Title

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Journal

Chemical Science, 4(10)

ISSN

2041-6520

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Publication Date

2013

DOI

10.1039/c3sc51658j

Peer reviewed

Chemical Science

RSC Publishing

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2013, **4**, 3857

Electrophilic α-oxygenation reaction of β-ketoesters using *N*-hydroxycarbamates: control of the ambident reactivity of nitrosoformate intermediates†

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Received 13th June 2013
Accepted 23rd July 2013

DOI: 10.1039/c3sc51658j

www.rsc.org/chemicalscience

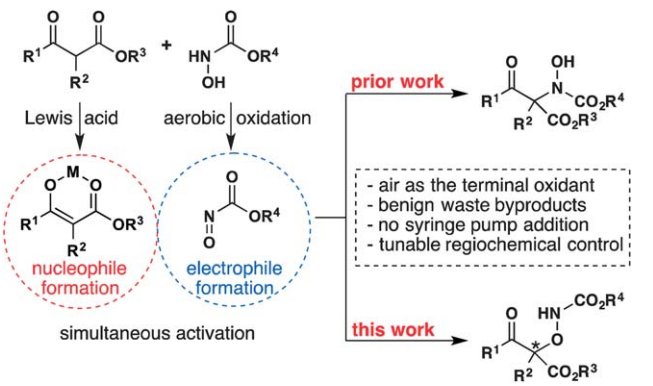
A copper-catalyzed aminooxylation of β-ketoesters using transient nitrosoformate intermediates is reported. The transformation is highly practical, efficient and highlights the ambident reactivity of nitrosocarbonyl compounds through a rare example of a nitrosocarbonyl aldol reaction. Along with a broad substrate scope, the reaction conditions that help control the regiochemistry are explored and the use of *N*-carbamate protected hydroxylamine is showcased by subsequent one-pot annulation reactions.

Introduction

The efficient and direct α-functionalization of carbonyl compounds with heteroatoms utilizing an electrophilic reagent is a significant challenge in organic synthesis.[1] Although examples of the nitroso aldol reaction have existed since 1924,[2] the pioneering work of Yamamoto and co-workers has ushered in a renaissance in the field, culminating in the report of a number of methodologies using arylnitroso compounds to install either an oxygen or nitrogen heteroatom.[3] These successes have inspired the search for alternative nitroso compounds that bear N-substituents that are easier to manipulate but have similar versatility.[4] In principle, nitrosocarbonyl compounds can function in this role.[5] However, due to their high reactivity, nitrosocarbonyls must be generated *in situ*[6] and identifying the conditions compatible with enolate formation has been a significant synthetic challenge, evidenced by the fact that there are only two protocols available to perform a nitrosocarbonyl aldol reaction.[7]

Recently, Yamamoto and co-workers described an elegant asymmetric *O*-nitrosocarbonyl aldol reaction of β-dicarbonyl compounds with *N*-Boc-hydroxylamine as the nitrosocarbonyl precursor.[7a] Key to the success of this process was the identification of manganese dioxide as the mild oxidant and syringe pump addition of the hydroxylamine. Simultaneously, we reported the first example of an *N*-nitrosocarbonyl aldol reaction. The method synergistically combined our previously developed catalytic aerobic oxidation of hydroxylamines with a well-established Lewis acid activation of β-ketoesters (Scheme 1).[8,7b]

Although conditions are known to reverse the regioselectivity (*O- vs. N*-selectivity) for the nitroso aldol reaction using stable arylnitroso compounds,[3] the ability to tune the reaction conditions to regioselectively control whether nucleophiles react on nitrogen or oxygen with highly reactive and transient nitrosocarbonyls has to date remained unexplored. In this article, we report our efforts at controlling the regioselectivity of the nitrosocarbonyl aldol reaction under aerobic oxidation conditions and we dissect the factors contributing to the regiochemical switch from N to O (Scheme 1). Importantly, the method involves the use of molecular oxygen as the terminal oxidant. From an environmental and economical perspective molecular oxygen represents an ideal oxidant due to its low cost, availability, and lack of toxic byproducts. Additionally, the process involves simultaneous mixing of all reagents at room temperature, is fully catalytic in both the oxidation and enolization processes, can be rendered asymmetric and incorporates a functional *N*-carbamate protected hydroxylamine, which can be used for subsequent transformations.



