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Catalytic Enantioselective [3 + 2] Cycloaddition of α-Keto Ester Enolates and Nitrile Oxides

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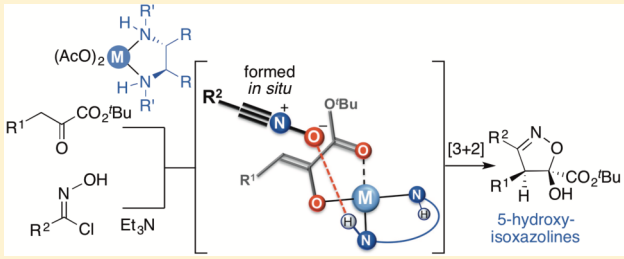
Supporting Information

ABSTRACT: An enantioselective [3 + 2] cycloaddition reaction between nitrile oxides and transiently generated enolates of α-keto esters has been developed. The catalyst system was found to be compatible with in situ nitrile oxide-generation conditions. A versatile array of nitrile oxides and α-keto esters could participate in the cycloaddition, providing novel 5-hydroxy-2-isoxazolines in high chemical yield with high levels of diastereo- and enantioselectivity. Notably, the optimal reaction conditions circumvented concurrent reactions via O-imidoylation and hetero-[3 + 2] pathways.



INTRODUCTION

Heterocycles are routinely encountered as structural units of biologically active unnatural[1] and natural[2] organic compounds. The contemporary chemist has at his or her disposal myriad modern methods to synthesize heterocyclic structures, yet the time-honored cycloaddition reaction between an olefin and reactive 1,3-dipoles is central because of its chemical efficiency and the breadth of structures accessible.[3,4] The development of new catalytic asymmetric 1,3-dipolar cycloaddition reactions holds significant potential for the preparation of enantioenriched five-membered heterocyclic scaffolds.[5] In particular, new activation modes allow the union of 1,3-dipoles with unprecedented reaction partners. Herein we describe a catalytic asymmetric [3 + 2] cycloaddition between in situ-generated nitrile oxides and catalytically generated transition metal enolates of α-keto esters.

Our groups have reported that late transition-metal complexes act as catalysts for reactions that proceed via the soft enolization of carbonyl compounds.[6] Transformations developed under this paradigm include Michael,[6a] halogenation,[6b,c] Mannich,[6d] and aldol[6e] reactions of β-keto esters as well as Michael additions[6h,f] and halogenations[6g−i] using α-keto esters as pronucleophiles.[7] The integration of unconventional electrophiles under this mechanistic construct carries with it the possibility to create heretofore unknown compounds: 1,3-dipolar synthons emerged as attractive targets. Sustmann classified 1,3-dipolar cycloadditions based on the relevant FMO interactions:[8] type III cycloadditions are controlled by the HOMO of the dipolarophile and the LUMO of the dipole (Scheme 1, top). Drawing a parallel with electron-rich dipolarophiles,[5a−d] we postulated that transition-metal enolates could engage dipoles in [3 + 2] cycloadditions. Precedent for achieving catalytic asymmetric dipolar cycloadditions by way of HOMO-raising activation exists. Yanagisawa and co-workers reported the cycloaddition of nitrones and alkenyl acetates and proposed the intermediacy of catalytically formed tin(IV) enolates.[9] Additionally, enamine catalysis has been used to facilitate asymmetric [3 + 2] cycloadditions of aldehydes and azomethine imines.[10,11] Building on this concept, we recently developed a catalytic asymmetric [3 + 2] cycloaddition of α-keto ester enolates and nitrones[12] inspired by the structural characterization of a Ni(II)−diamine catalyst that merges Ni(II)−enolate and hydrogen-bonding activation modes.[13] However, the scope of the process was limited to isolable (*E*)-nitrones, specifically dihydroquinoline derivatives. The generation of heretofore unknown isoxazolines via the reaction of an ephemeral metalloenolate with a transient nitrile oxide emerged as an attractive yet challenging next step (Scheme 1, bottom).[14]

