A Review on Generation and Reactivity of the N-Heterocyclic Carbene-Bound Alkynyl Acyl Azolium Intermediates

Ziyang Dong †, Chengming Jiang † and Changhai Zhao *

Key Laboratory of Radiopharmaceuticals, Ministry of Education, College of Chemistry, Beijing Normal University, Beijing 100875, China
* Correspondence: cgzhao@bnu.edu.cn; Tel.: +86-158-0115-4568
† These authors contributed equally to this work.

Abstract: N-heterocyclic carbene (NHC) has been widely used as an organocatalyst for both umpolung and non-umpolung chemistry. Previous works mainly focus on species including Breslow intermediate, azolium enolate intermediate, homoenoate intermediate, alkynyl acyl azolium intermediate, etc. Notably, the NHC-bound alkynyl acyl azolium has emerged as an effective intermediate to access functionalized cyclic molecular skeleton until very recently. In this review, we summarized the generation and reactivity of the NHC-bound alkynyl acyl azolium intermediates, which covers the efforts and advances in the synthesis of achiral and axially chiral cyclic scaffolds via the NHC-bound alkynyl acyl azolium intermediates. In particular, the mechanism related to this intermediate is discussed in detail.

Keywords: N-heterocyclic carbene; alkynyl acyl azolium; annulation; intermediate; mechanism

1. Introduction

Early in 1943, N-heterocyclic carbene (NHC) was discovered and applied to catalytic reactions in the form of coenzyme vitamin B1 [1]. Later in 1958, Breslow proposed an appropriate mechanism for a vitamin B1-catalyzed benzoin condensation reaction [2], which has inspired synthetic chemists to focus on NHCs in the field of catalytic organic reactions for decades. Due to its unique properties in organic chemical reaction processes, NHCs have been widely used as organometallic ligands as well as organocatalysts, owing to their extensive and diverse synthesis and versatility [3–11]. Generally, NHC-bound intermediates involving organocatalytic reactions are divided into the following types: Breslow intermediates, azolium enolate intermediates, homoenoate intermediates, azolium dienolate intermediates, and radical intermediates, as well as acyl azolium intermediates [12–16]. These intermediates have been explored for both umpolung and non-umpolung chemistry such as benzoin condensation, Stetter reaction, hydroacylation, [n + m] annulation, and so on.

Over recent decades, acyl azolium has represented a central reactive species for reaction designs in the modern era of NHC-based catalysis. Overall, acyl azolium intermediates can be categorized into the following types: alkyl acyl azoliums [17], alkenyl acyl azoliums [18–20], dienyl acyl azoliums [21–23], and alkynyl acyl azoliums [20] (Scheme 1A). Among them, NHC-based alkynyl acyl azolium intermediates, initially identified independently by Chi [24], Du [25], and Wang [26] between 2017 and 2018, were less commonly studied. Although only a few reaction models involving the species have been developed, alkynyl acyl azolium intermediates have been recognized as a new NHC-bound specie for the discovery of new reactions. Until now, three procedures have been disclosed to produce alkynyl acyl azoliums intermediates according to their precursors (i) via the addition of NHCs to ynals and subsequent oxidation of the Breslow intermediates (Scheme 1B, I); (ii) via the reaction of NHCs with activated alkynoic acid esters (Scheme 1B, II); (iii) via the reaction of NHCs with in situ activated alkynoic acids (Scheme 1B, III).
Typically, alkynyl acyl azoliums exhibit bielectrophilicity, and they have been investigated for [3 + n] annulations with diverse binucleophile reagents to afford heterocyclic molecules (Scheme 1B, IV).

However, despite recent developments gradually enabling the diverse transformation of these species, the area is in the early stages of its development. The main challenge to exploring the reactivity of alkynyl acyl azoliums intermediates is attributed to the difficulty to control the chemo- and regioselectivities, which would result in undesired byproducts. For instance, the NHC-bound alkynyl acyl anion intermediates Int. I, allene intermediates Int. II, and alkenyl acyl azoliums intermediates Int. III might also be formed during the generation of alkynyl acyl azoliums intermediates (Scheme 1C). Furthermore, the control of the regioselectivity of the [3 + n] annulations between binucleophile and alkynyl acyl azolium intermediates is another challenge to explore in this reaction (Scheme 1C, IV, V).

