

N-Heterocyclic Carbene-Catalyzed Formal [6+2] Annulation Reaction via Cross-Conjugated Aza-Trienolate Intermediates

Kuruva Balanna, Krishnaprasad Madica, Subrata Mukherjee, Arghya Ghosh, Thomas Poisson, Tatiana Besset, Garima Jindal, Akkattu Biju

▶ **To cite this version:**

Kuruva Balanna, Krishnaprasad Madica, Subrata Mukherjee, Arghya Ghosh, Thomas Poisson, et al.. N-Heterocyclic Carbene-Catalyzed Formal [6+2] Annulation Reaction via Cross-Conjugated Aza-Trienolate Intermediates. Chemistry - A European Journal, 2019, 26 (4), pp.818-822. 10.1002/chem.201905177 . hal-02455771

HAL Id: hal-02455771

https://normandie-univ.hal.science/hal-02455771

Submitted on 8 Dec 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

N-Heterocyclic Carbene-Catalyzed Formal [6+2] Annulation Reaction via Cross-Conjugated Aza-Trienolate Intermediates

Kuruva Balanna,[a] Krishnaprasad Madica,[a] Subrata Mukherjee,[a] Arghya Ghosh,[a]Thomas Poisson,[b, c] Tatiana Besset,[c] Garima Jindal,*[a] and Akkattu T. Biju*[a]

[a] Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012 (India)

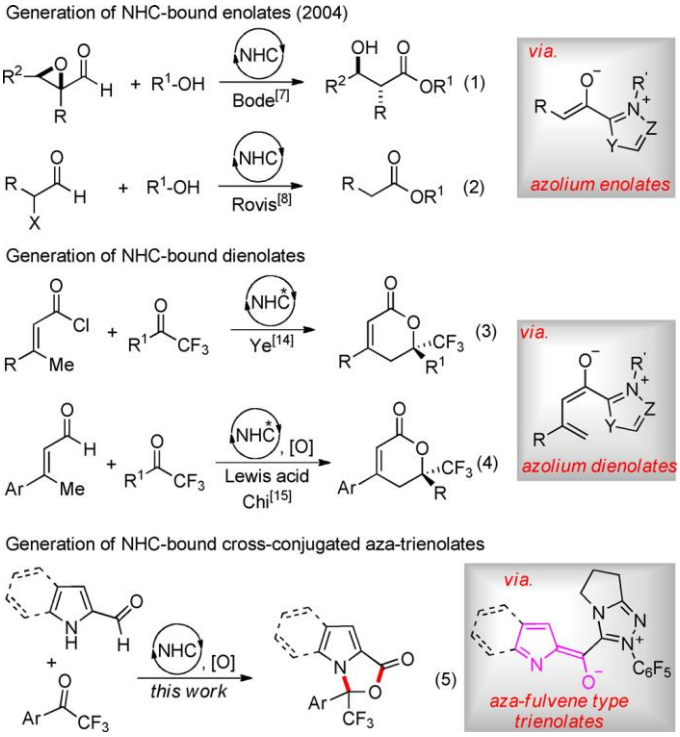
[b] Institut Universitaire de France, 1 rue Descartes, 75231 Paris (France)

[c] Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France.

E-mail: *gjindal@iisc.ac.in*, *atbiju@iisc.ac.in*

Abstract: : The diverse reactivity of N-heterocyclic carbenes (NHCs) in organocatalysis is due to the possibility of different modes of action. Although NHC-bound enolates and dienolates are known, the related NHC-bound cross-conju- gated aza-trienolates remain elusive. Herein, we demonstrate the NHC-catalyzed formal [6**+**2] annulation of nitro- gen-containing heterocyclic aldehydes with *a*,*a*,*a*-trifluoroacetophenones leading to the formation of versatile pyrrolooxazolones (29 examples). The catalytically generated cross-conjugated aza-trienolates (aza-fulvene type) underwent smooth [6**+**2] annulation with electrophilic ketones to afford the product in moderate to good yields under mild conditions. Preliminary DFT studies on the mechanism were also provided.

