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Mn^{VI}-NP–Catalyzed Generation of Nitrile Oxides: Easy Access to Isoxazolines and Isoxazoles via Stereoselective 1,3-Dipolar Cycloaddition Reactions

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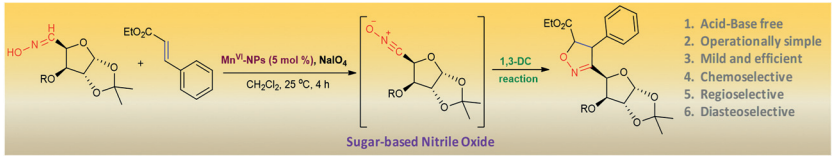

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Abstract The versatility and effectiveness of Mn^{VI}-NPs as a catalyst is examined for the generation of nitrile oxides from aldoximes and subsequent 1,3-dipolar cycloaddition reactions. This synthetic protocol features fast reaction convergence under benign reaction conditions, operational simplicity, and the use of inexpensive precursors; it avoids the use of acids or bases. The strategy offers excellent chemo-, regio-, and diastereoselectivity in the 1,3-dipolar cycloaddition reaction of *in situ* generated nitrile oxides with alkenes and alkynes.

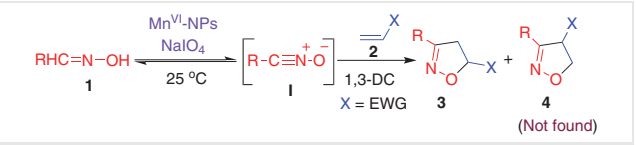
Key words manganese, nanoparticles, nitrile oxides, 1,3-dipolar cycloadditions, isoxazolines, isoxazoles

Applications of nanoparticles (NPs) have been explored in the chemical, biological, and materials fields.[1] It has been observed that the chemical reactivity of a bulk material is significantly improved by transformation into low-dimensional NPs.[2] Fabrication of Mo^{VI} nanowires has been reported, along with their applications in the construction of lithium-ion batteries, solar cells, and lubricating materials.[3] Recently, we have developed high-valency Mn-NPs with a highly active surface, strong oxidizing ability, improved magnetism, and catalytic properties, which helped us to construct new O–C/N–C/S–C and C–C bonds in approaches to biologically important flavones and their analogs.[4] The fabrication of Mn^{III}-NPs requires thermal decomposition of manganese oxalate at 450 °C,[5] and the preparation of Mn^{IV}-NPs needs extra stabilization from co-metal ions (Zn^{+2}, Ni^{+2}, Cu^{+2} and Mg^{+2}).[6] We were surprised to find that there are only a few reports on applications of Mn-NPs in fundamental organic transformations.[7] High-valency bulk Mn reagents have found many applications in synthetic organic chemistry as oxidants.[8] $KMnO_4$ is an inexpensive oxidizing agent, but its strong oxidizing properties prevent it from wide utility in organic synthesis. Copper, ruthenium, barium, ammonium, phosphonium, and crown ether stabilized permanganates have found only limited success.[9] Even with these reagents, explosions have been reported under certain reaction conditions.[9a] The transformation of the strong metal oxidant $KMnO_4$ into Mn^{VI}-NPs with an appropriately polarized surface could permit smooth exchange of electrons for oxidative organic reactions.[4] The 1,3-dipolar cycloaddition reaction is an atom-economical process that can construct bonds in a regio- and stereoselective way.[10–15] Recently, much effort has been devoted toward the development of improved variants of the Huisgen reaction.[10,11] For instance, several groups have recently demonstrated the 1,3-dipolar cycloaddition reaction as an outstanding tool for the construction of *N*-heterocycles involving nitrilium betaines with highly functionalized substituents.[13,14] Nitrile oxides have been identified as an important class of 1,3-dipoles that undergo 1,3-dipolar cycloaddition reactions with variety of unsaturated bonds in a unique regio- and stereocontrolled fashion to afford isoxazolines and isoxazoles.[12a,d,13a,15] These types of cycloadducts have been found to show antidepressant, antipsychotic, anti-anxiety, and anticancer activities.[16] They have also been utilized for the construction of natural products, pharmaceuticals, and agrochemicals.[17] Isoxazolines and isoxazoles offer high synthetic potential because a range of functionalities can be accessed by reductive cleavage of the N–O bond, followed by hydrolysis of the intermediates and nucleophilic and electrophilic functionalizations.[15a,18] Thus, a nitrile oxide cycloaddition with excellent regio- and stereoselectivity provides an important synthetic alternative to the stereoselective aldol condensation and related reactions. However,