RESULTS AND DISCUSSION

At the outset, we perceived a number of unique challenges to our reaction plan. Foremost among these is the inherent instability of nitrile oxides toward dimerization (Scheme 1, path A)[15,3b] and the need to generate them in situ via base-mediated dehydrohalogenation of the corresponding hydroximoyl chloride or by the dehydration of nitroalkanes.[16] Additionally, our laboratories have observed that α-keto esters **1** react via a homoaldol reaction (path B) in the absence of other viable pathways. The known hetero [3 + 2]-cycloaddition of nitrile oxides with α-keto esters defines a third relative-rate concern

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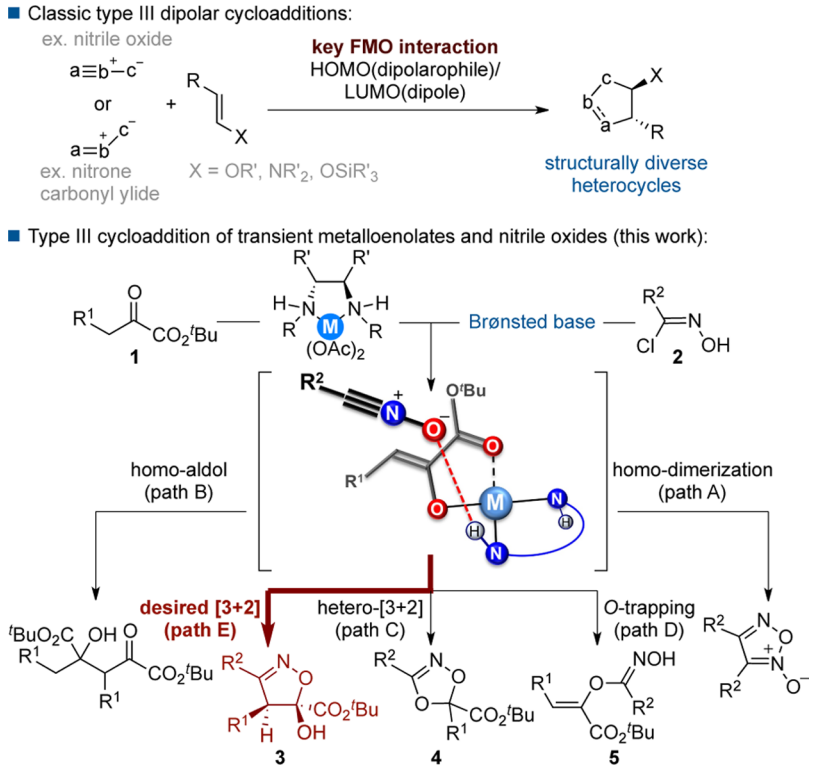
Scheme 1. Dipolar Cycloaddition by Dual Reagent Activation



(path C),[17] especially since the latter will be present in great excess relative to the derived metalloenolate. Finally, the inherent competition of O- versus C-trapping of metalloenolates (path D vs E) must be effectively managed for a successful outcome.

We hypothesized that the Ni(II) catalyst developed for the cycloaddition of nitrones with α-keto ester **1**[12] would display a similar efficiency with nitrile oxides and that running the reaction at −40 °C would preclude the undesired dioxazole coproduct **4** (Table 1). Catalytic amounts of tertiary amine bases have been shown to accelerate reactions involving Ni(II)−enolates of α-keto esters,[6h] thus nitrile oxides were generated in situ from hydroximoyl chlorides using triethylamine. Hydroximoyl chloride **2a** was chosen as a model substrate. As shown in entries 1 and 2, when utilizing $Ni(OAc)_2$ complexes of ligands **A** and **B** in the reactions, the conditions did not favor the formation of the desired 5-hydroxy-2-isoxazoline **3a**. In addition to the anticipated dioxazole coproduct **4a**, the intervention of the O-imidoylation pathway was concurrently observed (**5a**).[18] However, we were encouraged by the promising levels of stereoselectivity observed for **3a** (Table 1, entry 1: −82% ee, 11:1 dr and entry 2: −53% ee, 11:1 dr) without interference by the forecasted homodimerization (path A) and homoaldol (path B) pathways. A solvent screen (entries 3−5) revealed that the chemoselectivity could be dramatically improved (Table 1, entry 5: 10:1 **3a**/**5a**) if *N*,*N*-dimethylformamide was employed as the solvent. In contrast, the use of ^{i}PrOH as the solvent induced a preference for **5a** (Table 1, entry 6: 1:2 **3a**/**5a**). Further screening of conditions with Ni(II) failed to yield satisfactory results (See Supporting Information for details).

