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Asymmetric *N*-Heterocyclic Carbene (NHC) Catalyzed Acyl Anion Reactivity

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1. Introduction

The generation of acyl anion equivalents has been of interest to the synthetic community since the early 1960's. Of the numerous methods available to generate acyl anions (or acyl anion equivalents), their catalytic production from aldehydes has been through the use of cyanide and *N*-heterocyclic carbenes (NHCs). The latter has emerged as a prominent method to catalyze the formation of acyl anion equivalents from aldehydes in an umpolung process facilitating the discovery of new transformations and the development of asymmetric variants. This rapidly growing field of organocatalysis¹ has been the subject of many reviews which detail the contributions from numerous researchers in this area.² The present review will discuss the advent and development of NHCs in the generation of acyl anion equivalents and their use in synthesis.

2. Carbenes

In 1832, Wöhler and Liebig reported the homodimerization of aldehydes in the presence of cyanide to provide benzoin products.³ In 1943, Ukai demonstrated that stoichiometric amounts of thiazolium salts in the presence of base are capable of generating acyl anion equivalents from aldehydes to yield benzoin products.⁴ Initially proposed by Breslow, the currently accepted mechanism for generation of the acyl anion equivalent occurs via deprotonation of the azolium thereby generating an ylide or nucleophilic carbene (Scheme 1).⁵

Carbenes have long been studied, but our understanding of their stability and reactivity has dramatically improved in recent decades.⁶ They have typically been considered highly reactive intermediates, and only recently has it been shown that their reactivity can be harnessed and controlled upon appropriate steric and electronic manipulation. Carbenes are neutral compounds bearing a divalent carbon with six electrons in the valence shell. The two nonbonding electrons can either be spin paired (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 towards π -donation by proximal atoms around the divalent carbon.

This π -donation results in the overall increase of s-character and aids in stabilization and nucleophilicity of the carbene. An additional stabilizing event involving a σ -withdrawing effect with a concomitant increase in s-character is also plausible. This is typically observed in crystal structures of isolable carbenes by a decrease in the X-C-X bond angle and an increase in the C-X bond length (Figure 2).⁸

The advent of nucleophilic singlet carbenes in organic synthesis has been 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 different electrophiles and nucleophiles.⁹ In 1991, Arduengo's report of an isolable NHC renewed interest in the use of such compounds as ligands and catalysts.¹⁰

3. Benzoin Reaction

The benzoin reaction became the platform for which the efficiency of novel chiral azolium carbenes would be measured. In 1966, Sheehan and Hunneman were first to make use of a chiral thiazolidine carbene (**1**) in facilitating benzoin formation in 22% optical purity.¹¹ 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, to which low enantioselectivities observed with such carbenes is attributed.¹² The introduction of bicyclic thiazolium salts only led to modest improvement in enantioselectivities.¹³ The emergence of triazolidine carbenes, developed by Enders and Teles,¹⁴ and bicyclic triazolidine carbenes by Leeper¹⁵ resulted in acceptable enantioselectivities for the benzoin product (Chart 1).

4. Stetter Reaction

The application of NHCs to other areas of acyl anion chemistry was pursued concurrently with the development of the benzoin reaction. In 1974, Stetter demonstrated that thiazolidine carbenes could be employed to facilitate the addition of an aldehyde via its acyl anion equivalent to activated double bonds to generate functionalized ketones (Scheme 2).¹⁶ Although Stetter had previously demonstrated this process with cyanide, the use of a thiazolidine carbene displayed improved proficiency for aliphatic aldehydes, which were not compatible under the cyanide conditions. In 1995, Ciganek illustrated an intramolecular Stetter reaction to generate chromanones.¹⁷ The asymmetric Stetter reaction did not receive considerable attention by the synthetic community for many years, and the only example prior to our work was that of Enders, who showed that triazolium precursor **6** provides the desired chromanone product in 74% ee and 42% yield (eq 1).¹⁸



4.1 Catalyst Development

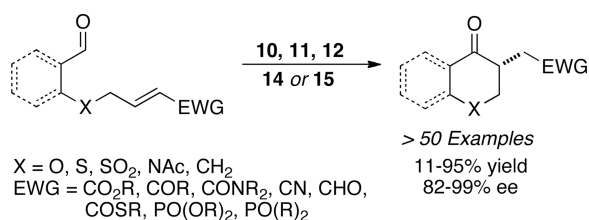
In 2000, our laboratory began a program to study chiral NHCs for use in organic synthesis. We envisioned accessing structurally and electronically diverse carbene precursors from readily available starting materials. The triazolium scaffold was prioritized over that of thiazolium and imidazolium precursors based on the number of sites available for structural and electronic modification and their proficiency as bicyclic carbenes in the benzoin reaction. Thiazolium precursors lead to blocking a single quadrant while corresponding triazolium-derived catalysts can effect three quadrants (Figure 3), presumably leading to improved selectivities.

We conceived that the chiral backbone could be readily introduced from amino alcohols (morpholine series) or amino acids (pyrrolidine series) and would provide steric blocking of quadrant **II** (Figure 3). We also envisaged that substitution in quadrants **I** and **IV** could arise from the hydrazine component which would enable an additional modulation of electronic and steric parameters (Figure 4). The use of substituted aryl hydrazines would give rise to differences in reactivity given its proximity to the carbene carbon.

The intramolecular Stetter reaction was the platform wherein the effectiveness of our catalysts would be measured. We quickly identified amino indanol as the optimal chiral amino alcohol in the morpholine series, which could be coupled with a variety of structurally and electronically diverse hydrazines to furnish bench stable triazolium salts (Chart 2).¹⁹ In the pyrrolidine series, a variety of sidechains (ultimately derived from amino acids such as phenyl alanine and valine) were identified as efficient chiral scaffolds which could also incorporate a variety of hydrazines to furnish bench stable triazolium salts (Chart 2).

4.2 Asymmetric Intramolecular Stetter Reaction

Our work on the intramolecular Stetter reaction has been reviewed extensively and therefore will not be the focus of this review.²⁰ A variety of salicylaldehyde derived substrates and aliphatic aldehydes bearing a range of linkers, including ether, thioether, sulfone, and protected amines, are effective in this process. An electron-withdrawing group on the prochiral alkene is still a necessary requirement²¹ but encompasses esters, thioesters, amides, ketones, aldehydes, nitriles, phosphine oxides, and phosphonates (eq 2).²²



(eq 2)

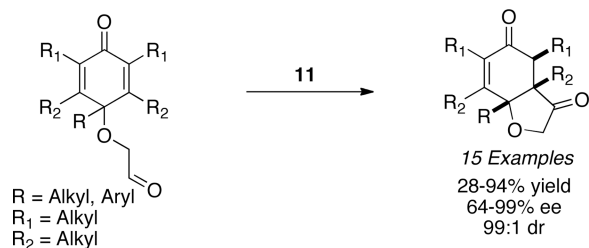
Michael acceptors bearing a second β -substituent also participate in the reaction in the presence of precatalyst **11** to furnish quaternary stereocenters (eq 3).²³ Contiguous stereocenters could also be generated by using precatalyst **15** with a variety of salicylaldehyde substrates to yield a highly enantioselective and diastereoselective process. The reaction is not limited to salicylaldehyde derived substrates as aliphatic aldehydes also partake in the reaction with high levels of enantio- and diastereoselectivity, the latter being attributed to an intramolecular proton transfer event (eq 4).²⁴ In advancing the scope of the Stetter reaction, we next focused on the synthesis of hydrobenzofuranones arising from a Stetter reaction on cyclohexadienones. These substrates are readily accessible in two steps and when subjected to optimized reaction conditions with triazolium salt **10** provide hydrobenzofuranones in excellent enantio- and diastereoselectivity (eq 5).²⁵ With these successes in the intramolecular Stetter reaction in hand, we turned our attention to the intermolecular version.



