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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Electrophilic α-Amination Reaction of β-Ketoesters Using *N*-Hydroxycarbamates: Merging Aerobic Oxidation and Lewis Acid Catalysis

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Supporting Information

ABSTRACT: The copper-catalyzed α-amination of carbonyl compounds using nitrosoformate intermediates as the electrophilic source of nitrogen is reported. The reaction merges aerobic oxidation and Lewis acid catalysis. The scope of the reaction is broad in terms of both the N-substituted hydroxylamines and the β-ketoesters. The new methodology harnesses the power of nitrosoformate intermediates and demonstrates their potential as a viable electrophilic source of nitrogen in α-functionalization reactions.

The efficient and direct synthetic construction of α-amino carbonyl compounds using an electrophilic source of nitrogen has been a long-standing challenge in organic synthesis.[1] Recently, nitrosobenzene and its analogues have been recognized as an attractive electrophile for α-heteroatom functionalization reactions of carbonyl compounds.[2] Nitrosoarenes can serve as both an electrophilic source of nitrogen or oxygen depending on the reaction conditions.[3] The aminoxylation reaction to afford α-oxygenated carbonyl compounds has been extensively developed and now represents a versatile method to gain access to the α-oxycarbonyl synthon (Figure 1a).[4] In contrast, while the N-selective nitroso aldol reaction has made considerable progress,[3d−f,5] the products of the hydroxyamination reaction are synthetically limited because it is often difficult to cleave the *N*-aryl bond to allow for subsequent nitrogen-bond forming transformations (Figure 1b).[5f,6] Notably absent from nitroso aldol methods are examples with nitrosocarbonyl intermediates, which can easily be modified and would represent a desirable alternative to arylnitroso compounds in electrophilic amination. In this communication, we present the development of the first N-selective nitroso aldol reaction utilizing nitrosoformate esters, generated in situ, as the electrophilic source of nitrogen (Figure 1c).[7] This new process is highly N-selective, uses an operationally convenient procedure, air, as the sole oxidant, and provides direct entry into α-amino carbonyl derivatives with functional groups that are easy to manipulate.

Recently, we reported the formation of nitroso compounds using a copper-catalyzed aerobic oxidation of N-substituted hydroxylamines.[8] In these reactions, the highly reactive and transient nitroso intermediates are generated catalytically under mild reaction conditions, which appears to help avoid previously reported problems associated with their in situ formation and subsequent chemistry.[9] On the basis of these studies and the limitations associated with the N-selective arylnitroso aldol reaction, we were encouraged to investigate if the transient electrophilic nitrosoformate intermediate could be trapped with an enolate equivalent.

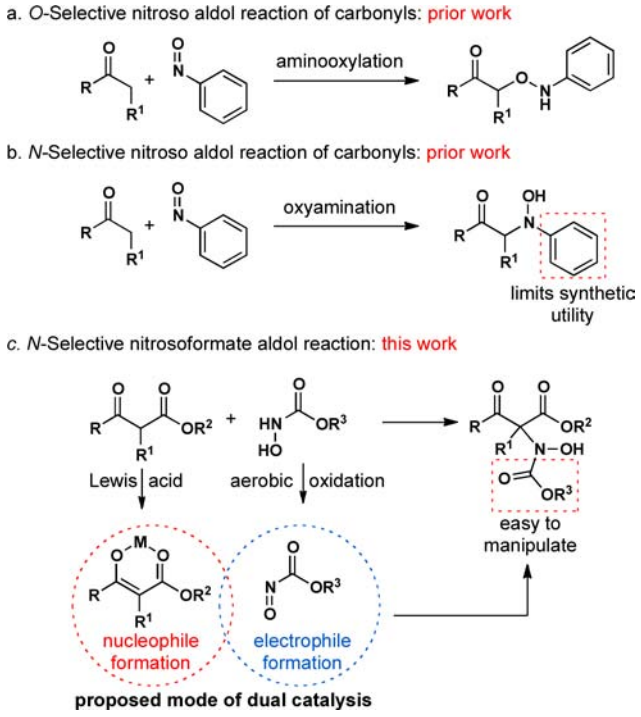


Figure 1. α-Functionalization of carbonyl compounds.

