N-acylation of oxazolidinones *via* aerobic oxidative NHC catalysis†

Linda Ta,‡ Anton Axelsson‡ and Henrik Sundén*

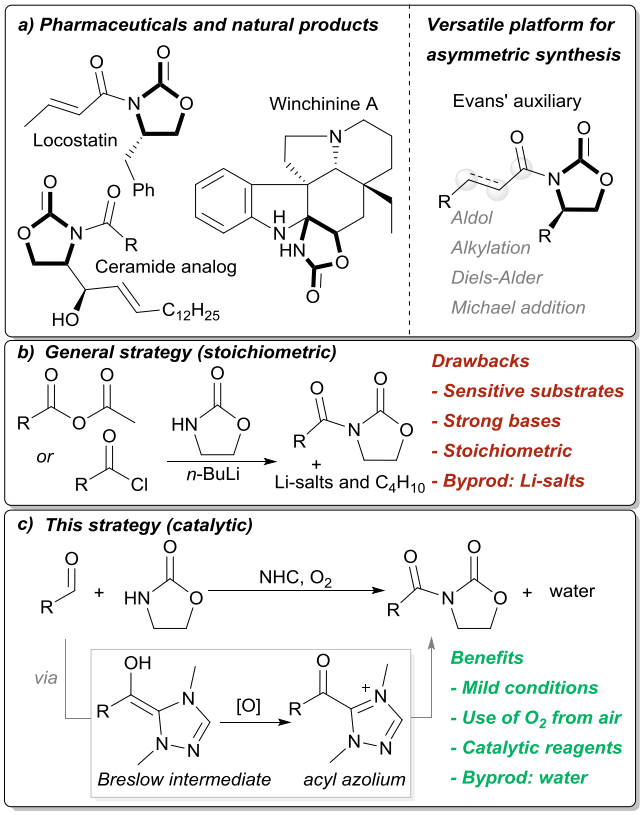
The first *N*-acylation of synthetically useful oxazolidinones with aldehydes using aerobic oxidative NHC catalysis is reported. The reaction offers a broad scope of functionalized oxazolidinones in good to excellent yields. The methodology allows a mild entry to acylated oxazolidinones avoiding the use of hazardous and reactive prefunctionalized substrates.

Functionalized oxazolidinones are important organic molecules that exhibit interesting biological activities. The oxazolidinone-moiety can, for example, be found in pharmaceuticals, such as Locostatin, a Raf-kinase inhibitor and natural products (Scheme 1a).[1] Synthetically, *N*-acylated oxazolidinones have mostly been used as chiral auxiliaries, first popularized by Evans and have been employed in different asymmetric transformations[2] such as aldol,[3] alkylation,[4] Diels-Alder reactions[5] and Michael additions[6] and in total synthesis[7] (Scheme 1a) and still attracts considerable attention within the synthetic community today.[8]

The general synthesis of *N*-acylated oxazolidinones proceeds by deprotonation normally using a strong base, such as *n*-BuLi, in combination with an acid chloride or anhydride (Scheme 1b). However, the use of highly reactive substrates, which requires special precautions as well as the usage of strong bases, capable of epimerizing chiral oxazolidinones at the C-5 position limits these protocols.[9] Alternative methods includes the use of coupling reagents,[10] acyl fluorides,[11] carbonylazoles,[12] DMAP,[13] metal catalysis,[14] and electrochemistry.[15] However, these procedures still requires highly reactive reagents, coupling reagents, high reaction temperatures and reagents in excess in order to drive the reaction to completion. Thus, adverse to the *principles of green chemistry*, these methodologies are not sustainable in terms of atom economy, energy efficiency, less hazardous synthesis and catalysis.[16] Clearly, a more environmentally benign acylation of oxazolidinones would be highly desirable (Scheme 1c).

The use of *N*-heterocyclic carbene (NHC) catalysis has emerged as an environmentally friendly method *in lieu* of transition metal catalysis, and displays a plethora of reaction pathways taking the field of organic synthesis forward.[17] In combination with an oxidant, NHC catalysis can utilize readily available aldehydes as acyl donors *via* the acyl azolium intermediate (Scheme 1c), thus circumventing the need to generate sensitive activated acyl-donors in advance.

The acyl azolium intermediate is generally formed *via* internal oxidation of the Breslow intermediate or by addition of an external oxidant, such as the Kharasch oxidant **8**. (Table 1) Conventional methods has enabled the formation of numerous novel methodologies,[18] where *O*-nucleophiles are well investigated,[18c, 19] on the contrary, methodologies for acylation of *N*-nucleophiles remain scarce.[20] These methodologies suffer from using **8** in stoichiometric amounts, generating stoichiometric quantities of waste in the downstream process.



