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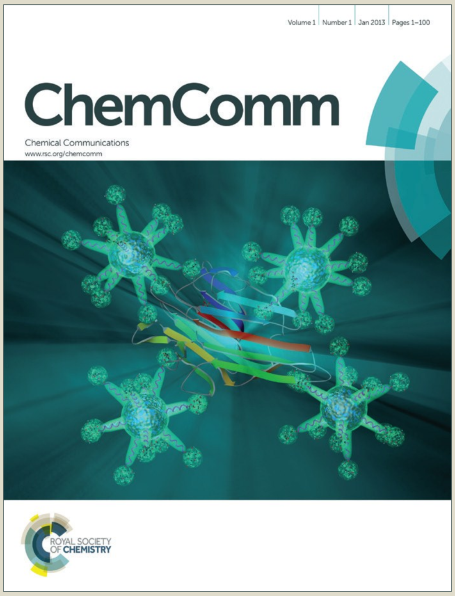

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Reaction of N-heterocyclic carbenes with chalcones leading to the synthesis of *deoxy*-Breslow intermediates in their oxidized form†

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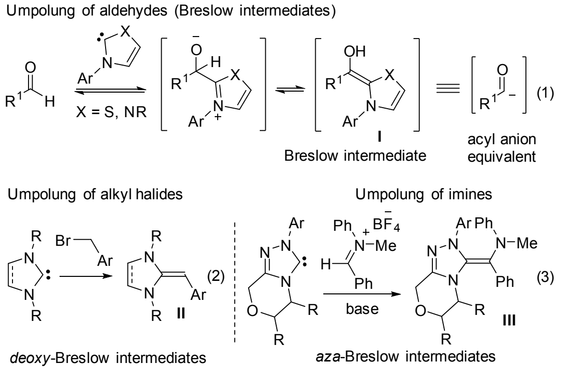
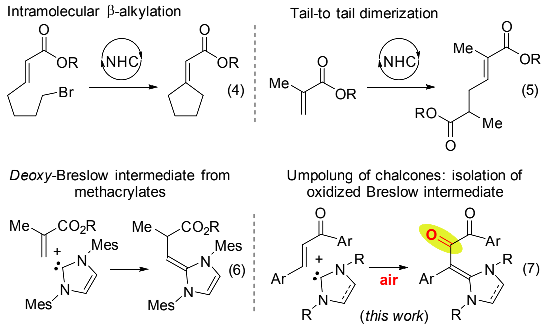
The synthesis of *deoxy*-Breslow intermediates in the oxidized form has been developed by the reaction of N-heterocyclic carbenes (NHCs) with chalcones. Moreover, the initial tetrahedral adduct formed from the 1,4-addition of NHCs to chalcones is also isolated.

NHCs have found various applications as versatile catalysts in several organic transformation.[1,2] One of the significant modes of action of NHCs in organocatalysis is the umpolung of aldehydes. The resultant nucleophilic acyl anion equivalents (Breslow intermediates)[3] can add to electrophiles including aldehydes and ketones (benzoin reaction),[4] imines,[5] Michael acceptors (Stetter reaction)[6] and even unactivated C-C multiple bonds (Scheme 1, eq 1).[7] Moreover, the addition of NHCs to enals can generate the extended Breslow intermediates (homoenolates).[8] Although Breslow was not able to isolate the key intermediate,[3] the existence of **I** was suggested by the isolation of the protected enaminol by Nair,[9] and the characterization of the key intermediates was reported by Berkessel.[10] 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[11] and Mayr (eq 2).[12] Moreover, the isolation of aza-Breslow intermediates **III** by the reaction of NHCs with iminium salts was disclosed by Rovis (eq 3).[13]



Scheme 1. Umpolung using NHCs.

