Attractive Aerobic Access to the α,β-Unsaturated Acyl Azolium Intermediate: Oxidative NHC Catalysis Via Multistep Electron Transfer

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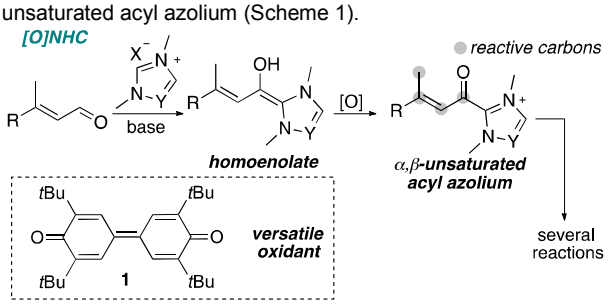
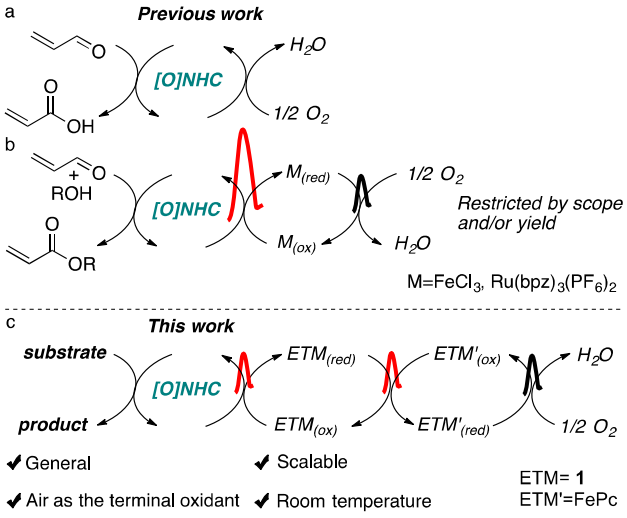
To replace high molecular weight oxidants with air (O_2) we introduce multistep electron transfer NHC catalysis. The method provides a general and selective oxidation of the α,β-unsaturated aldehyde derived homoenolate to the synthetically useful α,β-unsaturated acyl azolium intermediate. Several independent oxidative NHC-catalyzed reactions are viable with this strategy and the products can be isolated in high to excellent yields.

Within the vibrant field of N-heterocyclic carbene (NHC) catalysis[1] oxidative reaction paths have gained widespread attention in recent years. Several synthetic methodologies have emerged relying on the addition of a stoichiometric oxidant.[2] Of particular importance is the in situ oxidation of the homoenolate to the α,β-unsaturated acyl azolium (Scheme 1).



Scheme 1. Oxidation of the homoenolate to the α,β-unsaturated acyl azolium.

As a reaction intermediate, the unsaturated acyl azolium have been exploited in, for example, oxidative esterifications,[3] macrocyclization,[4] annulation reactions[5] and cyclo-additions[6] creating possibilities for broad molecular complexity. However, the majority of these reactions rely on the addition of a high molecular weight oxidant such as Kharasch oxidant **1**.[7,8] Taking into account, the price, separation and disposal of waste



Scheme 2. a) Direct oxidation with O_2. b) High energy barrier for the catalytic aerobic oxidative esterifications. c) Aerobic multistep electron transfer NHC catalysis, reliant on the combination of ETMs, lowers the energy barrier for oxidations with O_2.

(hydroquinone) of the oxidant it is clear that oxidants, such as **1,** presents a significant obstacle in terms of scale-up, sustainability and economy. A more atom efficient strategy would be to use environmentally friendly oxidants such as air (O_2).[9] It is highly desirable to use O_2 as a terminal oxidant since it is inexpensive, non-toxic, has a high efficiency of weight per oxidant, with formation of water as the sole byproduct. In oxidative NHC catalysis, direct oxidations with O_2 involving α,β-unsaturated aldehydes are reported to give carboxylic acids (Scheme 2a).[10] Furthermore, introduction of a catalytic oxidant, $FeCl_3$[11] or $Ru(bpz)_3(PF_6)_2$,[12] enables aerobic oxidative esterifications (Scheme 2b). However, these reactions are hampered by a high energy barrier for the oxidation of the NHC-aldehyde-adduct to the acyl azolium, reflected in high reaction temperatures, long reaction times or low reactivity. Clearly, mild and efficient protocols for aerobic oxidations accessing the unsaturated acyl

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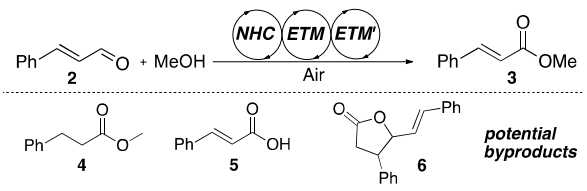
azolium intermediate would open up new possibilities for green chemistry and would therefore be most desirable.

