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Atom-Economic Silver-Catalyzed Difunctionalization of Isocyano Group with Cyclic Oximes Toward Pyrimidinediones

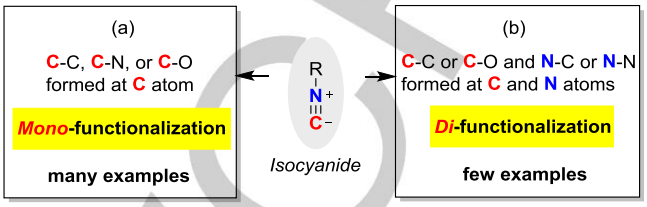
Hong-Wen Liang, Zhen Yang, Kun Jiang, Ying Ye, and Ye Wei*

Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday

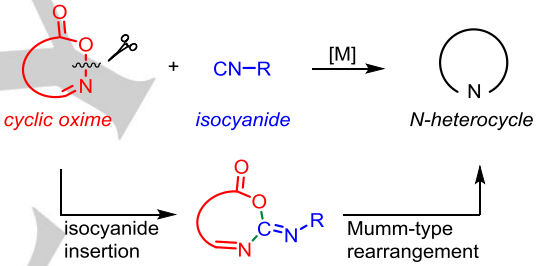
Abstract: An unprecedented silver-catalyzed difunctionalization of isocyano group with cyclic oximes is described. This method allows efficient and atom-economic assembly of a vast array of structurally novel and interesting pyrimidinediones and tolerates a range of functionalities. The resulting products can be easily converted into some useful compounds. Furthermore, our method can also be applied for the late-stage modification of a few biologically active molecules.

Owing to the unique reactivity, isocyanides have been explored as versatile building blocks for organic synthesis.[1] Such substrates can participate in a range of reactions, such as multicomponent reactions[2] (e.g. Ugi and Passerini reactions), insertion reactions,[3] and cycloaddition reactions.[4] In terms of the isocyano group functionalization,[5] most of these reactions merely involve the functionalization of the isocyanide terminal carbon atom, and the isocyanide nitrogen atom remains intact (Scheme 1a). Considering the potential reactivity of nitrogen and carbon functionalities toward new chemical bond formation, we can envision that exploration of both the nitrogen and carbon atoms of the isocyano group as reactive sites to *simultaneously construct new chemical bonds in one step* (difunctionalization of isocyano group) would provide opportunities for the creation of structurally new and important molecules. In this context, a few groups have recently reported their pioneering work toward cycloaddition reactions between isocyanides and propargylamines,[6] between isocyanides and enamides,[7] and between two isocyanides (Scheme 1b).[8] These reactions simultaneously generated new C−C, C−N, and/or N−N bonds at the isocyano group. Despite these advances, the reported reactions are still restricted to a narrow substrate scope, thus limiting the molecule diversity. Clearly, such a difunctionalization strategy will only be widely used in organic synthesis when diverse compounds can be generated with high efficiency. Thus, exploiting new reactivity profile of the isocyano group and developing new synthetic strategies involving the difunctionalization of the isocyano group are highly significant and desirable.

The pyrimidinedione scaffold is ubiquitous in a large number of molecules, such as pharmaceuticals, agrochemicals, and functional materials.[9] For instance, thymine and uracil are indispensable for DNA and RNA, respectively.[10] 5-Fluorouracil and tipiracil are drugs used for the treatment of cancer.[11] Consequently, many synthetic methods have been developed to construct the pyrimidinediones:[12] for example, the reactions of substituted ureas with diketene, and the reactions of 1,3-oxazine-2,4-diones with amines. However, many of these reactions require the use of strong base/acid or high temperature or involve multiple synthetic steps, which would result in low functional group tolerance and atom/step economy. Herein, we develop an unprecedented silver-catalyzed protocol for the expedient synthesis of pyrimidinediones, which utilizes cyclic oximes and isocyanides as the starting materials. In the reactions, multiple new chemical bonds are generated in one step involving the difunctionalization of the isocyano group. More significant, the reaction features excellent atom economy, operationally simple procedure, good functional group tolerance, and amenability to late-stage synthetic applications.



Scheme 1. Functionalization of Isocyano Group.



Scheme 2. Proposed reaction process of a cyclic oxime with an isocyanide.

