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$Cu(OAc)_2$-Triggered Cascade Reaction of Malonate-Tethered Acyl Oximes with Indoles, Indole-2-alcohols, and Indole-2-carboxamides

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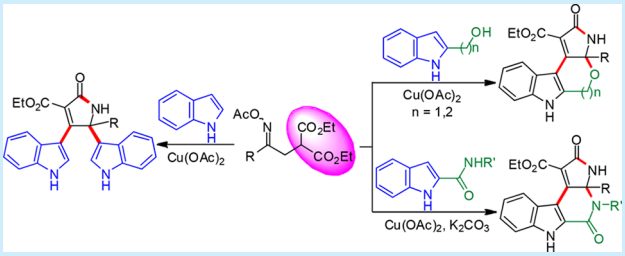
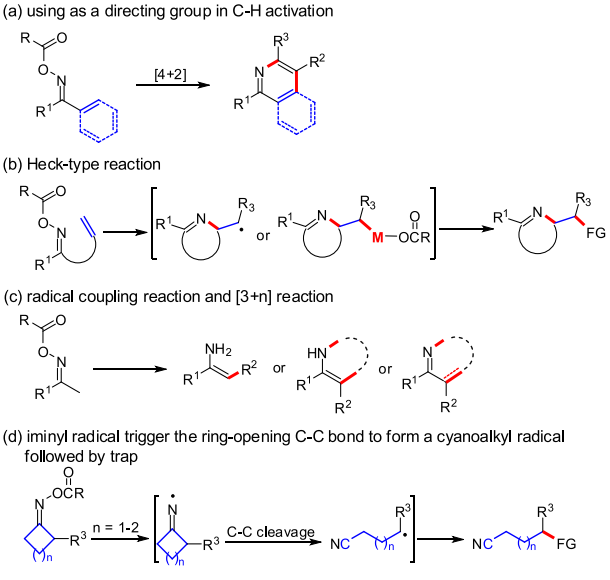
Supporting Information

ABSTRACT: A $Cu(OAc)_2$-promoted cascade reaction of malonate-tetherd acyl oximes with indoles, indole-2-alcohols, or indole-2-carboxmides provides facile access to polysubstituted 3-pyrrolin-2-ones. The reaction features the generation of two adjacent electrophilic centers at the same time as cyclization to lactam. The subsequent double addition with nucleophiles followed by oxidation realizes the difunctionalization of the imine sp^2-carbon and the adjacent α-sp^3-carbon.



Oximes are a class of important organic compounds widely used in Beckmann rearrangement,[1] Semmler−Wolff reaction,[2] and Neber rearrangement[3] owing to the relatively low dissociation energy of the N−O bond. Introducing an acyl group on the oxygen atom avoids the reaction from O−H functionalization and makes the cleavage of N−O bond easier. Acyl oximes have emerged as versatile building blocks for the synthesis of structurally diverse N-heterocycles via N−O bond cleavage and C−N bond formation catalyzed by transition metals.[4−12] In addition, acyl oximes can also act as internal oxidants while participating in the reaction, avoiding the use of a stoichiometric amount of external oxidant. A variety of the synthetic transformations were developed in recent years. The reaction types of acyl oximes are mainly as follows: (1) The imine serves as the directing group in *ortho*-C_{Ar}−H activation reaction, and a formal [4 + 2] product is produced (Scheme 1a).[5] Zhao et al. has developed a highly *para*-selective C_{Ar}−H difluoromethylation of acyl oximes.[6] (2) A transition-metal-catalyzed intramolecular Heck-type reaction through the addition of an imine radical or imine−metal complex to the tethered alkene group was followed by further elimination[7] or functionalization (Scheme 1b).[8] (3) Radical coupling reaction at the α-carbon of acyl oximes[9] or [3 + *n*] reaction[8f,10] generates various coupling products or five/six-membered nitrogen-containing heterocycles (Scheme 1c). (4) The iminyl radical generated from acyl cyclobutanone/cyclopentanone oxime triggered ring-opening C−C bond cleavage to form cyanoalkyl radicals which were further functionalized in a series of radical transformations (Scheme 1d).[8f,11] Acyl oxime can also take part in the intramolecular aromatic cyclization reaction via an iminyl radical, iminyl cation, or imine−metal pathway.[12] Recently, γ-C(sp^3)−H functionalization of oximes based on the 1,5-hydrogen transfer of a generated iminyl radical was developed.[11k,13] From the structural perspective of acyl oximes, most of them are linked to an intramolecular alkene, arene unit or have a cyclobutane/cyclopentane skeleton, whereas other types of acyl oximes have rarely been investigated. In view of the above points, we introduce a nucleophilic site on the α- carbon of acyl oxime. In the presence of a transition-metal catalyst, an iminyl radical or imine−metal intermediate can be generated, which adds to the alkene or alkyne followed by cyclization to generate the [4 + 2] product (Scheme 2a). The nucleophilic atom can be carbon, nitrogen, and oxygen atom, which will lead to structurally diverse products. In sharp contrast to the reported [4 + 2] or [3 + 3] reaction of acyl oxime, the six-membered heterocyclic products are mainly limited to pyridines.