High activation barriers are a general problem for direct catalytic oxidation with air or pure O_2. This often results in unselective reactions with kinetic byproducts,[13] thus making general usage of oxygen problematic as a terminal oxidant. A possible way to circumvent this is to mimic the respiratory chain and to create a low energy path for electrons to flow from the substrate to oxygen.[14] This has been envisioned and accomplished in transition metal-catalysis by introducing one or several electron transport mediators (ETMs) between the substrate specific catalyst and O_2. The most prominent example is the Wacker oxidation where $CuCl_2$ acts as an ETM, shuffling electrons from Pd^0 to O_2.[13, 15] Bäckvall and co-workers[13] have extended the generality of this strategy to a broad range of aerobic transition metal-catalyzed reactions such as, 1,4-oxidation of 1,3-dienes,[16] oxidative carbocyclization of allene-substituted olefins[17] and aerobic oxidations of alcohols.[18] Others have adapted this principle for a variety of oxidation reactions.[19]

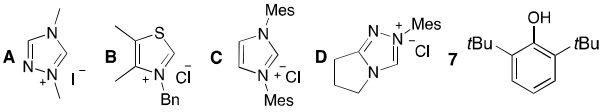
Here we present, as a part of our interest in NHC catalysis,[20] a strategy for oxidative NHC-catalyzed reactions relying on an electron transport chain involving two ETMs that enables efficient aerobic access to the synthetically useful α,β-unsaturated acyl azolium intermediate (Scheme 2c).

As a model reaction we choose to investigate the oxidative esterification of α,β-unsaturated aldehydes (Table 1).[21]

Table 1. NHC-catalyzed aerobic oxidative esterification of cinnamaldehyde[a]



Entry	NHC	ETM	ETM' (FePc, Eq.)	Time(h)	Yield(%)[b]	Selectivity(%)[c]
1	**A**	**1** (1 eq.)	-	4	74	78
2	**A**	**1** (0.01eq.)	-	7	24	40
3	**A**	**1** (0.01 eq.)	0.0055	4	80	88
4	**A**	**7** (0.02 eq.)	0.0055	4	85	89
5	**B**	**7** (0.02 eq.)	0.0055	-	-	-
6	**C**	**7** (0.02 eq.)	0.0055	22	65	65
7	**D**	**7** (0.02 eq.)	0.0055	4	68	68
8	**A**[d]	**7** (0.02 eq.)	0.0055	4	19	19
9	**A**[e]	**7** (0.02 eq.)	0.0055	4	67	74



[a] The reactions were performed in open reaction vessels at room temperature (r.t) in MeCN (1 mL) with **2** (66.1 mg, 0.5 mmol, 1 eq), TBD (34.8 mg, 0.25 mmol, 0.5 eq), MeOH (0.0809 ml, 2 mmol, 4 eq), NHC (2.3 mg, 0.01 mmol, 0.02 eq), ETM (see table) and ETM' (see table). [b] Yield determined by NMR against internal standard. [c] Yield over conversion. [d] 0.2 eq. of NHC was used. [e] 0.05 eq. of NHC was used. TBD=1,5,7-Triazabicyclo[4.4.0]dec-5-ene.

α,β-Unsaturated aldehydes, in the presence of NHCs, are known to undergo several distinct reactions to give, for example, saturated esters (**4**), [22] unsaturated carboxylic acids (**5**),[10a, 10b] and γ-butyrolactones (**6**).[23] Thus, selectivity towards the unsaturated ester **3** would give a good measure of the selectivity in the oxidation event. Initial screening, in open reaction vessels, revealed that quinone **1** alone was indeed possible to use in substoichiometric quantities[24] in the oxidative esterification of aldehyde **2**. The reaction gave **3** in 24% yield after 7h along with several byproducts from competing reaction paths (entry 2). To test our hypothesis of the possibility to combine oxidative NHC catalysis and a coupled system of ETMs for electron transfer, we investigated the effect of an additional ETM. A drastic improvement was achieved when performing the reaction in the presence of **1** and iron phthalocyanine (FePc [0.0055 equiv.]) with almost full conversion after 4h (entry 3). Notably, the reaction proceeds with a slightly better efficiency as compared to the stoichiometric reaction (entry 1). Further screening revealed that quinone **1** could be replaced with 2,6-di-*tert*-butylphenol (**7**) with equivalent efficiency (85% yield). Phenol **7** is the precursor in the synthesis of **1** and under our reaction conditions **1** is readily formed in situ.[7] Additionally, **7** is a much cheaper reagent than **1** and therefore became the ETM-precursor of choice (entry 4). Thereafter, different NHC precatalysts were investigated (Table 1, entries 5-7) with **A** proving superior as precatalyst. Furthermore, the loading of the NHC precatalyst is important: loadings higher than 0.02 equiv. results in lowered reaction efficiency (compare entry 4 with 8 and 9).

