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N-Heterocyclic Carbene Catalysis via the α,β-Unsaturated Acyl Azolium

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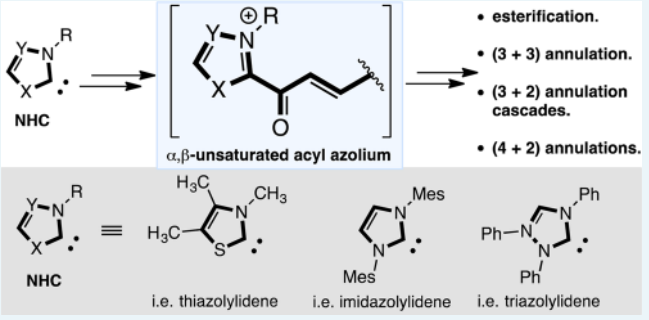
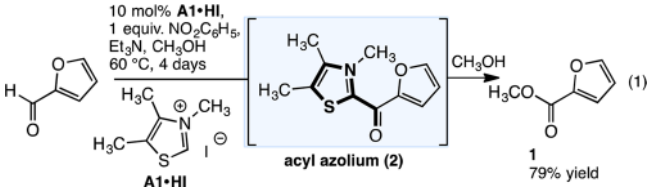
ABSTRACT: First reported less than a decade ago, the α,β-unsaturated acyl azolium has emerged as a central reactive intermediate for reaction discovery using *N*-heterocyclic carbene catalysis. In this Perspective, an introduction to the four main reactivity patterns accessible from this intermediate is provided. The Perspective is handled in a largely chronological fashion, with an emphasis on alternate approaches to the key intermediate and first-in-class reaction cascades. Finally, a brief discussion of emerging trends in this field of catalysis is presented. Although not exhaustive, the Perspective provides an overview of this active area of research and serves as a guide for future investigations.



KEYWORDS: *organocatalysis, enantioselective catalysis, N-heterocyclic carbene catalysis, Lewis-base catalysis, reaction cascade*

1. INTRODUCTION

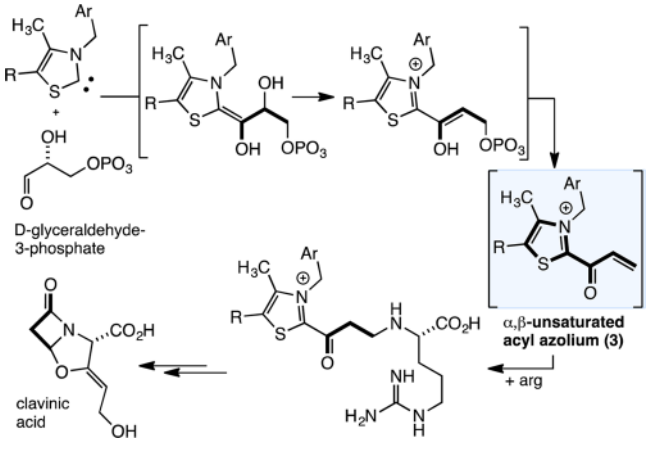
N-Heterocyclic carbene (NHC)-mediated reversal of carbonyl polarity, reported more than 60 years ago, remains a major field of study.[1,2] In contrast, NHC catalysis via normal polarity intermediates has received less attention.[2e] In 1977, Castells reported the NHC-catalyzed oxidative conversion of furfural to methyl ester **1** in 79% yield:[3]



This reaction is an early example of NHC catalysis via normal polarity intermediates and is thought to involve formation of the acyl anion equivalent, followed by oxidation to afford acyl azolium **2**. In this case, the acyl azolium acts as an "activated acid" in a fashion analogous to acyl ammonium species developed by Wegler, Steglich, and others.[4] While the significance of acyl azolium formation in biosynthesis has received ongoing attention,[5] remarkably, the methodological opportunities arising from this chemistry remained overlooked for almost three decades.

In 1999, Townsend proposed a biosynthesis of clavinic acid, based on a series of labeling studies, involving α,β-unsaturated acyl azolium **3**.[6] It was postulated that this intermediate undergoes conjugate addition with arginine and subsequent hydrolysis (Scheme 1). While directly related methodologies have not been reported, catalysis via the α,β-unsaturated acyl azolium over the past decade has developed into a highly active field of organocatalysis. Despite significant attention, a review focused on the chemistry of this species is yet to be reported.[7]

Scheme 1. Townsend's Biosynthesis of Clavinic Acid



Herein, we provide a critical perspective on the chemistry of the α,β-unsaturated acyl azolium (i.e., **3**). Although not exhaustive, common reactivity patterns are introduced, along with insight into future directions. The perspective's structure is summarized in Scheme 2 and commences with an examination of early approaches to α,β-unsaturated acyl azolium (i.e., **4**) and acylation chemistry (i.e., **4** → **5**) (Section 2). In Section 3 bond formation at the β-carbon and acyl carbons (i.e., **4** → **6**) is introduced. Reaction designs that take advantage of bond forming events at the β-, α-, and acyl atoms, (i.e., **4** → **7**) are discussed in Section 4, while Section 5 covers reaction discovery via γ-deprotonation of the acyl azolium, allowing

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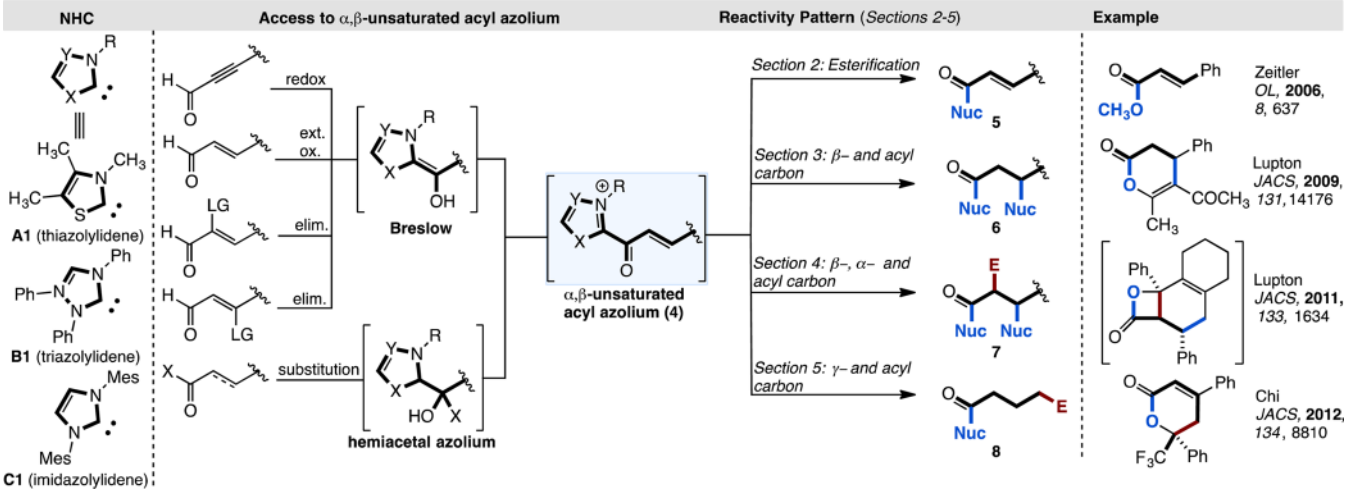
Scheme 2. Overview of Approaches to the α,β-Unsaturated Acyl Azolium and Common Reactivity Patterns

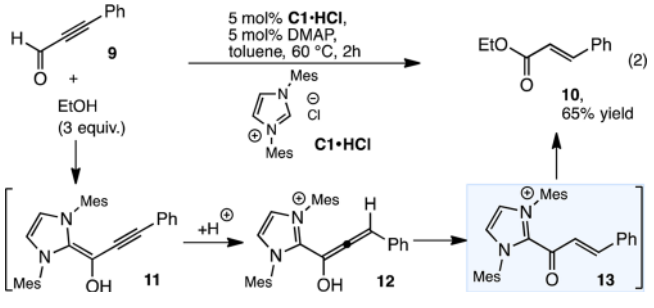


annulations of the γ- and acyl carbons (i.e., **4** → **8**). Finally, comments regarding the future of the field are included in Section 6.

2. ESTERIFICATION OF THE α,β-UNSATURATED ACYL AZOLIUM

The simplest reactions of the α,β-unsaturated acyl azolium provide esterified products. In 2006, Zeitler reported the redox isomerization of alkynal aldehydes (i.e., **9**) to α,β-unsaturated esters (i.e., **10**) in the presence of the IMes NHC (**C1**) and an appropriate alcohol (as described by eq 2 in Scheme 3).[8] The

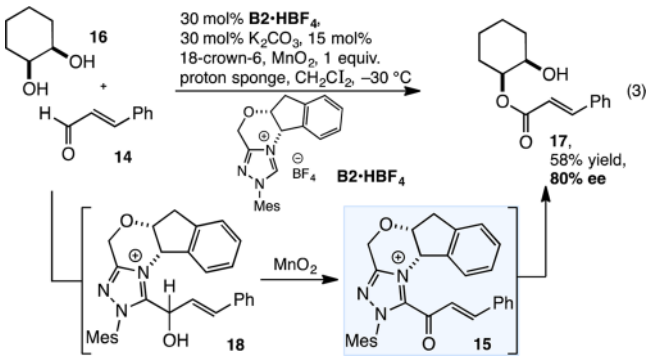
Scheme 3. Zeitler's Redox Isomerization Approach to the α,β-Unsaturated Acyl Azolium



reaction was proposed as proceeding via the acyl anion equivalent **11**, which is protonated to give allene **12**; tautomerization then gives the α,β-unsaturated acyl azolium **13** (see Scheme 3). This defined the first access to these species and demonstrated that facile acylation can be achieved. While only the reactivity about the carbonyl was exploited, this study paved the way for many important contributions that exploit the olefinic reactivity (*vide infra*).

The application of external oxidants to access the acyl azolium, as introduced previously (eq 1), has been studied for more than 40 years with a series of oxidants reported, although, in most cases, focused on the biological role of this pathway.[5] In 2007, Scheidt exploited MnO_2 as the terminal oxidant to allow conversion of both allylic alcohols and α,β-unsaturated aldehydes (i.e., **14**) to the α,β-unsaturated acyl azolium (i.e., **15**).[9,10] While a series of simple esterifications was developed, the use of chiral NHCs (i.e., **B2**) allowed desymmetrization of mesodiol **16** to provide enantioenriched ester **17** (see eq 3 in Scheme 4). It was proposed that formation of the Breslow

Scheme 4. Scheidt's MnO_2 Formation of α,β-Unsaturated Acyl Azolium and Desymmetrization



intermediate was slower than benzylic oxidation of **18**, thereby allowing the formation of acyl azolium **15** and subsequent esterification.