(eq 3)



(eq 4)

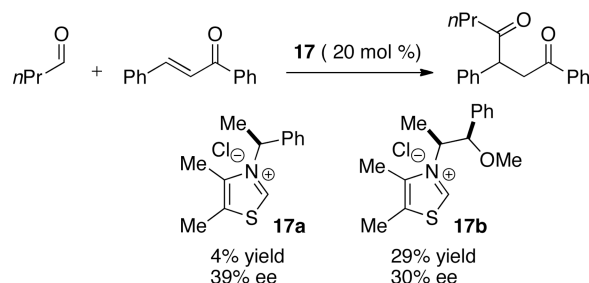


(eq 5)

4.3 Asymmetric Intermolecular Stetter Reaction

The intermolecular addition of acyl anion equivalents into activated double bonds had been thoroughly studied by Stetter,²⁴ but the asymmetric variant of this reaction has been nearly non-existent. The use of chiral NHCs in this process has not been fruitful as benzoin products dominate. One solution to the benzoin product is the use of acyl silanes to generate acyl anion equivalents via Brook rearrangement. Johnson has shown that in the presence of a chiral metallophosphite, acyl silane, and an activated prochiral olefin, one can obtain sila-Stetter products.²⁶ Scheidt has also shown the addition of acyl silanes into chalcones which give rise to racemic products in the presence of a NHC.²⁷ In 2006, this process was rendered enantioselective by generation of the acyl anion in the presence of stoichiometric carbene and chiral thiourea.²⁸ While the use of acyl silanes is an elegant solution, it only maneuvers around the problem at hand.

Prior to our work in this area, only three examples were known of an asymmetric intermolecular Stetter reaction, all reported by Enders. The reaction of butanal and chalcone in the presence of precatalysts **17** provides the 1,4-dicarbonyl product in low yield and poor ee (eq 6).²⁹ Enders introduced an improved triazolium catalyst for the Stetter reaction of aromatic aldehydes and chalcones (Table 1).³⁰ The benzyl substituent on the triazolium was found to be key to providing observable yields.



(eq 6)

Following our successes in the intramolecular asymmetric Stetter reaction, we turned our attention to relaying the lessons learned there to the problem of the intermolecular reaction. Based on Stetter's extensive work,³¹ we identified glyoxamides as competent aldehyde partners and β -substituted alkylidene malonates as reactive electrophiles. During catalyst optimization it was noted that while precatalyst **16** produces the desired product in 50% yield and 51% ee, the phenyl analogue **14** does not provide any product. These results again stress the significance of the N-aryl substituent in impacting carbene catalyzed reactions.³² A morpholine-derived glyoxamide results in superior reactivity with a variety of substituents tolerated at the β -position of the alkylidene malonate to provide α -ketoamides (Table 2). Under the reaction conditions, the glyoxamide 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.³³

This reaction was further developed to generate contiguous stereocenters in a highly enantioselective and diastereoselective manner. We hypothesized that a highly diastereoselective protonation event should result in a second stereocenter if the two activating carbonyls are different. The resultant stereocenter would be difficult to maintain under the basic reaction conditions unless one of the activating carbonyls was a tertiary amide which would insulate the stereocenter due to $A_{1,3}$ strain. The use of alkylidene ketoamides with glyoxamide under the mediation of precatalyst **16** leads to the desired Stetter product in 68–97% yield and 81–97% ee and high diastereoselectivity (Table 3).³⁴

The above studies, although inherently limited to glyoxamide as the sole nucleophile, taught us much about necessary reactivity for our azolium catalysts in the asymmetric intermolecular Stetter reaction. To wit, electron-deficient aldehydes and more activated Michael acceptors provide higher yields with the triazolium catalysts. We thus focused our efforts at using nitroalkenes as electrophiles and heteroaryl aldehydes as nucleophiles. We found that triazolium salts derived from the pyrrolidine series bearing the electron deficient pentafluorophenyl group are necessary to obtain reactivity and a sterically demanding substituent such as an *iso*-propyl group is necessary in quadrant **II** (Figure 3) to obtain moderate enantioselectivity. Further modification of the pyrrolidine core 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 while a variety of aliphatic substituents can be tolerated on the nitroalkene (Table 4).³⁵

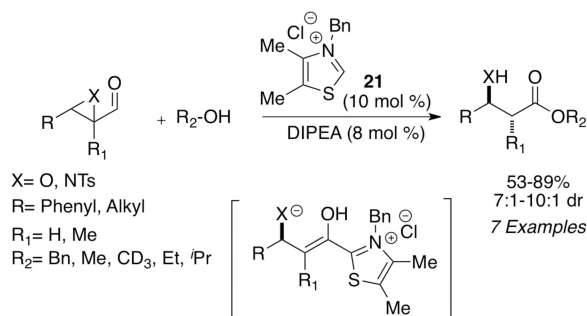
5. Redox Reaction

During our efforts in the intramolecular Stetter reaction, we inadvertently discovered a unique reactivity of acyl anion equivalents which was reminiscent of the observation by Wallach where chloral generates dichloroacetic acid when treated with aqueous cyanide.³⁶ The mechanism of the Wallach method was long debated and the currently accepted mechanism is that proposed by Nowak (Scheme 3).³⁷ The net process is an internal redox wherein one functionality gets reduced while a second is oxidized. An acylation using these intermediates thus constitutes an example of redox economy.³⁸

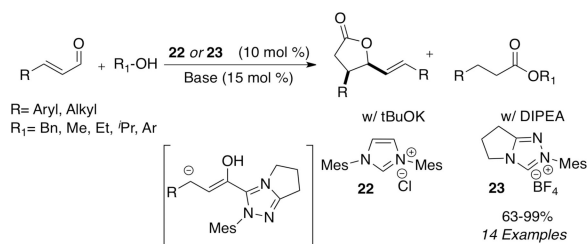
5.1 Redox Esterification

We saw this as an opportunity to implement this methodology as a mild acylating process using α -reducible aldehydes and NHCs. A resurgence in the development of α -halogenation of aldehydes³⁹ led to their use as substrates with alcohols as nucleophiles. 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 (60–99%). Enantioenriched ethyl lactate may also be used with acylation proceeding with minor epimerization, while the use of racemic lactate with chiral carbene occurs with enantioenrichment suggesting acylation occurs on the acyl azolium (Table 5).⁴⁰