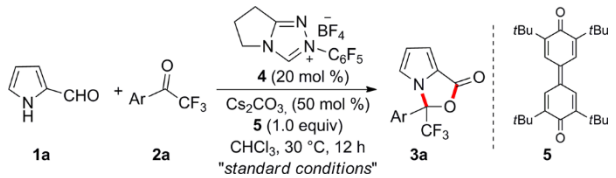
Over the past three decades, catalysis using N-heterocyclic carbenes (NHCs) has emerged as a flexible synthetic tool for the unconventional access to target molecules.[1] This catalytically active species is responsible for the umpolung of aldehydes, thus leading to the generation of nucleophilic Breslow intermediates.[2] The two fundamental reactions proceeding via NHC-generated acyl anions are the benzoin condensation[3] and Stetter reaction.[4] Moreover, addition of NHCs to α,β-unsaturated aldehydes could result in the generation of homoenolate equivalents,[5] and α,β-unsaturated acylazoliums under oxidative conditions.[6] A variety of carbocycles and heterocycles can easily be accessed by intercepting the homoenolates/a,bunsaturated acylazoliums. In 2004, the Bode[7] and Rovis[8] groups independently uncovered the generation of azolium enolates from NHCs by the addition to α-epoxyaldehydes and α-chloroaldehydes, respectively. The reaction afforded β-hydroxyesters or saturated esters upon quenching the NHC-enolates with alcohols (Scheme 1, eq. 1, 2). Moreover, the azolium enolates can also be generated by the treatment of NHCs with ketenes,[9] enals,[10] carboxylic acids,[11] and aliphatic aldehydes[12] or esters[13] bearing a C-H protons. In 2011, Ye and co-workers extended the NHC-enolate concept to the generation of NHC bound dienolates.[14] The in situ formed dienolates were intercepted with activated ketones in a [4+2] fashion to form unsaturated d-lactones (Scheme 1, eq. 3). Subsequently, Chi and coworkers reported an elegant generation of azolium dienolates from enals under oxidative conditions employing NHC/Lewis acid cooperative catalysis (Scheme 1, eq. 4).[15] Interestingly, however, the application of this concept for the generation of NHC-bound cross-conjugated aza-trienolates followed by their trapping with electrophiles, to the best of our knowledge is unknown. This will be interesting given that the related cross conjugated enamines and their aza version are known in secondary amine catalysis.[16] Herein, we demonstrate the NHC-catalyzed generation of cross-conjugated aza-trienolates from nitrogen-containing heterocyclic aldehydes followed by their interception with α,α,α-trifluoroacetophenones in a [6+2] fashion resulting in the synthesis of pyrrolooxazolones derivatives
(eq. 5).



Scheme 1. Generation and reaction of various NHC-enolates.

The present studies commenced with the treatment of pyrrole carboxaldehyde 1a with α,α,α–trifluoroacetophenone **2a** in the presence of the NHC catalyst generated from the triazolium salt **4** using Cs2CO3 base under oxidative conditions using the bisquinone **5** in $CHCl_3$. Interestingly, under these conditions, the [6+2] annulation product formed by the trapping of the aza-fulvene type trienolate generated from **1a** and **4** (under oxidative conditions) with the electron-poor carbonyl of **2a**, the pyrrolooxazolone **3a**, was formed in 83% yield (Table 1, entry 1). Impressed by this reactivity, various parameters such as NHC source, base, solvent have been examined. Compared with the carbene generated from **4**, reaction performed using other carbene precursors **6–9** resulted in the reduced yield of **3a** (entries 2–5). Moreover, Cs_2CO_3 was found to be the best base for this transformation, as the reactions carried out using other inorganic (K_2CO_3 and KOtBu) and organic (DBU and DABCO) bases returned inferior yields of **3a** (entries 6–9). The reactions carried out in solvents such as THF, 1,2-dichloroethane and toluene did not improve the yield of **3a** indicating that $CHCl_3$ is the optimal solvent for this [6+2] annulation (entries 10–12). Notably, reducing the loading of **4** to 10 mol% resulted in the formation of **3a** in 55% yield with 12% recovery of **1a** (entry 13). Control experiments performed without NHC precursor **4** or the oxidant **5** did not afford **3a** indicating the role of carbene as well as the oxidant in this reaction (entries 14,15).[17]

