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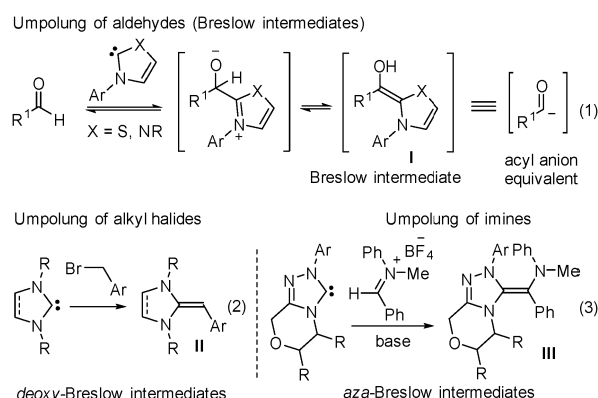
# Reaction of N-heterocyclic carbenes with chalcones leading to the synthesis of deoxy-Breslow intermediates in their oxidized form†

Anup Bhunia,<sup>a</sup> Shridhar Thorat,<sup>b</sup> Rajesh G. Gonnade<sup>b</sup> and Akkattu T. Biju\*<sup>a</sup>

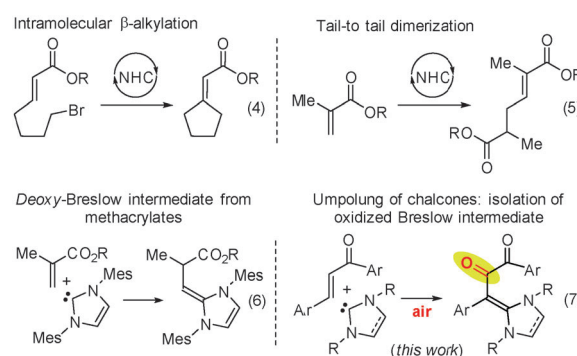
The synthesis of deoxy-Breslow intermediates in their oxidized form has been developed *via* the reaction of N-heterocyclic carbenes (NHCs) with chalcones. Moreover, the initial tetrahedral adduct formed from the 1,4-addition of NHCs to chalcones is also isolated.

NHCs have found various applications as versatile catalysts in several organic transformations.<sup>1,2</sup> One of the significant modes of action of NHCs in organocatalysis is the umpolung of aldehydes. The resultant nucleophilic acyl anion equivalents (Breslow intermediates)<sup>3</sup> can add to electrophiles including aldehydes and ketones (benzoin reaction),<sup>4</sup> imines,<sup>5</sup> Michael acceptors (Stetter reaction)<sup>6</sup> and even unactivated C–C multiple bonds (Scheme 1, eqn (1)).<sup>7</sup> Moreover, the addition of NHCs to enals can generate the extended Breslow intermediates (homoenolates).<sup>8</sup> Although Breslow was not able to isolate the key intermediate,<sup>3</sup> the existence of **I** was suggested by the isolation of the protected enaminol by Nair,<sup>9</sup> and the characterization of the key intermediates was reported by Berkessel.<sup>10</sup> Surprisingly, however, the umpolung triggered by NHCs is mostly limited to aldehydes, and the use of other electrophiles has received only limited attention. Recently, the umpolung of alkyl halides leading to the isolation of deoxy-Breslow intermediates **II** was reported by the groups of Jacobi von Wangelin<sup>11</sup> and Mayr (eqn (2)).<sup>12</sup> Moreover, the isolation of aza-Breslow intermediates **III** by the reaction of NHCs with iminium salts was disclosed by Rovis (eqn (3)).<sup>13</sup>

In 2006, Fu reported an unprecedented NHC-catalyzed umpolung of Michael acceptors for the intramolecular  $\beta$ -alkylation of  $\alpha,\beta$ -unsaturated esters (Scheme 2, eqn (4)).<sup>14</sup> Subsequently, Matsuoka and Glorius independently disclosed the umpolung of methacrylates for efficient tail-to-tail dimerization reactions (eqn (5)).<sup>15,16</sup> Moreover,



Scheme 1 Umpolung using NHCs.



