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Amine-urea Mediated Asymmetric Cycloadditions between Nitrile Oxides and *o*-Hydroxystyrenes by Dual Activation, and Their Computational Studies

Hiroyuki Suga,* Yohei Hashimoto, Yasunori Toda, Kazuaki Fukushima, Hiroyoshi Esaki, and Ayaka Kikuchi

Abstract: The first example of cinchona alkaloid-based amine-urea-mediated asymmetric 1,3-dipolar cycloadditions between nitrile oxides and *o*-hydroxystyrenes, based on the dual activation methodology involving both LUMO and HOMO activations, is described. In addition to stoichiometric asymmetric induction, a catalytic amount of amine-urea enables the cycloadditions in an enantioselective manner. Computational studies strongly support the HOMO activation of *o*-hydroxystyrenes and LUMO activation of nitrile oxides via hydrogen-bonding interactions by a Brønsted acid/base bifunctional catalyst.

1,3-Dipolar cycloadditions (1,3-DCs) between nitrile oxides and olefins have served as a highly efficient methodology for the synthesis of isoxazolines.[1] These isoxazolines can then be converted to γ-aminoalcohols and β-hydroxy ketones via reductive cleavage of the N-O bond, while retaining stereochemistry. Thus, the sequence of 1,3-DC followed by N-O reductive cleavage has been utilized for the construction of various natural products that possess continuous stereogenic centers.[2] It is therefore necessary to develop enantioselective 1,3-DCs of nitrile oxides, as well as chiral substrate-based diastereoselective 1,3-DCs.[3] For non-linear 1,3-dipoles, such as nitrones and azomethine imines, a number of enantioselective cycloadditions using chiral Lewis acids have been reported,[4] and these types of transformations have also been reported using several organocatalysts.[5] By contrast, there are only a few examples of enantioselective 1,3-DCs of nitrile oxides (linear 1,3-dipoles) using chiral Lewis acids[6] or metal catalysts[7]. This can be due to their linear structure, which lacks an enantioface and higher reactivity, allowing non-catalytic reaction to proceed easily in the background (Figure 1a and 1b). Furthermore, to the best of our knowledge, enantioselective 1,3-DCs of nitrile oxides that involve organocatalytic variants or even in the presence of stoichiometric amounts of chiral organic media, have yet to be demonstrated.[8] To overcome the intrinsic challenge and achieve high enantioselectivity, we propose a novel dual-activation strategy involving LUMO activation by a Brønsted acid and HOMO activation by a Brønsted base in inverse electron-demand 1,3-DCs between nitrile oxides **1** and *o*-hydroxystyrenes **2** employing chiral amine-urea **3** (Figure 1c).[9] Double hydrogen-bonding interactions between the urea moiety of **3** and the oxygen atom of **1** would construct a plane to distinguish the orientations of dipolarophile **2**.[9m] Although inverse electron-demand 1,3-DCs of azomethine imines with *o*-hydroxystyrenes catalyzed by a chiral Brønsted acid have been reported by Shi and co-workers,[5f] this approach can empower bifunctional amine-urea catalysis as the premier organocatalytic method for asymmetric transformation of linear 1,3-dipoles.

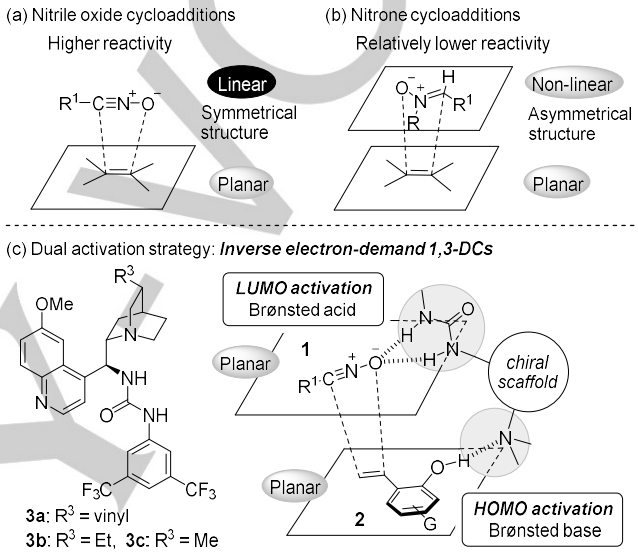

Figure 1. Working hypothesis based on dual activation by bifunctional organocatalyst.