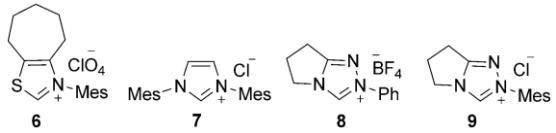
Table 1. Optimization of the reaction conditions.[a]



1a 2a 3a 5

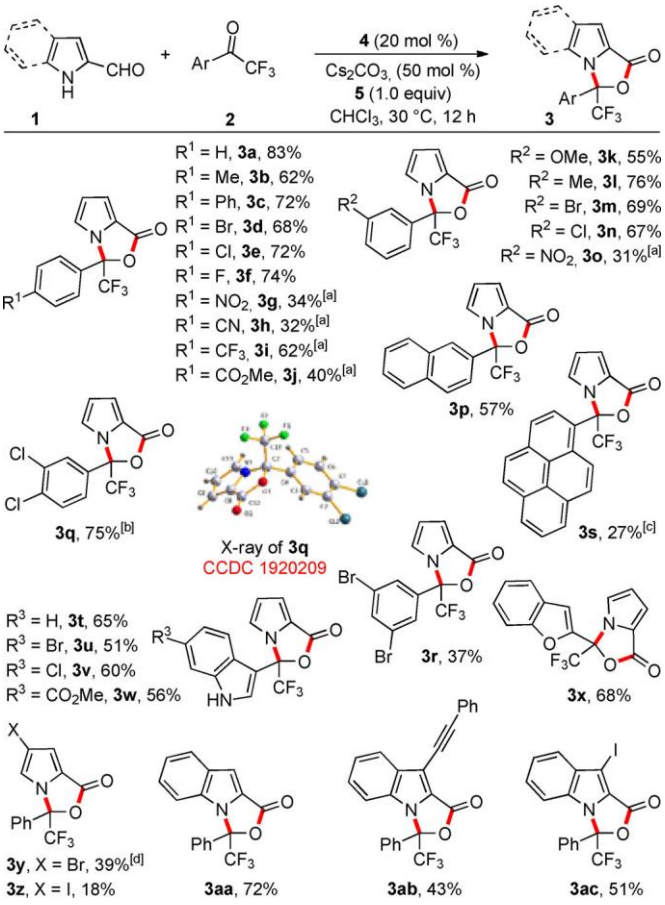
Entry	Variation of the standard conditions	Yield of 2a [%][b]
1	*none*	*83*
2	6 instead of 4	31
3	7 instead of 4	<5
4	8 instead of 4	18
5	9 instead of 4	16
6	K_2CO_3 instead of Cs_2CO_3	41
7	KO*t*Bu instead of Cs_2CO_3	<5
8	DBU instead of Cs_2CO_3	<5
9	DABCO instead of Cs_2CO_3	30
10	THF instead of $CHCl_3$	16
11	DCE instead of $CHCl_3$	22
12	toluene instead of DMF	19
13	10 mol% of 4 instead of 20 mol%	55
14	reaction without 4	<5
15	reaction without 5	<5

[a] Standard Conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), **4** (20 mol%), Cs_2CO_3 (50 mol%), **5** (1.0 equiv), $CHCl_3$ (2.0 mL), 30 °C, and 12 h. [b] Yield of chromatographically purified product is given.