Scheme 1 Controlling the regioselectivity of the nitrosocarbonyl aldol reaction.

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† Electronic supplementary information (ESI) available: Complete experimental details, spectral data and crystallographic data (CIF) for all compounds described. CCDC 932616 and 907696. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3sc51658j

Results and discussion

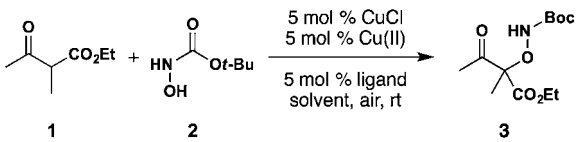
We envisaged that if our *N*-nitrosocarbonyl aldol reaction conditions could be tuned without disturbing the aerobic oxidation process, the regioselectivity of the nitroso aldol reaction could be reversed. The initial optimization commenced from our previously reported conditions.[7b] We found that, of the *N*-protected hydroxylamines screened, *N*-Boc-hydroxylamine (**2**) with β-ketoester **1** provided the aldol product with an increased amount of the *O*-regioisomer.[9] However, the reaction was still predominantly N-selective (entry 1). By switching from methanol as the solvent to a more sterically encumbered alcohol, such as ethanol or isopropyl alcohol, the process could be rendered more *O*-selective (entries 2 & 3). Switching from copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) to copper(II) chloride and copper(II) acetate monohydrate ($Cu(OAc)_2 \cdot H_2O$) further increased O-selectivity while maintaining a high yield (entries 4 & 5). To our gratification, the O-selectivity and the rate could be increased significantly by the addition of 5 mol% of 2-ethyl-2-oxazoline (EtOx),[10] with $Cu(OAc)_2 \cdot H_2O$ being the optimal Cu(II) source (entries 6–8). Removal of the Cu(I) source led to a dramatic decrease in rate (entry 9), while removal of the Cu(II) source adversely affected both the selectivity and yield of the reaction (entry 10). Although the formation of a single discrete catalyst from the mixed metal system cannot be ruled out, we believe the observed trends in reactivity (Table 1) are suggestive of a dual catalytic process.

With optimized reaction conditions in hand (5 mol% CuCl, 5 mol% $Cu(OAc)_2 \cdot H_2O$, 5 mol% 2-ethyl-2-oxazoline, *i*-PrOH, air, rt), we investigated the scope of our aminooxylation reaction by varying the β-ketoester component (Table 2). In contrast with our previously developed *N*-nitrosocarbonyl aldol reaction, the regioselectivity was noticeably influenced by the substitution of the β-ketoester.[7b] As a general trend, with more steric bulk at the 4-position (R^1) of the β-ketoester, the regioselectivity of the transformation was reduced; methyl (**3**, 10 : 1, O : N) proved to be much more regioselective than benzyl (**6**, 7 : 1, O : N), ethyl (**7**, 3 : 1, O : N), and isopropyl (**8**, 2 : 1, O : N). With regards to substitution at the 2-position of the β-ketoester, the converse was true: increasing the steric bulk at R^2 rendered the transformation completely *O*-selective (entries **9–11**). However, to obtain excellent yields of **9** and **10**, 3 equivalents of the corresponding β-ketoester was required in order to outcompete the condensation between the *in situ* formed nitrosocarbonyl species and the *N*-Boc-hydroxylamine. The scope of the β-ketoester could also be extended to include non-alkyl substituents at R^2, such as F, with no reduction in efficiency or regioselectivity (entry **12**). Varying the steric component at the ester position (R^3) also had an effect on the regiochemistry. The methyl ester (**13**, 11 : 1, O : N) proved to be more *O*-selective than the ethyl ester (**3**, 10 : 1, O : N), whereas the allyl (**14**, 7 : 1, O : N) and the *t*-Bu (**15**, 5 : 1, O : N) esters showed a reduction in regioselectivity.

In all cases, the combined yield of both regioisomers was high (>90%) and the *O*-selective product could easily be isolated in moderate to excellent yield after column chromatography.[11] It is particularly noteworthy that simultaneous mixing of all reagents at room temperature can be used, even in the most challenging cases. Presumably, the slow rate of oxidation relative to enolization is the key to avoiding deleterious side reactions; the transient nitrosocarbonyl is immediately trapped by the nucleophilic β-ketoester upon formation.

