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N-Heterocyclic Carbene-Catalyzed Formal [3+2] Annulation of Alkynyl Aldehydes with Nitrosobenzenes: A Highly Regioselective Umpolung Strategy

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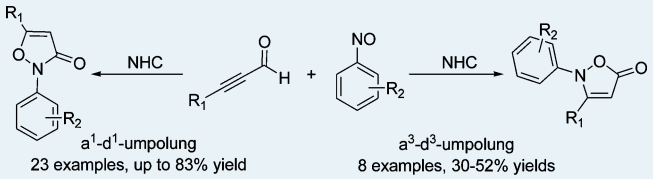
Supporting Information

ABSTRACT: N-Heterocyclic carbene-catalyzed formal [3+2] annulation of alkynyl aldehydes and nitrosobenzenes has been reported. This transformation provided the novel C−X bond formation under mild conditions in moderate to satisfactory yields. The catalytic protocol allows for a rapid construction of 2,5-disubstituted isoxazol-3(2H)-ones and 2,3-disubstituted isoxazol-5(2H)-ones from the same materials via a highly regioselectively umpolung stratgy.



KEYWORDS: *N-heterocyclic carbene, [3+2] annulation, regioselective, umpolung, alkynyl aldehydes, nitrosobenzenes*

N-Heterocyclic carbene (NHC)-catalyzed umpolung of aldehydes has been investigated thoroughly over the past decade.[1] For this, benzoin condensation[2] and Stetter reaction[3] are the most common types. Also, umpolung of enals via a homoenolate intermediate (a^3-d^3 umpolung) was another useful umpolung strategy and had become increasingly attractive for C−C bond[4] and C−X bond[5] formation, while investigation of the a^3-d^3 umpolung of alkynyl aldehydes via an allenolate intermediate was mainly focused on the β-protonation followed by esterification[6] or other transformations.[7] However, it is a challenge to construct a C−C or C−X bond via a^3-d^3 umpolung of alkynyl aldehydes probably because of its low nucleophilicity. Recently, Snyder et al. and our group reported NHC-catalyzed/Lewis acid-mediated conjugate umpolung of alkynyl aldehydes for the synthesis of the tricyclic framework of the securinega alkaloids[8] and butenolides,[9] respectively. However, highly regioselective umpolung of alkynyl aldehydes has rarely been investigated.

Isoxazol-3(2H)-one and isoxazol-5(2H)-one are regioisomeric skeletons of some of the synthetic biologically active compounds and materials (Figure 1).[10] Thus, their synthesis attracted our attention, and we are likely to synthesize them from aldehydes and nitrosobenzenes. This would be directly related to the regioselectivity of alkynyl aldehydes. In the literature, there are several excellent works about the annulation of aldehydes and nitrosobenzenes. In 2008, Ying and co-workers reported a NHC-catalyzed C−N bond formation via which α,β-unsaturated aldehydes and nitrosobenzenes gave *N*-phenylisoxazolidin-5-ones, followed by an acid-catalyzed esterification and Bamberger-like rearrangement in one pot leading to *N*-methoxyphenyl-protected β-amino acid esters (eq 1, Scheme 1).[5a] Then, Cheng and co-workers reported NHC-catalyzed annulation of *o*-vinylarylaldehydes with nitrosobenzenes proceeded via a cascade azabenzoin and oxo-Michael addition to produce multifunctional 2,3-benzoxazinones in good to excellent yields (eq 2, Scheme 1).[11] Recent work by Ma's group reported the NHC-catalyzed cyclization of β-halopropenals and arylnitroso compounds to 2,3-disubstituted isoxazol-5(2H)-ones (eq 3, Scheme 1).[5f] All of this work led to only one type of product skeleton, and the regioselective type

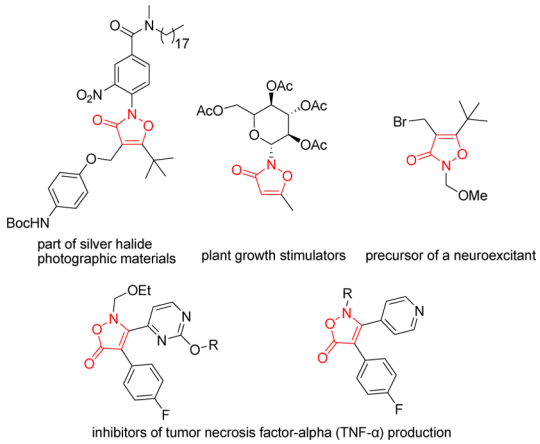


Figure 1. Isoxazol-3(2H)-one and isoxazol-5(2H)-one skeletons in the materials and biologically active compounds.

