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N-Heterocyclic Carbene (NHC)-Catalyzed Direct Amidation of Aldehydes with Nitroso Compounds

Fong Tian Wong, Pranab K. Patra, Jayasree Seayad,* Yugen Zhang,* and Jackie Y. Ying

Institute of Bioengineering and Nanotechnology, 31 Biopolis Way, The Nanos, Singapore 138669, Singapore

ygzhang@ibn.a-star.edu.sg; jayasree@ibn.a-star.edu.sg

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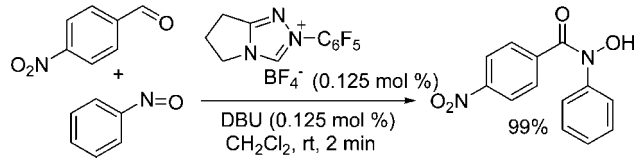
ABSTRACT



NHC-catalyzed direct amidation of aldehydes with nitroso compounds is a powerful method for the synthesis of *N*-arylhydroxamic acids. A variety of aryl, alkyl, alkenyl, and heterocyclic aldehydes were found to give excellent yields of the corresponding *N*-arylhydroxamic acids. This chemistry was also extended to the synthesis of chiral *N*-arylhydroxamic acids by kinetic resolution of α-branched aldehydes, a domino amidation−redox amination reaction of acrolein, and a three-component reaction for the synthesis of *N*-arylaziridines.

N-Heterocyclic carbene (NHC) catalysis is an efficient method for metal-free carbon−carbon bond formation via the nucleophilic "Breslow intermediate"[1] **ii** (Scheme 1) or the homoenolate equivalent species.[2] Depending on the electrophiles, different types of reactions are possible via both intermediates. Key examples for the former path are benzoin condensation,[3] wherein an aryl aldehyde acts as the electrophile, and Stetter reaction,[4] in which a Michael accepter takes the role. More recent examples include redox reactions of α-functionalized aldehydes to form the corresponding esters[5] or amides.[6] Examples of C−C bond-forming reactions using a homoenolate equivalent include lactonization,[2] cyclopentannulation,[7] azannulation,[8] etc. We have recently developed a NHC-catalyzed homoenolate intermediate based C−N bond formation by the reaction of α,*β*-unsaturated aldehydes with nitrosobenzene forming *N*-phenylisoxazolidin-5-ones.[9] These *N*-phenylisoxazolidin-5-ones were further converted to the corresponding *N*-*p*-methoxyphenyl (*N*-PMP)-protected *β*-amino acid esters via a simple acid-catalyzed Bamberger-like rearrangement in a mild one-pot

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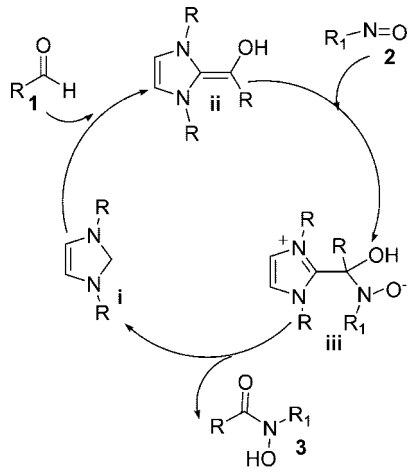
Scheme 1. Prosposed Amidation of Aldehydes Using Nitrosobenzene



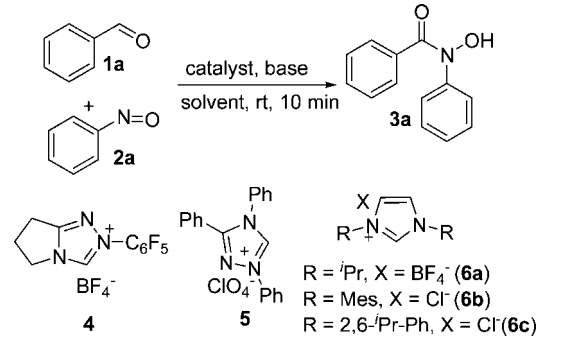
synthetic protocol. In another recent study, Chan and Scheidt reported the NHC-catalyzed amination of homoenolates using diazenes.[10]

Nitroso compounds exhibit a high reactivity of the nitroso group.[11] The polarization of the nitrogen−oxygen bond, resembling that of the carbon−oxygen bond in a carbonyl group, results in susceptibility of the nitroso group to additions of nucleophiles. By exploiting the higher reactivity of the nitroso group relative to its carbonyl counterpart toward nucleophilic attack, we envisaged a possibility that involved reaction of the intermediate **ii** with nitrosobenzene-forming hydroxamic acid instead of acyloin.