In 2006, Fu reported an unprecedented NHC-catalyzed umpolung of Michael acceptors for the intramolecular β-alkylation of α,β-unsaturated esters (Scheme 2, eq 4).[14] Subsequently, Matsuoka and Glorius independently disclosed the umpolung of methacrylates for efficient tail-to-tail dimerization reactions (eq 5).[15,16] Moreover, the Glorius group isolated the tetrahedral intermediate formed from the reaction of NHC and methacrylate.[16a] Interestingly, Zhang and Chen very recently uncovered the isolation of *deoxy*-Breslow intermediates formed from NHC-methacrylate reaction (eq 6).[17] However, the umpolung of Michael acceptors having a β-substituent has received only scant attention,[18] 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 the oxidized form (eq 7). It is important to note, however, in this context that chalcones are widely used Michael acceptors for acyl anions[19] and homoenolates[20] in NHC-catalysis.



Scheme 2. Umpolung of Michael acceptors using NHC

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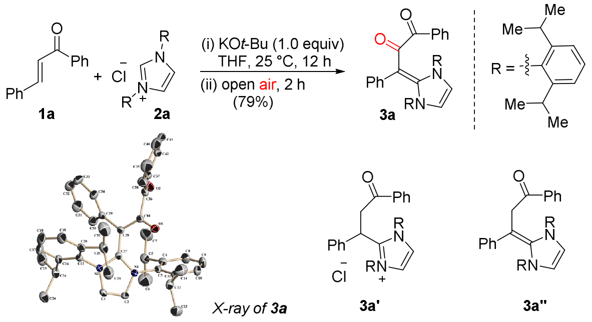
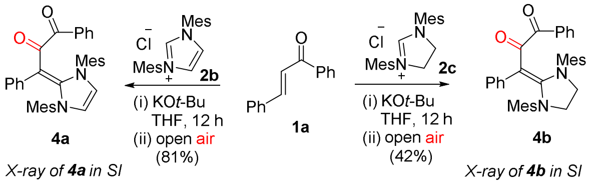
†Electronic Supplementary Information (ESI) available: Details on experimental procedure, characterization data of all compounds, and single crystal X-ray data of compounds **3a**, **4a**, **4b**, **5a** and **7a**. CCDC 1061964 to 1061968. See DOI: 10.1039/x0xx00000x

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



Scheme 3. Synthesis of oxidized form of *deoxy*-Breslow intermediate

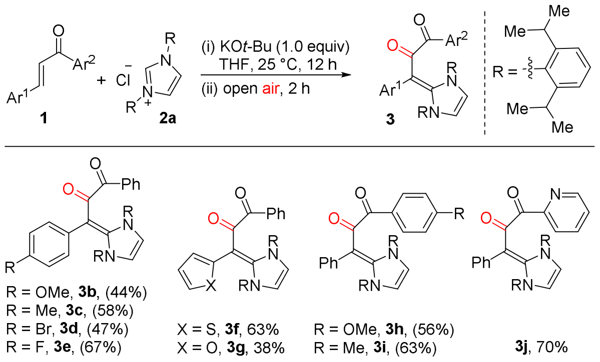
In addition to the use of **2a** in this reaction, treatment of chalcone **1a** with the carbene generated from *N*-mesityl imidazolium salt **2b** (IMes.HCl) afforded the diketone derivative **4a** in 81% yield (Scheme 4). Moreover, employing the carbene generated from **2c** (SIMes.HCl) in this reaction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



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

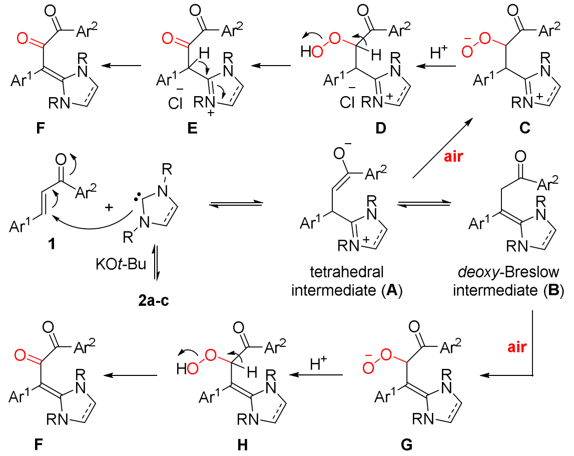
We then examined the generality of this reaction with substituted chalcones (Table 1). Gratifyingly, various chalcones bearing electron-releasing and electron-withdrawing groups at the 4-position of the β-aryl ring are tolerated well in the reaction with NHC generated from **2a**, and in all cases the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

