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N-Heterocyclic carbene (NHC)-catalyzed intramolecular benzoin condensation–oxidation†

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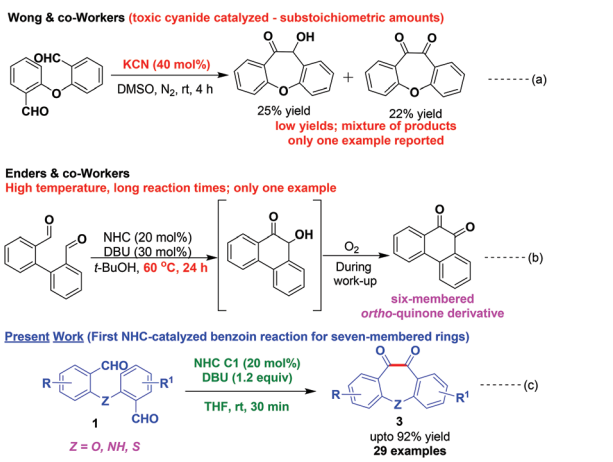
NHC-Catalyzed intramolecular benzoin condensation–oxidation is developed for the expedient synthesis of diverse cyclic 1,2-diketones incorporated in dibenzo-fused seven-membered heterocycles in good to excellent yields, under ambient conditions. The presented carbene-catalyzed transformation appears to proceed through the benzoin intermediate followed by aerobic oxidation.

N-Heterocyclic carbene (NHC)-organocatalyzed umpolung reactions have gained considerable attention for C–C bond formation involving various potentially useful unconventional organic transformations for synthesizing diverse building blocks and also have been elegantly applied in target-oriented organic syntheses.[1] Among these, NHC-catalyzed benzoin condensation is the earliest and a well-established transformation.[1,2] The intramolecular benzoin condensation is of particular interest to access carbo- and heterocycles.[2,3] However, NHC-catalyzed intramolecular benzoin condensation is mostly limited to constructing more feasible five-membered and six-membered rings while the construction of seven-membered rings is not known, to best of our knowledge. Continuing our interest in NHC catalysis[4] and the synthesis of fused heterocyclic systems,[5] we became interested to construct dibenzo-fused seven-membered heterocycles by using intramolecular benzoin condensation as a strategy. Dibenzo-fused seven-membered heterocycles such as dibenzoxepines, dibenzothiepines and dibenzazepines constitute valuable therapeutics that are useful in the treatment of several diseases and possess a wide range of biological profiles.[6–9]

On the other hand, 1,2-diketones are important precursors that are useful in the straightforward synthesis of biologically valuable heterocycles such as imidazoles, pyrazines and quinoxalines.[10] The conventional approaches to access 1,2-diketones include the oxidation of alkenes, alkynes, α-hydroxyketones and 1,2-diols.[11] Although there exist several methods to access 1,2-diketones, those methods rely on the use of transition metal compounds, toxic reagents, stoichiometric oxidants, long reaction times, harsh reaction conditions, and lengthy synthetic protocols.[11–13] Besides, however, those reported approaches are limited to access acyclic 1,2-diketones while straightforward methods to access cyclic 1,2-diketones are very scarce. Wong and co-workers described a cyanide catalyzed intramolecular benzoin reaction for the synthesis of the dibenzo[*b*,*f*]oxepine-10,11-dione derivative (22% yield) along with the benzoin derivative (25% yield). This method provides very low yields and uses substoichiometric amounts of toxic cyanide (Scheme 1a).[13*a*] Enders and co-workers reported an example of the α-diketone product by employing aromatic dialdehyde under NHC catalysis and obtained α-hydroxy ketone. During the work-up process, the product underwent oxidation to obtain the six-membered α-diketone, an *ortho*-quinone derivative (Scheme 1b).[13*b*]



Scheme 1 Prior work and present work.

