceeds with minor epimerization. The catalytic synthesis of α-chloro esters can be accomplished through the use of nucleophilic chiral Lewis bases such as the cinchona alkaloids, DMAP ("planar chiral"), and NHCs. In 2001, Lectka and coworkers reported the α-halogenation of acid chlorides catalyzed by cinchona alkaloids to generate α-chloro esters (Scheme 5).[8] The acid chloride **293** is

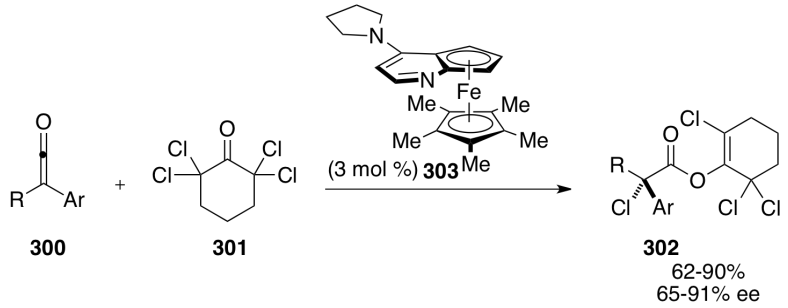
treated with base to generate ketene **296** which reacts with BQ **295** to furnish a nucleophilc enolate **297**. Enolate **297** reacts with quinone **277** to generate the acyl ammonium salt **298** and pentachlorophenol **299**. Phenol **299** liberates the acyl ammonium **298** upon nucleophilic attack to regenerate the Lewis base and furnish the α-chloro ester **294** (Scheme 5).

Scheme 5.



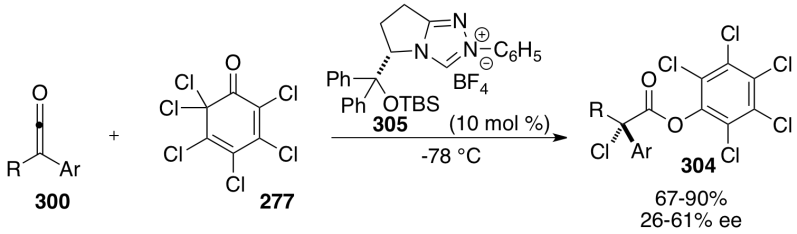
Fu and coworkers identified nucleophilic chiral PPY* **303** to catalyze the α-chlorination of ketenes **300** (Scheme 6).[9] Hexachloroacetone and 2,2,6,6 tetrachlorocyclo-hexanone **301** were identified as efficient electrophilic chlorine sources. The mechanism for this process is proposed to proceed via a chiral enolate or a chiral chlorinating agent which could not be distinguished (Scheme 6). However, at -78 °C no reaction is observed between PPY* **303** and 2,2,6,6-tetrachlorocyclohexanone **301** suggesting that a chiral chlorinating reagent might not be generated. Furthermore, a linear correlation is observed between catalyst ee and product enantioselectivity suggesting only one catalyst is operative.

Scheme 6.



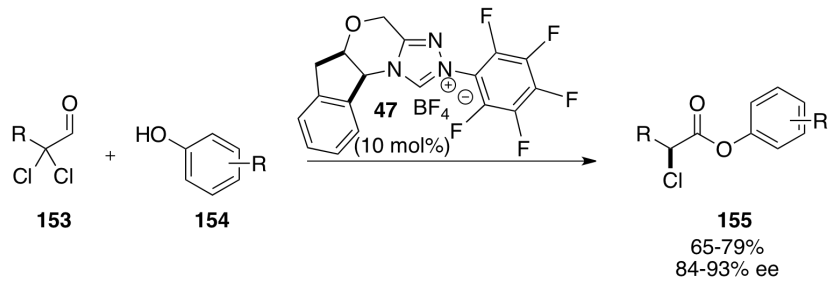
More recently, Smith and coworkers have reported the α-chlorination of ketenes using chiral NHCs to afford α-chloro esters in moderate enantioselectivities (Scheme 7).[10] Different halogenating reagents were surveyed and hexachloro cyclohexadienone is the most efficient, providing good yields of the product. Noteworthy, is the temperature dependence, as reactions conducted at elevated temperatures all result in the undesired reaction of carbene with the electrophilic chlorinating reagent.

Scheme 7



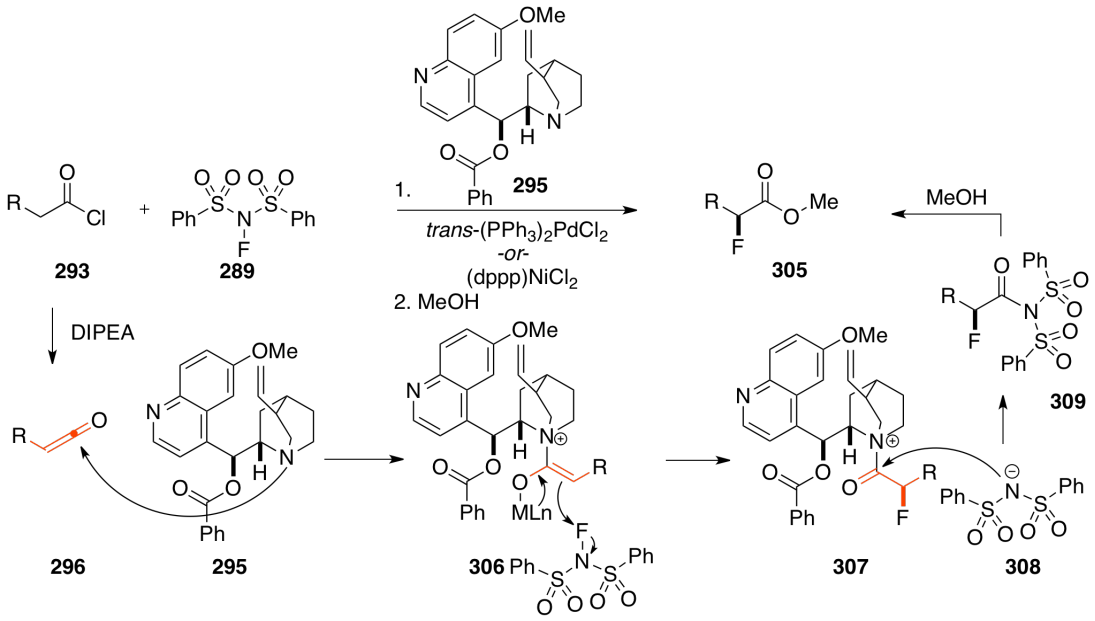
An alternative strategy to access enantioenriched α-chloro esters has been via an asymmetric protonation of α,α-dichloro aldehydes **153** catalyzed by NHC **47** in the presence of phenols **154** (Scheme 8).[11] Rovis and Reynolds identified NHC **47** to be optimal with a variety of phenols participating in the reaction to provide the enantioenriched α-chloro ester **155** in excellent enantioselectivity and yield. The reaction requires 10 equivalents of phenol as a reservoir to suppress base catalyzed epimerization.

Scheme 8



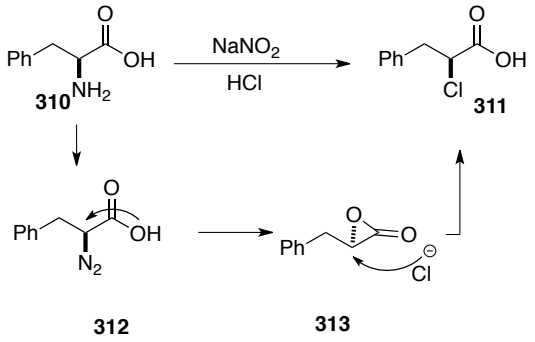
The synthesis of α-fluoro carboxylic acids can also be obtained via hydrolysis of α-fluoro esters. In 2008, Lectka and coworkers reported the α-fluorination of ketenes via dual metal-ketene enolate activation in the presence of Lewis base **295** (Scheme 9).[12] NFSi **289** was identified as a competent fluorinating agent and at elevated temperatures formation of a chiral fluorinating agent arising from the reaction of NFSi **289** with chiral catalyst **295** is observed. This requires that the reaction be conducted at -78 °C. The use of a metal complex was crucial in obtaining reproducible results and good yields. Formation of N-acyl bis sulfonamide intermediate **309** is proposed and is susceptible to hydrolysis by MeOH or other nucleophiles (Scheme 9).

Scheme 9



The direct catalytic asymmetric synthesis of α-halo acids has been less fruitful compared to the methods previously discussed. The synthesis of α-chloro carboxylic acids is still executed upon derivatization of amino acids **310** via diazotization of the amine with sodium nitrite in a solution of HCl to furnish the α-chloro carboxylic acid **311** (Scheme 10).[13] The reaction proceeds with stereoretention; thus, the (R) enantiomer of the amino acid provides the (R) enantiomer of the chloro acid (Scheme 10). This is postulated to proceed via a α-lactone **313** followed by ring opening with chloride to afford the chloro acid **311** (Scheme 10).

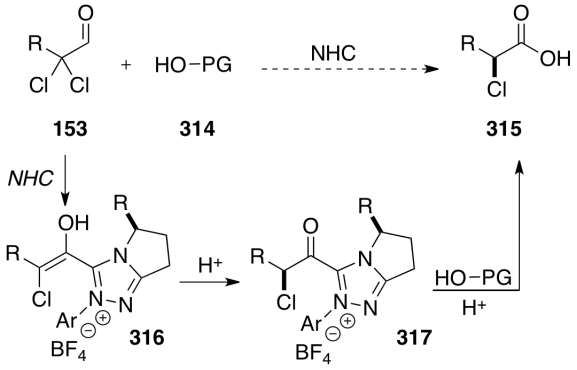
Scheme 10



3.3 Plan of Investigation

The catalytic asymmetric synthesis of α-chloro carboxylic acids has been unexplored prior to our work in this area. The synthesis of α-halo carboxylic acid provides distinct advantages over the synthesis of α-halo aldehydes or esters, as an insulated chiral center is generated with the most acidic proton now present on the carboxyl group thus preventing base catalyzed epimerization. The acid also circumvents product stability associated with α-halo aldehydes as carboxylic acids are not susceptible to oxidation. A process was envisioned where an α,α-dichloro aldehyde **153** can be treated with a chiral NHC to afford enol **316**. Enol **316** can be protonated to furnish the acyl azolium **317** which can be hydrolyzed by a masked hydroxide nucleophile **314** to furnish the enantioenriched α-chloro carboxylic acid (Scheme 11). The enantiodetermining event can be proposed to occur upon protonation of nucleophilic enol **316** or at the acyl azolium **317** if epimerization pathways are operative. The ideal nucleophile would be water; however, caution would need to be taken since it has been shown to engage in deleterious reactions with carbenes.

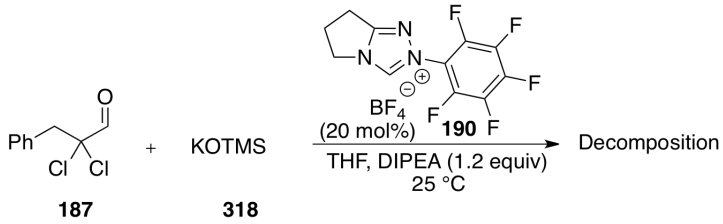
Scheme 11.



3.4 Synthesis of enantioenriched α-chloro carboxylic acids.

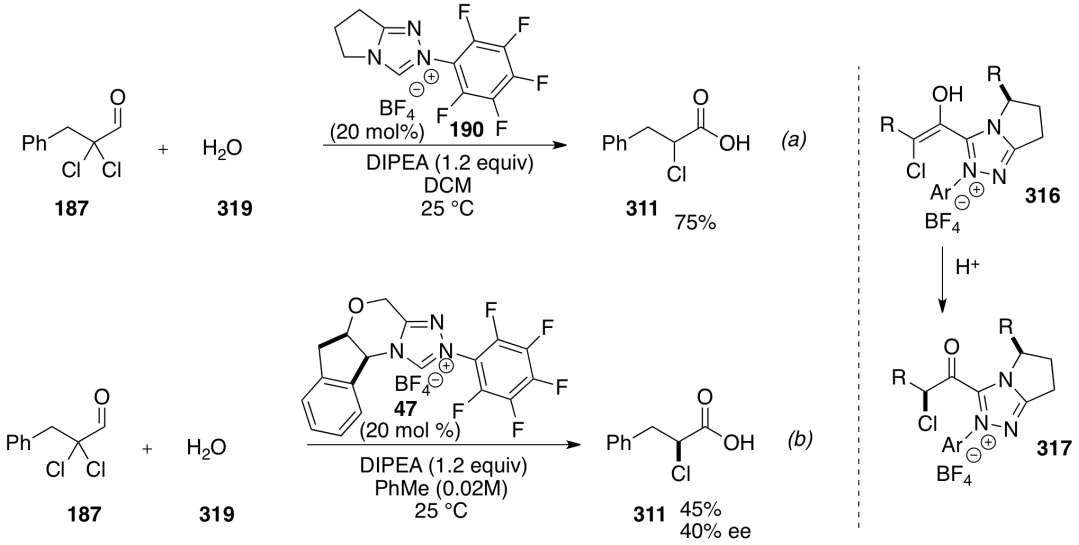
Potassium trimethylsilanolate **318** was initially investigated as a nucleophile in generating the α-chloro acid upon hydrolysis of the acyl azolium. However, all attempts at optimizing the reaction did not result in any product formation.

Scheme 12.



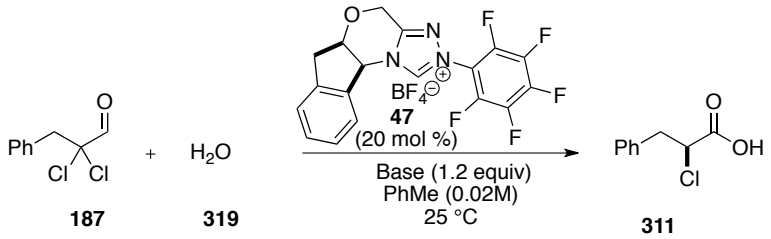
Concurrently, water was identified as a competent nucleophile providing the α-chloro acid with achiral triazolium salt **190** in 75% yield (Scheme 13). The reaction conducted with chiral triazolium salt **45** furnishes the desired product in 45% yield and 40% ee with the enantiodeterming step being attributed to protonation of enol **316** by the ammonium salt of DIPEA **(**Scheme 13).

Scheme 13.



If protonation of enol **316** is the enantiodetermining step of the reaction, presumably change of proton source could potentially influence selectivity. A variety of bases were surveyed in the reaction to see their effect on enantioselectivity. Strong bases resulted in lower enantioselectivities, while weak bases provided higher ee's, presumably due to the acidity of the conjugate acid. Ultimately, DABCO was identified as the optimal base in providing the desired product with an improved enantioselectivity of 63-76% (Table 1). The equivalence of DABCO has a marked effect on the enantioselectivity with 1.2 being optimal (entry 4, Table 1). Having identified the base which provided the improved enantioselectivity of the α- chloro acid, the effect of solvent on the reaction was next studied.

Table 1.

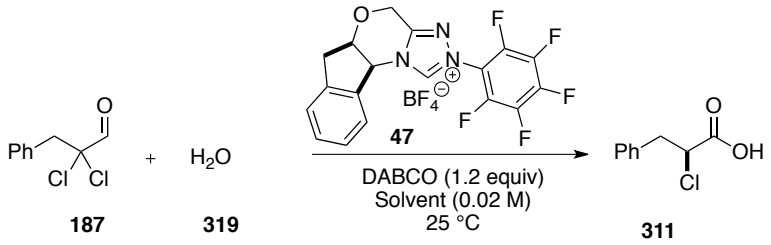


entry	base	yield (%)	ee (%)
1	Pyridine	45	60
2	DMAP	42	59
3[a]	DABCO	74	63
4[b]	DABCO	76	80
5[c]	DABCO	80	76
6	Quinucilidine	82	45
7	Et_3N	41	43
8	DIPEA	45	40
9	DBU	57	57
10	Proton Sponge	60	50
11	K_2CO_3	10	70
12	KH/ K_2CO_3	44	55

a=(60 mol %), *b*=(1.2 equiv), *c*=(1.6 equiv)

The solvent can have a profound impact on the reaction, as the miscibility of water will vary with polarity of the reaction medium. It was hypothesized that an increase in miscibility should result in an increase in yield as the effective concentration of water is increased in the organic phase. A survey of non-polar and polar solvents reveals that higher yields and enantioselectivities are obtained with non-polar solvents. However, solvents that are appreciably miscible with water only provide trace amounts of product and lower enantioselectivities. In order to overcome the inherent lack of nucleophilicity associated with water, it was reasoned that hydroxide should be more nucleophilic and thus, more efficient at hydrolyzing the acyl azolium.

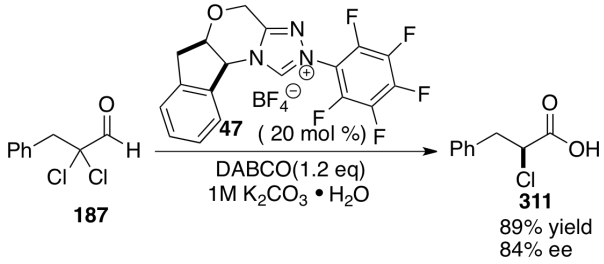
Table 2.



entry	solvent	yield (%)	ee (%)
1	hexanes	42	61
2	toluene	74	80
3	diethly ether	10	NA
4	methyl t-butyl ether	12	NA
5	tetrahydrofuran	NR	NA
6	dioxane	NR	NA
7	dichloroethane	65	70
8	dimethyl formamide	45	20
9	*N*-Methyl pyrrolidone	32	34
10	dimethylsulfoxide	NR	NA
11	acetonitrile	NR	NA

Indeed, the use of 1M potassium carbonate provides the desired product in 89% yield and 84% ee (Scheme 14).

Scheme 14



The effect of the N-aryl substituent on the carbene precursor was next surveyed to its effect on enantioselectivity. Substitution at the *para* position on the aromatic ring suppressed reactivity entirely, regardless of the electronic nature of the substituent (Figure 1). Monosubstitution at the *ortho*-postion was sufficient to facilitate reactivity but did not provide any appreciable increase in enantioselectivity. The presence of ortho-

disubstitution such as **320** and **324** provided acceptable levels of reactivity with **320** leading to an overall increase in enantioselectivity. Moreover, electron rich catalysts such as **52**, **53** and **268** and electron deficient catalysts **325** and **326** did not provide any reaction. Based on these results catalyst **320** was chosen as the optimal catalyst to continue further reaction optimization.