Herein, we summarized the efforts and advances in the NHC-catalyzed [3 + n] annulation reactions involving alkynyl acyl azoliums intermediates with focus on their generation and reactivity as well as the mechanism of the reactions. We present these achievements in generally chronological order and some seminal efforts or closely related works are mentioned as well. All the NHCs described in this article are summarized in Scheme 2.
2. Discussion

In 2018, Wang described the generation of alkynyl acyl azolium intermediates through the addition of NHC catalyst to ynals and subsequent oxidation of the Breslow intermediates (Scheme 3) [26]. The reaction of alkynyl acyl azoliums with binucleophile cyclic 1,3-diones 1 affords the axially chiral α-pyrene-aryls 3, along with byproducts 4, 5 and 6 which are derived from the annulation of α,β-unsaturated acyl azoliums intermediate Int. III, regioselective annulation between alkynyl acyl azoliums intermediate and oxygen nucleophile of cyclic 1,3-diones 1, as well as Knoevenagel reaction of 3 with 1, respectively.

Mechanistically, the reaction proceeds via the addition of NHC catalyst to ynal 2 followed by oxidation of the Breslow intermediate to form NHC-bound alkynyl acyl...
azolium intermediate 7. Nucleophilic addition of cyclic 1,3-diones 1 to 7 are promoted by Lewis acid Mg(OTf)_2 affords allenolate intermediate 9. Subsequent proton transfer forms alkenyl acyl azolium intermediate 10. Then, nucleophilic attack of acyl azolium forms an O—C bond and affords intermediate 11. The release of NHC catalyst finally delivers the targeted product 3. Importantly, the addition of Lewis acid was essential to modulate the regioselectivity. The chelation of the oxygen atom with magnesium ion promoted carbon nucleophilic addition of 1,3-dione to alkynyl acyl azoliums intermediate 7 and the formation of byproduct was inhibited. In addition, the attempt of oxidative dehydrogenation of 4 under their standard reaction conditions did not deliver product 3, which suggested that the direct annulation of cyclic 1,3-dione with unsaturated acyl azolium intermediate pathway was excluded (Scheme 4).

![Scheme 4. Mechanism of the NHC-catalyzed [3 + 3] atroposelective annulation of ynals and 1,3-diones.](image)

In 2020, Qi and co-workers developed a similar NHC-catalyzed [3 + 3] annulation of alkynyl acyl azoliums intermediate by replacing the binucleophile of pyrrol-4-one 13 [27]. In this reaction, the simple ynal 12a underwent [3 + 3] annulation smoothly and afforded the non-axially chiral pyrones in good yield. By optimizing a particular class of chiral indanol-derived NHCs and other conditions, the formation of axially chiral pyrones was also proven to be feasible by using 3-(2-methoxynaphthalen-1-yl)propiolaldehyde (12b) in the presence of chiral NHC catalyst A2 (Scheme 5).

Chi, Jin and co-workers also disclosed a [3 + 3] annulation of NHC-bound alkynyl acyl azoliums with N-Ts imine 16 [24]. In this case, the alkynyl acyl azolium intermediate was generated by the reaction of NHC catalyst with activated alkynoic acid ester. The alkynyl acyl azolium intermediates have great potential for reaction discovery due to the highly reactive carbon–carbon triple bond. In this work, they explored the reactivity of alkynyl acyl azoliums with binucleophile N-Ts imine 16 in order to access a variety of functionalized pyridines 17 (Scheme 6).
Scheme 5. NHC-catalyzed [3 + 3] atroposelective annulation of ynal and pyrrol-4-one.

Mechanistically, the addition of NHC catalyst to the ester 15 affords the key alkynyl acyl azolium intermediate 19. The nucleophilic conjugated addition of enamide 20 to 19 delivers the allenolate azolium intermediate 21, which undergoes a proton transfer to form

Scheme 6. NHC-catalyzed [3 + 3] annulation of activation of alkynoic acid ester and N-Ts imine.

Proposed mechanism
alkenyl acyl azolium intermediate $22$. Subsequent lactamization occurs to release the NHC catalyst and delivers the N-Ts δ-lactams $18$. Finally, isomerization of N-Ts δ-lactam $18$ at a slightly elevated temperature produces the pyridines $17$. This work pioneered the use of activated alkynoic acid ester as the precursor to generate the alkenyl acyl azolium intermediate.

In 2020, Qi and co-workers explored even further the reactivity of alkenyl acyl azolium intermediate for the [3 + 3] annulation reaction (Scheme 7) [28]. In this work, the N-Ts-protected 2-aminoacrylate $24$ serves as a nucleophile for conjugated addition and affords a range of pyridines $25$ in moderate yields.