Scheme 1. Main Reaction Types of Acyl Oximes



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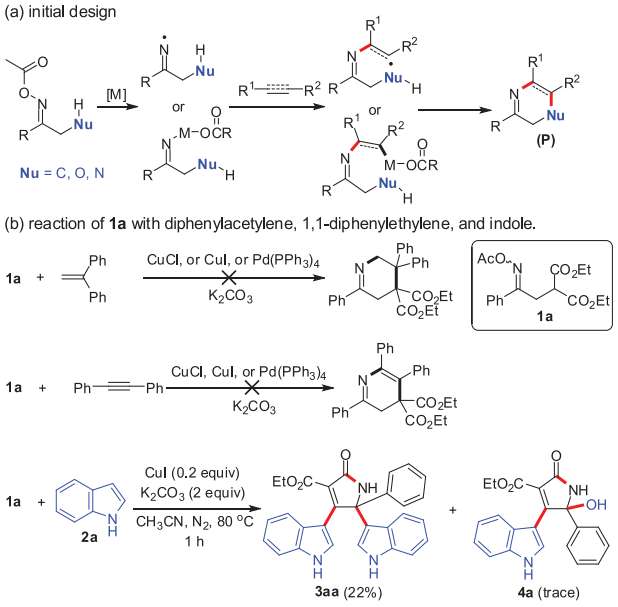
Scheme 2. Initial Design and the Primary Results



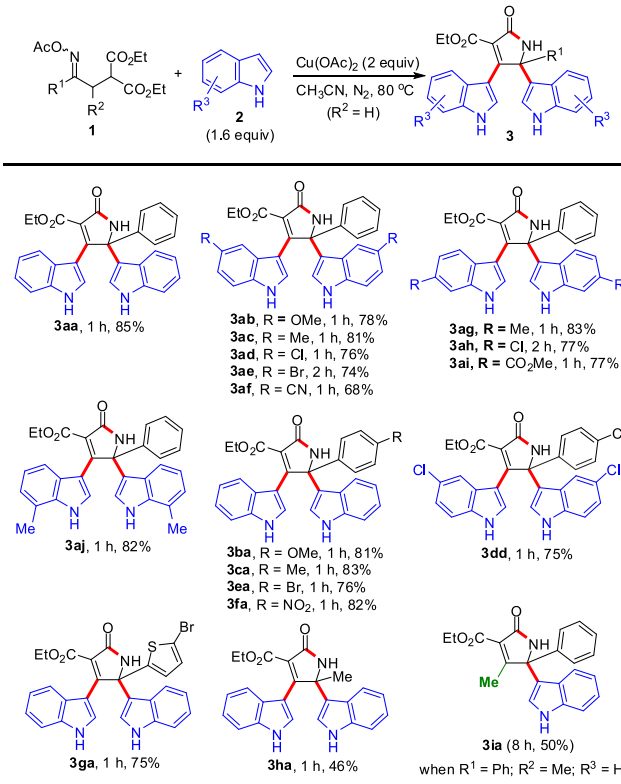
With this concept in mind, we prepared acetyl oxime **1a** bearing a malonate group because malonate is a good nucleophile and is liable to generate free radicals oxidized by transition metals. In a preliminary attempt, the reaction of **1a** with diphenylacetylene or 1,1-diphenylethylene catalyzed by CuCl, CuI, or $Pd(PPh_3)_4$ in the presence of a base under a nitrogen atmosphere was carried out. Disappointingly, no anticipated [4 + 2] product was formed (Scheme 2b). When it was treated with indole **2a** under similar conditions (see Supporting Information (SI), Table S1), no desired [4 + 2] product was generated either. To our surprise, the formation of 3-pyrrolin-2-one product **3aa** bearing two indole units along with the aminal product **4a** was observed. The formation of 3-pyrrolin-2-ones from oximes and the difunctionalization of the imine sp^2-carbon and the adjacent α-sp^3-carbon of acyl oximes was unprecedented. An important point to note was that the introduction of a malonate group on the α-carbon of acyl oximes resulted in the emergence of a novel reaction mode of the acyl oximes.

