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DOI: 10.1002/adsc.201300034

## **Cooperative N-Heterocyclic Carbene (NHC) and Ruthenium Redox Catalysis: Oxidative Esterification of Aldehydes with Air** *as the Terminal Oxidant*

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Received: January 15, 2013; Revised: February 15, 2013; Published online: April 8, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300034.

**Abstract:** The paper describes a cooperative NHC (N-heterocyclic carbene) and ruthenium-based redox catalysis for the mild aerobic oxidative esterification of various aromatic and heteroaromatic aldehydes. The ruthenium(II) complex  $\text{Ru}(\text{bpz})_3(\text{PF}_6)_2$  (bpz = 2,2'-bipyrazine) as catalyst is shown to be compatible with free NHCs. The NHC is used in these cascade reactions for the umpolung of the aldehyde to form the corresponding Breslow intermediate which in turn gets oxidized to an acylazolium ion by the ruthenium redox catalyst. Air is used as a terminal

### Introduction

Cooperative catalysis using an organocatalyst and a transition metal-based catalyst may offer novel reactivity which cannot be achieved by either of them individually.<sup>[1]</sup> NHCs have attracted great attention in the past decade and various NHC-catalyzed reactions have been developed.<sup>[2]</sup> However, the successful merger of NHC catalysis with transition metal catalysis is still a challenging topic. This is due to the fact that NHCs act as good ligands for most transition metals and their coordination to the metal generally results in the loss of their reactivity as organocatalysts (organocatalyst poisoning).<sup>[3]</sup> Therefore, only few examples on successful cooperative NHC- and metalbased catalysis have appeared to date.<sup>[4]</sup> Herein, we report the oxidative esterification of aldehydes by using cooperative NHC and Ru(II) redox catalysis with air as the terminal oxidant under mild reaction conditions. During the course of these studies we also developed a protocol for the mild NHC-catalyzed aerobic oxidation of aldehydes to carboxylic acids.

Acylazolium ions<sup>[5]</sup> are reactive intermediates which can be trapped by different nucleophiles in a range of NHC-catalyzed reactions such as esterification,<sup>[6]</sup> amidation<sup>[7]</sup> and Michael addition.<sup>[8]</sup> Formation oxidant for oxidation (regeneration) of the ruthenium catalyst. In addition, we will show that in the absence of the ruthenium redox catalyst and alcohol, NHC-catalyzed aerobic oxidation of aldehydes delivers the corresponding acids in good to excellent yields. Mechanistic studies and DFT calculations supporting our suggested mechanisms are provided.

**Keywords:** carbenes; cooperative catalysis; organocatalysis; oxidation; ruthenium

of acylazolium ions can be achieved by employing substrates able to undergo internal redox processes.<sup>[6,9]</sup> It was also found that MnO<sub>2</sub>,<sup>[10]</sup> azobenzene,<sup>[11]</sup> ribo-flavin,<sup>[12]</sup> phenazine,<sup>[13]</sup> TEMPO<sup>[14]</sup> and quinones<sup>[15]</sup> are effective external oxidants for oxidation of the Breslow intermediate to give the corresponding reactive acylazolium ion intermediate.<sup>[5]</sup> However, the internal redox active substrates need to be specially designed and the necessity to add an organic or inorganic stoichiometric external oxidant in the latter processes lead to an increase of costs and chemical waste which will hamper application of these strategies on a larger scale. We therefore envisioned that this chemistry would be more attractive if air could be used as cheap terminal oxidant for the oxidation of the Breslow intermediate.<sup>[16]</sup> Indeed, O<sub>2</sub> has already been successfully applied as terminal oxidant to NHC-catalyzed esterifications. However, reactive nucleophiles such as boronic acids<sup>[4h]</sup> and phenols<sup>[4i]</sup> are required or esterification occurs via oxidation to the acid and subsequent trapping with an alkyl halide.<sup>[17]</sup> To the best of our knowledge, only one paper describing an NHC-catalyzed esterification between aldehydes and aliphatic alcohols with air as the terminal oxidant showing very limited substrate scope was published.<sup>[18]</sup> Since alcohols are known to react efficiently



**Scheme 1.** NHC-catalyzed oxidative esterifications of aldehydes *via* cooperative NHC/metal-based catalysis.

with acylazolium ions the problem in these aerobic oxidative esterifications must lie in the generation of the acylazolium ion. Importantly, NHC-catalyzed oxidation of aldehydes to the corresponding acids with air as the terminal oxidant is documented.<sup>[19,20,21]</sup> However, these oxidations do not necessarily need to proceed via acylazolium ions. Oxidation of the Breslow intermediate with O<sub>2</sub> can lead via single electron transfer and in cage recombination to the peroxy adduct without formation of the acylazolium ion (Scheme 1). Proton transfer and carbene fragmentation will provide the corresponding peracid which upon reaction with the aldehyde will eventually afford two equivalents of the acid. Hence the challenge was to identify a catalyst which (i) does not react with the carbene by ligation (NHC poisoning), (ii) reacts with the Breslow intermediate faster than  $O_2$  does (to suppress peracid formation), and (iii) can after successful oxidation of the Breslow intermediate be regenerated by air oxidation (Scheme 1).