Initially, cycloadditions between isolable nitrile oxide **1a** and *o*-hydroxystyrene (**2a**) were carried out in toluene in the presence of various chiral amine-ureas (See Supporting Information (SI) for details). After screening numerous variations of the reaction, the optimal enantioselectivity was achieved at 0 °C using amine-urea **3a** (R^3 = vinyl) at a concentration of 0.2 M (Scheme 1, 89% ee for **4aa**). To assess the influence of the hydroxy group on the enantioselectivity, we examined the relationship between the position of the hydroxy group and the corresponding hydrogen-bond donors. In contrast to **2a**, attempts using *m*- and *p*-hydroxystyrene (**2b** and **2c**), and *o*-methoxystyrene (**2d**) resulted in little or no asymmetric induction in the presence of **3a**. Likewise, the reaction involving homoallylic alcohol (**2e**) did not exhibit any significant

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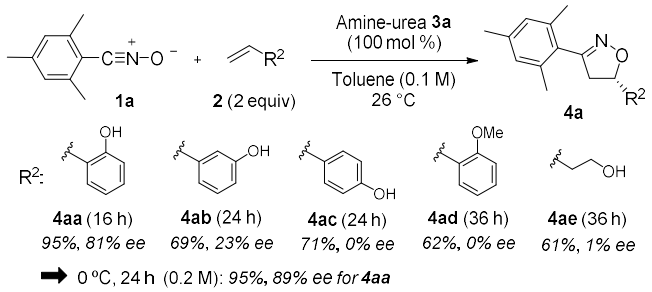
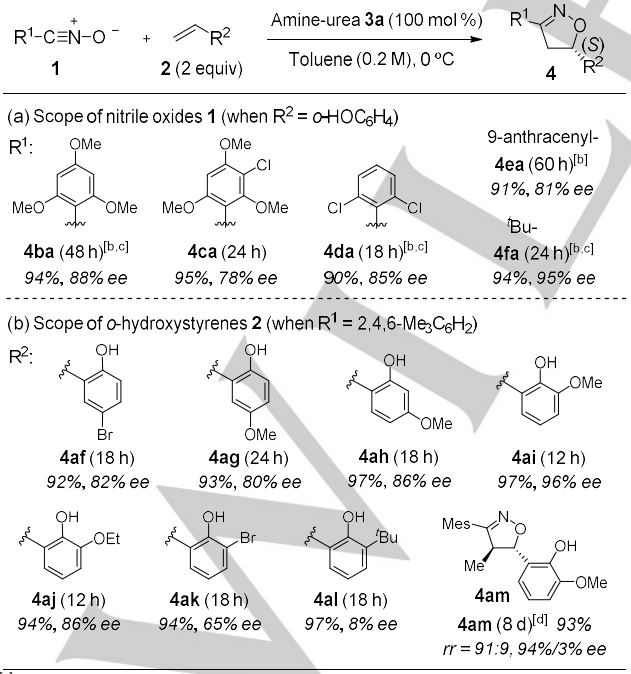
Scheme 1. Initial studies



asymmetric induction. These results suggest that the acidity and the position of the hydroxy group are crucial for obtaining high levels of enantioselection.