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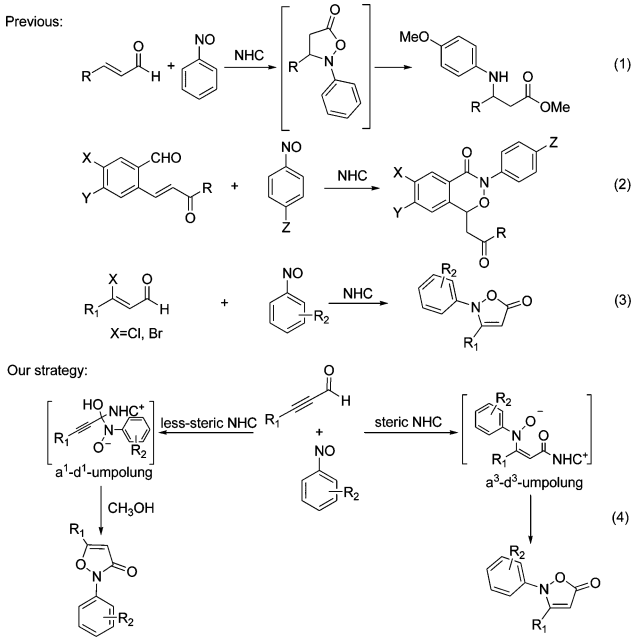
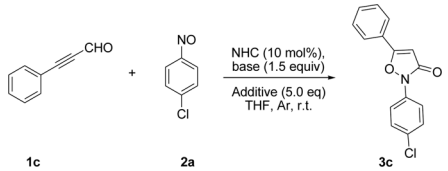
Scheme 1. Representative Annulations of Nitrosobenzenes with Aldehydes



has not been developed. Inspired by these pioneering works, we considered how to obtain the two regioisomers by controlling the reaction conditions, electronic and steric effects, or other factors. However, if such controls could be efficiently utilized, it would become an ideal platform for the divergent synthesis of different types of skeletons from the same reactants. Combined with our group works, regioselective umpolung (a^3-d^3 and a^1-d^1) of alkynyl aldehydes followed by formal [3+2] annulation attracted our attention; however, this strategy has rarely been reported. Herein, we disclose the novel NHC-catalyzed formal [3+2] annulation of alkynyl aldehydes with nitrosobenzenes by a highly regioselective umpolung strategy (eq 4, Scheme 1).

There have been excellent contributions from Bode's group and Smith's group recently about catalyst selection.[12] Because the key issue of the two pathways lies in the generation of either d^1-synthon or d^3-synthon from alkynyl aldehyde and NHC catalyst, we envisioned that the steric hindrance of catalysts could control the reaction pathways and therefore overcome the competition problem and thus exclusively lead to either of the desired products. Less steric NHCs could be beneficial for the a^1-d^1 umpolung, while steric catalysts might be favored for the a^3-d^3 umpolung (eq 4, Scheme 1). In view of the difficulty of the two pathways, our investigation began with a^1-d^1 umpolung. Initial screening revealed that a catalytic amount of base was not effective. Then 3-phenylpropiolaldehyde **1c** and 4-chloronitrosobenzene **2a** were treated with 10 mol % thiazolium salts **A**−**C** and 1.5 equiv of DBU; under these conditions, 2,5-disubstituted isoxazol-3(2H)-one **3c** was obtained in very low yield (Table 1, entries 1−3). Fortunately, the product was isolated in 28% yield in the presence of triazolium-based NHC precatalyst **D**, and other triazolium salts **E**−**G** gave higher yield than NHC salt **D** (Table 1, entries 4−7). After an extensive evaluation of other bases, we found that the yield decreased even in the presence of economical NHC precursor **E** (Table 1, entries 8−14). A further survey of other solvents (CH_2Cl_2, toluene, Et_2O, CH_3CN, EtOAc, $CHCl_3$, acetone, DCE, and 1,4-dioxane) was not effective. On the basis