Independently and concurrently, Bode showed that epoxy aldehydes are viable substrates in the NHC redox reaction with a variety of alcohols identified as competent nucleophiles (eq 7) to furnish β -hydroxy esters.⁴¹ Since the two initial reports by Bode and ourselves, the carbene catalyzed redox process has been developed to include other α -reducible aldehydes which participate in the esterification process. Bode⁴² and Scheidt⁴³ have independently shown that enals in the presence of imidazolium salt **22** or triazolium salt **23** can either generate a lactone dimer or saturated ester upon choice of reaction conditions. The use of a strong base such as *t*-butoxide leads to generation of the lactone dimer (eq 8), 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 protioacylation product (pKa of ${}^i\text{Pr}_2\text{EtNH}^+$ = 13 in THF). A variety of alcohols are tolerated in the reaction to produce the saturated esters in 63–99% yield (eq 8).

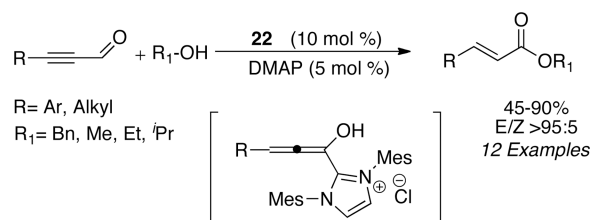


(eq 7)

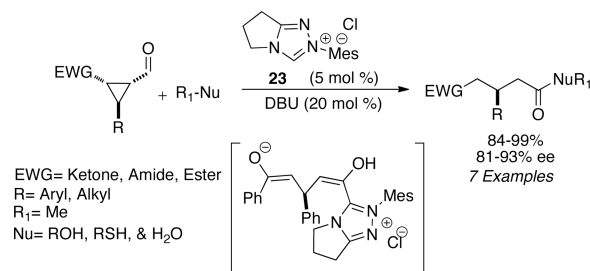


(eq 8)

The synthesis of (*E*)- α,β -unsaturated esters can also be accomplished via redox esterification of propargylic aldehydes. Zeitler had identified imidazolium salt **22** 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) (eq 9). A variety of alcohols participate in the reaction and aromatic, heteroaromatic, and aliphatic substituents are tolerated on the propargylic aldehyde (45–90%) (eq 9).⁴⁴ Bode has also found that formylcyclopropanes are competent in the *N*-heterocyclic redox esterification with a variety of nucleophiles including alcohols, thiols, and water (eq 10). Subjection of the chiral substrates under optimized reaction conditions with precatalyst **23** proceeds with minor epimerization to furnish the 1,5 dicarbonyl adducts in good yields (84–93%) (eq 10).⁴⁵



(eq 9)



(eq 10)

Treatment of α,α -dichloro aldehydes with phenols in the presence of NHC precursor **12** allows access to enantioenriched α -chloro aryl esters, via asymmetric protonation⁴⁶ of the enol.⁴⁷ 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 (Table 6), with the current limitation being β -branching on the aldehyde. A variety of substituted phenols work in the reaction which provides distinct advantages and complementarity to other methods generating enantioenriched α -chloro aryl esters (Table 7).⁴⁸

5.2 Redox Amidation

Expanding the scope of this mild acylation process to incorporate amine nucleophiles would afford amides. Amines have been previously studied as coupling partners with acyl azoliums derived from thiazolium and imidazolium carbenes and were determined to be less competent when compared to alcohols and hydroxide.⁴⁹ We had initially shown that aniline was an effective nucleophile with α -bromo aldehyde and carbene **20** to furnish the desired amide in excellent yield (Table 4); however, other amines failed in the reaction or only provided the amide in low yields. Others working in this area expressed similar sentiments⁵⁰ and further investigation into this process revealed that two byproducts of the reaction are imine formation and hydration product arising from water incorporation in the redox reaction.

This problem was solved by addition of a nucleophilic additive which acts as an acyl transfer agent thus liberating the carbene **24** from the acyl azolium.⁵¹ The acylated additive then undergoes the desired *N*-acylation to yield the respective amide. Common peptide coupling reagents were identified to participate in this process with HOAt displaying optimal reactivity.⁵² Exclusion of water was key to prevent hydration. A variety of primary and secondary amines participate as nucleophiles in the acylation process as well as the respective hydrochloride salts (Table 8). The scope of the reducible aldehyde includes α,α -dichloro aldehydes, epoxy aldehydes, and enals (Table 9).⁵³

Concurrent to our work, Bode and coworkers reported a similar concept in facilitating *N*-acylation in the redox reaction using stoichiometric imidazole and triazolium carbene **23**. Imine formation is suppressed by stoichiometric generation of the acyl imidazole followed by sequential addition of the amine to generate the amide. Primary and secondary amines are tolerated, however, amine hydrochloride salts are not compatible. The reducible aldehyde substrate scope entails formylcyclopropanes, α -chloro aldehydes, and α,β -unsaturated aldehydes to generate the respective amide (Scheme 4).⁵⁴ Recently, Bode and coworkers have extended the substrate scope to include α' -hydroxyenones as surrogates for α,β -unsaturated aldehydes with 1,2,4-triazole used in substoichiometric quantities to facilitate amidation (Scheme 4).⁵⁵

5.3 Redox Azidation

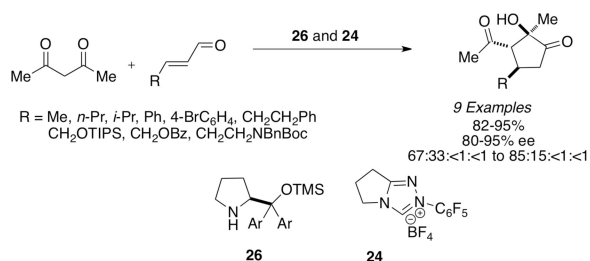
We also sought to generate carbamoyl azides and oxazolidinones from epoxy aldehydes in the presence of NHCs and azide as the nucleophile. Using triazolium salt **24** we were able to attenuate product selectivity based on reaction conditions. Using a combination of azidotrimethylsilane and sodium azide in a 2.5:1 ratio provides the carbamoyl azide selectively in 20–84% yields and diastereoselectivities of 2.6:1 to 6.5:1. The use of pseudo HN_3 conditions (which require a 1:1:1 ratio of azidotrimethylsilane to ethanol to sodium azide) affords the oxazolidinone products in 53–83% yields and moderate diastereoselectivities (1:1 to 6.5:1). The varying levels of diastereoselectivities are attributed to epimerization occurring at the acyl azide, as the α -proton is significantly acidic (Table 10).⁵⁶

