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Facile construction of 2-pyrones under carbene catalysis

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2-Pyrones are valuable structural motifs in organic chemistry, found in numerous natural products and pharmaceuticals. The synthesis of these heterocycles has been significantly advanced by the application of N-Heterocyclic Carbene (NHC) catalysis. This review examines the recent advancements in NHC-catalyzed synthesis of 2-pyrones, highlighting key methodologies, mechanisms, and synthetic applications. NHC catalysis has revolutionized the synthesis of 2-pyrones, providing efficient, selective, and versatile methods for constructing these valuable heterocycles.

1. Introduction

2-Pyrones are often found as common scaffolds in various natural products and biologically active molecules with a wide range of activities, such as antibiotic, antifungal, cytotoxic, neurotoxic and phytotoxic activities[1–9] (Fig. 1). Luteoreticulin[10] and salinipyrones A[11,12] are representative examples. Functionalized pyrones also show potential applications in organic materials due to their privileged photophysical properties.[13,14] Moreover, due to their privileged heterocyclic structure (conjugated dienes), lactones and arenes (30–35% resonance energy of benzene[15]), 2-pyrones as facile raw materials were widely used in organic synthetic chemistry, polymer, and medicinal chemistry.[16–27] Therefore, a lot of organic chemists paid much more attention in development of strategies for the construction of 2-pyrones. And a lot of facile and efficient methods have been developed promoted by transition-metals and organocatalysis.[28,29]

Notably, organocatalysis meets the development requirements of green chemistry and is widely used in the field of organic synthesis due to their advantages, such as easy catalyst modification, mild reaction conditions, and no residual transition metals. N-heterocyclic carbenes, as one of the most effective organocatalysts, have attracted widespread attention from chemists due to their unique and diverse catalytic activated modes, and have achieved great success in recent years. NHC could activate easily available substrates, such as aldehydes, enals and activated esters, to form several highly reactive and widely used intermediates, such as such as α,β-unsaturated acyl azoliums, alkynyl acyl azoliums, Breslow intermediates, homoenolate and enolate intermediates.[30–46] Notably, N-heterocyclic carbene catalysis has also used for the development of a large number of efficient synthetic methods for constructing 2-pyrones. For clarity, this mini-review systematically summarizes the methods for constructing 2-pyranone using N-heterocyclic carbene catalytic strategies, based on the catalytic activation modes of N-heterocyclic carbene (Fig. 2), which are classified into four categories: α,β-unsaturated acyl azoliums, alkynyl acyl azoliums, Breslow intermediates and enolate intermediates. Meanwhile, related substrates are also summarized in Fig. 2c. We evaluate and highlight the progress of this area in this review article, hoping that this short summary will benefit readers in the broad community of chemistry and beyond.

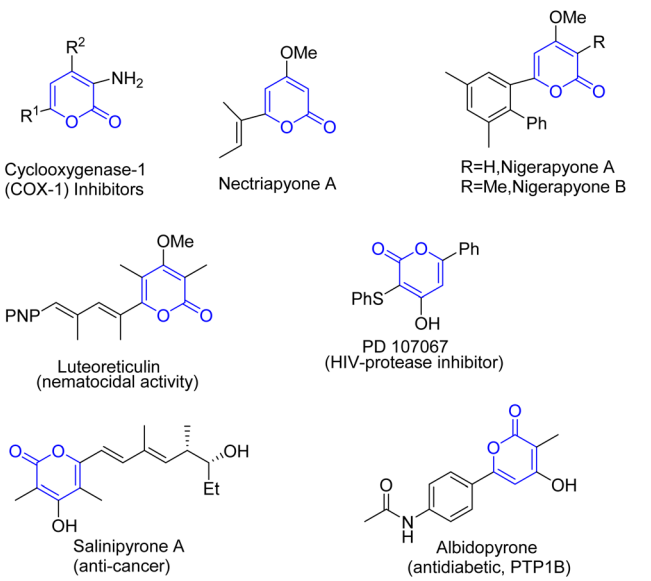

Fig. 1 Representative biologically important α-pyrones.

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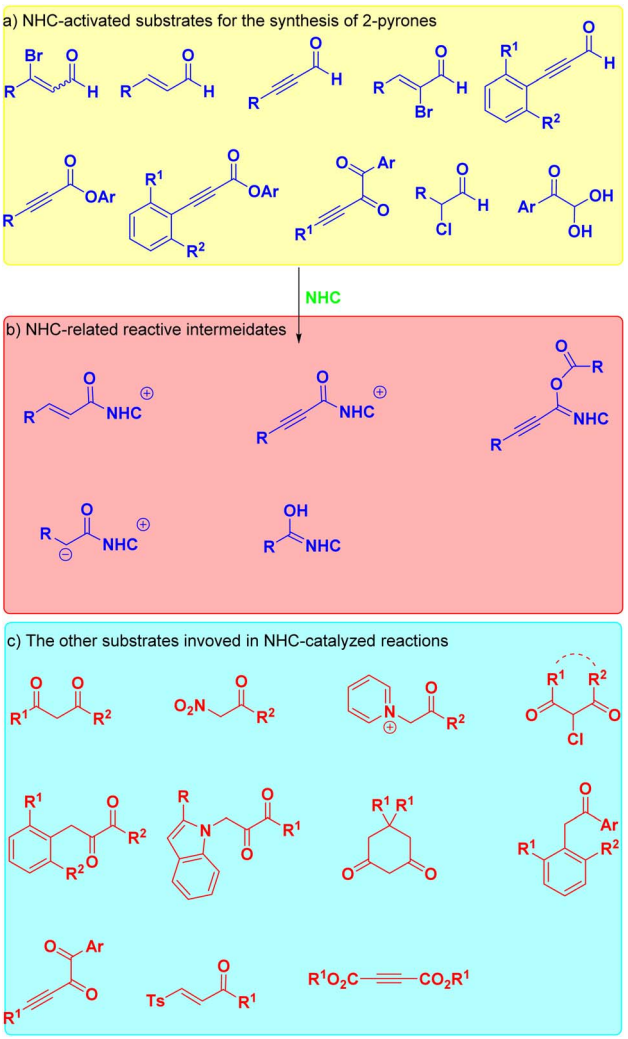
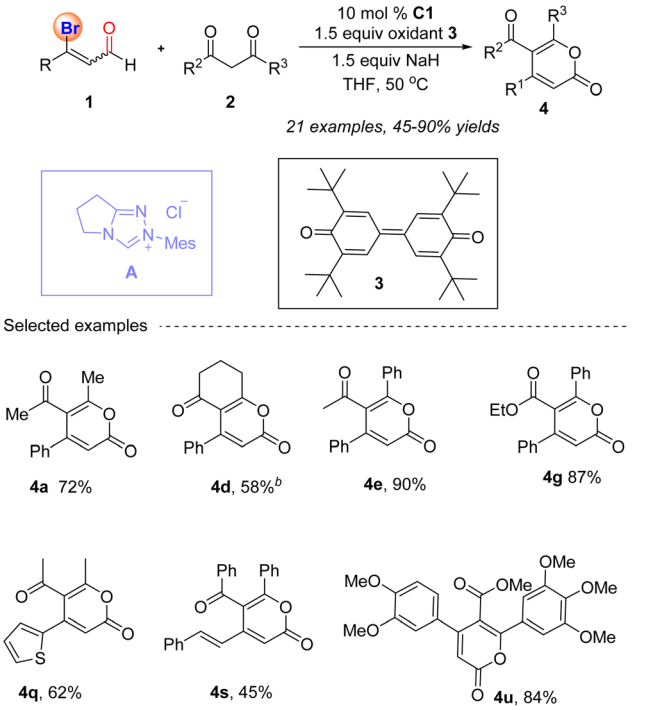