Scheme 7. NHC-catalyzed [3 + 3] annulation of ynals and N-Ts 2-aminoacrylates.

A possible mechanism is proposed for the reaction. Addition of NHC catalyst to ynal $23$ delivers Breslow intermediate $26$, then oxidation of $26$ with DQ yields the alkenyl acyl azolium intermediate $27$. Subsequent 1,4-addition of N-Ts-protected 2-aminoacrylate $24$ to $27$ produces allenolate azolium intermediate $28$, which undergoes proton transfer and lactamization to afford N-Ts δ-lactam $30$ and regenerates the NHC catalyst. Finally, thermodynamic aromatization achieves the product pyridines $25$. Interestingly, 1,2-addition of $24$ to $27$ and Claisen rearrangement with $31$ pathways cannot be excluded.

Besides [3 + 3] annulation reactions, Du and co-workers also developed an NHC-catalyzed [3 + 2] annulation of alkenyl acyl azolium intermediate in 2017 [25]. In this process, activated esters $15$ were used to generate the alkenyl acyl azolium intermediates, which reacted with β-diacyl $32$ to afford the desired Z-2-vinylfuran-3(2H)-one $33$ with
various substituents in moderate to excellent yields. The reaction was compatible with both electron-withdrawing and electron-donating groups with regard to esters. However, undesired six-membered ring byproduct 39 was also observed with low to moderate yields in some cases (Scheme 8).

Mechanistically, the reaction starts by nucleophilic addition of NHC catalyst to the ester 15 to afford the key alkynyl acyl azolium intermediate 34. Deprotonation of β-diacyl 32 by DIPEA followed by complexation with LiCl yields acyl enolate 35, which undergoes 1,2-addition to obtain 36. Subsequent intramolecular proton transfer generates intermediate 37. Two pathways may be involved in the intramolecular nucleophilic addition process. The 5-membered Z-2-vinylfuran-3(2H)-ones 33 are obtained when the addition of hydroxyl occurs at the α-carbon of the triple bond. On the other hand, 6-endo-dig cyclization of 37 yields the byproducts 4H-pyran-4-ones 39. DFT calculations indicated that the α-carbons are positively charged and that the β-carbons were negatively charged in both intermediate 36 and 37. Therefore, attack of the α-carbon by oxygen anion is more favorable for yielding five-membered products in the intramolecular addition process. Due to the less-steric hindrance between alkenyl hydrogen and carbonyl, Z-isomers are able to be obtained with high stereoselectivity (Scheme 8).

To further investigate the reactivity of NHC-bound alkynyl acyl azolium intermediates, Wang and co-workers extended binucleophile to amidines 40 [29]. In this case, they explored another NHC catalyzed [3 + 3] annulation of alkynyl acyl azoliums to construct multiply substituted pyrimidin-4-ones (Scheme 9). The reaction was compatible with both electron-withdrawing and electron-donating groups on ynals and amidines. Furthermore, the desired products were obtained in good yields even with the bulkier amidines, which enabled this reaction to be applied for further diversification.
Mechanically, the catalytic cycle begins with the addition of NHC catalyst to ynal 23 to form Breslow intermediate 42, which undergoes an oxidation to afford alkynyl acyl azolium intermediate 43. The coordination of the Lewis acid Mg(OTf)₂ with amidine 40 and intermediate 43 produces complex 44. Then, Michael addition affords allenolate intermediate 45, which undergoes intramolecular proton transfer to generate alkenyl acyl azolium intermediate 46; subsequently, intramolecular 6-exo-dig cyclization delivers the final product, pyrimidin-4(1H)-one 41, and regenerates the NHC catalyst.

In 2018, based on the works of NHC-catalyzed reactions with in situ activation of saturated or alkenoic acids [30–35], Du and co-workers reported the formation of alkynyl acyl azolium intermediate 50 via the in situ activation of alkynoic acids of 47 by NHC catalyst [36]. This seminal work achieved the NHC-catalyzed formal [3 + 3] annulation of alkynoic acids 47 and 2-mercaptoimidazoles 48 to access the heterocyclic imidazo[2,1-b][1,3]thiazinone frameworks (Scheme 10).