The organic oxidants azobenzene and TEMPO were developed independently by Connon (eq 4 in Scheme 5)[11] and Studer (eq 5 in Scheme 5),[12] respectively, for oxidative access to the α,β-unsaturated acyl azolium. While both gave acceptable yields of the expected cinnamate ester, the use of TEMPO was limited to the formation of TEMPO cinnamate **19** with rapid consumption of the azolium by $TEMPO^-$. This limitation was addressed by the use of the Kharasch oxidant **O1**, which Studer found to be compatible with a variety of alcohols (eq 6 in Scheme 5).[13] Benzoquinone **O1** has become the most common oxidant used in acyl azolium catalysis. This study also identified the acyl azolium's preference for esterification over amidation. Specifically, when equimolar quantities of benzylalcohol and benzylamine were subjected to the reaction conditions, only ester **20** formed. This feature of acyl azolium catalysis is notable in subsequent studies where amides and lactams have generally proved more challenging to access than esters and lactones (*vide infra*).

While early studies on the chemistry of the α,β-unsaturated acyl azolium focused on acylation chemistry they also defined

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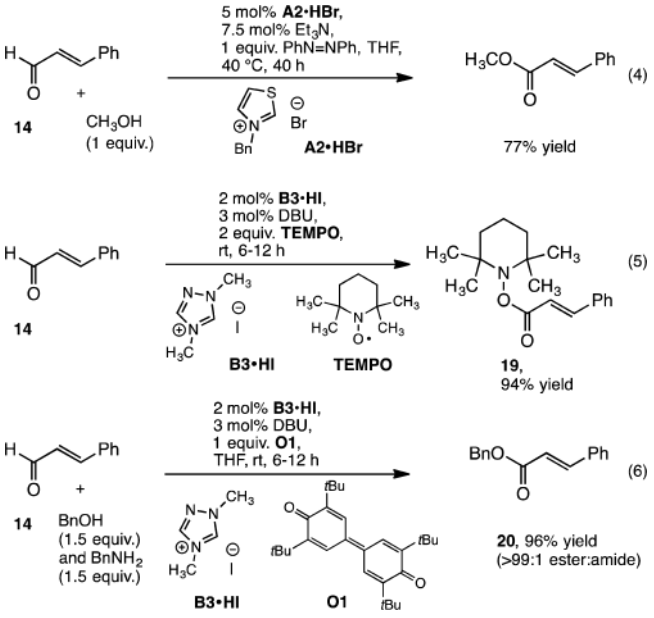
Scheme 5. Connon and Studer Oxidative Formation of α,β-Unsaturated Acyl Azolium

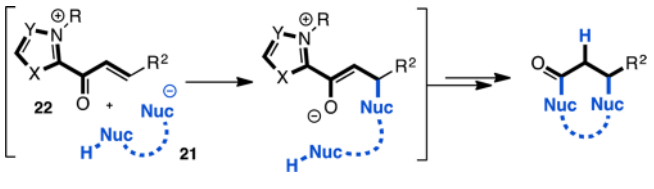


two of the most common approaches to access this intermediate (see eq 2 in Scheme 3 and eq 6 in Scheme 5).

3. CASCADES INVOLVING BOND FORMATION AT THE β- AND ACYL CARBONS

In 2009, the electrophilicity of the β-carbon of the α,β-unsaturated acyl azolium was exploited in reaction discovery. Subsequently, a range of reactions have been developed that allow *bis*-nucleophiles (**21**) to react with α,β-unsaturated acyl azoliums (**22**) in annulative reactions involving bond formation at the β- and acyl carbons (see Scheme 6). In addition to

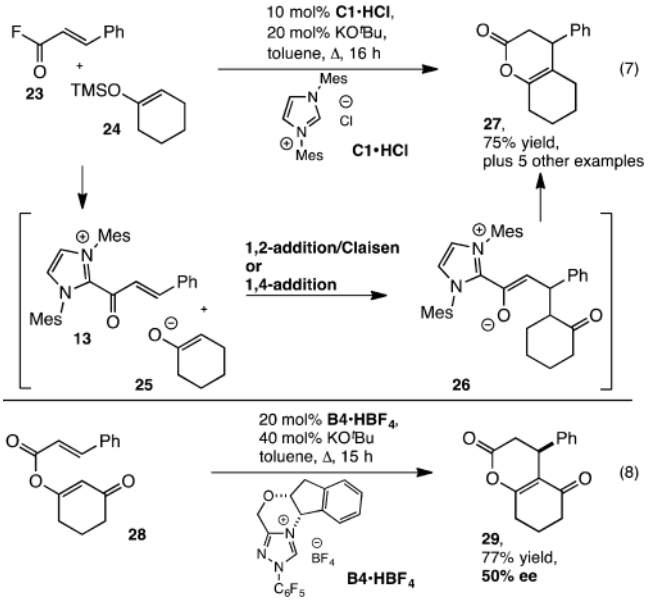
Scheme 6. Summary of the Mechanism Described in Section 3



allowing access to more-complex materials (compared to the esters of Section 2), such reactions have often been performed in an enantioselective fashion. In most cases, the *bis*-nucleophiles examined are enols or enamines, giving dihydropyranones (Section 3.1) or dihydropyrimidones (Section 3.2). In addition, several alternate *bis*-nucleophiles have been introduced (Section 3.3).

3.1. Annulation with Enolate *bis*-Nucleophiles. The first annulation of the α,β-unsaturated acyl azolium was reported by Lupton and co-workers in 2009 (eq 7 in Scheme 7). In addition to introducing annulative reactions, a new method to access the α,β-unsaturated acyl azolium, via the addition of an NHC to an acid fluoride (i.e., **23**) and desilylation of a silyl enol ether (i.e., **24**), was introduced.[14a] The unmasked nucleophile (i.e., **25**) then adds to the β-position of the acyl azolium, either by direct 1,4-addition, or by 1,2-addition to the carbonyl, followed by Claisen rearrange-

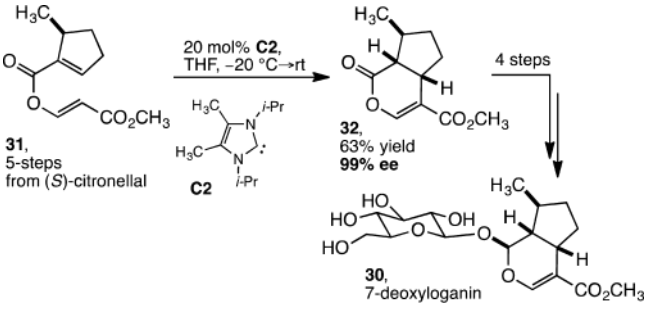
Scheme 7. Lupton's Annulation of the α,β-Unsaturated Acyl Azolium with Enolates



ment. The azolium enolate (**26**), following tautomerization, cyclizes to give dihydropyranone (**27**) with regeneration of the catalyst (Scheme 7). Although an enantioselective variant of this reaction was not possible,[14b] the related transformation of enol ester **28** to pyranone **29**, using indanol-derived NHC (**B4**), could be achieved (eq 8 in Scheme 7). Crossover experiments indicated that a fragmentation/addition pathway from the enol ester was unlikely; instead, a Claisen rearrangement or tight ion pair mechanism was favored.[15b]

By exploiting access to dihydropyranones from enol esters (i.e., eq 8 in Scheme 7), Lupton and Candish applied the NHC-catalyzed synthesis of dihydropyranones to the synthesis of 7-deoxyloganin (**30**) (see Scheme 8).[15,16] Beginning with (*S*)-

Scheme 8. Lupton's Total Synthesis of 7-Deoxyloganin (30)



citronellal as a chiral-pool starting material, enantiopure enol ester **31** was prepared in five steps. Treatment of this precursor with tetraalkyl imidazole catalyst **C2** gave pyranone **32** in 63% yield. The natural product was prepared in four additional steps.

In 2010, the annulation of α,β-unsaturated acyl azoliums was also reported by Studer, using aldehyde substrates and his previously developed oxidative conditions (i.e., eq 6 in Scheme 5).[17] Thus, the addition of triazolylidene NHC **B3** to cinnamaldehyde (**14**) gives homoenolate **33**, which is oxidized to the acyl azolium **35** by quinone **O1**. The enolate of 1,3-diketone **34** undergoes 1,4-addition to the α,β-unsaturated acyl

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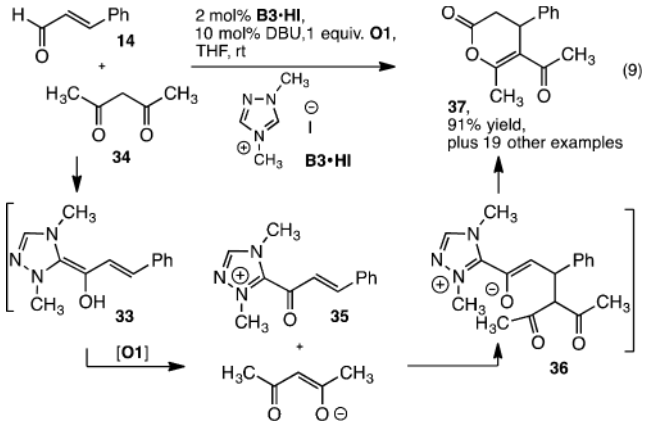
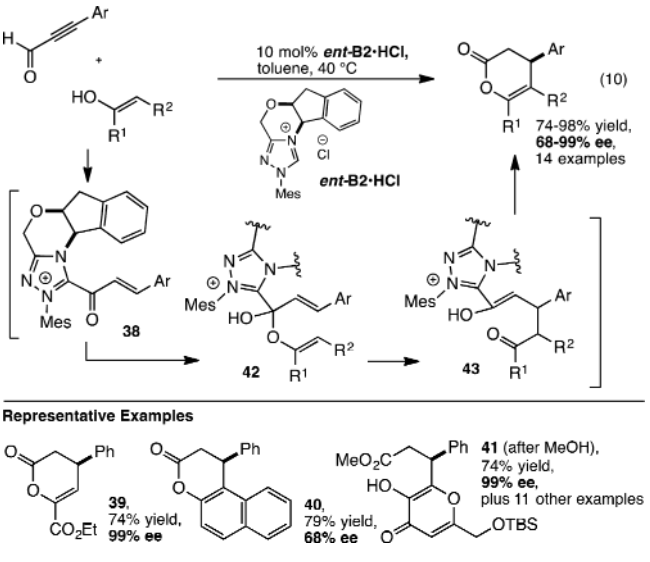
azolium **35** to provide acyl azolium enolate **36**, followed by tautomerization and cyclization to give dihydropyranone **37** (see Scheme 9). Control experiments indicated that the 1,4-addition of soft carbon nucleophiles was favored in this system over 1,2-addition to the carbonyl, and a mechanism involving Claisen rearrangement was discounted. Zeng and Zhong more recently reported a variation of this approach that makes use of aerobic oxidation to generate the α,β-unsaturated acyl azolium,[18a] while Sunden concurrently reported a similar reaction, which made use of iron(II) phthalocyanine as an electron transfer mediator, to assist in the aerobic oxidation step.[18b]

