

ENANTIOSELECTIVE CYCLOADDITIONS BETWEEN ALIPHATIC NITRILE OXIDES AND 2-HYDROXYSTYRENES CATALYZED BY CHIRAL AMINE-UREA

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‡ Dedicated with respect to Professor Kiyoshi Tomioka on his 70th birthday

Abstract – Chiral amine-urea-catalyzed enantioselective 1,3-dipolar cycloadditions of nitrile oxides with 2-hydroxy-3-methoxystyrene are described. Aliphatic aldehyde-derived hydroximoyl chlorides were used as nitrile oxide precursors, providing optically active isoxazolines with moderate to good enantioselectivities.

Nitrile oxides are generally unstable and reactive species, and are widely used as 1,3-dipoles not only for the preparation of isoxazolyl-type heterocycles but also for their applications in organic synthesis.¹ 1,3-Dipolar cycloadditions (1,3-DCs) between nitrile oxides and alkenes provide isoxazolines, which can be derivatized to γ -aminoalcohols and β -hydroxy ketones via N-O bond cleavage without loss of stereochemistry. Thus, these sequential transformations have been employed for the construction of contiguous stereogenic centers in natural product synthesis.² Several efforts have been devoted to stereoselective 1,3-DCs of nitrile oxides to obtain isoxazolines in optically active form;³ however, only a few enantioselective protocols have been exploited to date.^{4,5} This may be due to some inherent issues of nitrile oxides: (a) a linear structure that lacks an enantioface to distinguish the orientations of dipolarophiles, and (b) a higher reactivity that allows non-catalytic reactions to compete. In addition, one critical issue in the reported methods is that aromatic aldehydes and pivalaldehyde-derived nitrile oxides have been employed as adaptive scope to achieve high yields and/or high enantioselectivities in most

cases. Recently, we have demonstrated the first example of asymmetric inverse electron-demand 1,3-DCs between nitrile oxides and 2-hydroxystyrenes by a bifunctional chiral amine-urea catalyst, where a novel dual-activation system involving LUMO activation by a Brønsted acid and HOMO activation by a Brønsted base has been introduced (Figure 1).⁶ Since our organocatalytic approach was proven to be effective, we applied this strategy to enantioselective 1,3-DCs of nitrile oxides including aliphatic entries in order to expand the scope of substrates.

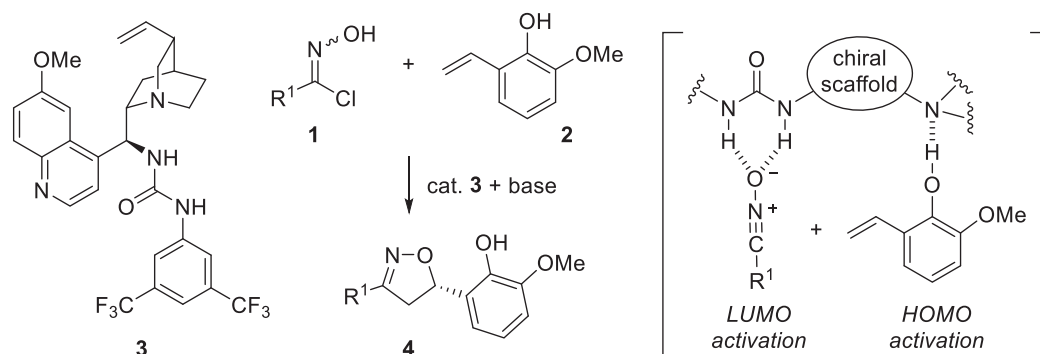


Figure 1. Dual activation strategy by a bifunctional catalyst for enantioselective 1,3-DCs