Mechanistically, alkynoic acid 47 is activated in situ by pyBOP followed by the addition of NHC catalyst to afford alkynyl acyl azolium intermediate 50. Michael addition of 2-mercaptoimidazoles 48 to intermediate 50 forms allenolate azolium intermediate 51. Subsequent proton transfer produces alkenyl acyl azolium intermediate 52, which undergoes 6-exo-trig cyclization to give formal [3 + 3] annulation product δ-lactam 49 with release of the NHC catalyst.
In 2019, based on previous works on the annulations of alkenyl acyl azolium intermediates with indolin-3-ones [37,38], Du and co-workers achieved [3 + 3] annulation of alkenyl acyl azolium intermediates with 3-oxo indolin-2-ides (Scheme 11) [39]. In the presence of DBU and NHC iminium salt A8, 4-nitrophenyl alkynyl acid esters 15 and indolin-3-ones 53 underwent the [3 + 3] annulation smoothly and yielded pyrano[3,2-b]indol-2-ones 54 in an efficient and rapid manner. The benzofuran-3(2H)-one 60 was also explored as binucleophile for the [3 + 3] annulation reaction under standard conditions, which produce the corresponding 4-phenyl-2H-pyrano[3,2-b]benzofuran-2-one 61 product in 30% yield.

Mechanistically, the reaction is initiated by the addition of NHC catalyst to activated alkynoic acid esters 15 followed by the elimination of 4-nitrophenolate to afford alkynyl acyl azolium intermediate 56. Michael addition of 3-oxo indolin-2-ide 59 to intermediate 56 forms allenolate azolium intermediate 57. Subsequent proton transfer produces alkenyl acyl azolium intermediate 58 which undergoes 6-exo-trig cyclization to give corresponding formal [3 + 3] annulation product 54 with the release of the NHC free carbene. Although the nucleophilic addition of resonant isomer enolate 59′ of 59 to alkenyl acyl azolium intermediate 56 could produce byproduct 55, its formation could be completely inhibited by optimizing the base and solvent. When the reaction carried out at 90 °C or tetrahydrofuran was used as the solvent, byproduct 55 was obtained in 30–45% yields. Reducing the heat from 90 °C to room temperature and replacing tetrahydrofuran with other solvent (toluene, acetonitrile, or dichloromethane) could essentially completely inhibit the formation of byproduct 55, and the targeted product 54 could be obtained with high chemoselectivity.
Scheme 11. [3 + 3] annulation of alkynyl acyl azolium intermediates and 3-oxo indolin-2-ide or 3-imino benzofuran-2-ide.

Additionally, NHC-catalyzed [3 + 3] annulations of 4-nitrophenyl alkynyl acid esters 15 and benzofuran-3-amines 62 were also demonstrated by Du and co-workers to obtain functionalized benzofuro[3,2-b]pyridin-2-ones 63 (Scheme 11) [40]. The reaction conditions are generally consistent, except for the binucleophile (53, 60, and 62); the reaction mechanism is similar to the previous work. Deprotonation of benzofuran-3-amine 62 generates enamine ion 64, which resonates with the 3-oxo indolin-2-ide 59 analogue 3-imino benzofuran-2-ide 64′. 1,4-Conjugate addition of 64′ with alkynyl acyl azolium intermediate 56 and followed by lactamization affords the desired product 63.

Based on the successful synthesis of achiral δ-lactones 54 or δ-lactams 63 via [3 + 3] annulations of alkynyl acyl azolium intermediate 56 with α-oxo ide 59 or α-imino ide 64′ [40], a related asymmetric annulation reaction was developed by Wei, Du, and co-workers in...
2021 [41]. In the presence of potassium carbonate and NHC iminium salt A9, a steric hindrance alkynyl acid ester 66 activated by 4-nitrophenyl reacts with 2-sulfonamidoindolines 65 yielding axially chiral δ-lactam 68, and subsequently thermodynamic aromatization produces an enantioenriched 4-aryl α-carboline 67 containing a chiral C–N axis (Scheme 12).

Scheme 12. Catalytic atroposelective formal [3 + 3] annulation between alkynyl acyl azolium intermediate and 2-sulfonamidoindolines.