3-Pyrrolin-2-ones are important motifs occurring in many natural products such as PI-090, myceliothermophins A–E, oteromycin, amooramides A–L, salannolactams, and munronin D,[14] which display a broad range of biological activity as anticancer, antimalarial, anti-HIV agents, ASK1, Mdm2 inhibitors, or nonpeptide CCK ligands.[15] Therefore, the development of new methods for their efficient synthesis with structural diversity is still of high interest.

Inspired by the result, we further optimized the conditions for the preparation of **3aa** (see SI, Table S1). The formation of **3aa** indicated that an oxidative process was involved in this reaction. Hence, $Cu(OAc)_2$ was used instead of CuCl or CuBr, and the amount of indole was increased to 2 equiv to optimize the reaction condition. The reaction proceeded faster in CH_3CN, and the yield was improved significantly to 68%. However, a small amount of indole **2a** remained unreacted probably due to the slight decomposition of **1a**. Pleasingly, when the amount of **2a** was decreased to 1.6 equiv, a full conversion of **1a** and **2a** was observed, resulting in a further improvement of the yield of **3aa** to 86%. Solvent screening revealed that CH_3CN was the best choice. Using DMSO as the solvent, a considerable amount of aminal product **4a** was formed, whereas the reaction in CH_3CN only produced a trace amount of **4a**. In the absence of base, the reaction proceeded equally well to give a comparable yield of **3aa** (Table S1, entry 16). Using $Cu(OTf)_2$, $CuCl_2$, or $Cu(ClO_4)_2$ instead of $Cu(OAc)_2$ generated only a trace of **3aa**, and the transformation of most of **1a** into the ketone was observed. Under open air conditions, neither **3aa** nor **4a** was generated. Additionally, reducing the loading of $Cu(OAc)_2$ to a catalytic amount with a combination of external oxidant such as (*t*-BuO)$_2$, $K_2S_2O_8$, or *t*-BuOOH was infeasible.

Based on the above optimization study, the generality of the $Cu(OAc)_2$-promoted reaction of acetyl oximes with indoles was investigated (Scheme 3). A variety of acetyl oximes derived from

Scheme 3. $Cu(OAc)_2$-Promoted Reaction of Indoles with Acetyl Oximes 1[a]



[a]Yield was calculated based on **2**.

α-malonate-substituted ketones participated in the reaction with different substituted indoles, affording the corresponding 3-pyrrolin-2-ones. Various functional groups including bromo, chloro, cyano, ester, and nitro groups as well as thiophene heterocycles were well tolerated in the reaction. No electronic effect was observed for the substituent on the phenyl ring. When R^1 was a methyl group, the desired product **3ha** was obtained in low yield. In addition, introducing a methyl group to the α-imine carbon led to the formation of 1:1 adduct **3ia** in 50% yield.

We reasoned that the formation of byproduct **4a** might be derived from the nucleophilic addition of water. Thus, introducing a tethered nucleophilic site on the 2-position of indole might lead to a cycloaddition reaction to generate various polycyclic indole derivatives. It would be very interesting as many polycyclic indoles have been reported to exhibit numerous

