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Catalytic Enantioselective *O*-Nitrosocarbonyl Aldol Reaction of *β*-Dicarbonyl Compounds

Mahiuddin Baidya, Kimberly A. Griffin, and Hisashi Yamamoto*

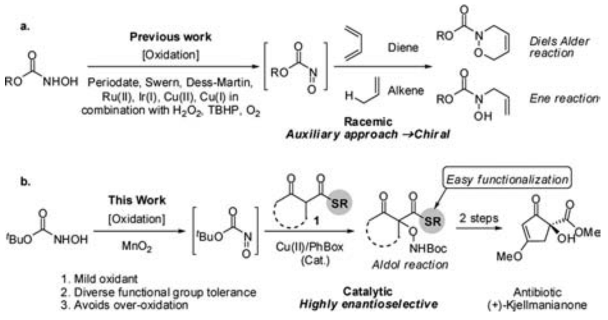
Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, United States

Supporting Information

ABSTRACT: The first example of a Cu-catalyzed asymmetric *O*-nitrosocarbonyl aldol reaction is described. This novel protocol allows convenient access to highly enantioenriched *α*-hydroxy-*β*-ketoesters including the antibacterial natural product kjellmanianone (up to 99% ee). MnO_2 was introduced as a mild efficient oxidant for the in situ generation of nitrosocarbonyl species from hydroxamic acid derivatives.

Since the pioneering work by Kirby in 1973, nitrosocarbonyl compounds have occupied a prominent position in organic chemistry.[1−3] Yet, these species are very unstable and highly reactive, posing a significant challenge to the synthetic chemist. Traditionally, they are generated in situ as a transient intermediate via oxidation of hydroxamic acid derivatives.[4,5] During the past few years, aerobic oxidizing processes have emerged, allowing convenient use of these intermediates for organic synthesis.[6] However, despite their high synthetic potential, the success of nitrosocarbonyl compounds is still immature and limited to hetero-Diels−Alder and ene reactions.[2,3] Heretofore, the more exciting nitrosocarbonyl aldol reaction is not known and no catalytic enantioselective reactions utilizing nitrosocarbonyl compounds have been reported. In this report we describe our progress addressing these challenges (Scheme 1).

Scheme 1. Reactions of Nitrosocarbonyl Compounds



The *α*-hydroxy-*β*-dicarbonyl moiety is an important structural feature found in many biologically relevant molecules and drug candidates.[7] Examples include the antibacterial kjellmanianone, hamigeran A, and doxycycline.[8] Moreover, this functional unit appears in key intermediates in the synthesis of complex molecules, such as indoline alkaloids vindoline and 11-demethoxyvindoline.[9] The most convenient synthetic route to chiral *α*-hydroxy-*β*-dicarbonyl products is the asymmetric oxidation of *β*-dicarbonyl compounds. The first enantioselective *α*-hydroxylation of *β*-ketoesters was developed by Davis and coworkers three decades ago, where a stoichiometric amount of enantiopure *N*-sulfonyloxaziridines (Davis reagent) was employed.[10] Despite considerable efforts in this area, to the best of our knowledge there are only a few methods dealing with asymmetric catalysis.[11,12] All of these catalytic processes are good, but only highly enolizable cyclic *β*-ketoesters are demonstrated to give high yields and enantioselectivities, indicating limited substrate scopes. Recently Ti-catalyzed *α*-hydroxylation reported by Togni and co-workers employed both cyclic and acyclic *β*-ketoesters as substrates; however, asymmetric induction was considerably low.[11b] Further, these transformations rely on oxaziridines and peroxides as oxygen atom sources, for which extra precaution is needed. Thus, the development of a mild, robust, and highly enantioselective catalytic protocol with a wide substrate scope is necessary.

We envisioned that development of an enantioselective *O*-nitrosocarbonyl aldol reaction of *β*-dicarbonyl compounds would open a new direction of nitroso chemistry, and subsequent selective N−O bond heterolysis could be a facile route to enantioenriched *α*-hydroxy-*β*-dicarbonyl compounds (Scheme 1b). Herein, we will report the first example of a Cu-catalyzed enantioselective *O*-nitrosocarbonyl aldol reaction of *β*-dicarbonyl compounds with commercially available *N*-Boc-hydroxylamine as the nitrosocarbonyl precursor and manganese dioxide as a mild oxidant.[13] In addition, for preliminary demonstration of the utility of this strategy, a concise enantioselective synthesis of antibacterial natural product kjellmanianone was accomplished.[8a]

Among the *β*-dicarbonyl compounds, we preferred *β*-ketothioesters **1** for these studies. The choice of thioesters relative to oxoesters is advantageous because the thioester moiety can be easily functionalized, allowing straightforward access to the products with a series of functional groups such as ketones, aldehydes, esters, and amides upon a single transformation.[14] Most importantly, the key to the success of this process is the identification of MnO_2 as an oxidizing reagent compatible with the catalytic cycle. This extremely mild oxidant efficiently generates nitrosocarbonyl compounds in situ through the oxidation of hydroxamic acid derivatives and also avoids overoxidation of the products.