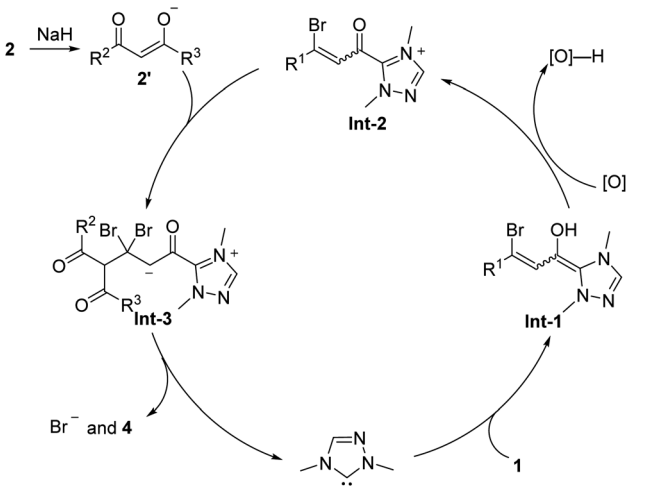
Fig. 2 Substrates and related intermediates in NHC-catalyzed construction of 2-pyrones: (a) NHC-activated substrates for the synthesis of 2-pyrones; (b) NHC-related reactive intermeidates; (c) the other substrates invoved in NHC-catalyzed reactions.

2. Unsaturated acyl intermediates with alpha-leaving group ketones

In 2013, the Ma group reported a highly efficient method for synthesizing multi-substituted 2-pyrones **4** through NHC **A** catalyzed [3 + 3] cyclization reaction of β-bromo unsaturated aldehydes **1** and 1,3-dicarbonyl compounds **2** by using NaH as a base in THF at 50 °C (Scheme 1).[47] Initially, the carbene generated *in situ* adds to 3-bromoenals, forming the conjugated β-bromo Breslow intermediate **Int-1** (Scheme 2), which reacts with an external oxidant to form β-bromo unsaturated acyl azoliums **Int-2**. The azoliums **Int-2** are then attacked by deprotonated 1,3-dicarbonyl compounds **2′**, likely forming 1,4-adducts **Int-3**. The intermediates **Int-3** then undergo cyclization and bromide elimination, resulting in the production of 2*H*-pyran-2-ones **4** and the release of the carbene catalyst. It is worth noting that the oxidant **3** used in this conversion have been introduced for the first time by the Studer group into the



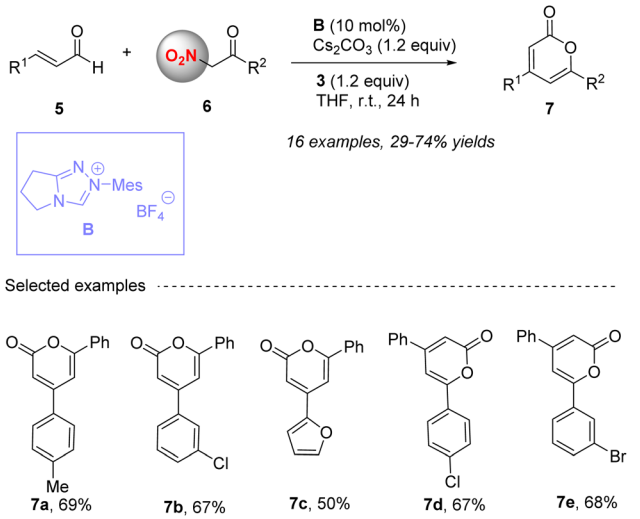
Scheme 1 NHC-catalyzed synthesis of 2-pyrones from 3-bromoenals and 1,3-dicarbonyl compounds.



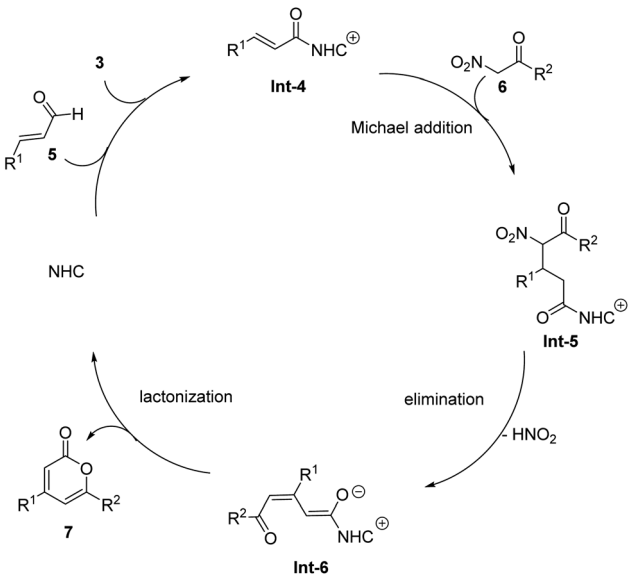
Scheme 2 Proposed mechanism for Ma's work.[47]

field of NHC catalysis, which can efficiently oxidize nucleophilic homoenolate into electrophilic unsaturated intermediate.[48]

In 2016, the Studer group achieved the [3 + 3] cyclization reaction of unsaturated aldehydes **5** and aroyl-substituted nitromethane **6**, efficiently constructing 4, 6-diaryl-2-pyrones **7** (Scheme 3).[49] In this reaction, NHC **B** was proved as the suitable catalyst with Cs_2CO_3 as a base in THF. Unsaturated aldehydes undergo a similar process under NHC activity and oxidation of **5** to obtain unsaturated acyl intermediates **Int-4** (Scheme 4). It is worth noting that in this reaction, the nitro group in the aroyl-substituted nitromethane is both an activating group and



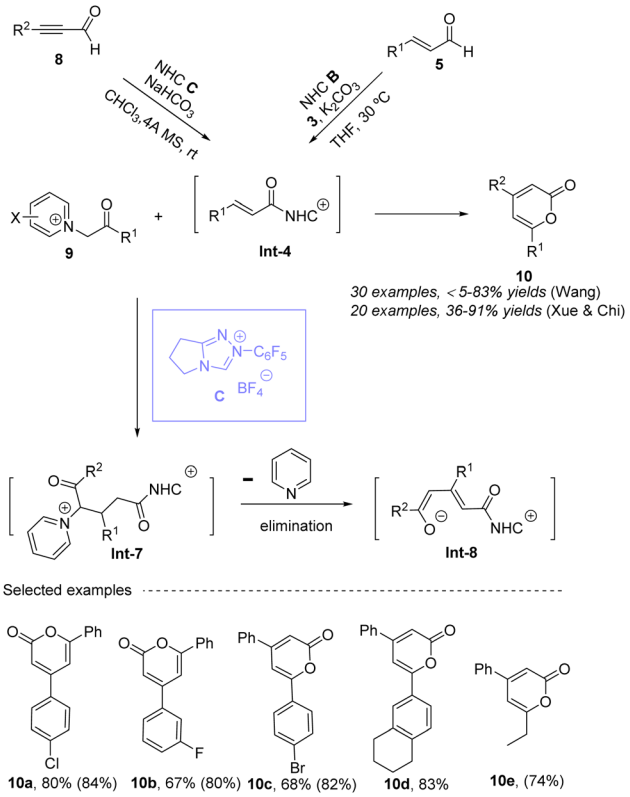
Scheme 3 The synthesis of 4,6-disubstituted 2-pyrones from aryl-substituted nitromethanes and enals under NHC catalysis.



