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An insight into the mechanism of the aerobic oxidation of aldehydes catalyzed by N-heterocyclic carbenes†

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N-Heterocyclic carbene catalysis for the aerobic oxidation and esterification of aromatic aldehydes was monitored by ESI-MS (MS/MS) and the key intermediates were intercepted and characterized using the charge-tag strategy.

The electron richness and structure of the N-heterocyclic carbenes (NHCs) provide a unique class of σ-donor species, which have found widespread applications in organocatalysis.[1] The most successful uses of these azolylidene catalysts involve the polarity reversal of aldehydes, in which the NHC promotes the formation of an acyl anion equivalent commonly referred to as the Breslow intermediate (**II** of Fig. 1). This NHC-catalysis has been recently enriched with oxidative protocols to access a wide range of organic compounds, especially acids and esters.[2] The key oxidation event characterizing these transformations takes place on the Breslow intermediate **II**, which may be converted by air as the terminal oxidant into an electrophilic acyl azolium ion **III**[3] (stoichiometric external oxidants such as MnO_2, azobenzene, riboflavin, phenazine, TEMPO, and quinones can also be employed),[2] and/or into an azolium peroxidic species **V**.[3] In the former case **III** is prone to transfer the acyl group to an alcohol forming the corresponding ester (*oxidative pattern*);[3a,b,e] in the latter case **V** is supposed to intercept a second molecule of aldehyde or **II** to generate the carboxylic acid *via* formation of the corresponding peracid and/or the anionic intermediate **VI** (*oxygenative pattern*).[3c–g,i] Eventually, the acid is converted into the ester by *O*-alkylating reagents and base (Fig. 1).[3f,g,4] A number of mechanistic studies have been performed on the NHC-catalyzed aerobic oxidation of aldehydes;[3b,c,e,g,h,4a,5b] nevertheless, key questions concerning the fate of the Breslow intermediate are still unanswered, including a precise characterization of the postulated intermediates and a rationalization of the proposed mechanistic dichotomy.

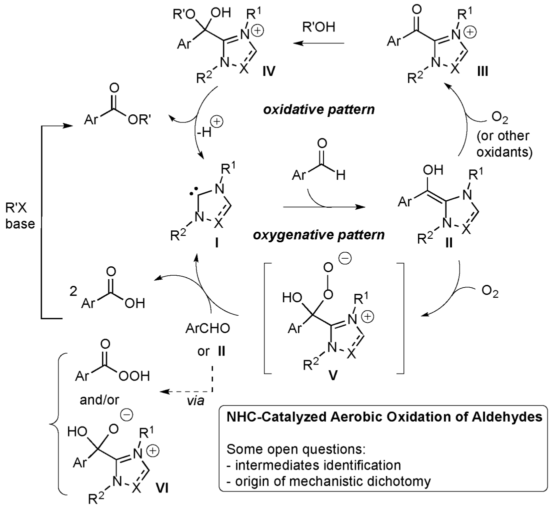

Fig. 1 Most commonly proposed mechanisms for the NHC-catalyzed aerobic oxidation of aldehydes.

In an attempt to provide responses to these issues and as part of our ongoing research on the chemistry of NHCs,[6] we envisaged the use of charge-tagged N-heterocyclic carbenes as mass spectrometric probes to identify the species involved in the different oxidation steps and their dynamic equilibria. The charge-tag strategy entails the use of reagents, catalysts or ligands bearing a cationic or anionic unit installed remotely from the reaction site.[7] It is noteworthy, also, that mass spectrometry (MS) has gained great benefit from the advent of electrospray ionization (ESI), since molecules of high polarity and complexity can be gently transferred directly from solution to gas-phase, thus permitting the detection of elusive and highly reactive intermediates.[8]

In the present study, the 3,3′-dimethyl-1,1′-(hexane-1,6-diyl) diimidazolium glutarate **1** has served as the precursor of carbene catalysts **2**, which displays the second imidazolium ring as a positive label for MS detection (Scheme 1). By this approach, we provide evidence of the key intermediates **III, V,** and **VI** as well as justification of preferential oxidative or