the generation of nitrile oxides and their subsequent 1,3-dipolar cycloaddition reactions are challenging under benign reaction conditions because of the tendency of nitrile oxides to undergo dimerization and poor selectivity in the cycloaddition step. Nitrile oxides are generally prepared by acid- or base-mediated dehydration of primary nitro compounds[19] or oxidation of aldoximes by a chlorinating agent in the presence of base.[20] Other approaches include the use of oxidizing agents such as hypervalent iodine ($PhICl_2$, (diacetoxyiodo)benzene, [hydroxy(tosyloxy)iodo]benzene, PhIO),[13a,21] KI/I_2,[22] *t*-BuOX,[23] and chloramine-T.[24] In this context, the use of a metallic oxidant offers an advantage over bases or acids because the latter generate an aldehyde and form dimerized byproducts of the *in situ* generated nitrile oxide[25] and can lead to racemization of the sensitive stereogenic centers.[26] $Hg(OAc)_2$, $Pb(OAc)_4$, MnO_2, and ceric ammonium nitrate[27c] have been efficiently utilized for the generation of nitrile oxides.[27] However, elevated temperatures (80 °C), and large excesses of the metal oxidant (six to ten equivalents) are generally employed in the conventional procedures. High-valency Mn-NPs possessing a highly active surface could offer an ideal reagent for the smooth generation of nitrile oxides from aldoximes and could achieve excellent regio- and stereoselectivity in the 1,3-dipolar cycloaddition reaction.

A surfactant-assembled supramolecular architecture can play dual roles. It can absorb precursors and undergo subsequent chemical transformations inside its core, in this case oxidative transformation of the organic substrate by controlled electron transfer to the surface of the high-valency metal-NPs. We envisaged that such a process could be utilized as an ideal protocol for the chemo-, regio-, and stereoselective transformation of aldoximes to nitrile oxides and subsequent inter- and intramolecular 1,3-dipolar cycloaddition reactions toward valuable *N*-heterocycles such as isoxazoles.[28] As we reported earlier, a combination of the cationic surfactant cetyl trimethyl ammonium bromide, $KMnO_4$, trimethylsilylchloride, and water in CH_2Cl_2 produces a reverse micelle architecture,[2a,b] wherein the desired Mn^{VI}-NPs are formed at the core of the supramolecular assembly.[4]

To develop an operationally simple method, we examined the *in situ* transformation of 4-chlorophenyl aldoxime (**1a**) to the corresponding nitrile oxide (**I**) by using $Br(Me_3SiO)Mn^{VI}O_2$-NPs (Scheme 1). Formation of nitrile oxide **I** was confirmed by trapping it with ethyl acrylate (**2a**) to afford Δ^2-isoxazoline **3a** (Scheme 1).[13a] With this system, the use of $KMnO_4$ as an oxidant produced (**3a**) in a yield of 60%. However, an improved yield of 79% was obtained by using a catalytic amount of the $Br(Me_3SiO)Mn^{VI}O_2$-NPs (5 mol %) with an additional oxidant such as $NaIO_4$. Likewise, the use of $NaIO_4$ alone led to 65% conversion. The $Br(Me_3SiO)Mn^{VI}O_2$-NPs could be recovered and used successfully for a subsequent 1,3-dipolar cycloaddition reaction with a comparable yield.



Scheme 1 Generation of nitrile oxides and their regioselective cyclization to Δ^2-isoxazolines **3**

With these developed reaction conditions, the versatility of the intermolecular 1,3-dipolar cycloaddition approach with Mn^{VI}-NPs (Scheme 1) was tested with several aldoximes **1** and alkenes **2** to afford the corresponding functionalized Δ^2-isoxazolines **3a–h** (Figure 1) Both electron-rich and electron-deficient aromatic substituents and functional groups, such as esters, nitriles, and vinyl sulfones, are tolerated in this protocol. The results indicate that the reaction time (3.5–5.0 h) and yield (71–85%) are almost independent of nature of the substrates used (Figure 1). The regioisomeric products (**4**) were not found in the reaction mixture.