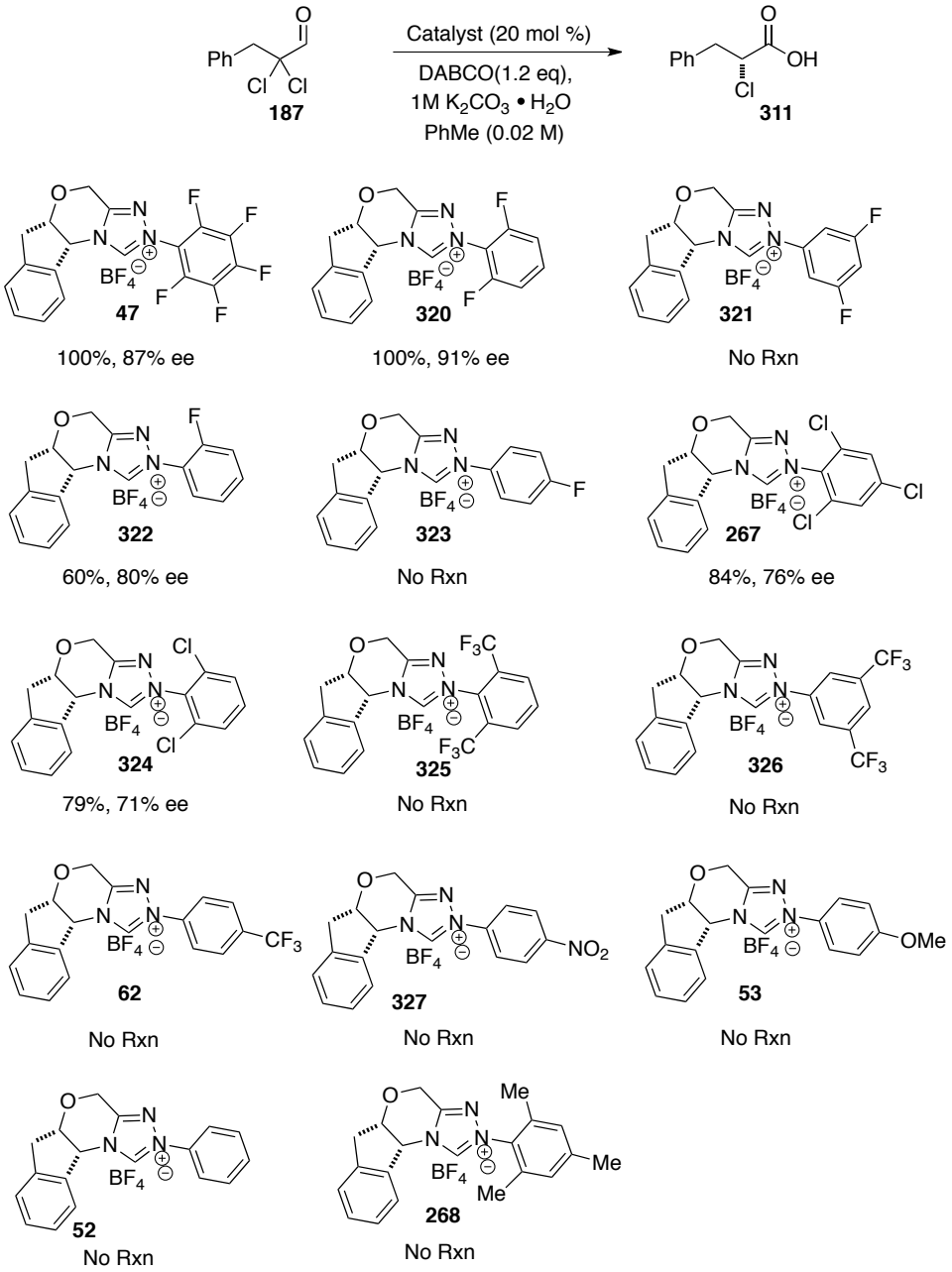
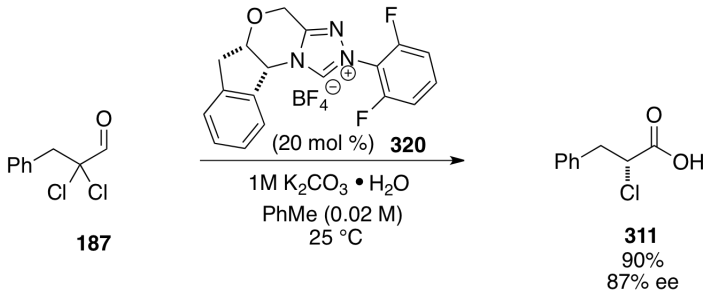


Figure 1.

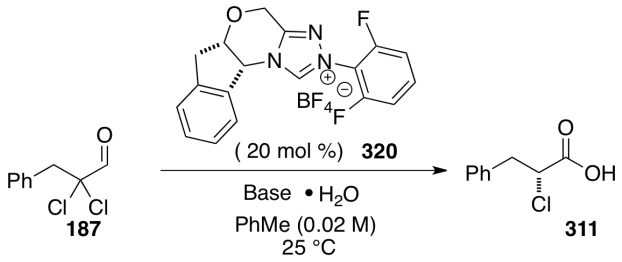
The conjugate acid of DABCO was hypothesized to be intimately involved in the enantiodetermining step, as delivering the proton to the nucleophilic enol **316**. Thus in the absence of DABCO, a significant decrease in enantioselectivity should be expected. A control experiment conducted in the absence of DABCO under the optimized conditions provides the desired product in 90% yield and 87% ee (Scheme 15). This was quite surprising that the enantioselectivities were not significantly affected in the absence of DABCO and left the question as to what species was involved in protonation of enol **316**.

Scheme 15.



As the enantiodetermining step was hypothesized to arise from protonation of enol **316**, and the reaction conducted in the absence of DABCO still provided high enantioselectivities, we sought to further understand the role of base by surveying additional inorganic bases.

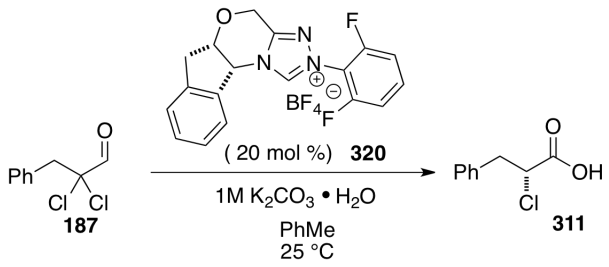
Table 3.



entry	base	yield (%)	ee (%)
1	Na_2CO_3	68	65
2	Li_2CO_3	64	61
3	Cs_2CO_3	81	86
4	$NaHCO_3$	60	70
5	$KHCO_3$	81	76
6	$CsHCO_3$	88	82
7	K_3PO_4	84	71
8	K_2HPO_4	74	73
9	KH_2PO_4	62	75
10	KOAc	15	55
11	NaOAC	22	45

The base screen revealed that a variety of inorganic bases were efficient at facilitating product formation. The cation had a significant impact on reactivity as lithium and sodium salts provided the product in low yields and enantioselectivities (entry 1 and 2, Table 3). Alternatively, potassium and cesium salts provided the product in higher yields and moderate to high enantioselectivities with potassium carbonate still providing optimal results (entry 3, Table 3). However, the base screen was not conclusive in identifying the role of the base, as majority of bases provided enantioselectivities within a reasonable margin from one another. A concentration study also confirmed that higher enantioselectivities were obtained under more dilute conditions (entry 3 and 4, Table 4) whereas an increase in concentration results in a decrease in enantioselectivity (entry 1 and 2, Table 4) suggesting possibility of epimerization at the acyl azolium.

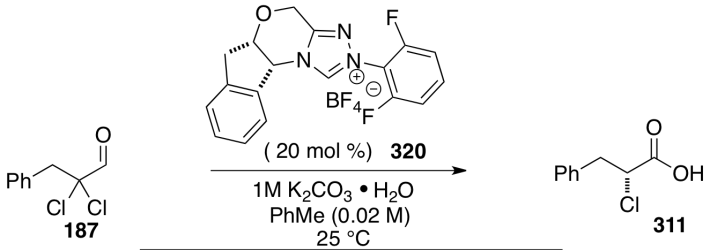
Table 4.



entry	conc (M)	yield (%)	ee (%)
1	0.074	89	82
2	0.050	84	86
3	0.037	87	87
4	0.024	89	87

To further evaluate the high levels of enantioselectivity obtained without the presence of a strong proton donor an aliquot study was designed. The aliquot study would reveal if epimerization was occurring during the course of the reaction, if high enantioselectivities were obtained at the onset of the reaction and decreased over time. Additionally, a linear relationship should be expected for product formation over time implicating catalyst efficiency is unwavering during the course of the reaction. The hygroscopicity of the α,α-dichloro aldehyde makes the reaction difficult to monitor by thin layer chromatography or other methods as decomposition becomes quite prevalent; thus, a series of reactions were concurrently run and individually stopped at specific time points to monitor conversion and enantioselectivity.

Table 5.



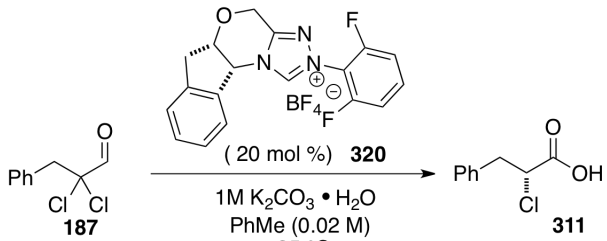
entry	time (hr)	yield (%)	ee (%)
1	2	NR	NR
2	4	NR	NR
3	6	24	86
4	8	79	87
5	10	82	87
6	12	84	87
7	24	88	87

The aliquot study revealed that conversion of starting material to product is not linear over time. Moreover, an induction period is present where the reaction does not take place for a period of time and then rapidly proceeds (entry 1 and 2, Table 5). The induction period is presumably attributed to the catalyst as it is solely responsible for facilitating the reaction. Furthermore, no change in enantioselectivity is observed over time suggesting that epimerization presumably does not occur (entry 3 to 7, Table 5). Since only aldehyde and catalyst exist in the reaction to react with hydroxide, further studies were conducted in identifying the proton donor and cause of the induction effect. Unfortunately the hydrate of the aldehyde could not be observed by spectroscopic methods and thus, efforts were redirected on identifying the role of the catalyst in the reaction.

To identify the possibility of multiple catalysts involved in the reaction a catalyst loading study was conducted. If multiple catalysts were involved in the reaction a variation in enantioselectivity would be observed with an increase or decrease in catalyst loading. Indeed, an increase in product enantioselectivity is observed with an increase in

catalyst loading (entry 3 and 4, Table 6). Additionally, a decrease in enantioselectivity is also observed with a decrease in catalyst loading suggesting that more than one catalyst may be operative (entry 1, Table 6). Having identified the catalyst as the likely culprit for the induction period, it still remained undetermined what the role of the catalyst was.

Table 6.

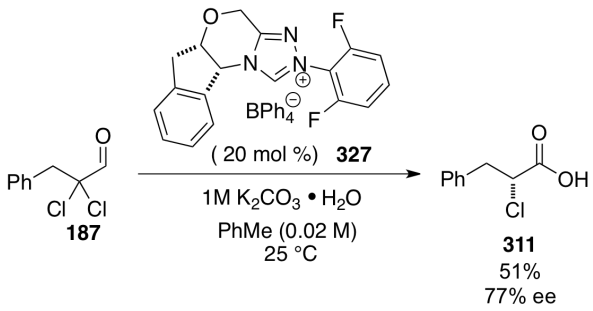


187 311

entry	catalyst (mol %)	yield (%)	ee (%)
1	10	72	80
2	20	89	87
3	30	90	90
4	40	89	92

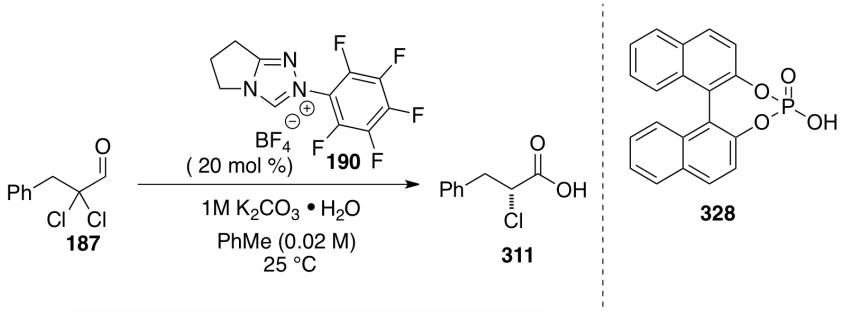
Since the reaction is biphasic it was hypothesized that the counterion could have a role in transferring hydroxide from the aqueous phase to the organic phase. Therefore, replacing tetrafluoroborate with a more organic soluble salt should provide the product in lower yields. Indeed, going from the tetrafluoroborate salt to tetraphenyl borate provides the product in lower yields of 55% (Scheme 16). Unexpectedly we also observed that the enantioselectivity had significantly decreased to 77% suggesting that counterion could be involved in the enantiodetermining event (Scheme 16).

Scheme 16



To validate the effect of the counterion on the enantiodeterming event, a chiral phosphoric acid **328** was introduced with achiral salt **190** to see if an enantioenriched product is obtained. The catalytic (20 mol%) use of phosphoric acid provides racemic product presumably due to the aqueous solubility of the chiral phosphate salt (entry 1, Table 7). The addition of 1.5 equivalent of chiral phosphoric acid **328** to the reaction with achiral triazolium **190** provides the product in 10% ee. However, observing enantioselectivity does not provide proof that the chiral phosphoric acid is involved as a counterion in the enantiodetermining step, as it can play a role as a chiral proton source in protonation of enol.

Table 7.

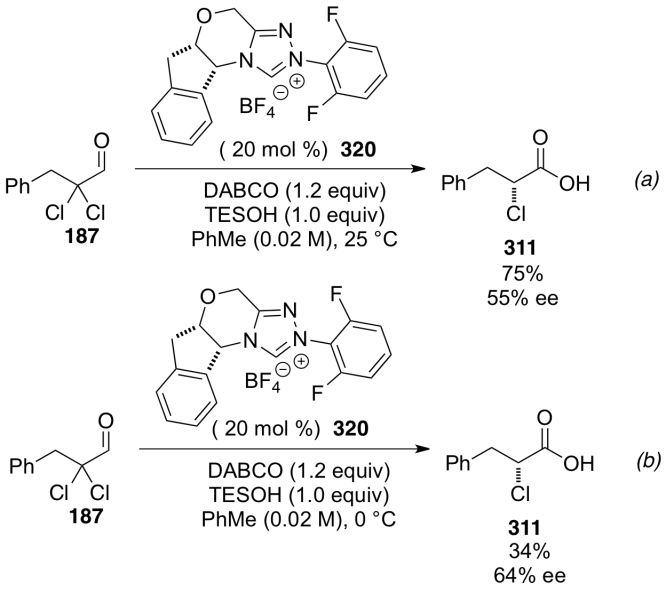


entry	**328** (mol %)	yield (%)	ee (%)
1	20	72	0
2	150	89	10

To further evaluate the effect of hydroxide with the catalyst triethylsilanol was chosen as the nucleophile. If hydroxide and the catalyst are both involved in the

enantiodetermining step a decrease in enantioselectivity would be expected with triethylsilanol as the nucleophile. The reaction conducted at 25 °C with triethysilanol affords the product **311** in 75% yield but does so with a significant reduction in enantioselectivity 55% (Scheme 17, a). When the reaction is conducted at 0 °C, the product is formed with enhanced enantioselectivity of 64% albeit in lower yields (Scheme 17, b). The dramatic difference in enantioselectivity observed when changing the nucleophile from hydroxide to triethylsilanol suggests that hydroxide is intimately involved in the enantiodetermining event.

Scheme 17



A working hypothesis was developed on the aforementioned experiments that intimately tied the induction effect, with the increase in enantioselectivity with catalyst loading, with the need for a water soluble anion, and hydroxide as a nucleophile where the azolium salt behaves as a phase transfer reagent and proton source to catalytically generated enol. Treatment of azolium salt **329** to 1M K_2CO_3 can result in the formation of

330 through ion exchange and thus behave as a phase transfer reagent in shuttling hydroxide from the aqueous phase to the organic phase. Furthermore, the addition of hydroxide to the azolium could generate hydrates **331** and **332** which could be responsible for protonation of enol.

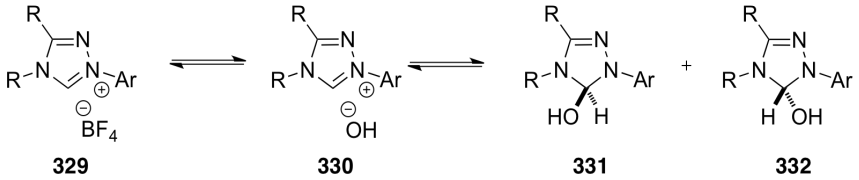
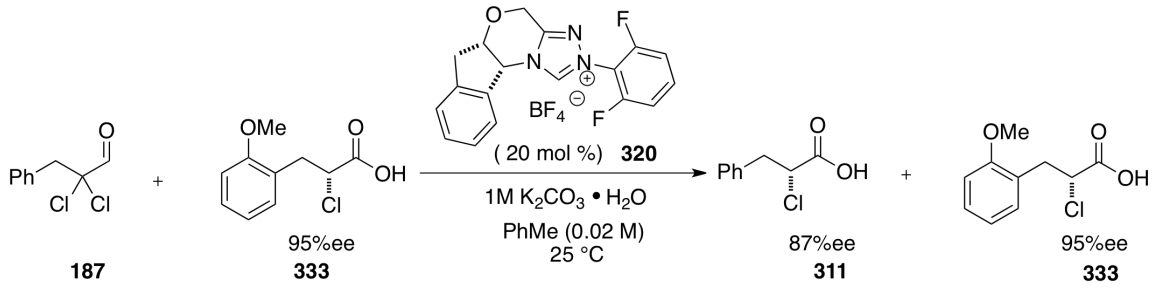


Figure 2

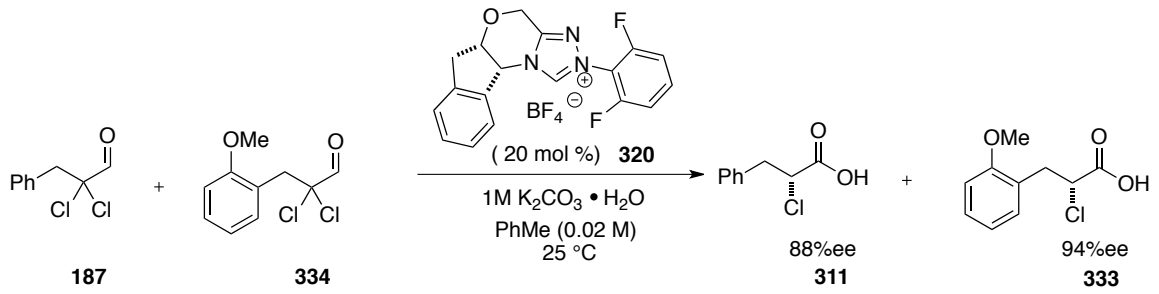
An additional possibility for the high enantioselectivities is the product playing a role as a chiral Brønsted acid in the protonation of enol due to slow partitioning of the acid from the organic phase to the aqueous phase as the potassium carboxylate. If the product is involved in the protonation of enol use of a chiral α-chloro carboxylic acid **333** in the reaction mixture in the presence of an alternative α,α-dihalo aldehyde **187** should provide the respective acid **311** with an increase or decrease in enantioselectivity due to match/mismatch (Scheme 18). However, the carboxylic acid **311** is furnished in 87% ee suggesting that the product is not involved in protonation of enol. Additionally, the experiment confirms that epimerization of the product from a catalytically generated intermediate is also not viable.