Switching to $Cu(OAc)_2{\cdot}H_2O$ as the metal source in THF completely eliminated the O-addition byproduct while favoring the opposite enantiomer of **3a** (Table 1, entry 7: 54% ee, 11:1 dr),[19] although the concurrence of the undesired hetero [3 + 2]-pathway was still observed. Diamine complexes of Ni(II) and Cu(II) exhibit distinct coordination geometries,[20] thereby leading to different coordination modes for the derived enolates. We postulate that these differences are manifested in opposite enantiofacial selectivity and preferential chiral recognition of geometrically different nitrones and nitrile oxides by the Ni(II) and Cu(II) complexes, respectively, via hydrogen bonding with the H-bond-donating diamine ligand.[12] A detailed discussion of this effect can be found in the SI. Along these lines, the inclination of Ni(II) enolates to undergo O-trapping may, in part, result from a kinetic preference for this pathway induced by the distinct geometry of Ni(II)-enolates.

Even though exchanging the cyclohexyl-substituted ligand **B** with the benzyl-type ligand **C** did not lead to an improvement in chemoselectivity, a noticeable enhancement in enantioselectivity was observed (Table 1, entry 8: 74% ee). Further solvent screening was performed. Whereas no improvement in chemoselectivity occurred in DCM (Table 1, entry 9: 1:5 **3a**/**4a**), **3a** was favored slightly in PhMe (Table 1, entry 10: 1.6:1 **3a**/**4a**). Along with others, we have noted that reactions involving transition-metal enolates display enhanced rates in alcoholic solvent.[6h,21] In fact, the use of ^{i}PrOH gave a >20:1 preference for the desired product **3a** (Table 1, entry 11: 77% yield, 70% ee, 11:1 dr). The protic solvent may promote fragmentation of less-active catalyst oligomers,[22] or catalyst turnover from the Cu(II)-alkoxide intermediate proceeding [3 + 2]-cycloaddition via protonolysis.

Having overcome the issue of low chemical yield, we shifted our focus toward the influence of ligand structure on enantioselectivity. The electronic features of the benzyl-type ligands **D** and **E** have little influence on enantioselection (Table 1, entry 12: 66% ee and Table 1, entry 13: 64% ee). However, the results with ligand **F** suggest that nonbonding interactions

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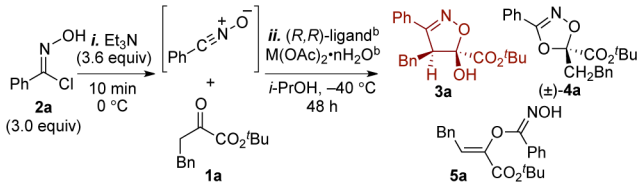
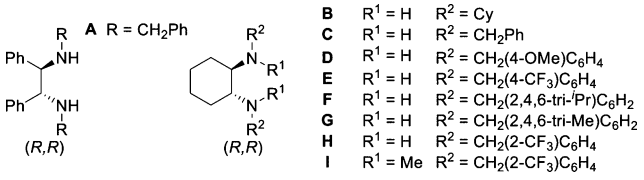
Table 1. Reaction Optimization