Encouraged by these results, we further explored the scope of the transformation by using cyclic β-ketoesters (Table 3). The reaction was tolerant of both 5- and 6-membered rings (entries **19** & **20**) as well as substitution on the cyclic backbone (entry **21**). In addition a wide variety of carbamate-derived protecting groups can be used: Cbz, Fmoc, Troc, Nppoc and Moz all gave the *O*-aldol product in good yield. In contrast to the acyclic

Table 1 Copper catalyzed *O*-nitrosocarbonyl aldol reaction

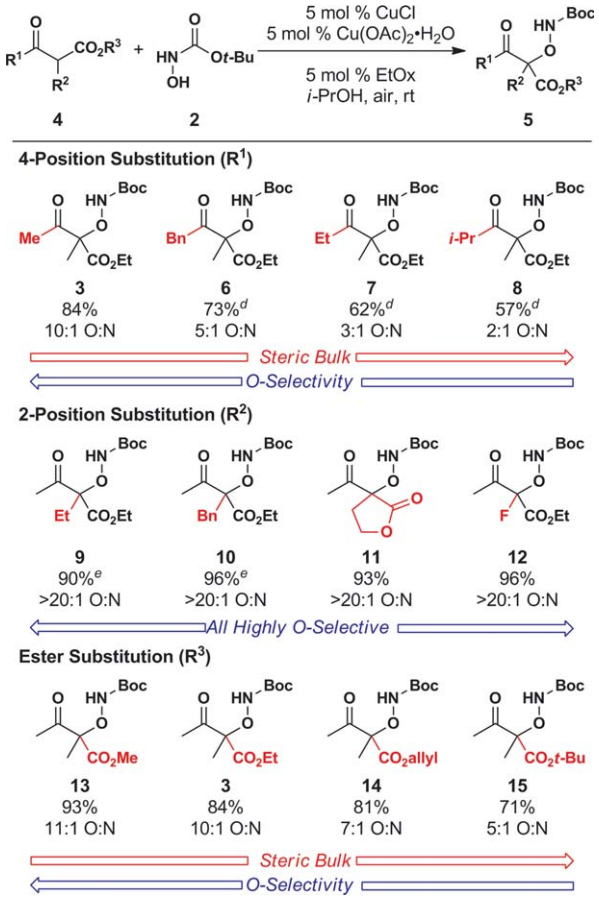


1 2 3

Entry	Cu(II) source	Ligand[a]	Solvent	Time [h]	Yield [%][b]	O/N ratio[c]
1	$Cu(OTf)_2$	—	MeOH	24	96	1 : 4
2	$Cu(OTf)_2$	—	EtOH	24	82	1 : 1
3	$Cu(OTf)_2$	—	*i*-PrOH	48	83	2 : 1
4	$CuCl_2$	—	*i*-PrOH	120	90	3 : 1
5	$Cu(OAc)_2 \cdot H_2O$	—	*i*-PrOH	196	97	3 : 1
6	$Cu(OTf)_2$	EtOx	*i*-PrOH	24	93	1.5 : 1
7	$CuCl_2$	EtOx	*i*-PrOH	20	75	6 : 1
8	$Cu(OAc)_2 \cdot H_2O$	EtOx	*i*-PrOH	18	94	10 : 1
9[d]	$Cu(OAc)_2 \cdot H_2O$	EtOx	*i*-PrOH	52	90	20 : 1
10	—	EtOx	*i*-PrOH	8	53	5 : 1