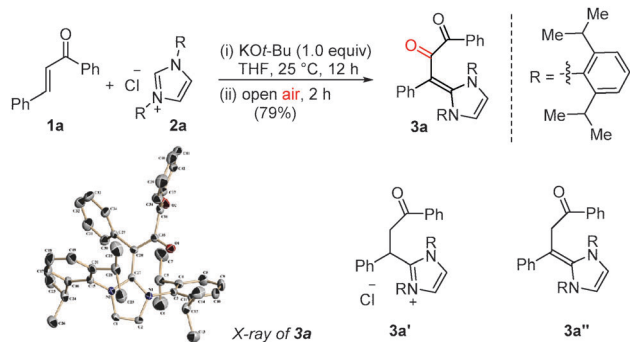
Scheme 2 Umpolung of Michael acceptors using NHCs.

the group of Glorius isolated the tetrahedral intermediate formed from the reaction of an NHC and methacrylate.<sup>16</sup> Interestingly, Zhang and Chen very recently uncovered the isolation of deoxy-Breslow intermediates formed from NHC-methacrylate reaction (eqn (6)).<sup>17</sup> However, the umpolung of Michael acceptors having a  $\beta$ -substituent has received only scant attention,<sup>18</sup> and the umpolung of chalcones, to the best of our knowledge, is not reported. Herein, we report reaction of NHCs with chalcones leading to the isolation of deoxy-Breslow intermediates in their oxidized form (eqn (7)). It is

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† Electronic supplementary information (ESI) available: Details of the experimental procedure, characterization data of all compounds, and single crystal X-ray data of compounds **3a**, **4a**, **4b**, **5a** and **7a**. CCDC 1061964 to 1061968. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc05800g



Scheme 3 Synthesis of the oxidized form of deoxy-Breslow intermediates.

important to note, however, in this context that chalcones are widely used Michael acceptors for acyl anions<sup>19</sup> and homoenolates<sup>20</sup> in NHC-catalysis.

The present study commenced with the treatment of chalcone **1a** with the imidazolium salt **2a** in the presence of KO<sup>t</sup>Bu as the base in THF at 25 °C. Stirring the reaction mixture under argon for 12 h followed by stirring in an open atmosphere for 2 h afforded the oxidized form of deoxy-Breslow intermediate **3a** in 79% yield (Scheme 3).<sup>21</sup> Under these conditions, tetrahedral intermediate **3a'** or deoxy-Breslow intermediate **3a''** (formed from the conjugate addition of NHCs derived from **2a** to **1a**) was not isolated. The structure of **3a** was unequivocally confirmed by single crystal X-ray analysis.<sup>22</sup> Diketone **3a** was possibly formed by the aerobic oxidation of the NHC-chalcone adduct under basic conditions.

In addition to the use of **2a** in this reaction, treatment of chalcone **1a** with the carbene generated from *N*-mesityl imidazolium salt **2b** (IMes-HCl) afforded diketone derivative **4a** in 81% yield (Scheme 4). Moreover, employing the carbene generated from **2c** (SIMes-HCl) in this reaction furnished **4b** in 42% yield. The structures of **4a** and **4b** were confirmed by single crystal X-ray analysis.<sup>22</sup>

We then examined the generality of this reaction with substituted chalcones (Table 1). Gratifyingly, various chalcones bearing electron-releasing and electron-withdrawing groups at the 4-position of the β-aryl ring are tolerated well in the reaction with the NHC generated from **2a**, and in all cases the oxidized form of the deoxy-Breslow intermediate was isolated in moderate to good yields (**3b–3e**). Moreover, chalcones with heteroaryl substitution at the β-position furnished the corresponding diketones in moderate yields (**3f, 3g**).<sup>23</sup> Besides, substitution is tolerated at the benzoyl moiety of a chalcone, and even a pyridine moiety did not create any problems in the reactivity. In all cases, the desired product was synthesized in moderate to good yields (**3h–3j**).

A tentative mechanism for the formation of the oxidized form of deoxy-Breslow intermediates is shown in Scheme 5.