entry	ligand	$M(OAc)_2$	solvent	yield of **3a** [%][c]	ratio **3**:**4**:**5**[d]	dr (**3a**)[d]	ee major [%][e]
1[f]	**A**	$Ni(OAc)_2$	THF	34	1:0.3:1	11:1[g]	−82
2[f]	**B**	$Ni(OAc)_2$	THF	20	1:1:1	11:1[g]	−53
3[f]	**A**	$Ni(OAc)_2$	DCM	22	1:0.3:1	18:1	n.d.
4[f]	**A**	$Ni(OAc)_2$	PhMe	25	1:0.6:1	13:1	n.d.
5[f]	**A**	$Ni(OAc)_2$	DMF	65	10:1:1	11:1	−58
6[f]	**A**	$Ni(OAc)_2$	^{i}PrOH	24	1:_:2	13:1	−78
7[h]	**B**	$Cu(OAc)_2$	THF	<17	1:5:_	11:1[g]	54
8[h]	**C**	$Cu(OAc)_2$	THF	15	1:4:_	12:1	74
9[h]	**C**	$Cu(OAc)_2$	DCM	16	1:5:_	12:1	74
10[h]	**C**	$Cu(OAc)_2$	PhMe	38	1.6:1:_	10:1	70
11[h]	**C**	$Cu(OAc)_2$	^{i}PrOH	77	>20:1:_	11:1	70
12[h]	**D**	$Cu(OAc)_2$	^{i}PrOH	86	8:1:_	9:1	66
13[h]	**E**	$Cu(OAc)_2$	^{i}PrOH	72	>20:1:_	10:1	64
14[h]	**F**	$Cu(OAc)_2$	^{i}PrOH	79	>20:1:_	10:1	83
15[h]	**G**	$Cu(OAc)_2$	^{i}PrOH	82	>20:1:_	10:1	91
16[I]	**G**	$Cu(OAc)_2$	^{i}PrOH	75	>20:1:_	13:1	90
17[I,j]	**G**	$Cu(OAc)_2$	^{i}PrOH	83	>20:1:_	13:1	91
18[I,j]	**H**	$Cu(OAc)_2$	^{i}PrOH	86	>20:1:_	11:1	92
19[j,k]	**I**	$Cu(OAc)_2$	^{i}PrOH	9	1:3:0.2	12:1	8



[a]Reactions were run on a 0.1 mmol scale; $M(OAc)_2$ refers to hydrate. [b]Used 20 mol % ligand and metal acetate unless otherwise noted. [c]Isolated yield. [d]Determined by ^{1}H NMR analysis of the crude reaction mixture, unless noted otherwise; _ = not observed [e]HPLC analysis using a chiral stationary phase, n.d. = not determined. [f]Isolated complex used. [g]Isolated dr. [h]Catalyst complexed in situ. [I]Used 5 mol % of isolated complex. [j]Consisted of 1.5 equiv **2**, 2.5 equiv Et_3N. [k]Scale of 0.2 mmol. Catalyst complexed in situ; 5 mol % loading.

are important (Table 1, entry 14: 83% ee). Ligand **G** provided satisfactory levels of enantioselectivity (entry 15: 91% ee), and we were pleased to find that the catalyst loading could be reduced to 5 mol % without adversely influencing reactivity or selectivity (entry 16). Additionally, the amounts of hydroximoyl chloride **2a** and Et_3N could be reduced to 1.5 equiv and 2.5 equiv, respectively (entry 17). The 2-CF_3-substituted benzyl-type ligand **H** also provided high selectivity for this substrate (entry 18: 92% ee) and was later found to be uniquely suited for achieving high enantioselectivity with 2-substituted benzenenitrile oxides. Finally, the reduced yield and stereocontrol obtained with *N*-Me ligand **I** suggest the secondary diamine as a key design feature of the present catalyst system (entry 19: 9% yield, 8% ee).