5.4 Redox Hydration

In recent years, the generation of α -halo acyl derivatives has received considerable attention. To the best of our knowledge, however, no catalytic asymmetric method is available to generate α -halo acids directly.⁵⁷ We identified chiral NHC precatalyst **25**⁵⁸ in promoting the redox hydration of α,α -dichloro aldehydes with 1M potassium carbonate in water. The reaction can also generate α -deuterio labeled chloro acids by simply using D_2O (Table 11). The hydration process has been extended to α -fluoro enals to generate enantioenriched fluoro carboxylic acids (Table 12). The α -deuterio, α -fluoro acids can also be obtained from the use of α -fluoro, α -bromo aldehydes as the reducible aldehyde.⁵⁹

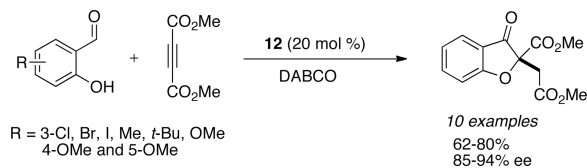
6. Cascade Catalysis

Having shown cooperative catalysis to be fruitful in resolving our amidation chemistry, we turned our attention to coupling other branches of organocatalysis with carbene catalysis.⁶⁰ The generation of substituted cyclopentanones was achieved using secondary amine catalysis coupled with carbene catalysis with readily available starting materials in a Michael/Benzoin cascade reaction. Substitution is tolerated on the enal and the 1,3-dicarbonyl to provide the respective cyclopentanones in excellent enantioselectivities and modest diastereoselectivities (eq 11 and Table 13). Importantly, both catalysts are present throughout the course of the reaction and the protocol involves immediate charging of all reactants and reagents with no slow addition necessary.⁶¹



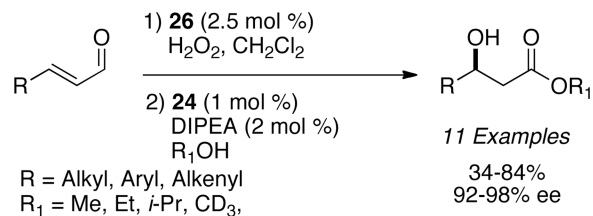
(eq 11)

Our laboratory has also extended the Michael/benzoin cascade to a Michael/Stetter cascade reaction with salicylaldehydes and activated acetylenes to provide hydrobenzofuranones. The reaction scope is tolerant of substitution on the salicylaldehyde with dimethylacetylene dicarboxylate (DMAD) as the Michael acceptor to provide the respective benzofuranones in good yields (62–80%) and enantioselectivities (85–94%). The Michael acceptor is currently limited to acetylene dicarboxylates and activated allenes (eq 12).⁶²

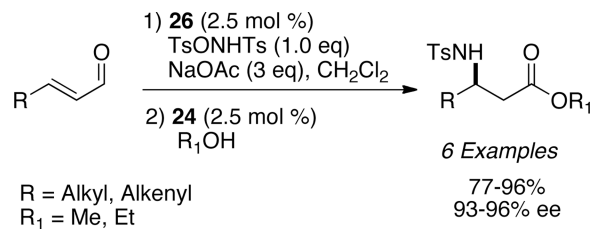


(eq 12)

Córdova⁶³ and Jørgensen⁶⁴ have independently shown secondary amine catalysis coupled with carbene catalysis in the realm of redox reactivity to furnish β -hydroxy and β -amino esters. The optimized reaction conditions rely on the consumption of the enal with secondary amine catalysis to furnish the epoxy or aziridinyl aldehyde prior to the addition of azolium salt and alcohol to furnish the respective esters.



(eq 13)



(eq 14)

7. Conclusion

This review has presented an overview of *NHC* catalyzed formation of acyl anion equivalents from aldehydes and their reactivity in the Stetter, α -redox reaction and cascade catalysis. Although this field is still in its infancy compared to other areas of organocatalysis, the further development of novel carbene precursors will pave the way to new reactivity and its utilization in natural product synthesis, and industrial processes.

Acknowledgments

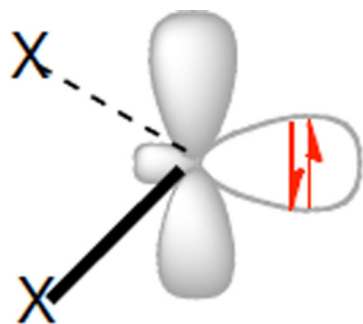
We gratefully acknowledge our many coworkers without whose intellectual and experimental contributions none of this would have been possible. Special thanks go to Mark Kerr and Javier Read de Alaniz who initiated the early work with these catalysts. We thank NIGMS (GM72586) for support. H.U.V. thanks Lilly for a graduate fellowship. T.R. thanks Amgen and Roche for support. We thank Donald Gauthier (Merck) for a generous gift of aminoindanol.

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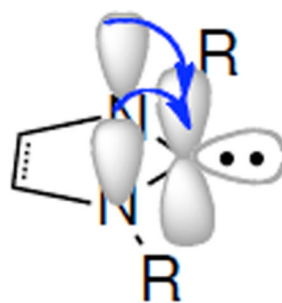
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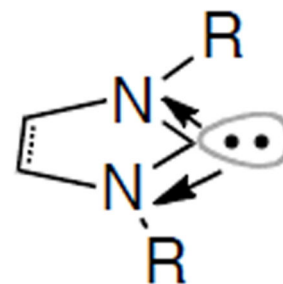
Singlet Carbene