Scheme 9. Studer's Oxidative Dihydropyranone Synthesis



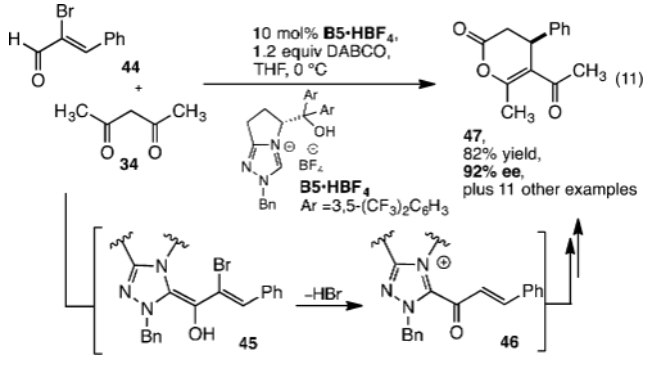
The first highly enantioselective synthesis of pyranones from an α,β-unsaturated acyl azolium intermediate was reported by Bode in 2010, utilizing redox isomerization of an ynal to give the reactive intermediate **38** (see Scheme 10).[19] Bode's synthesis employed the chiral indanol catalyst ***ent*-B2** and several stabilized enols as the nucleophilic component, achieving enantioselectivities of up to 99% enantiometric excess (*ee*). Examples include dihydropyranone **39** from an α-keto ester, the tricyclic napthol-derived product **40**, and a series of adducts of kojic acid, which was found to form an unstable dihydropyranone and was isolated as the methyl ester **41**, following workup with methanol. Based on kinetic studies performed with the kojic acid substrate, Bode suggests that a 1,4-addition mechanism is unlikely in this system, favoring Claisen rearrangement from intermediate **42** to give **43** (see Scheme 10).[20] You and co-workers later reported that an NHC derived from L-phenylalanine with ynals provides dihydopyranone from naphthol nucleophiles in 46%–96% *ee*.[21] In 2011, Xiao used the redox isomerization of ynals to synthesize pyranones from 1,3-dicarbonyls.[22] They found that the addition of a desiccant to the reaction was essential for achieving high yields and enantioselectivities. It was also reported that the same products could be isolated in high enantioselectivity from the α,β-unsaturated aldehyde, employing quinone oxidant **O1** previously used by Studer.[13,17] Also in 2011, the You group reported a similar oxidative annulation from the α,β-unsaturated aldehyde, catalyzed by a camphor-derived imidazolidinone NHC.[23]

Scheme 10. Bode's Enantioselective Dihydropyranone Synthesis



Alternate access to the α,β-unsaturated acyl azolium intermediate was developed by Ye in 2011 and reported in the context of an enantioselective synthesis of dihydropyranones (eq 11 in Scheme 11).[24] This approach uses α-bromoenals (i.e., **44**) with the elimination of HBr from the nucleophilic homoenolate **45** able to give acyl azolium **46**. Ye was able to successfully demonstrate this reaction with both 1,3-diketones (i.e., **34**) and β-ketoesters as the *bis*-nucleophile to give dihydropyranones with high enantioselectivity (**47**). Both enantiomers of the product could be isolated from the same catalyst precursor (L-pyroglutamic acid) by changing the oxygen substituent, from a TMS ether (not shown), to the free hydroxyl (i.e., **B5**).

Scheme 11. Ye's Enantioselective Dihydropyranone Synthesis from α-Bromoenals



In 2013, Biju described the synthesis of dihydropyranones and pyridinones from α-bromoenals and 1,3-dicarbonyls or enamides, giving the expected adducts with high enantioselectivity using ***ent*-B2** catalyst.[25a] Slightly modified reaction conditions allowed enolizable aldehydes to be converted to the expected dihydropyranones.[25b]

Also making use of a halide elimination strategy to access the α,β-unsaturated acyl azolium, Ma described the synthesis of dihydropyranones **47** from β-bromoenals (i.e., **48**) and 1,3-dicarbonyls (i.e., **34**) (see Scheme 12).[26] In addition, this study demonstrated that the same starting materials could be used to access 2-pyranones **48** in the presence of the quinone oxidant **O1**. α,β-Dibromoaldehydes have also been used as precursors to dihydropyranones, as reported by Yao in 2012.[27]

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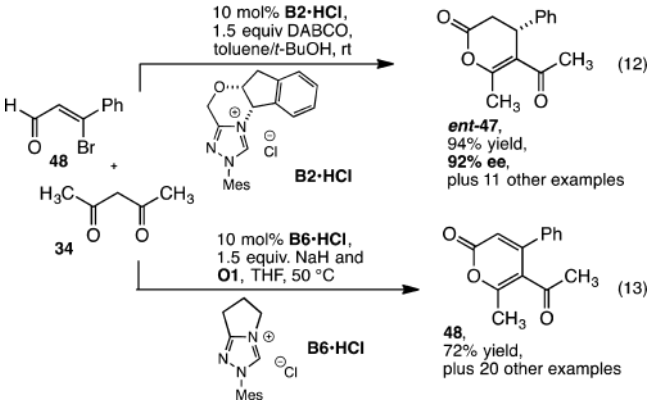
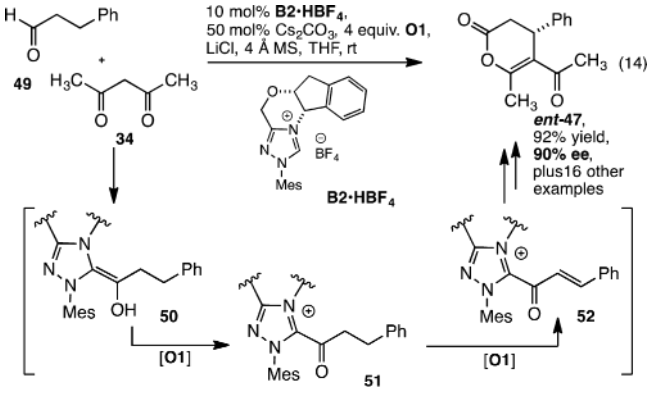
Scheme 12. Ma's Synthesis of Dihydropyranones and Pyranones from β-Bromoenals



An additional approach to α,β-unsaturated acyl azoliums was reported by Chi in 2013. Exploiting 4 equiv of oxidant **O1**, saturated aldehydes (i.e., **49**) could be converted to enantioenriched dihydropyranone ***ent*-47** (eq 14 in Scheme 13).[28] In this study, it was proposed that the addition of NHC

Scheme 13. Chi's Enantioselective Dihydropyranone Synthesis from Saturated Aldehydes

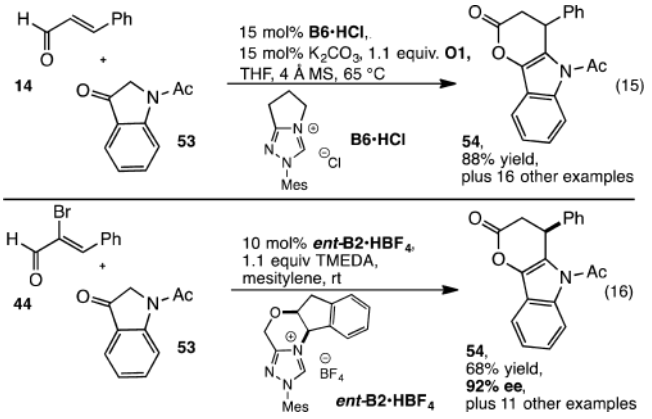


catalyst **B2** to aldehyde **49** results in the formation of the Breslow intermediate **50**, which is oxidized to acyl azolium **51**. Tautomerization of this intermediate, followed by a second oxidation, provides the α,β-unsaturated acyl azolium **52**, which reacts with the 1,3-dicarbonyl to give the expected product ***ent*-47**.

Exploiting less-common 1,3-dicarbonyl *bis*-nucleophiles, in 2013, Lu reported the use of indolin-3-one (**53**) to give dihydropyranindolone **54** (Scheme 14).[29a] Lu utilized Studer's oxidative route to the α,β-unsaturated acyl azolium intermediate (eq 15 in Scheme 14), while also noting that redox isomerization of the corresponding ynal returned the same products, albeit in significantly reduced yields. In a single example, this report describes the use of the chiral catalyst **B2**, giving **54** with moderate enanatioselectivity (87:13 enantiometric ratio (er)). The following year, Enders reported a highly enantioselective variant of this reaction, making use of α-bromoenals (i.e., **44**) and triazolylidene NHC ***ent*-B2** to access the α,β-unsaturated acyl azolium (eq 16 in Scheme 14).[29b]

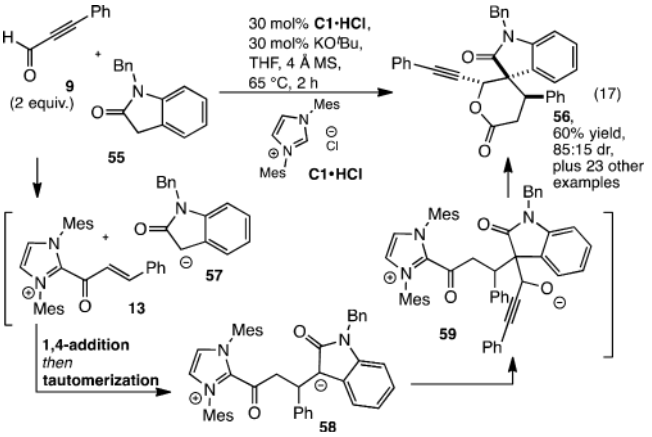
Lu has also developed a related three-component coupling reaction that exploits oxindoles. When the α,β-unsaturated acyl azolium is generated from an ynal (i.e., **9**) in the presence of oxindole (i.e., **55**) the formation of tetrahydrapyranones (**56**)

Scheme 14. Lu and Enders' Dihydropyranone Synthesis from Indolin-3-ones



was observed (see Scheme 15).[30] In this transformation, the oxindole enolate **57** undergoes 1,4-addition to acyl azolium **13**,

Scheme 15. Lu's Intercepted α,β-Unsaturated Acyl Azolium Annulation



resulting in the azolium enolate which tautomerizes to give **58**. Rather than lactonization, as observed with most reactions of the α,β-unsaturated acyl azolium, the addition of a second equivalent of ynal **9** gives alkoxide **59**. This intermediate then cyclizes to deliver **56** with good diastereoselectivity. The use of electron-poor oxindoles increased this selectivity.