The chemistry and biochemistry of hydroxamic acids are well documented. They are strong metal ion chelators[12] and possess extensive pharmacological, toxicological, and pathological properties.[13] Some of them are being examined in human clinical trials as drugs for the treatment of several diseases.[14] *N*-Arylhydroxamic acids[15] are also known to be proximate carcinogens[16] and demand simple synthetic protocols. Recently, many synthetic approaches to hydroxamic acids have appeared in the literature, mostly involving acylation of hydroxylamines.[17] Other known synthetic pathways to *N*-arylhydroxamic acids involve oxidation of arylacyl amides[18] and reaction of aromatic nitroso compounds with oxoacids in the presence of thiamine-dependent enzymes[19] or acidic media.[20] Herein we report a very simple and efficient synthesis of *N*-arylhydroxamic acids by NHC-catalyzed amidation of aldehydes[21] via acyl anion addition to aryl nitroso compounds.

In our preliminary experiments, we found that benzaldehyde and nitrosobenzene reacted rapidly in the presence of the NHC catalyst generated from the triazolium salt **4**[22] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), forming *N*-hydroxy-*N*-phenylbenzamide **3a** in excellent yields. No formation of benzoin was observed under these conditions. Optimization studies using different imidazolium and triazolium salts indicated that sterically less hindered triazolium salts provided higher yields of the product (Table 1). The

Table 1. Catalyst Optimization



entry	catalyst (mol %)	solvent	base	yield (%)[a]
1	**4** (20)	CH_2Cl_2	DBU[b]	99
2	**5** (20)	CH_2Cl_2	KO^{t}Bu	50
3	**6a** (20)	CH_2Cl_2	KO^{t}Bu	trace
4	**6b** (20)	CH_2Cl_2	KO^{t}Bu	55
5	**6c** (20)	CH_2Cl_2	KO^{t}Bu	trace
6	**4** (20)	CH_2Cl_2	KO^{t}Bu	95
7	**4** (20)	THF	KO^{t}Bu	85
8	**4** (0.5)	CH_2Cl_2	DBU	99
9	**4** (5)	CH_2Cl_2	DBU	99
10	none	CH_2Cl_2	DBU	0

[a] GC yield. [b] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

only observable side product was traces of azoxybenzene, which was minimized by optimizing the reaction parameters.

The scope of the reaction was examined by varying the aldehydes (**1a**−**1q**), as well as the nitroso compounds (**2a**, **2r**−**2u**). As shown in Table 2, a variety of aryl, alkyl, alkenyl, and heterocyclic aldehydes gave excellent yields (55−99%) of the corresponding *N*-arylhydroxamic acids (**3a**−**3u**).

We have also scaled up the synthesis of *N*-hydroxy-4-nitro-*N*-phenylbenzamide, **3c**, to a 5 g scale using 0.125 mol % of catalyst **4**. The reaction was rapidly completed within 2 min, resulting in a turnover frequency (TOF) of 24 000

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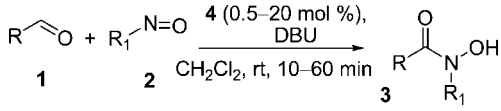
Table 2. NHC-Catalyzed Synthesis of *N*-Arylhydroxamic Acids



entry	R	R_1	yield (%)[a]
1	C_6H_5 (**a**)	C_6H_5 (**a**)	96
2	4-$OMeC_6H_4$ (**b**)	C_6H_5	99
3	4-$NO_2C_6H_4$ (**c**)	C_6H_5	99
4	4-BrC_6H_4 (**d**)	C_6H_5	95
5	1-methyl-1*H*-imidazol-2- (**e**)	C_6H_5	98
6	$C_6H_5CH(CH_3)$ (**f**)	C_6H_5	89
7	$C_6H_5CH_2CH_2$ (**g**)	C_6H_5	78
8	C_6H_{11} (**h**)	C_6H_5	97
9	C_3H_5 (**i**)	C_6H_5	99
10	*n*-C_4H_9 (**j**)	C_6H_5	99
11	$C_6H_5CH{=}CH$ (**k**)	C_6H_5	95
12	$C_6H_5CH{=}C(CH_3)$ (**l**)	C_6H_5	96
13	4-$OMeC_6H_4CH{=}CH$ (**m**)	C_6H_5	87
14	4-$NO_2C_6H_4CH{=}CH$ (**n**)	C_6H_5	99
15	3-OMe-4-$OTfC_6H_3CH{=}CH$ (**o**)	C_6H_5	80
16	$EtOOC{-}CH{=}CH$ (**p**)	C_6H_5	99
17	$CH_2{=}CH$ (**q**)	C_6H_5	99
18	C_6H_5	4-$(Me)_2NC_6H_4$ (**r**)	93
19	C_6H_5	3,5-Me-4-$(OH)C_6H_2$ (**s**)	55
20	C_6H_5	2,6-$F_2C_6H_3$ (**t**)	82
21	C_6H_5	2-MeC_6H_4 (**u**)	77

[a] Isolated yields.

h^{-1}. The product precipitated as a yellow solid after the reaction and was obtained by filtration in excellent yields and purity (Figure 1).