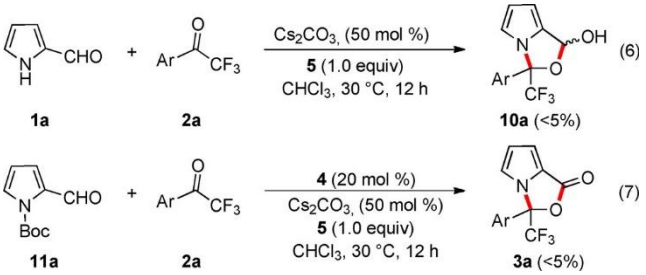
6 7 8 9

Having the optimized reaction conditions in hand, the scope and limitations of this [6+2] annulation have been examined (Scheme 2). A series of α,α,α-trifluoroacetophenone derivatives bearing electron-donating,-neutral and -withdrawing groups at the 4-position of the aromatic ring are well tolerated under the present NHC-catalyzed conditions and the desired pyrrolooxazolones are formed in moderate to good yields (**3a–3j**). Notably, substrates having electron-withdrawing groups required 36 h for completion of the reaction. This sheds light on a stepwise pathway in which the initially generated cross-conjugated aza-trienolates adds to the electrophilic carbonyl group of **1** forming an alkoxide, which undergoes an intramolecular acylation to afford the product. Moreover, α,α,α-trifluoroacetophenones having substituent at the 3-position of the ring worked well under the present conditions furnishing the desired products in moderate to good yields (**3k– 3o**). Disappointingly, reactions performed using 2-aryl substituted α,α,α-trifluoroacetophenones provided only traces of the product. Interestingly, the disubstituted α,α,α-trifluoroacetophenones afforded the desired products under the optimized conditions. In the case of the dichloro derivative **3q**, the structure was confirmed using single-crystal X-ray analysis.[18] The reaction using pyrenyl trifluoromethyl ketone afforded the product **3s** in 27% yield. In addition, a series of heteroaryl trifluoromethyl ketones readily underwent smooth [6+2] annulation affording the target products in good yields (**3t–3x**) thus demonstrating the versatility of the present reaction. The introduction of substituent on pyrrole carboxaldehyde **1a** affected the outcome of the reaction. For instance, the aldehyde having bromine at the 4-position returned only 39% yield of the product **3y**, and iodine at the 4-position afforded **3z** in 18% yield.

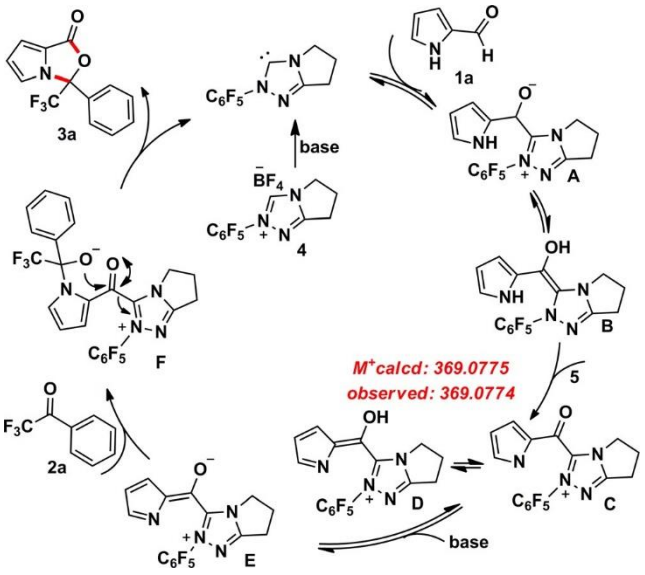


Scheme 2. Scope of the NHC-catalyzed formal [6+2] annulation reaction. General conditions: **1** (0.5 mmol), **3** (0.75 mmol), **4** (20 mol%), Cs_2CO_3 (50 mol%), **5** (1.0 equiv), $CHCl_3$ (4.0 mL), 30°C, and 12 h. Yields of the isolated products are given. [a] Reaction run for 36 h. [b] Structure confirmed by X-ray analysis. [c] Run for 24 h. [d] The product contained _3% of oxidant 5.