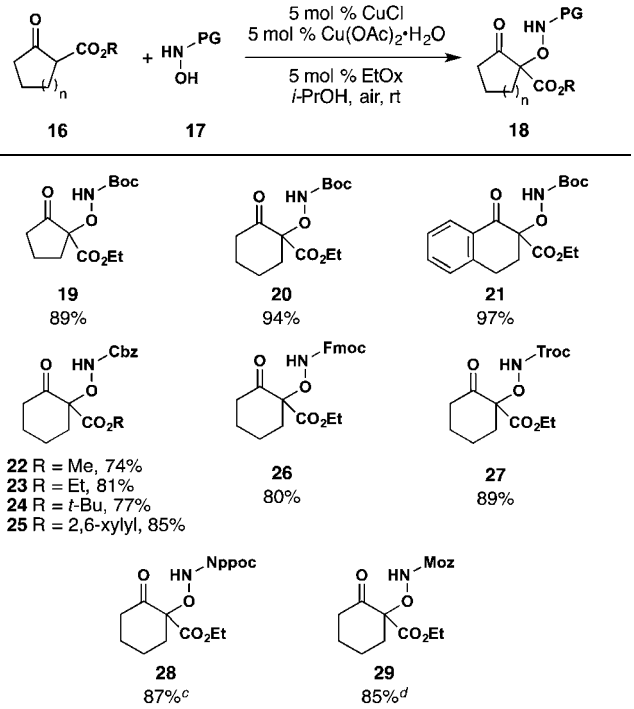
[a] EtOx = 2-ethyl-2-oxazoline. [b] Isolated yield of the *O*- and N-product mixture. [c] Determined by ^{1}H NMR spectroscopy of the mixture of crude material. [d] No CuCl was added to the reaction.

Table 2 Acyclic β-ketoester scope for the *O*-nitrosocarbonyl aldol[a,b,c]



[a] All reactions were performed with reagent-grade *i*-PrOH, and unless otherwise noted, using 1.2 equiv. of **4** and 1 equiv. of **2**. [b] All yields are isolated yields of the *O*-regioisomer. [c] Regioselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Reaction was conducted with 2 equiv of **4**. [e] Reaction was conducted with 3 equiv of **4**. EtOx = 2-ethyl-2-oxazoline.

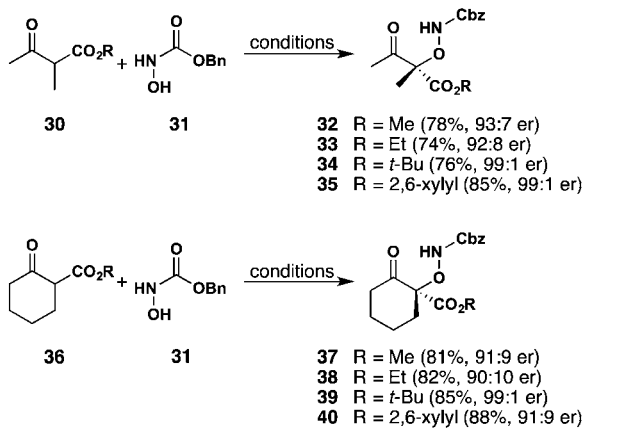
Table 3 Cyclic β-ketoester scope for the *O*-nitrosocarbonyl aldol[a,b]



[a] All reactions were performed with reagent-grade *i*-PrOH using 1.2 equiv. of **16** and 1 equiv. of **17**. [b] All yields are isolated yields of the *O*-regioisomer. [c] Nppoc = 2-(2-nitrophenyl)propoxy-carbonyl. [d] Moz = 4-methoxybenzyloxy-carbonyl. EtOx = 2-ethyl-2-oxazoline.

substrates, changes to the ester component (entries **22**–**25**) were well tolerated as methyl, ethyl, and *tert*-butyl all proceeded in good yield and with perfect regiocontrol. The notable exception was the reaction derived from the ester bearing a 2,6-dimethyl phenol (**25**). In this case, we observed a 3% yield of the N-regioisomer. Further investigations are underway to help elucidate the difference in reactivity between the acyclic and cyclic substrates.

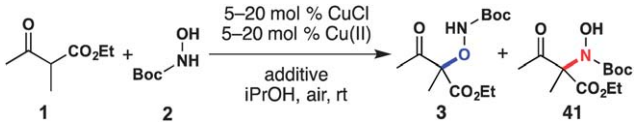
Inspired by the work of Yamamoto and co-workers,[7a] we set out to control the absolute stereochemistry of the *O*-selective nitrosocarbonyl aldol products. To our satisfaction, the reaction can be rendered asymmetric by simply substituting the 2-ethyl-2-oxazoline ligand with a 6 mol% (*R*,*R*)-PhBox ligand (Scheme 2).[12] Not surprisingly, the choice of β-ketoester played a role in achieving higher levels of enantioinduction.[7a] Initially, we were pleased to observe that the reaction with commercially available β-ketoester **1** afforded good levels of enantioselectivity in the formation of product **33** (92 : 8 er). Replacement of the ethyl ester moiety with the more sterically demanding *tert*-butyl ester significantly improved the enantioselectivity from 92 : 8 er to 99 : 1 er, respectively. The product derived from an ester bearing a 2,6-dimethyl phenol (**35**) also resulted in excellent enantioselectivity (99 : 1 er) and was slightly more efficient (85% yield). To our delight the same asymmetric reaction conditions could be extended to the cyclic substrates (entries **37**–**40**). Once again, the *tert*-butyl ester moiety provided the highest levels of



