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NHC-Catalyzed *O*-Selective Addition of Nitrosoarenes with Aldehydes

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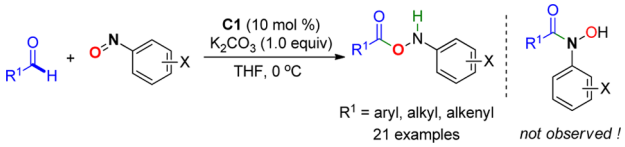
ABSTRACT



An NHC-catalyzed *O*-selective addition of nitrosoarenes with aldehydes probably upon a dual-activation mode was developed, generating a variety of *O*-acyl hydroxylamines without any detectable competing amidation byproducts.

Selective transformations of the same starting materials into two or more different products simply by the choice of catalyst provide an expedient approach to molecular diversity synthesis.[1] Nitroso compounds are versatile reagents utilized as a nitrogen and/or an oxygen source in organic synthesis.[2] Due to their high reactivity based on the polarization of the N−O bond and specific structure by the equilibration between the monomer and azodioxy dimer, the control of chemo- and regioselectivity for various catalytic reactions using nitroso derivatives is a challenge of fundamental importance.[3]

N-Heterocyclic carbene (NHC) catalysis has developed to a powerful tool for chemical synthesis during the past decade.[4] Notably, a variety of NHC-catalyzed reactions of aldehydes with nitroso compounds, such as amidation,[5] cycloaddition,[6] and three-component reactions involving enone components[7] have been achieved primarily upon the nucleophilic attack of Breslow intermediate **I** or **II** at the nitrogen atom of nitroso groups (Scheme 1a).[8] Moreover, Lobo and Prabhakar have also studied a model reaction of 2-(α-hydroxyalkyl)-3,4-dimethylthiazoliums, a precursor of **I**, with nitrosoarenes in the presence of base and find the formation of a mixture of *O*- and *N*-acylhydroxylamine products.[9] Heretofore, the catalytic *O*-selective attack of Breslow intermediate **I** on nitroso electrophiles to form C−O bonds remains to be exploited. We envisaged that if an appropriate Lewis acid/hydrogen-bonding donor could

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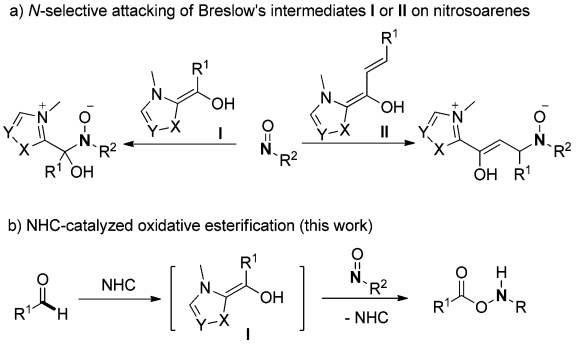
10.1021/ol4012458

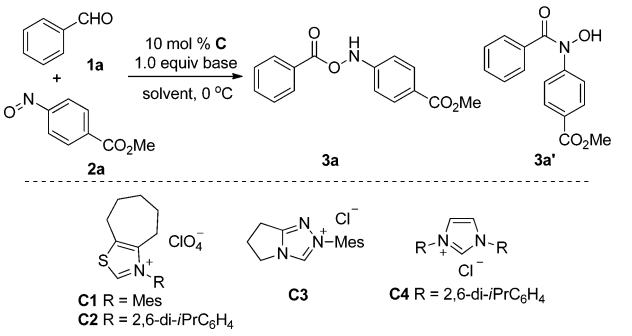
activate the nitrosoarene without disturbing the oxidative NHC catalysis,[10] the *O*-selective acylation of nitroso groups would be achieved. Herein, we want to report an NHC-catalyzed oxidative esterification of aldehydes[11] with nitrosoarenes by using thiazolium carbene as a single dual-activation catalyst[12] to realize the selective formation of *O*-acyl hydroxylamines (Scheme 1b).

Scheme 1. NHC-Catalyzed Reaction of Aldehydes and Nitrosoarenes



We began our investigation by examining the reaction between benzaldehyde (**1a**) and methyl 4-nitrosobenzoate (**2a**) in the presence of K_2CO_3 and NHC precursors **C** (Table 1, entries 1−4). After assessing four commonly encountered NHC catalysts, we were delighted to find that thiazolium salt **C1**[13] was the most effective in promoting the desired C−O bond-forming process to furnish *O*-acyl hydroxylamine **3a** in 86% yield without any detectable amount of amidation product **3a′**.[14] In contrast, triazolium salt **C3** gave a mixture of **3a** (45%) and **3a′** (12%) as the product (entry 3). When employing **C1** as the precatalyst, the base played a critical influence on this reaction. Switching the base to *t*-BuOK afforded **3a** in a diminished yield due to the decomposition of the product (Table 1, entry 5). In contrast, when DBU or Et_3N was used instead, no productive reaction was detected by TLC (entries 6 and 7). Moreover, a stoichiometric amount of K_2CO_3 with respect to **1a** is essential to accomplish this conversion (Table 1, entry 8). Finally, among those solvents tested, THF was the choice, as it led to the best result (Table 1, entries 1 and 9−11).