Scheme 4 Proposed mechanism for Studer's work.[49]

a good leaving group. After HNO_2 elimination, it can increase an unsaturation degree, and then undergo lactonization to obtain the final 2-pyrones **7** with moderate to good yields.

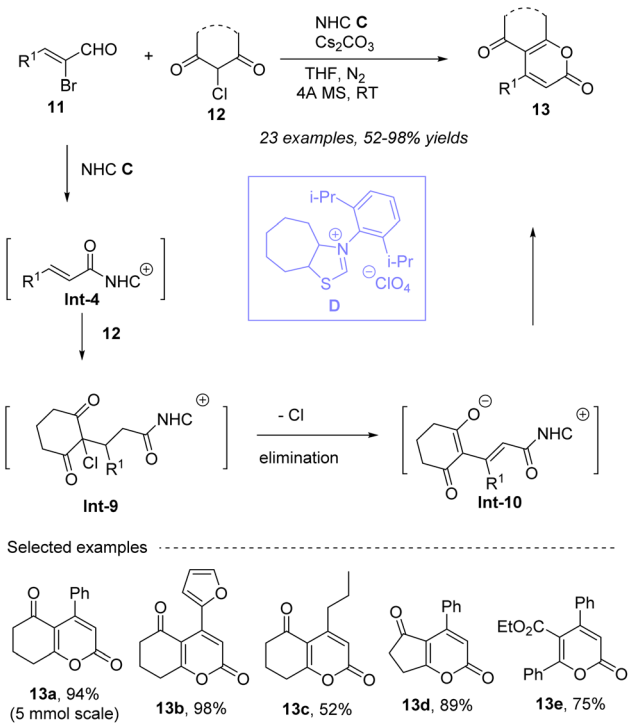
In 2018, Wang's group reported a cyclization strategy using NHC catalysis of ynals **8** and ylides **9**, which directly constructed a series of 4,6-disubstituted 2-pyrones **10** with good to high yields (Scheme 5).[50] A series of easily prepared and inexpensive ylides **9**, including *N*-pyridinium, *N*-quinolinium, and *N*-imidazolium ylides, were screened, and *N*-pyridinium ylides have been proven to be more efficient one. NHC activates ynals following by a proton transfer to generate α,β-unsaturated acyl intermediates **Int-4**, and then undergoes elimination of pyridinium intermediate followed by intramolecular cyclization to give the desired 2-pyrones **10**. It is worth noting that *N*-pyridinium serves as both an activating group and a good leaving



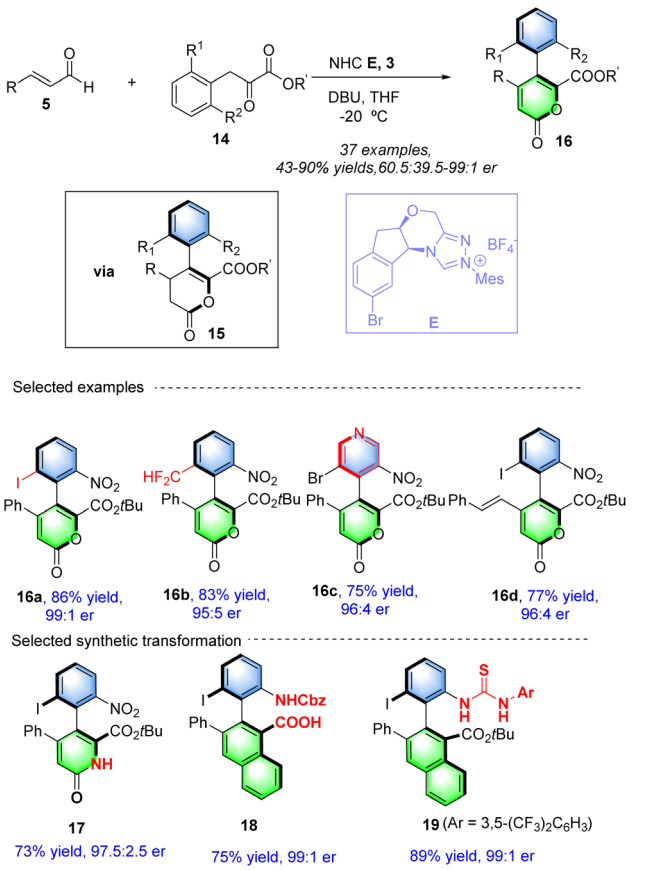
Scheme 5 The synthesis of 4,6-disubstituted 2-pyrones from ylides and ynals (or enals) under NHC catalysis.

group in this conversion. The method is tolerant of various functional groups on both the enal and pyridinium bromide substrates, making it versatile and adaptable to different synthetic needs. Very nearly, Xue, Chi and co-workers[51] realized similar work, also using the *N*-pyridinium ylides **9** to react with α,β-unsaturated acyl intermediate **Int-4**. The different from Wang group's work, they used enal **5** and oxidant **3** to generate α,β-unsaturated acyl intermediate **Int-4**, the reaction undergoes similar process to give the desired 2-pyrones **10** with good to excellent yields. Delightingly, for 2′-pyridinium ylides, switching of aryl group to alkyl group also worked well. Notably, both of alkyl ynals and alkyl enals are not compatible with this transformation. For these two works, the optimal conditions, such as catalyst, bases and solvents, are different.

In 2022, Xu, Chen and co-workers[52] applied inexpensive and easily prepared 2-chloro-1,3-diketones **12** as nucleophiles to construct 4,5,6-trisubstituted α-pyrones **13** efficiently under mild conditions (Scheme 6). Carbene which generated from NHC **D** deprotonated by Cs_2CO_3 in THF, activates brominated unsaturated aldehydes **11** to form α,β-unsaturated acyl intermediates **Int-4**, which are then subjected to Michael addition by 2-chloro-1,3-diketones **12**. Subsequently, the departing chlorine increases by one degree of unsaturation, followed by lactonization to give variables 4,5,6-trisubstituted 2-pyrones **13** in generally good to excellent yields. The reactions do not require external oxidants, making the process more environmentally friendly. 2-Pyrones bearing various substituents and



Scheme 6 Oxidant free synthesis of 2-pyrones from 2-chloro-1,3-diketones and bromoenals under NHC catalysis.

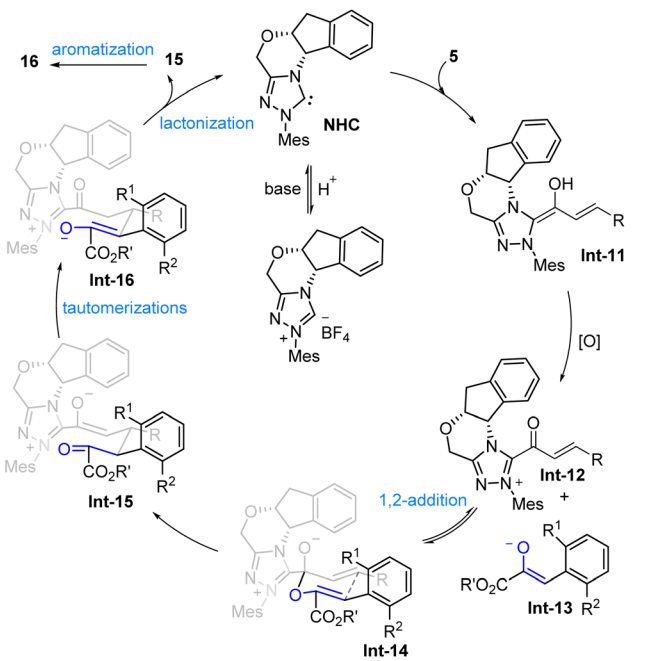


Scheme 7 NHC-catalyzed synthesis of axially 2-pyrones from enals and α-aryl pyruvates.