With this in mind, we set out to merge aerobic oxidation with Lewis acid catalysis. The use of synergistic catalysis is a powerful approach to reaction design and has emerged as a highly attractive strategy for developing new and valuable transformations.[10] As shown in Figure 1c, we envisioned that the concurrent activation of latent nucleophilic (β-ketoester) and electrophilic (nitrosoformate) partners could be achieved. The union of these catalytic processes would result in a direct α-amination reaction of β-ketoesters. The central challenge was to identify conditions that would allow for the compatible formation of the electrophile and nucelophile in situ, would facilitate subsequent C−N bond formation, and would avoid

Received: November 1, 2012
Published: November 5, 2012

dx.doi.org/10.1021/ja310784f | J. Am. Chem. Soc. 2012, 134, 18948−18951

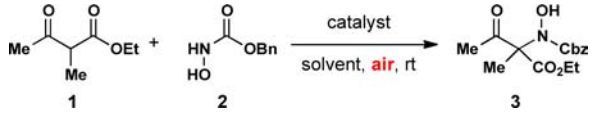
decomposition of the highly reactive nitrosoformate ester intermediate. In this regard, we felt copper complexes held tremendous promise and would be an excellent choice to initiate our investigations. In addition to our studies on Cu(I)-catalyzed nitroso formation, Shea and Whiting have developed a Cu(II)-catalyzed aerobic oxidation of *N*-hydroxycarbamates to nitrosoformates.[11] Moreover, copper(II) complexes have proven effective as a means of enolate generation in metal-catalyzed functionalization of β-ketoesters.[12]

The reaction of ethyl β-keto ester **1** with carbobenzyloxy (Cbz)-protected hydroxylamine **2** was chosen as a test reaction (Table 1). Our initial studies revealed that the proposed α-amination with nitrosoformate could be accomplished by the addition of copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) to our original optimized conditions (entries 1), albeit in a modest 3:1 N/O-selectivity.[13] To our gratification, promising levels of N/O-selectivity were obtained by changing the solvent from THF to MeOH (entry 2). A further increase in N-selectivity (11:1 to 14:1) resulted when pyridine was removed from the reaction (entry 3). We found that other polar protic solvents, such as ethanol and isopropanol, negatively affected the N-selectivity (entries 4 and 5). In the absence of either $Cu(OTf)_2$ or CuCl, we observe a slight decrease in the N/O-selectivity or efficiency, respectively (entries 6 and 7). The conditions that provided the optimal balance between efficiency and selectivity was 5 mol % CuCl and 5 mol % $Cu(OTf)_2$ (entry 8). It is conceivable that two separate catalysts simultaneously activate the nucelophile and electrophile; however, other possibilities cannot be ruled out at this time. Importantly, the optimized protocol is practical and operationally simple. It involves simultaneous addition and mixing of all reagents, at room temperature, open to air, with reagent grade solvent and inexpensive and readily available metal catalysts.

With optimized reaction conditions in hand (5 mol % CuCl and $Cu(OTf)_2$, MeOH, air, rt), we investigated the scope of the α-amination reaction by initially varying the ester group on the β-ketoesters and the N-substituent on the hydroxylamine (Table 2). There appears to be no substantial steric restrictions of the ester moiety. Methyl, ethyl, allyl and *t*-butyl derivatives all proceed in high yield, with comparable reaction rates (**3** and **7**–**9**). X-ray crystal structure analysis of **9** was used to establish that the reaction had taken place on nitrogen.[14] In addition, steric and electronic modifications to the N-substituent on the hydroxylamine were also well tolerated. *N*-Hydroxycarbamates bearing protecting groups that could be orthogonally deprotected, Cbz, Boc, Fmoc, Troc, and Nppoc, all participated in greater than 79% yield (**10**–**13**). In all cases, the O-selective adduct was observed in minor amounts and could be separated by column chromatography.[15]

Encouraged by these results, we further explored the scope of the transformation with a series of substituted β-keto esters. β-Keto esters with alkyl, benzyl, or aryl substituents at R^1 all afforded excellent yields of the desired hydroxyamination product (Table 3). Notably, a more sterically bulky α-branched substrate underwent smooth conversion to give **21** in 91% yield. Next, the electronic nature of aryl substitutents at R^1 was investigated and found to have minimal effect on the reaction outcome. Both electron rich and electron deficient aryl groups were found to be compatible (**22**–**26**). Importantly, initial studies suggest that there is some leeway in the steric bulk of the α-substituent (**27**–**32**). For example, α-substitution (R^2) with methyl, ethyl and benzyl groups all proceeded in excellent yield. The methodology can also be used for cyclic β-ketoesters (**29** and **30**) but the O-regioisomer became more competitive in such cases, affording O-selective products in 25% and 40%, respectively. In general, the rate of the reaction slowed and higher ratios of the O-selective adduct were observed as the steric bulk of the α-substitution increased (**29**–**31**). Unsubstituted carbonyl compound (**32**, R^2 = H) can be activated toward electrophilic substitution. Interestingly, in this case we observed N–O bond heterolysis and presumably the formation of an α-imino β-ketoester that is trapped by methanol to afford **32**.[16]