This is an indication of the role p-electron cloud of aldehyde on this [6+2] annulation. Furthermore, unsubstituted indole 2- carboxaldehyde afforded the desired product **3aa** in 72% yield. Finally, substitution at the 3-position of indole 2-carboxaldehyde did not affect the outcome of the reaction and the target products are formed in moderate to good yields (**3ab– 3ac**). To gain insight into the mechanism of the reaction, we performed a few experiments. When the reaction of **1a** and **2a** was performed in the absence of NHC pre-catalyst **4**, the desired product **3a** was not formed indicating the role of NHC in this [6+2] annulation (Scheme 3, eq 6). Moreover, the acetal **10a** (likely formed by the N-H addition of **1a** to **2a** followed by intramolecular cyclization) was not observed under these conditions showing that the direct N-H addition of initially formed acylazolium and cyclization in a [3+2] pathway is not operating in this case.[19] In addition, when the reaction was performed using N-Boc protected aldehyde **11 a**, the product **3a** was not formed signifying the role of N-H moiety in forming the NHC-bound cross-conjugated aza-trienolates (eq 7).



Scheme 3. Control experiment and reaction using N-Boc aldehyde.



Scheme 4. Tentative mechanism of the reaction.

Mechanistically, the free carbene generated from **4** adds to the aldehyde 1a forming the Breslow intermediate **B** (*via* the tetrahedral intermediate **A**),[2a, 20] which is subsequently oxidized by the bisquinone **5** to the NHC-acylazolium intermediate **C** (Scheme 4). The intermediate **C** could tautomerize to the cross-conjugated aza-trienol **D**. The intermediate **C** or its tautomer **D** was detected in high resolution mass spectrum (ESI) of a stoichiometric reaction carried out using **1a**, **4**, Cs_2CO_3 under oxidative conditions.[17, 21] Under basic conditions, deprotonation of intermediate **C**/**D** could generate the key cross-conjugated aza-trienolates (aza-fulvene type) **E**. Efforts to isolate the intermediate **C**, **D**, or **E** failed in our hands. The nucleophilic aza-trienolate **E** could add to the carbonyl group of **2a** resulting in the generation of the acyl azolium **F**, which could undergo an intramolecular acylation to form the desired product **3a** with the regeneration of the NHC catalyst. To get further insight into the proposed mechanism, we have carried out a preliminary DFT study with the B3LYP functional.[22] Given that the formation of a Breslow intermediate and its subsequent oxidation is well documented,[1c, d] we focused on the newly proposed intermediate **E** and its reaction with the ketone **2a**. Two different configurations, i.e., *E* and *Z*, were optimized for intermediate *E*. Further calculations were performed with the *E* isomer as it was about 5 kcalmol^{-1} lower in energy than the *Z* isomer. The conversion of **E** to **F** proceeds via transition state **TS(E–F)** and the activation free-energy was found to be about 15 kcalmol^{-1} making this a facile step. The optimized geometries of transition state and the intermediates **E–2a** (pre-reacting complex between **E** and **2a**), and **F** are shown in Figure 1. It should be noted that intermediate **F** is pre-organized for the final C-O bond formation, where the C-O distance is 2.17 Å. The final step leading to the product **3a** and generation of the free carbene takes place via a concerted late transition state **TS(F–3a)** where the C-O bond distance is 1.50 Å, and the activation barrier is 8.6 kcalmol^{-1}. We also looked at the thermodynamic stability of the intermediate **C**, Scheme 3. Control experiment and reaction using *N*-Boc aldehyde. its enol form **D** and the deprotonated form **E**.[23] It was found

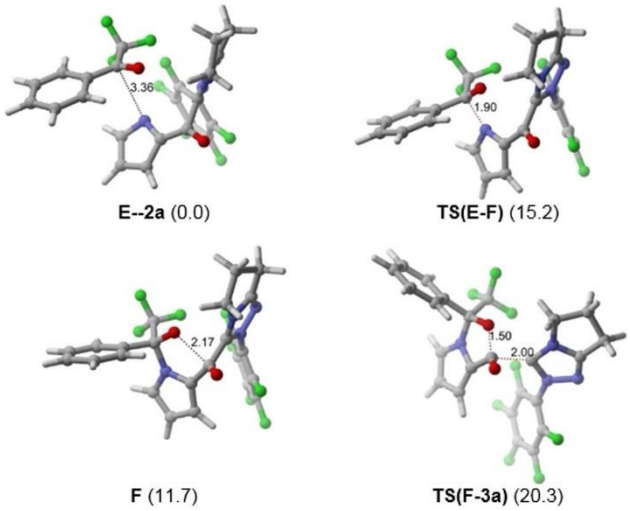
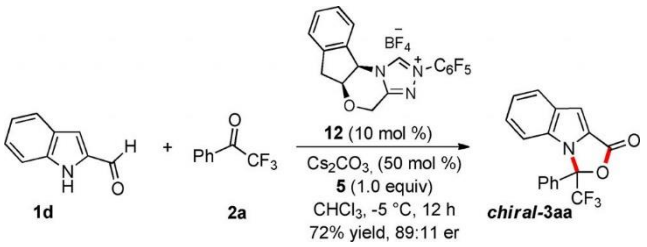