$$\theta = 103^\circ$$

$$\text{X-C-X}$$



π -donation



σ -withdrawing

Figure 2.
Stabilization of Singlet Carbenes

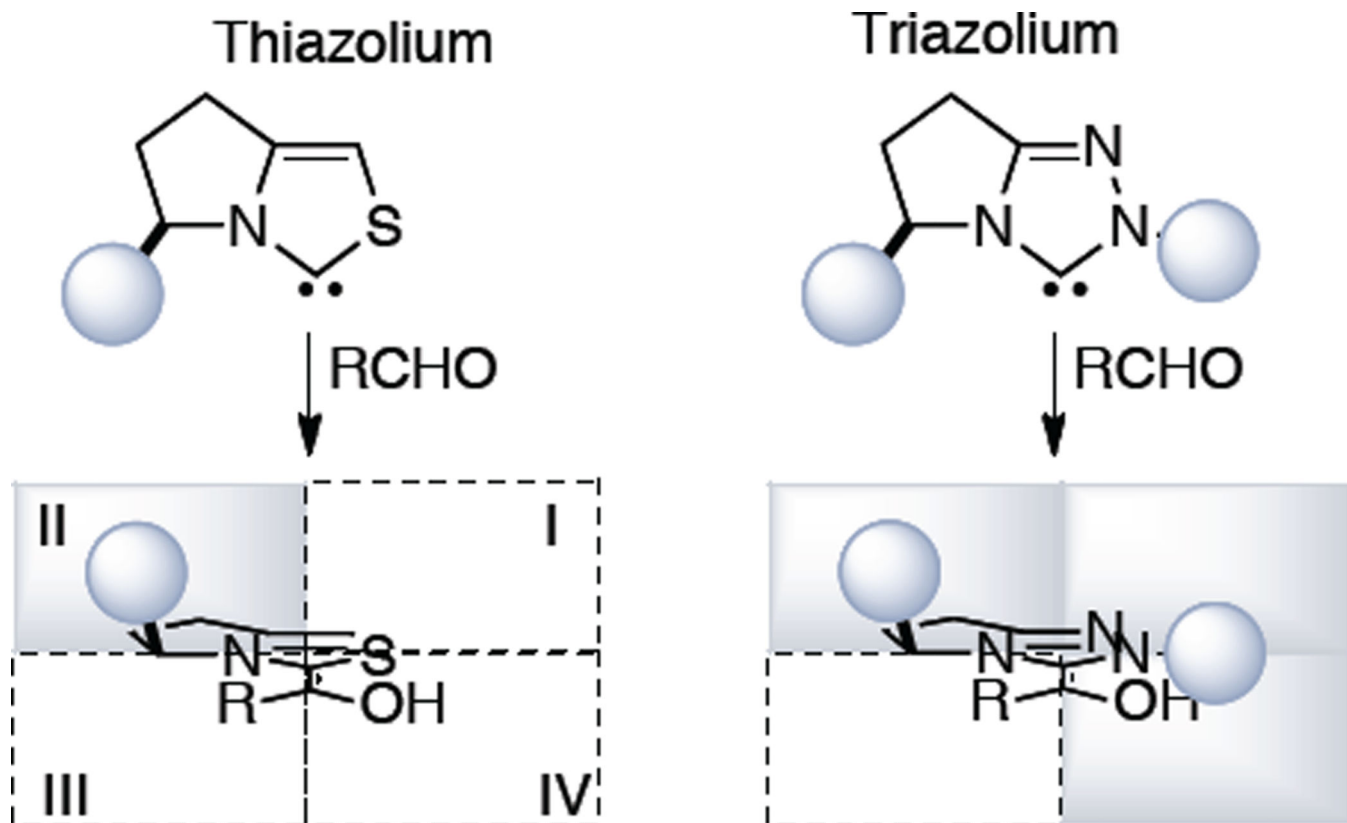


Figure 3.
Mapping Steric Space About Carbene

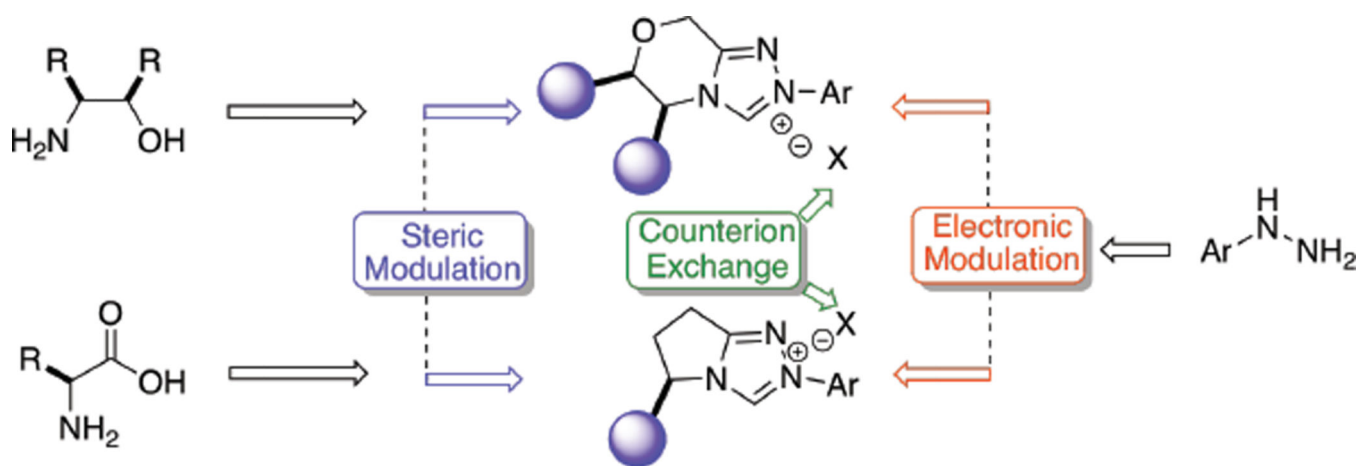
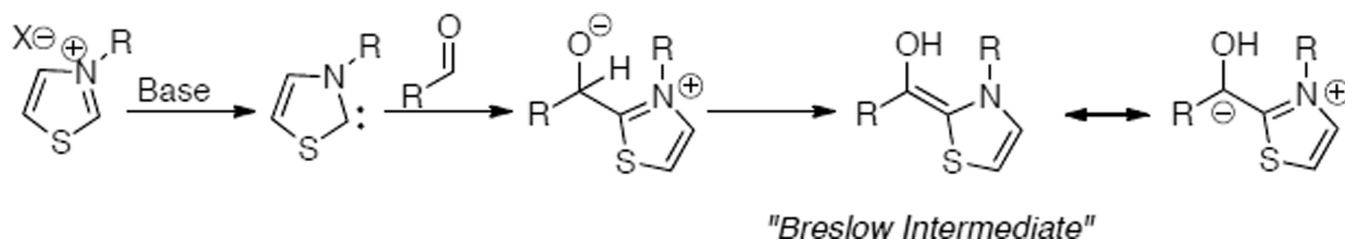
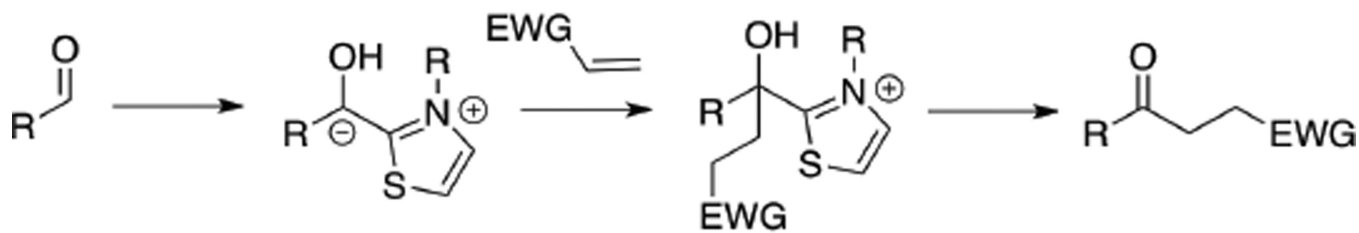