Scheme 1 a) Various uses for functionalized oxazolidinones. b) Previous reports for *N*-acylation of oxazolidinones. c) This approach.

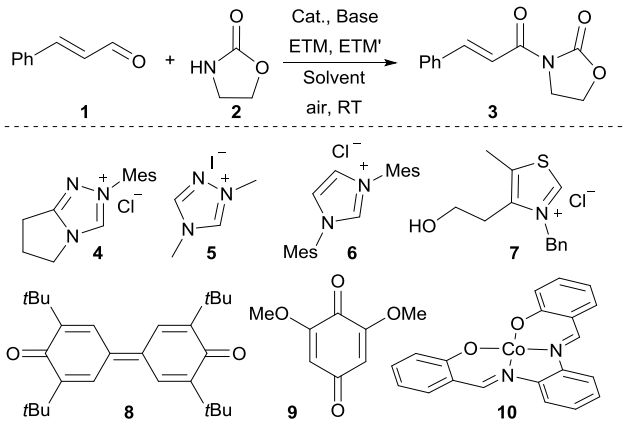
Recently, we have shown that **8** can be replaced with aerial O_2, an oxidant that generates water as the sole by-product, using a system of electron transfer mediators (ETMs) for the synthesis of various esters and dihydropyranones.[21] The system of ETMs circumvents the high energy barriers normally associated with direct aerobic oxidation by creating a low energy pathway for the electrons to flow from the substrate to oxygen.[22] It is worth noting, that by using an ETM-system, one can typically avoid side-reactions associated with aerobic NHC catalysis, such as, acid formation, homo-coupling and internal redox reactions. This selectivity can be attributed to a kinetic preference for oxidation of the homoenolate to the acyl azolium by the ETMs.

Herein, we report the first aerobic oxidative NHC-catalyzed *N*-acylation of oxazolidinones using aldehydes as mild acylation reagents. The reaction can be carried out under ambient reaction conditions and offers a broad scope of synthetically useful acylated oxazolidinones.

The starting point for this study was a survey of different NHC-precatalysts. Triazolium salts **4** and **5** were both good candidates (Table 1, entry 1 and 2) with **5** delivering **3** in slightly higher yields (53% vs. 47%). Imidazolium salt **6** (entry 3) was not as efficient in comparison (32%) and thiazolium salt **7** (entry 4) showed no activity in the reaction. Next, evaluations of different solvents were made. Ethyl acetate (EtOAc) gave comparable results with acetonitrile (MeCN) delivering the product in 55% yield (entry 6). On the other hand, dichloromethane (DCM) (entry 7) and methyl ethyl ketone (MEK) (entry 8) resulted in lower yields As EtOAc is considered a more sustainable and greener solvent alternative,[23] it became the solvent of choice.

At this point the system was still not efficient enough. The side-products isolated, γ-butyrolactone[24] the saturated *N*-acyloxazolidinone product as well as cinnamic acid, indicated a slow oxidation step of the Breslow intermediate (Scheme 1c). Further optimization with different bases and ETM-systems were investigated. The most effective base proved to be DBU (entry 9) capable of delivering **3** in 90% yield, while the weaker organic base, triethylamine (TEA) (entry 10) failed to generate any product at all. We also noted that it was possible to lower the amount of NHC catalyst (from 5 mol% to 1 mol%), base (from 0.5 eq. to 0.2 eq.). Furthermore, the reaction seemed to be sensitive to any changes in concentration; doubling the amount of EtOAc (3.2 ml, 77% yield) give lower yields in comparison with the optimized amount (1.6 ml, 90% yield). Different ETM-systems (entry 11–12) were tested and showed that **8** together with FePc were the most suited combination. With a stoichiometric amount of **8** the product was obtained in 84% yield, less efficient in comparison with our developed aerobic method (entry 13).