Table 1 summarizes the scope of asymmetric 1,3-DCs. For isolable nitrile oxides, the reactions proceeded smoothly to afford the corresponding cycloadducts in high yields with 78 – 95% ee (Table 1a). X-ray crystal structure analysis was employed to determine the absolute configuration of enantiomerically pure **4da**, in which the methine carbon at the 5-position was determined to possess an (*S*)-configuration (see SI). Next, the scope of the *o*-hydroxystyrenes was examined (Table 1b). Although the inclusion of substituents such as 5-Br, 5-OMe, 4-OMe, or 3-OEt led to comparable enantioselectivities, the inclusion of a 3-OMe substituent produced a dramatic increase in enantioselectivity (96% ee for **4ai**). Conversely, decreased enantioselectivies were observed for **4ak** and **4al**. The 1,3-DC of **1a** with *trans*-β-substituted *o*-hydroxystyrene **2m** exhibited intriguing results in terms of not only enantioselectivity but also regioselectivity. In the absence of **3b** (Figure 1, R^3 = Et), the reaction favored the 5-methyl regioisomer **4am**' (**4am**/**4am**' = 27:73, 83% combined yield).[10] In the presence of **3b**, however, the reaction afforded the 4-methyl regioisomer **4am** with high regioselectivity (**4am**/**4am**' = 91:9, 93% combined yield) and enantioselectivity (94% ee, **4am**). Notably, no *cis*-cycloadducts were observed from *trans*-alkene **2m**, implying that this reaction proceeded through a concerted pathway.

Table 1. Scope of asymmetric 1,3-DCs[a]



[a]All reactions were carried out using 0.1 mmol of **1**. Isolated yields are shown. [b]0.1 M. [c]-20 °C. [d]Amine-urea **3b** was used (at 26 °C).

To gain insight into the mechanism of asymmetric induction, the 1,3-DC between **1a** and **2i** was studied using density functional theory (DFT). Recently, Houk et al. reported on computational studies of an asymmetric conjugate addition reaction catalyzed by a cinchona alkaloid-derived amine-urea.[9c,11] For protonated **3c** (Figure 1, R^3 = Me), the *anti*-open and *syn*-open conformers were proved to be favored over other conformers.[12] On the basis of Houk's system, four possible transition states (TSs) [(a) *anti*-open TS (*S*), (b) *syn*-open TS (*S*) (c) *anti*-open TS (*R*), (d) *syn*-open TS (*R*)] were generated (Figure 3, see SI for full computational details). We ruled out the TS models in which the phenoxide generated from **2** coordinates with the urea moiety of protonated **3**, while this activation mode has often been used to explain (thio)urea-tertiary amine organocatalysis.[13] This is because no proton transfer between **1** and **2** is required during the course of the 1,3-DC.

All calculations were performed using the M06-2X/def2-TZVPP-IEFPCM (toluene)//M06-2X/6-31G(d)-IEFPCM (toluene) level of theory with Gaussian09 D.01.[14,15] The intrinsic reaction coordinate (IRC) approach was used to search for pre-reaction complexes (PCs) and products. First, TSs providing (*S*)-products were considered since (*S*)-**4** was experimentally obtained as a major enantiomer (**4da** in Table 1). Although *anti*-open TS (*S*) was favored over *syn*-open TS (*S*) by only $\Delta\Delta G^{\ddagger}$ = 0.7 kcal mol^{-1}, *anti*-open PC (*S*) was favored over *syn*-open PC (*S*) by ΔG = 2.3 kcal mol^{-1} (Figure 2a vs. 2b, and Figure 3). Hydrogen-bonding interactions between the amine N and the phenol H (1.74 – 1.76 Å) and between the nitrile oxide O and the urea H (1.87 – 2.20 Å) were apparent in the TSs. From these results and the energy profiles, it is highly likely that the reaction involving *anti*-open TS (*S*) is the preferred pathway for the 1,3-DC between **1a** and **2i**. Regarding the TSs, the 1,3-DC proceeds through a concerted but asynchronous pathway, where the C-O bond lengths (2.41 – 2.45 Å) are longer than C-C bonds (2.14 – 2.15 Å). To further explore the mechanism behind the high enantioselectivities of asymmetric 1,3-DCs, energies were calculated for *anti*-open TS (*R*), which corresponds to the (*R*)-isomer of the cycloadduct. The $\Delta\Delta G^{\ddagger}$ energy for the *anti*-open TS (*R*)-conformation was higher than that of the (*S*)-conformation by 6.2 kcal mol^{-1} (Figure 2a vs. 2c). The energy profiles also indicate that the *anti*-open (*S*) arrangement is favored over the *anti*-open (*R*) in terms of their pre-reaction complexes as well as their TSs. Moreover, even in comparison with the *syn*-open TS (*R*), it was confirmed that the *anti*-open TS (*S*) is the lowest energy TS (Figure 2a vs. 2d). On the other hand, in order to validate our working hypothesis, i.e. the dual-activation strategy, we calculated the HOMO–LUMO gap between **1a** and **2i** (see SI for details). The gap is smaller for LUMO_**1a**–HOMO_**2i** than for LUMO_**2i**–HOMO_**1a** (155.5 vs. 174.3 kcal mol^{-1}), which suggests that the 1,3-DCs proceed in an inverse electron-demand fashion. Importantly, both the LUMO_**1a** and HOMO_**2i** can be activated by **3a** engaging the two reactants (overall 11.2 kcal mol^{-1} preferred).