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



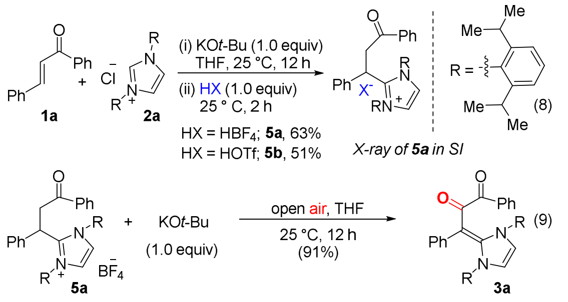
General conditions: **1** (0.5 mmol), **2a** (0.5 mmol), KO*t*-Bu (0.5 mmol), THF (3.0 mL), 25 °C, 12 h stirring under argon atmosphere followed by 2 h stirring in open air, yields of isolated product are given.

A tentative mechanism for the formation of the oxidized form of deoxy-Breslow intermediate is shown in Scheme **5**. Likely, the reaction began by the conjugate addition of the NHC generated from **2a-c** to the chalcone **1** to generate the azolium enolate **A**. This intermediate undergoes a proton transfer to form the 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 the α-hydroperoxy ketone anion **C**, which is subsequently protonated to generate the α-hydroperoxy ketone **D**. The intermediate **D** undergoes an elimination of a molecule of water under basic conditions to form the azolium diketone **E**. Deprotonation of the intermediate **E** results in the formation of the oxidized form of *deoxy*-Breslow intermediate **F**.[24] Alternatively, the intermediate **B** under basic conditions can react with molecular oxygen to form the α-hydroperoxy ketone anion **G**, which on protonation generates the α-hydroperoxy ketone **H**. Elimination of a molecule of water from intermediate **H** delivers **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.[25]



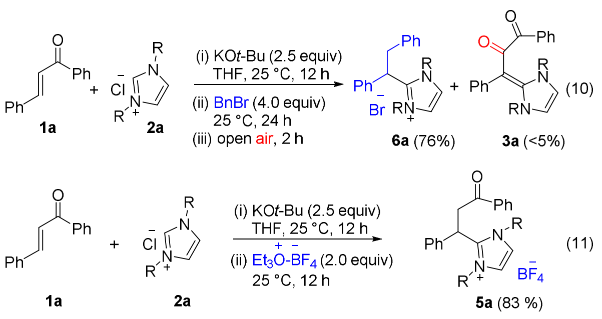
Scheme 5. Proposed mechanism of the reaction

To shed light on this unique transformation, we have carried out a series of mechanistic experiments. Efforts to isolate either the keto form of **A** or the intermediate **B** were unsuccessful in our hands. Moreover, given the importance of the basic medium in the aerobic oxidation to form the diketone **3**, experiments were performed using Brønsted acid quenching instead of exposure to air. Thus, the reaction of **1a** with NHC generated from **2a** using KO*t*-Bu for 12 h followed by quenching the reaction mixture using HBF_4 resulted in the formation of the salt **5a** in 63% yield (Scheme 6, eq 8). Similar results were obtained by quenching the reaction with TfOH leading to the isolation of the 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 NHC to chalcone. The structure of **5a** was confirmed by single crystal X-ray analysis.[22] Interestingly, treatment of the salt **5a** with KO*t*-Bu in open air resulted in the formation of the oxidized form of deoxy-Breslow intermediate **3a** in 91% yield (eq 9). These studies indicate the intermediacy of the tetrahedral intermediate **5** 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**.