Scheme 2 Asymmetric *O*-nitrosocarbonyl aldol reaction. Conditions: 5 mol% CuCl, 5 mol% $Cu(OAc)_2 \cdot H_2O$, 6 mol% (*R*,*R*)-PhBox, *i*-PrOH, air, rt.

enantioselectivity (**39**, 99 : 1 er). Interestingly, we observed a decrease in the enantioselectivity when the β-ketoester of 2,6-dimethyl phenol was employed (**40**). Single crystal X-ray analysis of a derivative of **35** was used to determine the absolute stereochemistry.[13]

While models have been developed to rationalize the ambident reactivity of arylnitroso compounds for the aldol reaction,[14] similar guiding principles for nitrosocarbonyl species are non-existent. Therefore, we sought to better understand the source of the regiochemical switch by studying the steric and electronic environment about the Lewis acid. From our optimization studies (Table 1, entries 6 and 8) a dramatic difference was observed in the regiochemistry when the Lewis acid was switched from $Cu(OTf)_2$ to $Cu(OAc)_2 \cdot H_2O$ when the EtOx ligand was present. Based on that observation, we screened a number of Cu(II) Lewis acids using our optimized reaction conditions to determine what role the counterion played in selectivity. Weakly coordinating counterions, such as -OTf and -BF_4 favour an unselective aldol reaction, whereas strongly associating carboxylate counterions favour reaction on oxygen (1.5 : 1 *vs.* >10 : 1, O : N, see Fig. 1A). Additionally, with two electronically similar carboxylate counterions, the increased steric bulk of the 2-ethylhexanoate counterion further enhances the O-selectivity from 10 : 1 to 14 : 1.



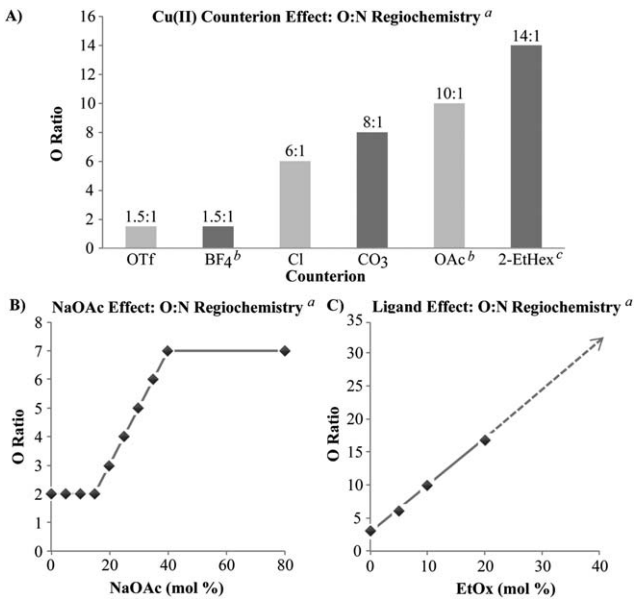


Fig. 1 (A) Role of the counterion derived from the Cu(II) Lewis acid on the O- and N-selectivity. (B) Addition of NaOAc to an unselective reaction leads to an increase in O-selectivity. (C) Addition of EtOx ligand results in an increase in O-selectivity (EtOx = 2-ethyl-2-oxazoline). [a] Regioselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] The hydrate of the Cu(II) source was used. [c] 2-EtHex = 2-ethylhexanoate.

In order to better understand the influence of the acetate–metal complex on the regiochemistry, a varying amount of NaOAc was added to an unselective reaction, 1.5 : 1 (O : N). For this study the conditions in Table 1, entry 6, were used.[15] At low concentrations of NaOAc (0–15 mol%), the reaction showed no increase in O-selectivity (2 : 1, O : N; see Fig. 1B). However, above 15 mol% the regiochemistry linearly increased up to 40 mol% (7 : 1, O : N), which equalled the molar concentration of the copper catalysts. Employing greater than 40 mol% of NaOAc showed no additional influence on the regiochemistry (Fig. 1B). The same effect was observed when using (*R*,*R*)-PhBOX as the ligand instead of EtOx. Without the addition of NaOAc the reaction gave a 9 : 1 selectivity (O : N) and with 40 mol% NaOAc the reaction was completely O-selective (not depicted).