Table 1 Optimization of reaction conditions



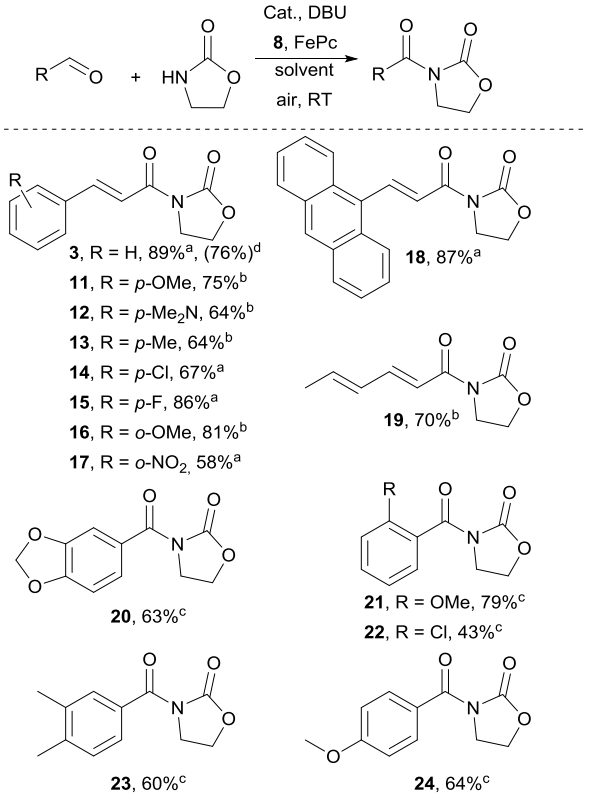
Entry	Cat.	Solvent	Base	ETM	ETM'	Yield[d]
1.[a]	4	MeCN	TBD	8	FePc	47
2.[a]	5	MeCN	TBD	8	FePc	53
3.[a]	6	MeCN	TBD	8	FePc	32
4.[a]	7	MeCN	TBD	8	FePc	0
5.[a]	5	Anisole	TBD	8	FePc	24
6.[a]	5	EtOAc	TBD	8	FePc	55
7.[a]	5	DCM	TBD	8	FePc	35
8.[a]	5	MEK	TBD	8	FePc	32
9.[b]	**5**	**EtOAc**	**DBU**	**8**	**FePc**	**90/89[e]**
10.[c]	5	EtOAc	TEA	8	FePc	0
11.[c]	5	EtOAc	DBU	8	10	39
12.[c]	5	EtOAc	DBU	9	FePc	78
13.[f]	5	EtOAc	DBU	8	-	84

Reaction conditions: [a] cinnamaldehyde (1 eq.), 2-oxazolidinone (1.5 eq.), cat (5 mol%), base (0.5 eq.), ETM (5mol%), ETM' (3 mol%), solvent (0.16 M). [b] As footnote a, but with cat (1 mol%), base (0.2 eq.), ETM (3 mol%), ETM' (2 mol%), solvent (0.31 M). [c] As footnote a, but with cat (1mol%). [d] Yield (%) is determined by ^{1}H NMR with durene as internal standard. [e] Isolated yield. [f] As footnote b, but performed under N_2 with **8** (1 eq). FePc = Iron(II)phthalocyanine, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Reactions performed by excluding the different ETMs and O_2 showed that they are essential for an efficient reaction (for full optimization of reaction conditions, see ESI).

The generality of the reaction was investigated with α,β-unsaturated aldehydes and benzaldehydes bearing different substituents (Scheme 2). Under our optimized reaction conditions, the reaction works well with both electron donating groups (compounds **11–13**, **16**) and electron withdrawing groups (compounds **14**, **15**, and **17**) with both *para*- and *orto*-substitution on the aromatic ring giving good yields. A gram-scale synthesis of **3** was also viable and could be obtained without using any chromatography. An aldehyde bearing an anthracene-moiety was converted to compound **18** in 87% yield. Moreover, a non-aromatic α,β-unsaturated aldehyde was viable, generating **19** in 70% yield. It was also noted that α,β-unsaturated aldehydes with electron donating groups on the aromatic ring required a more electron-rich catalyst **4** to furnish the products. The benzaldehydes, being less activated than their α,β-unsaturated counterpart, required slightly higher loadings of catalyst **4**. Good yields were obtained with benzaldehydes containing electron donating groups (**20**, **21**, **23**, and **24**) whereas electron withdrawing groups was only able to give compound **22** in acceptable yields (43%). The low yields were attributed to the formation of the benzoic acids *via* direct oxygenative oxidation of the Breslow intermediate with O_2.[18b]

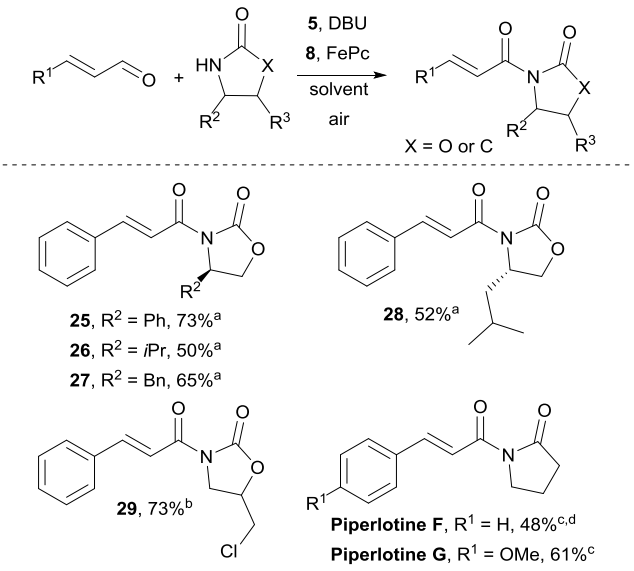
Next, the oxazolidinone-part was investigated (Scheme 3).