Figure 1. Optimized geometries of stationary points; E–2a, TS(E–F), and F. All distances are in Å. Relative free energies (kcalmol^{-1}) are given in paren theses. (Atom colour code: Grey: C, White: H, Green: F, Blue: N, Red: O).

that the keto form **C** is _19 kcalmol_1 lower in energy than the enol form. Further, intermediate **E** which arises as a result of deprotonation with the Cs_2CO_3 base, was found to be _47 kcalmol_1 lower in energy than **C**. We have also performed the preliminary studies on the enantioselective version of this [6+2] annulation. Thus, treatment of the indole aldehyde **1d** with **2a** using the carbene generated from the chiral triazolium salt **12** using Cs_2CO_3 as the base resulted in the formation of the desired product chiral-**3 aa** in 72% yield and 89:11 er (Scheme 5).



Scheme 5. Preliminary study on the enantioselective version.

In conclusion, we have demonstrated the NHC-catalyzed formal [6+2] annulation of nitrogen-containing heterocyclic aldehydes with α,α,α-trifluoroacetophenones allowing the synthesis of pyrrolooxazolones in moderate to good yields.[24] The key to the success of the present reaction is the generation of cross-conjugated aza-trienolates (aza-fulvene type) from NHC and heteroaldehydes (supported by DFT studies). Mild reaction conditions, broad scope, new mode of carbene reactivity are the notable features of the present annulation. Further studies on NHC-bound cross-conjugated aza-trienolates are ongoing in our laboratory.

Acknowledgements

Generous financial support by IFCPAR-CEFIPRA (no. 5505-1) is gratefully acknowledged. G. J. thanks Supercomputer Education and Research Centre (SERC), IISc Bangalore for computing time. K. B. and K. M. thank UGC for the PhD scholarship and DS Kothari post-doctoral fellowship, respectively, and

A.G. thanks CSIR for the research fellowship. We thank Dr. M. Venkateswarulu and Mr Ravi Teja for collecting the X-ray data of **3q** and Mr. Arun Patel from the help with ^{1}H NMR experiments.

Keywords: [6+2] annulations · conjugated aza-trienolates · heterocycles · N-heterocyclic carbenes · organocatalysis

[1] a) For recent reviews on NHC organocatalysis, see: K. J. R. Murauski, A. A. Jaworski, K. A. Scheidt, Chem. Soc. Rev. 2018, 47, 1773; b) M. H. Wang, K. A. Scheidt, Angew. Chem. Int. Ed. 2016, 55, 14912; Angew. Chem. 2016, 128, 15134; c) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, Chem. Rev. 2015, 115, 9307; d) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, Nature 2014, 510, 485; e) J. Mahatthananchai, J. W. Bode, Acc. Chem. Res. 2014, 47, 696; f) S. J. Ryan, L. Candish, D. W. Lupton, Chem. Soc. Rev. 2013, 42, 4906; g) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, Chem. Eur. J. 2013, 19, 4664; h) M. F_vre, J. Pinaud, Y. Gnanou, J. Vignolle, D. Taton, Chem. Soc. Rev. 2013, 42, 2142; i) H. U. Vora, P. Wheeler, T. Rovis, Adv. Synth. Catal. 2012, 354, 1617; j) A. Grossmann, D. Enders, Angew. Chem. Int. Ed. 2012, 51, 314; Angew. Chem. 2012, 124, 320; k) D. T. Cohen, K. A. Scheidt, Chem. Sci. 2012, 3, 53; l) X. Bugaut, F. Glorius, Chem. Soc. Rev. 2012, 41, 3511; m) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, Angew. Chem. Int. Ed. 2012, 51,
11686; Angew. Chem. 2012, 124, 11854; n) A. T. Biju, N. Kuhl, F. Glorius, Acc. Chem. Res. 2011, 44, 1182; o) D. Enders, O. Niemeier, A. Henseler, Chem. Rev. 2007, 107, 5606.