Figure 4.
Catalyst Design

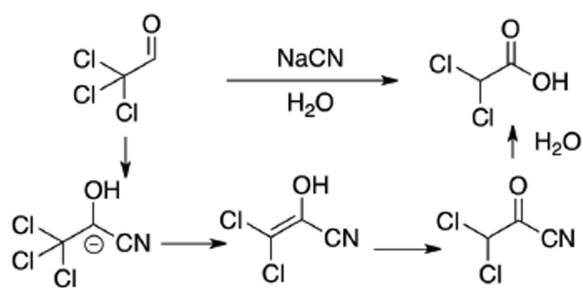


Scheme 1.
Formation of Acyl Anion Equivalent

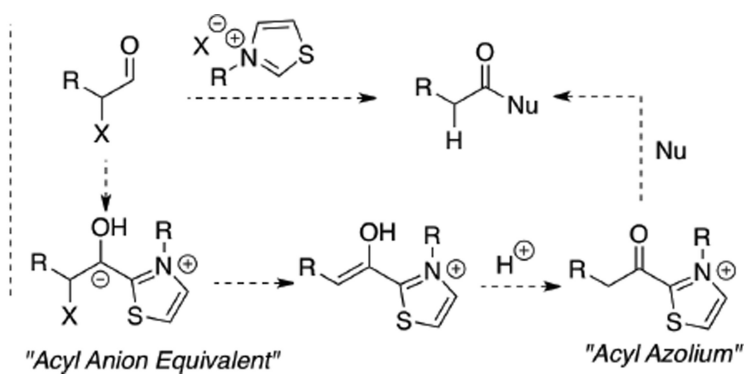
Stetter 1974

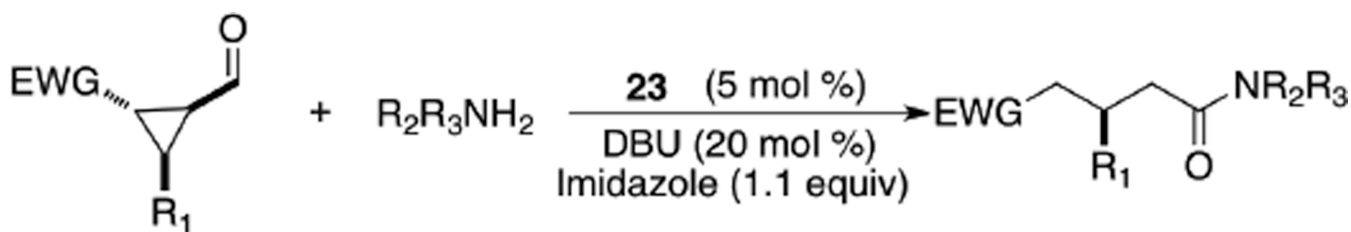


Scheme 2.
Stetter Reaction

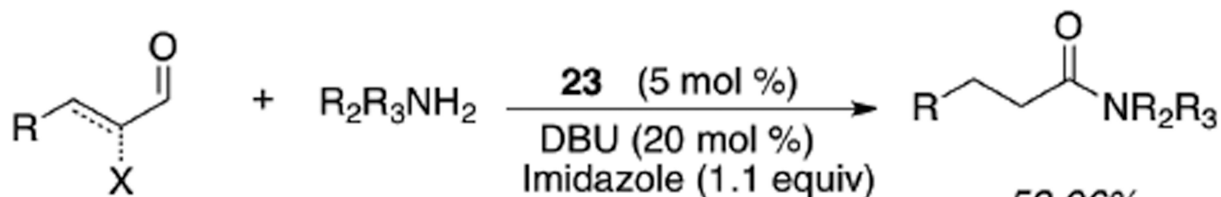


Scheme 3.
Redox Mechanism



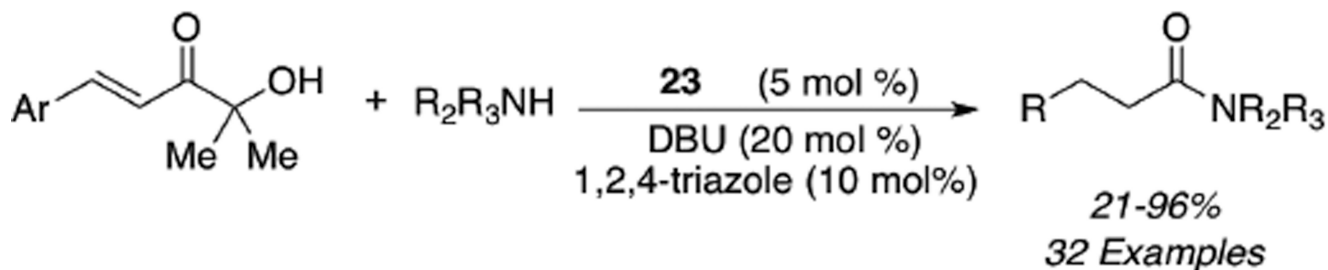


65-99%
11 Examples



R = Aryl, Alkyl, CO₂Et

52-96%
9 Examples



21-96%
32 Examples

Scheme 4.
NHC-Amidation

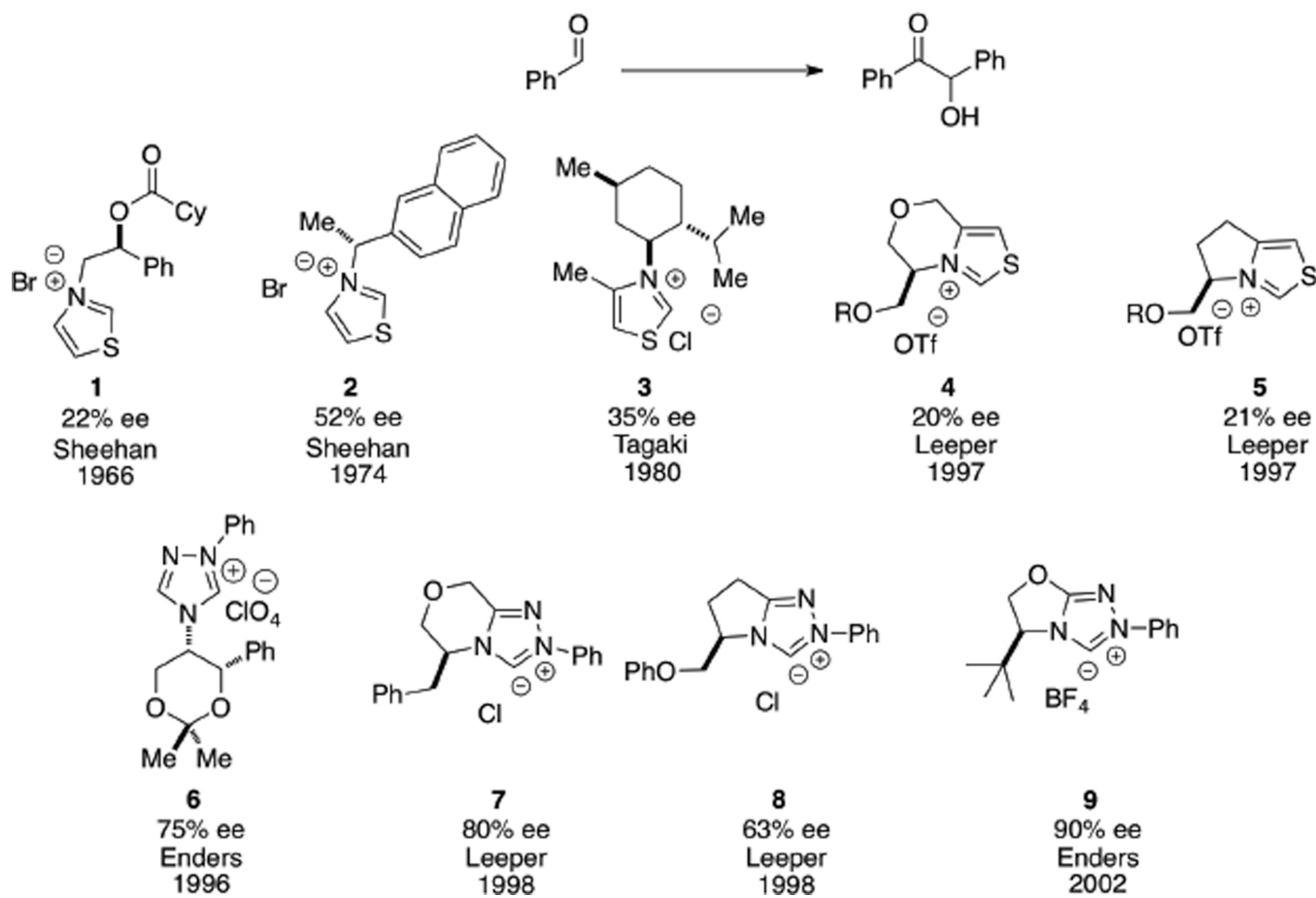
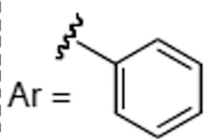
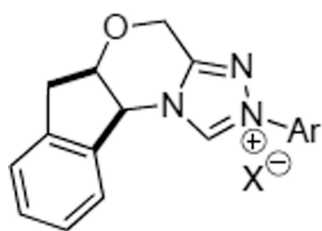
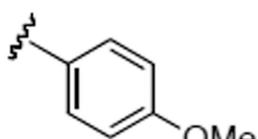


Chart 1.
Development of Azollum Salts in the Benzoin Reaction

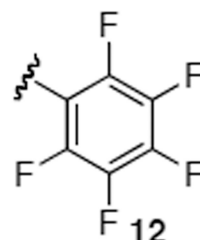
Morpholine Series:



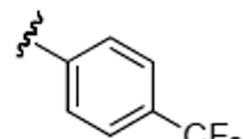
10



11

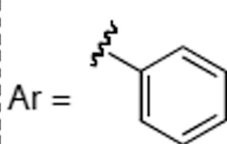
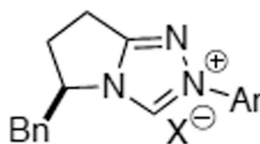


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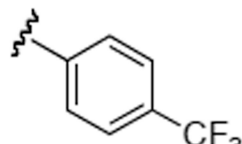


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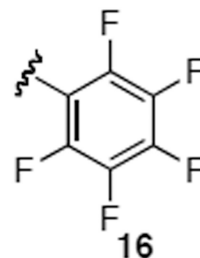
Pyrrolidine Series:



14



15

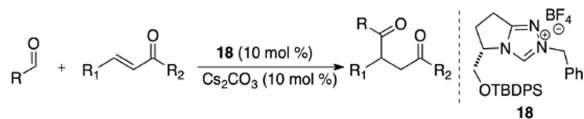