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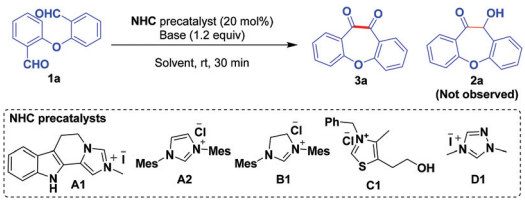
Furthermore, it is a challenging task to access cyclic 1,2-diketones incorporated in medium-sized rings such as seven-membered rings under mild conditions obviating the use of transition metal compounds/toxic reagents. Herein, we describe an NHC-catalyzed intramolecular benzoin condensation–oxidation protocol to access cyclic 1,2-diketones incorporated in dibenzo-fused seven-membered heterocycles (Scheme 1c).

We reasoned that an intramolecular benzoin condensation between two aldehyde groups could provide cyclic α-sec-hydroxyketone that could undergo oxidation of the secondary hydroxyl group to eventually furnish the cyclic 1,2-diketone functionality. We envisaged that an intramolecular benzoin reaction of readily available 2,2′-oxydibenzaldehyde **1a**, by using NHC catalysis, would provide access to a dibenzo-fused oxepine core. Accordingly, **1a** was subjected to NHC catalysis using a readily accessible NHC precatalyst **A1** [5f] in the presence of DBU as a base. Interestingly, under the reaction conditions, we isolated the corresponding cyclic 1,2-diketone dibenzo[*b*,*f*] oxepine-10,11-dione **3a**, and the benzoin derivative **2a** was not observed (Table 1, entry 1). In order to obtain higher yields of the cyclic 1,2-diketone **3a**, we performed an optimization assay using different NHC precatalysts, bases and reaction conditions.

The commercially available imidazolium-based NHC precatalyst **A2** delivered the cyclic 1,2-diketone **3a** in a high yield (Table 1, entry 2). The imidazolinium-based NHC precatalyst **B1** provided a moderate yield of **3a** (Table 1, entry 3). The thiazolium-based NHC precatalyst **C1** was found to be a superior catalyst to give **3a** in an excellent yield (Table 1, entry 4). It was reported that thiazolium-derived NHCs are efficient for certain benzoin condensation reactions.[14] Note that with **C1** the reaction could be scaled up to the gram scale in a high yield. The triazolium-based NHC precatalyst **D1** was also effective for this study to afford **3a**, albeit in a moderate yield (Table 1, entry 5).

Table 1 Optimization study[a]

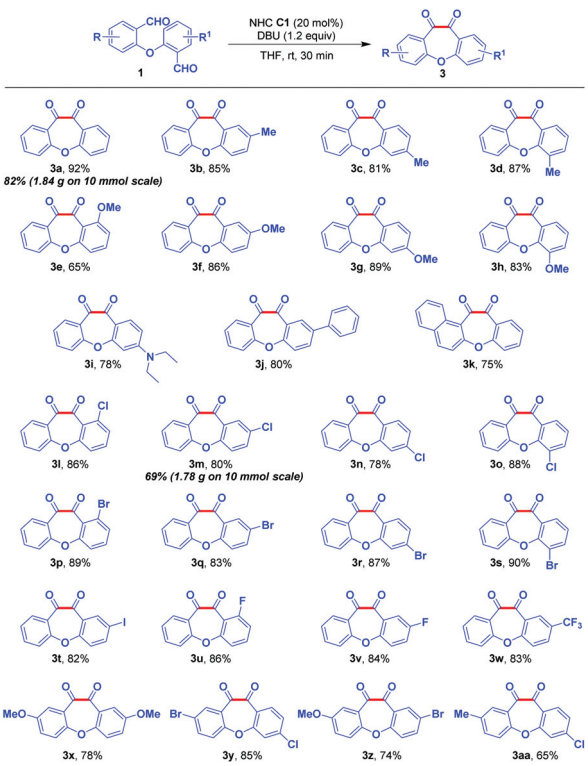


Entry	NHC precatalyst	Base	Solvent	%Yield of **3a**[b]
1	**A1**	DBU	THF	42
2	**A2**	DBU	THF	85
3	**B1**	DBU	THF	48
4	**C1**	**DBU**	**THF**	**92 (82%)**[c]
5	**D1**	DBU	THF	58
6	**C1**	K_2CO_3	THF	45
7	**C1**	NaH	THF	35
8	**C1**	DBU	DMSO	85
9	**C1**	DBU	EtOAc	31