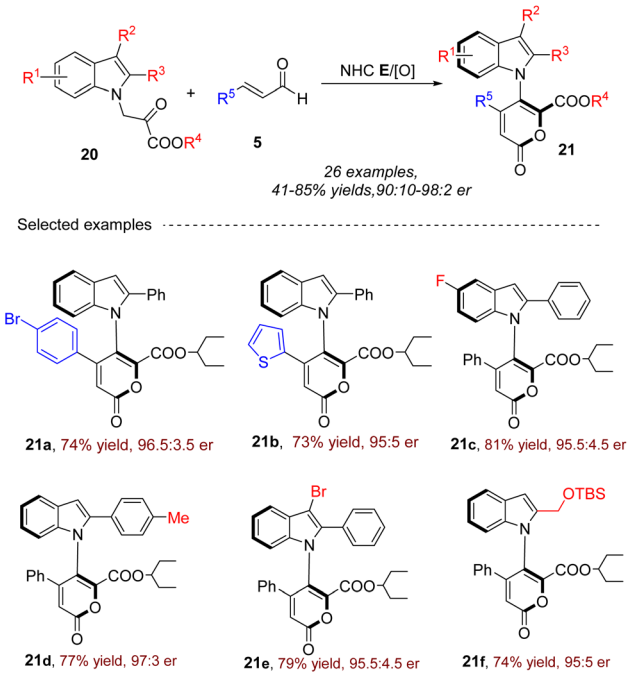
substitution patterns are accessible. Besides 6-membered ring scaffold of 2-chloro-1,3-diketones, 6-membered ring or acyclic scaffolds are compatible with this transformation. Notably, alkyl bromoenal also worked well.

In 2022, our group[53] realized an NHC-catalyzed atroposelective [3 + 3] annulation reactions from readily available enals **5** and α-aryl pyruvates **14** though Coates-Claisen type rearrangement, after the automatic aromatization, assembling wide-ranging of atropisomerically enriched 5-aryl 2-pyrones **16** in good to excellent enatioselectivities (Scheme 7). Chiral NHC **E** could give the best outcomes in the term of yields and enationselecitivities by using DBU as a base in THFat −20 °C. Comparison experiments and reported results reveal that the presented strategies involving an atroposelective annulation/heteroaromatization sequence to construct axially chiral aryl-heteroaryl molecules features an inherent advantage in comparison to these rely on alkynylacyl azolium intermediates. The method is compatible with a wide range of substrates, including enals with various electron-withdrawing and donating groups, leading to high yields and enantiomeric ratios. Pleasingly, the resulting axially chiral 2-pyrones were easily converted into widely used biaryl atropisomers in excellent yields without any loss of enantioselectivities *via* Diels–Alder reaction with benzynes, such as biaryl amino acids and BINAM derivatives, demonstrating the practical utility of the synthesized molecules. Notably, the intermediate could be oxidized to 2-pyrones under reaction conditions (Scheme 8).

In 2023, our group[54] further developed a carbene-catalyzed oxidative [3 + 3] annulation of indole-1-pyruvate esters **20** and



Scheme 8 Proposed mechanism for Fu's work.[53]

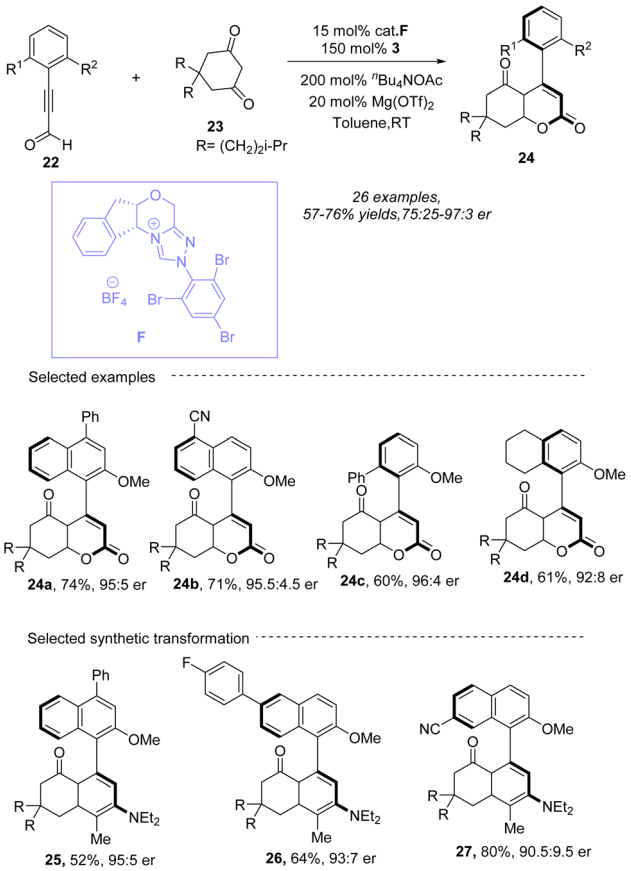


Scheme 9 The synthesis of 5-indo-1-yl pyran-2-ones with an N–C axis from indole-1-pyruvate esters and enals.

enals **5** to construct a variety of axially enantioenriched 5-indo-1-yl pyran-2-ones **21** with an N–C axis under similar optimal conditions with our previous work (Scheme 9).[53] This strategy features direct asymmetric 2-pyrone ring from enals under oxidative NHC catalysis. The method is applicable to a broad range of substrates, including variously substituted indole-1-pyruvate esters and enals. The resulting products exhibit high enantiomeric ratios, making them suitable for further asymmetric synthesis applications. The reaction mechanism is similar with previous work. The resulting products could be converted into important axially chiral *N*-arylindoles.