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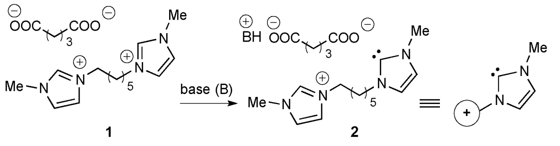
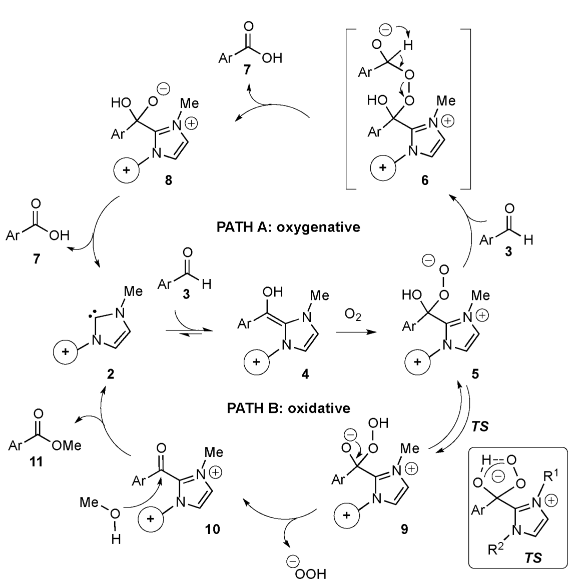


Scheme 1 Generation of the charge-tagged NHC **2**.

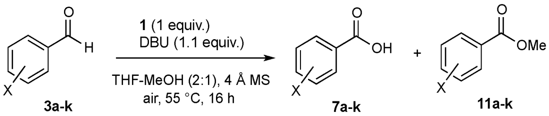
oxygenative patterns with dependence on aldehyde stereoelectronic features.

Our investigation began with the ESI-MS monitoring of the reaction between pre-catalyst **1** and the model 2-bromo benzaldehyde **3a** using acetonitrile–MeOH (5 : 1) as the eluent. Firstly, it was observed that significant amounts of **2** could be produced without the need of an external base, the relative intensity of **2** (*m*/*z* 247) being about 70% in the absence of aldehyde. Upon addition of **3a** the intensity of **2** quickly decreased in parallel with an increase (up to 100%) of the signal at *m*/*z* 447 (^{79}Br isotope) unequivocally assigned, by accurate mass analysis, to the Breslow intermediate **4a** containing an additional oxygen atom [**4a** + O]$^+$ (Fig. 2 and Scheme 2). Noteworthily, when this ionic species was mass selected and subjected to collision induced fragmentation (MS/MS), the release of the neutral carboxylic acid **7a** and formation of the NHC **2** were observed. Significantly, this decomposition perfectly fits with the reactivity found in solution (Table 1), thus corroborating the structure proposed in Fig. 2 for the [**4a** + O]$^+$ ion.



Scheme 2 Proposed mechanism for the aerobic oxidation of aldehydes: path A, *oxygenative*, path B, *oxidative*.

Table 1 Oxidation–esterification of aldehydes **3a–k**



Entry	Aldehyde	X	**8**[a] (ab. %)	**10**[b]	**7**/**11**[c] (%)
1	**3a**	2-Br	100	N	45/5 (37/8)[d]
2	**3b**	2-Cl	80	N	32/8
3	**3c**	2-NO$_2$	[5][e]	N	40/0
4	**3d**	2-OMe	60	N	24/0
5	**3e**	4-Br	<1	Y	11/78 (19/72)[d]
6	**3f**	4-Cl	8	Y	10/76
7	**3g**	4-NO$_2$	<1	Y	5/84
8	**3h**	4-OMe	10	Y	6/32
9	**3i**	3-Br	8	Y	10/72
10	**3j**	2,6-Cl$_2$	80	N	25/5
11	**3k**	2,4,6-Me$_3$	100	N	28/0

[a] Relative abundance as determined by ESI-MS (see ESI). [b] N = not detected; Y = detected and characterized. [c] Isolated yield. [d] Reaction performed with bmim(OTf). [e] Very unstable species that spontaneously undergoes fragmentation.