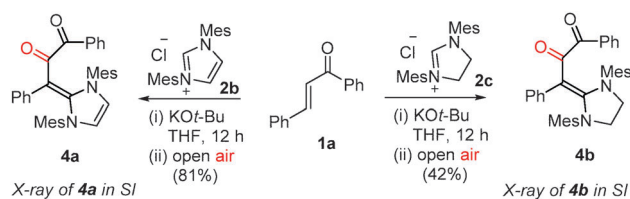
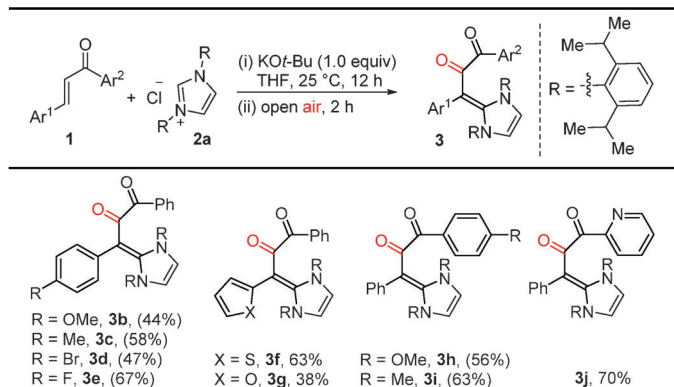
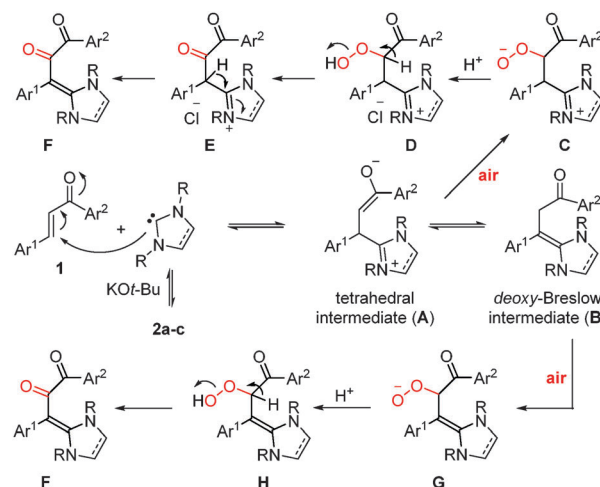
Scheme 4 Oxidized form of deoxy-Breslow intermediates from **2b** and **2c**.

Table 1 Scope of the synthesis of oxidized deoxy-Breslow intermediates



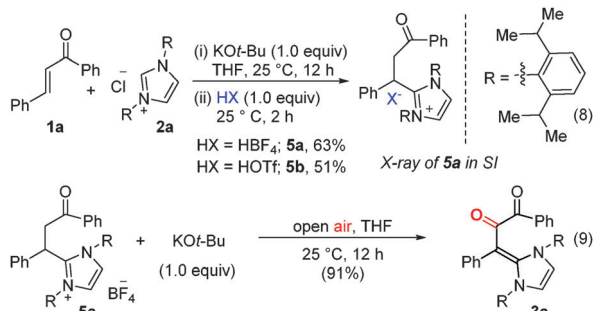
General conditions: **1** (0.5 mmol), **2a** (0.5 mmol), KO<sup>t</sup>Bu (0.5 mmol), THF (3.0 mL), 25 °C, stirring for 12 h under an argon atmosphere followed by stirring for 2 h in open air, yields of the isolated product are given.



Scheme 5 Proposed mechanism of the reaction.

Likely, the reaction began with the conjugate addition of the NHC generated from **2a–c** to chalcone **1** to generate azolium enolate **A**. This intermediate undergoes a proton transfer to form enamine intermediate **B**. The steps leading to the generation of **A** and **B** appear to be reversible. In an irreversible step, **A** captures a molecule of oxygen to generate α-hydroperoxy ketone anion **C**, which is subsequently protonated to generate α-hydroperoxy ketone **D**. Intermediate **D** undergoes an elimination of a molecule of water under basic conditions to form azolium diketone **E**. Deprotonation of intermediate **E** results in the formation of the oxidized form of deoxy-Breslow intermediate **F**.<sup>24</sup> Alternatively, intermediate **B** under basic conditions can react with molecular oxygen to form α-hydroperoxy ketone anion **G**, which on protonation generates α-hydroperoxy ketone **H**. Elimination of a molecule of water from intermediate **H** affords **F**. Notably, the aerobic oxidation of ketones at the α-position leading to the synthesis of diketones using air as the sole oxidant under basic conditions is well demonstrated in the literature.<sup>25</sup>