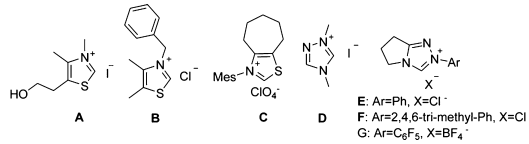
Table 1. Screening of Reaction Conditions for the Synthesis of 2,5-Disubstituted Isoxazol-3(2H)-one[a]



1c 2a 3c

entry	catalyst	base	additive	t (min)	yield (%)[b]
1	**A**	DBU[c]	–	60	trace
2	**B**	DBU	–	60	not determined
3	**C**	DBU	–	60	trace
4	**D**	DBU	–	60	28
5	**E**	DBU	–	60	48
6	**F**	DBU	–	60	50
7	**G**	DBU	–	60	29
8	**E**	K_2CO_3	–	60	4
9	**E**	DABCO[d]	–	60	trace
10	**E**	^{t}BuOK	–	60	trace
11	**E**	Et_3N	–	60	trace
12	**E**	Cs_2CO_3	–	60	trace
13	**E**	NaOAc	–	60	trace
14	**E**	TBD[e]	–	60	28
15	**E**	DBU	CH_3OH	40	65
16	***E***	*DBU*	*CH_3OH*	*60*	*78*
17	**E**	DBU	EtOH	60	74
18	**E**	DBU	^{i}PrOH	60	70
19	**E**	DBU	^{t}BuOH	60	70
20	**E**	DBU	H_2O	60	59

[a]Reaction conditions: **1c** (0.3 mmol), **2a** (0.2 mmol), catalyst (10 mol %), base (0.3 mmol, 1.5 equiv), THF (2.0 mL). [b]Isolated yield. [c]DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [d]DABCO = 1,4-diazabicyclo[2.2.2]octane. [e]TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.



of the analysis of the reaction mechanism, to facilitate the 5-endo-dig cyclization of the intermediate, different types of alcohols were tested as inexpensive and easily accessible additives for the promotion of the reaction. Compared to the reaction time and the variety and amount of alcohols, CH_3OH (5.0 equiv) was an appropriate proton source and **3c** was isolated in 78% yield (Table 1, entries 15−19). To our surprise, the yield was only slightly smaller than that of CH_3OH even though H_2O was used as an additive (Table 1, entry 20). Finally, 10 mol % NHC precursor **E**, DBU as a base, and 5.0 equiv of CH_3OH used as a proton source in THF were chosen as an optimal condition for evaluating the substrate scope.

As shown in Scheme 2, a broad range of β-substituted alkynyl aldehydes and nitrosobenzenes could readily participate in this reaction under the optimized condition. For alkynyl aldehydes bearing β-aryl substituents, electron-rich and unsubstituted reactants had little influence on the reaction yields (Scheme 2, **3a**−**c** and **3m**), but electron-poor substrates gave moderate yields (Scheme 2, **3d**). The same situation was discovered in the *m*-substituted phenylpropioaldehydes (Scheme 2, **3e**−**3g**), as well. Surprisingly, *o*-substituted phenylpropioaldehydes demonstrated different results, of which both EDG- and EWG-substituted substrates gave slightly higher yields, and it

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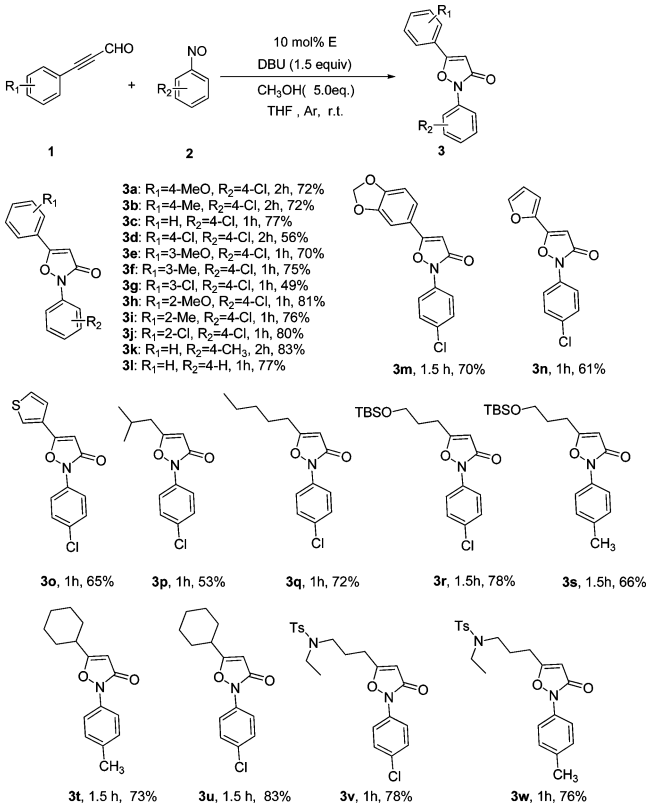
Scheme 2. Substrate Scope for the a^1-d^1 Umpolung[a]