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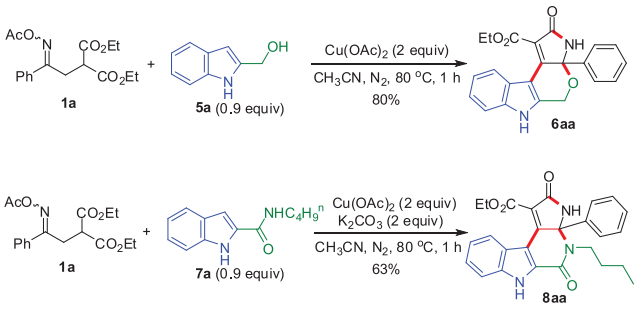
biological activities.[16] Accordingly, indole-2-methanol **5a** and 2-indoleformamide **7a** were introduced in the reaction with **1a** (Scheme 4). The reaction of **1a** with **5a** in the presence of 2

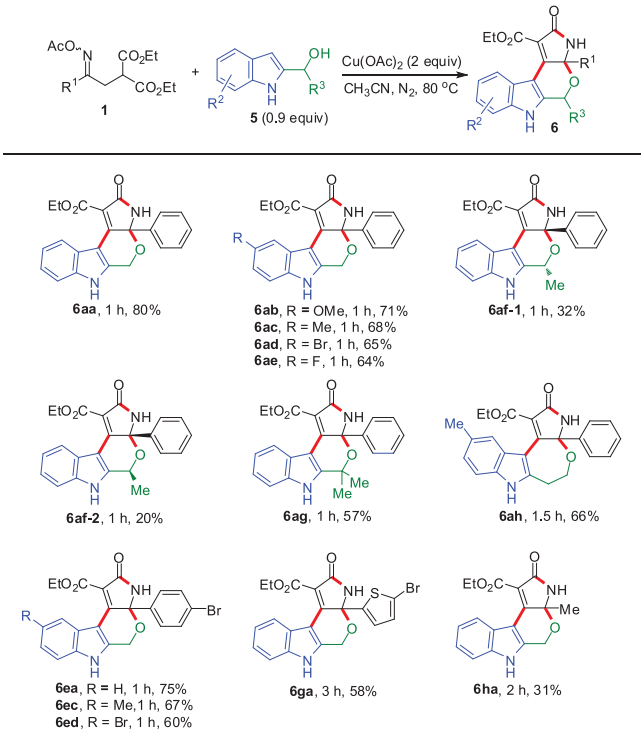
Scheme 4. Reaction of 1a with 5a or 7a



equiv of $Cu(OAc)_2$ proceeded rapidly at 80 °C, affording the anticipated product **6aa** in 80% yield within 1 h. However, the reaction of **1a** with **7a** in the presence of 2 equiv of $Cu(OAc)_2$ proceeded very slowly, and only a trace amount of the desired product **8aa** was formed after 2 h. We were pleased to find that adding 2 equiv of K_2CO_3 as the base accelerated the reaction remarkably, and the reaction was completed within 1 h to afford 63% yield of **8aa**. It was noteworthy that the reaction of **1a** with **5a** or **7a** showed excellent regioselectivity with indole-3-carbon coupling with sp^3-carbon and heteroatom attack on the imine carbon.

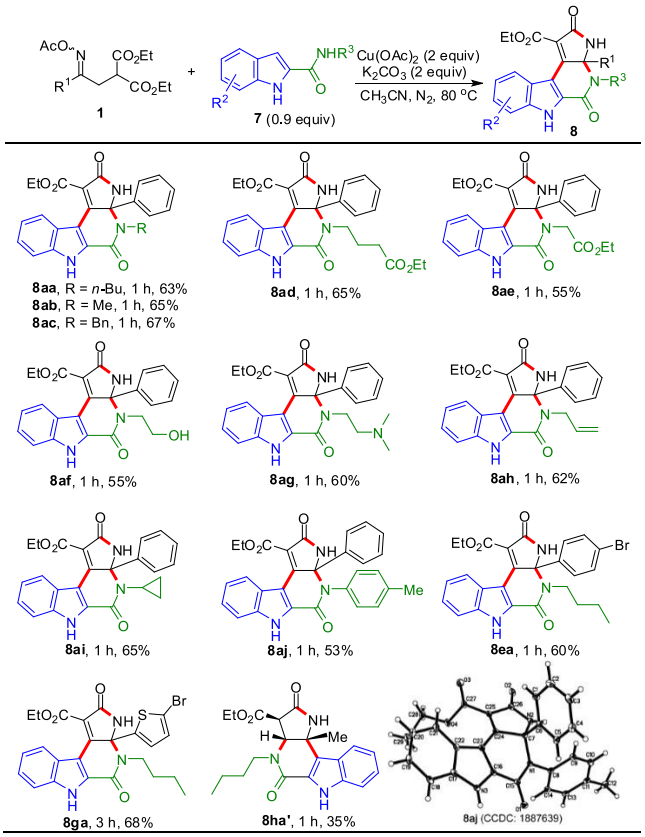
To evaluate the generality of this process, various indole-2-alcohols and indole-2-carboxamides were subjected to the reaction with **1** (Schemes 5 and 6). For the indole-2-alcohols **5**,