#### **Results and Discussion**

As a test reaction we chose oxidation of benzaldehyde in the presence of benzyl alcohol to benzyl benzoate. Initial screening of the reaction conditions revealed that promising results could be obtained in acetonitrile with carbene precursor **1** (5 mol%, see Figure 1) and triazabicyclodecene (TBD, 1.2 equiv.) as a stoichiometric base (Table 1). In the absence of any metal-based cocatalyst we isolated the benzyl ester in 24% yield along with benzoic acid (72%, entry 1; studies on acid formation will be discussed below). We tested various redox active catalysts and found the ester in traces upon using Cu-based salts (entries 2–4). Pleasingly, the ferrocenium salts Cp<sub>2</sub>FeBF<sub>4</sub>



**Figure 1.** Various carbene precursors tested in the oxidation of benzaldehyde to benzyl benzoate (yields are given in brackets).

and Cp<sub>2</sub>FePF<sub>6</sub> afforded the targeted ester in 55% yield (entries 5 and 6). In agreement with a recent Rovis study we found that Ru-based catalysts are compatible with free NHCs.<sup>[4g]</sup> Whereas Ru(bpy)<sub>3</sub>Cl<sub>2</sub> did not show any catalyst activity (entry 7, compare with the background esterification in entry 1; bpy=2,2'-bipyridine) significant activity was achieved with Ru(bpm)<sub>3</sub>Cl<sub>2</sub> and Ru(bpz)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> [entries 8 and 9; all further studies were conducted with Ru(bpz)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub>; for structures see Figure 1]. Interestingly, at lower NHC catalyst loading (2.5 mol%) the yield further increased to 76% (entry 10). Reactions were run by leaving the reaction vessel open to the air atmosphere and esterifications performed under an O<sub>2</sub> atmosphere (balloon technique, around 1 bar) delivered

Table 1. Oxidative esterification of benzaldehyde under various conditions.



Entry	Metal catalyst (mol%)	<b>1</b> (mol%)	Base	Time [h]	Yield [%] <sup>[a,b]</sup>
1	none	5	TBD	2	24
2	$Cu(OAc)_2(5)$	5	TBD	4	traces
3	$CuBr_2(5)$	5	TBD	4	traces
4	$CuCl_2$ (5)	5	TBD	4	traces
5	$Cp_2FeBF_4$ (5)	5	TBD	2	55
6	$Cp_2FePF_6$ (5)	5	TBD	2	55
7	$Ru(bpy)_3Cl_2/H_2O(5)$	5	TBD	4	26
8	$Ru(bpm)_3Cl_2(5)$	5	TBD	2	67
9	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	TBD	2	70
10	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	2.5	TBD	2	76
11	$Ru(bpz)_{3}(PF_{6})_{2}(3)$	2.5	TBD	2	66
12	$Ru(bpz)_{3}(PF_{6})_{2}$ (10)	2.5	TBD	2	78
13	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	DBU	2	53
14	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	MTBD	2	76
15	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	$Cs_2CO_3$	2	57
16	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	$Rb_2CO_3$	1	50
17	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	tBuOK	1	50
18	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	KHMDS	1	67
19	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	TBD <sup>[c]</sup>	1	38
20	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	$K_2CO_3$	2	-
21	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	DIEA	2	_
22	$Ru(bpz)_{3}(PF_{6})_{2}(5)$	5	DABCO	2	_
23	$\operatorname{Ru}(\operatorname{bpz})_3(\operatorname{PF}_6)_2(5)$	5	Et <sub>3</sub> N	2	-

<sup>[a]</sup> Reactions were carried out on a 0.25-mmol scale of aldehyde with 10 equiv. of benzyl alcohol (2.5 mmol) in 1 mL acetonitrile at room temperature.

<sup>[b]</sup> Isolated yields.