[a] Reaction conditions: **1a** (0.25 mmol), NHC precatalyst (20 mol%), base (0.3 mmol), solvent (2.5 mL). [b] Yields are of isolated products. [c] 82% yield (1.84 g) on a 10 mmol scale.

The use of other bases, instead of DBU, such as K_2CO_3 and NaH, proved to be less efficient in this transformation (Table 1, entries 6 and 7). Probably, DBU combines well in THF and also as a strong base it promotes efficient conversion of the NHC pre-catalyst to NHC. Furthermore, DBU may also enhance the oxidation of the corresponding benzoin intermediate to the diketone product. We also performed the reaction of **1a** in various solvents under NHC catalysis conditions (Table 1, entries 8 and 9) and THF was found to be the best medium to provide the desired product **3a** in an excellent yield (Table 1, entry 4). Product **3a** was not observed when we conducted the reaction of **1a** in the absence of NHC or a base. These results suggest the essentiality of an NHC precatalyst and a base for this transformation (see the ESI† for an extensive optimization survey).

By choosing the optimal conditions from Table 1 (entry 4), we intended to examine the generality of this transformation. We subjected 2,2′-oxydibenzaldehydes, bearing EDGs on one of the benzene rings at different positions, to the optimized NHC catalysis conditions to give the corresponding products **3b–i** in high yields (Scheme 2). The dialdehydes comprising the phenyl and naphthyl groups are also well tolerated for this transformation to afford the corresponding diketones **3j** and **3k** in 80% and 75% yields, respectively (Scheme 2). The dialdehydes, having halogen substituents, worked efficiently to provide the corresponding diketones **3l–v** in good to excellent yields (Scheme 2). The dialdehyde bearing an EWG such as



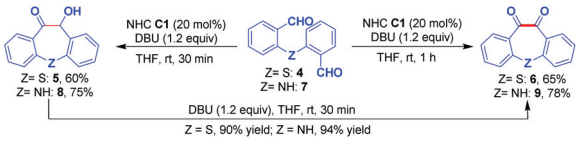
Scheme 2 Scope of the NHC-catalyzed intramolecular benzoin condensation–oxidation.

CF_3 also served well in this transformation to afford the respective cyclic 1,2-diketone **3w** in 83% yield (Scheme 2). However, our efforts to access the dialdehyde starting material bearing a strong EWG such as NO_2 using an S_NAr reaction were not successful. We were also interested in investigating the scope of dialdehyde **1** bearing substituents on both the benzene rings (Scheme 2). The dialdehyde, bearing EDGs on the benzene rings, served as a good substrate to deliver the corresponding diketone **3x** in 78% yield. The dialdehyde containing halo substituents such as –Br and –Cl on the benzene rings gave the corresponding diketone **3y** in 85% yield. The dialdehydes bearing an EDG and halo groups on the benzene rings afforded the corresponding products **3z** and **3aa** in good yields.