Scheme 5. $Cu(OAc)_2$-Promoted Reaction of Indole-2-alcohols 5 with Acetyl Oximes 1[a]



[a]Yield was calculated based on **5**.

Scheme 6. $Cu(OAc)_2$-Promoted Reaction of Indole-2-Carboxamides with Acetyl Oximes



the substituent R^2 on the phenyl ring had no influence on their reactions with **1**. All the primary, secondary, and tertiary alcohols could react with **1a** to give the corresponding products **6**. When an asymmetrical alcohol **5f** (R^3 = Me) was subjected to the reaction with **1a**, two diastereomeric products **6af-1** and **6af-2** were obtained with a ratio of 1.6:1. It was exciting that indole-2-ethanol **5h** was also tolerated in the reaction to give **6ah** in 66% yield. When R^1 was an alkyl group, the product **6ha** was formed in 31% yield. The reaction of indole-2-carboxamides **7** with **1** proceeded well to give the corresponding products **8** in moderate yields with either *N*-aryl or alkyl substitutions. The reaction displayed a broad functional group tolerance such as bromo, ester, amino, hydroxyl, allyl, and cyclopropyl as well as thiophene heterocycle. Surprisingly, when R^1 was changed from an aryl to a methyl group, only the inverse addition product **8ha′** was obtained in 35% yield with the recovery of a lot of indole-2-carboxamide **7h** (37%). The structure of **8aj** was also unambiguously established by X-ray crystallography.

To confirm the role of the malonate group, the reactions of acetyl oximes **1j**−**1l** with **2a** were performed (Scheme 7). When one of the two ester groups was replaced by hydrogen or methyl, no reaction occurred. Extension of the distance between malonate and imine carbon to two CH_2 units also led to failure of the reaction. These results illustrated that both the ester groups and the distance to the imine carbon were crucial to the reaction. During the reaction of **1a** with indole **2a**, no key intermediate was detected, probably due to its rapid reaction with **2a**. For the self-reaction of **1a** in the absence of **2a** under standard conditions, no key intermediate was generated and most of the **1a** was recovered after 3 h of stirring. A radical capture experiment was also carried out under standard

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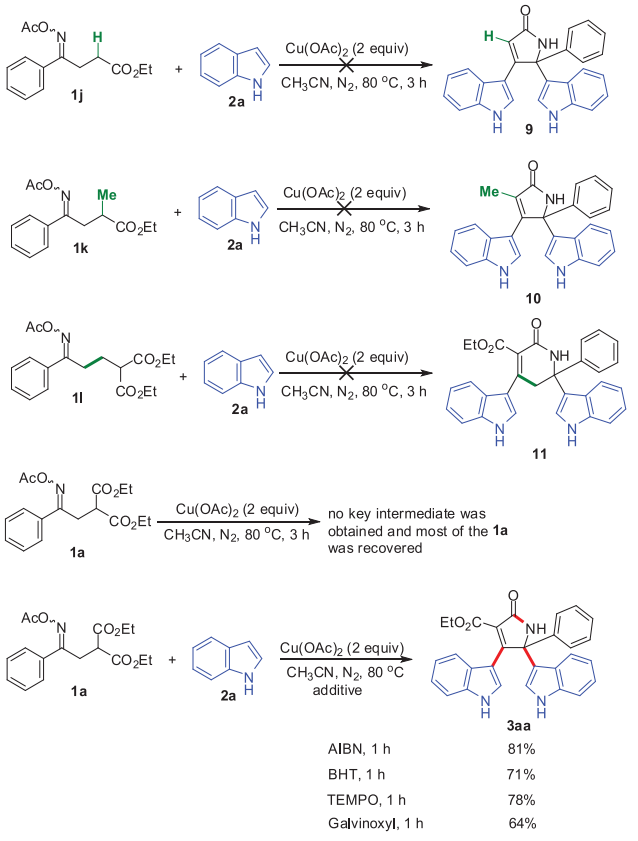
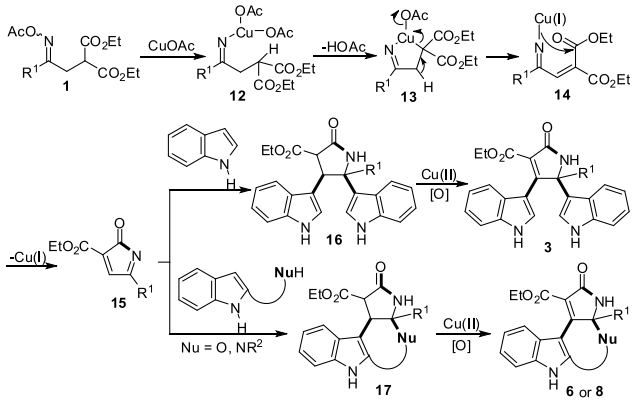
Scheme 7. Control Experiments