In the previous work, we found that 2-hydroxystyrenes, specifically 2-hydroxy-3-methoxystyrene (**2**), undergo nitrile oxide 1,3-DCs in an enantioselective manner under the influence of amine-urea **3** (30 mol%), wherein unstable nitrile oxides can be generated in situ from hydroximoyl chlorides **1**.⁶ Treatment of **1a** (R¹ = *c*-hexyl) with triethylamine in toluene followed by filtration provided a solution of nitrile oxide, which was used for cycloaddition at $-20\text{ }^{\circ}\text{C}$, affording isoxazoline **4a** in 88% yield with 90% ee (Table 1, entry 1). We therefore investigated the scope of aliphatic nitrile oxides under the same conditions. The reaction of **1b** (R¹ = *n*-pentyl), bearing a linear-chain alkyl group, proceeded smoothly with good enantioselection (entry 2). Relatively high selectivity was observed when using *i*-butyl and benzyl hydroximoyl chlorides **1c** and **1d**, albeit with low yields of **4d** (entries 3 and 4). Alkenyl and aryl hydroximoyl chlorides **1e** – **1i** were also examined, but led to decreased enantioselectivities.⁷ Thus, we calculated the frontier molecular orbitals of the nitrile oxides to characterize their reactivity for 1,3-DCs in conjunction with their stereochemical outcome. All calculations were performed using the M06-2X/def2-TZVPP-IEFPCM(toluene)//M06-2X/6-31G(d)-IEFPCM(toluene) level of theory with Gaussian09 E.01.⁸ Our recent study disclosed that the nitrile oxide LUMO can be activated by the urea moiety of **3**, and it was hypothesized that lower enantioselectivities observed in aryl groups would be due to their higher reactivity, i.e., the lower LUMO energy. Indeed, as shown in Figure 2a, the LUMO energy for benzonitrile oxide (**5b**) was lower than that of cyclohexanecarbonitrile oxide (**5a**) by 2.6 eV (ca. 60 kcal mol⁻¹). The competitive reaction between **5a** and **5b** also clearly showed the reactivity difference in 1,3-DCs with **2** (Figure 2b, **4a/4f** = 1:1.4).⁹ Based on these results, our dual activation strategy seems to

be more suitable for nitrile oxides bearing aliphatic substituents, because the lower reactivity prevents the background reaction. This is in contrast to Lewis acid catalysis for 1,3-DCs of nitrile oxides with electron-deficient alkenes, in which the nitrile oxide HOMO reacts with the alkene LUMO in an electron-demand fashion.⁴

Table 1. Scope of nitrile oxides

entry	1 (R ¹ =)	4	yield (%) ^a	ee (%) ^b
1	1a : <i>c</i> -hexyl	4a	86	90
2	1b : <i>n</i> -pentyl	4b	78	73
3	1c : <i>i</i> -butyl	4c	89	82
4	1d : benzyl	4d	49	87
5	1e : (<i>E</i>)-cinnamyl	4e	81	51
6	1f : phenyl	4f	97	57
7	1g : 4-MeC ₆ H ₄	4g	98	48
8	1h : 3-MeC ₆ H ₄	4h	98	53
9	1i : 2-MeC ₆ H ₄	4i	96	54

^aIsolated yield. ^bDetermined by chiral HPLC analysis.

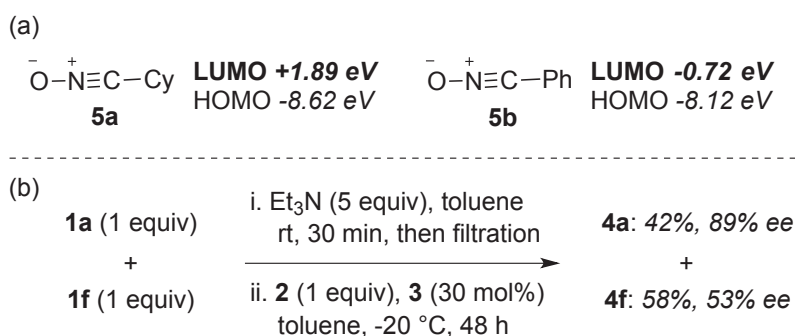


Figure 2. (a) HOMO-LUMO energies. (b) Competitive reaction.

In conclusion, we have developed chiral amine-urea-catalyzed enantioselective 1,3-DCs between in situ generated nitrile oxides and 2-hydroxystyrenes. This system is applicable to aliphatic nitrile oxides to afford the corresponding enantio-enriched isoxazolines. According to DFT calculations, the higher levels of asymmetric induction could be due to the LUMO energy differences between alkyl and aryl substituents on the nitrile oxides. Further extension of this unique catalysis for a range of applications is currently underway in our laboratory.

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