Another annulation of the α,β-unsaturated acyl azolium that diverts from the conventional mechanism was reported by Alexakis with the preparation of bicyclic tetrahydropyrone **60** (see Scheme 16).[31] While NHCs bearing *N*-phenyl, benzyl, and pentafluorophenyl substituents were examined, *N*-mesityl NHC **B6** provided pyrone **60** with optimal diastereoselectivity and yield (eq 18 in Scheme 16). The *bis*-enol tautomer of diketone **62** is thought to undergo conjugate addition with the α,β-unsaturated acyl azolium, and, upon tautomerization of the resulting azolium enolate, acyl azolium **63** is formed. Cyclization of the diketone fragment provides hemiacetal **64**, which leads to lactone product **60**.

While β-disubstituted α,β-unsaturated acyl azoliums were reported in Lupton's original dihydropyranone synthesis, they have seen limited subsequent application. In 2016, Lu and Du synthesized a range of spirocyclic quaternary carbon containing dihydropyranones **65** exploiting isatin-derived α-bromoenal **66** with β-ketoesters (i.e., **67**) (see Scheme 17).[32]

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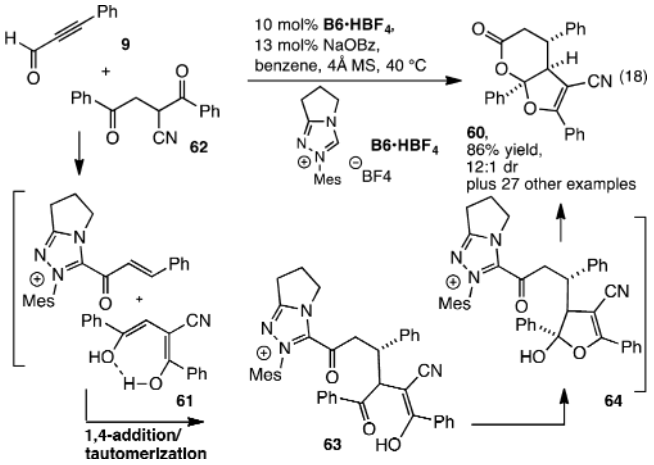
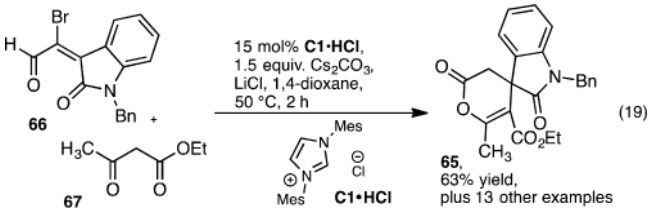
Scheme 16. Alexakis' Intercepted α,β-Unsaturated Acyl Azolium Annulation



Scheme 17. Lu and Du's Synthesis of Spirocyclic Oxindole

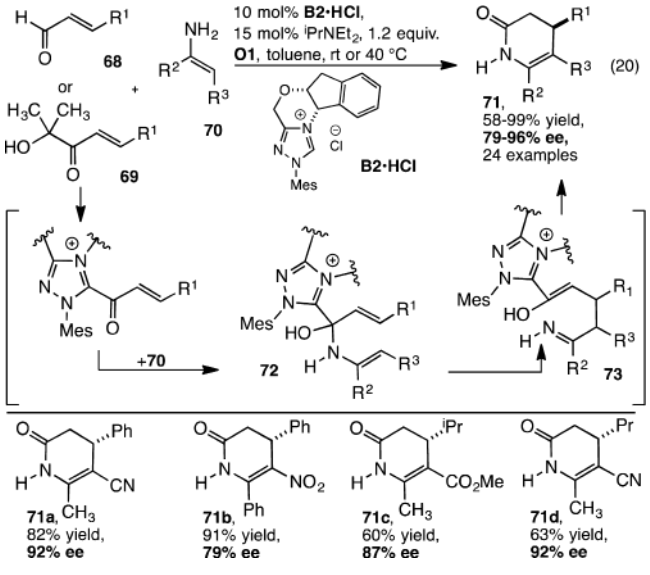


Over the last seven years, the synthesis of dihydropyranones has developed as a testing ground for new methods to access α,β-unsaturated acyl azoliums. Although the synthesis of simple dihydropyranones, particularly from 1,3-dicarbonyl *bis*-nucleophiles, is now relatively routine, new frontiers exist, especially relating to the use of unusual *bis*-nucleophiles and diversion from the conventional reaction pathway, allowing novel reaction cascades.

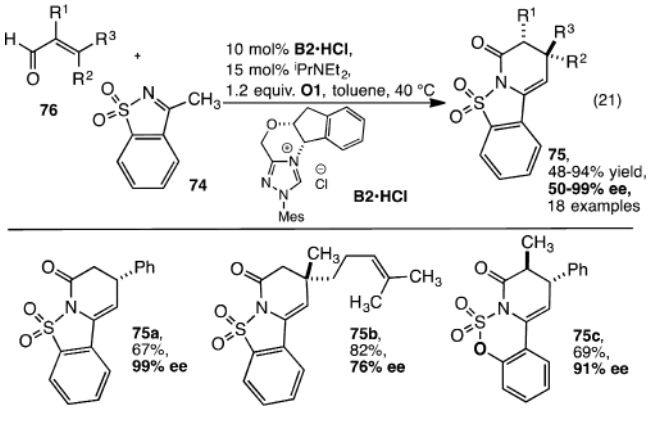
3.2. Annulation with Enamine *bis*-Nucleophiles. Shortly following the first dihydropyranone synthesis from α,β-unsaturated acyl azolium intermediates, Bode developed a related synthesis of dihydropyridinones (see Scheme 18).[33] Accessing the acyl azolium intermediate from either α,β-unsaturated aldehydes **68**, or from α′-hydroxyenones (**69**), annulation with many stabilized enamine *bis*-nucleophiles (i.e., **70**) was achieved. Using this approach, various dihydropyridinones (i.e., **71a**–**71d**) were prepared in good yield and enantioselectivity, using the chiral indanol catalyst **B2** (Scheme 18). Akin to Bode's dihydropyranone synthesis (Scheme 10), this reaction is thought to proceed via a hemiaminal intermediate **72**, which undergoes sigmatropic rearrangement to give **73**. The reaction is completed by tautomerization and lactamization.

In 2012, Bode published a second dihydropyridinone synthesis, this time employing cyclic *N*-sulfonylimines (**74**) as enamine precursors (see Scheme 19).[34] This led to a series of tricyclic *N*-sulfonyl dihydropyridinones **75** in up to 99% *ee*. This method tolerated many trisubstituted α,β-unsaturated aldehydes **76**, allowing for the synthesis of quaternary stereocenters (i.e., **75b**) and adjacent stereocenters (i.e., **75c**). In the latter case, the selectivity was enhanced by applying the six-membered analogue of imine **74** as the starting material. Ye reported a similar transformation, using α-bromoenones to generate the α,β-unsaturated acyl azolium.[35]

Scheme 18. Bode's Enantioselective Synthesis of Dihydropyridinones

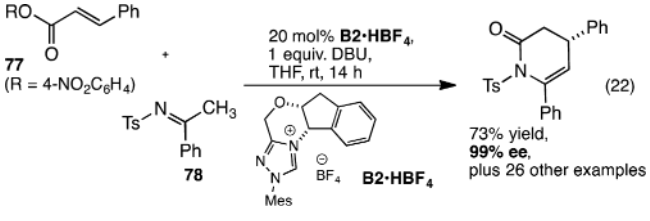


Scheme 19. Bode's Annulation of *N*-Sulfonlyimines



In 2013, Chi reported that dihydropyridinones can be synthesized from the α,β-unsaturated acyl azolium intermediates, generated, in turn, from ester **77** (see Scheme 20).[36] The

Scheme 20. Chi's Enantioselective Dihydropyridinone Synthesis



use of carboxylic acid oxidation-state substrates, such as these phenolic esters and Lupton's acyl fluorides, avoids the need for elimination or oxidation events. This approach gives pyridinone products from various tosyl imines (i.e., **78**) with exceptional enantioselectivity, achieving 99% *ee* in the majority of cases. The reaction can employ trisubstituted alkenes, giving products bearing quaternary stereocenters, albeit with reduced enantioselectivity. Yang and Zhong later reported a similar reaction employing activated *N*-hydroxyphthalimide esters as the

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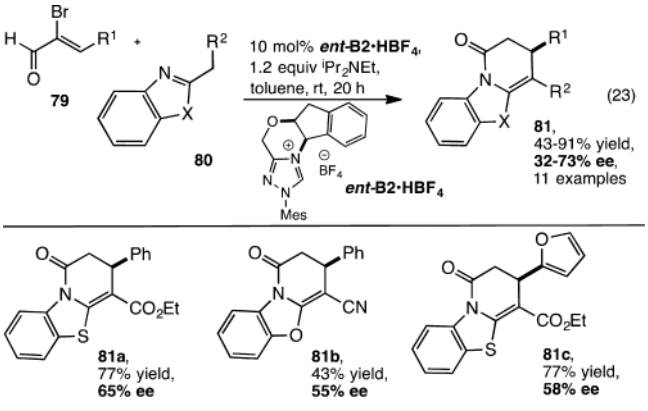
azolium precursor. In this case, the products were isolated with almost exclusively >99% *ee*, with all examples including a quaternary carbon stereocenter.[37]

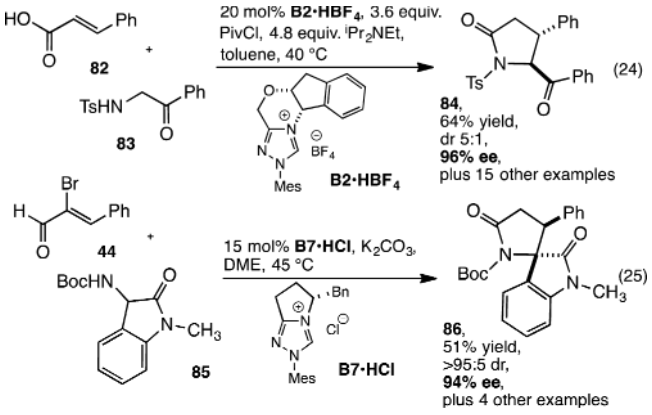
In 2015, Enders reported a dihydropyridinone synthesis from various imine/enamine substrates and α-bromoenones (i.e., **79**) as the α,β-unsaturated acyl azolium precursors (Scheme 21).[38] Specifically benzothiozolyl enamine precursors (i.e., **80**) gave a variety of fused tricyclic dihydropyridinone products **81**, although with moderate levels of enantioselectivity.