Our research interests[13] in transition metal-catalyzed oxime N−O bond transformations[14] inspired us to investigate the insertion reactions of isocyanide into the cyclic oxime N−O bond to construct *N*-heterocycles. The proposed reaction process is shown in Scheme 2. An isocyanide inserts into the N−O bond of a cyclic oxime with the assistance of a transition metal to furnish an imidate, which subsequently undergoes a Mumm-type rearrangement[15] to generate a *N*-heterocycle. To this end, considerable experimentations were surveyed,[16] and finally we found that the reactions between isocyanides and isoxazol-5-ones[17] catalyzed by a silver salt afforded pyrimidinediones. Note that the isoxazol-5-ones can be readily prepared by several methods (Scheme 3), including (1) condensation of *β*-ketoesters with hydroxylamine hydrochloride, (2) Knoevenagel condensation of isoxazol-5(4*H*)-ones with carbonyl compounds, followed by nucleophilic addition, (3) nucleophilic substitution of the isoxazol-5(4*H*)-ones with alkyl halide.

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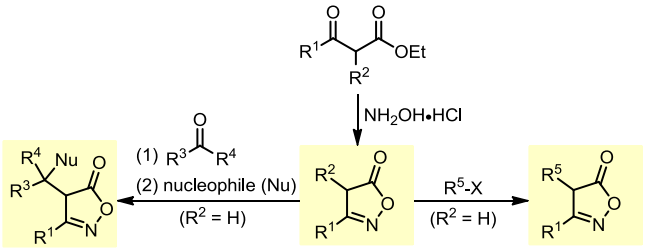
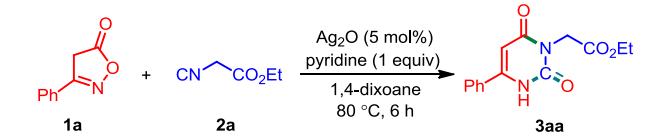


Scheme 3. Synthetic methods for the isoxazol-5-ones.



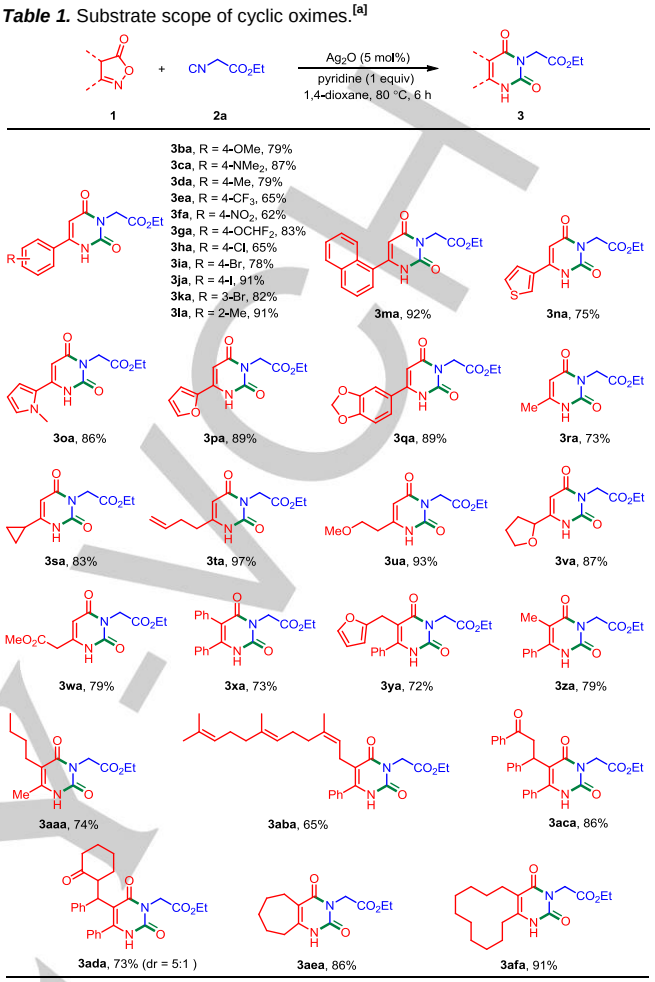
1a (1.61 g, 10 mmol) **2a** (1.70 g, 15 mmol) **3aa** (2.36 g, 8.6 mmol, 87%)

Scheme 4. Gram-scale reaction.