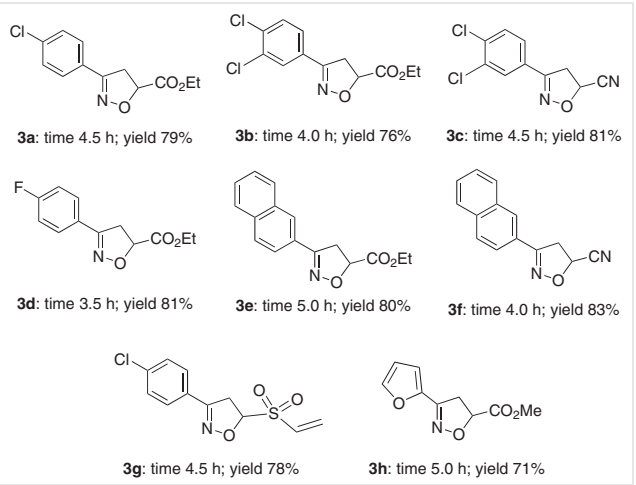


Figure 1 Synthesized Δ^2-isoxazolines **3**

Carbohydrates are inexpensive, abundant, biocompatible, and valuable precursors for the installation of multiple chiral centers in target molecules.[29] The synthesis of sugar-based chiral compounds has gained importance in the areas of catalysis, asymmetric synthesis, and organic nanostructured materials.[30,31] Sugar-derived nitrile oxides have been used for the construction of pseudo-disaccharides and higher carbon-chain monosaccharides,[32c] cyclization to give chiral benzimidazoles, benzoxazoles, and benzthiazoles,[32b] and the multistep synthesis of bioactive natural products[32a] and bioactive isoxazolines.[33,34] Jäger and co-workers reported efficient routes to L-furanomycin and L-carbafuranomycin from sugar-derived nitrile oxides by utilizing the *N*-chlorosuccinimide/HCl protocol.[35] However, HCl is incompatible with sugar moieties possessing labile glycoside linkages.

Thus, pursuing our interest in the construction of sugar-derived heterocycles,[13a,c,d,31,36] we have successfully utilized Mn^{VI}-NPs for the generation of chiral nitrile oxides bearing sugar moieties and their subsequent intermolecular 1,3-dipolar cycloaddition reaction with achiral olefins **2**. Gratifyingly, excellent chemo-, regio-, and stereoselectivities were observed by using sugar-derived aldoximes **1f** and **1g** with *trans*-ethylcinnamate (**2e**: X = CO_2Et and Y = Ph). In general, sugar-based chiral nitrile oxides are known to produce chiral isoxazolines (**5a/6a** and **5b/6b**).[12a] In this case, the Mn^{VI}-NPs played an important role in controlling the stereoselection during the cycloaddition step to furnish a single stereoisomer with 100% *de* (Figure 2, entries 1 and 2). Earlier, however, we observed that the selectivity is lower with oth-