Scheme 21. Enders' Enantioselective Benzothiazolyl Annulation



3.3. Annulation with Other *bis*-Nucleophiles. In addition to the use of enolates and enamines in annulations of α,β-unsaturated acyl azolium intermediates, alternate *bis*-nucleophiles have been exploited in annulative reactions. In 2014, Ye demonstrated that the α,β-unsaturated acyl azolium could be accessed from the mixed anhydride, generated *in situ* from a carboxylic acid **82** and pivolyl chloride (Scheme 22).

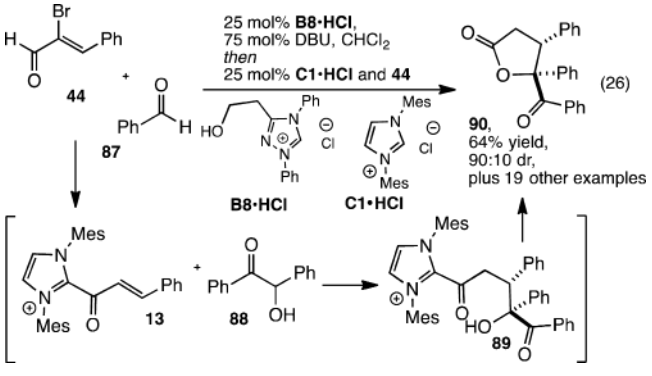
Scheme 22. Ye and Du's Enantioselective γ-Lactam Synthesis



This intermediate was shown to react with α-tosylaminoketones **83**, which gave rise to the pyrrolidinone products **84** (eq 24 in Scheme 22).[39] A similar strategy was reported by Lu and Du in 2015, with 3-aminooxindoles **85** serving as the *bis*-nucleophile, which reacted with the azolium intermediate generated from α-bromoenals **44** to give spirocyclic oxindole **86**. While the generality of this reaction was examined with achiral NHC **B6** a handful of enantioselective reactions were reported using chiral NHC **B7** (eq 25 in Scheme 22).[40a] Ye and co-workers have also reported a related transformation, although with a more comprehensive examination of enantioselectivity.[40b]

γ-Lactones can also be accessed from the α,β-unsaturated acyl azolium. In 2015, Huang reported a novel three-component coupling (see Scheme 23).[41] In this reaction, it is

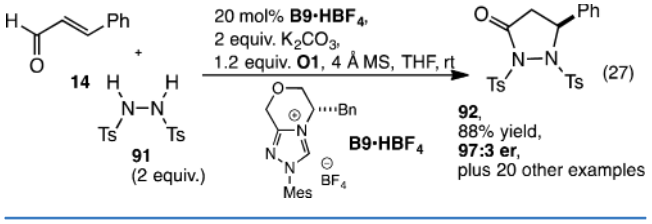
Scheme 23. Huang's Benzoin Condensation α,β-Unsaturated Acyl Azolium Cascade



proposed that benzaldehyde (**87**) is dimerized via a benzoin reaction mediated by triazolylidene NHC **B8** to give benzil **88**. Subsequent addition of α-bromoenal **44** and imidazolium precatalyst **C1·HCl** leads to the formation of the α,β-unsaturated acyl azolium intermediate **13**, which reacts with the enol form of benzil **88**. Cyclization of the resultant acyl azolium **89** completes the catalytic cycle, giving γ-lactones **90** with good levels of diastereoselectivity.

Very recently, Chi has exploited protected hydrazines (i.e., **91** as *bis*-nucleophiles for annulations of the α,β-unsaturated acyl azolium (see Scheme 24).[42] Formation of the acyl azolium

Scheme 24. Chi's Annulation of α,β-Unsaturated Acyl Azolium with Protected Hydrazine



from aromatic and aliphatic α,β-unsaturated aldehydes (**14**) was achieved using morpholinone NHC **B9** and oxidant **O1**. Subsequent annulation gives rise to a series of pyrazolidone products (i.e., **92**) with high enantiopurity (eq 27 in Scheme 24).

The annulation of the α,β-unsaturated acyl azolium has been reported by Biju with *bis*-carbon nucleophiles in the form of dienolate **93** (eq 28 in Scheme 25).[43] Following acyl azolium formation, Michael addition of dienolate **93** gives acyl azolium enolate **95**. Tautomerization and Claisen condensation then affords the cyclohexanone products **96** with high enantiopurity (see Scheme 25).

4. CASCADES INVOLVING BOND FORMATION AT THE β-, α-, AND ACYL CARBONS

While early studies focused on the α,β-unsaturated acyl azoliums as useful *bis*-electrophiles, more recently, the potential to develop reactions with C−C bond formation from the acyl

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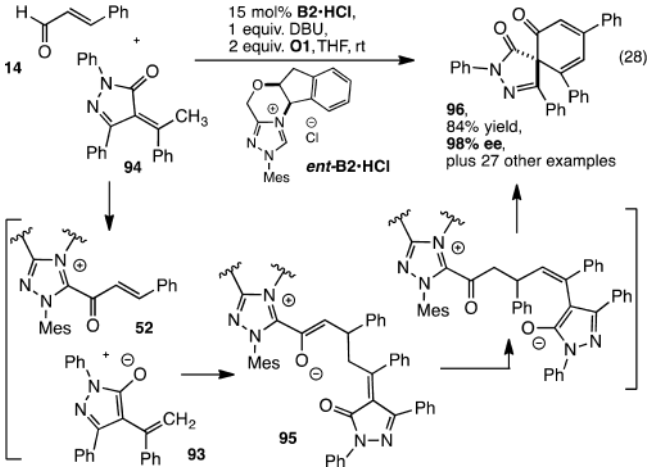
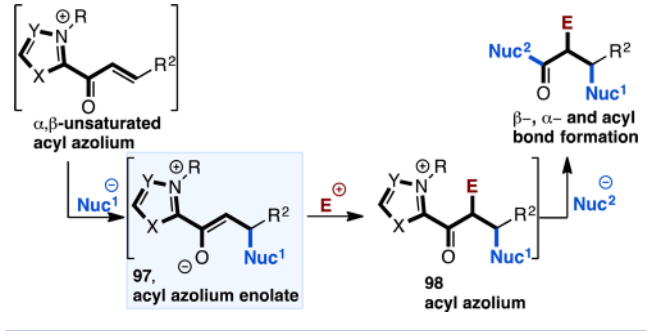
Scheme 25. Biju's All-Carbon Annulation of α,β-Unsaturated Acyl Azolium



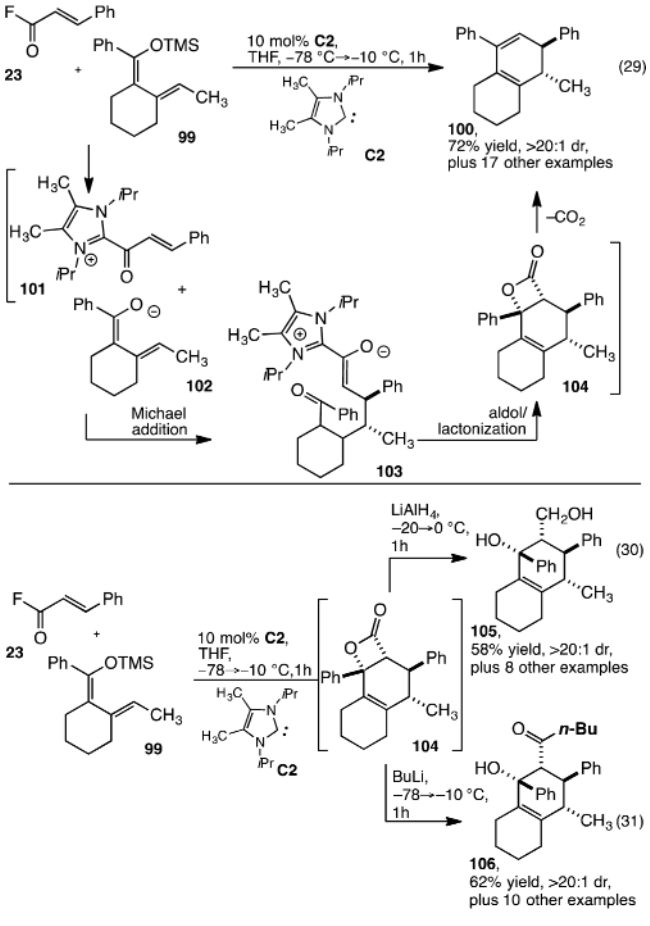
azolium enolate (i.e., **97**) have also been developed. In these cases, cascades involving Michael additions, followed by aldol-like reactions of the α-carbon and acylation of the resultant acyl azolium **98**, have been developed. When an appropriate substrate is used with all reaction partners tethered, multiple-ring systems can be accessed by cascade reactions with bond formations at the β-, α-, and acyl carbons. This class of reaction of the α,β-unsaturated acyl azolium can be generalized by the cascade shown in Scheme 26.

Scheme 26. Summary of the Mecahnism Described in Section 4



4.1. (4 + 2) Annulation/β-Lactonization. In 2011, Lupton and co-workers reported the NHC-catalyzed all-carbon (4 + 2) annulation between α,β-unsaturated acyl fluorides **23** and silyl dienol ethers **99** to provide cyclohexadienes **100** (Scheme 27).[44] In this case, nucleophilic substitution of imidazolylidene NHC **C2** with **23** provides α,β-unsaturated acyl azolium **101**, with the liberated fluoride ion desilylating **99** to reveal dienolate **102**. Secondary kinetic isotope effect analysis and computational studies implicate a mechanism involving stepwise annulation, via Michael addition, giving **103**. Subsequent aldol cyclization/lactonization affords β-lactone **104** with decarboxylation, giving cyclohexadiene **100** as a single diastereoisomer.[45] While defining the reactivity pattern outline above (Scheme 26), decarboxylation ablates much stereochemical information. However, in subsequent studies, it was demonstrated that, by performing the reaction at temperatures below −20 °C, it was possible to intercept the β-lactone intermediate **104** with either reducing agents (eq 30 in Scheme 27) to produce diols (i.e., **105**), or alkyl lithium reagents (eq 31

Scheme 27. Lupton's (4 + 2) Annulation of Dienolates and the α,β-Unsaturated Acyl Azolium



in Scheme 27) to afford β-hydroxy ketones (i.e., **106**). In both cases, the reactions proceeded to produce cyclohexenes bearing up to 4-contiguous stereogenic centers as a single diastereoisomer.