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Chart 2.
Triazolium Salts

Table 1

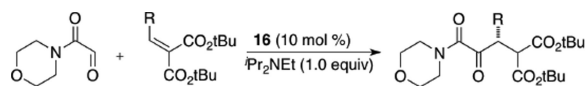
Intermolecular stetter



R	R ₁	R ₂	yield (%)	ee (%)
Ph	Ph	Ph	89	66
4-MeC ₆ H ₄	Ph	Ph	85	78
3-MeC ₆ H ₄	Ph	Ph	73	70
4-ClC ₆ H ₄	Ph	Ph	89	67
4-BrC ₆ H ₄	Ph	Ph	72	56
2-Naphthyl	Ph	Ph	87	70
2-Furyl	Ph	Ph	82	56
Ph	4-MeC ₆ H ₄	Ph	83	64
Ph	4-ClC ₆ H ₄	Ph	85	56

Table 2

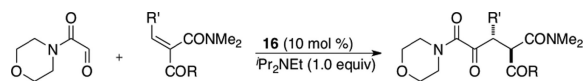
Intermolecular Glyoxal Stetter Reaction



R	yield (%)	ee (%)
Et	84	90
Me	68	87
Pr	83	90
Bu	70	90
CH ₂ CH ₂ Ph	81	88
^t Bu	51	91
CH ₂ CH ₂ OBn	91	80
CH ₂ CH ₂ CH ₂ Cl	84	81
CH ₂ CH ₂ CH(SCH ₂ CH ₂ CH ₂ S)	88	84
CH ₂ CH ₂ CHCH ₂	97	89

Table 3

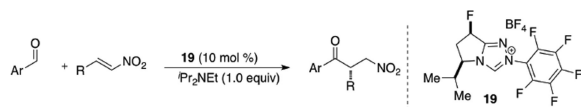
Contiguous Stereocenters in the Glyoxamide Stetter Reaction



R	R'	yield (%)	ee (%)	dr
Et	Et	84	90	12:1
Et	Me	68	87	7:1
Et	Pr	83	90	6:1
Et	Bu	70	90	12:1
Et	iBu	81	88	11:1
Et	CH ₂ CH ₂ Ph	51	91	19:1
Et	CH ₂ CH ₂ OBn	91	80	11:1
Et	CH ₂ CH ₂ CH ₂ Cl	84	81	10:1
Et	CH ₂ CH ₂ CHCH ₂	88	84	14:1
Et	CH ₂ CH ₂ CCH	97	89	4:1
Et	CH ₂ CH ₂ C(SCH ₂ CH ₂ CH ₂ S)	97	89	9:1
Pr	Et	97	89	11:1
Pr	CH ₂ CH ₂ Ar	97	89	5:1
CH ₂ CH ₂ CHCH ₂	Et	97	97	9:1

