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# Proline as Lewis Base Catalyst: Diastereoselective Synthesis of Isoxazoline-*N*-oxide through [3 + 2] Cycloaddition

**Haifeng Duan, Xiaohua Sun, Wenyan Liao, Jeffrey L. Petersen, and Xiaodong Shi***

*C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506*

*xiaodong.shi@mail.wvu.edu*

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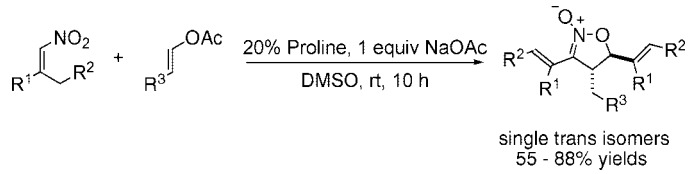
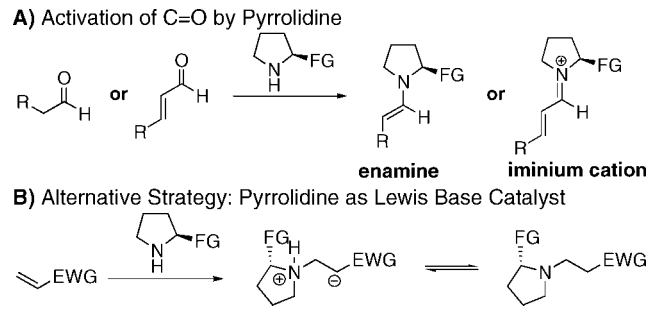
## ABSTRACT




**A catalytic cascade synthesis of isoxazoline-*N*-oxide was developed through proline-catalyzed nitroalkene activation. A large substrate scope was obtained with good to excellent yields. Mechanistic studies revealed intramolecular cyclization as the rate-determining step, giving only trans isomers in all cases.**

During the past decade, organocatalyst-promoted reactions have rapidly evolved into one of the most important approaches in organic synthesis.[1] Among the reported small organic molecule catalysts, chiral amines, in particular pyrrolidine derivatives (also referred to as proline analogues), are dominant due to good accessibility and high efficiency. The mechanism of these catalysts is generally through the amine activation of the carbonyl group to form a corresponding iminium cation or enamine intermediates (Scheme 1A). Application of this strategy, remarkable works targeting

**Scheme 1**




the C−C bond formation,[2] C−heteroatom bond formation,[3] and oxidation or reduction process[4] have been developed

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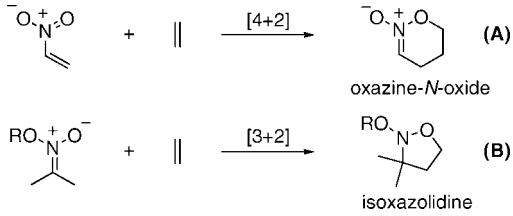
with excellent stereoselectivity. Meanwhile, with the presence of nitrogen lone-pair electrons, amines are also good nucleophilic catalysts.[5] Some tertiary amines, such as DABCO, quinine, and DMAP have been well studied as Lewis base catalysts.[6] But the application of secondary and primary amines as a Lewis base is much less developed. One general concern is that the deprotonation of the ammonium hydrogen will convert the Zwitterion intermediate into the neutral Michael adduct, thereby decreasing the reactivity of the carbon nucleophile (Scheme 1B).

Recently, our group reported a catalytic cascade intermolecular double Michael addition between $\beta$-alkyl nitroalkenes and enones. Experimental and computational studies suggested that L-proline served as an effective Lewis base catalyst for activation of the nitroalkene.[7] This result initiated our interest in investigating whether this strategy can be extended to other functional group transformations and eventually to be an alternate application of the well-studied proline-based catalysts. In this paper, we report a one-step stereoselective synthesis of isoxazoline-*N*-oxide through proline-catalyzed [3 + 2] cycloaddition of nitroalkenes and vinyl esters.