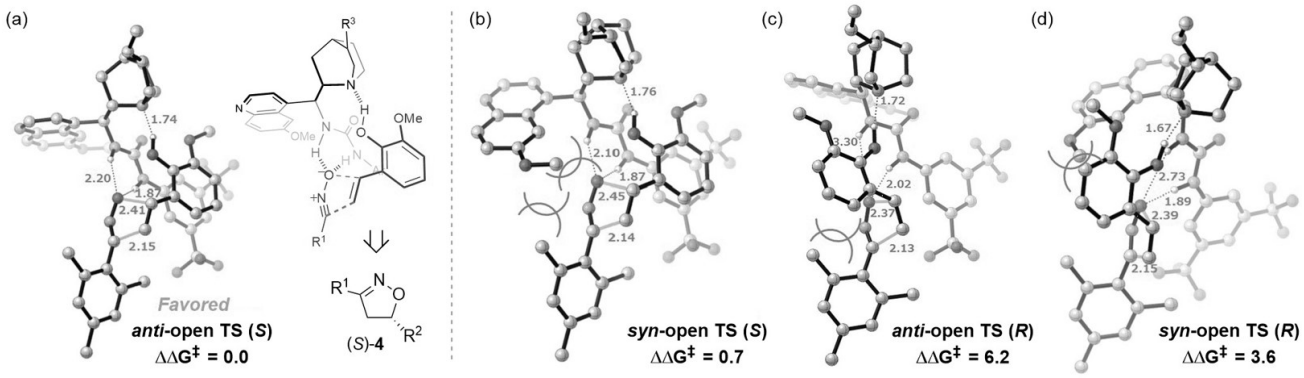


Figure 2. TSs corresponding to the *anti*-open and *syn*-open conformers of protonated **3a**. M06-2X/def2-TZVPP-IEFPCM (toluene)//M06-2X/6-31G(d)-IEFPCM (toluene). Noncritical hydrogen atoms omitted for clarity. Energy in kcal mol^{-1}.