[2] a) R. Breslow, J. Am. Chem. Soc. 1958, 80, 3719; see also: b) T. Ukai, R. Tanaka, T. J. Dokawa, Pharm Soc. Jpn. 1943, 63, 296 .

[3] a) For selected reviews on benzoin reaction, see: R. S. Menon, A. T. Biju, V. Nair, Beilstein J. Org. Chem. 2016, 12, 444; b) X. Bugaut in Comprehensive Organic Synthesis II, Vol. 1 (Eds.: G. A. Molander, P. Knochel), Elsevier, Oxford, 2014, pp. 424– 470; c) D. Enders, T. Balensiefer, Acc. Chem. Res. 2004, 37, 534.

[4] a) For selected reviews on Stetter reaction, see: S. R. Yetra, A. Patra, A. T. Biju, Synthesis 2015, 47, 1357; b) J. Read de Alaniz, T. Rovis, Synlett 2009, 1189; c) T. Rovis, Chem. Lett. 2008, 37, 2; d) H. Stetter, Angew. Chem. Int. Ed. Engl. 1976, 15, 639; Angew. Chem. 1976, 88, 695.

[5] a) For reviews, see: R. S. Menon, A. T. Biju, V. Nair, Chem. Soc. Rev. 2015, 44, 5040; b) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, Chem. Soc. Rev. 2011, 40, 5336; for the pioneering reports, see: c) C. Burstein, F. Glorius, Angew. Chem. Int. Ed. 2004, 43, 6205;
Angew. Chem. 2004, 116, 6331; d) S. S. Sohn, E. L. Rosen, J. W. Bode, J. Am. Chem. Soc. 2004, 126, 14370; e) A. Chan, K. A. Scheidt, Org. Lett. 2005, 7, 905; f) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, J. Am. Chem. Soc. 2006, 128, 8736.

[6] a) For reviews on a,b-unsaturated acylazoliums, see: S. Mondal, S. R. Yetra, S. Mukherjee, A. T. Biju, Acc. Chem. Res. 2019, 52, 425; b) C. Zhang, J. F. Hooper, D. W. Lupton, ACS Catal. 2017, 7, 2583; for leading reports, see: c) S. De Sarkar, A. Studer, Angew. Chem. Int. Ed. 2010, 49, 9266; Angew. Chem. 2010, 122, 9452; d) S. J. Ryan, L. Candish, D. W. Lupton, J. Am. Chem. Soc. 2009, 131, 14176; e) J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, J. Am. Chem. Soc. 2010, 132, 8810;
f) K. Zeitler, Org. Lett. 2006, 8, 637.

[7] K. Y.-K. Chow, J. W. Bode, J. Am. Chem. Soc. 2004, 126, 8126.

[8] a) N. T. Reynolds, J. Read de Alaniz, T. Rovis, J. Am. Chem. Soc. 2004, 126, 9518; b) N. T. Reynolds, T. Rovis, J. Am. Chem. Soc. 2005, 127, 16406.

[9] a) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, Org. Lett. 2008, 10, 277; b) H.-M. Zhang, Z.-H. Gao, S. Ye, Org. Lett. 2014, 16, 3079.

[10] a) M. He, J. R. Struble, J. W. Bode, J. Am. Chem. Soc. 2006, 128, 8418; b) Z. Fu, H. Sun, S. Chen, B. Tiwari, G. Li, Y. R. Chi, Chem. Commun. 2013, 49, 261.