The hetero cycloaddition between aliphatic nitro compounds and alkenes is recognized as an important strategy in complex molecule synthesis.[8] Two typical transformations are the conjugated nitroalkene/alkene [4 + 2] (Scheme 2, A) addition[9] and nitronate/alkene [3 + 2] addition[10] (Scheme 2, B), which have been well studied as an efficient approach for synthesis of oxazine-*N*-oxide and isoxazolidine derivatives.

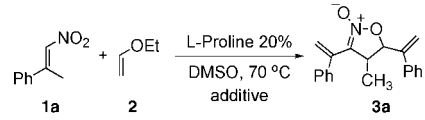
**Scheme 2.** [4 + 2]/[3 + 2] Cycloaddition of Nitro Compounds




Although five-membered isoxazoline-*N*-oxides are known to be important building blocks for synthesis of biologically active compounds and pharmaceutical agents,[11] there is still a lack of an efficient protocol for their synthesis. The conventional strategy for the preparation of these heterocyclic compounds is the intramolecular O-alkylation of aliphatic nitro compounds.[12] However, the lack of general methods to prepare the starting materials, low overall yield, and the narrow substrate scope limited the application of this approach. With high synthetic efficiency, the cycloaddition approach is of great interest for the preparation of isoxazoline.[13] Currently, most of the approaches focus on the development of the alternative method for the preparation of nitronate. On the basis of our previous success in the proline as Lewis base activation of $\beta$-alkyl-nitroalkene, we wondered if this strategy could be applied to the nitroalkene-alkene [3 + 2] cycloaddition. This alternative route will not only avoid preparation of nitronate but also help us to understand the mechanism of proline as a Lewis base catalyzed reaction.

To evaluate this hypothesis, nitroalkene **1a** and vinyl ethyl ether **2** were first applied. The results are summarized in Scheme 3.

**Scheme 3.** Cycloaddition of Nitroalkene and Vinyl Ether




| additive | yield |
|---|---|
| none | 0% |
| 1 equiv $BF_3$-THF | 0% |
| 1 equiv $BF_3$-THF; 1 equiv NaOAc | 56% |

With only proline as the catalyst, no cyclization was observed between **1a** and **2**, even on heating at 70 °C. Addition of $BF_3$−THF also did not give any cycloaddition product. However, the addition of 1 equiv of NaOAc along with the $BF_3$−THF at 70 °C for 10 h gave isoxazoline-*N*-oxide **3a** in 56% yield. It is expected that the nitro-carbanion from amine addition to nitroalkene is crucial for the sequential [3 + 2] reaction. Thus, the addition of NaOAc

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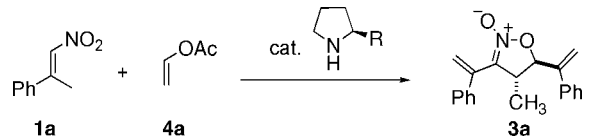
may provide the necessary buffer for the desired reaction. Meanwhile, addition of only proline and NaOAc, without $BF_3$−THF, produced only trace amounts of **3a**. Considering that the OEt in **2** was eliminated during the process (which is consistent with the fact that the $BF_3$−THF is required for the transformation), we then postulated that a better leaving group on the alkene may help this transformation by providing easier elimination step. The reaction between nitroalkene **1a** and vinyl ester **4a** was then carried out. The results are given in Table 1.