Table 1. Optimization of Reaction Conditions[a]



entry	C	base	solvent	time (h)	yield[b] (%) 3a	3a′
1	**C1**	K_2CO_3	THF	6	86	–
2	**C2**	K_2CO_3	THF	6	53	–
3	**C3**	K_2CO_3	THF	3	45	12
4	**C4**	K_2CO_3	THF	12	–	–
5	**C1**	*t*-BuOK	THF	0.5	77	–
6	**C1**	DBU	THF	12	–	–
7	**C1**	Et_3N	THF	12	–	–
8[c]	**C1**	K_2CO_3	THF	12	44 (40)[d]	–
9	**C1**	K_2CO_3	Toluene	6	51	–
10	**C1**	K_2CO_3	CH_2Cl_2	6	55	–
11[e]	**C1**	K_2CO_3	*i*-PrOH	12	22	–

[a] Unless otherwise noted, a mixture of **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst **C** (10 mol %), K_2CO_3 (0.2 mmol), and solvent (2 mL) under N_2 was stirred at 0 °C. [b] Isolated yield. [c] K_2CO_3 (0.1 mmol). [d] Recovery of **1a** is in parentheses. [e] Some unidentified byproducts were formed.

The reactions of a range of aldehydes **1** with nitroso compound **2a** were next examined. As shown in Figure 1, a set of electron-deficient benzaldehyde derivatives with various substitution patterns all carried out this reaction smoothly to form the corresponding products **3b**−**f** in good yields. Picolinaldehyde also readily participated in this process to give **3g** in 91% yield. Unfortunately, those targeted products derived from aromatic aldehydes bearing an electron-donating group such as 4-methoxybenzaldehyde is too fragile under the current reaction conditions, only furnishing some unidentified byproducts. Gratifyingly, aliphatic aldehydes, such as *n*-octanal and 2-bromocyclopent-1-enecarbaldehyde, were found to be suitable substrates, and the desired products **3h** and **3i** were obtained in 56% and 49% yield, respectively. Finally, in each case, the current NHC-catalyzed reaction affords *O*-acyl products of methyl 4-nitrosobenzoate without any detectable *N*-acyl products.

To further explore the scope and synthetic application of the current NHC-catalyzed *O*-selective conversion of

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(13) Lebeuf, R.; Hirano, K.; Glorius, F. *Org. Lett.* **2008**, *10*, 4243.

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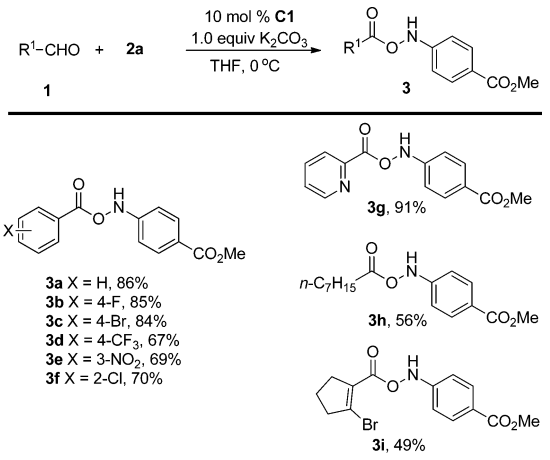


Figure 1. NHC-catalyzed formation of *O*-acyl hydroxylamines **3**.