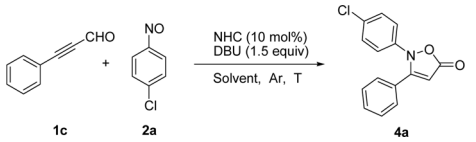


[a]Reaction conditions: **1** (0.75 mmol), **2** (0.5 mmol), catalyst (10 mol %), base (0.75 mmol, 1.5 equiv), THF (5.0 mL), isolated yield.

was revealed that the yields may not be affected by the electron or steric effect (Scheme 2, **3h**−**3j**). Also, other nitrosobenzenes gave high yields (Scheme 2, **3k** and **3l**). Substitution patterns on both the aldehydes and nitrosobenzenes affected the yields to some extent. We were also pleased to obtain the corresponding products in moderate yields even when heterocyclic substituted propioaldehydes were used (Scheme 2, **3n** and **3o**). Significantly, *β*-alkyl-substituted alkynyl aldehydes were well tolerated and gave the products in good to moderate yields with either 4-CH_3- or 4-Cl-substituted nitrosobenzenes (Scheme 2, **3p**−**3w**). This demonstrates that the substrate scope of this catalytic system is remarkably broad.

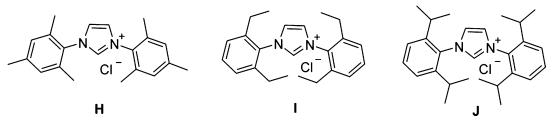
On the other hand, a^3-d^3 umpolung of enals was another interesting area for constructing C−C and C−X bonds, but there are only a few examples of a^3-d^3 umpolung of alkynyl adehydes. Recently, our group developed the novel C−C bond formation of a^3-d^3 umpolung of alkynyl adehydes and obtained butenolides.[9] After that, this area attracted our attention, and we tried to construct the C−X bond in a similar manner. To avoid the unwanted formation of the a^1-d^1 umpolung product, the steric imidazolium-derived NHCs might be superior to other NHC scaffolds. To test this hypothesis, we investigated 3-phenylpropiolaldehyde **1c** and 4-chloronitrosobenzene **2a** as model substrates, and after using the steric imidazolium-based NHC precatalysts **H**−**J**, we found **J** was the optimal one even though **4a** was isolated in only 20% yield (Table 2, entries 1−3). Then other solvents were tested, and it was shown that DMF was appropriate for this transformation (Table 2, entries 4−10). The yield was slightly increased when the amount of catalyst loading was 20 mol % (Table 2, entry 11) and the

Table 2. Screening of Reaction Conditions for the Synthesis of 2,3-Disubstituted Isoxazol-5(2H)-one[a]



entry	catalyst	solvent	*t* (min)	yield (%)[b]
1	**H**	THF	60	7
2	**I**	THF	60	9
3	**J**	THF	60	20
4	**J**	DCM	60	7
5	**J**	toluene	60	15
6	**J**	CH_3CN	60	13
7	**J**	$CHCl_3$	60	mixtures
8	**J**	Et_2O	60	mixtures
9	**J**	DMF	60	31
10	**J**	DMSO	60	30
11[c]	**J**	DMF	60	42
12[c]	***J***	*DMF*	*20*	*42*

[a]Reaction conditions: **1c** (0.3 mmol), **2a** (0.2 mmol), catalyst (10 mol %), base (0.3 mmol, 1.5 equiv), solvent (2.0 mL). [b]Isolated yield. [c]When 20 mol % **J** was used.



reaction time was shortened to 20 min (Table 2, entry 12). Unfortunately, further screening of other bases (such as K_2CO_3, DABCO, Et_3N, Li_2CO_3, Cs_2CO_3, TBD, NaOAc, and DIPEA) did not further improve the yield. Additionally, other attempts to change the loading of the catalyst, the reaction temperature, the amount of bases, and the method as described in ref 4m to further improve the yield proved to be futile possibly because of the low nucleophilicity of the allenolate intermediate.