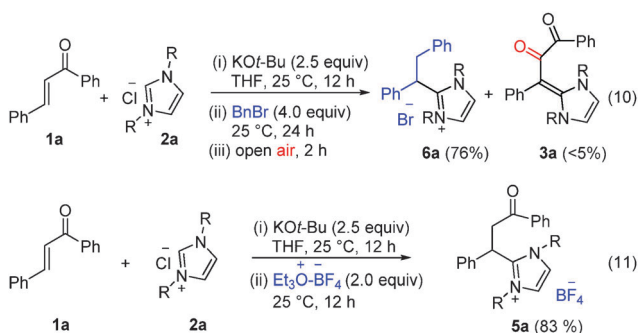
To shed light on this unique transformation, we have carried out a series of mechanistic experiments. Efforts to isolate either



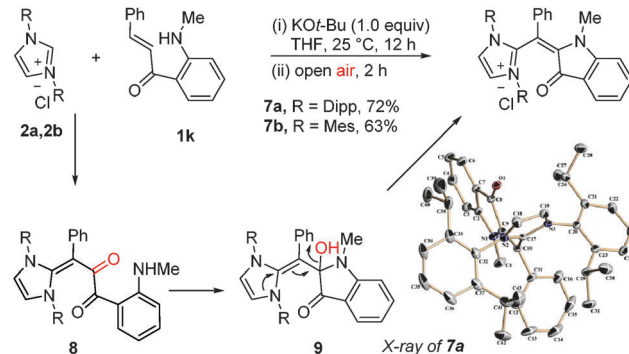
Scheme 6 Mechanistic experiments.

the keto form of **A** or intermediate **B** were unsuccessful in our hands. Moreover, given the importance of the basic medium in the aerobic oxidation to form diketone **3**, experiments were performed using Brønsted acid quenching instead of exposure to air. Thus, the reaction of **1a** with the NHC generated from **2a** using  $\text{KO}^t\text{-Bu}$  for 12 h followed by quenching the reaction mixture using  $\text{HBF}_4$  resulted in the formation of the salt **5a** in 63% yield (Scheme 6, eqn (8)). Similar results were obtained by quenching the reaction with  $\text{TfOH}$ , leading to the isolation of triflate salt **5b** in 51% yield. The salts **5a** and **5b** correspond to the keto form of the tetrahedral intermediate (**A**) formed by the addition of NHCs to chalcones. The structure of **5a** was confirmed by single crystal X-ray analysis.<sup>22</sup> Interestingly, treatment of the salt **5a** with  $\text{KO}^t\text{-Bu}$  in open air resulted in the formation of the oxidized form of deoxy-Breslow intermediate **3a** in 91% yield (eqn (9)). These studies indicate the intermediacy of the tetrahedral intermediate **A** in the formation of the diketone **3a**. This also sheds light on the reversible nature of the generation of the tetrahedral intermediate **A** and deoxy-Breslow intermediate **B**.

Given the nucleophilic nature of enolate intermediate **A** and deoxy-Breslow intermediate **B** formed by the initial addition of NHCs to chalcones (Scheme 5), we have performed experiments using external electrophiles. Treatment of chalcone **1a** with imidazolium salt **2a** in the presence of  $\text{KO}^t\text{-Bu}$  and stirring the reaction mixture under argon for 12 h followed by addition of benzyl bromide and stirring under argon for 24 h and stirring in an open atmosphere for an additional 2 h afforded imidazolium salt **6a** in 76% yield along with traces of **3a** (Scheme 7, eqn (10)). The isolation of **6a** under the present conditions



Scheme 7 Electrophile trapping experiments.