<sup>[c]</sup> 0.6 equiv. of TBD were used.

lower yields. Increasing the Ru(bpz)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> concentration (10 mol%) did not give a better result but decreasing Ru loading to 3 mol% led to a lower yield (entries 11 and 12). The major side product in all these transformations was benzoic acid. Importantly, such Ru(II) complexes have been extensively used in visible light photoredox catalysis.<sup>[22]</sup> However, control experiments demonstrated that irradiation with visible light is not necessary in our case. In fact we noted slightly diminished yields upon running the esterification under irradiation. This result clearly showed that Ru(bpz)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (E<sub>1/2</sub>=1.98)<sup>[23]</sup> in its ground state is a strong enough oxidant to oxidize the Breslow intermediate. Further control experiments revealed that the NHC **1**, TBD, and air are all crucial for successful esterification.

We found that the nature of the base has a strong influence on the reaction outcome. Along with TBD, other bases such as DBU (1,8-diazabicycloundec-7-ene), MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene,  $pK_a > 24$  in CH<sub>3</sub>CN),<sup>[24]</sup> Cs<sub>2</sub>CO<sub>3</sub>, Rb<sub>2</sub>CO<sub>3</sub>, *t*-BuOK, KHMDS showed activity in the esterification

(entries 13–18). Decreasing the amount of TBD to 0.6 equiv. had a detrimental effect on the yield (entry 19) and no reaction occurred with  $K_2CO_3$ , DIEA (diethylamine), DABCO (1,4-diazabicyclo-[2.2.2]octane) and Et<sub>3</sub>N (entries 20–23). Other solvents such as THF, DMSO, and DMF provided worse results (solvent screening was conducted with DBU as base, see the Supporting Information).

Under the optimized conditions (1.2 equiv. TBD, 5 mol% of Ru(bpz)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> and 2.5 mol% of NHC under air)<sup>[25]</sup> we tested various carbene precursors **2–8** in the oxidative esterification of benzaldehyde with benzylalcohol. Surprisingly, only the electron-rich bulky triazolium salt  $2^{[26]}$  provided a good yield (76%, Figure 1). Less bulky triazolium salts such as **3**, **4** and the electron poorer congener **5** gave only traces of the targeted ester. Imidazolium salt **6**, salt **7** and the thiazolium salt **8** did not show high activity in the oxidative esterification and products were identified in trace amounts.

Using carbene precursor 1 we then evaluated the substrate scope of this methodology by varying the al-

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 [a] Reactions were carried out on a 0.25 mmol scale of aldehyde with 0.25 mL alcohol (2.5 mmol) in 1 mL acetonitrile at room temperature.
 [b] Isolated yields.

<sup>[c]</sup> Cyclohexanecarboxylic acid formed as major product in 70% yield.

Scheme 2. Substrate scope.

dehyde as well as the alcohol component. As shown in Scheme 2, aromatic aldehydes were converted to the corresponding benzyl esters in good to excellent yields. As expected, sterically more shielded aldehydes provided lower yields and heteroaromatic aldehydes containing a furan, pyrrole or a thiophene moiety were good substrates for this esterification. Additionally, other alcohols such as methanol, ethanol and propargyl alcohol also work well for this reaction. However, aliphatic aldehydes turned out to be not good substrates for this oxidative esterification. 3-Phenylpropanal provided only traces of the targeted ester and cyclohexylcarbaldehyde in the reaction with benzylalcohol gave only 15% yield of the corresponding benzyl ester. The major product formed was cyclohehexanecarboxylic acid which was obtained in 70% yield.

A possible mechanism for the cooperative NHC/  $Ru(bpz)_3(PF_6)_2$ -catalyzed cascade reaction is depicted in Scheme 3. The Breslow intermediate 9 generated upon reaction of the carbene with the aldehyde gets oxidized by  $Ru(bpz)_3(PF_6)_2$  through a single electron transfer (SET) process to afford the radical cation 10.<sup>[27]</sup> Oxygen acts as the terminal oxidant by oxidation of the intermediate Ru(I) complex to give the  $Ru(bpz)_{3}^{++}$  complex along with the superoxide radical anion. Reaction of 9 with dioxygen initiates a process eventually leading to the acid as will be discussed below. Deprotonation of 10 with the base or with the superoxide radical anion will provide the tertiary radical 11, which will be further oxidized to the acylazolium ion 12. This oxidation can be achieved with  $Ru(bpz)_{3}^{++}$  or with the hydroperoxyl radical. Trapping of the acylazolium ion 12 by the alcohol will eventually provide the ester thereby releasing the NHC catalyst. This step is catalyzed by the NHC.<sup>[15a]</sup> We assume that the base is not only used to release the NHC catalyst but also likely involved in the formation of the Breslow intermediate.

As mentioned above, the major side product identified in these oxidative esterifications was the acid,



Scheme 3. Suggested mechanism for oxidative esterification.