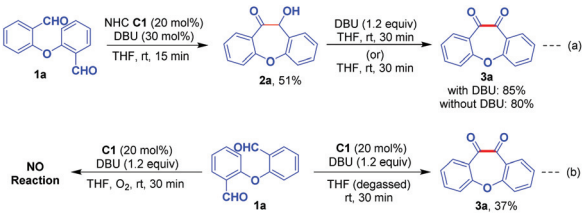
Later, we thought of examining the scope of the heteroatom connection in dialdehyde **1**. We performed the reaction of 2,2′-thiodibenzaldehyde **4** under the optimized NHC catalysis conditions and observed the formation of the corresponding benzoin derivative **5** in 60% yield instead of the expected dibenzo[*b*,*f*]thiepine-10,11-dione **6** (Scheme 3, **LHS**). When the reaction time was prolonged to 1 hour, the 1,2-diketone product **6** was formed in 65% yield (Scheme 3, **RHS**). We also treated benzoin **5** with DBU (1.2 equiv.), in the absence of NHC, in THF at room temperature in open air for 30 minutes to furnish **6** in 90% yield (Scheme 3). We then performed the reaction of 2,2′-azanediyldibenzaldehyde **7** under the optimal NHC-catalyzed conditions and isolated the corresponding benzoin **8** in 75% yield (Scheme 3, **LHS**). Prolonging the reaction time to 1 hour provided the cyclic 1,2-diketone 5*H*-dibenzo[*b*,*f*]azepine-10,11-dione **9** in 78% yield (Scheme 3, **RHS**). The reaction of **8** with DBU in open air, in the absence of NHC, furnished **9** in an excellent yield (Scheme 3).

To probe the reaction mechanism of the present transformation, we decided to isolate the benzoin intermediate **2a**. We treated **1a** with the NHC **C1** (20 mol%) in the presence of DBU (1.2 equiv.) in THF and stirred the reaction mixture for 15 minutes. However, we failed to obtain the corresponding benzoin intermediate **2a**. When the reaction was conducted with a reduced amount of DBU (30 mol%), we isolated the benzoin derivative **2a** in 51% yield (Scheme 4).

These results indicate that the sequential transformation proceeds through the benzoin intermediate (Schemes 3 and 4). Subsequently, the benzoin derivative **2a** was treated with DBU (1.2 equiv.) in THF under an open air atmosphere to obtain the diketone **3a** in 85% yield. Note that in the absence of DBU also the desired diketone **3a** was observed in 80% yield (Scheme 4a). The reaction of **1a** with NHC was not successful under an oxygen/open air atmosphere (Scheme 4b, **LHS**),



Scheme 3 NHC-catalyzed intramolecular benzoin condensation–oxidation of **4**/**7**.

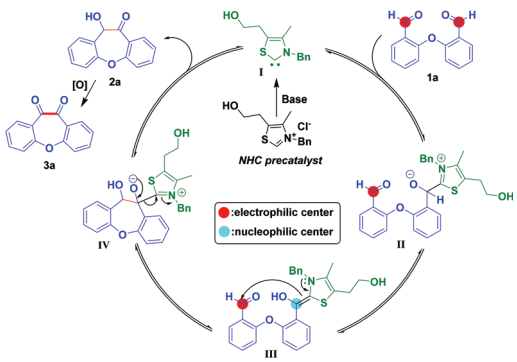


Scheme 4 Control experiments.

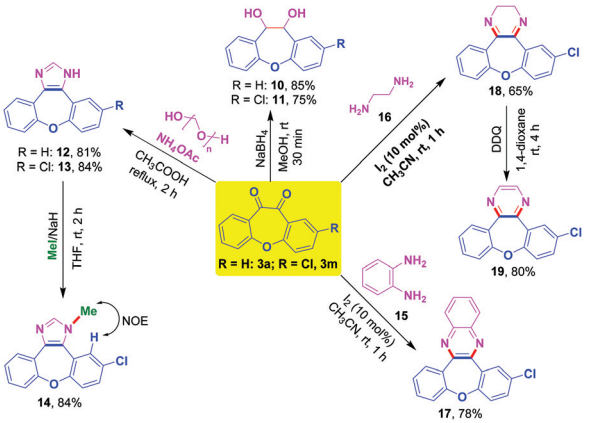
which may suggest that the reaction does not proceed through intramolecular oxidative coupling of the dialdehyde. By using degassed THF, under an argon atmosphere, the yield of **3a** drastically dropped, which may suggest that the oxidation of the benzoin intermediate is assisted by the dissolved oxygen in THF[15] (Scheme 4b, **RHS**). It turns out that the first step, *i.e.* benzoin condensation needs an inert atmosphere;[2] subsequently, the secondary hydroxyl group undergoes oxidation with molecular oxygen dissolved in the reaction solvent.[15]