Scheme 18.



A crossover experiment was subsequently conducted to see if a catalytically generated intermediate was capable of acting as a proton donor by utilizing two different aldehydes. However, both aldehydes **187** and **334** provided the respective carboxylic acids **311** and **334** in 88 and 94% ee (Scheme 19) suggesting that intermediates in the reaction are not responsible for the high enantioselectivities.

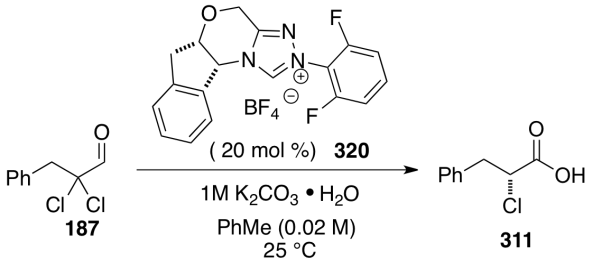
Scheme 19.



Residual water can play a role as a proton donor and its exclusion from the organic phase should result in variation of enantioselectivity. If water is responsible for the high selectivities its exclusion should provide the product with lower enantioselectivity. However, if an additional proton source is present exclusion of water should provide the product with higher enantioselectivity. In fact, a study of drying reagents revealed that addition of saturated brine led to an increase in enantioselectivity suggesting a different proton contributor (Table 8). Use of saturated sodium iodide

resulted in no reaction and use of hydroxide led to lower enantioselectivities presumably due to epimerization.

Table 8.



entry	solution	yield (%)	ee (%)
1	NaCl	72	89
2	NaBr	89	87
3	NaI	NR	NR
4	NaOH	63	51
5	1M NaOH	80	82

Having excluded additional proton donors, effort was placed on confirming the role of catalyst as a phase transfer reagent and proton source. Studies conducted on azoliums in the presence of nucleophiles have revealed that certain nucleophiles such as amines, alcohols, and water have a propensity to add into the C2 carbon of the salt to furnish a neutral species.[14] Thus, addition of hydroxide could lead to the formation of two diastereomeric hemiaminals. Becker has observed the formation of such a hemiaminal in the study of azolium and estimated its pka to be around that of phenol.[15] The formation of hemiaminal is also thermodynamically favored based on the computational work conducted on the hydration of imidazolium salts.[16]

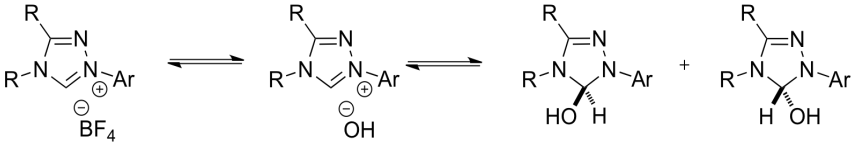
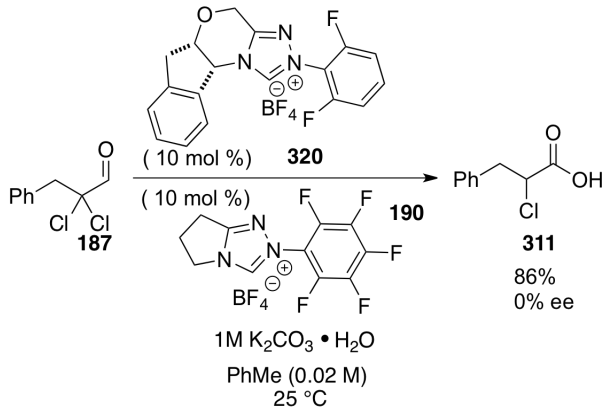


Figure 3.

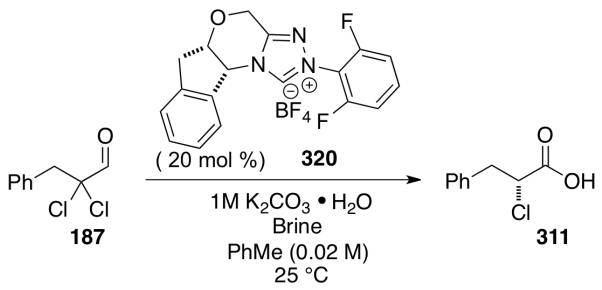
An initial investigation into the probability of hydrates **331** and **332** being involved in the protonation step was conducted by the combination of achiral and chiral catalyst, with the expectation of obtaining enantioenriched product (Figure 3). However, racemic product is obtained suggesting that reaction with achiral triazolium **190** is kinetically faster than formation of hemiaminals **331** and **332** from azolium salt **320** (Scheme 20).

Scheme 20.



A nonlinear effect study was next conducted to gain further insight into the formation of hydrates **331** and **332**, based on the catalyst loading study (Table 6). Mixing two different antipodes of catalyst resulted in an azolium salt with ee's of 90% to 40%. Four runs were conducted where the ee of the catalyst was varied from 100% to 40% with the expectation that product enantioselectivity should be linear with catalyst enantioselectivity if one catalyst is operative. However, the data was inconclusive as enantioselectivities of the product differed on each run (Table 9). This is not too surprising as Kagan outlines that reactions conducted in a biphasic medium can lead to inconclusive data from a non linear experiment.[17]

Table 9



entry	catalyst (ee %)	run 1 (ee %)	run 2 (ee %)	run 3 (ee %)	run 4 (ee %)
1	100	91	91	90	90
2	90	79	80	80	80
3	80	70	74	72	66
4	70	69	70	65	50
5	60	71	59	57	49
6	50	60	62	50	42
7	40	55	57	40	32

Disappointed by the failure of the nonlinear effect study, we sought to characterize the hydrates by spectroscopic means. Reaction of the azolium salt **320** with 1M potassium carbonate can give rise to 5 intermediates (Figure 4). If deprotonation of the azolium salt occurs it generates carbene **335**, which could exist in equilibrium as the azolium salt with hydroxide as its ion pair **330**. Hydroxide could also add to generate hydrates **331** and **332**, which are susceptible to decomposition to furnish the N-formyl derivative **336**. Unfortunately, all attempts to identify hydrates **331** and **332** by NMR, MS, UV-VIS failed and could not provide conclusive evidence for their formation.

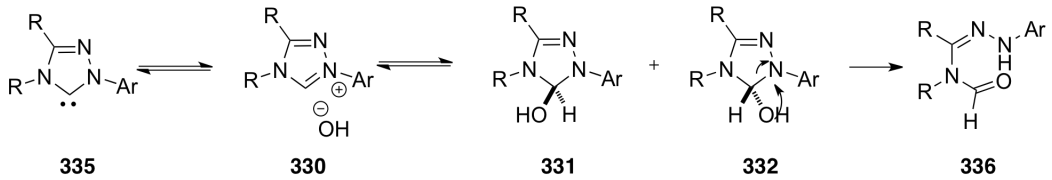


Figure 4

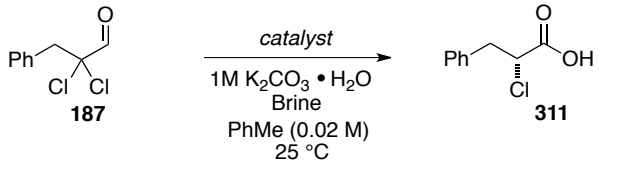
A mixed catalyst study was next pursued to gain a better understanding of the role of the catalyst in the reaction. It was assumed that catalyst **268** and **326** were not competent in the reaction, presumably due to formation of the hydrate **331** and **332** and or decomposition to furnish **336**. If hydrates are generated from precatalyst **268** and **326** the pka's of the hydrates should be different based on the *N*-aryl substituent with **326** being more acidic than **268** (Table 10).

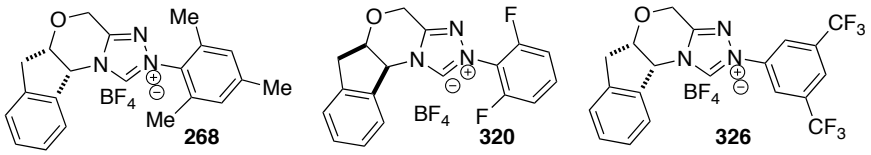
The mixed catalyst study began with the combination of catalyst **320** with electron rich azolium **268**. At higher molar ratios of the electron rich azolium **268**, we obtain **311** with the stereochemical outcome from catalyst **320** albeit in diminished ee of 65% and 55% conversion (entry 4, Table 10). This was surprising since 5 mol % of catalyst **320** provides product in 78% ee and 15% conversion suggesting that electron rich azolium is shuttling hydroxide from the aqueous phase to the organic phase (entry 2, Table 10). Additionally, the drop in enantioselectivity is a result of a match/mismatch suggesting hydrate of electron rich azolium is involved in the enantiodetermining step. With a 1:1 molar ratio we obtain the desired product in 87% ee and 100% conversion (entry 5, Table 10). The increase in reactivity and enantioselectivity is attributed to catalyst **320** in protonating enol as it should be the more acidic hydrate. This was the first time that we were able to obtain higher enantioselectivities with lower catalyst loadings presumably due to the catalyst behaving as a phase transfer reagent.

When mixing more electron deficient precatalyst **326** with precatalyst **320** at a molar ration of 15:5 we obtain **311** in 56% ee and a 100% conversion (entry 6, Table 10). A molar ratio of 1:1 provides product **311** in 88% ee and 100% conversion (entry 7, Table 10). We hypothesized that a match mismatch situation is again responsible for the

enantioselectivities. It is noteworthy that the more acidic hydrate is responsible for protonating enol. At 5 mol% of catalyst **320**, the more acidic hydrate from precatalyst **326** leads to a lower enantioselectivity (entry 6, Table 10) to that compared of **268** (entry 4, Table 10). To further validate this hypothesis, and preclude a match/mismatch situation, the same antipode of catalyst at a molar ratio of 15:5 of electron rich precatalyst **268** and **320 ent** provides product in 80% ee and 60% conversion (entry 8, Table 10). Incorporating the electron deficient precatalyst **326** with **320 ent** in a molar ratio of 15:5 also provides the product in 88% ee and 100% conversion (entry 9, Table 10). The increase in enantioselectivity is attributed to the formation of the more acidic hydrate which kinetically out competes hydrates generated from precatalyst **320**. The increase in reactivity is attributed to phase transfer behavior by the carbene.

Table 10



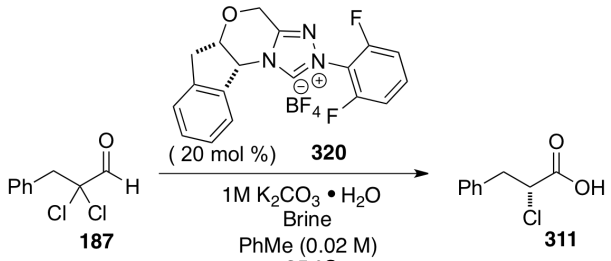


entry	268	320	326	conv (%)	ee (%)
1	15 mol %	--------	--------	NR	NA
2	--------	5 mol %	--------	15	78
3	--------	--------	15 mol %	NR	NA
4	15 mol %	5 mol %	--------	55	(+) 65
5	10 mol %	10 mol %	--------	100	(+) 87
6	--------	5 mol %	15 mol %	100	(+) 56
7	--------	10 mol %	10 mol %	100	(+) 88
8[a]	15 mol %	5 mol%	--------	60	(-) 80
9[a]	--------	5 mol %	15 mol %	100	(-) 88

[a] *The same enantiomer was used.*

Based on the results obtained from the mixed catalyst study we hypothesized that catalyst loading could be reduced by introduction of a phase transfer reagent. A survey of phase transfer reagents reveals that when employed in catalytic quantities an effect is observed in enantioselectivity and yield (Table 11). However, the use of a chiral phase transfer reagent with an achiral triazolium salt affords racemic product.

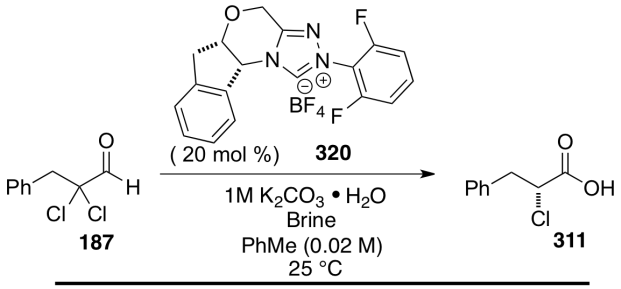
Table 11



entry	phase transfer	yield (%)	ee (%)
1	TBAI	90	89
2	TBACl	78	80
3	TBAOH	81	78

An additional screen reveals that catalyst loading can be reduced in the presence of phase transfer reagent while still maintaining enantioselectivity. However, an excess of tetrabutylammoniun iodide does not furnish any product.

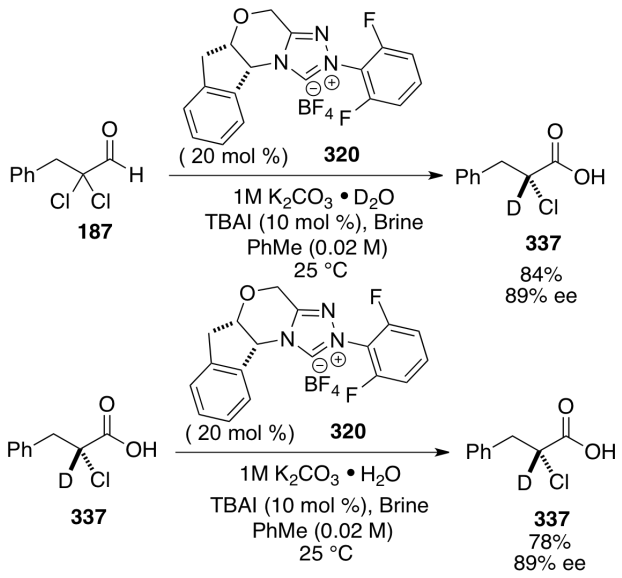
Table 12



entry	catalyst (mol %)	TBAI (mol %)	yield (%)	ee (%)
1	5	5	68	88
2	5	10	NR	NA
3	5	15	NR	NA
4	10	5	80	88
5	10	10	89	88
6	10	15	NR	NA

Additionally, it was confirmed that product epimerization does not occur under the newly developed conditions, as a α-deuterio α-chloro carboxylic acid was synthesized by simply using D_2O instead of water in the reaction (Scheme 21). When the enantioenriched deuterio acid is resubjected to the reaction under protic conditions we obtained the deuterio acid confirming that upon generation of product the stereocenter is insulated (Scheme 21).

Scheme 21.



Having developed optimized conditions, studies were conducted to survey the scope of aldehydes in this reaction. A variety of α,α-dichloro aldehydes participate in the reaction to furnish enantioenriched α-chloro carboxylic acids. Substitution of D_2O in place of water leads to an asymmetric deuteration reaction affording enantioenriched isotopically labeled chloroacids. *ortho*-methoxy **334** and *para*-N-Boc-amino **338** groups are tolerated on the aromatic ring, yielding the respective products in 78-80% and 78-95% ee (Figure 5). It is interesting to note that presence of an additional proton donor in **338** significantly reduces the ee, presumably due to competitive protonation. Analogues bearing aliphatic groups **339** and **340** and functional groups **341** and **343** all provide the acid in good yield and ee (Figure 5).

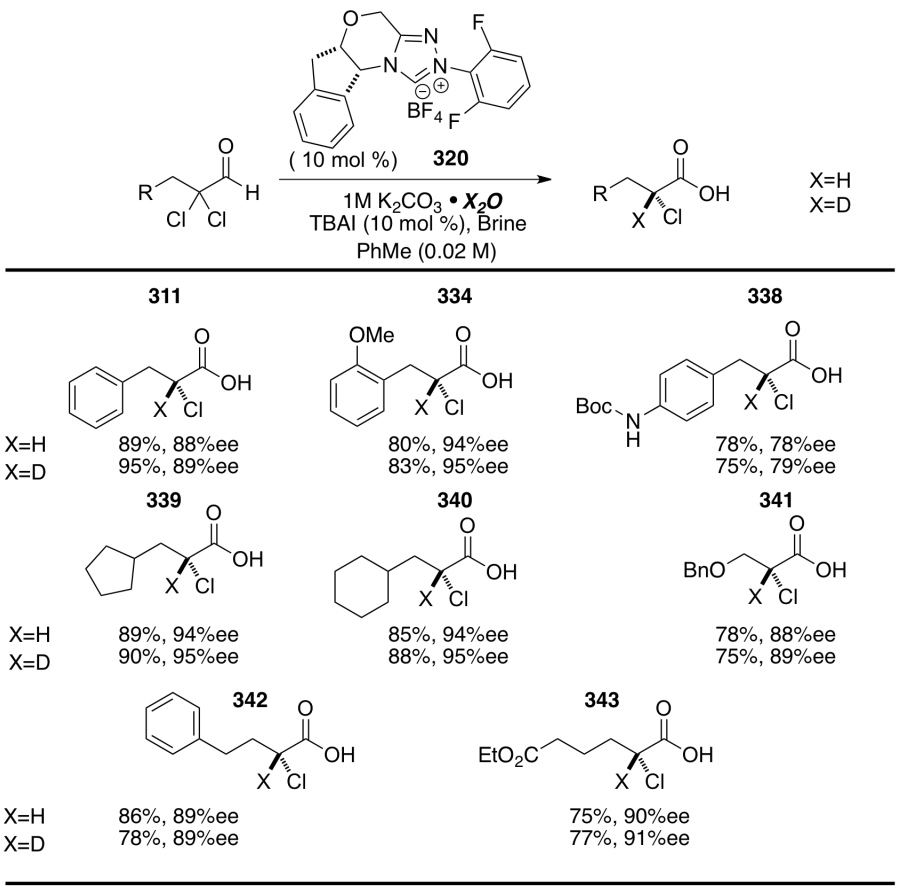
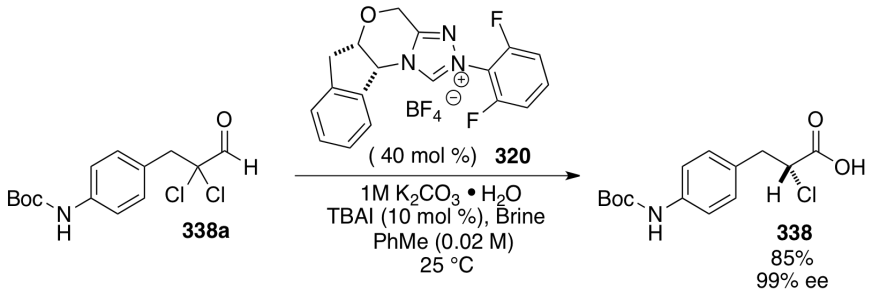


Figure 5

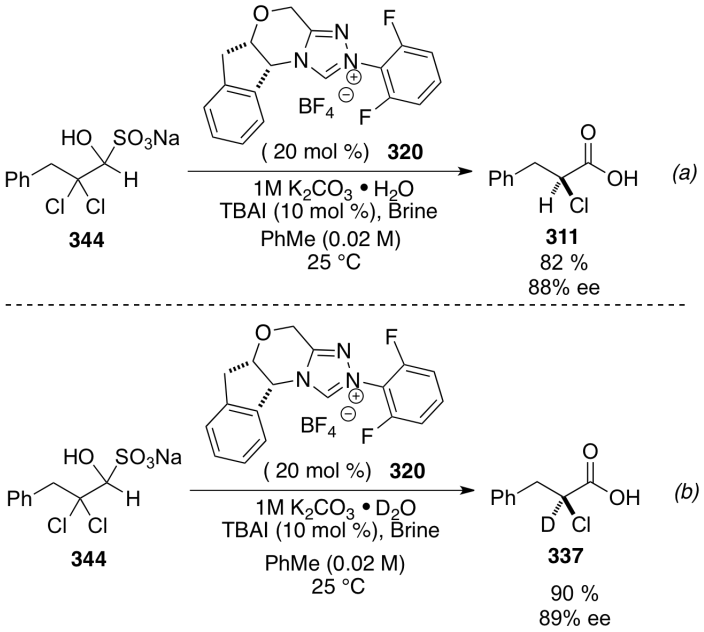
To further validate the role of the catalyst in the enantiodetermining event a subsequent reaction conducted with **338a** and 40 mol % of azolium **320** leads to desired product **338** in 99% ee and 85 % yield (Scheme 22). This suggests that an increase in concentration of the hydrate maybe involved in leading to higher enantioselectivities.