3. Alkynyl acyl azoliums with enols

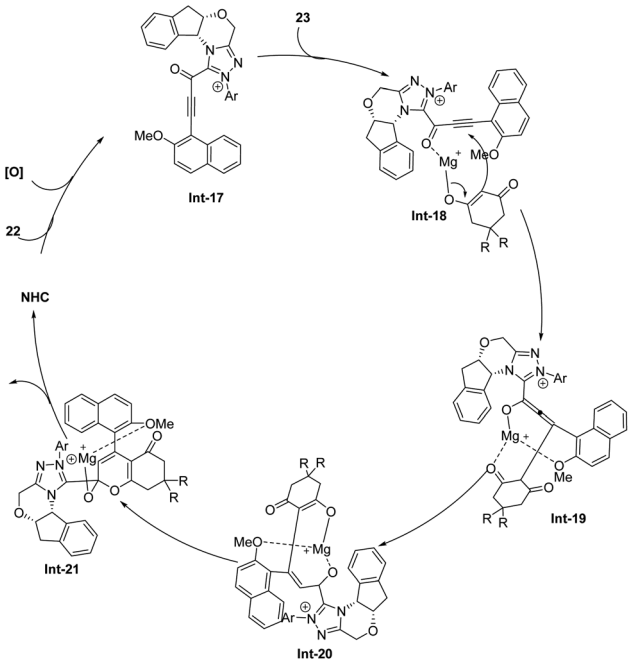
Wang group[55] reported a novel method for synthesizing axially chiral α-pyrone-aryls **24** through an N-heterocyclic carbene (NHC)-catalyzed [3 + 3] atroposelective annulation (Scheme 10). This method involves the reaction of cyclic 1,3-diones **23** with ynals **22** in the presence of an NHC precatalyst, base, Lewis acid, and oxidant. The process leads to the formation of axially chiral 2-pyrones in moderate to good yields with high enantioselectivities under NHC **F** catalysis by using nBu_4NOAc as a base in toluene. Notably, $Mg(OTf)_2$ as the additive in this reaction could suppress unexpected intermediates and reaction pathways which results in the formation of byproducts. A wide range of cyclic 1,3-diones and ynals are compatible with this transformation. The use of readily available starting materials and mild reaction conditions makes the method economically attractive and practical for large-scale synthesis. The study also explores the mechanistic pathways and demonstrates the synthetic utility of the products. The addition of the NHC catalyst to ynal followed by oxidation results in the formation of



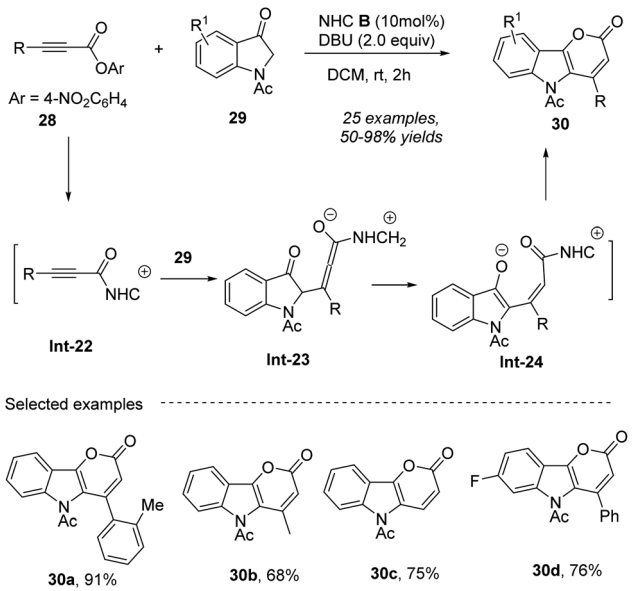
Scheme 10 NHC-catalyzed synthesis of axially 2-pyrones from ynals and cyclic 1,3-dicarbonyl compounds.

alkynyl acyl azolium intermediate **Int-17** (Scheme 11), which subsequently reacts with cyclic 1,3-dione **23** to form intermediate **Int-18**. Intermediate **Int-18** undergoes a Michael addition to the alkynyl azolium moiety, forming an allenolate intermediate **Int-19**. After a proton transfer from the 1,3-dione to the allenolate, intermediate **Int-20** is formed. The subsequent formation of the O–C bond results in intermediate **Int-21**, releasing the NHC catalyst and ultimately generating product **24**. This innovative approach not only expands the toolkit for organic synthesis but also provides a practical and efficient method for producing valuable chemical scaffolds with significant potential in pharmaceuticals and material science.

In 2019, Du and co-workers[56] presented a novel method for the efficient construction of pyrano [3,2-*b*]indol-2-one skeletons **30** in moderate to high yields (up to 95%) under DBU as a base in DCM (Scheme 12), in which the formal [3 + 3] annulation of alkynoic acid esters **28** with indolin-3-ones **29** to construct 2-pyrone ring was facilitated by N-heterocyclic carbene (NHC) **B** catalysis. The nucleophilic attack of carbene on substrate **28** leads to the formation of alkynyl acylazolium **Int-22**. Next, the conjugate addition of the C-centered nucleophile derived from **29** with DBU, to intermediate **Int-22** results in the formation of intermediate **Int-23**. This intermediate then undergoes a proton transfer to produce intermediate **Int-24**. Finally, the lactone formation of **Int-24** yields the desired product **30**. The resulting



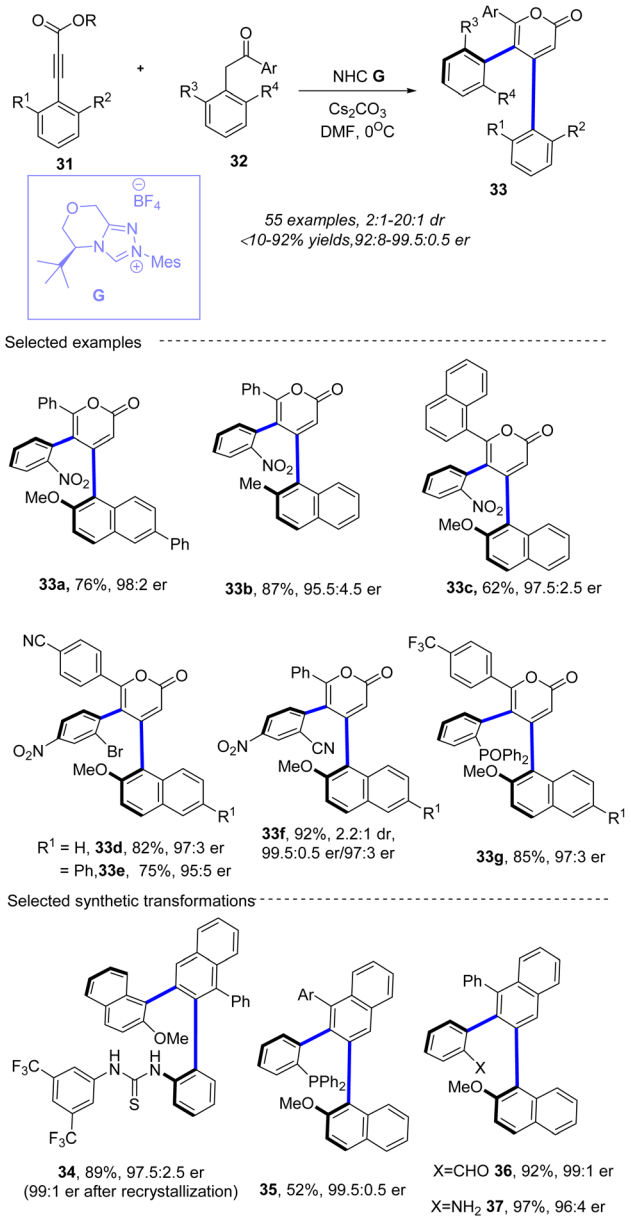
Scheme 11 Proposed mechanism for Wang's work.[55]



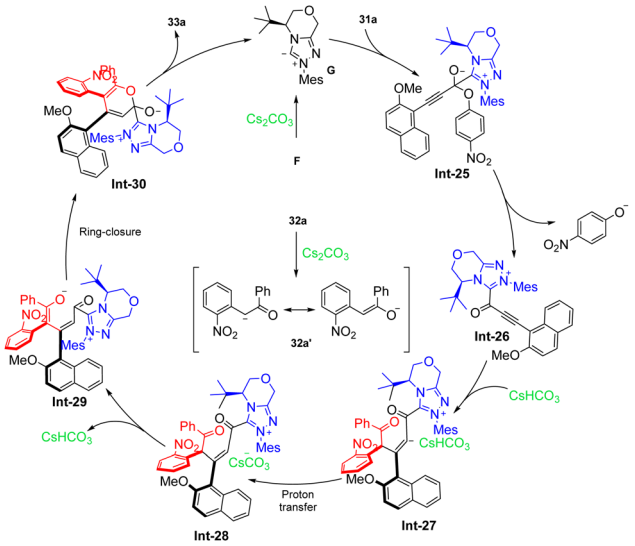
Scheme 12 Access to functionalized pyrano [3,2-*b*]indol-2-ones from alkynoic acid esters and indolin-3-one under NHC catalysis.

pyrano [3,2-*b*]indol-2-ones **30** can serve as valuable intermediates for the synthesis of other complex molecules with significant biological activities. The use of readily available starting materials and mild reaction conditions makes the method economically attractive and practical for large-scale synthesis.