We began our investigation using acyclic *β*-ketothioester **1a** as a model substrate with $Cu(OTf)_2$ as the catalyst in

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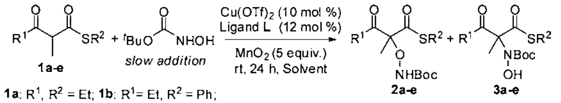
combination with commercially available bidentate bisoxazoline ligands (Table 1).[15] Gratifyingly, when a solution of *N*-Boc-hydroxylamine was slowly injected via a syringe pump into the mixture of 10 mol % $Cu(OTf)_2$ and 12 mol % (*R*, *R*)-PhBox ligand **L1** in the presence of substrate **1a** and oxidant MnO_2 (5 equiv) in CH_2Cl_2 at room temperature, the *O*-nitrosocarbonyl aldol product **2a** was formed in 70% yield with 79% ee (Table 1, entry 1).

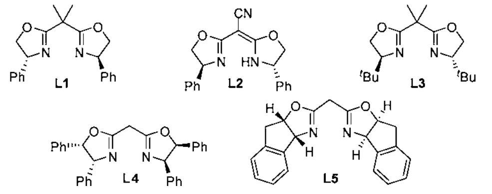
Table 1. Screening of Reaction Conditions



1a: R^1, R^2 = Et; **1b**: R^1= Et, R^2 = Ph;
1c: R^1, R^2 = Ph; **1d**: R^1= Ph, R^2 = ^tBu,
1e: R^1= Et, R^2 = 2,6-xylyl

				2		3	
entry[a]	1	L	solvent	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[c]
1	1a	L1	CH_2Cl_2	70	79	<1	N.D.
2	1a	L1	$CHCl_3$	46	79	14	14
3	1a	L1	CH_3CN	34	75	28	9
4	1a	L1	toluene	25	74	6	14
5	1a	L1	THF[d]	48	75	10	6
6	1a	L1	MeOH	31	70	48	0
7	1a	L2	CH_2Cl_2	71	88	<1	N.D.
8[e]	1a	L2	CH_2Cl_2	11	87	<1	N.D.
9	1a	L3	CH_2Cl_2	31	0	14	2
10	1a	L4	CH_2Cl_2	37	81	7	0
11	1a	L5	CH_2Cl_2	28	36	26	17
12	1b	L1	CH_2Cl_2	76	90	<1	N.D.
13	1b	L2	CH_2Cl_2	15	83	<1	N.D.
14	1c	L1	CH_2Cl_2	65	89	<1	N.D.
15	1d	L1	CH_2Cl_2	8	69	N.D.	N.D.
16	**1e**	**L1**	**CH_2Cl_2**	**73**	**99**	**<1**	**N.D.**

[a] All reactions were performed at 0.1 mmol scale. [b] Yield of the isolated product. [c] Determined by HPLC on chiral stationary phase. [d] Reaction did not proceed at −40 °C in THF. [e] Reaction was performed with 100 mg of 4 Å molecular sieves as additive. N.D. = not determined.



Only trace amounts of *N*-nitrosocarbonyl aldol product **3a** were observed. The high preference for *O*-selectivity over *N*-selectivity is rather remarkable. Slow addition of *N*-Boc-hydroxylamine is crucial to avoid condensation between the in situ formed nitrosocarbonyl species and excess *N*-Boc-hydroxylamine, a strong nucleophile. Screening of other solvents resulted in diminished yields and enantioselectivities with poor *O*- vs *N*-selectivity (entries 2−6). Notably, in MeOH, selectivity was inverted favoring the *N*-nitrosocarbonyl aldol product. The reaction completely shut down upon lowering the temperature to −40 °C in THF. In order to improve enantioselectivity further, various substituted ligands were tested. Box-ligands **L3−L5** were not particularly effective for this reaction (entries 9−11). The semicorrin ligand **L2** showed similar reactivity as observed for **L1**; however, enantioselectivity was improved up to 88% (entry 7). Addition of 4 Å molecular sieves reduced the yield significantly (entry 8).