Scheme 22



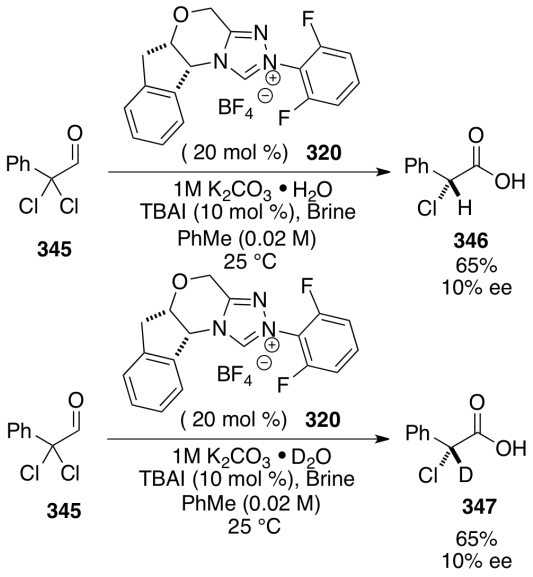
Due to instability and hygroscopicity of the α,α-dichloro aldehydes, a bench stable bisulfite derivative **339** can be subjected to the reaction to afford the respective acid **311** and **337** in comparable yields and ee's for both protio (Scheme 23, a) and deuterio hydration reactions (Scheme 23, b) .

Scheme 23



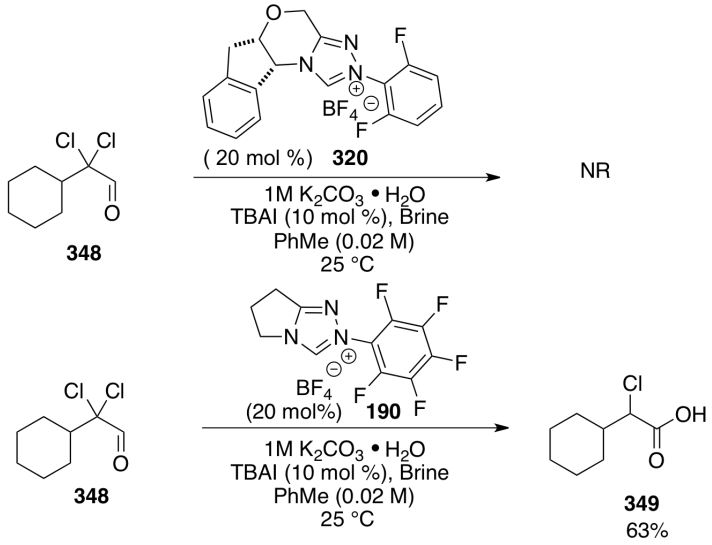
Further investigation into viable dihalo aldehydes revealed that doubly activated α-chloro carboxylic acids as the proton is benzylic and α to a carbonyl, did not furnish any appreciable enantioselectivity under protio and deuterio reaction conditions (Scheme 24). This was surprising as the esters have been obtained in high enantioselectivity by Lectka. This result suggests that epimerization may occur on the acyl azolium .

Scheme 24



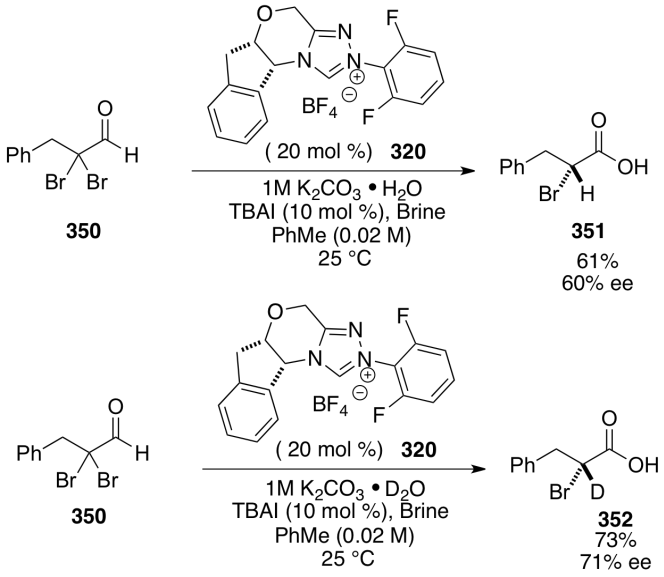
Moreover, β,β-dialkyl substitution is not tolerable as **349** does not afford any product under the optimized reaction conditions with NHC **320** (Scheme 25). This is presumably due to sterics of the catalyst as reaction catalyzed by achiral carbene **190** affords racemic product in 63% yield (Scheme 25).

Scheme 25



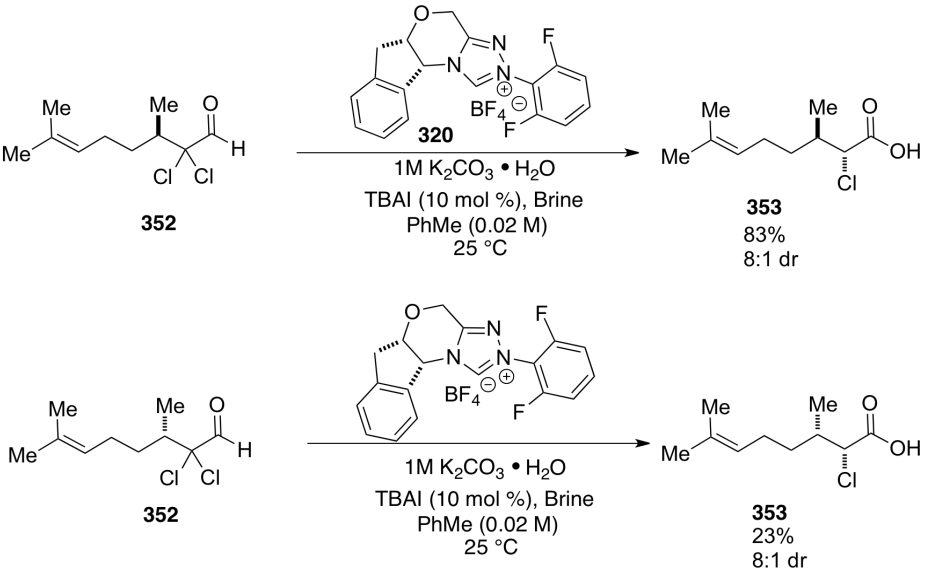
Lastly, we expected the process to be amenable to the synthesis of α-bromo carboxylic acids. Subjection of α,α-dibromo aldehydes **350** to the protio and deuterio reaction conditions afforded the enantioenriched α-bromo carboxylic acid in lower enantioselectivities, (60% and 71%) compared to that of the α-chloro carboxylic acid (Scheme 26).

Scheme 26



Validation of whether the reaction proceeds via catalyst or substrate control was experimentally confirmed. Subjection of **353** to the protio reaction provides the product in 8:1 dr confirming that the reaction proceeds via catalyst control.

Scheme 27



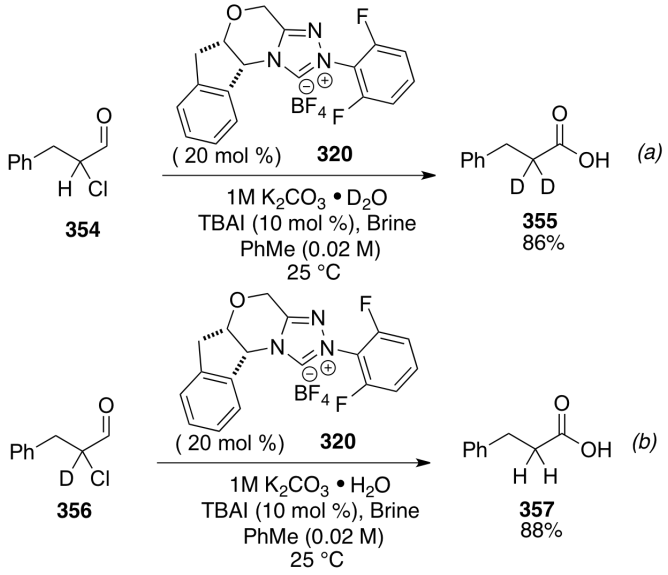
In summary, enantioenriched α-chloro carboxyl acids can be obtained in moderate to excellent yields and enantioselectivities from α,α-dichloro aldehydes under a biphasic reaction system where water is the nucleophile. Investigations into the mechanism have revealed that hydrates **331** and **332** of azolium salt **320** may be responsible for protonating the nucleophilic enol and that the azolium salt **320** participates in shuttling hydroxide from the aqueous phase to the organic phase.

Investigation into the substrate scope revealed that an external proton source can have a dramatic influence on the enantioselectivity. β,β-disubstituted aldehydes do not work under the developed reaction conditions and doubly activated aldehydes provide low enantioselectivities presumably due to epimerization at the acyl azolium. In advancing the scope of the hydration process we focused our efforts in identifying other α-reducible aldehydes.

3.5 Synthesis of α-deuterio carboxylic acids

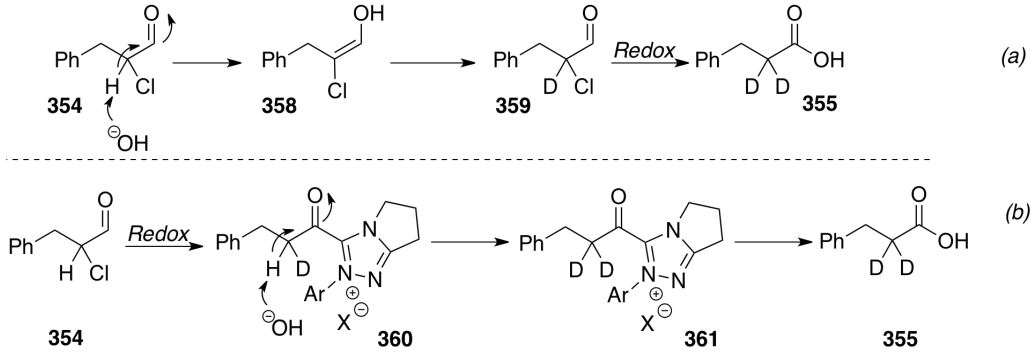
The synthesis of enantioenriched α-deuterio carboxylic acids was undertaken via an asymmetric monodeuteration from α-chloro aldehydes. Subjection of α-chloro aldehyde **354** to the optimized reaction conditions afforded the α,α-di dueterio hydrocinnamic acid **355** (Scheme 28). This unexpected result was confirmed upon subjecting α- deuterio α-chloro aldehyde **356** to the protio reaction conditions which provided hydrocinnamic acid in 88% yield (Scheme 28).

Scheme 28.



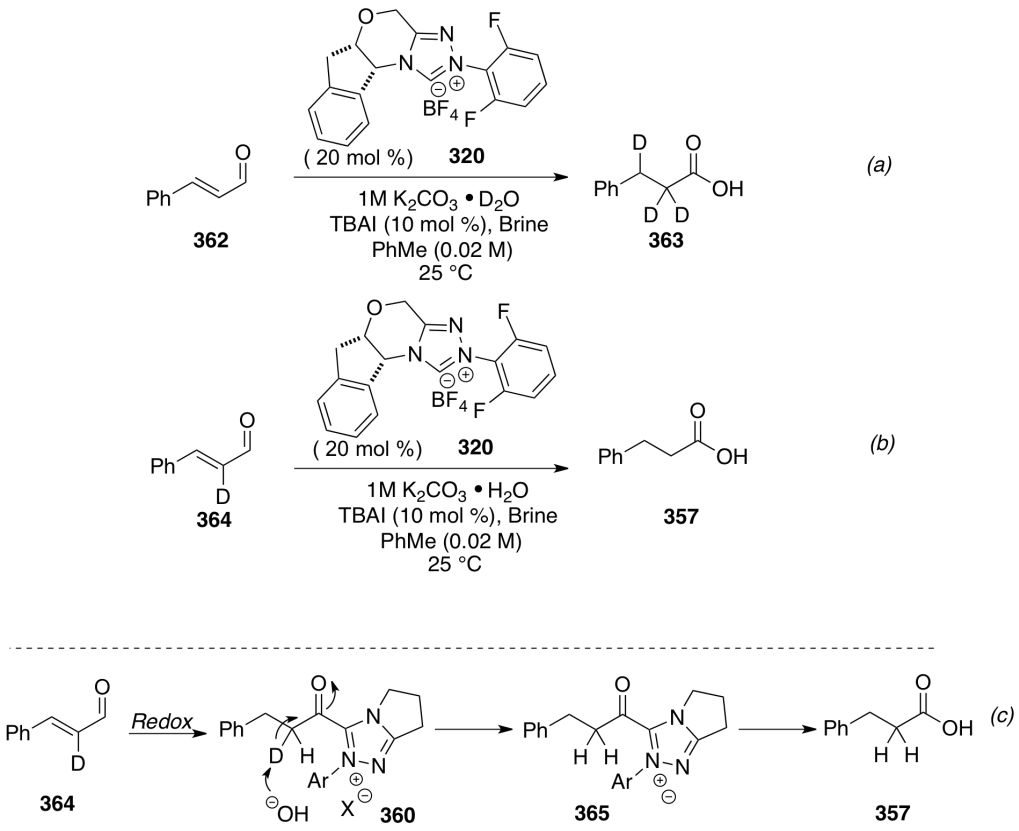
The observed products can arise from two distinct epimerization pathways, in which the aldehyde **354** is epimerized prior to the redox reaction (Scheme 29, a) or epimerization occurring on the acyl azolium **361** (Scheme 29, b).

Scheme 29.



To determine which pathway was operative, enals were chosen as the reducible aldehyde as epimerization at the aldehyde is not possible. Subjection of *trans*-cinnamyl aldehyde **362** to the reaction results in the formation of **363** (Scheme 30, a). This provides further evidence that epimerization occurs on the acyl azolium and the turn over limiting step is the hydrolysis of the acyl azolium. When *trans*-cinnamyl aldehyde with an α-deuterium **364** is subjected to the protio reaction conditions hydrocinnamic acid **357** is obtained thus confirming a racemization process occurring at the acyl azolium.

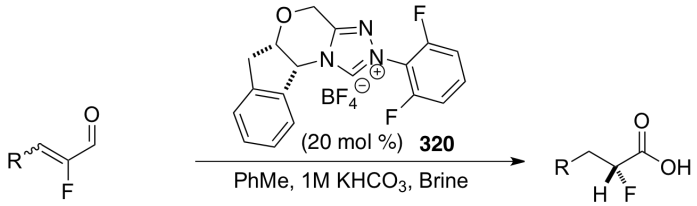
Scheme 30.

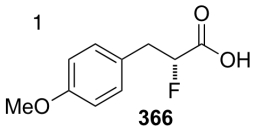
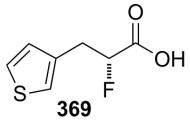
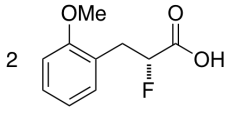
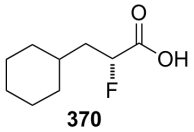
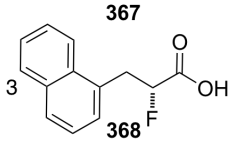


Section 3.6 Synthesis of α-Fluoro carboxylic acids

Additionally, we were able to extend this hydration process to encompass other reducible aldehydes such as enals to provide saturated acids and enantioenriched α-fluoro carboxylic acids which arise from α-fluoroenals. Noteworthy deviations from the previously developed procedure: TBAI was found to decompose the enal, and higher yields were observed with the use of 1M $KHCO_3$ instead of 1M K_2CO_3. A variety of α-fluoroenals participate in the reaction to afford the fluoro acid in high enantioselectivities (Table 13).

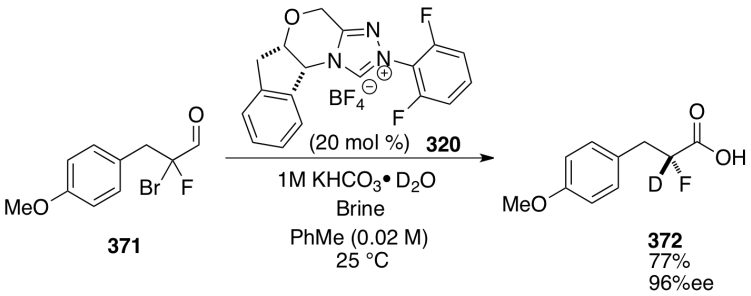
Table 13.



Entry		Yield (%)	ee (%)	Entry		Yield (%)	ee (%)
1	 **366**	74	93	4	 **369**	70	90
2	 **367**	80	96	5	 **370**	65	96
3	 **368**	77	94				

Noteworthy is that the (Z)-α-fluoro-p-methoxy phenylacrylaldehyde provide the respective product in 93% ee and 84% yield whereas the (E)- α-fluoro-p-methoxy phenylacrylaldehyde provides the product in 93% ee and 42% yield. An asymmetric deuteron can also be installed if a α-bromo,α-fluoro aldehyde is used to afford an α-deuterio,α-fluoro carboxylic acid.