An illustrative example is the gram-scale reaction of 3-phenyl-5-isoxazolone with ethyl isocyanoacetate (Scheme 4). The reaction of 3-phenyl-5-isoxazolone **1a** with ethyl isocyanoacetate **2a** proceeded smoothly with Ag_2O as a catalyst and pyridine as an additive, giving rise to pyrimidinedione **3aa** in 87% yield. The structure of **3aa** was unambiguously confirmed by single-crystal X-ray diffraction.[18] In this reaction, two C−N bonds and one C=O bond were newly formed at the isocyano group, and all atoms of the two reactants were incorporated into the final product, thus exhibiting excellent atom economy.

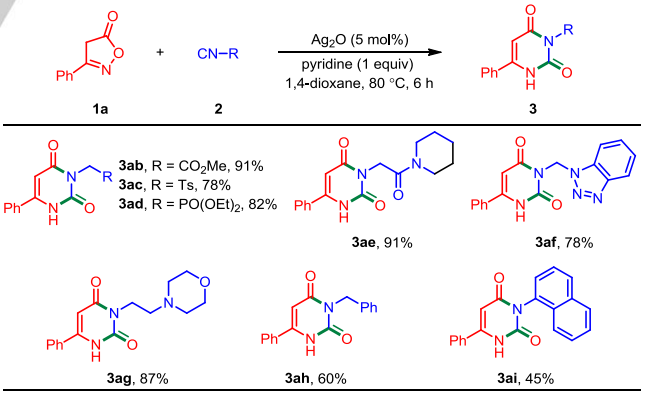
To evaluate the feasibility of the current isocyano group difunctionalization protocol toward the pyrimidinedione synthesis, a wide spectrum of cyclic oximes were surveyed (Table 1). It is found that both the electronic nature and position of the substituents on the aryl ring have negligible effect on the reaction efficiency. For instance, substrate **1** containing electron-donating (OMe, NMe_2, and Me) or electron-withdrawing groups (CF_3, NO_2, $OCHF_2$, Cl, Br, and I) at different positions (*para* or *meta*) of the aryl ring reacted with **2a** efficiently to generate the corresponding products **3ba**−**3ka** in 62−92% yields. Furthermore, the sterically hindered *ortho*-methyl group substituted substrate did not affect the reaction, because the desired product was generated in 91% yield (**3la**). In addition, cyclic oxime with a naphthyl functionality also exhibited excellent reactivity (**3ma**). Note that our method was also amenable to several heterocycle-derived cyclic oximes, which include the ones derived from thiophene (**3na**), pyrrole (**3oa**), furan (**3pa**), and benzodioxole (**3qa**). Besides the pyrimidinediones bearing (hetero)arenes at the C6 position, the products containing methyl, cyclopropyl, olefinic, ether, or ester groups were also obtained in 73−97% yields (**3ra**−**3wa**). More importantly, this method not only provided C6-substituted pyrimidinediones, but also afforded C5- and C6-disubstituted products **3xa**−**3afa** in moderate to excellent yields. The functionalities at the C5 position include phenyl (**3xa**), furylmethyl (**3ya**), methyl (**3za**), *n*-butyl (**3aaa**), and ketone groups (**3aca** and **3ada**). Of note is that a polyenic moiety stemmed from farnesol, an important natural product and biologically active compound,[19] was successfully introduced into the desired product (**3aba**).

Table 1. Substrate scope of cyclic oximes.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (1.5 equiv), Ag_2O (5 mol%), pyridine (1 equiv), 1,4-dioxane (2 mL), 80 °C, 6 h, under Ar.