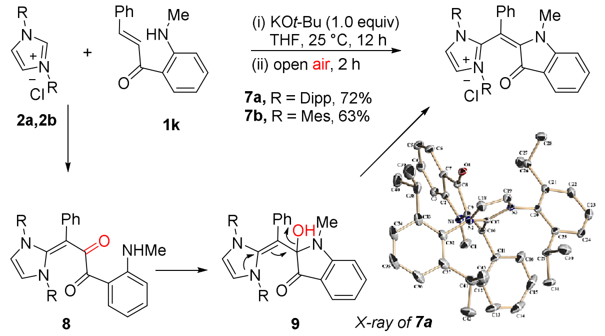
Scheme 6. Mechanistic experiments

Given the nucleophilic nature of the enolate intermediate **A** and the *deoxy*-Breslow intermediate **B** formed by the initial addition of NHC to chalcones (Scheme 5), we have performed experiments using external electrophiles. Treatment of chalcone **1a** with the imidazolium salt **2a** in the presence of KO*t*-Bu and stirring the reaction mixture under argon for 12 h followed by addition of benzyl bromide and 24 h stirring under argon and an additional 2 h stirring in open atmosphere afforded the imidazolium salt **6a** in 76% yield along with traces of **3a** (Scheme 7, eq 10). The isolation of **6a** under the present conditions 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 the tetrahedral intermediate **A**. Surprisingly, this reaction furnished the imidazolium salt **5a** in 83% yield (eq 11).



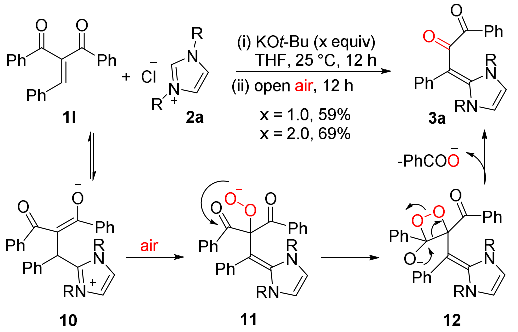
Scheme 7. Electrophile trapping experiments

Gratifyingly, when the reaction of 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 2-benzylidene 1-methylindoline 3-one derivative having an imidazolium salt (**7a**) in 72% yield proceeding via the carbinol intermediate **9** (Scheme 8). The structure of **7a** was confirmed by single crystal X-ray analysis.[22] Moreover, the reaction worked well with NHC generated from **2b** affording the corresponding product **7b** in 63% yield.



Scheme 8. Reaction of NHCs with 2'-aminochalcones

We also examined the reaction of NHCs with α-substituted electron deficient chalcones. Interestingly, the reaction of α-benzoyl chalcone **1l** with NHC derived from **2a** using KO*t*-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 KO*t*-Bu the yield was improved to 69%. Notably, one of the benzoyl moiety was cleaved under the reaction conditions.



Scheme 9. Reaction of NHCs with α-substituted chalcone

Mechanistically, the reaction proceeds via the generation of the tetrahedral intermediate **10**, which on exposure to air under basic conditions forms the α-hydroperoxy diketone anion **11**. The intermediate **11** cyclizes to form the 1,2-dioxetane intermediate **12**, which on carbon-carbon bond cleavage results in the formation of **3a**. Alternatively, the 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 basic medium using air as the oxidant is known in the literature.[25b,25c]

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

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Notes and references

1 For an overview, see (*a*) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485.

2 For recent reviews on NHCs in organocatalysis, see: (*a*) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev*., 2015, **115**, DOI: 10.1021/acs.chemrev.5b00060; (*b*) R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.,* 2015, **44**, DOI:10.1039/C5CS00162E; (*c*) J. Mahatthananchai, and J.W. Bode *Acc. Chem. Res.*, 2014, **47**, 696; (*d*) S. De Sarkar, A. Biswas, R. C. Samanta and A. Studer, *Chem. Eur. J.*, 2013, **19**, 4664; (*e*) S. J. Ryan, L. Candish and D.W. Lupton, *Chem. Soc. Rev.*, 2013, **42**, 4906; (*f*) A. Grossmann and D. Enders, *Angew. Chem. Int. Ed.*, 2012, **51**, 314; (*g*) X. Bugaut and F. Glorius, *Chem. Soc. Rev.*, 2012, **41**, 351; (*h*) J. Izquierdo, G. E. Hutson, D. T. Cohen and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2012, **51**, 11686; (*i*) D. T. Cohen and K. A. Scheidt, *Chem. Sci.*, 2012, **3**, 53; (*j*) C. E. I. Knappke, A. Imami and A. Jacobi von Wangelin, *ChemCatChem*, 2012, **4**, 937.