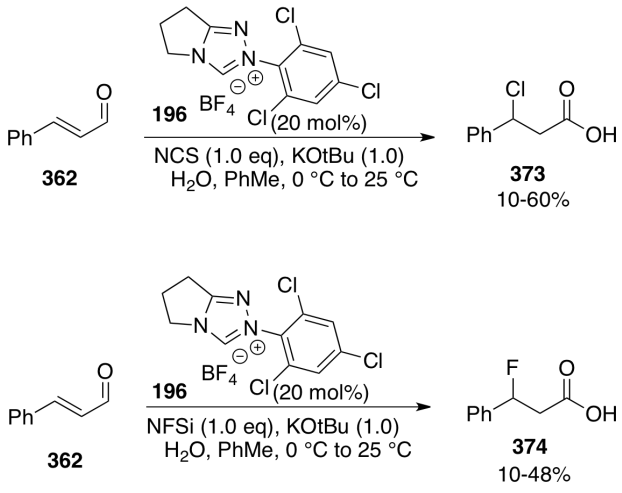
Scheme 31.



Section 3.7 Synthesis of β-halo carboxylic acids.

The synthesis of β-halo carboxylic acids was next studied. It was envisioned that a chiral NHC coupled with homoenolate chemistry and an electrophilic halogenating reagent could provide access to enantioenriched β-halo carboxylic acids. Preliminary results suggest that the reaction is achievable. Utilizing achiral NHC in combination with trans-cinnamyl aldhyde and NCS as the chlorinating agent we can obtain the β-chloro carboxylic acid in 10-60% yield (Scheme 32). The reaction provides irreproducible yields and it is not known what contributes to this. The same is true for fluorination with NFSi which provides the β-fluoro carboxylic acid in 10-48% yield (Scheme 32).

Scheme 32.



Section 3.8 Conclusion

In conclusion a mild catalytic synthesis of enantioenriched α-chloro carboxylic acids was developed. The reaction is also amenable to installing an α-deuteron to provide enantioenriched isotopically labeled acids. Preliminary, mechanistic investigations suggest that the NHC plays a role in supplying hydroxide from the aqueous phase to the

organic phase. Additonally, enantioselectivities can be attributed to the formation hydrates arrived from the addition of hydroxide to the NHC. Investigations into the synthesis of enantioenriched α-deuterio carboxylic acids has provided evidence that epimerization occurrs at the acyl azolium, suggesting that hydrolysis is the turnover limiting step. The synthesis of enantioenriched α-fluoro carboxylic acids has also been accomplished where fluoroenals were identified as a new redox substrate.

Section 3.9 References

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Chapter 2 Experimental

N-heterocyclic Carbene Catalyzed Synthesis of Amides

General Methods. All reactions were carried out under an atmosphere of argon in flame dried glassware with magnetic stirring. Tetrahydrofuran was degassed with argon and passed through two columns of neutral alumina. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV quench, $KMNO_4$, or aqueous ceric ammonium molybdate dips followed by heating. Infrared Spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift is parts per million (δ, ppm) for chloroform ($CHCl_3$) taken as 7.26 ppm, integration, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), and coupling constants (Hz). ^{13}C spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on a Fisions VG Autospec.

Anhydrous HOAt was purchased from Advanced Chem Tech and anydrous HOBt was purchased from AK Scientific Inc. The representative cocatalysts were also dehydrated of any residual water by drying over phosphorus pentoxide and heating to 100 °C in a drying pistol under reduced pressure as needed. Amines were purchased from

Aldrich Chemical Co. and used without further purification. Aldehydes were obtained from Aldrich Chemical Co. or synthesized from the corresponding alcohol. α,α-dichloroaldehydes were prepared from an adaptation of the literature procedure and were purified over calcium hydride and distilled.[i] α,β-Unsaturated aldehydes were purchased from Aldrich Chemical Company and Alfa Aesar and used with further purification as needed. Enantioenriched α,β-epoxyaldehydes were prepared according to literature procedure from the corresponding allylic alcohol.[ii] The enantioenriched epoxy alcohol was then oxidized to the corresponding α,β-epoxyaldehyde according to literature procedure. [iii] α,β-Aziridinealdehyde was synthesized according to the literature procedure.[iv] Compounds **7a**,[v] **7d**[vi], and **7e**[6] match characterization data from previous reports.

It was found that addition of tert-Butanol was essential to reactivity as it buffers the reaction (1-5 ml).

General Procedure A: Synthesis of α-chloro amides.

A 10 ml flame dried round bottom flask with magnetic stir bar was charged with azolium salt (0.011 g, 0.030 mmol, 0.2 equiv) and HOAt (0.004 g, 0.030 mmol, 0.2 equiv). To the flask under argon, was added 1ml of anhydrous THF followed by triethylamine (0.020 g, 0.21 mmol, 1.4 equiv). The mixture was stirred for 20 min, followed by the addition of α,α-dichloro aldehyde (0.030 g, 0.150 mmol, 1.0 equiv). This solution was stirred for an additional 10 minutes at 25 °C. Benzyl Amine (0.017 g, 0.16 mmol, 1.05 equiv) was taken up in 4 ml of anhydrous THF and added to the reaction vessel dropwise over a period of 2 hours (sufficient to attain a final concentration of 0.03M in substrate). The reaction mixture was then stirred for 6 hours or until consumption of starting

material. The mixture is concentrated under reduced pressure to yield a yellow oil. The crude reaction mixture is taken up in a minimal amount of DCM and subjected directly to column chromatography in 4:1 hexanes/EtOAc to yield the desired product in 92% yield.

When hydrochloride salts of amines are used, a variation to the general procedure is followed.

General Procedure B: Synthesis of α-chloro amides.

A 10 ml flame dried round bottom flask with magnetic stir bar was charged with $MgSO_4$ (0.018 g, 0.147 mmol, 1.0 eq) and flame dried under vacuum. To the cooled flask are added azolium salt (0.009 g, 0.030 mmol, 0.2 equiv), HOBt (0.004 g, 0.030 mmol, 0.2 equiv) and L-alanine *tert*-butyl ester hydrochloride (0.028 g, 0.155 mmol, 1.05 equiv). To the flask under argon was added 5 ml of anhydrous THF followed by triethylamine (0.036 g, 0.354 mmol, 2.4 equiv). The mixture was stirred for 30 min, followed by the slow addition of the α,α-dichloro aldehyde (0.030 g, 0.147 mmol, 1.0 equiv) to the reaction vessel. The reaction mixture is stirred for 6 hours or until consumption of starting material. The reaction mixture is concentrated under reduced pressure to yield a yellow oil. The crude mixture is taken up in a minimal amount of DCM and subjected directly to column chromatography and eluted with 2:1 Hexanes/EtOAc to yield the desired product in 85 % yield.

General Procedure C: Synthesis of β-hydroxy amides.

A 5 ml flame dried round bottom flask with magnetic stir bar was charged with azolium salt (0.012 g, 0.033 mmol, 0.01 equiv) and imidazole (0.003 g, 0.033 mmol, 0.01 equiv). To this under argon was added via syringe anhydrous t-BuOH (sufficient to attain 0.1 M concentration in substrate.) The flask was placed in to a 40 °C oil bath and stirred for 5 min at which time DIPEA (0.013 g, 0.100 mmol, 0.30 equiv) was added. The homogeneous mixture was stirred for an additional 20 min at 40 °C. To the reaction vessel was added substrate (0.054 g, 0.033 mmol, 1.0 equiv), and stirred for 10 min followed by the dropwise addition of benzyl amine (0.037 g, 0.350 mmol, 1.05 eq). The reaction was stirred for 24 h and solvent was removed under reduced pressure. The resultant oil was taken up in a minimal amount of DCM and subjected directly to column chromatography and eluted with 3:2 Hexanes/EtOAc to yield the desired product in 86 % yield.

When hydrochloride salts of amines are used, the following variation to the general procedure is applied.

General Procedure D: Synthesis of β-hydroxy amides.

A 5 ml flame dried round bottom flask with magnetic stir bar was charged with azolium salt (0.012 g, 0.033 mmol, 0.01 equiv), imidazole (0.003 g, 0.033 mmol, 0.01 equiv) and L-Alanine *tert*-butyl ester hydrochloride (0.063 g, 0.350 mmol, 1.05 equiv) . To this under argon was added via syringe anhydrous t-BuOH (sufficient to attain 0.1 M concentration in substrate.) The flask was placed in to a 40 °C oil bath and stirred for 5 min at which time DIPEA (0.056 g, 0.434 mmol, 1.30 equiv) was added. The

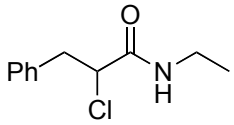
homogeneous mixture was stirred for an additional 20 min at 40 °C. To the reaction vessel was added substrate (0.054 g, 0.333 mmol, 1.0 equiv), and the reaction was stirred for 24 h at which point solvent was removed under reduced pressure. The resultant oil was taken up in a minimal amount of DCM and subjected directly to column chromatography and eluted with 70:30 Hexanes/EtOAc to yield the desired product in 75 % yield.

General Procedure E: Synthesis of Amides from enals

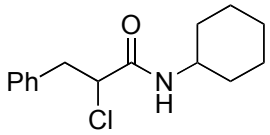
A 5 ml flame dried roundbottom flask with magnetic stir bar was charged with azolium salt (0.027 g, 0.080 mmol, 0.10 equiv) and HOAt (0.010 g, 0.080 mmol, 0.10 equiv). To this under argon was added anhydrous THF via syringe (sufficient to attain a 1M concentration in substrate.) The flask was heated at 45 °C upon which DIPEA (0.010 g, 0.079 mmol, 0.10 equiv) was added and stirred for 15 min followed by the addition of *trans*-cinnamyl aldehyde (0.100 g, 0.756 mmol, 1.0 equiv). To the homogeneous solution was added benzyl amine dropwise over a period of 30 min (0.085 g, 0.756 mmol, 1.0 equiv). The reaction vessel was heated at 45 °C for 24 hours and solvent was removed under reduced pressure. The crude oil was taken up in a minimal amount of DCM and subjected directly to column chromatography and eluted with 70:30 hexanes/EtOAc to yield the desired product in 82% yield.

N-benzyl-2-chloro-3-phenylpropanamide (189): Title compound was prepared according to general procedure A. Rf =0.40 (4:1 Hex/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21-7.31 (m, 8H), 7.12-7.14 (m, 2H), 6.67 (br s, 1H), 4.58 (dd, 1H, J = 4.4, 7.6

Hz), 4.38 (dd, 1H, *J* = 5.6, 14.8 Hz), 4.40 (dd, 1H, *J* = 5.6, 14.8 Hz), 3.45 (dd, 1H, *J* = 4.4, 14.4 Hz), 3.24 (dd, 1H, *J* = 7.6, 14.4 Hz); **^{13}C NMR**: (100 MHz, CDCl3) δ 168.2, 137.5, 136.3, 130.0, 129.0, 128.6, 127.9, 127.4, 61.7, 44.1, 41.5; IR (NaCl, neat) 3284, 3064, 3030, 1659, 1557 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{16}ClNO$ 273.0920. Found 274.0995.

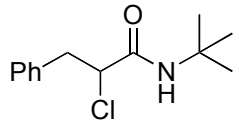


N-ethyl-2-chloro-3-phenylpropanamide (217): Title compound was prepared according to general procedure A, with the exception that the amine was used as a 2.0M solution purchased from Aldrich. Rf = 0.60 (4:1 Hex/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21-7.31 (m, 5H), 6.36 (br s, 1H), 4.51(dd, 1H, *J* = 4, 8 Hz), 3.42 (dd, 1H, *J* = 4.4, 14.4 Hz), 3.26 (ddq, 2H, *J* = 2.1, 5.7, 7.2 Hz), 3.19 (dd, 1H, *J* = 8, 14.4 Hz), 1.07 (d, 3H, *J* = 7.2 Hz); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 168.1, 136.4, 129.9, 128.5, 127.4, 61.9, 41.5, 35.0, 14.7; IR (NaCl, neat) 3288, 3087, 3030, 2976, 2933, 1656, 1557 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}ClNO$ 212.0842. Found 212.0838.

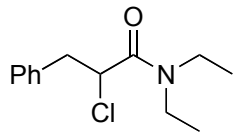


N-cyclohexyl-2-chloro-3-phenylpropanamide (218): Title compound was prepared according to general procedure A. Rf = 0.53 (4:1 Hex/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21-7.30 (m, 5H), 6.26 (br s, 1H), 4.53 (dd, 1H, *J* = 4.0, 12.0 Hz), 3.68-3.80 (m, 1H), 3.42 (dd, 1H, *J* = 8.0, 20.0 Hz), 3.23 (dd, 1H, *J* = 8.0, 20.0 Hz), 1.75-1.85 (m, 2H), 1.52-1.69 (m, 3H), 1.26-1.39 (m, 2H), 1.00-1.14 (m, 3H); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 167.2, 136.3, 130.0, 128.5, 127.3, 61.9, 48.8, 41.5, 32.8, 25.6, 24.8; IR (NaCl,

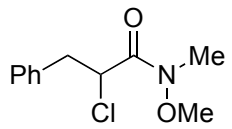
neat) 3301, 3062, 2919, 2851, 1650, 1550 cm^{-1}, HRMS (FAB+) calcd for $C_{15}H_{20}ClNO$ 266.1312. Found 266.1308.



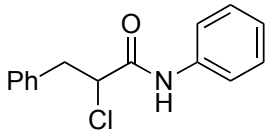
N-*tert*-butyl-2-chloro-3-phenylpropanamide (219): Title compound was prepared according to general procedure A. Rf = 0.25 (9:1 Hex/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22-7.30 (m, 5H), 6.17 (br s, 1H), 4.41 (dd, 1H, *J* = 4, 8 Hz), 3.37 (dd, 1H, *J* = 4.0, 12.0 Hz), 3.19 (dd, 1H, *J* = 8, 16 Hz), 1.29 (s, 9H); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 167.3, 136.4, 130.0, 128.5, 127.3, 62.1, 51.9, 41.4, 28.6; IR (NaCl, neat) 3413, 3305, 3065, 3031, 2969, 2930, 1658, 1556 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{19}NOCl$ 242.1120. Found 242.1119



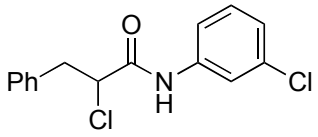
N,N-diethyl-2 chloro-3-phenylpropanamide (220): Title compound was prepared according to general procedure A. Rf = 0.34 (9:1 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21-7.27 (m, 5H), 4.51 (dd, 1H, *J* = 8, 8 Hz), 3.47 (dd, 1H, *J* = 8, 12 Hz), 3.24-3.37 (m, 3H), 3.11 (dd, 1H, *J* = 8, 12 Hz), 3.10 (dq, 1H, *J* = 8, 19.2 Hz), 1.04 (dd, 3H, *J* = 8, 14 Hz), 0.98 (dd, 3H, *J* = 7.2, 14.4 Hz); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 167.7, 137.10, 129.8, 128.7, 127.3, 54.2, 42.4, 41.4, 41.3, 14.8, 12.8; IR (NaCl, neat) 3030, 2976, 2934, 1650, 1495, 1454 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{19}NOCl$ 240.1149. Found 240.1146.



N-methoxy-N-methyl-2-chloro-3-phenylpropanamide (221): Title compound was prepared according to general procedure B. Rf = 0.30 (9:1 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21-7.30 (m, 5H), 4.92 (m, 1H), 3.54 (s, 3H), 3.40 (dd, 1H, *J* = 8.0, 13.6 Hz), 3.15 (s, 3H), 3.12 (m, 1H); **^{13}C NMR**: (100 MHz, CDCl3) δ 136.8, 129.7, 128.7, 127.3, 61.8, 53.0, 40.7, 32.5; IR (NaCl, neat) 3029, 2923, 2851, 1668 cm^{-1} ; HRMS (FAB+) calcd for $C_{11}H_{14}ClNO_2$ 228.0791. Found 228.0801.

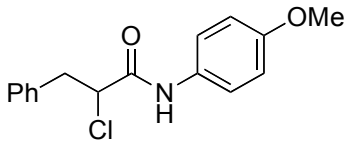


N-phenyl-2-chloro-3-phenylpropanamide (225): Title compound was prepared according to general procedure A. Rf = 0.56 (3:1 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.44-7.46 (d, 2H, J = XX Hz), 7.23-7.34 (m, 7H), 7.12-7.16 (m, 1H), 4.66 (dd, 1H, *J* = 4.8, 7.6 Hz), 3.51 (dd, 1H, *J* = 4.4, 14.4 Hz), 3.28 (dd, 1H, *J* = 8, 14.4 Hz); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 166.4, 136.9, 136.1, 129.9, 129.3, 128.7, 127.6, 125.4, 120.5, 62.1, 41.6; IR (NaCl, neat) 3243, 3194, 3132, 3061, 3022, 2973, 1665, 1600, 1544, 1497 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{16}ClNO$ 260.0842. Found 260.0838.

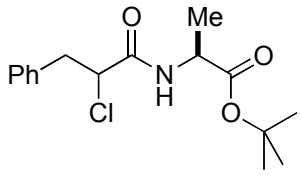


N-(3-chlorophenyl)-2-chloro-3-phenylpropanamide (226): Title compound was prepared according to general procedure A. Rf = 0.046 (3:1 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.57-7.58 (m, 1H), 7.21-7.32 (m, 7H), 7.1-7.13 (m, 1H), 4.65 (dd, 1H), 3.49 (dd, 1H, *J* = 4.8, 14.4 Hz), 3.28 (dd, 1H, *J* = 7.6, 14.4 Hz); **^{13}C NMR**: (100 MHz, CDCl3) δ 166.5, 138.0, 135.9, 135.0, 130.3, 129.9, 128.7, 127.6, 125.5,

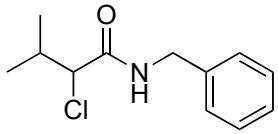
120.5, 118.4, 61.9, 41.5; IR (NaCl, neat) 3284, 3124, 3064, 3026, 2984, 2959, 2897, 1693, 1655, 1591, 1547 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{13}Cl_2NO$ 294.0452. Found 294.0460.



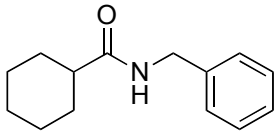
N-(4-methoxyphenyl)-2-chloro-3-phenylpropanamide (227): Title compound was prepared according to general procedure A. Rf = 0.60 (3:1 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.24-7.34 (m, 7H), 6.83-6.86 (m, 2H), 4.65 (dd, 1H, *J* = 4.4, 7.6 Hz), 3.77 (s, 3H), 3.49 (dd, 1H, *J* = 4.4, 14 Hz), 3.28 (dd, 1H, *J* = 7.6, 14 Hz); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 166.3, 157.2, 136.2, 130.0, 128.7, 127.5, 122.5, 114.4, 62.0, 55.7, 41.6; IR (NaCl, neat) 3277, 3143, 3087, 2959, 2838, 1686, 1662, 1607, 1553 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{16}ClNO_2$ 289.0869. Found 289.0872.