This transformation has limitations related to undesired enol ester formation, thereby limiting compatibility with homochiral triazolylidene NHCs. To address these problems, enol ester **107** was examined and found to allow conversion to the corresponding β-lactones **108** with various chiral catalysts (Scheme 28).[46] The optimal catalyst was found to be triazolylidene **B10** bearing a *tert*-butyl *N*-substitutent.[47] Crossover studies indicate that the reaction involves fragmentation of the dienyl ester **107** to dienolate **109** and acyl azolium **110**. Vinylogous Michael addition then provides azolium enolate **111**, which isomerizes to **112** via the intermediacy of allyl anion **113**, as supported by deuterium labeling studies. Aldol cyclization/lactonization, followed by release of the catalyst, completes the reaction and provides the β-lactones **108** (eq 32 in Scheme 28).

Interestingly, when substituents were placed at both C3 and C4 of the dienyl esters (i.e., **114**), the corresponding proton transfer/olefin isomerization process is prevented and β-lactones **115** forms. As a result of the instability of **115**, facile decarboxylation occurs to give cyclohexadienes **116** (eq 33 in Scheme 28).[48] In this case, the optimal catalyst was found to be the morpholinone-derived **B11**, bearing a dimethoxyphenyl *N*-substitution.

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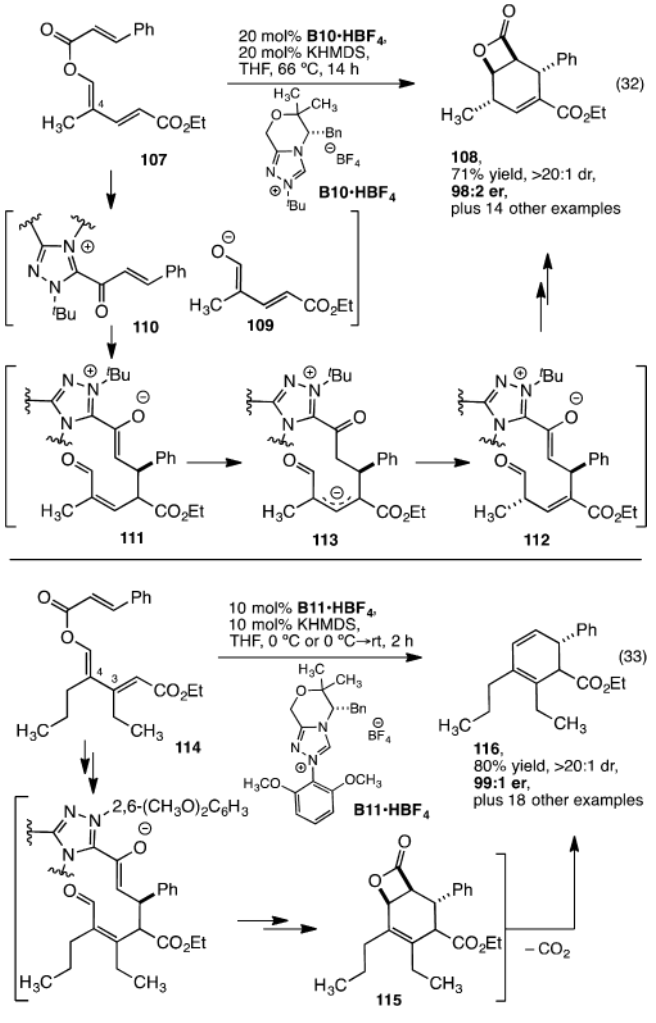
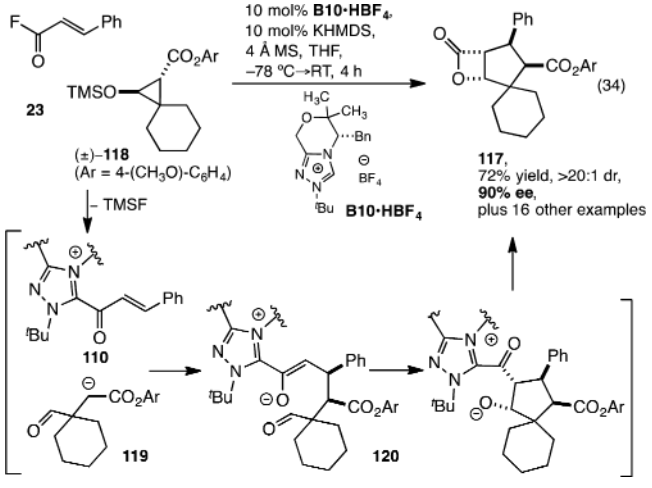
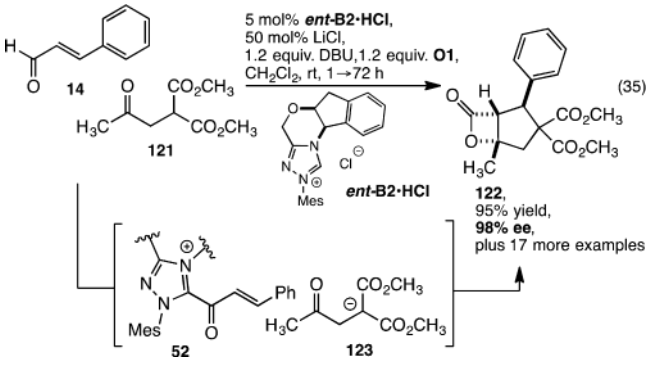
Scheme 28. Lupton's Enantioselective Cycloisomerisations of Trienyl Esters



Scheme 29. Lupton's Enantioselective Synthesis of Cyclopentyl Fused β-Lactones



Scheme 30. Studer's Enantioselective Synthesis of Cyclopentyl Fused β-Lactones



4.2. (3 + 2) Annulation/β-Lactonization. In 2013, Lupton and co-workers reported a synthesis of cyclopentyl fused β-lactones **117** by NHC-catalyzed (3 + 2) annulation of α,β-unsaturated acid fluorides **23** and donor–acceptor cyclopropanes **118** (see Scheme 29).[49] While achiral imidazolylidene catalyst **C1** gave racemic lactones **117** with good yields and high diastereoselectivity (all dr >20:1),[49a] catalyst **B10** allowed the reaction to proceed with good to excellent enantioselectivity without erosion of diastereoselectivity.[49b] Mechanistic studies suggest that the reaction commences with the addition of NHC to acyl fluoride **23**, giving acyl azolium **110** and enolate **119** by fluorodesilylation and retro aldol reaction. Formation of **120** is thought to occur via 1,2-addition of enolate **119** to acyl azolium **110** and ester enolate Claisen rearrangement. This mechanism is supported by substituent and salt effects. Finally, aldol cyclization and lactonization provides β-lactone **117**.

In 2014, Studer and co-workers reported a related NHC-catalyzed (3 + 2) annulation between enals (i.e., **14**) and ketone-malonates (i.e., **121**) (see Scheme 30).[50] Lithium chloride plays an important role in enhancing the enantioselectivity of the reaction, allowing malonates (i.e., **121**) to be converted to the corresponding β-lactones (**122**) with excellent enantioselectivity (eq 35 in Scheme 30). Extension of the tether between malonate and ketone moiety and application of precatalyst **B9·HCl** allowed cyclohexyl-fused β-lactone to be formed with diminished enantioselectivity (80% *ee*), but comparable yield. Mechanistically, the reaction is believed to involve the formation of α,β-unsaturated acyl azolium **52** from enal **14** under oxidative conditions and enolate **123** via the deprotonation of malonate **121**. Michael addition of **123** to **52**, and then aldol reaction and lactonization, gave the β-lactone product **122**.

In the same year, Biju and co-workers reported the application of α-bromo enals (**44**) as precursors to acyl azoliums, enabling a related (3 + 2) annulation with keto-malonates (**124**) (eq 36 in Scheme 31).[51] By replacing the methyl in Studer's studies with a phenyl group (**124**, cf. **121**), decarboxylation becomes more facile and, hence, cyclopentenes are isolated. Returning to aliphatic substituents, β-lactone **126** could be prepared with high enantiopurity. In addition, one of the malonate esters could be replaced with a cyano or keto group with products **125a** and **125b** being formed with moderate diastereoselectivity and good enantioselectivity.

4.3. (3 + 2) Annulation/δ-Lactonization. In addition to reactions that culminate in β-lactonization (see Sections 4.1 and 4.2), δ-lactone formation by transformations that terminate with a Michael addition/lactonization have been developed (see Scheme 32). The first example of such chemistry was reported by Studer and co-workers with an oxidative NHC-catalyzed cascade that allowed the synthesis of δ-lactone-fused indanes **127** from enone-functionalized enals **128** and 1,3-

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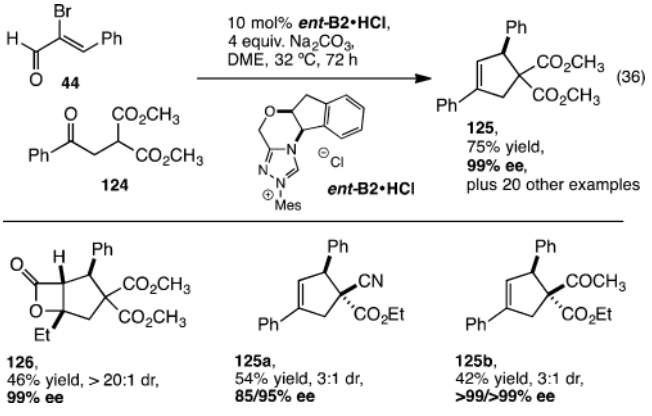
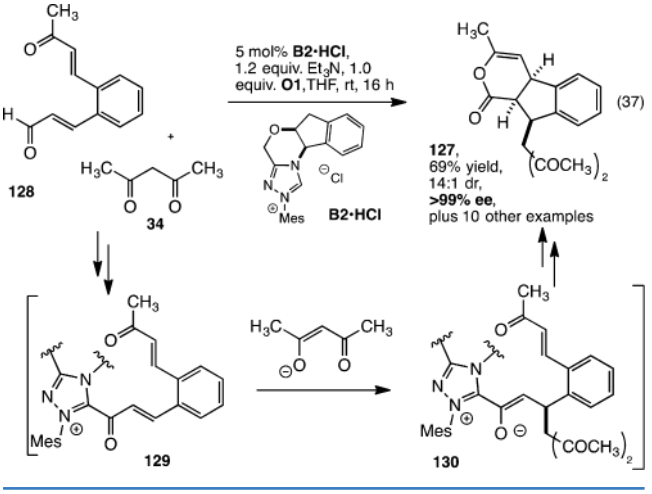
Scheme 31. Biju's Enantioselective Synthesis of Cyclopentenes