With suitable reaction conditions in hand, we sought to learn how the steric and electronic parameters of the reaction partners might affect the process (Table 2). Nitrile oxides bearing electron-withdrawing groups in the 4-position were tolerated under the optimized conditions. For instance, 4-$CF_3C_6H_4$-substituted **3b** and 4-FC_6H_4-substituted **3c** were obtained in good chemical yields with high levels of diastereo- and enantioselectivity (Table 2, **3b**: 91% yield, 90% ee, 10:1 dr and **3c**: 88% yield, 91% ee, 10:1 dr). Electron-rich aromatic nitrile oxides also participated, and 4-PhC_6H_4-substituted **3d** and 4-MeC_6H_4-substituted **3e** were obtained with similarly high levels of diastereo- and enantioselectivity (Table 2, **3d**: 58% yield, 88% ee, 11:1 dr and **3e**: 75% yield, 90% ee, 13:1 dr). Mesityl ligand **G** displayed lower levels of enantioselection when 2-substituted aryl nitrile oxides were used; however, the 2-CF_3 analogue **H** promoted high selectivity with these substrates. This effect was not as marked with smaller substituents, as 2-FC_6H_4-subsituted **3f** was obtained with high levels of enantioselectivity using both catalysts (Table 2, ligand **G**: 90% ee and ligand **H**: 92% ee). The difference in selectivity increased upon moving from 2-OMe to the more sterically demanding 2-Me substitution (Table 2, **3g**: 80% ee vs 92% ee and **3h**: 76% ee vs 90% ee). The enantioselectivity difference was accentuated in the case of 2-BrC_6H_4-substituted **3i**, which was obtained in 62% ee using the mesityl-substituted ligand **G**, whereas the 2-$CF_3C_6H_4$-substituted ligand **H** provided 91% ee. Heteroaromatic nitrile oxides were compatible with the optimized reaction conditions; the 2-keto glutaric acid-derived 3-pyridyl-substituted **3j** could be formed, albeit with lower enantioselectivity (Table 2, **3j**: 90% yield, 74% ee). Cycloadduct **3k** was obtained in good yield with excellent diastereoselectivity, and with high levels of enantioselectivity

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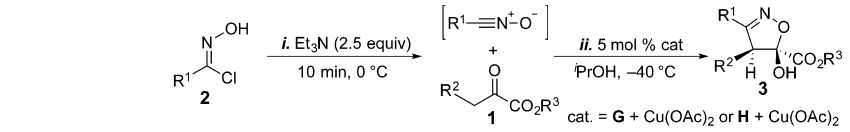
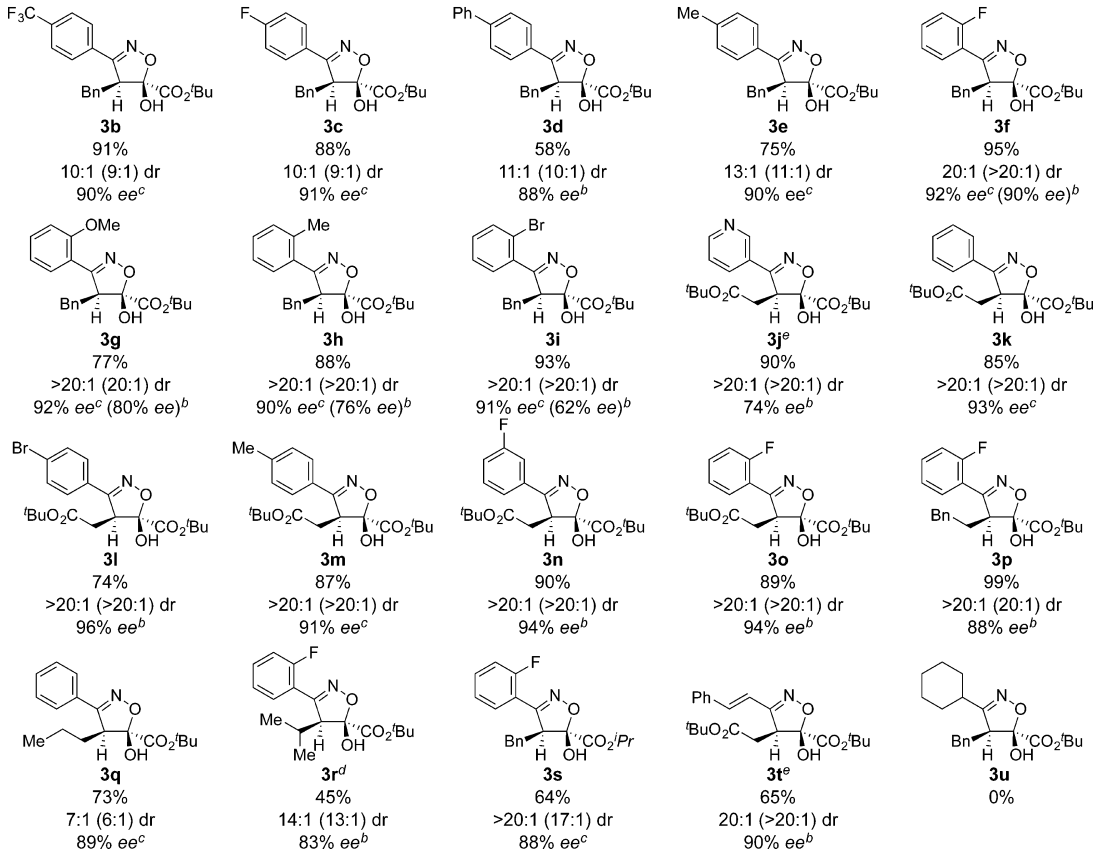
Table 2. Scope of Reaction[a]