Based on the experiments with NaOAc, we decided to re-examine the effects of the EtOx ligand on the regiochemistry (Fig. 1C). Previously we only evaluated the reaction without EtOx and with 5 mol% EtOx (Table 1). The same trend was also observed when the amount of EtOx ligand was varied from 0 to 40 mol%.[16] However, to our gratification, the reaction was completely O-selective in the presence of 40 mol% EtOx (depicted by dotted arrow). Combined, these studies elucidate that weakly Lewis acidic metal complexes bearing strongly coordinating counterions and ligands are important for the O-selective process.[17]

On the basis of the absolute configuration of the products and the combined results obtained during our investigations, we tentatively propose a reaction mechanism that involves the approach of the nitrosocarbonyl to the catalyst-coordinated β-ketoester, as shown in Fig. 2. We speculate that the decreased Lewis acidity and the increased steric environment associated with the catalyst-β-ketoester complex during the bond-forming event largely govern the reversal in selectivity. Assuming that the reaction proceeds through a square-pyramidal or octahedral geometry (not depicted),[17a,b,d,e] it is conceivable that the counterion occupies the axial position, which would prevent the coordination of the nitroso species to the Lewis acid and force the nitroso electrophile to approach over the β-ketoester. Using large and more associating counterions, excess ethyl oxazoline or sterically bulky PhBox ligand further enhances this effect. Presumably, the reaction predominately occurs on oxygen because this helps avoid unfavourable steric interactions between the protecting-group of the nitroso species and the β-ketoester-metal complex. This hypothesis is consistent with the observation that the use of an *N*-Boc-protected hydroxylamine gave the best results for the O-selective process[8] and

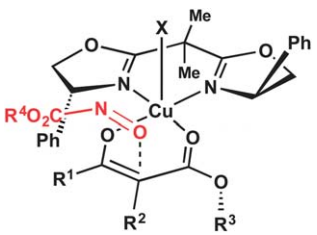
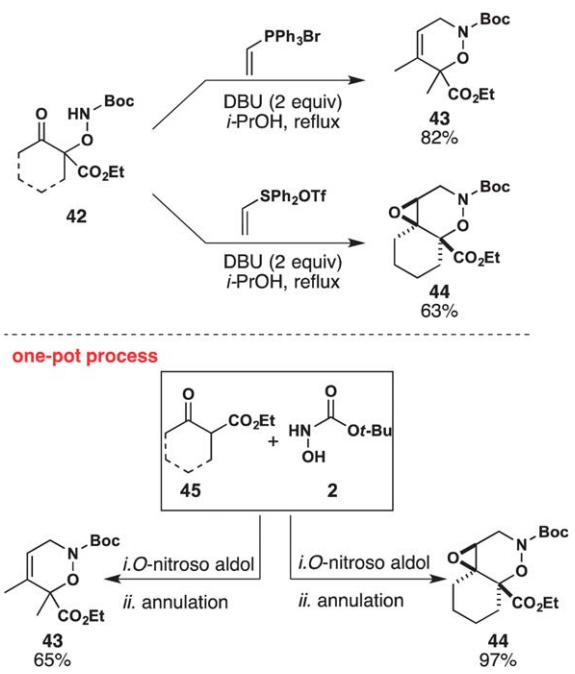


Fig. 2 Tentative model for the O-nitrosocarbonyl aldol reaction. X = counterion.

helps rationalize why the sterics of the β-ketoester can have a significant affect on the regiochemical outcome, specifically at the R^1 and R^3 positions of the β-ketoester (see Table 2). Further investigations are underway to help elucidate the complexities of the regiochemical outcome of the nitrosocarbonyl aldol reaction and explore other possible models.