Adv. Synth. Catal. 2013, 355, 1098-1106

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which is likely formed via O2 oxidation of the Breslow intermediate 9 without involvement of Ru catalysis.<sup>[19-21]</sup> Notably, with aliphatic aldehydes this route was the major reaction pathway. It seems that whereas Breslow intermediates derived from aromatic aldehydes are efficiently oxidized by the Ru catalyst, the aliphatic congeners are not readily oxidized with the metal catalyst and reactions mainly occur via O<sub>2</sub> oxidation to eventually provide the corresponding acids. We therefore assumed that aromatic and aliphatic aldehydes in the absence of the Ru catalyst and alcohol under otherwise identical conditions might be cleanly oxidized to the corresponding acids and reinvestigated the oxidation of benzaldehyde in the absence of  $Ru(bpz)_3(PF_6)_2$  and benzyl alcohol. To our delight, benzoic acid was formed at room temperature in acetonitrile under air in the presence of 5 mol% of NHC 1 and 1.2 equiv. of TBD in 92% isolated yield (2 h). In two control experiments we showed that both 1 and the base TBD were necessary for successful oxidation. However, water was not necessary for this acidification (reaction run in the presence of molecular sieve provided the same yield while the presence of water caused a lower yield). The NHC catalyst loading could be decreased to 2.5 mol% without affecting the yield (Scheme 4). By running the reaction at 1 mol% catalyst loading we still obtained a good yield, however the reaction time had to be prolonged (80%, 6 h).

Under optimized conditions (2.5 mol% 1, 1.2 equiv. TBD) various aromatic and heteroaromatic aldehydes were successfully oxidized to the corresponding acids in good to excellent yields. Except for the F-substituted systems, which showed very high yields, aromatic aldehydes bearing electron-withdrawing groups generally delivered lower yields (see Br-, Cl-, CN- and NO<sub>2</sub>-substituted derivatives). Interestingly, aliphatic branched aldehydes, in particular cyclic congeners, could be oxidized to the corresponding carboxylic acids in good to excellent yields while the linear aliphatic aldehyde provided a lower yield. It is currently not clear to us why branched aldehydes are good substrates whereas sterically less hindered linear aliphatic aldehydes deliver lower yields. Note that for the oxidative esterification discussed above, the aliphatic branched aldehydes were not efficiently converted to the corresponding benzyl esters.

We suggest the following mechanism for these aerobic oxidations (Scheme 5). Reaction of the carbene with the aldehyde provides the Breslow intermediate 9 which is oxidized by  $O_2$  to give the radical cation 10 along with the superoxide radical anion. In cage recombination of the two radicals leads to zwitterion 13, which upon carbene fragmentation provides the peracid 14. The acid 14 then further reacts with the starting aldehyde to give two equivalents of the isolated acid. Peracid 14 might also react with Breslow in-



[a] Reactions were carried out on a 0.25 mmol scale of aldehyde in 1 mL acetonitrile at room temperature.
 [b] Isolated yields.

**Scheme 4.** NHC-catalyzed aerobic oxidation – substrate scope.

termediate 9 *via* hydroxyl transfer to salt 15 which upon fragmentation will deliver two equivalents of the acid and the NHC.



**Scheme 5.** Suggested mechanism for NHC-catalyzed aerobic oxidation to acids.

We currently rule out formation of the acylazolium ion 12 under the applied conditions for the following reasons. We showed that by running the oxidation in the presence of molecular sieves the same yield was achieved (Scheme 6). The acylazolium ion should efficiently react even with traces of water. Moreover, we experimentally showed that running the oxidation of ortho-fluorobenzaldehyde in the presence of 4 equiv. of  $H_2^{18}O$  provided the corresponding acid in 51% yield containing 60% of monolabeled acid. In another experiment the same aldehyde was first treated with 4 equivalents of  $H_2^{18}O$  overnight to give partially labeled aldehyde (43% <sup>18</sup>O-incorporation) which was then subjected to the oxidation conditions upon addition of base and carbene catalyst. We obtained the acid in 52% isolated yield containing 53% of <sup>18</sup>Omonolabeled acid. Importantly, only traces of <sup>18</sup>Odouble labeled acid were identified by mass spectrometry which clearly shows that labeling in these two experiments occurred prior to the oxidation step at the aldehyde stage. We also showed that exchange of the OH group in ortho-fluorobenzoic acid does not occur under the applied reaction conditions. These mechanistic studies allow us to conclude that the reaction does likely not proceed via the acylazolium ion. If so, double labeling must have been observed.