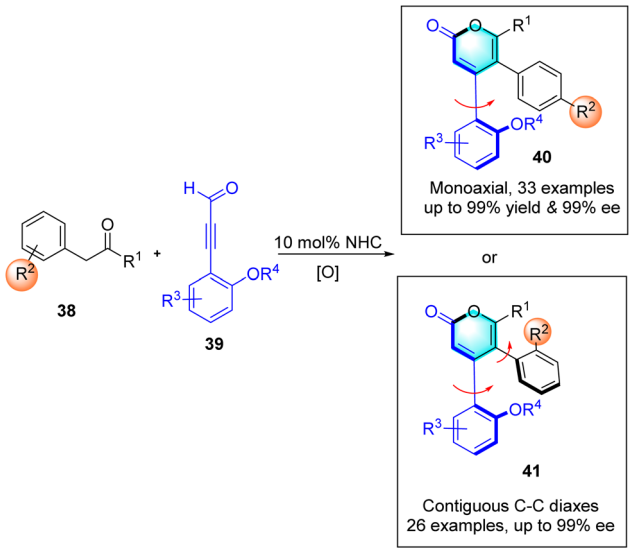
In 2022, Du, Wei and co-workers[57] reported a novel method for synthesizing triaryl 2-pyrones **33** with multiple stereogenic axes promoted by NHC **G** in the presence of Cs_2CO_3 in DMF (Scheme 13). The research demonstrates a single-step construction of 1,2-diaxially chiral triaryl 2-pyrones under N-heterocyclic carbene organocatalysis. The method involves an asymmetric [3 + 3] annulation of well-designed alkynyl acylazolium precursors with enolizable sterically hindered 2-aryl ketones, resulting in the formation of desired 1,2-diaxially chiral triaryl α-pyrones in excellent diastereoselectivities (most cases >20 : 1 dr) and enantioselectivities (up to 99.5 : 0.5 er). The reaction is initiated by nucleophilic addition to **31** by the NHC organocatalyst, which is generated by deprotonation of pre-NHC **F**, producing intermediate **Int-25**. The cleavage of the C_1–O_1 bond occurs, forming intermediate **Int-26.** Subsequently, Michael addition of **32a′** to intermediate **Int-26** generates **Int-26′**, which undergoes proton transfer followed by deprotonation leads to the formation of **Int-29.** Lactonization of **Int-29** results in the formation of the final product **33a** and regenerates carbene. Density functional theory (DFT) calculations are



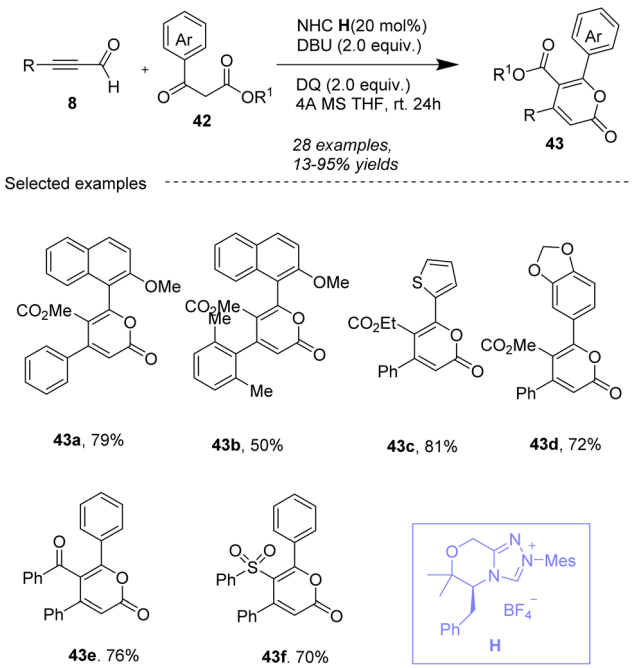
Scheme 13 NHC-catalyzed synthesis of 1,2-diaxially chiral triaryl 2-pyrones.



Scheme 14 Proposed mechanism for Du's work.[57]



Scheme 15 NHC-catalyzed synthesis of 1,2-diaxially chiral triaryl 2-pyrones.



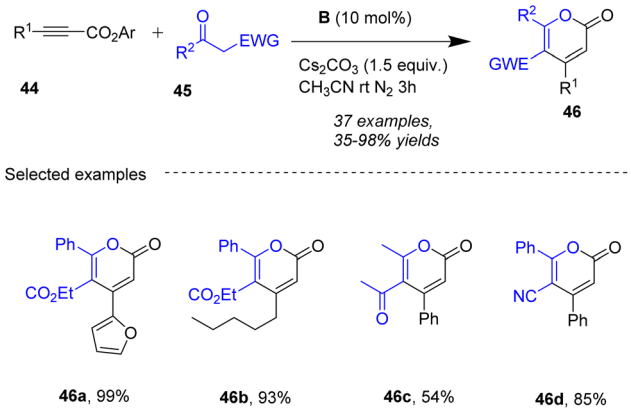
Scheme 16 NHC-catalyzed synthesis of 2-pyrones from ynals with β-keto esters.

performed to rationalize the high diastereoselectivity and enantioselectivity in this [3 + 3] annulation process. TS3 are in four stereoselective pathways. The Gibbs free energy barriers for TS3RS, TS3SR, TS3RR, and TS3SS are 7.7, 11.4, 13.9, and 16.4 kcal mol^{-1}, respectively, indicating that the 4*R*,5*S*-configurational pathway is the most energetically favorable. Thus, with the aid of $CsHCO_3$, only the favorable pathway associated with intermediate M3RS is discussed further. Subsequently, intermediate M3RS transforms to intermediate M5RS *via* a protonated base-assisted[1,3]-proton shift through stepwise transition states TS4RS ($\Delta G^{\ddagger}$ = 4.9 kcal mol^{-1}) and TS5RS ($\Delta G^{\ddagger}$ = 2.5 kcal mol^{-1}). Following this, the C_1–O bond forms through transition state TS6RS ($\Delta G^{\ddagger}$ = 2.2 kcal mol^{-1}), resulting in the ring-closure intermediate M6RS. Finally, the C_1–C bond is broken to dissociate the product PRS (**3a**) with the catalyst through transition state TS7RS ($\Delta G^{\ddagger}$ = 2.3 kcal mol^{-1}). Overall, the pathway associated with the 4*R*,5*S*-configurational product is the most energetically favorable, with an energy barrier difference ($\Delta\Delta G^{\ddagger}$ TS3SR–TS3RS) of 3.7 kcal mol^{-1}, corresponding to an enantiomeric excess (ee) value of 99.4% according to Boltzmann distribution equations (Scheme 14). The resulting 1,2-diaxially chiral triaryl α-pyranones can be further transformed into useful compounds, such as chiral catalysts **34** and ligands **35–37**. Notably, Wong, Lu and co-workers also realized similar transformations in which the synthesis of triaryl-2-pyrones with monoaxial or contiguous C–C diaxes the enals has been established *via* oxidative NHC catalysis (Scheme 15).[58]