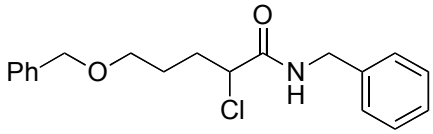
(2S)-*tert*-butyl-2-(2-chloro-3-phenylpropanamido) propanoate (229): Title compound was prepared according to general procedure B as a 2:1 ratio of diastereomers. Rf = 0.35 (9:1 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19-7.28 (m, 5H), 6.94 (d, 1H, *J* = 4 Hz), 4.43 (dd, 1H, *J* = 4, 12 Hz), 4.33-4.40 (m, 1H), 3.46 (dd, 1H, *J* = 4.4, 14 Hz), 3.06 (dd, 1H, *J* = 8.8, 14.4 Hz), 1.42 (s, 9H), 1.32 (d, 3H, *J* = 7.6 Hz); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 171.7, 167.8, 136.6, 129.7, 128.6, 127.3, 82.5, 61.5, 49.3, 41.6, 28.1, 18.6; IR (NaCl, neat) 3306, 3064, 3031, 2979, 2934, 1733, 1661, 1525 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{22}ClNO_3$



N-benzyl-2-chloro-3-methylbutanamide (232): Title compound was prepared according to general procedure A. Rf = 0.28 (4:2 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23-7.34 (m, 5H), 6.94 (br s, 1H), 4.48 (dd, 1H, *J* = 6, 14.8 Hz), 4.43 (dd, 1H, *J* = 5.6, 14.8 Hz), 4.34 (d, 1H, *J* = 3.6 Hz), 2.59 (dqq, 1H, *J* = 3.6, 6.8, 7.2 Hz), 1.05 (d, 3H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 6.8 Hz); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 168.6, 137.8, 129.0, 127.9, 68.7, 44.1, 32.5, 20.4, 16.7; IR (NaCl, neat) 3284, 3067, 2966, 2874, 1648, 1545 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{17}NOCl$ 226.0993. Found 226.0990.

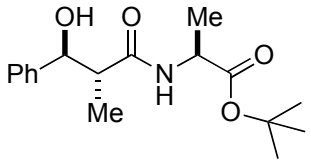


N-benzylcyclohexanecarboxamide (231): Title compound was prepared according to general procedure A. Rf = 0.23 (4:2 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21-7.31 (m, 5H), 5.80 (br s, 1H), 4.39 (d, 2H, *J* = 6 Hz), 2.05-2.10 (m, 1H), 1.74-1.87 (m, 4H), 1.62-1.64 (m, 1H), 1.38-1.47 (m, 2H), 1.18-1.24 (m, 3H); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 176.2, 138.7, 128.9, 127.9, 127.6, 45.8, 43.6, 29.9, 25.9; IR (NaCl, neat) 3282, 3085, 3029, 2926, 2851, 1639, 1551 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{20}NO$ 218.1539. Found 218.1538.

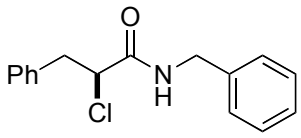


N-benzyl-5-(benzyloxy)-2-chloropentanamide (230): Title compound was prepared according to general procedure A. Rf = 0.42 (4:2 Hex:EtoAc); **^{1}H NMR** (400 MHz,

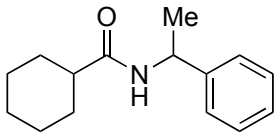
$CDCl_3$) δ 7.23-7.34 (m, 9H), 6.82 (br s, 1H), 4.47 (s, 2H), 4.39-4.45 (m, 4H), 3.49 (d, 2H, *J* = 6 Hz), 2.22-2.32 (m, 1H), 1.98-2.09 (m, 1H), 1.71-1.86 (m, 2H); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 168.9, 138.5, 137.7, 129.0, 128.6, 127.9, 127.9, 127.8, 73.1, 69.6, 61.3, 44.1, 33.0, 26.4; IR (NaCl, neat) 3274, 2963, 2874, 1647, 1547 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{23}NO_2Cl$ 332.1411. Found 332.1407.



(S)-tert-butyl 2-((2R, 3S)-3-hydroxy-2-methyl-3-phenylpropanamido)propanoate (258): Title compound was prepared according to general procedure D. Rf = 0.40 (7:3 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23-7.32 (m, 5H), 6.22 (d, 1H, *J* = 6.8 Hz), 4.66 (d, 1H, *J* = 8 Hz), 4.42 (m, 1H), 4.03 (br s, 1H), 2.52 (m, 1H), 1.43 (s, 9H), 1.35 (d, 3H, *J* = 7.2 Hz), 0.99 (d, 3H, *J* = 7.2 Hz); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 175.3, 172.9, 142.1, 128.1, 128.0, 126.8, 82.6, 49.1, 48.7, 28.1, 18.2, 14.8; IR (NaCl, neat) 3315, 3063, 2978, 2934, 1731, 1650, 1537 cm^{-1}.



(S)-N-benzyl-2-chloro-3-phenylpropanamide (242): Title compound was prepared using enantionenirched 2-Pentafluorophenyl-6,10b-dihydro-4H,5aH-5-oxa-3,10c-diaza-2-azonia-cyclopenta[c]fluorine tetrafluoroborate and under the general procedure A with the addition of 1.0 equiv of t-BuOH. $[\alpha]_D^{23}$ = + 10.0 (CH_2Cl_2). HPLC analysis CHIRACEL OJ-H Column, 80:20 hexanes to isopropanol: 1.0 ml/min. Major 14.40 min, minor 12.35 min.



N-(1-phenylethyl)cyclohexanecarboxamide (250): Title compound was prepared using enantionenirched 2-Pentafluorophenyl-6,10b-dihydro-4H,5aH-5-oxa-3,10c-diaza-2-azonia-cyclopenta[c]fluorine tetrafluoroborate and under the general procedure A. Rf = 0.32 (9:1 Hex:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20-7.32 (m, 5H), 5.63 (d, 1H, *J* = 6.4 Hz), 5.10 (ddd, 1H, *J* = 6.8, 14, 14 Hz), 2.00-2.07 (m, 1H), 1.74-1.86 (m, 4H), 1.61-1.65 (m, 1H), 1.34-1.45 (m, 5H), 1.15-1.27 (m, 3H); **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 175.3, 143.6, 128.8, 127.5, 126.3, 48.4, 45.8, 29.9, 29.8, 25.9, 21.9; IR (NaCl, neat) 3277, 3062, 3029, 2971, 2928, 2853, 1639, 1540 cm^{-1}. HPLC Analysis CHIRACEL OJ-H, 90:10 hexanes to isopropanol, 1.0 ml/min. Major 9.27 min, minor 8.15 min.

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[ii] Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, 109, 5765-5780.

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[iv] Ali, S. I.; Nikalje, M. D.; Sudalai, A. *Org. Lett.* **1999**, *1*, 705-707.

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Chapter 3 Experimental

General Methods

All reactions were carried out under an atmosphere of argon using flame-dried glassware with magnetic stirring. Toluene was degassed and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on SiliCycle® Silica Flash® 40-63μm 60A. Thin Layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light, $KMnO_4$, bromocrescol Green dips followed by heating.

^1H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. ^1H NMR data are reported as the following: chemical shift in parts per million (δ, ppm) from chloroform ($CHCl_3$) taken as 7.26 ppm, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet) and coupling constant (Hz). ^{13}C NMR are reported as the following: chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on a Fisons VG Autospec.

^1H NMR and ^{13}C NMR spectra of the azolium salts were recorded on a Varian 400 MHz spectrometers at ambient temperature. ^1H NMR data are reported as the following: chemical shift in parts per million (δ, ppm) from chloroform ($CHCl_3$) taken as 7.26 ppm, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet,

m=multiplet) and coupling constant (Hz). ^{13}C NMR are reported as the following: chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm.

α,α-dichloro aldehydes were prepared according to literature procedure from the corresponding aldehyde and freshly distilled prior to use or purified by generating the bisulfite adduct. Aldehydes **2a**, **2e**, and **2g** match spectroscopic data and physical properties to those previously reported in the literature. Bisulfite adducts were prepared according to literature procedure from the corresponding α,α-dichloro aldehydes and dried under vacuum prior to use. α-Fluoro enals were prepared according to literature procedure. Bisulfite adducts were prepared according to literature procedure from the corresponding α-Fluoro enals and dried under vacuum prior to use. α-Bromo α-fluoro aldehyde was prepared according to literature procedure and distilled prior to use.

Distilled water was used without further purification. Deuterium Oxide was purchased from Cambridge Isotope Laboratories, Inc and was used without further purification. Anhydrous Potassium Carbonate was purchased from Fisher Scientific and used without further purification. Sodium Chloride was purchased from Fisher Scientific and used without further purification. Diazomethane was prepared according to literature procedure from Diazald.

All racemic products were obtained upon treating the respective aldehyde with achiral triazolium salt using DCM as solvent and 1M K_2CO_3.

General Procedure (A) for the synthesis of α-proteo, α-chloro carboxylic acid: To a flame dried 25 ml round bottom flask with magnetic stir bar was added triazolium salt **320** (0.012, 0.029 mmol, 10 mol %) and TBAI (0.011, 0.029 mmol, 10 mol %). To the

flask was added aldehyde **187** (0.060, 0.295 mmol, 1.0 eq) followed by toluene (0.02M with respect to aldehyde). The flask was purged with argon and brine was added to the reaction vessel (of equal volume to 1.0 eq of 1M K_2CO_3 in H_2O). The reaction is stirred under an atmosphere of argon for 5 minutes followed by addition of 1.0 equiv of 1M K_2CO_3 in H_2O. The reaction is stirred vigorously until completion (12-28 hours) followed by addition of 3.0 equiv of AcOH to the reaction vessel. The reaction mixture is loaded on a plug of silica and eluted with EtOAc with 5% AcOH. The crude solution is reduced *in vacuo* to yield an oil. The crude oil is taken up in toluene and the solution is reduced *in vacuo* to remove residual AcOH. The crude oil is then taken up in toluene and purified via column chromatography via gradient elution. The oil is dissolved in 1:1 DCM and MeOH and to the vessel is added CH_2N_2 dropwise with stirring until bubbling subsides and the solution is yellow. Excess diazomethane is quenched via the addition of AcOH. The reaction is concentrated *in vacuo* to yield the methyl ester.

General Procedure (B) for the synthesis of α-deutero, α-chloro carboxylic acid: To a flame dried 25 ml round bottom flask with magnetic stir bar was added triazolium salt **320** (0.012 g, 0.0295 mmol, 10 mol %) and TBAI (0.011 g, 0.0295 mmol, 10 mol %). To the flask was added aldehyde **187** (0.060 g, 0.295 mmol, 1.0 eq) followed by toluene (0.02M with respect to aldehyde). The flask was purged with argon and brine (saturated solution of NaCl in D_2O) was added to the reaction vessel (of equal volume to 1.0 eq of 1M K_2CO_3 in D_2O). The reaction is stirred under an atmosphere of argon for 5 minutes followed by addition of 1.0 equiv of 1M K_2CO_3 in D_2O. The reaction is stirred until completion (8-10 hours) followed by addition of 1.0 equiv of AcOH to the reaction

vessel. The reaction mixture is loaded on to a plug of silica and eluted with EtOAc with 5% AcOH. The crude solution is reduced *in vacuo* to yield an oil. The oil is dissolved in 1:1 DCM and MeOH and to the vessel is added CH_2N_2 dropwise with stirring until bubbling subsides. The reaction is concentrated *in vacuo* to yield a crude oil. The crude mixture is purified by flash chromatography to yield the desired product.

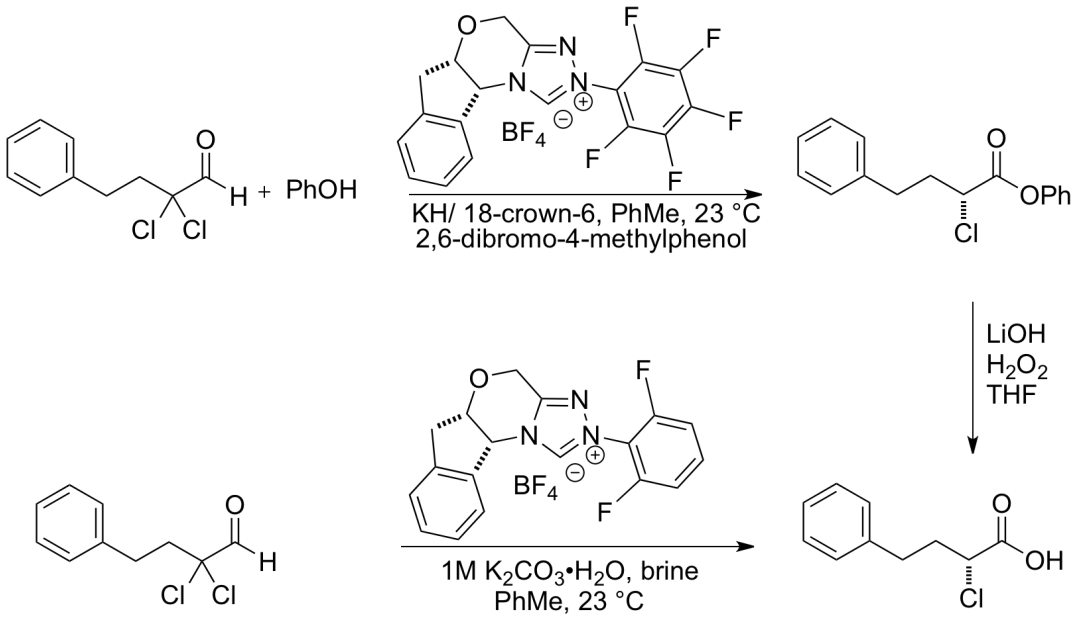
General Procedure (C) for the synthesis of α-proteo, α-fluoro carboxylic acid: To a flame dried 25 ml round bottom flask with magnetic stir bar was added triazolium salt **320** (0.028 g, 0.066 mmol, 20 mol %). To the flask was added aldehyde (0.060 g, 0.333 mmol, 1.0 eq) followed by toluene (0.02M with respect to aldehyde). The flask was purged with argon and brine was added to the reaction vessel (of equal volume to 1.0 eq of 1M $KHCO_3$ in H_2O). The reaction is stirred under an atmosphere of argon for 5 minutes followed by addition of 1.0 equiv of 1M $KHCO_3$ in H_2O. The reaction is stirred until completion (8-10 hours) followed by addition of 1.0 equiv of AcOH to the reaction vessel. The reaction mixture is loaded on a plug of silica and eluted with EtOAc with 5% AcOH. The crude solution is reduced *in vacuo* to yield an oil. The oil is dissolved in 1:1 DCM and MeOH and to the vessel is added CH_2N_2 dropwise with stirring until bubbling subsides. The reaction is concentrated *in vacuo* to yield a crude oil. The crude mixture is purified by flash chromatography to yield the desired product.

General Procedure (D) for the synthesis of α-deutero, α-fluoro carboxylic acid: To a flame dried 25 ml round bottom flask with magnetic stir bar was added triazolium salt **320** (0.028 g, 0.066 mmol, 20 mol %). To the flask was added aldehyde **371** (0.060 g,

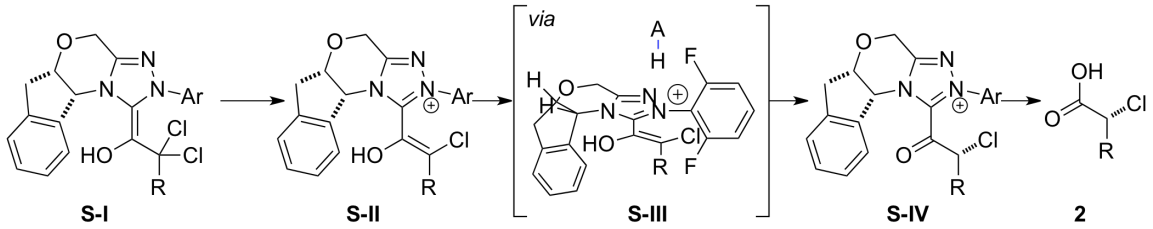
0.333 mmol, 1.0 eq) followed by toluene (0.02M with respect to aldehyde). The flask was purged with argon and brine (saturated solution of NaCl in D_2O) was added to the reaction vessel (of equal volume to 1.0 eq of 1M K_2CO_3 in D_2O). The reaction is stirred under an atmosphere of argon for 5 minutes followed by addition of 1.0 equiv of 1M K_2CO_3 in D_2O. The reaction is stirred until completion (8-10 hours) followed by addition of 1.0 equiv of AcOH to the reaction vessel. The reaction mixture is loaded on a plug of silica and eluted with EtOAc with 5% AcOH. The crude solution is reduced *in vacuo* to yield an oil. The oil is dissolved in 1:1 DCM and MeOH and to the vessel is added CH_2N_2 dropwise with stirring until bubbling subsides. AcOH is added dropwise to quench any unreacted diazomethane. The reaction is concentrated *in vacuo* to yield a crude oil. The crude mixture is purified by flash chromatography to yield the desired product.

Determination of Absolute Stereochemistry

In our prior work,[i] we have shown we can access the enantioenriched α-chloroester shown below and determined its absolute stereochemistry by chemical correlation to an amino acid. We have taken this phenyl ester and hydrolyzed it to the α-chloro acid. HPLC elution indicates the same major enantiomer as that observed in the hydration reaction.

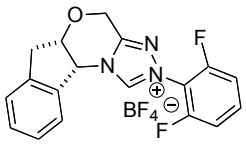


A model to account for absolute stereochemistry is shown below. Structure **S-I** is presumed to be the major olefin isomer generated as an intermediate, following the computational work of Houk.[ii] Chloride elimination affords **S-II** having the chloride substituent cis to the azolium. Protonation then occurs from the top face, controlled by the bulky indanyl group on the catalyst to afford **S-IV**.

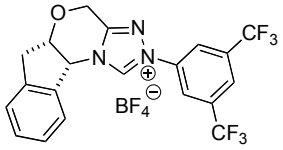


Catalyst Preparation and Characterization

All catalysts were prepared according to literature procedure. During the synthesis of catalyst **C5** it was noted that isolation and drying of the hydrazide was necessary to facilitate cyclization.

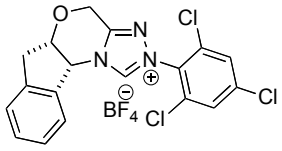


Triazolium Salt (**320**): $\mathbf{R_f}$ = 0.42 (EtOAc); $\mathbf{[\alpha]_D}^{24}$ = - 179.8° (10 mg/ml, MeOH); mp = 235 °C; **^{1}H NMR** (400 MHz, acetone-d_6) δ 11.10 (s, 1H), 7.90-7.87 (m, 1H), 7.65 (d, 1H, *J* = 7.2 Hz), 7.50-7.32 (m, 5H), 6.30 (d, 1H, *J* = 6.3 Hz), 5.37 (d, 1H, *J* = 16 Hz), 5.24 (d, 1H, *J* = 16.4 Hz), 5.20 (m, 1H); **^{13}C NMR** (100 MHz, acetone-d_6) δ 158.2, 155.6, 151.4, 145.8, 141.1, 135.7, 134.9 (t), 129.8, 127.5, 125.8, 124.4, 113.3 (d), 94.6, 77.6, 62.6, 60.2, 37.3; **IR** (KBr) 3133, 3115, 3072, 2955, 2916, 1627, 1605, 1588, 1540, 1484, 1210, 1067, 967 cm^{-1}; **HRMS** (FAB+) calcd for $C_{18}H_{14}F_2N_3O$, 326.1105. Found 326.1102.