Mechanistically, the reaction is initiated by the addition of NHC catalyst to activated alkynoic acid esters 66 followed by the elimination of 4-nitrophenolate to afford alkynyl acyl azolium intermediate 69. Deprotonation of 2-sulfonamidoindolines 65 by potassium carbonate and followed by Michael addition to intermediate 69 forms allenolate azolium intermediate 70. Subsequent proton transfer produces alkenyl acyl azolium intermediate 71 which undergoes lactamization to yield the corresponding formal [3 + 3] annulation δ-lactams 68 with release of the NHC catalyst. Further thermal treatment of δ-lactams 68 affords the aromatized product 67. DFT calculation indicates that in the process of nucleophilic attack to intermediate 69, the energy of transition state TS1_R is 1.8 kcal/mol lower than that of transition state TS1_S, so R configuration isomer plays a dominant role.
in the reaction. According to DFT calculations, the main reason for the lower energy of TS1_R than TS1_S is that the noncovalent interactions (LP . . . π, C–H . . . N, π . . . π, etc.) of the former are stronger than the latter.

The above works referred to the construction of achiral compounds or molecules with the C–C axis through NHC-bound alkynyl acyl azolium intermediates. However, investigation of the C–hetero chiral axis remained underexplored. In 2021, Jin, Chi, and co-workers realized NHC-catalyzed asymmetric synthesis of C–N axial chiral thiazine 73 via the [3 + 3] annulation of alkynyl acyl azolium intermediate and thioureas 72 (Scheme 13) [42]. In this approach, in the presence of NHC-free carbene A10 and Scandium trifluoromethanesulfonate additive, a variety of bulky aryl substituted thioureas 72 annulated with ynals 23 afforded thiazine 73 with moderate to good yields and high to excellent enantioselectivities.

![Scheme 13. NHC-catalyzed atroposelective [3 + 3] annulation of ynals and thioureas.](image-url)

Mechanistically, the reaction proceeds via the addition of NHC catalyst to activated ynal 23a in order to generate the Breslow intermediate 74. The subsequent oxidation by DQ generates alkynyl acyl azolium intermediate 75. Deprotonation of thiourea 23a, through DMAP and nucleophilic thiol-addition to intermediate 75, forms allenolate azolium intermediate 76. Subsequent proton transfer produces alkynyl acyl azolium intermediate 77, which complexes with Sc(OTf)3 to afford stereoisomeric intermediate 78. Under the action of chiral NHC, intermediate 78 undergoes 6-exo-trig cyclization to yield the corresponding formal [3 + 3] annulation product 73a with the release of the NHC catalyst. It is worth noting that although Scandium promotes the reaction, it has no effect on ee value.

In 2021, as a continuous work on NHC-catalyzed atroposelective [3 + n] annulation to access chiral C–N axis heterocyclic compounds, Chi and co-workers disclosed the atroposelective [3 + 2] annulation between ynals 23 and 4-arylurazole 79 using a desymmetrization
strategy (Scheme 14) [43]. A wide range of ynals 23 and symmetric urazole 79 with bulky 4-aryl bearing diverse substituents were well tolerated and underwent the desymmetric atroposelective [3 + 2] annulation to afford pyrazolo[1,2-a]triazoles 80 containing a C–N axis in good to excellent yield with high enantiomeric excess. The mechanism is similar to that reported previously, in which atroposelective nucleophilic addition of the deprotonated 79 to the alkynyl acyl azolium intermediate 75 occurs to yield formal [3 +2] annular product.

![Scheme 14. NHC-catalyzed atroposelective [3 + 2] annulation of ynals and urazoles.](image)

3. Conclusions

Since its discovery, NHC-based alkynyl acyl azolium intermediates have made significant progress in the past five years. Three methods to access the NHC-based alkynyl acyl azolium intermediates have been discussed, (1) via the oxidation of ynals, (2) via the activation of alkynoic acid ethers, and (3) via the in situ activation of alkynoic acids. These intermediates exhibit bielectrophilicity and react with binucleophiles via conjugated addition followed by 1,2-addition to yield structurally and functionally diverse cyclic molecules such as pyridines, lactones, and lactams containing a ring-fused structure, as well as multiple heteroatoms. Particularly, with the participation of alkynyl acyl azolium intermediates, the construction of C–N chiral axes and C–C chiral axes was achieved.

However, due to the formation of several other reactive species during the generation of alkynyl acyl azolium intermediates and the difficulty of controlling the regioselectivity of the nucleophilic addition, these reactions lead to the formation of several byproducts. Unfortunately, only a few reports concerning this topic have been produced. On the other hand, only four relatively successful cases for the synthesis of chiral compounds have been developed. In the future, more efforts will be required to explore new reactions for the synthesis of axially chiral molecules and to further investigate the mechanism by which NHC-based alkynyl acyl azolium intermediates participate.
Author Contributions: Conceptualization, C.Z.; writing—original draft preparation, Z.D., C.J. and C.Z.; writing—review and editing, C.Z.; supervision, C.Z. All authors have read and agreed to the published version of the manuscript.