**Table 1.** Screening of the Reaction Conditions[a,g]



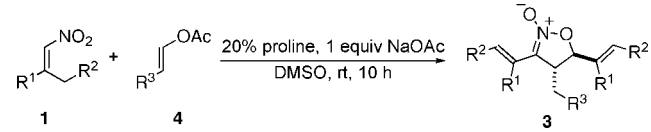

**1a** **4a** **3a**

| entry | cat. | base | solvent | temp | time (h)[b] | convn (%)[c] | yield (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | – | – | DMSO | 70 °C | 8 | 0 | 0 |
| 2 | – | NaOAc | DMSO | rt | 8 | 90 | 0 |
| 3 | – | NaOAc | DMSO | 70 °C | 8 | 95 | 5 |
| 4 | cat.-**1**[e] | – | DMSO | rt | 24 | 37 | 19 |
| 5 | cat.-**1** | NaOAc | DMSO | rt | 8 | 99 | 88 |
| 6 | cat.-**2** | NaOAc | DMSO | rt | 8 | 81 | 20 |
| 7 | cat.-**2** | NaOAc/ HOAC(20%) | DMSO | rt | 8 | 88 | 29 |
| 8 | $PPh_3$[f] | NaOAc | DMSO | rt | 8 | 95 | 8 |
| 9 | NMI [f] | NaOAc | DMSO | rt | 8 | 87 | 9 |
| 10 | DMAP [f] | NaOAc | DMSO | rt | 8 | 85 | 7 |
| 11 | Glycine | NaOAc | DMSO | rt | 8 | 90 | 54 |
| 12 | cat.-**3** | NaOAc | DMSO | rt | 8 | 99 | 45 |
| 13 | cat.-**1** | $Cs_2CO_3$ | DMSO | rt | 8 | 99 | 46 |
| 14 | cat.-**1** | NaO$^t$Bu | DMSO | rt | 8 | 99 | 43 |
| 15 | cat.-**1** | $Et_3N$ | DMSO | rt | 10 | 95 | 40 |
| 16 | cat.-**1** | NaOAc | MeOH | rt | 8 | 98 | 22 |
| 17 | cat.-**1** | NaOAc | THF | rt | 24 | 15 | 5 |
| 18 | cat.-**1** | NaOAc | $CH_3CN$ | rt | 24 | 10 | trace |

[a] Reactions were carried out with **1a**:**4a**:cat. = 1:2:0.2; concentration is 0.2 M of **1a**. [b] Monitored by TLC. [c] Based on the consumption of **1a** by NMR. [d] Determined by NMR. [e] cat.-**1**: R = COOH; cat.-**2**: R = H; cat.-**3**: R = $CH_2NHC(S)NHAr$. (Ar = 2,3-di-$CF_3$−Ph). [f] 1.0 equiv. [g] The reaction is 2:1 condensation of **1a** and **4a**. The 1:2 ratio gave the best results by avoiding polymerization of **1a**, which is the major side reaction for the reported transformation. The 2:1 ration of **1a** and **4a** also gave the desired **3a** with 30 to 50% lower yields due to the polymerization of **1a**.

As shown in Table 1, the thermo [4 + 2] cycloaddition between **1a** and **4a** was not observed even at higher reaction temperatures (entry 1). This is probably due to the steric hindrance of the 2,2-disubstituted nitroalkene **1a** and the presence of electron enriched alkene. The combination of proline as the catalyst and NaOAc as the additive was critical for good overall yield (entries 2−5). With only NaOAc as the additive, significant polymerization of **1a** was observed, and a very small amount of **3a** was produced (entries 2 and 3). This result suggested that rather than the base deprotonation of the methyl group of **1a**, nucleophilic addition of **1a** by a catalyst was the key step that accounted for the formation of **3a**. Meanwhile, secondary and primary amines were found as the only effective catalysts for this reaction. Tertiary amines and phosphorus nucleophilic catalysts resulted in significant amounts of polymerization. Interestingly, the amino acids gave better yields than the simple amine (entry 6). With pyrrolidine as the catalyst, poor yields were obtained even with the addition of 20% of acetic acid, which best mimics the basicity of the proline/NaOAc condition (entry 7). This effect was further emphasized when glycine and thiourea modified proline cat.-**3** were applied, and in both cases, reasonable good yields of **3a** were obtained. These results strongly imply the formation of an intramolecular H-bond of the amino acid activated nitronate intermediate, which may lead to future enantioselective reactions (at this moment, <10% ee was observed in all these cases). Other bases and solvents have also been investigated, while NaOAc as an additive in DMSO was identified as the optimal condition. Thus, various nitroalkenes and vinylesters were applied to investigate the substrate scope, and the results are shown in Table 2.