We also studied the spin distribution of four different radical cations of type **10** derived from *para*-substituted benzaldehyde derivatives (4-X-C<sub>6</sub>H<sub>4</sub>-CHO) with DFT calculations (TPSSh/def2-TZVP).<sup>[28]</sup> As *para*-substituents we chose groups that we expect to



Scheme 6. Control experiments.

differ with respect to their electronic substituent effect (X=H, F, CN, OMe). To simplify the model further, the carbene **1** was replaced by 1,4-dimethyl-1,2,4-triazol-5-ylidene. The optimized structures and the spin distributions are depicted in Figure 2. We did



**Figure 2.** DFT (TPSS-D3/def2-TZVP) structures of radical cations of type **10**. Spin density ( $\rho_{\alpha} - \rho_{\beta}$ ) surfaces are plotted with an isovalue of +/-0.003 a.u. (positive values in blue). In brackets: the spin density  $\rho_s$  of the carbon atom next to the OH group, obtained from a Mulliken population analysis.

not see large differences in the structures of these four intermediates and found a high spin density for all compounds investigated at the C-atom next to the OH group. This might explain the highly efficient coupling reaction of the radical cation 10 with the superoxide radical anion to give 13. The 4-methoxyphenyl substituted radical (X=OMe) is the only exception: its spin density value of the C-atom is smaller than that of the other three radical cations, due to a slightly larger extension of the spin density towards the triazole ring.

#### Conclusions

In summary, we have developed an efficient cooperative NHC and Ru(II)-based redox catalysis for the oxidative esterification of aromatic and heteroaromatic aldehydes in the presence of alcohols by employing aerobic oxygen as the terminal oxidant. Cooperative NHC and metal-based catalysis (merger of organocatalysis with redox catalysis) is rare due to the fact that most transition metals form stable complexes with carbenes which leads to carbene poisoning in the context of NHC catalysis. With the Ru-based catalysts we identified NHC compatible complexes. Such couples might be useful to conduct other processes proceeding via organocatalysis in cooperation with transition metal redox catalysis. The NHC and Ru(II)-catalysis presented herein proceeds via acylazolium ions, which are important and highly valuable intermediates in many NHC-catalyzed reactions. Therefore, our approach should allow in future the running of other reactions occurring via acylazolium ions with aerobic oxygen as the terminal stoichiometric oxidant. Our study has also demonstrated that in the absence of the Ru(II) complex and alcohol, aldehyde oxidation provides the corresponding acids in good to excellent yields. These transition metal-free aerobic oxidations of carbaldehydes occur with small amounts of O<sub>2</sub> present in the solvent and with low organocatalyst loading (2.5 mol%) and likely do not proceed via acylazolium ions. Notably, both the esterification and the acidification are conducted under very mild conditions. We believe that these methods should be attractive for academia as well as for industry.

### **Experimental Section**

#### General Procedure for the NHC-Catalyzed Oxidative Esterification of Aldehydes RCHO with Benzyl Alcohol

TBD (0.3 mmol, 1.2 equiv.) was added to a solution of Ru-(bpz)<sub>2</sub>(PF<sub>6</sub>)<sub>2</sub> (0.0125 mmol, 5 mol%), NHC precursor (2.5 mol%), aldehyde RCHO (0.25 mmol, 1.0 equiv.) and benzyl alcohol PhCH<sub>2</sub>OH (0.25 mL) in acetonitrile (1.0 mL) under air. The reaction mixture was stirred at room temperature for 1–16 h until complete consumption of the starting aldehyde as checked by TLC. The reaction mixture was loaded to a flash silica gel column and was eluted with a mixture of pentane and diethyl ether to afford the targeted ester.

# General Procedure for the NHC-Catalyzed Oxidation of Aldehydes to Acids

TBD (0.3 mmol, 1.2 equiv.) was added to a solution of NHC precursor (2.5 mol%), aldehyde RCHO (0.25 mmol, 1.0 equiv.) in acetonitrile (1.0 mL) under air. The reaction mixture was stirred at room temperature for 1–24 h until complete consumption of the starting aldehyde as checked by TLC. The reaction mixture was poured into 3 mL 1N NaOH solution and the aqueous phase was extracted three times with ethyl acetate. The aqueous layer was acidified upon adding 5 mL 3N HCl solution and the resulting solution was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over MgSO<sub>4</sub> and evaporation of solvent to afford the acid.

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of the acids and esters are provided in the Supporting Information.

### Acknowledgements

We thank the Alexander von Humboldt Foundation (stipend to J. F. Zhao) and the SFB858 (project Z1) for supporting this work. We also thank an anonymous referee for helpful suggestions.

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