Scheme 2 The scope of the reaction with different aldehydes. Reaction conditions: [a] with cat **5** (1 mol%). [b] with cat **4** (1 mol%). [c] with cat **4** (4 mol%). [d] gram-scale synthesis.

Different chiral and achiral oxazolidinones were tested. The *N*-acylation of chiral oxazolidinones substituted at C-4 position

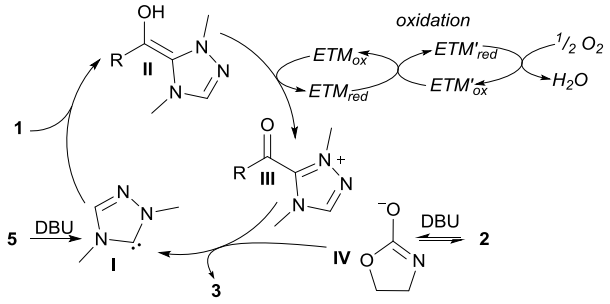
(compounds **25–28**) gave products in good yields. Due to the steric nature of the substituents, the reaction required an elevation of reaction temperature (60 °C) and a slight increase of equivalents of base. Reaction between the C-5 substituted oxazolidinone and cinnamaldehyde was able to deliver the product **29** in 73% yield under normal reaction condition,



Scheme 3 The scope of the reaction with different oxazolidinones. Reaction conditions: [a] with cat **5** (1 mol%), DBU (0.4 eq.), 60 °C. [b] with cat **5** (1 mol%). [c] with cat **5** (1 mol%), **8** (5 mol%), DBU (1.5 eq.), aldehyde (1 eq.), 2-pyrrolidinone (2 eq.). [d] with molecular sieves (4 Å, 0.2 g)

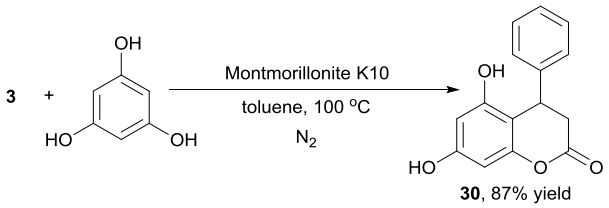
leaving the primary alkyl chloride unscathed. Furthermore, it was also possible to incorporate 2-pyrrolidinone as nucleophile for the synthesis of two natural products, Piperlotine F and Piperlotine G, an Nrf2 activator, in moderate to good yields.[25]

The postulated catalytic cycle (Scheme 4) starts with deprotonation of the NHC-precatalyst forming the active carbene species **I**. The catalyst then adds to cinnamaldehyde **1** to give Breslow intermediate **II**. With the help of the linked ETM-system, the Breslow intermediate is subsequently oxidized by O_2 *via* a multistep electron transfer step, to form the acyl azolium intermediate **III**. In the last step, the deprotonated oxazolidinone **IV** reacts with acyl azolium **III** forming **3** and regenerating the catalyst.



Scheme 4 The postulated catalytic cycle.

The synthetically useful *N*-acylated oxazolidinones were also applied in the synthesis of a 2-chromanone-scaffold found in the natural products of the calomelanol family (Scheme 5).[26] Compound **3** was reacted with phloroglucinol in toluene at 100 °C using montmorillonite K10 as catalyst giving compound **30** in 87% yield through a tandem Friedel-Craft alkylation lactonization.[27]



Scheme 5 Application of the *N*-acylated compounds.

In summary, the first oxidative NHC-catalyzed *N*-acylation of oxazolidinones and pyrrolidinone has been reported. In combination with an ETM system the reaction uses molecular oxygen as a terminal oxidant in an atom efficient manner. The reaction has a high functional group compatibility, providing a broad scope of *N*-acylated oxazolidinones. The method was also used for the synthesis of two natural products, Piperlotine F and Piperlotine G. The acylated oxazolidinones were further modified in the synthesis of a 2-chromanone using montmorillonite K10 as catalyst. The developed methodology offers a sustainable way of using readily available aldehydes as acylation reagents circumventing the need for highly reactive prefunctionalized substrates.

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