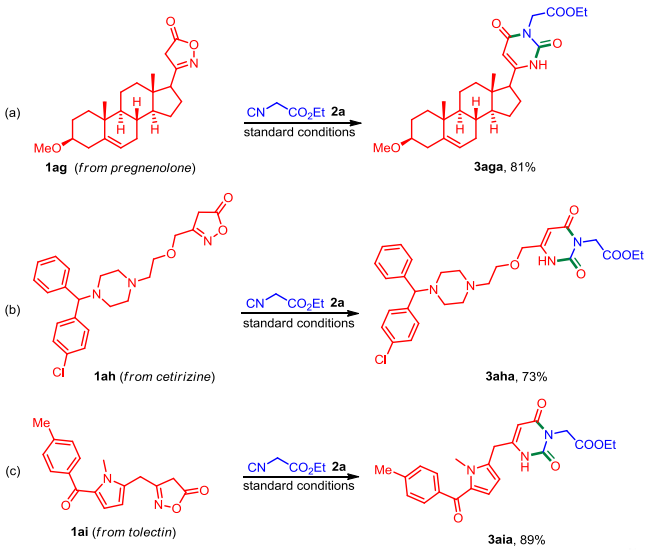
Table 2. Substrate scope of isocyanides.[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (1.5 equiv), Ag_2O (5 mol%), pyridine (1 equiv), 1,4-dioxane (2 mL), 80 °C, 6 h, under Ar.

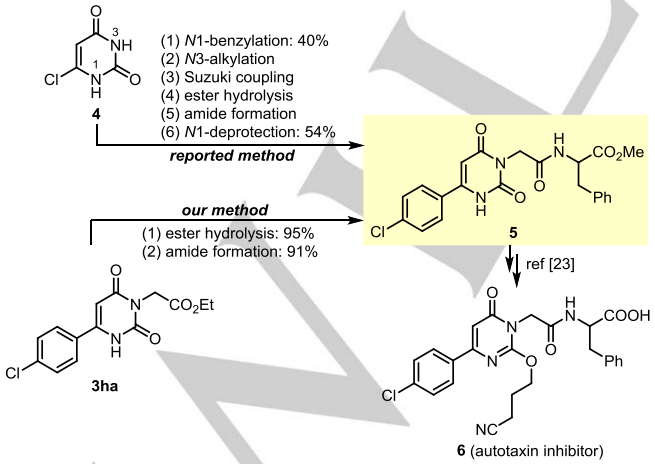
We next turned our attention to evaluate the substrate scope with respect to the isocyanides (Table 2). A variety of isocyanides with acidic *α* C−H bonds, including methyl isocyanoacetate, *p*-tolylsulfonylmethyl isocyanide, diethyl isocyanomethylphosphonate, 1-cyclohexyl-2-isocyanoethanone, and benzotriazol-1-ylmethyl isocyanide, reacted smoothly with **1a** to deliver a diverse set of pyrimidinediones **3ab**−**3af** in good to excellent yields. Similar efficiencies were observed for 2-

morpholinoethyl isocyanide and benzyl isocyanide, and the corresponding products were formed in 87 and 60% yields (**3ag** and **3ah**). Besides, our approach was also suitable for the isocyanide without a hydrogen at the *α* position. For instance, 1-isocyanonaphthalene displayed moderate reactivity in the synthesis of product **3ai**. Unfortunately, *tert*-butyl isocyanide showed very low reactivity (<10%) and cyclohexyl isocyanide did not react with **1a** at all.



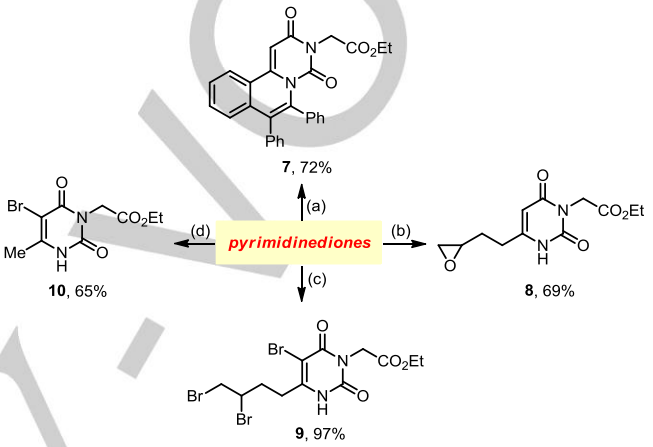
Scheme 5. Late-stage modification of some biologically active compounds.

To demonstrate the function of this newly developed method for the late-stage functionalization[20] of biologically active compounds, several cyclic oximes installed with different key moieties in biologically active compounds were tested under the standard reaction conditions. As depicted in Scheme 5, the pregnenolone-derived substrate **1ag** was subjected to this protocol, furnishing the desired product **3aga** in 81% yield. Furthermore, cetirizine, a drug used to treat allergies,[21] was first converted into the corresponding cyclic oxime **1ah**, which then reacted with **2a** to afford **3aha** in 73% yield. Similarly, starting from tolectin that is applicable in the treatment of rheumatoid arthritis,[22] a pyrimidinedione **3aia** was obtained in 89% yield.