Scheme 32. Studer's Enantioselective Synthesis of Indanes

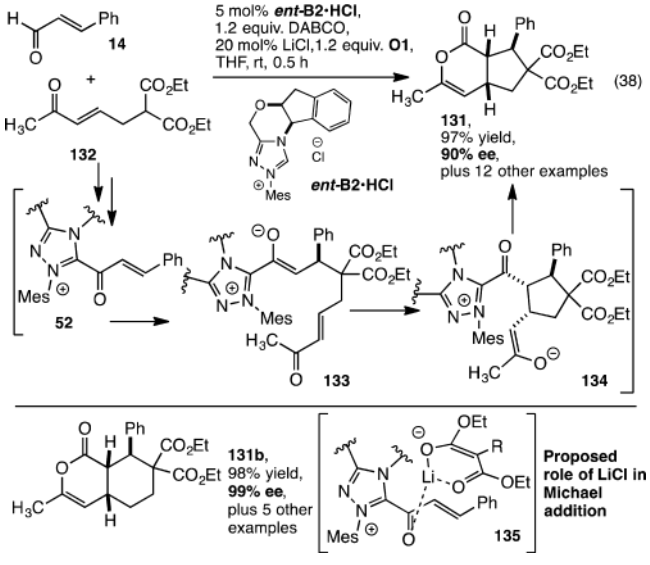


dicarbonyls (i.e., **34**) (eq 37 in Scheme 32).[52] This early example (2011) of a reaction involving functionalization at the β-, α-, and acyl carbon commences with an oxidative conversion of aldehyde **128** to acyl azolium **129**, which undergoes conjugate addition with the enolate of **34** to yield acyl azolium enolate **130**. Michael addition and lactonization then provides highly enantioenriched indane **127** and completes the reaction cycle.

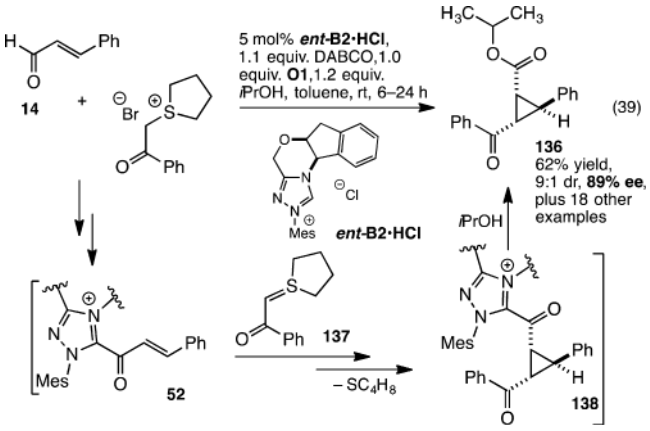
In 2015, the groups of Studer[53a] and Ye[53b] independently reported NHC-catalyzed construction of cyclopentane-fused δ-lactones **131** from enals and bifunctional malonates **132**, with LiCl as a co-catalyst (see Scheme 33). Oxidative conversion of enals (i.e., **14**) with NHC ***ent*-B2** leads to acyl azolium **52**, which reacts with the deprotonated malonate by Michael addition giving acyl azolium enolate **133**. A second Michael addition gives acyl azolium **134**, which cyclizes to deliver δ-lactone **131** (eq 38 in Scheme 33). Cyclohexanes (i.e., **131b**) were also prepared with higher enantioselectivity, while yields were not compromised. A templating role for the LiCl was postulated to rationalize the high enantioselectivity (i.e., **135**).

4.4. Three-Component Reactions. While most studies exploit bond formation about the β-, α-, and acyl positions of the acyl azolium terminate with cyclization, in 2012, Studer and co-workers reported an NHC-catalyzed synthesis of cyclopropyl ester **136**, in which the catalytic cycle is terminated by the addition of an alcohol (see Scheme 34).[54] Specifically, oxidative conversion of cinnamaldehyde **14** in the presence of

Scheme 33. Studer and Ye's enantioselective Cyclopentyl δ-Lactone Synthesis (Conditions of Studer Shown)



Scheme 34. Studer's Enantioselective Sulfur Ylide Cyclopropanation



NHC **B2** affords acyl azolium **52**, which reacts with ylide **137**. Esterification of acyl azolium **138** with external alcohol then gives ester **136** (eq 39 in Scheme 34).

5. CASCADES INVOLVING BOND FORMATION AT THE γ-CARBON AND ACYL CARBON

When the α,β-unsaturated acyl azolium bears a methyl group at the β-position (i.e., **139**), the sp^3 γ-C−H is relatively acidic and deprotonation results in the azolium dienolate intermediate (**140**) (see Scheme 35). While related intermediates have previously been accessed from the corresponding ketene, with notable work from Ye and Smith,[55] access from the α,β-unsaturated acyl azolium has delivered new opportunities for reaction design and discovery. In this section, annulations of the γ- and acyl carbons are examined, along with cascades that also involve bond formation at the α-carbon.

5.1. Annulations with Ketones and Imines. In 2012, Chi and co-workers reported the first example of this type of reactivity with the NHC-catalyzed oxidative γ-functionalization of enals to deliver unsaturated δ-lactones **141** (see Scheme 36). It is postulated that α,β-unsaturated acyl azolium **142** forms and is deprotonated to give a dienolate, which cyclizes with

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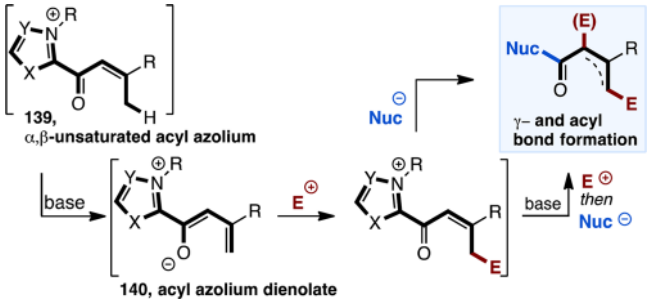
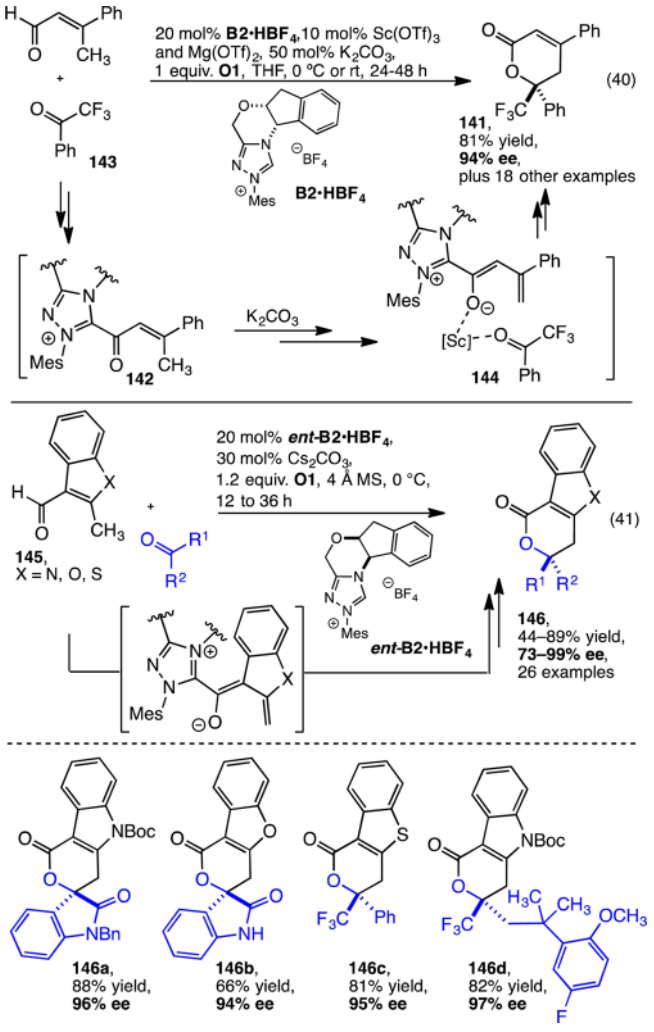
Scheme 35. Summary of the Mechanism Described in Section 5



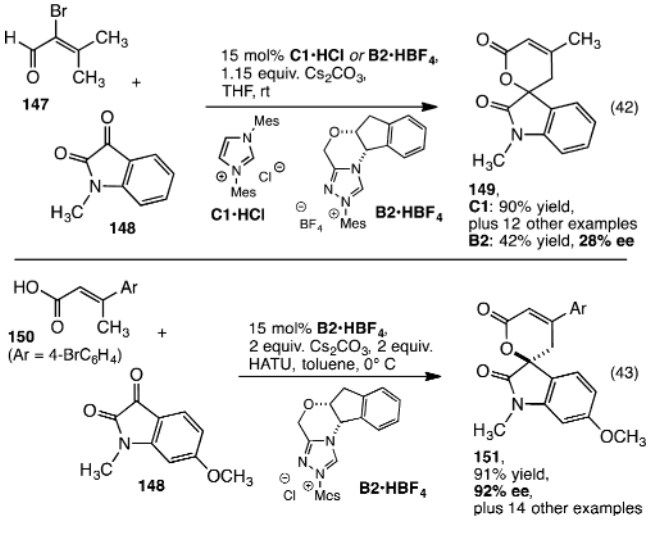
Scheme 36. Reaction with activated ketones



trifluoromethyl ketones **143** via the chelated intermediate **144** (eq 40 in Scheme 36).[56a] The reaction proceeded with moderate yield and enantioselectivity in the absence of Lewis acids, whose role was assigned as a coordinating reagent, bringing ketone electrophile and the acyl azolium dienolate proximal. Chi and co-workers subsequently expanded this transformation to 2-methylindole, benzofuran, and benzothiophene derivatives (**145**).[56b] Because of the increased acidity of the benzylic hydrogen, the reaction does not require Lewis acid co-catalysts, allowing ketone electrophiles, including trifluoromethyl ketones and isatins, to give a series of dihydropyranones **146a**–**146d** (eq 41 in Scheme 36).