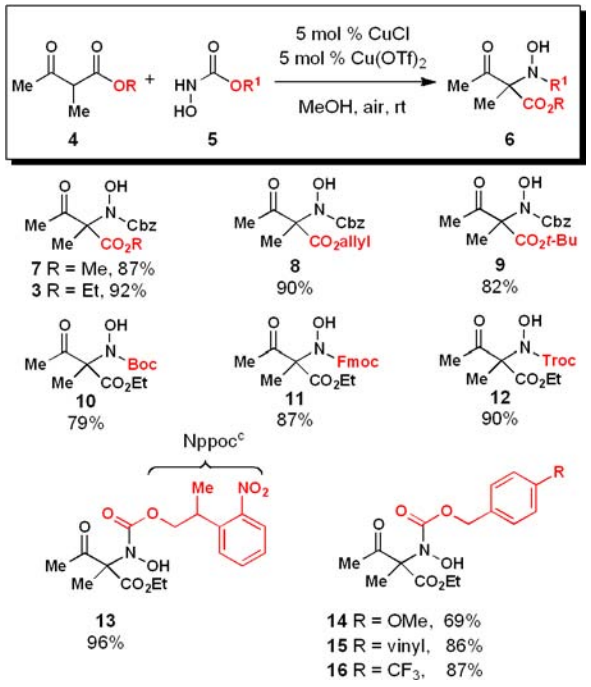
Table 1. Copper-Catalyzed Nitrosoformate α-Amination Reaction



entry	$CuCl/Cu(OTf)_2$	additive	solvent	time (h)	yield (%)[a]	N/O ratio[b]
1	10/10 mol %	pyr[c]	THF	56	86	3:1
2	10/10 mol %	pyr[c]	MeOH	9	91	11:1
3	10/10 mol %	–	MeOH	12	94	14:1
4	10/10 mol %	–	EtOH	24	90	4:1
5	10/10 mol %	–	iPrOH	53	80	2:1
6	10/0 mol %	–	MeOH	24	94	9:1
7[d]	0/10 mol %	–	MeOH	192	74	14:1
8	5/5 mol %	–	MeOH	24	97	14:1

[a]Isolated yield of the N- and O-product mixture. [b]Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c]Reaction conducted with 1.25 mol % of pyridine. [d]The reaction with 5 mol % catalyst was prohibitively long.

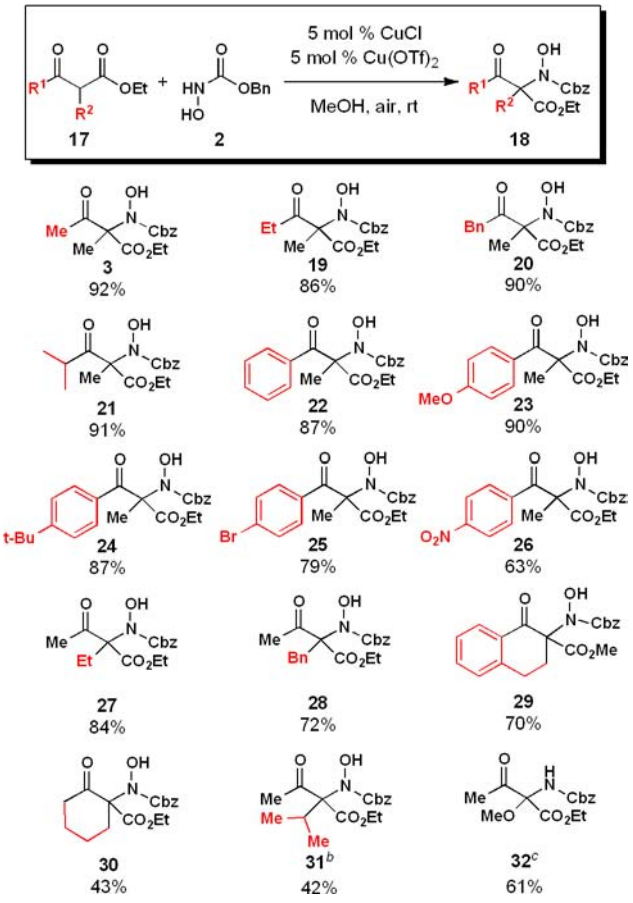
Table 2. Substrate Scope Studies for the Nitrosoformate α-Amination Reaction[a,b]



[a]All reactions were performed with reagent-grade MeOH, using 1.2 equiv of **4** and 1 equiv of **5**. [b]Yields are reported as isolated yields of the N-regioisomer.