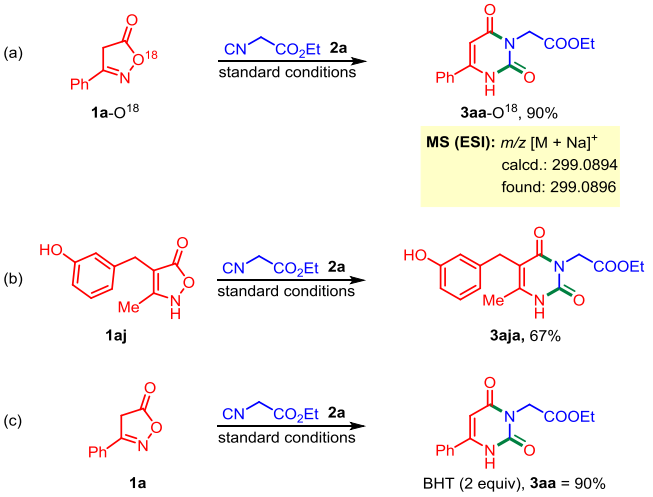
Scheme 6. Synthesis of a biologically active molecule.

Of note is that our method can be utilized to prepare a pyrimidinedione **5**, a precursor of compound **6** that displays autotaxin inhibitory activity (Scheme 6).[23] An existing approach for the synthesis of the pyrimidinedione **5** employs 6-chlorouracil **4** as a starting material, and such a method involves six synthetic steps, such as *N*-protection, Pd-catalyzed Suzuki reaction, and ammonium hexanitrate cerium-mediated *N*-deprotection steps. Moreover, the total yield of **5** is significantly lower than 20% yield after six steps. Compared with the known method, our protocol exhibited obvious advantages in terms of reaction efficiency and step economy. Specifically, the catalytic product **3ha** was easily transformed into the compound **5** in 86% total yield after ester hydrolysis and amide formation steps.



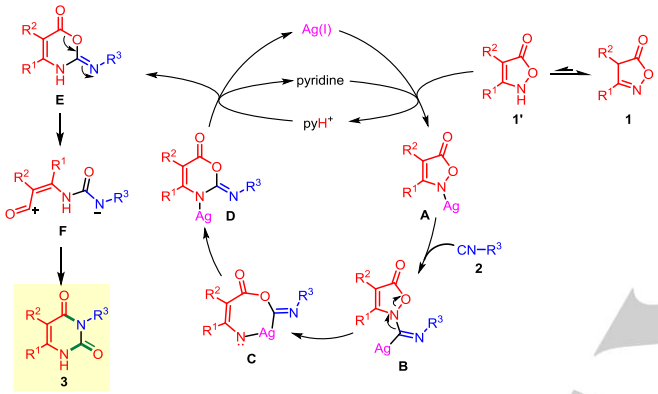
Scheme 7. Synthetic transformations of pyrimidinediones. Reaction conditions: (a) **3aa** (0.2 mmol), diphenylacetylene (1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (7.5 mol%), Na_2CO_3 (2 equiv), $Cu(OAc)_2$ (2 equiv), PhCl, 120 °C, 10 h. (b) **3ta** (0.2 mmol), 3-chloroperbenzoic acid (1.1 equiv), DCM, rt, 4 h. (c) **3ta** (0.2 mmol), Br_2 (2.2 equiv), DCM, rt, 12 h. (d) **3ra** (0.2 mmol), Br_2 (1.1 equiv), DCM, 65 °C, 2 h.

The synthetic value of our method was further demonstrated by the synthetic transformations of the obtained pyrimidinediones (Scheme 7). For example, compound **3aa** reacted with diphenylacetylene via Ru-catalyzed C−H cyclization process to provide a polycyclic *N*-heterocycle **7** in good yield. Besides, compound **3ta** can efficiently undergo epoxidation and multiple bromination to form epoxide **8** and polybrominated compound **9** in 69 and 97% yields, respectively. Similarly, mono-brominated product **10** was achieved for the pyrimidinedione **3ra**, of which a 65% yield being obtained.