Funding: Project supported by the National Natural Science Foundation of China (No. 22171027) and the Beijing Natural Science Foundation (No. 2212009).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Ukai, T.; Tanaka, R.; Dokawa, T. A new catalyst for acyloin condensation. *J. Pharm. Soc. Jpn.* 1943, 63, 296–300.
2. Breslow, R. On the mechanism of thiamine action. *Iv.1 evidence from studies on model systems*. *J. Am. Chem. Soc.* 1958, 80, 3719–3726. [CrossRef]
3. Zhao, Q.; Meng, G.; Nolan, S.P.; Szostak, M. N-heterocyclic carbene complexes in C–H activation reactions. *Chem. Rev.* 2020, 120, 1981–2048. [CrossRef]
4. Chen, C.; Liu, F.-S.; Szostak, M. Bian–NHC ligands in transition-metal-catalysis: A perfect union of sterically encumbered, electronically tunable N-heterocyclic carbene metal complexes. *Dalton Trans.* 2021, 50, 12058–12068. [CrossRef] [PubMed]
5. Nahra, F.; Cazin, C.S.J. Sustainability in Ru- and Pd-based catalytic systems using N-heterocyclic carbenes as ligands. *Chem. Rev.* 2021, 121, 3094–3142. [CrossRef] [PubMed]
6. Voloshkin, V.A.; Tzouras, N.V.; Nolan, S.P. Recent advances in the synthesis and derivatization of N-heterocyclic carbene metal complexes. *Angew. Chem. Int. Ed.* 2021, 60, 7973–7992. [CrossRef] [PubMed]
7. Neshat, A.; Mastrorilli, P.; Mousavizadeh Mobarakhe, A. Recent advances in catalysis involving bidentate N-heterocyclic carbene ligands. *Molecules* 2022, 27, 95. [CrossRef] [PubMed]
8. Danopoulos, A.A.; Simler, T.; Braunstein, P. N-heterocyclic carbene complexes of Copper, Nickel, and Cobalt. *Chem. Rev.* 2019, 119, 3730–3961. [CrossRef]
9. Flanagan, D.M.; Romanov–Michailidis, F.; White, N.A.; Rovis, T. Organocatalytic reactions enabled by N-heterocyclic carbens. *Chem. Rev.* 2015, 115, 9307–9387. [CrossRef] [PubMed]
10. Wang, J.; Zhao, C.; Wang, J. Recent progress toward the construction of axially chiral molecules catalyzed by an N-heterocyclic carbene. *ACS Catal.* 2021, 11, 12520–12531. [CrossRef]
11. Ohmiya, H. N-heterocyclic carbene-based catalysis enabling cross-coupling reactions. *ACS Catal.* 2020, 10, 6862–6869. [CrossRef]
12. Pareek, M.; Reddi, Y.; Sunoj, R.B. Tale of the breslow intermediate, a central player in N-heterocyclic carbene organocatalysis: Then and now. *Chem. Sci.* 2021, 12, 7973–7992. [CrossRef] [PubMed]
13. Mondal, S.; Ghosh, A.; Biju, A.T. N-heterocyclic carbene (NHC)-catalyzed transformations involving azolium enolates. *Chem. Rev.* 2022, 22, e202200054. [CrossRef] [PubMed]
14. Menon, R.S.; Biju, A.T.; Nair, V. Recent advances in employing homoenolates generated by N-heterocyclic carbene (NHC) catalysis in carbon–carbon bond-forming reactions. *Chem. Soc. Rev.* 2015, 44, 5040–5052. [CrossRef]
15. Gao, J.; Feng, J.; Du, D. Generation of azolium dienolates as versatile nucleophilic synthons via N-heterocyclic carbene catalysis. *Org. Chem. Front.* 2021, 8, 6138–6166. [CrossRef]
16. Chen, K.-Q.; Sheng, H.; Liu, Q.; Shao, P.-L.; Chen, X.-Y. N-heterocyclic carbene-catalyzed radical reactions. *Sci. China Chem.* 2021, 64, 7–16. [CrossRef]
17. Mahaththananchai, J.; Bode, J.W. On the mechanism of N-heterocyclic carbene-catalyzed reactions involving acyl azoliums. *Acc. Chem. Res.* 2014, 47, 696–707. [CrossRef]
18. Zhang, C.; Hooper, J.F.; Lupton, D.W. N-heterocyclic carbene catalysis via the α,β-unsaturated acyl azolium. *ACS Catal.* 2017, 7, 2583–2596. [CrossRef]
19. Mondal, S.; Yetra, S.R.; Mukherjee, S.; Biju, A.T. NHC-catalyzed generation of α,β-unsaturated acylazoliums for the enantioselective synthesis of heterocycles and carbocycles. *Acc. Chem. Res.* 2019, 52, 425–436. [CrossRef]
20. Zhao, C.; Blaszczyk, S.A.; Wang, J. Asymmetric reactions of N-heterocyclic carbene (NHC)-based chiral acyl azoliums and azolium enolates. *Green Syn. Catal.* 2021, 2, 198–215. [CrossRef]
21. Zhu, T.; Mou, C.; Li, B.; Smetankova, M.; Song, B.-A.; Chi, Y.R. N-heterocyclic carbene-catalyzed δ-carbon lumo activation of unsaturated aldehydes. *J. Am. Chem. Soc.* 2015, 137, 5658–5661. [CrossRef] [PubMed]
22. Gillard, R.M.; Fernando, J.E.M.; Lupton, D.W. Enantioselective N-heterocyclic carbene catalysis via the dienyl acyl azolium. *Angew. Chem. Int. Ed.* 2018, 57, 4712–4716. [CrossRef] [PubMed]
23. Xu, K.; Li, W.; Zhu, S.; Zhu, T. Atroposelective arene formation by carbene-catalyzed formal [4 + 2] cycloaddition. *Angew. Chem. Int. Ed.* 2019, 58, 17625–17630. [CrossRef] [PubMed]
24. Mou, C.; Wu, J.; Huang, Z.; Sun, J.; Jin, Z.; Chi, Y.R. Carbene-catalyzed lumo activation of alkyne esters for access to functional pyridines. *Chem. Commun.* 2017, 53, 13359–13362. [CrossRef] [PubMed]