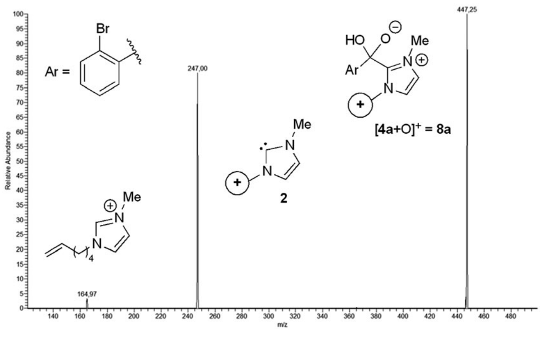


Fig. 2 MS/MS of the Breslow intermediate **4a** containing an additional oxygen atom (*m*/*z* 447) formed by the **1**/**3a** reaction.

In addition, the full scan acquisition highlighted the presence, although in a much lower relative intensity (*ca.* 2%), of a second important ion cluster (*m*/*z* 463), identified as the Breslow intermediate formally containing two oxygen atoms [**4a** + 2O]$^+$.[9] The MS/MS analysis of this ionic species disclosed even more important information consisting in the release of O$_2$ with formation of the genuine Breslow intermediate **4a** (*m*/*z* 431), species otherwise not detectable in the full mass spectrum. The detailed snapshots of the involved intermediates and their preferential decomposition substantiate the mechanism described in path A of Scheme 2. Accordingly, molecular oxygen adds to the Breslow intermediate **4** with formation of the zwitterionic peroxide **5** (heretofore named [**4a** + 2O]$^+$); reasonably, **5** then attacks a second molecule of aldehyde by a mechanism reminiscent of the Baeyer–Villiger oxidation to yield a first molecule of acid **7**.[10] The final event consists in the release of an additional molecule of **7** from the intermediate **8** (heretofore named [**4a** + O]$^+$) with regeneration of catalyst **2**. Remarkably, in our MS experiments we observed no evidence of the formation of free deprotonated peracids (Fig. 1), species that survive the (−)-ESI MS conditions, as proved by control experiments with genuine samples.

To corroborate the above findings, the reaction of 2-bromo benzaldehyde **3a** with pre-catalyst **1** (1 equiv.) was investigated in solution (anhydrous THF, molecular sieves, 55 °C) using DBU (1.1 equiv.) as the base. As hinted in the mechanistic proposal (path A), aldehyde **3a** was converted into the corresponding acid **7a** in 51% yield. However, when this reaction was performed in THF–MeOH (2 : 1), a low amount (5%) of methyl ester **11a** was detected together with the acid **7a** (45%; Table 1, entry 1). Extension of these conditions to aldehydes **3b–k** possessing *ortho*-, *meta*- or *para*-groups, with either electron-withdrawing or electron-donating properties, confirmed the concurring partial or almost complete esterification of the substrates (Table 1). Although the activity of pre-catalyst **1** in solution was limited,[11] its utilization represented the gateway for accessing key intermediates by ESI-MS. Replacement of the cationic imidazolium tag of **1** with an uncharged alkyl chain as in 1-butyl-3-methylimidazolium trifluoromethanesulfonate [bmim(OTf)] produced similar results in terms of isolated yields of acids **7** and esters **11** (entries 1 and 5).

This divergent reactivity was deeply examined by the ESI-MS monitoring of the reaction between **1** and a model aldehyde that predominantly affords the ester rather than the acid, *i.e.* the 4-bromo benzaldehyde **3e**.

The most resounding evidence in the (+)-ESI full spectrum was the *absence* of the oxidized Breslow intermediate **8e**. In contrast, the peroxidic Breslow intermediate **5e** remained detectable, whose MS/MS spectrum showed the release of O_2, thus confirming oxygen insertion on **4** to be still effective. Pleasantly, it was also possible to detect and characterize the crucial intermediate **10e** of the oxygenative mechanism (path B), which was intercepted as a doubly charged ion at *m*/*z* 215. The MS/MS spectrum of **10e** enlightened us about its structure since the observed fragments were the acyl cation (*m*/*z* 183) and the singly charged catalyst **2** (*m*/*z* 247; Fig. S16, ESI†). It is worth emphasizing that all aldehydes having preference for ester over acid formation showed the presence of the related acyl intermediate **10** and traces of the oxidized Breslow species **8**, while the detection of **8** in high relative abundance (Table 1, columns 4 and 5) was distinctive for preferential acid production.