3 R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719.

4 For selected recent reports, see: (*a*) C. G. Goodman and J. S. Johnson, *J. Am. Chem. Soc*., 2014, **136**, 14698; (*b*) S. M. Langdon, M. M. D. Wilde, K. Thai and M. Gravel, *J. Am. Chem. Soc*., 2014, **136**, 7539; (*c*) M.-Q. Jia and S.-L. You, *ACS Catal*., 2013, **3**, 622; (*d*) A. Takada, Y. Hashimoto, H. Takikawa, K. Hikita and K. Suzuki, *Angew. Chem., Int. Ed.*, 2011, **50**, 2297; (*e*) D. Enders, O. Niemeier, and T. Balensiefer, *Angew. Chem., Int. Ed*., 2006, **45**, 1463.

5 For selected recent reports, see: (*a*) M. M. D. Wilde and M. Gravel, *Org. Lett*., 2014, **16**, 5308; (*b*) J. Xu, C. Mou, T. Zhu, B.-A. Song and Y. R. Chi, *Org. Lett*., 2014, **16**, 3272; (*c*) L.-H. Sun, Z.-Q. Liang, W.-Q. Jia, and S. Ye, *Angew. Chem., Int. Ed.*, 2013, **52**, 5803; (*d*) D. A. DiRocco, and T. Rovis, *Angew. Chem., Int. Ed*., 2012, **51**, 5904; (*e*) D. Enders, A. Henseler and S. Lowins, *Synthesis*, 2009, **24**, 4125; (*f*) M. He and J. W. Bode, *J. Am. Chem. Soc.*, 2008, **130**, 418.

6 For selected reviews on Stetter reaction, see: (*a*) S. R. Yetra, A. Patra and A. T. Biju, *Synthesis,* 2015, **47**, 1357; (*b*) J. Read de Alaniz and T. Rovis, *Synlett,* 2009, 1189; (*c*) H. Stetter, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 639.

7 For an account, see: A. T. Biju, N. Kuhl and F. Glorius, *Acc. Chem. Res.,* 2011, **44**, 1182.

8 For initial reports, see: (*a*) C. Burstein and F. Glorius, *Angew. Chem. Int. Ed.*, 2004, **43**, 6205; (*b*) S. S. Sohn, E. L. Rosen and J. W. Bode, *J. Am. Chem. Soc.,* 2004, **126**, 14370.

9 V. Nair, S. Bindu, V. Sreekumar and N. P. Rath, *Org. Lett*., 2003, **5**, 665.

10 (*a*) A. Berkessel, V. R. Yatham, S. Elfert, and J.-M. Neudörfl, *Angew. Chem. Int. Ed.,* 2013, **52**, 11158; (*b*) A. Berkessel, S. Elfert, V. R. Yatham, J.-M. Neudörfl, N. E. Schlörer and J. H. Teles, *Angew. Chem. Int. Ed.,* 2012, **51**, 12370; (*c*) V. R. Yatham, J.-M. Neudörfl , N. E. Schlörer and A. Berkessel, *Chem. Sci.,* 2015, **6**, 3706.

11 (*a*) C. E. I. Knappke, J. M. Neudörfl and A. Jacobi von Wangelin, *Org, Biomol. Chem*., 2010, **8**, 1695; (*b*) C. E. I. Knappke, A. J. Arduengo III, H. Jiao, J. M. Neudörfl and A. Jacobi von Wangelin, *Synthesis*, 2011, **23**, 3784.

12 (*a*) B. Maji, M. Breugst and H. Mayr, *Angew. Chem., Int. Ed.,* 2011, **50**, 6915; (*b*) B. Maji, M. Horn and H. Mayr, *Angew. Chem., Int. Ed.,* 2012, **51**, 6231.