25. Cao, J.; Sun, K.; Dong, S.; Lu, T.; Dong, Y.; Du, D. Esters as alkynyl acyl ammonium and azolium precursors: A formal [2 + 3] annulation with amidomalonates via Lewis base/Lewis acid cooperative catalysis. *Org. Lett.* 2017, 19, 6724–6727. [CrossRef] [PubMed]

26. Zhao, C.; Guo, D.; Munkerup, K.; Huang, K.-W.; Li, F.; Wang, J. Enantioselective [3 + 3] atroposelective annulation catalyzed by N-heterocyclic carbienes. *Nat. Commun.* 2018, 9, 611. [CrossRef]

27. Wu, Y.-T.; Zhang, R.; Duan, X.-Y.; Yu, H.-F.; Sun, B.-Y.; Qi, J. Access to dihydropyran[3,2-b]pyrrol-5-ones skeletons by N-heterocyclic carbene-catalyzed [3 + 3] annulations. *Chem. Commun.* 2020, 56, 9854–9857. [CrossRef]

28. Li, J.-H.; Duan, X.-Y.; Tian, Z.-H.; Zheng, Y.-F.; Qi, J. N-heterocyclic carbene-catalyzed activation of ynals for the construction of functional pyridines. *Asian J. Org. Chem.* 2020, 9, 385–390. [CrossRef]

29. Xie, Y.; Wang, J. N-heterocyclic carbene-catalyzed annulation of ynals with amidines: Access to 1,2,6-trisubstituted pyrimidin-4-ones. *Chem. Commun.* 2018, 54, 4597–4600. [CrossRef]

30. Chen, X.-Y.; Gao, Z.-H.; Song, C.-Y.; Zhang, C.-L.; Wang, Z.-X.; Ye, S. N-heterocyclic carbene catalyzed cyclocondensation of α,β-unsaturated carboxylic acids: Enantioselective synthesis of pyrrolidinone and dihydropyridinone derivatives. *Angew. Chem. Int. Ed.* 2014, 53, 11611–11615. [CrossRef]

31. Lee, A.; Younai, A.; Price, C.K.; Izquierdo, J.; Mishra, R.K.; Scheidt, K.A. Enantioselective annulations for dihydroquinolones by in situ generation of azolium enolates. *J. Am. Chem. Soc.* 2014, 136, 10589–10592. [CrossRef] [PubMed]