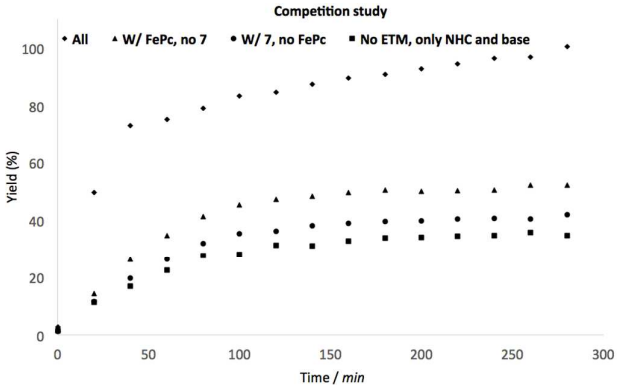


Figure 1. Kinetic profile of the oxidative esterification of **2** to **3**. See supporting information for experimental details.

Mechanistically, elimination experiments show that reactions performed without **7** stops after 100 minutes at 40% yield (Figure 1). If FePc is removed from the reactions a similar trend is observed. Without **7** or FePc the reaction reaches 30% yield and then stops. In all control experiments full conversion of starting material can be noted indicating competing background reactions. In the reactions performed without **7** a possible background reaction is the formation of a peracid. An indirect evidence of this is the isolation of carboxylic acid after aqueous work up. This is in agreement with previous reports that suggests that the homoenolate intermediate (Figure 2, **II**) is oxidized in the presence of O_2 to a peroxo-species (**III**) rather than to the acyl-azolium intermediate (**IV**).[10,12] Conversely, in the presence of both **7** and FePc, a low energy path is created so that the homoenolate intermediate (**II**) is oxidized by quinone **1** to the acyl azolium (**IV**). Intermediate **IV** reacts with the alcohol to give the unsaturated ester **V** regenerating the NHC. The proposed redox cascade is

rationalized by elimination experiments and the decreasing redox potential of the three oxidants, O_2, FePc (E = +0.74 V vs SCE)[25] and **1** (E = -0.52, -0.89 V vs SCE).[26,27]

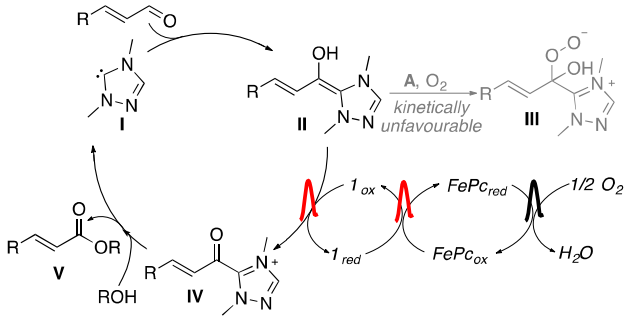
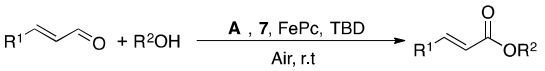
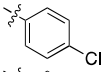
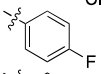
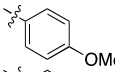
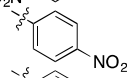
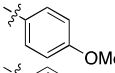
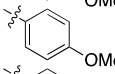
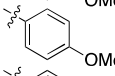
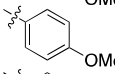
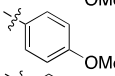
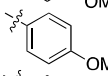
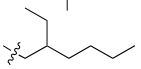
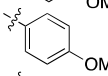
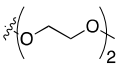
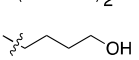


Figure 2. Catalytic cycle for the aerobic oxidative esterification of aldehydes.