Few mechanistic considerations would be appropriate in light of these results. Nucleophilic addition of carbene **2** to aldehyde **3**, irrespective of its electronic and steric features, results in the formation of the Breslow intermediate **4**. This new nucleophile then intercepts molecular oxygen affording the zwitterionic peroxide **5**. In analogy with Studer *et al.*,[3c] we suggest for this step oxidation of **4** by O_2 to give the radical cation $[\mathbf{4}]^{\bullet+}$ and the superoxide radical anion $[O_2]^{\bullet-}$. Accordingly, we calculated the structure of the complex between $[\mathbf{4}]^{\bullet+}$ and $[O_2]^{\bullet-}$ at the DFT level. The optimized structures for **4a** and **4e** along with spin densities are shown in Fig. 3. We found that a fraction of the $[O_2]^{\bullet-}$ spin density spreads on $[\mathbf{4}]^{\bullet+}$, mainly on the C-atom next to the OH group. This result fully conforms with those reported for triazolium-based systems.[3c]

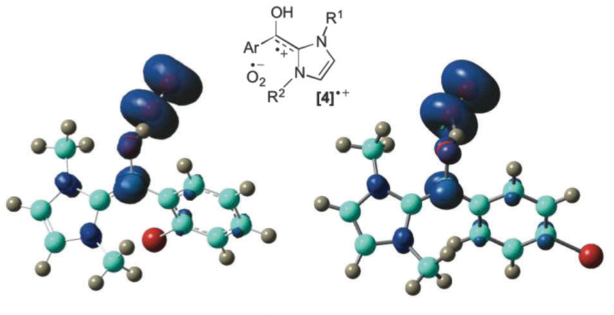


Fig. 3 Complexes between $[\mathbf{4}]^{\bullet+}$ and $[O_2]^{\bullet-}$ (Ar = 2-Br-Ph, left; and Ar = 4-Br-Ph, right. For model simplification, $R^1 = R^2$ = Me). The threshold value of the spin density is 0.03 a.u. The spin densities, calculated using the Mulliken population analysis, on the C-atom next to the OH group are 0.149 and 0.140 a.u. ($[\mathbf{4a}]^{\bullet+}$ and $[\mathbf{4e}]^{\bullet+}$ respectively). The total spin densities on $[\mathbf{4a}]^{\bullet+}$ and $[\mathbf{4e}]^{\bullet+}$ are 0.260 and 0.262 a.u., respectively.

Significantly, peroxide **5** appears as the common intermediate of both oxygenative and oxidative mechanisms. Indeed, DFT calculations showed the H-bonded transition state TS (Scheme 2, R^1 = Me; R^2 = Me; Ar = Ph) in the tautomeric equilibrium between **5** and **9**. In the oxidative mechanism, **5** is converted into the acyl cation equivalent **10** through the intermediate **9** by intramolecular proton transfer and liberation of the hydroperoxide anion.[3a,l] Path B is finally completed with acylation of MeOH to give the ester **11** and catalyst **2**. Both A and B reaction patterns fully conform to the *oxygenative* and *oxidative* classification proposed by von Wangelin *et al.*,[2b] and the divergent reactivity seems to be mainly directed by steric factors. Indeed, *meta*- and *para*-substituted aldehydes **3e–i** are good substrates for esterification. By contrast, path A is preferred by *ortho*-substituted aldehydes **3a–d**, **3j**, and **3k** that, however, give the corresponding acids with lower efficiency (24–45%).

We would like to stress that the mechanistic picture of Scheme 2 is proposed for imidazolium type catalysts and that paths A and B coexist in most of the investigated cases. As imidazolinium-, triazolium-, and thiazolium-based protocols have also been reported for the aerobic oxidation of aldehydes,[3,5a] further investigation on these systems is currently underway using the charge-tag strategy.

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11 Reaction of **3e** with catalytic **1** (20 mol%; 24 h): **7e** (24%), **11e** (65%). Reaction of **3e** with equimolar **1** at 25 °C (72 h): **7e** (28%), **11e** (45%). Background oxidation of **3a–i** under optimized conditions are reported in Table S1 (ESI†).