Triazolium Salt (**326**): R_f = 0.50 (EtOAc); $[\alpha]_D^{24}$ = - 165.0° (9 mg/ml, MeOH); mp = 220 °C; **^{1}H NMR** (400 MHz, acetone-d_6) δ 11.37 (s, 1H), 8.73 (s, 2H), 8.42 (s, 1H), 7.70 (dd, 1H, *J* = 7.6, 3.8 Hz), 7.45-7.40 (m, 2H), 7.32-7.28 (m, 1H), 6.22 (d, 1H, *J* = 4.10 Hz), 5.83 (d, 1H, *J* = 16.4 Hz), 5.22 (d, 1H, *J* = 16.4 Hz), 5.14 (t,

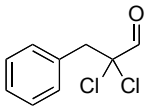
1H, *J* = 4.8 Hz), 3.54 (dd, 1H, *J* = 17.2, 4.8 Hz), 3.26 (d, 1H, *J* = 17.2 Hz); **^{13}C NMR** (100 MHz, acetone-d_6) δ 151.1, 142.6, 141.1, 137.2, 135.6, 133.3 (q, *J* = 34.6 Hz), 129.7, 127.4, 125.8, 124.6, 123.0 (br s), 123.0 (q, *J* = 270 Hz), 121.6, 77.7, 62.5, 60.2, 37.3; IR (KBr) 3133, 3115, 3106, 2953, 2914, 1666, 1593, 1540, 1369, 1281, 1182, 1140, 899 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{13}F_6N_3O$, 426.1036. Found 426.1044.



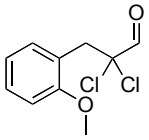
Triazolium Salt (**267**): R_f = 0.25 (EtOAc); $[\alpha]_D^{24}$ = - 63.3° (11 mg/ml, CH_3CN); mp = 260 ˚C ; **^{1}H NMR** (400 MHz, acetone-d_6) δ 11.15 (s, 1H), 8.00 (s, 2H), 7.63-7.61 (m, 1H), 7.47-7.35 (m, 3H), 6.38 (d, 1H, *J* = 4.10 Hz), 5.37 (d, 1H, *J* = 16.4 Hz), 5.27 (d, 1H, *J* = 16.4 Hz), 5.22 (t, 1H, *J* = 4.8 Hz), 3.57 (dd, 1H, *J* = 17.2, 4.8 Hz), 3.27 (d, 1H, *J* = 17.2 Hz); **^{13}C NMR** (100 MHz, acetone-d_6) δ 151.8, 146.1, 141.1, 139.3, 135.9, 134.4, 130.2, 129.8, 127.7, 126.0, 124, 77.6, 62.9, 60.2, 37.4; IR (KBr) 3124, 3089, 3068, 3050, 3007, 2911, 2855, 1588, 1566, 1536, 1466, 1414, 1149, 1054, 967 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{13}Cl_3N_3O$, 392.0019. Found 392.0124.

Characterization of α,α-dichloroaldehydes

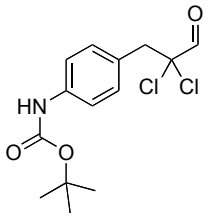
General Comments: Retention factors (R_f) were unobtainable due to streaking of the compound on TLC plates. High-resolution mass spectra were also not obtainable due to decomposition of the aldehyde. The aldehydes are stable for several weeks stored in the neat form under Ar in a freezer.



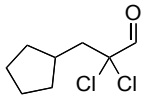
2,2-dichloro-3-phenylpropanal (311a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.34 (s, 5H), 3.58 (s, 2H).



2,2-dichloro-3-(2-methoxyphenyl)propanal (334a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.28-7.24 (m, 2H), 6.95-6.93 (m, 1H), 6.84-6.82 (m, 1H), 3.76 (s, 3H), 3.70 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.6, 157.3, 133.2, 130.0, 121.5, 120.9, 110.7, 89.0, 55.2, 43.2. IR (NaCl) 2941, 2840, 1750, 1491, 1524 cm^{-1}.

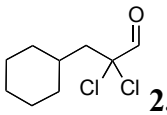


2,2-dichloro-3-(4-tert butylaminophenyl)propanal (338a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.32 (d, 2H, J = 8.4 Hz), 7.25 (d, 1H, J = 8.4 Hz), 6.48 (bs, 1H), 3.51 (s, 2H), 1.50 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.6, 152.8, 138.4, 132.2, 127.2, 118.4, 87.7, 81.0, 45.8, 28.5; IR (NaCl) 3411, 3328, 2986, 2923, 1748, 1732, 1710, 1560, 1166 cm^{-1}.

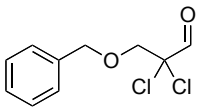


2,2-dichloro-3-cyclopentylpropanal (339a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 2.32 (d, 2H, J = 6.4 Hz), 2.11-2.0 (m, 1H), 1.87-1.80 (m, 2H), 1.60-1.43 (m,

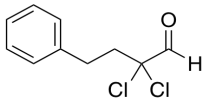
4H), 1.16-1.01 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.4, 89.0, 46.5, 37.1, 33.9, 25.0; IR (NaCl) 2951, 2869, 1743, 1717 cm^{-1}.



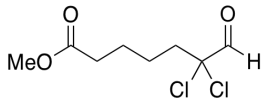
2,2-dichloro-3-cyclohexylpropanal (340a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 2.24 (d, 2H, *J* = 5.3 Hz), 1.81-1.61 (m, 6H), 1.32-1.00 (m, 5H).



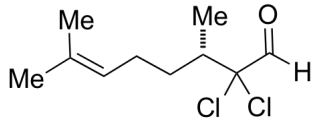
3-benzyloxy-2,2-dichloropropanal (341a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.35-7.24 (m, 5H), 4.65 (s, 2H), 4.02 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.4, 136.9, 128.8, 128.4, 128.0, 74.3; IR (NaCl) 3062, 3031, 2926, 2860, 1742, 1717, 1701, 1099 cm^{-1}.



2,2-Dichloro-4-phenyl-butyraldehyde (342a): ^{1}H NMR (400 MHz) δ 9.31 (s, 1H), 7.28-7.40 (m, 5H), 3.00-3.07 (m, 2H), 2.63-2.67 (m, 2H).

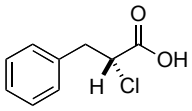


Methyl 6,6-dichloro-7-oxoheptanoate (343a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 3.70 (s, 3H), 2.25-2.40 (m, 4H), 1.65-1.71 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.9, 173.8, 94.2, 88.4, 51.8, 40.3, 33.8, 24.2; IR (NaCl) 2955, 2869, 1438 cm^{-1} .

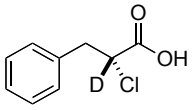


2,2-Dichloro-3,7-dimethyl-oct-6-enal (352): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 5.04-5.10 (m, 1H), 2.32-2.38 (m, 1H), 2.08-2.19 (m, 1H), 1.93-2.06 (m, 1H), 1.66-1.76 (m, 4H), 1.61 (s, 3H), 1.28-1.40 (m, 1H), 1.16 (d, 3H, *J* = 6.6 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 185.6, 132.8, 123.1, 94.5, 41.7, 31.8, 25.7, 25.3, 17.7, 14.5; IR (NaCl) 1747, 1453, 1382 cm^{-1} .

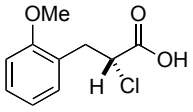
Characterization of α-chloro,α-proteo and α-chloro,α-deutero carboxylic acids



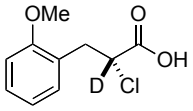
(R)-2-chloro-3-phenylpropionic acid (**311**; X=H): Title compound was prepared according to general procedure A. R_f = 0.32 (8:2 Hexanes:EtOAc w/ 3% AcOH); $[\alpha]_D^{24}$ = - 6.8° (10 mg/ml, MeOH); HPLC – analysis Chiracel OJ-H column 95:5 hexanes : isopropanol 1 ml/min for 30 min. Major: 13.69 min, Minor: 19.21 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.80 (bs, 1H), 7.17-7.29 (m, 5H), 4.50 (t, 1H, *J* = 10 Hz), 3.40 (dd, 1H, *J* = 8.8, 19.2 Hz), 3.20 (dd, 1H, *J* = 10.4, 18.8 Hz).



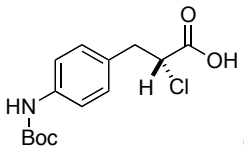
(R)- 2- deutero, chloro-3-phenylpropanoic acid (**311**; X=D): Title compound was prepared according to general procedure B. R_f = 0.32 (8:2 Hexanes:EtOAc w/ 3% AcOH); $[\alpha]_D^{24}$ = - 6.7° (13 mg/ 1 ml, MeOH); HPLC – analysis Chiracel OJ-H column 95:5 hexanes : isopropanol 1 ml/ min for 30 min. Major: 13.94 min, Minor: 19.50 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.16-7.28 (m, 5H), 3.30 (bd, 1H, *J* = 14.4 Hz), 3.10 (bd, 1H, *J* = 14.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.7, 135.8, 135.0, 129.6, 128.9, 127.6, 58.9 (t), 41.0; IR (NaCl) 3133, 3115, 3072, 2955, 2916, 1627, 1605, 1588, 1540, 1484, 1210, 1067, 967 cm^{-1}; HRMS (FAB+) calcd for $C_9H_8DClO_2$, 184.0281. Found 184.0288.



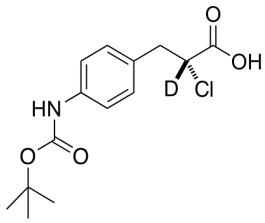
(R)-2-chloro-3-(methoxyphenyl) propanoic acid (**334**; X=H): R_f = 0.22 (7:3 Hexanes: EtOAc); $[\alpha]_D^{24}$ = -31.6° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 99:1 hexanes : isopropanol 1 ml/min for 30 min. Major: 14.20 min, Minor: 10.52 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.04 (bs, 1H), 7.28-7.15 (m, 2H), 6.91-6.84 (m, 2H), 4.65 (t, 1H, *J* = 7.4 Hz), 3.81 (s, 3H), 3.39 (dd, 1H, *J* = 13.6, 7.2 Hz), 3.16 (dd, 1H, *J* = 14, 8.0 Hz); **^{13}C NMR** (100 MHz, acetone-d_6) δ 175.7, 157.8, 132.0, 129.2, 123.9, 120.7, 110.5, 55.6, 55.4, 36.7, 30.0; IR (NaCl) 3133, 3115, 3072, 2955, 2916, 1627, 1605, 1588, 1540, 1484, 1210, 1067, 967 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{10}ClO_3$, 213.0324. Found 213.0325.



(R)-2-deutero, chloro-3-(methoxyphenyl) propanoic acid (**334**; X=D): R_f = 0.22 (7:3 Hexanes: EtOAc); $[\alpha]_D^{24}$ = -35.0° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 99:1 hexanes : isopropanol 1 ml/min for 30 min. Major: 16.33 min, Minor: 11.87 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.67 (bs, 1H), 7.27-7.15 (m, 2H), 6.90-6.83 (m, 2H), 3.81 (s, 3H), 3.40 (bd, 1H, *J* = 13.6 Hz), 3.18 (bd, 1H, *J* = 13.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.6, 157.8, 131.9, 129.2, 123.9, 120.7, 110.5, 55.6, 55.4, 36.7, 30.0; IR (NaCl) 3133, 3115, 3072, 2955, 2916, 1627, 1605, 1588, 1540, 1484, 1210, 1067, 967 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_9DClO_3$, 214.0387. Found 214.0389.

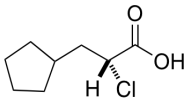


(R)-2-chloro-3-(4-tert-butoxycarbonylaminophenyl)propanoic acid (**338**; X= H): Title compound was prepared according to general procedure A. R_f = 0.42 (1:1 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -74.8° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 95:5 hexanes : isopropanol 1 ml/min for 50 min. Major: 43.56 min, Minor: 37.86 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 7.23 (d, 2H, *J* = 8.4 Hz), 7.12 (d, 2H, *J* = 8.4 Hz), 6.68 (bs, 1H), 4.42 (t, 1H, *J* = 7.2 Hz), 3.29 (dd, 1H, *J* = 14.0, 7.2 Hz), 3.13 (dd, 1H, *J* = 14.0, 7.2 Hz), 1.50 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 137.7, 130.4, 130.7, 119.1, 57.5, 40.5, 28.5; IR (NaCl) 3331, 2980, 2931, 2627, 2360, 1715, 1614, 1596, 1524, 1414, 1393, 1369, 1159 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}ClNO_4$, 298.0852. Found 298.0855.

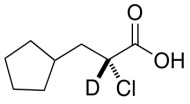


(R)- 2-deutero, chloro-3-(4-tert-butoxycarbonylaminophenyl) propanoic acid (**339**; X = D): Title compound was prepared according to general procedure B. R_f = 0.42 (1:1 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -78.9° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 95:5 hexanes : isopropanol 1 ml/min for 50 min. Major: 43.0 min, Minor: 37.60 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, 2H, *J* = 8.0 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 3.29 (bd, 1H, *J* = 14.0 Hz), 3.12 (bd, 1H, *J* = 14.0 Hz), 1.50 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.7, 137.7, 130.3, 130.1, 119.0, 58.6 (t), 40.4, 28.5; IR (NaCl) 3331, 2980, 2931, 2627, 2360, 1715, 1614, 1596, 1524, 1414,

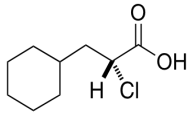
1393, 1369, 1159 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}DClNO_4$, 299.0914. Found 299.092.



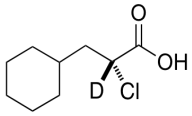
(R)- 2-chloro-3-cyclopentylpropanoic acid (**339**; X=H): Title compound was prepared according to general procedure A. R_f = 0.22 (1:1 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -95.0° (10 mg/ml, MeOH); GC – analysis Chiral BDM-1 column, 140 °C, 1 ml/min for 45 min. Major: 7.58 min, Minor: 5.77 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (bs, 1H), 4.29 (t, 1H, *J* = 7.6 Hz), 1.95-2.03 (m, 3H), 1.80-1.84(m, 2H), 1.52-1.63 (m, 4H), 1.06-1.16 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.0, 56.8, 41.1, 37.1, 32.6, 32.1, 25.3, 25.1; IR (NaCl) 2951, 2869, 1721, 1431, 1289, 1205 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{12}ClO_2$, 175.0531. Found 175.0532.



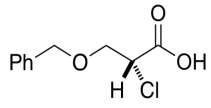
(R)- 2-deutero, chloro-3-cyclopentylpropanoic acid (**339**; X=D): Title compound was prepared according to general procedure B. R_f = 0.24 (1:1 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -98.5° (10 mg/ml, MeOH); GC – analysis Chiral BDM-1 column, 140 °C, 1 ml/min for 46 min. Major: 7.58 min, Minor: 5.70 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.24 (bs, 1H), 1.95-2.02 (m, 3H), 1.78-1.87(m, 2H), 1.53-1.64 (m, 4H), 1.12-1.19 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.2, 56.4 (t), 41.0, 37.1, 32.6, 32.1, 31.3, 25.2, 25.0; IR (NaCl) 3109, 2952, 2869, 2670, 2554, 1720, 1451, 1414, 1284, 1205 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{11}DClO_2$, 176.0594. Found 176.0594.



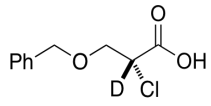
(R)- 2-chloro-3-cyclohexylpropanoic acid (**340**; X= H): Title compound was prepared according to general procedure A. R_f = 0.20 (1:1 Hexanes: EtOAc); $[\alpha]_D^{24}$ = -105.1° (10 mg/ml, MeOH); GC – analysis Chiral BDM-1 column, 100 °C, 1 ml/min for 120 min. Major: 85.92 min, Minor: 88.61 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.67 (bs, 1H), 4.36 (dd, 1H, *J* = 6.0, 8.8 Hz), 1.80-1.92 (m, 2H), 1.63-1.74 (m, 5H), 1.46-1.59 (m, 1H), 1.11-1.30 (m, 3H), 0.82-1.2 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.0, 55.2, 42.2, 34.5, 33.4, 32.1, 26.5, 26.2, 26.1; IR (NaCl) 3109, 2925, 2853, 2672, 1723, 1449, 1429, 1291, 1211 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{14}ClO_2$, 189.0688. Found 189.0688.



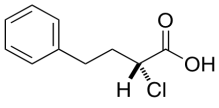
(R)- 2-chloro-3-cyclohexylpropanoic acid (**340**; X= D): Title compound was prepared according to general procedure B. R_f = 0.2 (1:1 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -108.2° (10 mg/ml , MeOH); GC – analysis Chiral BDM-1 column, 100 °C, 1 ml/min for 120 min. Major: 85.92 min, Minor: 88.61 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.21 (bs, 1H), 1.74-1.90 (m, 2H), 1.64-1.74 (m, 5H), 1.47-1.56 (m, 1H), 1.11-1.30 (m, 3H), 0.82-1.2 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.2, 54.6 (t), 42.1, 34.5, 33.4, 32.1, 26.5, 26.2, 26.1; IR (NaCl) 3098, 3036, 2925, 2853, 2669, 2537, 2342, 2360, 1721, 1449, 1415, 1292, 1282, 1213 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{13}DClO_2$, 190.0751. Found 190.0752.



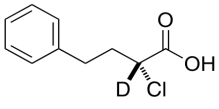
(R)- 2-chloro-3-cyclohexylpropanoic acid (**341**; X= H): Title compound was prepared according to general procedure A. R_f = 0.35 (7:3 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -27.3° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 99:1 hexanes : isopropanol 1 ml/ min for 10 min. Major: 8.28 min, Minor: 8.74 min 1 ml/ min for 10 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.10 (bs, 1H), 7.30-7.33 (m, 5H), 4.60 (s, 2H), 4.30 (dd, 1H, *J* = 5.6, 10.4 Hz), 3.89 (dd, 1H, *J* = 8.4, 10.4 Hz), 3.83 (dd, 1H, *J* = 6.0, 10.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.2, 128.7, 128.3, 128.0, 73.9, 71.0; IR (NaCl) 3439, 3165, 3032, 2926, 2871 2644, 2582, 1733, 1453, 1107 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{10}ClO_3$, 213.0324. Found 213.0321.