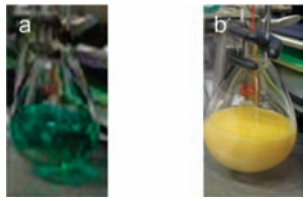
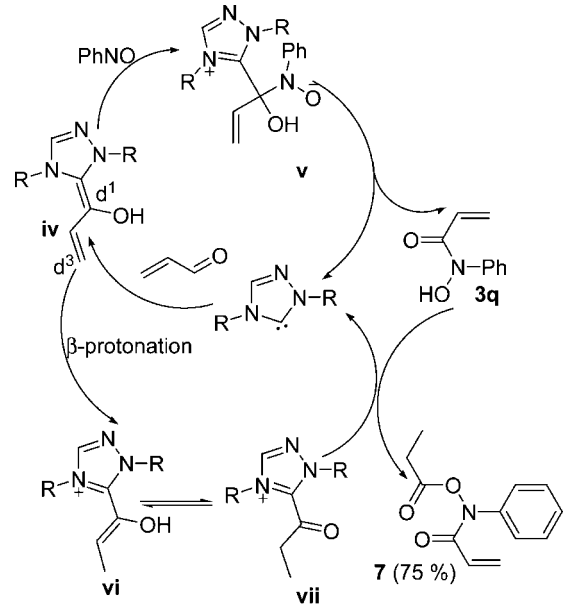


Figure 1. NHC-catalyzed synthesis of *N*-hydroxy-4-nitro-*N*-phenyl benzamide (**3c**). Scale up of 5 g product (a) before activation of the catalyst (**4**, 0.125 mol %), and (b) after reaction completion (in 2 min).

In the case of acrolein (**1q**), when used in excess to nitrosobenzene (3 equiv), a novel domino amidation−redox amination reaction took place, forming the corresponding *N*-propionyloxy-*N*-phenylacrylamide (**7**) as the major product (75%).

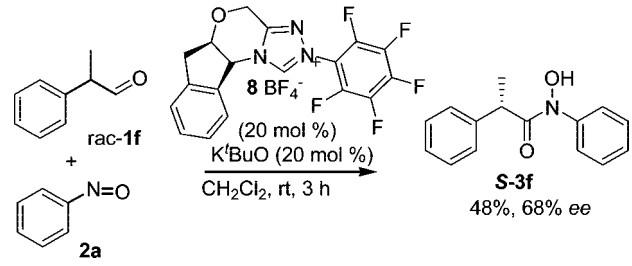
Here, two catalytic cycles seemed to operate, one forming the *N*-arylhydroxamic acid by the reaction of the d^1 nucleophile with the nitroso compound and the second through protonation of the d^3 nucleophile forming the activated ester **vii**, which then reacted with the hydroxamate nucleophile (**3q**) forming the product **7** and carbene catalyst (Scheme 2).

Scheme 2. Prosposed Domino Amidation−Redox Amination of Acrolein with Nitrosobenzene



A preliminary study on the synthesis of chiral *N*-arylhydroxamic acids[23] by kinetic resolution of the α-branched aldehyde **1f** by reaction with nitrosobenzene in the presence of NHC catalyst derived from the chiral triazolium salt **8**[24] resulted in 48% yield and 68% ee of the product (*S*)-**3f** (Scheme 3).

Scheme 3. NHC-Catalyzed Synthesis of Chiral *N*-Arylhydroxamic Acids by Kinetic Resolution of α-Branched Aldehydes



The applicability of this methodology was also extended to a three-component, one-step synthesis of *N*-arylaziridines by reaction of the aldehyde, nitroso compound, and a Michael acceptor. The reaction between hydroxamic acids and acrolyl

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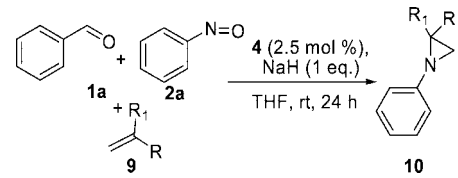
derivatives forming *N*-arylaziridines has been reported previously.[25] In our studies, we found that benzaldehyde, nitrosobenzene, and acrolyl derivatives **9a**−**9e** reacted in the presence of the NHC catalyst generated from the triazolium salt **4** and NaH, forming the corresponding *N*-arylaziridines **10a**−**10e** in high yields (Table 3).

In conclusion, we have developed a powerful NHC-catalyzed amidation of aldehydes with nitroso compounds to form a variety of *N*-arylhydroxamic acids. The reaction can be carried out with catalyst concentration as low as 0.125 mol %. The applicability of the protocol is extended to the synthesis of chiral *N*-arylhydroxamic acids by kinetic resolution of α-branched aldehydes, a domino amidation−redox amination reaction of acrolein, and a three-component synthesis of *N*-arylaziridines. Further optimization of the enantioselective variant and elaboration of the scope of the reaction is underway.

Table 3. NHC-Catalyzed Three-Component Synthesis of *N*-Arylaziridines



entry	R	R_1	yield (%)[a]
1	COOMe (**a**)	H	82
2	COO^{t}Bu (**b**)	H	87
3	CN (**c**)	H	71
4	COOMe (**d**)	Me	67
5	COOMe (**e**)	CH_2COOMe	69

[a] Isolated yields.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, HPLC traces, X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

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