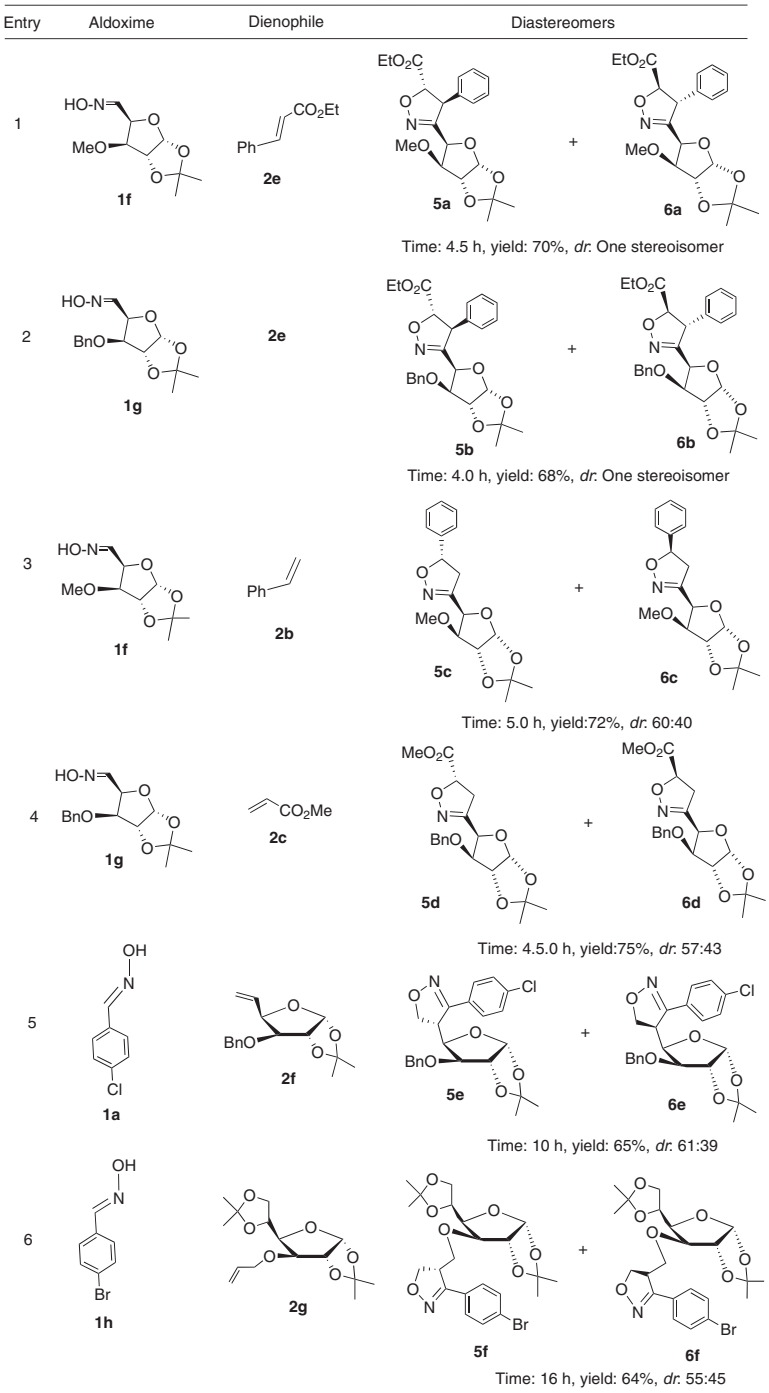
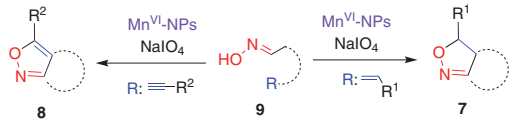


Figure 2 Preparation of sugar-based chiral isoxazolines **5**/**6**

er olefins and sugar-based aldoximes (Figure 2, entries 3 and 4). Bode and Carreira synthesized optically pure isoxazolines by using non-sugar chiral nitrile oxides.[15a]

The total reaction times were 4–16 h, and the optically pure cycloadducts were isolated by silica column chromatography in good yields (64–75%). Moderate diastereoselectivity was observed for 1,3-dipolar cycloaddition reactions of sugar-based chiral olefins with *in situ* generated achiral nitrile oxides (Figure 2, entries 5 and 6).

Owing to favorable entropy and conformational restriction in the transition state, excellent regio- and stereoselectivity can be achieved in intramolecular nitrile oxide cycloadditions.[15b,20d,37,38] We therefore extended the scope of this Mn^{VI}-NP-mediated synthetic protocol to the intramolecular variant with alkenes and alkynes to furnish fused isoxazolines **7** and isoxazoles **8**, as shown in Scheme 2.



Scheme 2 Intramolecular nitrile oxide cycloaddition toward isoxazolines **7** and isoxazoles **8**

As shown in Scheme 2, the intramolecular reaction provides the desired benzopyranoisoxazolines regardless of the presence or nature of the aromatic moieties on the dipolarophilic moiety. Complete *cis* stereoselectivity was observed in the intramolecular cycloaddition processes by using a *trans*-alkene (**7a–c**, Figure 3). Heterocycles (**7d–f**) were obtained under similar reaction conditions. The reaction times are 3.5–5.0 h and the yields are 68–76% in these examples. Synthesis of isoxazoles (**8a**,**b**) resulted from the reaction of aldoximes having a terminal alkyne. Likewise, we have extended this protocol to afford optically pure fused Δ^2-isoxazoles (**8c–f**) in good yields (62–72%).