13 (*a*) D. A. DiRocco, K. M. Oberg and T. Rovis, *J. Am. Chem. Soc.,* 2012, **134**, 6143; (*b*) X. Zhao, G. S. Glover, K. M. Oberg, D. M. Dalton and T. Rovis, *Synlett*, 2013, 1229.

14 C. Fischer, S. W. Smith, D. A. Powell and G. C. Fu, *J. Am. Chem. Soc.,* 2006, **128**, 1472.

15 (*a*) S. Matsuoka, Y. Ota, A. Washio, A. Katada, K. Ichioka, K. Takagi and M. Suzuki, *Org. Lett.,* 2011, **13**, 3722.

16 *(a*) A. T. Biju, M. Padmanaban, N. E. Wurz, *Angew. Chem., Int. Ed.,* 2011, **50**, 8412.

17 (*a*) Y. Zhang and E. Y.-X. Chen, *Angew. Chem., Int. Ed.,* 2012, **51**, 2465; see also (*b*) M. Hong and E. Y.-X. Chen, *Angew. Chem., Int. Ed.,* 2014, **53**, 11900.

18 (*a*) D. Enders, K. Breuer, J. Runsink and J. H. Teles, *Liebigs Ann.,* 1996, 2019; (*b*) D. Enders, K. Breuer, U. Kallfass, T. Balensiefer, *Synthesis*, 2003, 1292.

19 For selected reports, see: (*a*) J. Zhang, C. Xing, B. Tiwari and Y. R. Chi, *J. Am. Chem. Soc.,* 2013, **135**, 8113; (*b*) D. Enders, J. Han and A. Henseler, *Chem. Commun.,* 2008, 3989; (*c*) A. E. Mattson, A. R. Bharadwaj and K. A. Scheidt, *J. Am. Chem. Soc.,* 2004, **126**, 2314; (*d*) A. G. M. Barrett, A. C. Love and L. Tedeschi, *Org. Lett.,* 2004, **6**, 3377.

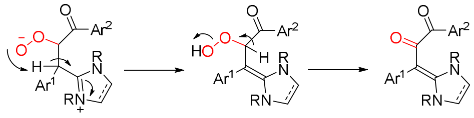
20 For selected reports, see: (*a*) Z. Fu, K. Jiang, T. Zhu, J. Torres and Y. R. Chi, *Angew. Chem. Int. Ed.*, 2014, **53**, 6506; (*b*) A. Bhunia, A. Patra, V. G. Puranik and A. T. Biju, *Org. Lett*., 2013, **15**, 1756; (*c*) X. Fang, X. Chen, H. Lv and Y. R. Chi, *Angew. Chem., Int. Ed.,* 2011, **50**, 11782; (*d*) H. Lv, J. Mo, X. Fang and Y. R. Chi, *Org. Lett.,* 2011, **13**, 5366; (*e*) B. Cardinal-David, D. E. A. Raup and K. A. Scheidt, *J. Am. Chem. Soc.,* 2010, **132**, 5345; (*f*) V. Nair, S. Vellalath, M. Poonoth, and E. Suresh, *J. Am. Chem. Soc.,* 2006, **128**, 8736.

21 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%.

22 CCDC-1061964 (**3a**), CCDC-1061965 (**4a**), CCDC-1061966 (**4b**) CCDC-1061967 (**5a**), and CCDC-1061968 (**7a**).

23 It may be mentioned that the β-furyl substituted enone **1g** on treatment with NHC derived from **2c** afforded the diketone **4b'** in 54% yield.

24 It is also likely that the intermediate **C** undergoes an intramolecular proton transfer to generate the neutral α-hydroperoxy ketone **C'**, which eliminates a molecule of water to afford the diketone **F**.



C **C'** **F**

25 For selected reports, see: (*a*) C. Qi, H. Jiang, L. Huang, Z. Chen and H. Chen, *Synthesis*, 2011, 387; (*b*) Y. Sawaki and Y. Ogata, *J. Am. Chem. Soc.,* 1975, **97**, 6983; (*c*) F. G. Bordwell and A. C. Knipe, *J. Am. Chem. Soc.,* 1971, **93**, 3416.