[11] A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra, K. A. Scheidt, J. Am. Chem. Soc. 2014, 136, 10589.

[12] a) X. Zhao, K. E. Ruhl, T. Rovis, Angew. Chem. Int. Ed. 2012, 51, 12330; Angew. Chem. 2012, 124, 12496; b) J. Mo, R. Yang, X. Chen, B. Tiwari, Y. R. Chi, Org. Lett. 2013, 15, 50; c) Y. Kawanaka, E. M. Phillips, K. A. Scheidt, J. Am. Chem. Soc. 2009, 131, 18028.

[13] a) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, Org. Lett. 2012, 14, 2154; b) S. Chen, L. Hao, Y. Zhang, B. Tiwari, Y. R. Chi, Org. Lett. 2013, 15, 5822.

[14] L.-T. Shen, P.-L. Shao, S. Ye, Adv. Synth. Catal. 2011, 353, 1943.

[15] a) J. Mo, X. Chen, Y. R. Chi, J. Am. Chem. Soc. 2012, 134, 8810; see also: b) X. Chen, S. Yang, B.-A. Song, Y. R. Chi, Angew. Chem. Int. Ed. 2013, 52, 11134; Angew. Chem. 2013, 125, 11340.

[16] a) K. S. Halskov, T. K. Johansen, R. L. Davis, M. Steurer, F. Jensen, K. A. Jørgensen, J. Am. Chem. Soc. 2012, 134, 12943; b) A. Dieckmann, M. Breugst, K. N. Houk, J. Am. Chem. Soc. 2013, 135, 3237; c) G. Bertuzzi, M. K. Thøgersen, M. Giardinetti, A. Vidal-Albalat, A. Simon, K. N. Houk, K. A. Jørgensen, J. Am. Chem. Soc. 2019, 141, 3288.

[17] For details, see the Supporting Information.

[18] CCDC 1920209 (3q) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[19] For a related observation on NHC-catalyzed annulation of salicylaldehydes with **2a**, see: X. Chen, H. Wang, K. Doitomi, C. Y. Ooi, P. Zheng, W. Liu, H. Guo, S. Yang, B.-A. Song, H. Hirao, Y. R. Chi, Nat. Commun. 2017, 8, 15598.

[20] a) For the isolation of NHC-aldehyde adducts, see: C. J. Collett, R. S. Massey, J. E. Taylor, O. R. Maguire, A. C. O'Donoghue, A. D. Smith, Angew. Chem. Int. Ed. 2015, 54, 6887; Angew. Chem. 2015, 127, 6991; b) C. J. Collett, R. S. Massey, O. R. Maguire, A. S. Batsanov, A. C. O'Donoghue, A. D. Smith, Chem. Sci. 2013, 4, 1514.

[21] 1H NMR analysis of 1:1:1:1 mixture of **1a**, **4**, Cs_2CO_3 and **5** under the present reaction conditions showed two broad signals in the downfield region (>9.0 ppm) shedding light on acylazolium **C** or the aza-trienol **D**.

[22] a) All calculations were carried out at the SMDChloroform/B3LYP/6-31G(d,p) level of theory; b) M. J. Frisch, et al. Gaussian 09, Revision C.01; Gaussian, Inc.: Wallingford, CT, 2013; c) Further computational details and coordinates of optimized geometries are given in the Supporting Information.

[23] M. Paul, M. Breugst, J.-M. Neudçrfl, R. B. Sunoj, A. Berkessel, J. Am. Chem. Soc. 2016, 138, 5044.

[24] While this manuscript was under review, Jin and co-workers demonstrated a closely related NHC-catalyzed reaction of nitrogen-containing heterocyclic aldehydes and activated ketones for the enantioselective synthesis of multi-functionalized cyclic N,O-acetals. For details, see: Y. Liu, G. Luo, X. Yang, S. Jiang, W. Xue, Y. R. Chi, Z. Jin, Angew. Chem. Int. Ed. 2019, 58, https://doi.org/10.1002/anie.201912160; Angew. Chem. 2019, 131, https://doi.org/10.1002/ange.201912160.