dx.doi.org/10.1021/ja310784f | J. Am. Chem. Soc. 2012, 134, 18948–18951

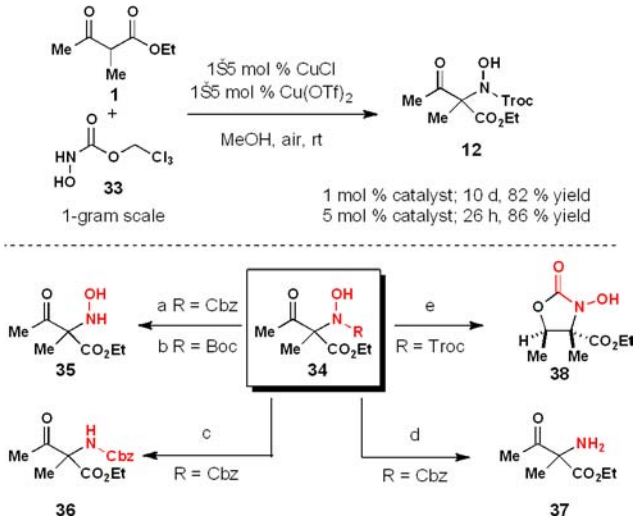
Table 3. β-Keto Ester Substrate Scope Studies for α-Amination Reaction[a]



[a]All reactions were performed with reagent-grade MeOH, using 1.2 equiv of **17** and 1 equiv of **2**. [b]Reaction was conducted with 20 mol % of each copper catalyst. [c]Unsubstituted β-keto ester (R^2 = H) was used as the starting material for this reaction.

To demonstrate the synthetic utility of this method, the reaction was performed on gram-scale (Scheme 1). The catalyst loading could be lowered to 1 mol % with no significant loss in overall yield, although the reaction required 10 days for completion. Although a number of synthetic transformations could be envisioned for the α-amination products, we focused on a series of functional group manipulations that highlight the utility of using a nitrosoformate intermediate as the electrophilic source of nitrogen. For example, hydrogenation of the Cbz-group with 5 mol % Pd/C or an acid catalyzed deprotection of Boc-group leads to α-hydroxylamine product (**35**). It is worth noting that the expected N−O bond cleavage under the reducing conditions was not observed. In addition, this compound was surprisingly stable to column chromatography; presumably these effects are due to steric hindrance. Alternatively, the N−O bond can be cleaved using Zn and 2N HCl to afford **36** in excellent yield. Most notably, the free amine can be obtained by a hydrogenation of **37**.[17] Given the difficulty in isolating **37** and its tendency to undergo self-condensation, we were unable to isolate the α-amination product directly from **12**. The ^{1}H NMR of the crude material from the deprotection of **12** showed the desired product **37**, but isolation resulted in substantial amounts of decomposition and poor mass recovery. Lastly, *N*-oxazolidinone **38** can be obtained directly by a reduction of the β-keto functionality with

Scheme 1. Synthetic Utility of α-Amination Adducts[a]



[a](a) Pd/C (5 mol %), MeOH, H_2 (73%); (b) TFA, CH_2Cl_2 (95%); (c) Zn, 2N HCl, reflux, (79% yield); (d) (1) Zn, 2N HCl, reflux (79%), (2) Pd/C (5 mol %), H_2 (90%) ; (e) (i) $NaBH_4$, MeOH, (ii) SiO_2 (71%).

sodium borohydride. The reduction was highly diastereoselective and the relative stereochemistry was established by X-ray crystal structure analysis of a corresponding O-acylated derivative.[18] As illustrated in Scheme 1, the hydroxylamine (**35**), the carbamate (**36**), the free amine (**37**), and the *N*-oxazolidinone (**38**) were all obtained in a straightforward manner using conditions that should be amenable to a more complex setting and would be difficult to access using current methodology.

In conclusion, we have developed the first α-amination of carbonyls using nitrosoformate intermediates generated in situ from readily available *N*-hydroxycarbamates. The new methodology harnesses the power of nitrosocarbonyl chemistry and demonstrates their potential as a new viable electrophilic source of nitrogen in α-functionalization reactions. The reactions are operationally simple to perform, take advantage of dual catalysis and the products are easy to modify. Further investigations are underway to render this process asymmetric.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by UCSB. Additional support was kindly provided by Eli Lilly, the Hellman Family Foundation and Bridge to the Doctorate Fellowship Program (D.S.).

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(13) Use of conditions developed for the ene reaction (5 mol % CuCl, 1.25 mol % pyr and THF) resulted in an N/O ratio of 1:1 and significant amount of decomposition of the nitrosoformate intermediate. Other Cu(II) Lewis acids were screened but $Cu(OTf)_2$ proved optimal.

(14) See Supporting Information for details.

(15) The aminooxylation product could be easily removed by column chromatography. The O- and N-selective adducts have ΔR_f of ~0.3 in 1:2 EtOAc/hexane. Flash column chromatography was performed using normal phase silica gel (60 Å, 230−240 mesh, Guduran).

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