**Table 2.** Reaction Substrate Scope[a]




**1** **4** **3**

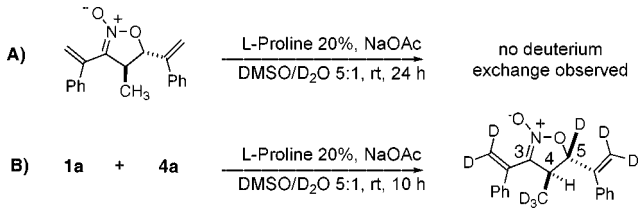
| entry | **1** | **4** ($R^3$) | yield (%)[b] |
|---|---|---|---|
| 1 | **1a**: $R^1$ = Ph; $R^2$ = H | **4a**: $R^3$ = H | **3a**: 88 |
| 2 | **1a** | **4b**: $R^3$ = Me | **3b**: 76 |
| 3 | **1a** | **4c**: $R^3$ = Et | **3c**: 71 |
| 4 | **1a** | **4d**: $R^3$ = $CH_2Ph$ | **3d**: 65 |
| 5 | **1b**: $R^1$ = p-Me-Ph; $R^2$ = H | **4a** | **3e**: 83 |
| 6 | **1b** | **4d** | **3f**: 66 |
| 7 | **1c**: $R^1$ = p-Cl-Ph; $R^2$ = H | **4a** | **3g**: 77 |
| 8 | **1c** | **4b** | **3h**: 58 |
| 9 | **1d**: $R^1$ = 2-naphthalene; $R^2$ = H | **4a** | **3i**: 75 |
| 10 | **1d** | **4d** | **3j**: 61 |
| 11 | **1e**: $R^1$ =Ph; $R^2$ = $CH_3$ | **4a** | **3k**: 75[c] |
| 12 | **1f**: $R^1$; $R^2$ = -$(CH_2)_4$- | **4a** | **3l**: 87[c] |
| 13 | **1f** | **4b** | **3m**: 80 |
| 14 | **1f** | **4c** | **3n**: 74 |
| 15 | **1f** | **4d** | **3o**: 70 |
| 16 | **1g**: $R^1$; $R^2$ = -$(CH_2)_3$- | **4a** | **3p**: 72 |
| 17 | **1g** | **4b** | **3q**: 65 |
| 18 | **1h**: $R^1$ = $CH_3$; $R^2$ = H | **4a** | **3r**: 55 |

[a] **1** (1.0 equiv), **4** (2.0 equiv), L-Pro (20%), and NaOAc (1 equiv) were dissolved in DMSO (0.2 M) and stirred at rt. [b] Isolated yields. [c] Structure was determined by X-ray crystallography.

Various 2,2-disubstituted nitroalkenes were suitable for this transformation. The substrate scope included dialkyl (both cyclic and acyclic) and aryl−alkyl nitroalkenes. Although the monoalkyl substituted nitroalkene could also conduct the $\beta$-elimination of LB catalyst, a significant amount of polymerization was observed giving only a trace amount of the desired isoxazoline product. Different $\beta$-substituted vinyl esters were also suitable for this reaction, giving easy access to the C-4 position of product **3**. Notably, among all cases, only trans diastereomers were formed, and the structure was confirmed by X-ray crystallography.[14]