Under the optimized condition, a variety of substituted alkynyl aldehydes and 4-chloronitrosobenzene were used for investigating the substrate generality of this method (Scheme 3). Generally, the yields were not high and EDG-substituted 3-phenylpropiolaldehydes were adaptive for the conversion. It is obvious that the yield was lower than in the former case when EDG-substituted alkynyl aldehydes were replaced by the reverse electronic property group, thus indicating a relatively strong electronic effect associated with the aromatic ring. Compared to the homoenolate intermediate, the allenolate intermediate is typically less reactive, and optimization of the yield for a^3-d^3 umpolung is often more difficult. It is understandable that the yields were not as high as that of the a^1-d^1 umpolung pattern. Additionally, we could show that steric different *β*-substituted alkynyl aldehydes on the aromatic ring were all well tolerated in this reaction.

The possible mechanism of the regioselective umpolung strategy was revealed as follows (Scheme 4). Initially, NHCs were produced in the presence of bases, followed by formation of Breslow intermediate **K**. Acyl anion equivalent (**L**) (cycle **I**) was generated when triazolium-based catalyst **E** was used and then reacted with 4-chloronitrosobenzene for C−N bond formation. After the NHC catalyst had been released, product **3c** was obtained by 5-endo-dig cyclization of intermediate **M** followed by proton transfer and the structure of product **3c** was unambiguously assigned on the basis of X-ray crystallographic

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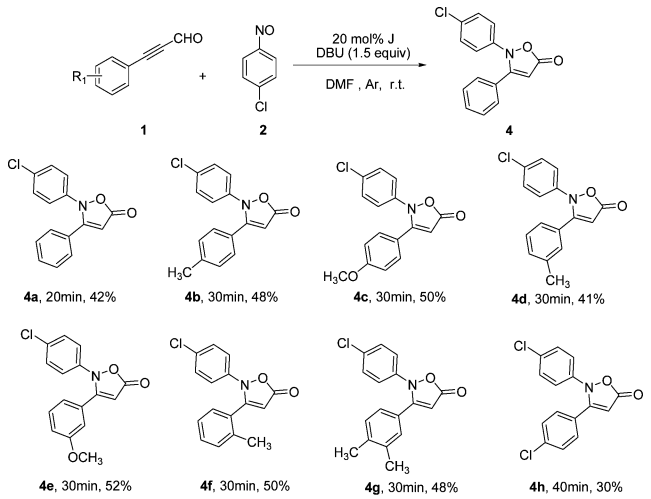
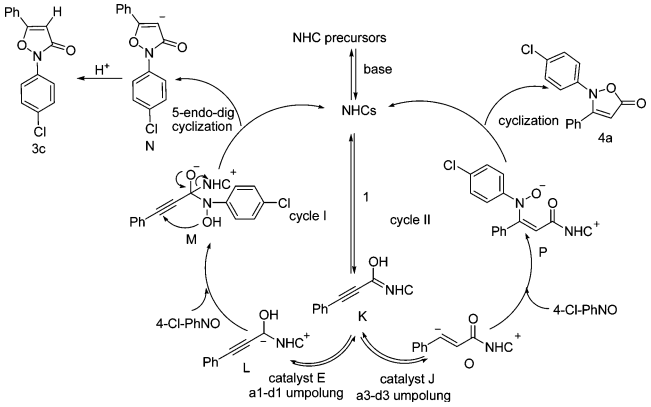
Scheme 3. Substrate Scope for the a^3-d^3 Umpolung[a]



[a]Reaction conditions: **1** (0.75 mmol), **2** (0.5 mmol), catalyst (20 mol %), base (0.75 mmol, 1.5 equiv), DMF (5.0 mL), isolated yield.