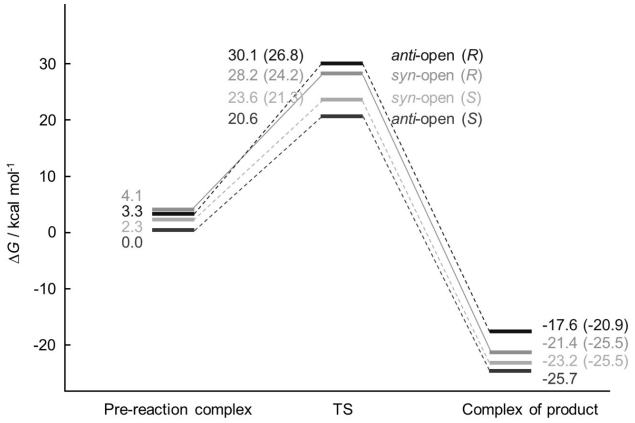


Figure 3. Energy profiles of the 1,3-DC. Energy in kcal mol^{-1}

Encouraged by the results of the DFT calculations, we finally attempted the *catalytic* enantioselective reactions shown in Scheme 2a. It is noteworthy that the use of a catalytic amount (30 mol %) of **3a** enhanced the asymmetric 1,3-DCs between **2i** and isolable nitrile oxides resulting in high yields and enantioselectivities (85 – 96% ee).[16,17] The catalysis was also applicable to the reactions between *o*-hydroxystyrenes and unstable nitrile oxides that are generated from hydroxymoyl chlorides **5** with a base, providing cycloadducts **4** in high yields with good to high enantioselectivities (Scheme 2b).

In conclusion, we have developed the first example of highly enantioselective cinchona alkaloid-based amine-urea-mediated 1,3-DCs between nitrile oxides and *o*-hydroxystyrenes involving the dual activation methodology. The high levels of asymmetric induction are strongly supported by DFT calculations of the energy differences between the *anti*-open TS (*S*) and *anti*-open TS (*R*). Asymmetric 1,3-DCs of other dipoles based on the methodology described herein are currently under investigation in our laboratory.

Acknowledgements

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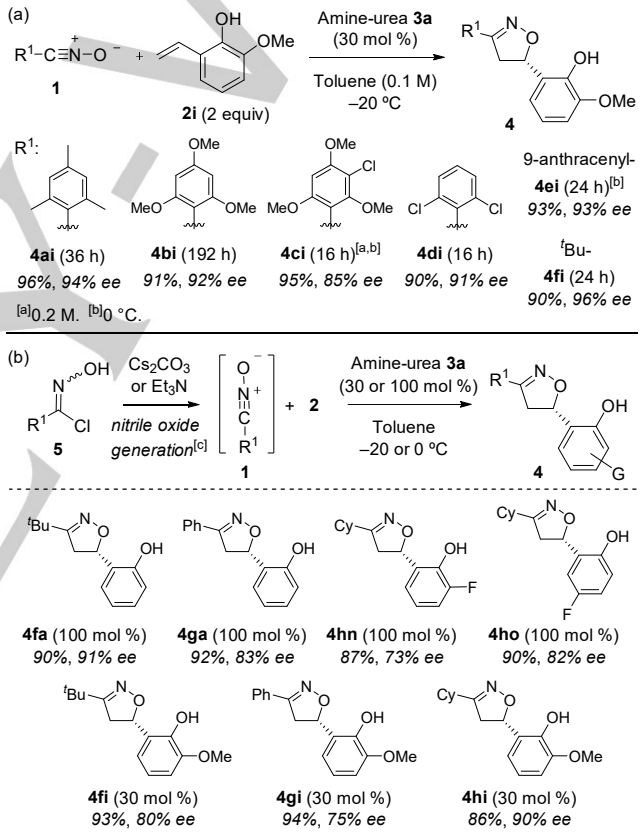
Scheme 2. Enantioselective 1,3-DCs of nitrile oxides



[c]See supporting information for details of the reaction conditions.

Keywords: nitrile oxide • 1,3-dipolar cycloaddition • isooxazoline • organocatalyst • bifunctional catalyst

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[16] Although the catalyst loading is relatively high, **3a** can be recovered and reused even if an equimolar amount of **3a** was used. For example, upon completion of the asymmetric 1,3-DC between **1a** and **2i**, the resulting product was purified by silica gel chromatography to afford **4ai** along with a nearly complete recovery of **3a** (see SI for details).

[17] The reaction of **1a** with **2i** in the presence of **3a** (10 mol %) afforded **4ai** in 92% yield with 84% ee.

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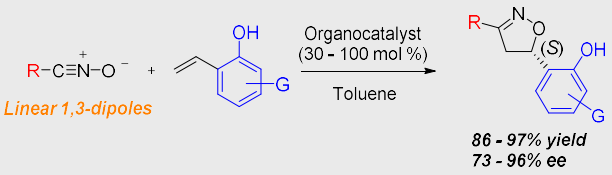

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