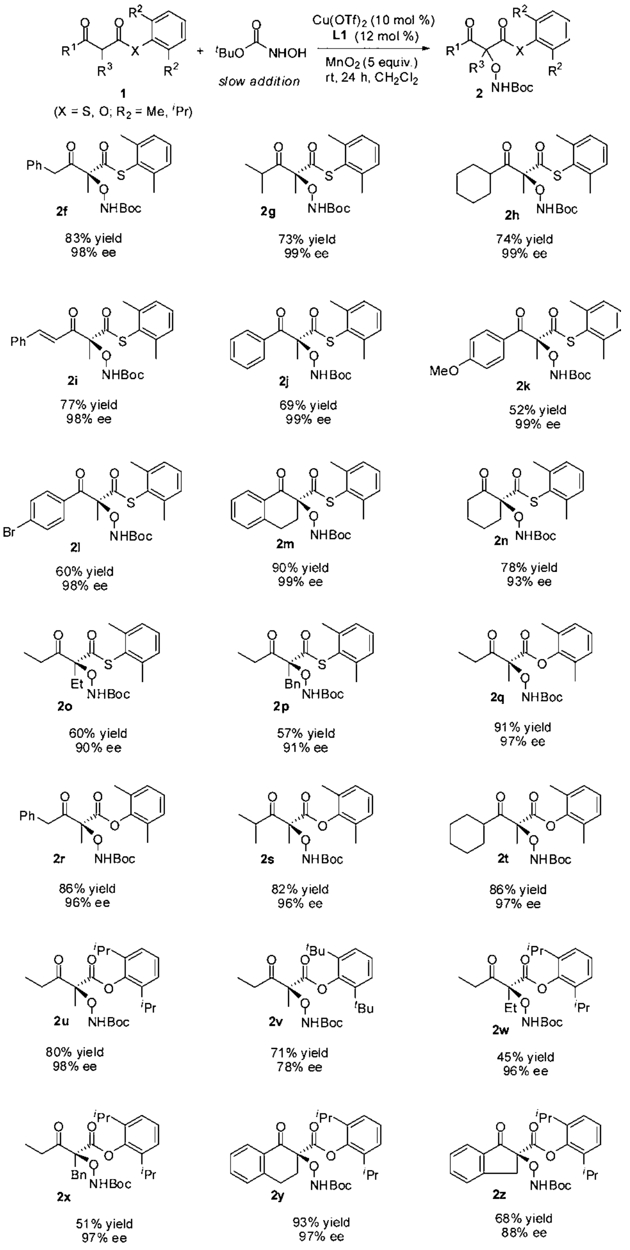
Next, we turned our attention to modification of the thioester moiety using ligands **L1** and **L2** while keeping other reaction conditions unchanged. Replacement of *S*-ethyl thioester **1a** with *S*-phenyl thioester **1b** significantly improved the outcome delivering the *O*-nitrosocarbonyl aldol product **2b** in 76% yield and 90% ee when **L1** was used as a ligand (Table 1, entry 12). In contrast, this reaction became sluggish for ligand **L2**, which performed better for *S*-ethyl thioester **1a** (entry 13 vs 7). When *S*-*tert*-butyl thioester **1d** was used with ligand **L1**, both yields and ee dropped drastically (entry 14 vs 15). Moreover, the aldol product **2c** was crystallized and X-ray analysis unambiguously confirmed the *O*-selectivity. These results suggest that the *S*-phenyl unit in the *β*-ketothioester is very important. Encouraged by this result, we have further tuned the *β*-ketothioester by introducing *S*-2,6-xylyl moiety. To our delight, *S*-2,6-xylyl thioester **1e** produced desired *O*-nitrosocarbonyl aldol product **2e** in very good yield (73%) with almost complete enantioselectivity (99%, entry 16). Thus, *S*-2,6-xylyl substituted *β*-ketothioesters are most appropriate for this reaction with the ligand **L1**.