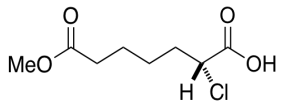
(R)- 2- deutero, chloro-3-cyclohexylpropanoic acid (**341**; X= D): Title compound was prepared according to general procedure B. R_f = 0.32 (1:1 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -30.1° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 99:1 hexanes : isopropanol 1 ml/ min for 10 min. Major: 8.32 min, Minor: 8.84 min 1 ml/min for 10 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.10 (bs, 1H), 7.24-7.35 (m, 5H), 4.60 (s, 2H), 3.89 (bd, 1H, *J* = 10.0 Hz), 3.83 (bd, 1H, *J* = 10.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9, 137.2, 128.7, 128.3, 128.0, 127.6, 127.9, 73.9, 70.9, 53.4 (t), 27.7; IR (NaCl) 3176, 3086, 3064, 2929, 2868, 2801, 1726, 1496, 1453, 1237, 1213 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_9DClO_3$, 214.0387. Found 214.0392.



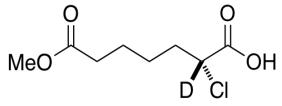
(R)- 2-deutero, chloro-3-cyclohexylpropanoic acid (**342**; X= H): Title compound was prepared according to general procedure A. R_f = 0.45 (7:3 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -25.8° (10 mg/ml, MeOH); HPLC – analysis Chiracel OJ-H column 90:10 hexanes : isopropanol 1 ml/min for 30 min. Major: 8.32 min, Minor: 8.84 min 1 ml/min for 10 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (bs, 1H), 7.13-7.24 (m, 5H), 4.20 (dd, 1H, *J* = 4.8, 8.4 Hz), 2.70-2.80 (m, 2H), 2.16-2.30 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.3, 139.8, 128.9, 128.8, 126.7, 56.4, 36.4, 32.1; IR (NaCl) 3031, 3086, 3064, 2929, 2868, 2801, 1721, 1496, 1453, 1237, 1213 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{10}ClO_2$, 197.0375. Found 197.0376.



(R)- 2-deutero, chloro-3-cyclohexylpropanoic acid (**342**; X=D): Title compound was prepared according to general procedure B. R_f = 0.45 (7:3 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -27.2° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 99:1 hexanes : isopropanol 1 ml/min for 10 min. Major: 8.32 min, Minor: 8.84 min 1 ml/min for 10 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.15 (bs, 1H), 7.13-7.26 (m, 5H), 2.68-2.81 (m, 2H), 2.16-2.33 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.5, 139.8, 128.9, 128.8, 128.5, 126.7, 56.1 (t), 36.3, 32.1; IR (NaCl) 3176, 3086, 3064, 2929, 2868, 2801, 1726, 1496, 1453, 1237, 1213 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_9DClO_2$, 198.0438. Found 198.0438.

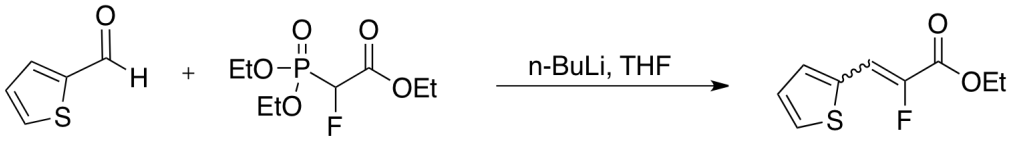


(R)-2-chloro-7-methoxy-7-oxoheptanoic acid (**343**; X=H): Title compound was prepared according to general procedure A. R_f = 0.18 (1:1 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -89.1° (10 mg/ml, MeOH); HPLC – analysis Chiracel AD-H column 95:5 hexanes : isopropanol 1 ml/min for 50 min. Major: 46.4 min, Minor: 48.3 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.05 (bs, 1H), 4.30 (bs, 1H), 3.65 (s, 3H), 3.32 (t, 2H, *J* = 7.2 Hz), 1.95-2.04 (m, 2H), 1.50-1.66 (m, 4H); **^{13}C NMR** (100 MHz, acetone-d_6) δ 175.1, 174.1, 59.8, 51.9, 34.5, 33.9, 25.6, 24.7, 24.3; IR (NaCl) 3467, 2954, 2869, 2360, 1732, 1636, 1457, 1439, 1368, 1177 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{12}ClO_4$, 207.043. Found 207.0431.

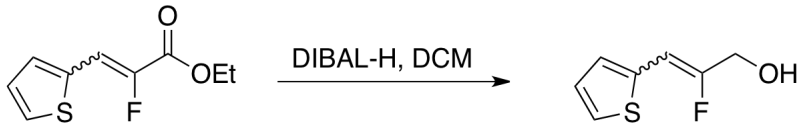


(R)-2-deutero, chloro-7-methoxy-7-oxoheptanoic acid (**343**; X = D): Title compound was prepared according to general procedure B. R_f = 0.17 (1:1 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -92.5° (10 mg/ml, MeOH); HPLC – analysis Chiracel AD-H column 95:5 hexanes : isopropanol 1 ml/min for 60 min. Major: 47.3 min, Minor: 49.6 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.17 (bs, 1H), 4.30 (bs, 1H), 3.65 (s, 3H), 2.28-2.36 (m, 2H), 2.01-2.07 (m, 1H), 1.89-2.00 (m, 1H), 1.58-1.70 (m, 3H), 1.43-1.57 (m, 2H), 1.47-1.56 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.9, 174.5, 56.9 (t), 51.9, 34.4, 33.9, 25.5, 24.6; IR (NaCl) 3467, 3182, 2953, 2868, 2633, 2537, 2360, 1737, 1720, 1457, 1439, 1367, 1223, 1169 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{11}DClO_4$, 208.0492. Found 208.0496.

Synthesis of α-Fluoro Enals



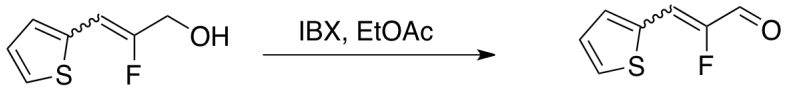
A flame dried 25 ml round bottom flask with stir bar was charged with 2-Fluoro-2-phosphonoacetic acid triethyl ester (1.50 g, 6.19 mmol, 1.0 eq.), and placed under an argon atmosphere. Anhydrous THF (20 ml) was then added to the reaction vessel and the clear solution was agitated and cooled to 0 °C. 4 ml of *n*-BuLi (1.6 M in hexanes) was slowly added to the reaction vessel. Upon complete addition the vessel was warmed to 25 °C and stirred for 30 min. 2- Thiophene carboxaldehyde was the added to the reaction vessel and stirred for 12 hrs. The reaction was quenched at 0 °C via the addition of 15 ml of 10% HCl. The mixture was extracted with EtOAc and washed with water and brine. The organic solution was dried with magnesium sulfate and filtered to yield a crude yellow solution, which was reduced *in vacuo* to yield a yellow oil. The oil is purified via column chromatography in 97:3 hexanes: ethyl acetate to 95: 5 hexanes: ethyl acetate to yield the desired product as a mixture of olefin isomers in an 80% yield.



A flame dried 25 ml round bottom flask with stir bar was charged with ester (0.934 g, 4.66 mmol, 1.0 eq). To the flask was added 15 ml of anhydrous DCM and the

solution stirred under an argon atmosphere. To the reaction vessel was added DIBAl-H (1M in PhMe, 18.64 ml, 3.0 eq) at 25 °C. The reaction was stirred until consumption of starting material was observed by TLC; the reaction vessel was then cooled to 0 °C and 15 ml of a saturated solution of Rochelle's salt was added and the vessel was allowed to warm to 25 °C. The solution was stirred until a phase separation was observed. The solution was extracted with DCM and washed with water and brine. The organic solution was dried with magnesium sulfate, filtered and reduced *in vacuo* to yield an oil. The oil was purified by column chromatography in 8:2 hexanes: ethyl acetate to yield the alcohol in 75% yield.

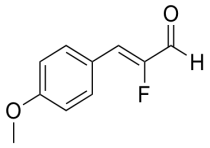
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, 1H, *J* = 1.2, 5.2 Hz), 6.92-6.99 (m, 2H), 6.42 (d, 1H, *J* = 18.8 Hz), 4.49 (d, 2H, *J* = 21.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.9, 174.5, 56.9 (t), 51.9, 34.4, 33.9, 25.5, 24.6;



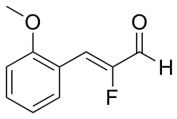
A 100 ml round bottom was charged with alcohol (0.50 g, 1.0 eq) and dissolved in 40 ml of EtOAc. IBX (2.21 g, 2.5 eq) was added to the flask. A reflux condenser was fitted to the flask and the heterogeneous mixture was stirred and heated at 70 °C until consumption of alcohol was observed by TLC. The flask was cooled to 25 °C and then cooled to 0 °C for 2 hours. The heterogeneous mixture was filtered over a pad of celite. The pad was further washed with cold EtOAc and the solution was reduced *in vacuo* to yield the desired aldehyde (80% yield). Characterization of this product is found on page 16.

Characterization of α-Fluoro enals.

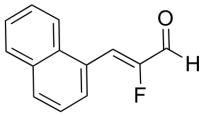
General Comments: High-resolution mass spectra were not attainable due to decomposition of the aldehyde. The aldehydes were stored under Ar in the freezer for several days. Decomposition is observed if the aldehyde is stored at ambient temperature or upon prolonged exposure to light.



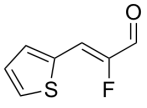
(E/Z)-2-fluoro-3-(4-methoxyphenyl)acrylaldehyde (**366a**): R_f = 0.24 (9:1 Hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.64 (d, 1H, *J* = 20.4 Hz), 4.30 (bs, 1H), 7.31 (d, 2H, *J* = 7.6 Hz), 7.23 (d, 1H, *J* = 1.2 Hz), 6.92 (d, 2H, *J* = 8.0 Hz), 3.81 (s, 3H; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.0 (d), 131.7, 55.6; IR (NaCl) 3008, 2958, 2937, 2841, 2562, 2361, 2052, 1683, 1629, 1604, 1570, 1511, 1464, 1443, 1331, 1302, 1239, 1171, 1029 cm^{-1};



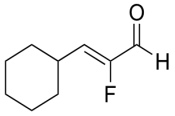
(E/Z)-2-fluoro-3-(2-methoxyphenyl)acrylaldehyde (**367a**): R_f = 0.21 (9:1 Hexanes: EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.32 (d, 1H, *J* = 18 Hz), 7.37-7.42 (m, 2H), 6.90-7.02 (m, 3H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.3 (d), 132.7, 132.1, 131.7 (d), 121.3, 111.1, 55.8; IR (NaCl) 3011, 2946, 2841, 1683, 1627, 1598, 1540, 1488, 1465, 1437, 1374, 1328, 1291, 1254, 1227 cm^{-1};



(E/Z)-2-fluoro-3-(naphthalene-1-yl)acrylaldehyde (**368a**): R_f = 0.31 (9:1 Hexanes: EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.52 (d, 1H, *J* = 19.6 Hz), 7.86-7.94 (m, 4H), 7.44-7.59 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.1 (d), 130.9, 130.0, 129.0, 127.5, 127.0, 126.1, 125.8, 125.4, 124.8; IR (NaCl) 3059, 2956, 2868, 1949, 1777, 1692, 1664, 1642, 1509, 1462, 1324, 1271, 1242, 1215, 1195 cm^{-1};

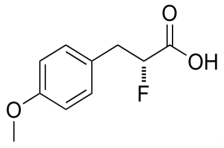


(E/Z)-2-fluoro-3-(thiophen-2-yl)acrylaldehyde (**369a**): R_f = 0.42 (9:1 Hexanes: EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.28 (d, 1H, *J* = 19.2 Hz), 7.46-7.48 (m, 1H), 7.26-2.27 (m, 1H), 7.06-7.10 (m, 1H), 6.92 (d, 1H, *J* = 33.2 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 182.2 (d), 152.0 (d), 133.5, 133.2, 132.5, 130.9, 120.3 (d); IR (NaCl) 3108, 2861, 1674, 1653, 1646, 1558, 1540, 1320, 1245, 1224, 885 cm^{-1};

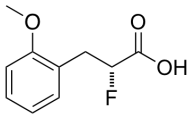


(E/Z)-2-fluoro-3-cyclohexyl acrylaldehyde (**370a**): R_f = 0.31 (8:2 Hexanes: EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (d, 1H, *J* = 18 Hz), 5.76 (dd, 1H, *J* = 9.6, 33.6 Hz), 2.66 (d, 1H, *J* = 10.4 Hz), 1.65-1.75 (m, 5H), 1.10-1.37 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.2 (d), 155.0 (d), 136.4 (d), 34.6, 32.0, 25.8, 25.5 ; IR (NaCl) 3467, 3182, 2953, 2868, 2633, 2537, 2360, 1737, 1720, 1457, 1439, 1367, 1223, 1169 cm^{-1};

Characterization of α-Fluoro carboxylic acids.

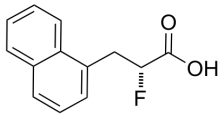


(R)-2-fluoro-3-(4-methoxyphenyl) propanoic acid (**366**): Title compound was prepared according to general procedure C. R_f = 0.23 (8:2 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -32.4° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 99:1 hexanes : isopropanol 1 ml/ min for 60 min. Major: 54.3 min, Minor: 57.6 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (d, 2H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 5.10 (ddd, 1H, *J* = 4.0, 7.6, 48.8 Hz), 3.22 (ddd, 1H, *J* = 4.0, 14.8, 28.0 Hz), 3.11 (ddd, 1H, *J* = 7.6, 14.8, 25.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.2 (d), 130.6, 126.8, 114.3, 55.5 (d), 37.7 (d); IR (NaCl) 2935, 2837, 1777, 1733, 1700, 1684, 1675, 1652, 1646, 1635, 1575, 1514, 1248 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{10}FO_3$, 197.0619. Found 197.0619.

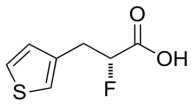


(R)-2-fluoro-3-(2-methoxyphenyl)propanoic acid (**367**): Title compound was prepared according to general procedure C. R_f = 0.20 (8:2 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -40.3° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 95:5 hexanes : isopropanol 1 ml/min for 60 min. Major: 41.3 min, Minor: 45.6 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23-7.27 (m, 1H), 7.16-7.18 (m, 1H), 6.85-6.91 (m, 2H), 5.22 (ddd, 1H, *J* = 4.4, 8.4, 48.8 Hz), 3.38 (ddd, 1H, *J* = 4.4, 14.4, 30.0 Hz), 3.10 (ddd, 1H, *J* = 8.4, 14.4, 18.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.8 (d), 157.7, 131.6, 128.9, 123.2, 120.8,

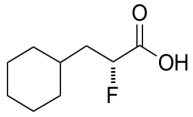
110.5, 55.4, 33.8 (d); IR (NaCl) 2940, 2839, 1733, 1602, 1495, 1465, 1439, 1247 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{10}FO_3$, 197.0619. Found 197.0623.



(R)-2-fluoro-3-(naphthalene-1-yl)propanoic aicd (**368**): Title compound was prepared according to general procedure C. R_f = 0.3 (7:3 Hexanes:EtOAc); $[\alpha]_D^{24}$ = -28.3° (10 mg/ml, MeOH); HPLC – analysis Chiracel OJ-H column 95:5 hexanes : isopropanol 1 ml/min for 60 min. Major: 42.0 min, Minor: 43.1 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, 1H, *J* = 8.8 Hz), 7.87 (d, 1H, *J* = 7.6 Hz), 7.79-7.81 (m, 1H), 7.48-7.58 (m, 2H), 7.42-7.43 (m, 2H), 5.28 (ddd, 1H, *J* = 3.2, 8.8, 48.8 Hz), 3.82 (ddd, 1H, *J* = 3.6, 15.2, 31.2 Hz), 3.55 (ddd, 1H, *J* = 8.8, 15.2, 20.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.1 (d), 134.2, 131.9, 131.1, 129.2, 128.5, 128.3, 126.7, 126.0, 125.7, 123.3, 89.6, 87.7, 35.8 (d); IR (NaCl) 3057, 2931, 1718, 1700, 1684, 1675, 790, 775 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{10}FO_2$, 217.067. Found 217.0675.

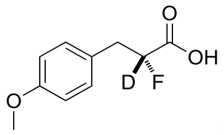


(R)-2-fluoro-2-thiophen-2-yl)propanoic acid (**369**): Title compound was prepared according to general procedure C. R_f = 0.44 (6:4 Hexanes: EtOAc); $[\alpha]_D^{24}$ = -93.4° (10 mg/ml, MeOH); HPLC – analysis Chiracel AD-H column 95:5 hexanes : isopropanol 1 ml/min for 60 min. Major: 35.6 min, Minor: 41.1 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19-7.23 (m, 1H), 6.94-6.96 (m, 2H), 5.18 (ddd, 1H, *J* = 4.0, 6.8, 48.4 Hz), 3.35-3.55 (m, 2H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.5 (d), 127.9, 127.4, 127.3, 125.4, 89.3, 87.3, 32.8 (d); IR (NaCl) 3108, 2974, 1700, 1684, 1456, 1436, 1418, 701 cm^{-1}; HRMS (FAB+) calcd for $C_7H_6FO_2S$, 173.0078. Found 173.0081.



(R)-2-fluoro-3-cyclohexyl propanoic aicd (**370**): Title compound was prepared according to general procedure C. R_f = 0.2 (1:1 Hexanes: EtOAc); $[\alpha]_D^{24}$ = -115.6° (10 mg/ml, MeOH); GC – analysis Chiral BDM-1 column, 100 °C, 1 ml/ min for 120 min. Major: 80.62 min, Minor: 83.61 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.02 (ddd, 1H, *J* = 3.6, 9.2, 49.6 Hz), 1.55-1.86 (m, 8H), 0.91-1.27 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.2 (d), 87.0 (d), 39.7 (d), 33.8, 32.4, 32.0, 26.5, 26.2, 26.1, 25.9, 25.5; IR (NaCl) 3010, 2925, 2852, 1733, 1684, 1652, 1448, 1276, 1232, 1097, 1074 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{14}FO_2$, 173.0983. Found 173.0988.

Characterization of α-fluoro,α-deutero carboxylic acid



(R)-2- deutero, fluoro-3-(4-methoxyphenyl)propanoic aicd (**372**): Title compound was prepared according to general procedure D. R_f = 0.18 (8:2 Hexanes: EtOAc); $[\alpha]_D^{24}$ = -36.0° (10 mg/ml, MeOH); HPLC – analysis Chiracel OD-H column 99:1 hexanes : isopropanol 1 ml/min for 60 min. Major: 43.6 min, Minor: 48.4 min; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (d, 2H, *J* = 8.4 Hz), 6.84 (d, 2H, *J* = 11.2 Hz), 3.77 (s, 3H), 3.08-3.25 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.3 (d), 159.0, 131.9, 130.6, 128.3, 126.8, 114.3, 80.1 (dt), 55.4, 37.6 (d); IR (NaCl) 3041, 2933, 2838, 1734, 1653, 1558, 1539, 1513, 1250, 1180, 800, 778 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_9DFO_3$, 198.0682. Found 198.068.

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[i] Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, 127, 16406-16407.
[ii] Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci.* USA **2004**, *101*, 5770-5775.