From the control experiments and previous literature reports,[2] we postulated a plausible mechanism for the NHC-catalyzed intramolecular benzoin condensation–oxidation to access dibenzo[*b*,*f*]oxepine-10,11-dione derivatives (Scheme 5). The catalytic cycle could be initiated by the abstraction of the proton from carbene precursor **C1** to generate the free NHC **I**, which would add to one of the electrophilic carbonyl carbons of dialdehyde **1a** to give intermediate **II**. Subsequently, a proton shift might take place on intermediate **II** to lead to the formation of the Breslow intermediate **III**. The Breslow intermediate's nucleophilic carbon would intramolecularly add to the other electrophilic carbonyl centre of aldehyde to provide intermediate **IV**. Expulsion of NHC would take place from intermediate **IV** to provide the corresponding benzoin derivative **2a**. The benzoin derivative would undergo an aerial oxidation[13b] process to furnish the desired diketone derivative **3a**.

To demonstrate the synthetic utility of the cyclic 1,2-diketones, we subjected the 1,2-diketone functionality to various organic transformations. The cyclic 1,2-diketones **3a** and **3m** were treated with sodium borohydride to give the corres-



Scheme 5 Plausible mechanism.



Scheme 6 Synthetic transformation of the cyclic 1,2-diketones **3a** and **3m**.

ponding 1,2-diols **10** and **11**, respectively, in high yields with excellent diastereoselectivity (Scheme 6). The cyclic 1,2-diketones **3a** and **3m** were treated with ammonium acetate and paraformaldehyde to furnish the corresponding imidazole-fused dibenzoxepine derivatives **12** and **13**, respectively, in very good yields (Scheme 6). The –NH group of imidazole **13** was methylated using methyl iodide to give compound **14** (Scheme 6). The tetracyclic compounds **12–14** can be considered as the imidazole congeners of asenapine,[7] which is used as an antipsychotic drug. Also these kinds of imidazole-fused dibenzoxepine derivatives were shown to have anti-inflammatory activities.[16]

To further demonstrate the synthetic utility of the cyclic 1,2-diketones, **3m** was treated with *o*-phenylenediamine **15** in the presence of 10 mol% of I_2 in CH_3CN at room temperature for 1 h to afford 7-chlorodibenzo[2,3 : 6,7]oxepino[4,5-*b*]quinoxaline **17** in 78% yield (Scheme 6). We also performed the reaction of **3m** and ethylenediamine **16** in the presence of 10 mol% of I_2 in CH_3CN at room temperature for 1 h to furnish the respective 6-chloro-2,3-dihydrodibenzo[2,3 : 6,7] oxepino[4,5-*b*]pyrazine **18** in 65% yield (Scheme 6). Subsequently, compound **18** was subjected to DDQ oxidation to furnish 6-chlorodibenzo[2,3 : 6,7]oxepino[4,5-*b*]pyrazine **19** in 80% yield (Scheme 6).

In summary, we have developed and described NHC-catalyzed intramolecular benzoin condensation–oxidation in one pot to synthesize diverse cyclic 1,2-diketones incorporated in dibenzo-fused seven-membered heterocycles, under very mild conditions, in good to excellent yields. Post-synthetic modifications of the thus generated 1,2-diketone functionality of dibenzo[*b*,*f*]oxepines allow further extension the diversity of these valuable cores including the synthesis of the imidazole congeners of an antipsychotic drug, asenapine.

Conflicts of interest

There are no conflicts to declare.

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