Finally, we wanted to showcase the increased synthetic utility offered by using nitrosocarbonyls. Typically, the utility of the O-selective nitroso aldol reaction has been highlighted by the transformation of the α-aminooxy-carbonyl to the corresponding α-hydroxy-carbonyl.[3b–e,j,7a] This approach provides efficient access to a highly valued synthetic target, α-hydroxy-carbonyl.[18] However, it also treats the substituted nitrogen group as a waste byproduct, which diminishes the atom economy and can restrict the synthetic utility of the overall transformation. This phenomenon is most likely a consequence of using nitrosobenzene as the electrophile and the difficulties associated with cleaving the *N*-aryl bond for subsequent transformations. Thus, we chose to take advantage of the appended nitrogen group by utilizing it in a series of annulation reactions (Scheme 3).[19] Treatment of the O-aldol product with DBU and vinyltriphenylphosphonium bromide efficiently affords the highly substituted 1,2-oxazine **43** *via* cascade Michael and Wittig reactions. This transformation provides an attractive and synthetically useful approach to access a 1,2-oxazine bearing a quaternary center and a nitrogen substituent that can be easily deprotected.[7b] This structural motif can be challenging to construct using the nitrosocarbonyl hetero-Diels–Alder reaction because moderate regioselectivity is often observed in these cases.[5f] Alternatively, the O-aldol product can be treated with vinyldiphenylsulfonium triflate to access the highly substituted epoxyoxazine **44** as a single diastereomer, determined by X-ray.[20] We were thrilled to discover that both annulation reactions could be carried out conveniently in a one-pot process by simply adding the reagents for the annulation reaction directly to the reaction mixture after the O-nitrosocarbonyl aldol reaction was complete. These one-pot annulation reactions are feasible because the aerobic oxidation conditions are mild and the oxidation byproducts produced do not interfere with the subsequent reaction.



Scheme 3 Combining the O-nitrosocarbonyl aldol reaction with annulation chemistry.

Conclusions

In conclusion, we have developed a highly practical and efficient O-selective nitrosocarbonyl aldol reaction through the use of dual catalysis. By modifying the reaction conditions we can control the regioselectivity of the process. This new methodology complements our previously disclosed N-selective nitroso aldol reaction and the two, as a set, showcase the ambident reactivity of nitrosocarbonyl compounds. The reaction is operationally simple to perform, utilizes reagent grade solvent, readily available copper salts, and is fully catalytic in both the oxidation and enolization processes. The molecular complexity that can be constructed using the annulation chemistry highlights the synthetic utility of this methodology and the mildness of the aerobic oxidation process. Further investigations are underway to investigate the mechanism and expand the scope of nitrosocarbonyl chemistry in synthesis.

Acknowledgements

This work was supported by UCSB. Additional support was kindly provided by Eli Lilly, the Hellman Family Foundation and NSF Bridge to the Doctorate Fellowship Program (D.S.) We also thank Dr Guang Wu (UCSB) for X-ray analysis.

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9 The regioselectivity (O : N) for the *N*-protecting groups screened were Boc (1 : 4), Troc (1 : 9), Fmoc (1 : 10), and Cbz (1 : 13).

10 EtOx ligand was initially chosen based on Shea's and Whiting's report (see, ref. 8*a*). Pyridine was also investigated but resulted in 7 : 1 O : N selectivity using optimized conditions found in Table 1, entry 8.

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

12 During the asymmetric studies we switched the source of the *N*-protected hydroxylamine from the *N*-Boc to *N*-Cbz derivative because the Cbz group simplified our analysis of the enantioselectivities.

13 See ESI.†

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15 The catalyst and EtOx loading was increased from 5 mol% to 20 mol% to more accurately study the effects of NaOAc, specifically when low concentrations were used.

16 For this study the following reaction conditions were used 20 mol% $Cu(OAc)_2 \cdot H_20$, 20 mol% CuCl, 0–40 mol% EtOx, IPA, air, rt.

17 For examples of Cu(II)-catalyzed reactions and the effects of counterion and metal geometry on reactivity, see: (*a*) D. A. Evans, M. C. Kozlowski, C. S. Burgey and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 1997, **119**, 7893; (*b*) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell and R. J. Staples, *J. Am. Chem. Soc.*, 1999, **121**, 669; (*c*) J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, 2000, **33**, 325; (*d*) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692; (*e*) G. Desimoni, G. Faita and K. A. Jørgensen, *Chem. Rev.*, 2006, **106**, 3561.

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20 See ESI.†