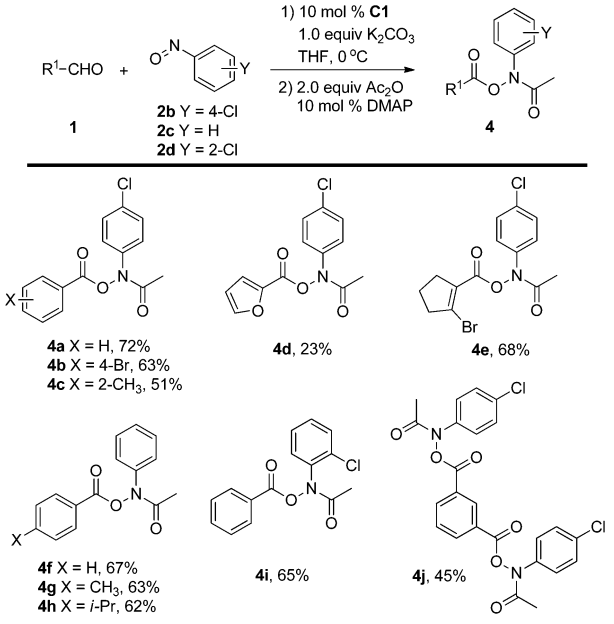
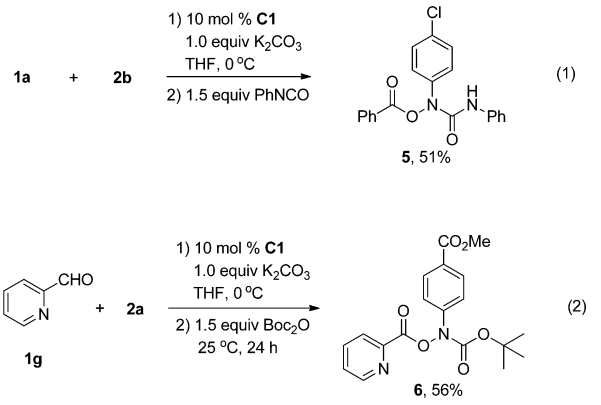


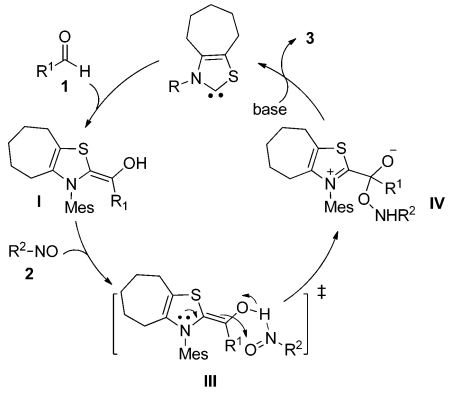
Figure 2. Formation of *N*,*O*-diacyl-*N*-arylhydroxylamines **4**.

nitrosoarenes, we subsequently investigated a two-step, one-pot approach to *N*,*O*-diacyl-*N*-arylhydroxylamines.[15] Employing acetic anhydride (2 equiv) and DMAP (10 mol %) as acylation reagents in the second amidation step,[16] a set of aldehydes and other three nitrosoarenes **2b**–**d** were generally well tolerated, giving the desired products **4** in reasonably good yields (Figure 2). However, due to the decomposition of corresponding *O*-acyl hydroxylamine intermediates, furfural only furnished the targeted product **4d** in quite low yield. Intriguingly, isophthalaldehyde had also successfully been employed in this process to produce the corresponding product **4j** in 45% yield. On the other hand, while electron-poor or electron-neutral nitrosoarenes carried out this reaction smoothly, those substrates with an electron-rich aryl moiety did not work in the reaction.



In addition, isocyanatobenzene and Boc_2O were also suitable acylation reagents instead of acetic anhydride for this one-pot protocol, giving the corresponding products **5** and **6** in 51% and 56% yield, respectively (eqs 1 and 2).

Scheme 2. Proposed Catalytic Cycle



Based on the experimental results, a proposed catalytic cycle is depicted in Scheme 2. Thus, the addition of in situ generated NHC to aldehydes **1** followed by proton transfer initially forms Breslow intermediates **I**. The latter nucleophilic species **I** then attack nitrosoarenes **2** at the oxygen atom to give intermediates **IV**. The *O*-selective nature of this step indicates a transition state of **III**, which involves a potential hydrogen-bonding interaction between the positively polarized proton of the enaminol and the nitrogen atom of the nitroso group.[17] Finally, the zwitterions **IV** release the NHC catalyst and give desired *O*-acyl hydroxylamines **3**.

In summary, we have described an NHC-catalyzed *O*-selective addition of nitrosoarenes with aldehydes, giving a type of *O*-acyl hydroxylamines without any detectable

(16) For optimization of conditions see the Supporting Information.

(17) Hydrogen-bonding interaction has been previously proposed for the organocatalytic *O*-nitrosoaldol reaction; for selected references, see: (a) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293. (d) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374.

competing amidation byproducts. Moreover, upon this reaction, a one-pot approach to various *N*,*O*-diacyl-*N*-arylhydroxylamines has been developed. It is proposed that a dual-activation mode of the distinct carbene catalyst generated from thiazolium salt **C1** is critical to achieving complete *O*-selectivities in the reaction.

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Supporting Information Available. Experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.