Table 4

N-heterocyclic Carbene Catalyzed Nitro Ketone Synthesis



Ar	R	Product	Yield (%)	ee (%)
2-pyridyl	cyclohexyl		95	95
2-pyrazyl	cyclohexyl		99	96
3-pyridazyl	cyclohexyl		88	94
2-thiazolyl	cyclohexyl		70	96
2-furyl	cyclohexyl		75	87
4-oxazolyl	cyclohexyl		76	86
2-pyridyl	cyclopentyl		98	90
2-pyridyl	cyclopropyl		72	87
2-pyridyl	iso-propyl		85	95
2-pyridyl	propyl		97	89
2-pyridyl	propyl		97	89
2-pyridyl	sec-butyl		97	89
2-pyridyl	cyclohexyl		97	89

Table 5

 α -Halo Aldehyde Redox Esterification

R	X	R ₁	yield (%)
H	Br	BnOH	60
Bn	Br	BnOH	80
Bn	Cl	BnOH	65
Cy	Br	BnOH	99
Bn	Br	MeOH	78
Bn	Br	EtOH	78
Bn	Br	PhCH ₂ CH ₂ CH ₂ CH ₂ OH	78
Bn	Br	<i>i</i> -PrOH	66
Bn	Br	CyOH	66
Bn	Br	PhOH	55
Bn	Br		65
Bn	Br		56
Bn	Br	PhNH ₂	91

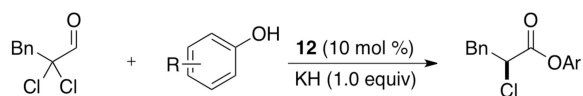
Table 6

Aldehyde Scope for Synthesis of Enantioenriched α -Chloro Aryl Esters

Substrate	yield (%)	ee (%)	Substrate	yield (%)	ee (%)
	79	93		71	88
	76	90		65	93
	73	85		65	89
	68	89		75	84
	74	90		71	84

Table 7

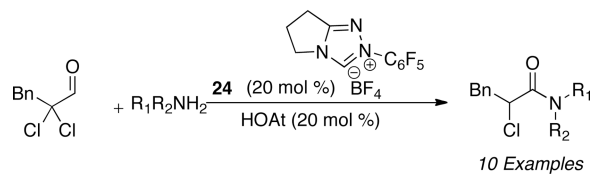
Scope of Phenols



Substituted Phenols	yield (%)	ee (%)
4-methyl	71	89
4-methoxy	71	91
4-chloro	75	83
2-methyl	62	90
2-chloro	75	91
2,6-dichloro	65	82
2,6-dibromo-4-methyl	85	76
2,4,6-trimethyl	0	NA
3,4-dimethyl	80	89

Table 8

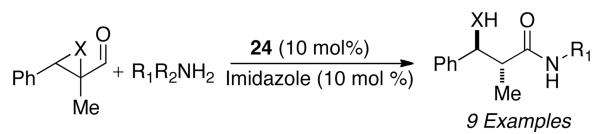
Amine Scope of MHC-Amidation



R₁	R₂	yield (%)
Et	H	89
Cy	H	85
<i>t</i> -Bu	H	73
Et	Et	89
Me	OMe	72
Ph	H	87
3-ClC ₆ H ₄	H	82
4-OMeC ₆ H ₄	H	83
Alanine	H	85

Table 9

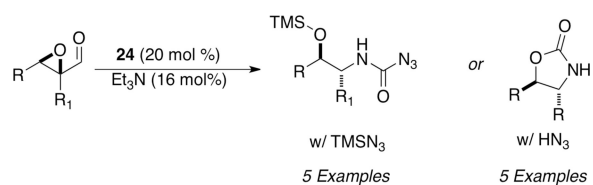
Substrate Scope of MHC-Amidation



X	R ₁	yield (%)	dr
O	Bn	86	>19:1
O	Alanine	75	15:1
NTs	Bn	72	>19:1

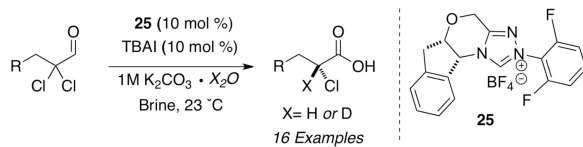
Table 10

Azidation of Aldehydes

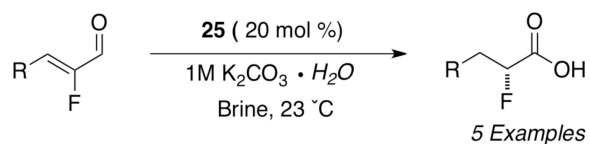


R	R₁	w/ TMSN₃ 5 Examples yield (%)^a (dr)^c	w/ HN₃ 5 Examples yield (%)^b (dr)^c
Ph	Me	75 (4:1)	75 (4:1)
Ph	C ₅ H ₁₁	83 (6.5:1)	83 (6.5:1)
Ph	Ph	84 (2.6:1)	47 (1:1)
4-ClC ₆ H ₄	Me	79 (3.6:1)	53 (3.5:1)
2-Naphthyl	Me	52 (5.6:1)	53 (3:1)
1-Naphthyl	Me	20 (2.6:1)	60 (5:1)
Cy	Me	78 (2.7:1)	78 (3:1)

Table 11

Synthesis of Enantioenriched α -Chloro Acids

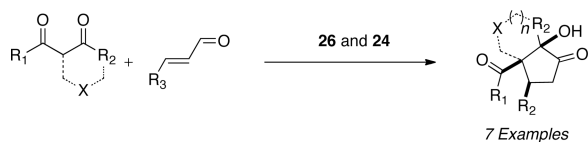
R	X	yield (%)	ee (%)
Ph	H/D	89/ 95	88/ 88
2-OMeC ₆ H ₄	H/D	80/ 83	94/ 95
4-BocNHC ₆ H ₄	H/D	78/ 75	78/ 79
Cyclopentyl	H/D	89/ 90	94/ 95
Cyclohexyl	H/D	85/ 88	94/ 95
CH ₂ OBn	H/D	78/ 75	88/ 89
CH ₂ CH ₂ Ph	H/D	86/ 78	88/ 89
CH ₂ CH ₂ CH ₂ CO ₂ Et	H/D	75/ 77	90/ 91

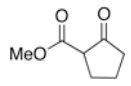
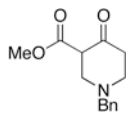
Table 12Synthesis of Enantioenriched α -Fluoro Acids

R	X	yield(%)	ee(%)
4-OMeC ₆ H ₄	H	74	93
2-OMeC ₆ H ₄	H	80	96
2-Naphthyl	H	77	94
2-Thiazolyl	H	70	90
Cyclohexyl	H	65	96

Table 13

Michael/Benzoin Cascade



R ₁	R ₂	R ₃	yield(%) (dr)	ee(%)
OMe	Me	Me	90 (64:33:3:<1)	91
OEt	Me	<i>n</i> -Pr	80 (60:30:8:2)	93
<i>O</i> -Bu	Me	Ph	86(60:35:5:<1)	97
OBn	Me	Me	90 (58:39:2<1)	82
Ets	Me	<i>n</i> -Pr	56 (69:22:6:3)	81
		Me	79 (80:20:<1:<1)	94
		Me	76 (85:15:<1:<1)	90