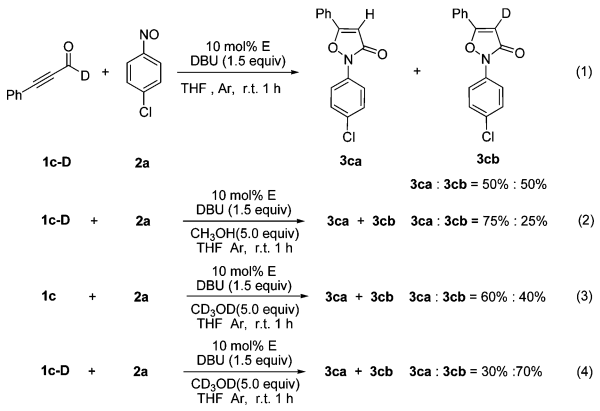
Scheme 4. Possible Mechanism for the Regioselective Umpolung



analysis (see the Supporting Information). On the other hand, a^3-d^3 umpolung (**O**) occurred via the allenolate intermediate, followed by reaction with 4-chloronitrosobenzene (cycle **II**). Finally, product **4a** was formed by lactonization of **P**.

To verify the role of CH_3OH and the possible mechanism of the a^1-d^1 umpolung strategy, deuterium phenylpropiolaldehyde **1c-D** was used with 4-chloronitrosobenzene **2a** in the absence of CH_3OH, and **3ca** and **3cb** were obtained in a 1:1 ratio (Scheme 5, eq 1). It was revealed that the aldehydic deuterium was transferred to the expected position as shown in **3cb**. On the other hand, theoretically, **3cb** would be more than 90% in the two products, but we could obtain only 50% **3cb** from the reaction, which may be due to the participation of a trace amount of H_2O in the system (it would be clarified as shown in Scheme 5, eq 4; 30% of the proton comes from H_2O and $[DBU\text{-}H]^+$). This confirmed our hypothesis that there may be three kinds of proton sources from **N** to **3c**, and they were $[DBU\text{-}H]^+$, aldehyde, and H_2O. Interestingly, the amount of **3ca** was increased when CH_3OH was added as another proton source (Scheme 5, eq 2); this may be due to the fast proton transfer when CH_3OH is added as a proton source. The proton of CH_3OH tracked to the position in **3cb**, which was shown in eq 3 of Scheme 5. Therefore, cyclization would not be fast enough in the absence of CH_3OH, and the yield was decreased.

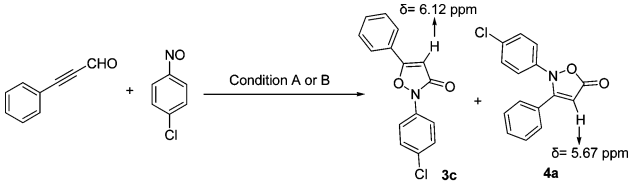
Scheme 5. Deuterium Experiment That Aimed to Determine the Role of Additive



However, we could not obtain the deuterium isotope effects of CD_3OD and CH_3OH because more than one kind of proton source existed in the system. Finally, it is obvious that the 5-endo-dig cyclization was promoted by CH_3OH to some extent.

Also, to prove that this highly regioselective umpolung strategy is effective, control experiments were performed using ^1H NMR analysis of the products (Scheme 6). It can be noted

Scheme 6. Controlled Experiments for the Regioselective Umpolung



Condition A: 10mol% E, DBU (1.5 equiv), CH_3OH(5.0 equiv), THF , Ar, r.t. **3c** : **4a** >99 : 1
Condition B: 20mol% J, DBU (1.5 equiv), DMF , Ar, r.t. **4a** : **3c** >30 : 1

that the ratio of the two regioisomers was more than 99:1 and 30:1 under each condition, and this revealed our highly regioselective umpolung strategy was successful.

In summary, we have developed a highly regioselective umpolung reaction using alkynyl aldehydes as nucleophiles in which regioselectivity was controlled by the reaction conditions. This catalytic protocol allows for a rapid construction of isoxazol-3(2H)-ones and isoxazol-5(2H)-ones from the same materials under mild conditions in moderate to acceptable yields. Further investigations of the use other electrophiles and the regioselective umpolung strategy are being pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, and crystallographic data for the products. 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.

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