conditions with addition of BHT, AIBN, TEMPO, or galvinoxyl. No obvious inhibition or sluggishness was observed, and no radical capture intermediate was detected, which indicated that the reaction might not proceed via a radical process (Scheme 7).

Based on the previously reported copper-catalyzed reaction of acyl oximes[8−10] and the above results, a plausible mechanism is described in Scheme 8. Our studies indicate that Cu(I) rather

Scheme 8. Plausible Mechanism



than Cu(II) initiated the reaction because using $Cu(OTf)_2$, $CuCl_2$, or $Cu(ClO_4)_2$ results in the failure of reaction, whereas using CuCl or CuI gives the normal product. Cu(I) might be formed in situ via reduction or disproportionation of $Cu(OAc)_2$, which has been reported in the literature.[7d,17] The oxidative addition of the in situ generated Cu(I) to the N−O bond produced Cu(III) intermediate **12**. Owing to the nucleophilicity of malonate, an intramolecular attack on Cu(III) may occur to form **13**, which undergoes β-hydride elimination to furnish **14**. A subsequent intramolecular attack on the ester group delivers the key intermediate 2*H*-pyrrol-2-one **15**. Distinctly, the indole also has a synergetic cooperation in the generation of **14** or **15** because, in the absence of indole, most of **1a** is recovered without detection of any key intermediate for the self-reaction of **1a**. Subsequently, double additions on the electron-deficient C═C and C═N double bonds provide **16** and **17**, which undergo further oxidation by Cu(II) to afford **3** and **6**/**8**, respectively. It is also possible that the addition of indole to C═C double bonds of **14** occurs prior to the cyclization to form **15**.

Finally, a preliminary biological activity test for the selected nine representative compounds was performed to evaluate the application against adenocarcinomic human alveolar basal epithelial cells (A549) using final concentrations ranging from 0.01 to 100 μM (see the SI). Compounds **3ai** and **3ga** exhibited a high degree of inhibition with more than 70% against A549 cell growth at 10 μM concentration. These results showed that **3ai** and **3ga** had an obvious cytotoxic activity, although it was a little weaker in comparison with that of adriamycin as a classic anticancer agent.

In summary, we have developed a novel reaction mode of acyl oximes through installing a malonate group on the α-carbon, thus providing a facile access to polysubstituted 3-pyrrolin-2-ones through a $Cu(OAc)_2$-promoted cascade reaction with indoles, indole-2-alcohols, or indole-2-carboxmides. The highlight of the method lies in the cyclization to lactam occurring at the same time as the generation of two adjacent electrophilic centers under mild conditions, which undergoes double addition with two molecular indoles followed by oxidation. When the indoles bear a nucleophilic site at the 2-position, a formal $[n + 2]$ (n = 4/5) reaction occurs to generate polycyclic indole derivatives with high regioselectivity. The exploration of new chemistry of the α-manolate-substituted acyl oximes is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00849.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for all new products (PDF)

Accession Codes

CCDC 1887639 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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