Experiments probing the scope of this process under optimized conditions are summarized in Table 2. A broad spectrum of *β*-ketothioesters, cyclic and acyclic, could be employed to afford tertiary *O*-nitrosocarbonyl aldol products **2** in very good yields and excellent stereoselectivities. While substitution at the position R^1 with aliphatic (**2f−h**), aromatic (**2j−l**), and vinyl (**2i**) groups in *β*-ketothioesters **1** has little effect on enantioselectivity, substitution at the position R^3 is sensitive. Moving from methyl (**2e**, Table 1) to ethyl (**2o**) and benzyl (**2p**), a slight drop in enantioselectivity was observed, yet it remained high (≥90%). In order to extend the reaction scope further, we also integrated commonly used *β*-ketoesters (**1q−z**). Gratifyingly, *β*-ketoesters are also efficient for this reaction and the desired products were isolated in better yields with similar asymmetric inductions (**2q−t**). At this point, we questioned whether the enantioselectivity of the aldol product **2** with ethyl and benzyl substitution at the R^3 position might be further improved via revision of the ester moiety (R^2). Thus, substituted *β*-ketoesters of various commercially available 2,6-disubstituted phenols were considered. Altering the methyl group at R^2 with isopropyl in *β*-ketoesters improved the enantioselctivity (**2q** vs **2u**); however, when the more bulky ^{t}Bu-group was installed (**2v**), both the yield and enantioselectivity decreased significantly. Thus, *β*-ketoesters (**1w−z**) of 2,6-diisopropyl phenol were employed and the desired products (**2w−z**) were isolated with improved enantioselectivities (up to 97%).

The transformation from *α*-aminooxy-*β*-ketoester **2** to *α*-hydroxy-*β*-ketoesters **4** is smooth and facile. Treatment of $Mo(CO)_6$ cleanly cleaved the N−O bond for both carboxylate ester and thioesters affording *α*-hydroxy products **4** in very good yields without affecting enantioselectivities (Scheme 2).[16]

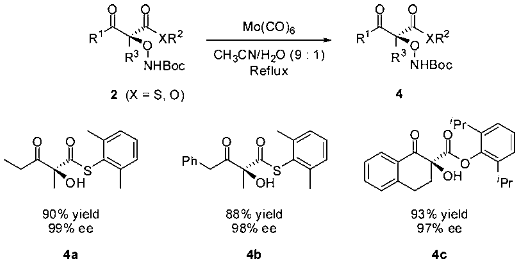
To highlight further the chemical utility, we applied this new catalytic *O*-nitrosocarbonyl aldol reaction to the enantioselective synthesis of kjellmanianone, a member of the cyclopentanoid class of antibiotics, which shows moderate activity against gram positive bacteria such as *E. coli* K12 and *Bacillus subtilis var. niger*.[17] As illustrated in Scheme 3, exposure of *β*-ketothioester **5** (prepared in two steps from commercial materials) to our oxidation protocol, followed by N−O bond heterolysis, and then silver trifluoroacetate promoted trans-

Table 2. Enantioselective *O*-Nitrosocarbonyl Aldol Reactions of *β*-Dicarbonyl Compounds[a–d]

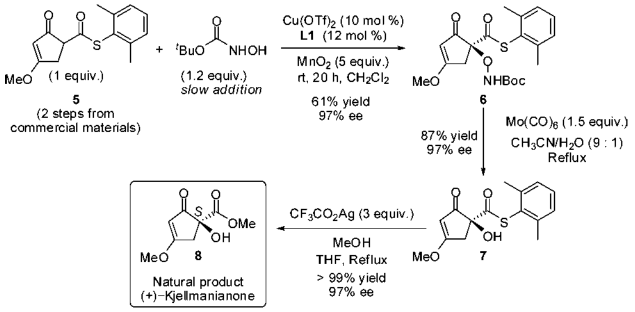


[a]All reactions were performed at 0.1 mmol scale. [b]Yield of the isolated product. [c]Determined by HPLC on chiral stationary phase. [d]Stereochemistries were assigned by analogy to compound **8**.

Scheme 2. Mo(CO)$_6$ Mediated N–O Bond Heterolysis and the Synthesis of *α*-Hydroxy-*β*-Ketoesters



Scheme 3. Rapid Enantioselective Synthesis of Antibacterial (*S*)-Kjellmanianone



esterification, rapidly furnished the antibiotic kjellmanianone **8** in 53% yield over three steps and 97% ee.[14a,b] The absolute configuration of the product was determined by comparing the optical rotation with literature data, and the stereochemistries of the other *α*-hydroxy-*β*-ketoesters were tentatively assigned by analogy.[17b]

In conclusion, we have developed the first catalytic asymmetric *O*-nitrosocarbonyl aldol reaction of both *β*-ketothioesters and *β*-ketoesters using a readily accessible Cu-catalyst and PhBox ligand. The value of this transformation has been highlighted via the expedient synthesis of antibacterial (*S*)-kjellmanianone. MnO$_2$ was introduced as a mild oxidant to generate transient nitrosocarbonyl species from a hydroxamic acid derivative. Further investigations are underway to clarify the mechanism of this transformation and to explore the scope of nitrosocarbonyl chemistry in catalytic asymmetric synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental details and characterization data for prepared compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

yamamoto@uchicago.edu

Notes

The authors declare no competing financial interest.

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