Scheme 8. Mechanistic investigations.

To shed light on the reaction mechanism of this transformation, several experiments were carried out (Scheme 8). Firstly, O^{18}-labelled substrate **1a**-O^{18} was subjected to the reaction to react with **2a** to investigate the oxygen atom source (Scheme 8a). The mass spectrometry result revealed that the O^{18} atom was incorporated into the final product **3aa**-O^{18}. As such, all of the atoms in the two starting materials were implanted into the target product. Secondly, an isoxazol-5(2*H*)-one derivative **1aj** was prepared, which reacted with **2a** under the standard reaction conditions to afford the corresponding product **3aia** in 67% yield (Scheme 8b). This observation implied that the isoxazol-5(2*H*)-one might be an intermediate in the Ag-catalyzed pyrimidinedione synthesis. Lastly, the model reaction of **1a** with **2a** took place under the standard reaction conditions in the presence of 2 equiv of BHT (2,6-di-*tert*-butyl-4-methylphenol), affording **3aa** in 90% yield, which implied that the Ag-catalyzed difunctionalization of isocyano group probably does not proceed via a radical process (Scheme 8c).



Scheme 9. Proposed mechanism.

Although the exact mechanism of this reaction remains elusive, on the basis of the above observations and the previous work, a plausible mechanism is illustrated to account for the unprecedented Ag-catalyzed pyrimidinedione synthesis from cyclic oximes and isocyanides. As depicted in Scheme 9, the cyclic oxime **1** may tautomerize to the isoxazol-5(2*H*)-one **1'**[24] that then reacts with Ag(I) salt by using pyridine as a base to generate a silver complex **A**. Subsequent isocyanide insertion affords an intermediate **B**, followed by ring opening to give rise to a silver-nitrene species **C**.[25] After intramolecular nitrene insertion into the C−Ag bond,[26] a species **D** could be delivered, which then occurs protonation to furnish an imidate **E**. The compound **E** could undergo ring opening[15] to produce a species **F**, which is then converted into the desired product **3** through intramolecular C−N bond formation. Note that another role of the pyridine might be to enhance the solubility of the silver salt by virtue of its good coordination ability to the silver salt.[27]

In summary, we outline an unprecedented silver-catalyzed difunctionalization of isocyano group with cyclic oximes for the rapid assembly of pyrimidinediones. Our method exhibits excellent atom economy, good functional group compatibility and broad substrate scope; thus, a great majority of structurally new and interesting pyrimidinediones have been generated. These molecules might be recognized as privileged scaffolds in drug discovery, and the realization of concise methods to access them would be of great interest. The exploration of more new synthetic strategies involving the difunctionalization of isocyano group is underway in our group.

Acknowledgements

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Keywords: oximes • isocyanides • *N*-heterocycles • silver • homogeneous catalysis

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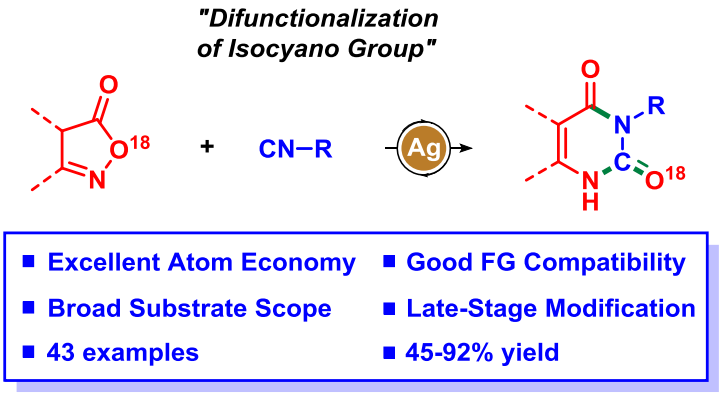

An unprecedented silver-catalyzed difunctionalization of isocyano group with cyclic oximes has been achieved. This method allows efficient and atom-economic assembly of a vast array of structurally novel and interesting pyrimidinediones and tolerates a range of functionalities. The resulting products can be easily converted into some useful compounds. Furthermore, our method can also be applied for the late-stage modification of a few biologically active molecules.

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