32. Jin, Z.; Jiang, K.; Fu, Z.; Torres, J.; Zheng, P.; Yang, S.; Song, B.-A.; Chi, Y.R. Nucleophilic α-carbon activation of propionic acid as a 3-carbon synthon by carbene organocatalysis. *Chem. Eur. J.* 2015, 21, 9360–9363. [CrossRef] [PubMed]

33. Jia, W.-Q.; Zhang, H.-M.; Zhang, C.-L.; Gao, Z.-H.; Ye, S. N-heterocyclic carbene-catalyzed [4 + 2] annulation of a,β-unsaturated carboxylic acids: Enantioselective synthesis of dihydropyridinones and spirocyclic oxindolodihydropyridinones. *Org. Chem. Front.* 2016, 3, 77–81. [CrossRef]

34. Zhu, L.; Yu, C.; Li, T.; Wang, Y.; Lu, Y.; Wang, W.; Yao, C. N-heterocyclic carbene-catalyzed [4 + 2] cyclization of α,β-unsaturated carboxylic acids bearing γ-H with isatins: An enantioselective synthesis of spirocyclic oxindole–dihydropyranones. *Org. Biomol. Chem.* 2016, 14, 1485–1491. [CrossRef]

35. Mondal, S.; Mukherjee, S.; Das, T.K.; Gonnade, R.; Biju, A.T. N-heterocyclic carbene-catalyzed aldol-lactonization of ketoacids via dynamic kinetic resolution. *ACS Catal.* 2017, 7, 3995–3999. [CrossRef]

36. Sun, K.; Jin, S.; Zhu, J.; Zhang, X.; Gao, M.; Zhang, W.; Lu, T.; Du, D. N-heterocyclic carbene-catalyzed in situ activation of alkynyl acids for C–S bond formation: Access to imidazo[2,1-b][1,3]thiazinones. *Adv. Syn. Catal.* 2018, 360, 4515–4522. [CrossRef]

37. Lu, Y.; Tang, W.; Zhang, Y.; Du, D.; Lu, T. N-heterocyclic carbene-catalyzed annulations of enals and ynals with indolin-3-ones: Synthesis of 3,4-dihydropyran[3,2-b]indol-2-ones. *Adv. Syn. Catal.* 2013, 535, 321–326.

38. Ni, Q.; Song, X.; Raabe, G.; Enders, D. N-heterocyclic carbene-catalyzed enantioselective annulation of indolin-3-ones with bromoenaos. *Chem. Asian J.* 2014, 9, 1535–1538. [CrossRef]

39. Sun, K.; Jin, S.; Fang, S.; Ma, R.; Zhang, X.; Gao, M.; Zhang, W.; Lu, T.; Du, D. N-heterocyclic carbene-catalyzed formal [3 + 3] annulation of alkylic acid esters with indolin-3-ones: Access to functionalized pyrano[3,2-b]indol-2-ones. *Org. Chem. Front.* 2019, 6, 2291–2295. [CrossRef]

40. Wang, X.; Shao, Y.; Zhang, S.; Lu, T.; Du, D. N-heterocyclic carbene-catalyzed formal [3 + 3] annulation of alkylnyl acylazoliums for the synthesis of benzofuro[3,2-b]pyridin-2-ones. *J. Org. Chem.* 2021, 86, 12336–12343. [CrossRef]

41. Ma, R.; Wang, X.; Zhang, Q.; Chen, L.; Gao, J.; Feng, J.; Wei, D.; Du, D. Atroposelective synthesis of axially chiral 4-aryl α-carbolines via N-heterocyclic carbene catalysis. *Org. Lett.* 2021, 23, 4267–4272. [CrossRef] [PubMed]

42. Li, T.; Mou, C.; Qi, P.; Peng, X.; Jiang, S.; Hao, G.; Xue, W.; Yang, S.; Hao, L.; Chi, Y.R.; et al. N-heterocyclic carbene-catalyzed atroposelective annulation for access to thiazine derivatives with C–N axial chirality. *Angew. Chem. Int. Ed.* 2021, 60, 9362–9367. [CrossRef] [PubMed]

43. Jin, J.; Huang, X.; Xu, J.; Li, T.; Peng, X.; Zhu, X.; Zhang, J.; Jin, Z.; Chi, Y.R. Carbene-catalyzed atroposelective annulation and desymmetrization of urazoles. *Org. Lett.* 2021, 23, 3991–3996. [CrossRef] [PubMed]