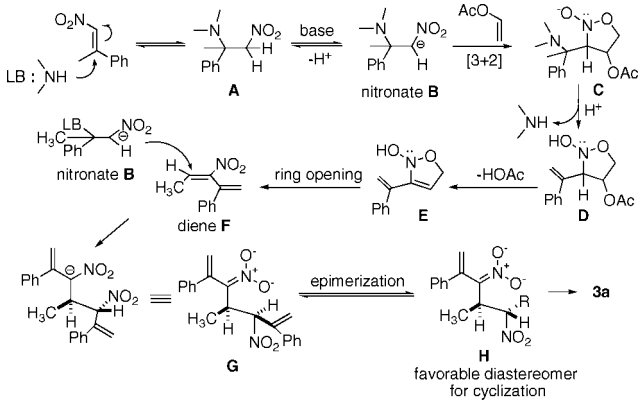
To further elucidate the reaction mechanism, especially the stereoselectivity, deuterium exchange studies have been performed, and the results are summerized in Scheme 4.

**Scheme 4.** Deuterium-Labeling Experiment




Recharging product **3a** into the reaction under the presence of $D_2O$, no deuterium exchange was observed, which implied that no epimerization of the C-5 stereogenic center occurred under the reaction condition (Scheme 4A). Therefore, the cyclization should be the key step that accounts for the formation of the single *trans* isomer. A reaction between **1a** and **4a** was then performed in the presence of $D_2O$. As expected, deuterium exchange was observed on the C-5 position along with the C-4 methyl and vinyl groups (Scheme 4B). Notably, no deuterium exchange was obtained with the C-4 hydrogen. Therefore, a mechanism with epimerization of intermediate **G** is proposed in Scheme 5.[15]

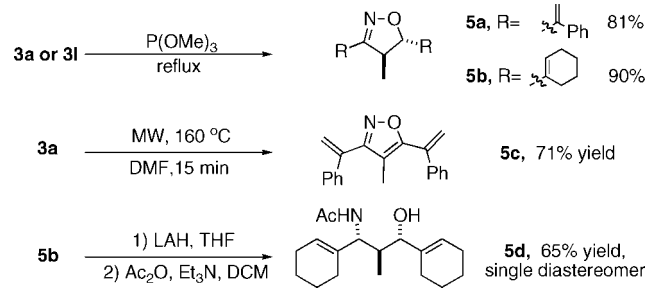
**Scheme 5.** Proposed Mechanism for the Formation of Isoxazoline-*N*-oxide **3**




As illustrated in Scheme 5, the reaction between **1a** and proline produced nitro carbanion intermediates **B**. It is likely that **B** underwent [3 + 2] dipolar cycloaddition with vinylester, forming five-membered intermediate **C**. The transformation from **C** to **F** can go through different mechanisms, where the retro-electro cycloaddition is just one possible path. Nevertheless, the formation of diene **F** is most likely through the elimination of AcOH, which is consistent with the requirement of base. Since the addition of nitronate **B** to diene **F** likely underwent a Mukaiyama-type transition state, the corresponding *anti* intermediate **G** would be formed. Through the fast epimerization of the C-5 proton, the cyclization of the *syn* isomer **H** gave the *trans* isomer as the only product. The fact that no proton exchange occurred on the C-4 position was consistent with the proposed mechanism.

As a very useful synthon, the isoxazoline-*N*-oxide can be readily converted into other synthetically attractive building blocks.[16] Some functional group transformations have been performed, and the results are shown in Scheme 6.

**Scheme 6**




In conclusion, a catalytic cascade one-step synthesis of isoxazoline-*N*-oxide was developed. A large variety of nitroalkenes and vinyl esters were found suitable for this transformation to give only *trans* isomers with good to excellent yields. Mechanistic studies revealed amine addition to the nitroalkene with nitronate cyclization as the rate-determining step. This strategy not only provides a new approach for the construction of substituted isoxazoline derivatives but also provides further evidence of secondary amine nucleophilic activation of nitroalkene, an alternative path of proline catalysis. Other secondary/primary amine-promoted nitroalkene cascade reactions are currently under investigation in our group and will be reported in due course.

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**Supporting Information Available:** Experimental and computational details, spectrographic data, and XRD information. This material is available free of charge via the Internet at http://pubs.acs.org.

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