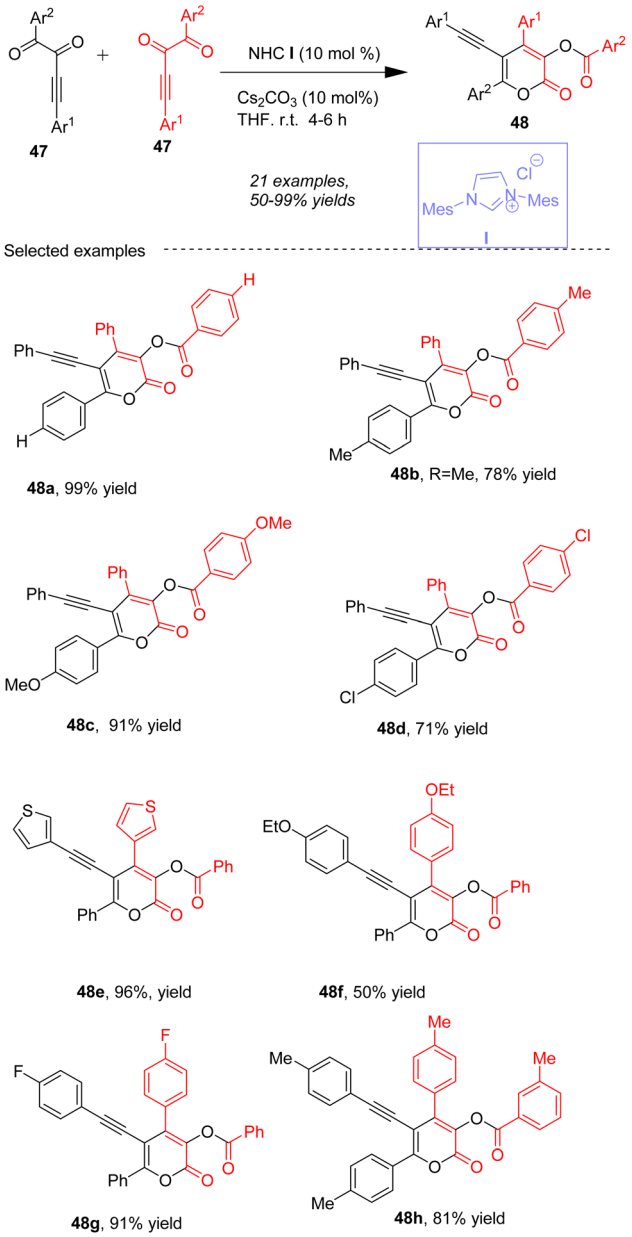
Zhao group[59] (Scheme 16) and Du group[60] (Scheme 17) further developed a novel strategy for the construction of functionalized 2-pyrones by using the similar strategies.

4. *O*-Acylated allenolate intermediates

Fang and co-workers[61] presented a novel method for the rapid synthesis of a variety of α-pyrones **48** through the Umpolung (polarity reversal) of alkynyl 1,2-diketones **47** under N-heterocyclic carbene (NHC) **I** catalysis in the presence of Cs_2CO_3 in THF (Scheme 18). The study introduces a new Umpolung pattern involving an *O*-acylated allenolate as the key intermediate and proposes an unprecedented reaction pathway characterized by group migrations and new bond formations. A variety of substrates, including both diaryl and alkyl-substituted alkynyl diketones are tolerated under reaction condition. Specifically, the nucleophilic attack of a carbonyl group of **47** by the carbene catalyst leads to intermediate **Int-31** (Scheme 19).



Scheme 17 NHC-catalyzed synthesis of 2-pyrones from alkynyl esters with alkynyl esters.



Scheme 18 NHC-catalyzed synthesis of 2-pyrones from alkynyl 1,2-diketones.

An *O*-acylated allenolate equivalent **Int-32** is formed after the first acyl transfer. Subsequently, the nucleophilic addition of **Int-32**/**33** to a second molecule of **47** affords intermediate **Int-34**, and intermediate **Int-35** is generated *via* the second acyl transfer. An unusual acyloxy migration occurs between intermediates **Int-35** and **Int-36**, and finally, a lactonization process releases the product **48**. Notably, a total of four bonds (one C–C bond and three C–O bonds) are formed in this cycle.

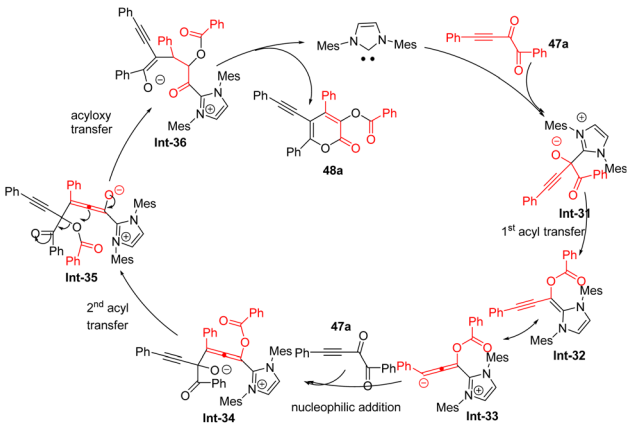
5. Enolate intermediates

In 2021, Tiwari group[62] reported the direct, transition metal-free synthesis of 3,6-disubstituted α-pyrones **51** in moderate to excellent yields (up to 97%) from widely accessible α-chloro aldehydes **49** and β-tosyl enones **50** (Scheme 20). The reactions proceed *via* a Michael addition/lactonization/elimination cascade, offering a regioselective addition of NHC-bound enolates to enones with bulky functionalities. It should be noted that β-tosyl enones have remained beyond the scope of carbene catalysis. Enolates which are generated from α-chloro aldehydes with carbene *via* a dechlorination process, undergo Michael addition to enones bearing a leaving group (Ts), lactonization and further detosylation to eventually produce 3,6-disubstituted α-pyrones **51**. A wide range of α-chloro aldehydes and β-tosyl enones are compatible with this transformation. The resulting 3,6-disubstituted α-pyrones can be further transformed into valuable compounds such as tetrasubstituted benzenes **54**, naphthalenes **53**, anthracenes **55**, and dihydroethenopentacenes **56**.