In conclusion, the catalytic application of Mn^{VI}-NPs has been demonstrated for the generation of nitrile oxides from aldoximes and subsequent 1,3-dipolar cycloaddition reactions under mild reaction conditions.[39] High degrees of chemo-, regio-, and diastereoselectivities are observed in both the inter- and intramolecular 1,3-dipolar cycloaddition reactions with alkenes and alkynes.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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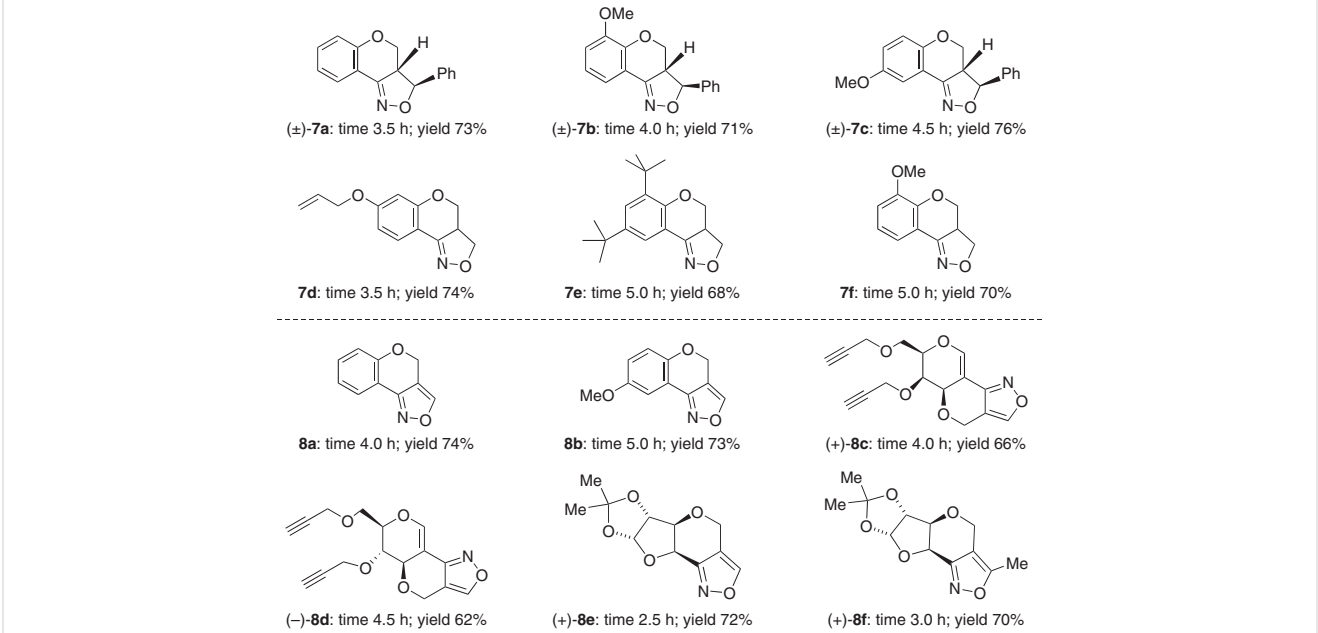

Figure 3 Synthesized isoxazolines **7** and isoxazoles **8**

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(39) **Representative procedure for preparation of 3b**: Oxime **1** (1 mmol) and alkene **2** (2.5 mmol) were dissolved in CH_2Cl_2 (10 mL), and Mn^{VI}-NPs (13 mg, 5 mol%) and $NaIO_4$ (214 mg, 1 mmol) were added. The mixture was then stirred for 3.5–5.0 h at 25 °C, with the progress of the reaction being monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure at room temperature. The reaction mixture was filtered and washed with a mixture of ethyl acetate and cold water. The filtrate was transferred to a separatory funnel and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with water (3 × 30 mL) and brine (1 × 30 mL) and then dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure at room temperature. The residue was purified by column chromatography over silica gel (60–120 mesh) with ethyl acetate–petroleum ether as the eluent to furnish pure Δ^2-isoxazoline **3b**.

3-(3,4-Dichlorophenyl)-4,5-dihydroisoxazole-5-carboxylic acid ethyl ester (3b): R_f = 0.6 (1:4 ethyl acetate–petroleum ether); yield: 76% (218 mg, 0.76 mmol); yellow solid; mp 70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (3 H, t, *J* = 7.2 Hz), 3.49–3.55 (2 H, m), 4.21 (2 H, q, *J* = 7.2 Hz), 5.09–5.16 (1 H, m), 7.39–7.68 (2 H, m), 7.78 (1 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 38.4, 62.2, 78.6, 125.9, 126.1, 128.7, 130.9, 133.2, 134.7, 154.3, 169.7. FT-IR (KBr): 1030, 1397, 1734, 3140 cm^{-1}. HRMS: *m*/*z* calcd for $C_{12}H_{12}Cl_2NO_3$ [M$^+$ + H]: 288.0194; found: 288.0190..