[a]The reactions were run on a 0.2 mmol scale, see SI for reaction times. Yields are for isolated products. Diastereomeric ratio (dr) values were determined by ^{1}H NMR analysis of the crude reaction mixture, isolated dr values were written in parentheses. The enantiomeric excess (ee) values were determined by HPLC using a chiral stationary phase. [b]Ligand **G** employed. [c]Ligand **H** employed. [d]20 mol % $Cu(OAc)_2$−diamine employed. [e]3.0 equiv of hydroximoyl chloride, 3.6 equiv of Et_3N.

(Table 2, **3k**: 85% yield, 93% ee). The absolute stereochemistry of **3k** was determined via X-ray crystallography, and the configurations of the remaining products are assigned by analogy. Other electronically diverse nitrile oxides reacted well with this α-keto ester (**3l**−**o**). The homobenzyl-substituted α-keto ester furnished the corresponding cycloadduct **3p** in an 88% ee with high diastereoselection when the 2-FC_6H_4-substituted hydroximidoyl chloride was employed. In contrast, the *n*-propyl-substituted product **3q** was formed with lower levels of diastereoselectivity. A γ-branched α-keto ester could be employed when the catalyst loading was increased to 20 mol % (Table 2, **3r**: 45% yield, 14:1 dr, 83% ee). A β-aryl-substituted α-keto ester (R^2 = 3-tolyl) provided low diastereo- and enantiocontrol during the formation of the cycloadduct (59% yield, 1.3:1 dr, 62% ee and 68% ee, see SI for details). Similarly, lower levels of enantiocontrol were observed for a product derived from a Me-substituted α-keto ester (R^2 = Me) and 2-fluorobenzonitrile oxide, although satisfactory levels of diastereocontrol were maintained (79% yield, 54% ee, 7:1 dr, see SI for details). The isoxazoline, derived from *tert*-butyl pyruvate (R^2 = H), was furnished in racemic form (58% yield, 2% ee, see SI for details). The identity of the ester influenced the enantiocontrol, as lower levels of enantioselectivity were obtained for product **3s** using the ^{i}propyl-substituted analogue of our model α-keto ester **1a** (Table 2, 88% ee). Finally, alkenyl nitrile oxides are viable partners under the reaction conditions, and the styryl isoxazoline **3t** was obtained in good yield, as a single diastereomer, with high levels of enantioselectivity (Table 2, 65% yield, 20:1 dr, 90% ee). Unfortunately, aliphatic nitrile oxides are not compatible at this stage of optimization (i.e. **3u**). Aliphatic nitrile oxides are less stable than their sp^2-carbon-substituted counterparts,[15] and we believe that competitive decomposition is to blame.