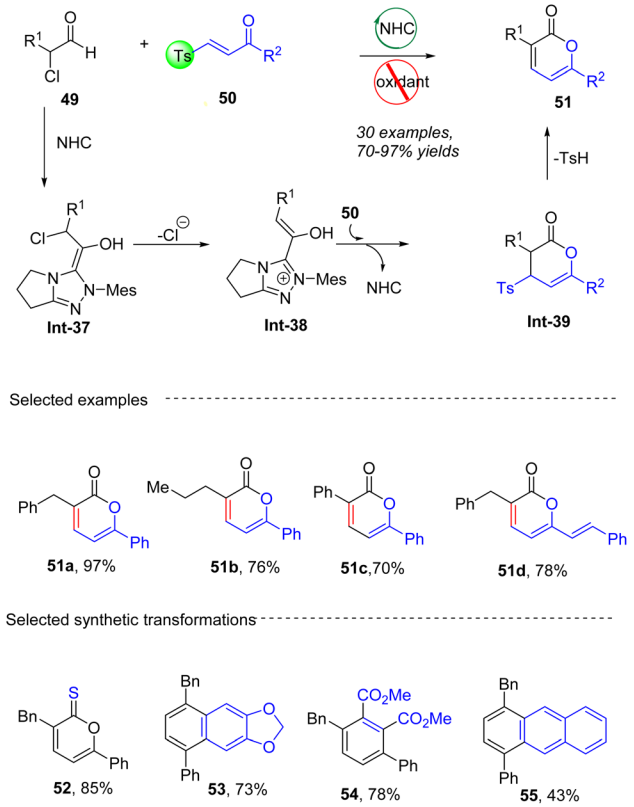
6. Breslow intermediates

In 2018, Tu, Jiang and co-workers[63] developed a new method for synthesizing trisubstituted 2-pyrones **58** using arylglyoxals **57** as a carbonyl source promoted by NHC J in the presence of NaH in CH_3CN (Scheme 21). The innovative method involves a thiazolium salt-catalyzed [3 + 2 + 1] cyclization, potentially offering higher yields and better functional group compatibility. The use of arylglyoxals as dual-role reagents enhances the versatility of the reaction, allowing for the incorporation of various functional groups and structural motifs into the final products. This approach is noteworthy for its potential in organic synthesis, offering a novel route to construct 2-pyrones with specific substitution patterns.

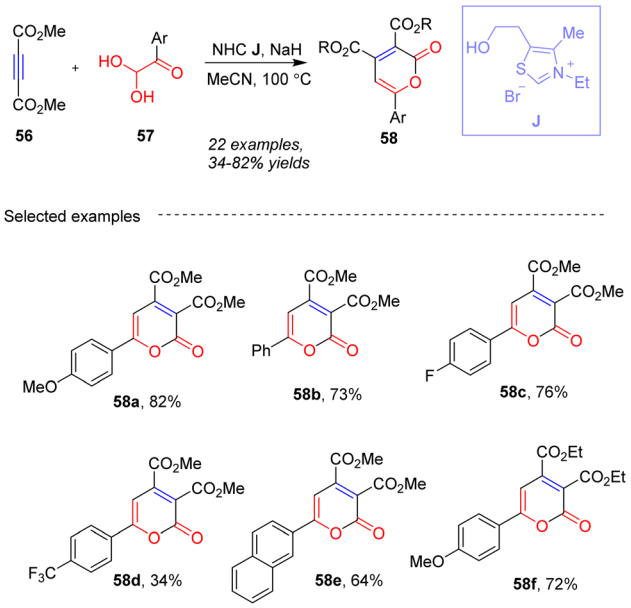
For this reaction (Scheme 22), thiazole carbene, generated *in situ* by the deprotonation of the thiazolium salt I at its most acidic position, reacts with 2-(4-methoxyphenyl)-2-oxoacetaldehyde **Int-40**, derived from substrate **57**, to form zwitterionic intermediate **Int-41** (detected by LC-MS, MS = 335.1). This is followed by an Umpolung process to convert **Int-41** into intermediate **Int-42**. Next, the addition of **Int-42** to the C–C bond of substrate **56** generates zwitterionic intermediate



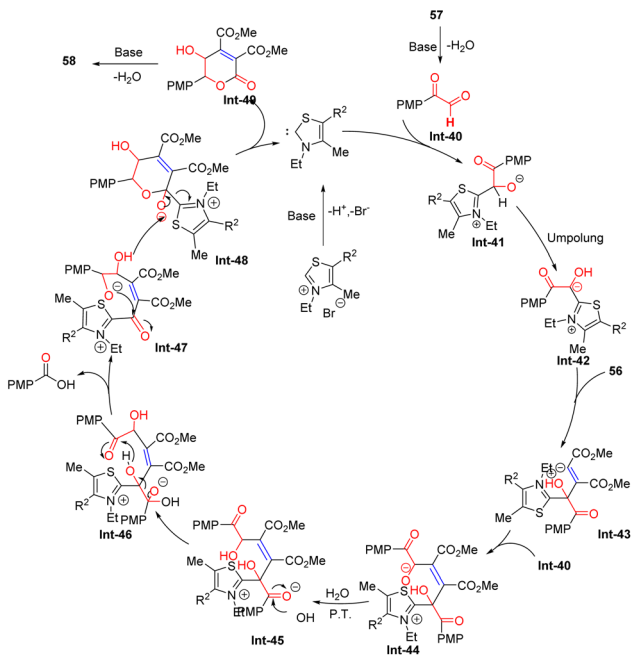
Scheme 19 Proposed mechanism for Fang's work.[61]



Scheme 20 NHC-catalyzed synthesis of 2-pyrones from α-chloro aldehydes and β-tosyl enones.



Scheme 21 NHC-catalyzed synthesis of 2-pyrones from arylglyoxals and substrates **56**.



Scheme 22 Proposed mechanism for Tu, and Jiang's work.[63]

Int-43 (detected by LC-MS, MS = 477.1), which undergoes an aldol-type reaction with **Int-40** to deliver intermediate **Int-44** (detected by LC-MS, MS = 641.2). Afterward, proton transfer between **Int-44** and H_2O gives intermediate **Int-45** (detected by LC-MS, MS = 642.2), which is intercepted by the hydroxyl anion to afford **Int-46**. This step eliminates 4-methoxybenzoic acid (detected by LC-MS, MS = 152.0) to produce intermediate **Int-47** (detected by LC-MS, MS = 507.2). Intermediate **Int-47** is then converted into the final product **58** through a sequence involving continuous intramolecular nucleophilic addition/elimination of thiazole carbene **I** and dehydration.

7. Conclusion and outlook

2-Pyrones have received significant attention in recent years because of their important biological activities and wide applications in synthetic chemistry. The synthesis of these compounds has been significantly enhanced by the application

of N-Heterocyclic Carbene (NHC) catalysis. Although significant progress has been made in this field, there are still many issues as follows: (i) most reactions require 10–20% catalyst loading. Further improvements in catalytic efficiency are essential to reduce catalyst loading and enhance overall reaction efficiency; (ii) the range of substrates used in these reactions is relatively limited. Expanding the variety of substrates remains a key challenge, necessitating innovative approaches and the development of new substrates to broaden the applicability of NHC-catalyzed synthesis; (iii) although various 2-pyrone structures have been synthesized, few mimic the structures of natural products or bioactive molecules. Achieving direct synthesis of such compounds through the development of new reaction types and substrate designs is crucial; (iv) despite the synthesis of numerous 2-pyrone molecules, relatively little research has been conducted on their biological activity. Increased focus on biological testing can uncover new bioactive compounds and enhance the relevance of synthesized 2-pyrones in medicinal chemistry. Addressing challenges such as catalytic efficiency, substrate diversity, direct synthesis of bioactive molecules, and biological activity testing will drive the future of 2-pyrone research. Continued exploration in this field promises to expand the synthetic utility and biological relevance of 2-pyrones, with far-reaching implications for organic and medicinal chemistry.

Data availability

Our manuscript entitled "Facile Construction of 2-Pyrones under Carbene Catalysis" should be a review article in RSC Advances. Therefore, there is no need to upload the compound characterisation checklist.

Conflicts of interest

There are no conflicts to declare.

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