Concurrently, Yao and colleagues reported a related nonenantioselective δ-lactone synthesis exploiting α-bromo-β-methyl enals (i.e., **147**) with isatins (**148**) (see Scheme 37).[57a]

Scheme 37. Yao's Acyl Azolium Dienolate Cyclizations with Isatin



While the achiral catalyst IMes (**C1**) gave spirocylic lactones **149** with generally high yields, chiral catalyst **B2** gave **149** with only modest yields and enantioinduction (eq 40 in Scheme 36). In 2016, the Yao group reported that acyl azolium dienolates can also be generated from α,β-unsaturated carboxylic acid (i.e., **150**) with HATU as the activating reagent.[57b] In this work, they were able to access chiral spirocyclic dihydropyranones **151** with far improved enantioselectivity (eq 43 in Scheme 37).

The azolium dienolate intermediates can also be generated from other α,β-unsaturated acyl azolium precursors (see Scheme 38). In 2013, Chi and co-workers reported the NHC-catalyzed annulation of α,β-unsaturated esters (**152**) with hydrazones (**153**) (eq 44 in Scheme 38).[58a] However, in 2015, Yao reported that saturated β-methyl carboxylic acids **154** with HATU as the acid activating reagent and quinones as oxidant allowed a related annulation (eq 45 in Scheme 38).[58b] Both reactions gave δ-lactams **155** with high enantiopurity via related reactive intermediates.

In 2014, Chi and co-workers reported a (4 + 3) annulation of the acyl azolium dienolate with azomethine imine (±)-**156** (eq 46 in Scheme 39).[59] Oxidative formation of acyl azolium **142**, as previously discussed, and deprotonation gives azolium dienolates **157**, which undergo a resolving nucleophilic addition to racemic azomethine imines **156** to form acyl azoliums **159**. Cyclization and the release of the catalyst provides the dinitrogen-fused seven-membered heterocyclic products **160** in high enantiopurity and unreacted enantioenriched imine **156**. By changing the stoichiometry of the reaction, a kinetic resolution of azomethine imines such as **156** could be achieved with an *S*-factor of up to 339.

5.2. Annulations with Electron-Poor Olefins. Besides annulations across C═O and C═N bonds (recall Section 5.1), the acyl azolium dienolate can participate in annulations of electron-poor C═C bonds (see Scheme 40). In 2014, the Chi group reported an oxidative NHC-catalyzed benzene synthesis

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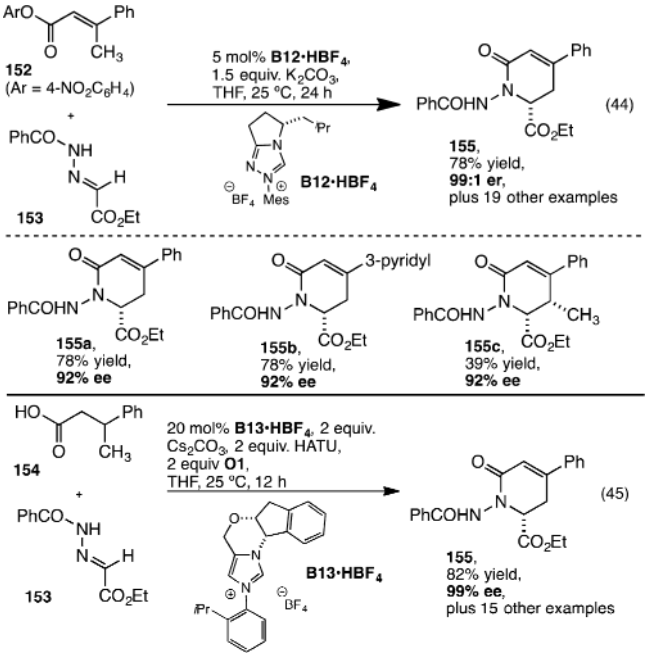
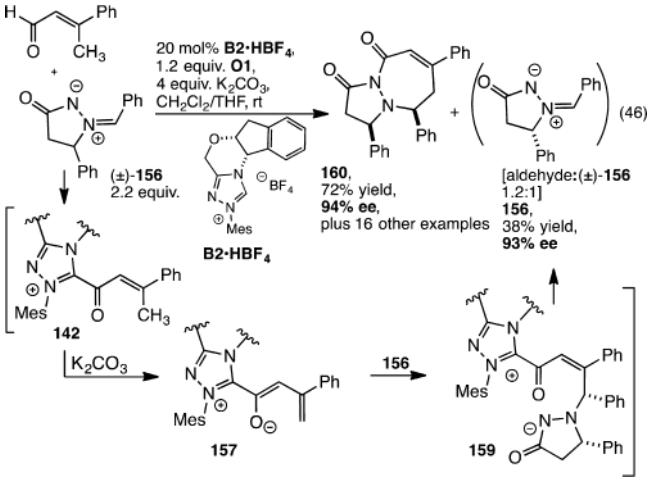
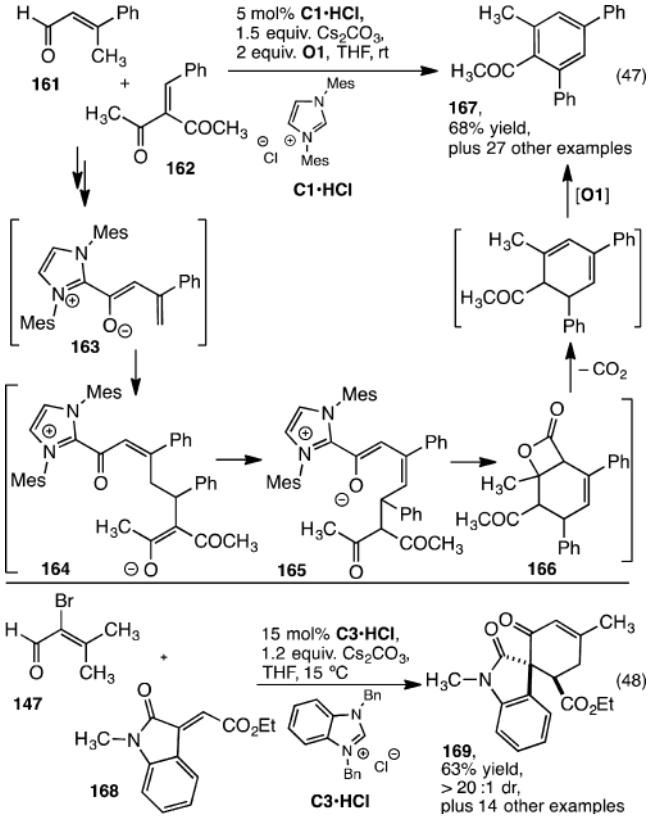
Scheme 38. Reaction with Hydrazones



Scheme 39. Chi's (4 + 3) Annulation



Scheme 40. Cyclization with C=C Double Bonds



by (3 + 3) cycloaddition of enal **161** with activated enone **162** (eq 47 in Scheme 40).[60] The reaction proceeds via azolium dienolate **163**, which reacts with enone **162** via Michael addition to form azolium intermediate **164**. Subsequent γ-deprotonation gives azolium dienolate **165**, which cyclizes to provide β-lactone **166**. Finally, decarboxylation and oxidation gives the aromatized products **167**. This reaction provides tetrasubstituted benzenes with moderate to high yields.

In 2015, a mechanistically simpler (4 + 2) annulation was reported by the Yao group (eq 48 in Scheme 40). In this reaction, the acyl azolium dienolate derived from **147** reacts with isatin-derived olefin **168** to give spirocylic product **169** with generally excellent diastereoselectivity (most >20:1) (eq 48 in Scheme 40).[61]

6. FUTURE DIRECTIONS

The α,β-unsaturated acyl azolium has played a central role in the modern era of *N*-heterocyclic carbene (NHC) organocatalysis. This species is at the heart of many reaction cascades, allowing chemoselective and generally stereoselective reactions to be discovered. Interestingly, the electrophilicity at the β-carbon of the α,β-unsaturated acyl azolium, as determined by Mayr and Studer, is not remarkable, and is similar to a Knoevenagel adduct, while being significantly less electrophilic than analogous iminium intermediates.[20c] Despite this modest reactivity, the development of new enantioselective reactions has proceeded at an impressive rate. Although progress has been made, the range of nucleophiles amenable to reaction discovery is somewhat limited. After some years of study, many classes of nucleophiles are clearly well-suited to reaction discovery, and are featured prominently in the reactions discussed above. One challenge for the future of this field will surely reside in delivering conjugate acceptors with greater reactivity, thereby allowing new nucleophiles for application in reaction discovery to be woven into reaction cascades. Despite these limitations in reactivity, there still remain many frontiers yet to be examined. For example, there remain few examples of amine addition to the α,β-unsaturated acyl azolium. Hui has reported an elegant hetero-Michael/Michael/lactonization,[62] while Chi has reported a pyrazolidinone synthesis.[42] Because 1,4-additions are at the heart of many reaction cascades with carbon nucleophiles, these discoveries will likely create many new opportunities in reaction design. Furthermore, there are many other types of nucleophiles yet to be examined that will likely deliver new reaction cascades in the future. In terms of the acyl azolium component, methods to access this material from readily available starting materials will remain an ongoing theme. Pioneering work by Chi and ourselves has introduced esters as substrates; however, these generally required preactivation, with the use of simple esters making it more challenging. Another approach to this challenge has been

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communicated by Scheidt, Ye, and Chi, with the *in situ* generation of activated esters from the corresponding carboxylic acids.[63] Finally, the application of vinylogous reactivity has been developed further, with Chi reporting, in 2015, the use of dienyl acyl azoliums to deliver polysubstituted aromatic compounds.[64]

A very exciting emerging theme in NHC organocatalysis relates to the formation of radical cationic intermediates from the oxidation of the acyl anion equivalent en route to the acyl azolium. In contrast to the oxidative conditions routinely used in the chemistry of the α,β-unsaturated acyl azolium, careful choice of oxidant by Chi, Rovis, Ye, and others have allowed the radical cation chemistry of this species to be exploited in reaction discovery.[65] Whether as a simple electron-donor or as a component incorporated into the product, this clearly represents an exciting area for investigation.

Finally, the applications of the materials prepared from the α,β-unsaturated acyl azolium has received limited attention. A handful of NHC-catalyzed reactions have been applied in natural product total synthesis;[2h,15] however, application of the many novel molecules in medicinal chemistry is yet to become routine. This transition is likely very near, as graduates trained in the nuances of these reactions begin to impact the pharmaceutical sector.

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Notes

The authors declare no competing financial interest.

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