Having established the scope of this transformation, we sought to study the reactivity of the C═N bond installed during the cycloaddition reaction (Scheme 2). We found that the 2-ketoglutaric acid-derived cycloadduct **3k** could be prepared on a gram scale (2.5 mol % catalyst). Under the action of $NaBH_4/NiCl_2$,[23] **3k** (90% ee) was converted to γ-lactam **6k** containing three vicinal stereocenters (2.5 mmol scale). Lactam **6k** was moderately enriched upon recrystallization, and the structure of this product was obtained via X-ray crystallography.[24]

The isoxazoline products delivered by the title reaction are hemiacetals that could in principle coexist with their ring-opened acyclic γ-oximo-α-keto ester isomers (**7**, Scheme 3).

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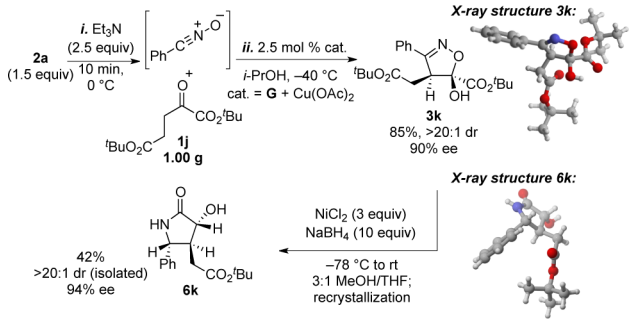
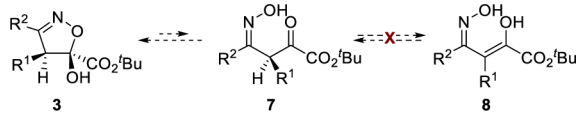
Scheme 2. Gram Scale Reaction and Isoxazoline Reduction



Scheme 3. Isoxazoline Hemiacetals Do Not Racemize via Tautomerization



Such structures would appear to be quite vulnerable toward racemization via facile keto−enol tautomerization because of the high C−H acidity of the methine proton (**7** ⇆ **8**). The obtention of isoxazoline adducts **3** and a downstream adduct such as **6k** with high enantiomeric enrichment allows us to draw conclusions regarding the intervention of the equilibria depicted in Scheme 3. We hypothesize that the lack of racemization stems from the high stability of the isoxazoline hemiacetal that disfavors ring opening. Circumstantial evidence against the formation of the acyclic oxime **7** is the constant product diastereomeric ratio as a function of time: ring opening/ring closure would presumably change the diastereomeric composition. The kinetic reluctance to form the oxime **7** may stem from the system's preference to avoid the creation of a highly electrophilic α-keto ester in the presence of multiple electronegative atoms/functional groups. The isoxazoline hemiacetal thus insulates a potentially labile stereocenter from undesired racemization.

SUMMARY

We have developed an enantioselective [3 + 2] cycloaddition reaction between nitrile oxides and transiently generated enolates of α-keto esters catalyzed by a chiral copper(II)−diamine complex. The catalyst system was found to be compatible with in situ nitrile oxide generation. This constitutes the first catalytic enantioselective preparation of this unique class of heterocycles, which can be transformed into interesting lactams. With this data in hand, we are currently assessing the reactivity of the 5-hydroxy-2-isoxazolines in other downstream transformations in addition to studying the mechanism of this transformation in detail. These results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b03782.

Experimental procedures and spectral, analytical, and computational data(PDF)
Crystallographic data for **3k** (CIF)
Crystallographic data for **6k** (CIF)

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Notes

The authors declare no competing financial interest.

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