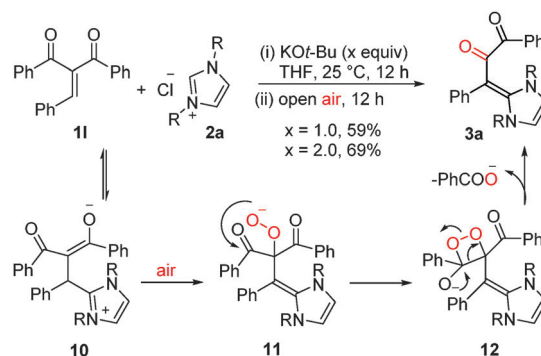
Scheme 8 Reaction of NHCs with 2'-aminochalcones.

sheds light on the reversibility of the formation of intermediates **A** and **B** from chalcones and NHCs. Moreover, we have performed the reaction in the presence of Meerwein's reagent, anticipating the alkylation of tetrahedral intermediate **A**. Surprisingly, this reaction furnished imidazolium salt **5a** in 83% yield (eqn (11)).

Gratifyingly, when the reaction of the NHC generated from **2a** was carried out using 2'-aminochalcone derivative **1k**, the initially formed oxidized form of the deoxy-Breslow intermediate (**8**) underwent an intramolecular cyclization reaction, leading to the formation of a 2-benzylidene 1-methylindoline 3-one derivative having an imidazolium salt (**7a**) in 72% yield proceeding *via* carbinol intermediate **9** (Scheme 8). The structure of **7a** was confirmed by single crystal X-ray analysis.<sup>22</sup> Moreover, the reaction worked well with the NHC generated from **2b**, affording the corresponding product **7b** in 63% yield.

We also examined the reaction of NHCs with  $\alpha$ -substituted electron deficient chalcones. Interestingly, the reaction of  $\alpha$ -benzoyl chalcone **1l** with the NHC derived from **2a** using  $\text{KO}^t\text{-Bu}$  as the base resulted in the formation of the oxidized form of deoxy-Breslow intermediate **3a** in 59% yield under the standard conditions (Scheme 9). With 2.0 equiv. of  $\text{KO}^t\text{-Bu}$  the yield was improved to 69%. Notably, one of the benzoyl moieties was cleaved under the reaction conditions.

Mechanistically, the reaction proceeds *via* the generation of tetrahedral intermediate **10**, which on exposure to air under basic conditions forms  $\alpha$ -hydroperoxy diketone anion **11**. Intermediate **11** cyclizes to form 1,2-dioxetane intermediate **12**, which on carbon-carbon bond cleavage results in the formation of **3a**. Alternatively,

Scheme 9 Reaction of NHCs with  $\alpha$ -substituted chalcone.



enolate intermediate **10** can be transformed to the corresponding deoxy-Breslow intermediate, which can also oxidize to afford **3a**. Closely related carbon-carbon bond scission proceeding *via* the intermediacy of 1,2-dioxetane under a basic medium using air as the oxidant is known in the literature.<sup>25b,c</sup>

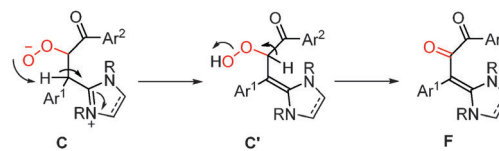
In conclusion, we have developed the reaction of NHCs with chalcones resulting in the synthesis of the oxidized form of the deoxy-Breslow intermediates. Moreover, the tetrahedral intermediate formed from the initial addition of NHCs to chalcones has been isolated. Further studies on the application of this concept in NHC-organocatalysis are currently ongoing in our laboratory.

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- Performing the reaction in air afforded **3a** in ~10% yield. However, generation of carbene from **2a** under Ar followed by stirring in open air improved the yield of **3a** to 31%.
- CCDC 1061964 (**3a**), 1061965 (**4a**), 1061966 (**4b**) 1061967 (**5a**), and 1061968 (**7a**).
- It may be mentioned that  $\beta$ -furyl substituted enone **1g** on treatment with the NHC derived from **2c** afforded diketone **4b'** in 54% yield.
- It is also likely that intermediate C undergoes an intramolecular proton transfer to generate neutral  $\alpha$ -hydroperoxy ketone C', which eliminates a molecule of water to afford diketone F.



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