Having found our optimal reaction conditions for the oxidative esterification of α,β-unsaturated aldehydes the scope of the reaction was investigated (Table 2). The reaction proceeds in good to excellent yield for a range of methyl cinnamates incorporating both electron donating and electron withdrawing substituents (entries 1-7). For example, halogen substituents are well tolerated on the aromatic ring and both 4-chloro and 4-fluoro methyl cinnamates can be isolated in 87% and 73% yield, respectively (entries 2 and 3). The reaction is also compatible with a broad range of alcohols yielding the corresponding α,β-unsaturated esters in high to excellent yields (72-98% yield, entries 8-16). For example, allyl and benzyl alcohols give their corresponding esters in 78% and 98% yield, respectively (entries 10 and 11). Moreover, methoxycinnamates such as, Amiloxate **19** and Octinoxate **20**, two out of several sunscreening agents that are based on a 4-methoxycinnamate core-structure, were both isolated in 72% yield.[28] Diols such as, 1,4-butanediol was efficiently converted to the unsaturated ester **22** in 74% yield with only traces of the diacylated byproduct found in the reaction mixture. Aliphatic α,β-unsaturated aldehydes proved to be difficult substrates and 2-hexenal and citral gave sluggish reactions. Nonetheless, conjugated aldehyde worked well and sorbic aldehyde, provided ester **23** in 69% yield. Furthermore, the reaction is scalable and compound **12** could be isolated in 1.5 g, 95% yield (entry 11). In addition, with regard to the oxidants, this reaction requires only 26.7 mg of **7** and 18.9 mg of FePc. In comparison, the anaerobic stoichiometric oxidation would need at least 2.48 g of quinone **1** to achieve a similar result. The oxidative esterifications run very clean, none of the expected byproducts can be detected on crude NMR, which simplifies purification. It also signifies the very high selectivity in each catalytic step of this multi-component reaction. Moreover, the method provides a mild direct access to unsaturated esters from aldehydes, which circumvents oxidation to the carboxylic acid that traditionally is the starting point in ester formations. Recycling experiments showed that addition of new starting materials to the reaction vessel was successful and compound **3** could be obtained in average 71% yield over three cycles (see supporting information). These results confirm that the catalytic system is not degraded over the course of the reaction and that it would be possible to design a system for recover and reuse.

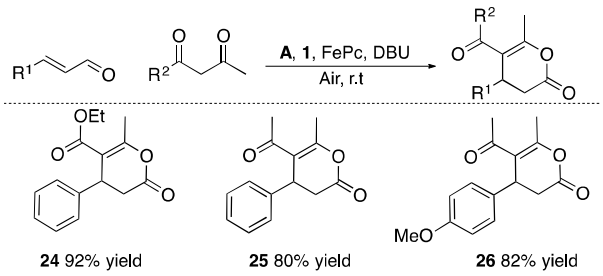
Table 2. Reaction scope of the oxidative esterification.[a]



Entry	Product	R^1	R^2	yield[b]
1	**3**			87%
2	**8**			87%
3	**9**			73%
4	**10**			72%
5	**11**			88%
6	**12**			64%
7	**13**			79%
8	**14**			89%
9	**15**			93%
10	**16**			78%
11	**17**			98% 95%[c]
12	**18**			96%
13	**19**			72%
14	**20**			72%
15	**21**			76%
16	**22**			74%
17	**23**			69%

[a] See supporting information for experimental details. [b] Isolated yields. [c] 1.5 g isolated

Encouraged by the efficiency of our simple aerobic multistep electron transfer NHC catalysis the reaction was further examined for compatibility with other reactions such as conjugate additions. Accordingly, 1,3-ketoesters and 1,3-diketones were investigated as nucleophiles in combination with cinnamaldehyde (Scheme 3).[5a, 5c, 29] The approach proved viable and lactone **24**–**26** could be isolated in 92, 80 and 82% yield, respectively. These reactions require a slightly higher loading of both ETMs and NHC but instead the loading of the base can be reduced.



24 92% yield **25** 80% yield **26** 82% yield

Scheme 3. Synthesis of lactones **23-25**. See supporting information for experimental details. Yields refer to isolated product.

In summary we have developed a new strategy relying on ETMs for aerobic oxidative NHC-catalyzed reactions. The in situ oxidation of the homoenolate to the unsaturated acyl azolium, is general, here exemplified with oxidative esterifications and oxidative Michael-additions of 1,3-dicarbonyl compounds to α,β-unsaturated aldehydes. The reactions have a broad substrate scope and the products can be isolated in good to excellent yields. The use of O_2 in the form of air as the terminal oxidant, offers an environmentally friendly and inexpensive way to scale-up the important chemistry of oxidative NHC catalysis. In the lab we are currently exploring other forms of aerobic oxidative multistep electron transfer NHC-catalyzed reactions.

Acknowledgements

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