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Bisoxazoline-Lewis Acid-Catalyzed Direct-Electron Demand *oxo*-Hetero-Diels−Alder Reactions of *N*-Oxy-pyridine Aldehyde and Ketone Derivatives

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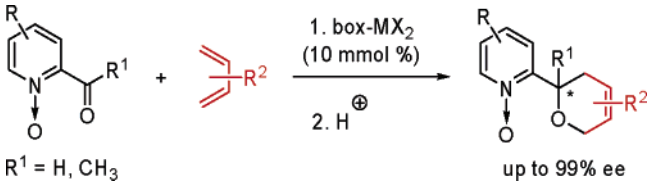

A general catalytic *oxo*-hetero-Diels−Alder reaction for pro-chiral aldehyde and ketone *N*-oxy-pyridines is presented. The catalytic and asymmetric *oxo*-hetero-Diels−Alder reaction of electron-rich dienes with *N*-oxy-pyridine-2-carbaldehyde and ketone derivatives, catalyzed by chiral copper(II)−bisoxazoline complexes, gives optically active six-membered oxygen heterocycles in moderate to good yields and with excellent enantioselectivities.

Introduction

Despite the fact that we are in the "Golden Age" of organocatalysis,[1] chiral metal complexes still continue to be the focus of intense activity in asymmetric catalysis.[2] Electrophilic activation of carbonyl compounds by metal-centered chiral Lewis acids is an efficient method for the enantioselective catalysis of nucleophile−electrophile reactions.

The Diels−Alder reaction (DA), the concerted [$\pi 4_s + \pi 2_s$] cycloaddition of a conjugate diene and a dienophile to form unsaturated six-membered rings, is a cornerstone in organic chemistry and has been a widely used synthetic procedure for the construction of stereochemically controlled compounds.[3] An important variant of the DA reaction, the *oxo*-hetero-Diels−Alder reaction (*oxo*-HDA), was developed by Danishefsky et al. They reported the Lewis-acid-catalyzed reaction of an activated diene, 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (Danishefsky's diene), with aldehydes to afford racemic 5,6-dihydro-γ-pyrones.[4] This was followed soon after by the asymmetric catalytic *oxo*-HDA reaction using chiral Eu(hfc)$_3$

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as the catalyst.[5] This reaction has since become the focal point for the synthesis of six-membered oxygen-containing heterocycles, which are playing an important role as intermediates in, for example, natural compound synthesis.[6] Since this initial report, a large number of highly stereoselective catalytic *oxo*-HDA reactions (aldehydes and ketones as dienophiles) catalyzed by Lewis and Brønsted acids have been developed.[7] In the direct-electron demand *oxo*-HDA reaction, the Lewis and Brønsted acid catalysts increase the reactivity of the dienophile activating the carbonyl group by lowering the $LUMO_{dienophile}$ energy and enhancing interaction with the $HOMO_{diene}$, thereby reducing the activation energy for the process.[8]

Aldehydes have been used as dienophiles in the majority of the developed *oxo*-HDA reactions, while the ketone functionality, for steric and electronic reasons, is a much poorer dienophile as compared to the aldehyde. Therefore, there are only few reports of successful *oxo*-HDA reactions of simple ketones to form oxygen-containing quaternary centers,[9] although the stereoselective formation of quaternary stereocenters is of great importance for the synthesis of optically pure natural products and pharmaceuticals.[10]

In this paper, we present that aldehyde and ketone *N*-oxy-pyridines undergo enantioselective *oxo*-HDA reactions with electron-rich dienes, leading to optically active γ-pyrones having the attractive 1-oxypyridine functionality, which can be converted to the corresponding pyridine derivatives.[11] The attractive features of this new reaction are (i) the introduction of chiral carbon atoms attached to 1-oxypyridines or pyridines, (ii) both aldehydes and ketones undergo the *oxo*-HDA reactions with dienes when using the same catalytic system, and finally (iii) it is shown that the reaction proceeds by the Mukaiyama-aldol pathway mechanism. As far as we know, only a single successful example of catalytic enantioselective *oxo*-HDA reaction between pyridine-2-carbaldehyde and activated diene has been reported. Feng, Jiang, and co-workers have showed that chiral titanium(IV)−BINOL complexes can catalyze the reaction in moderated yield and with 92% ee.[12] Furthermore, according to the best of our knowledge, there has not been reported any asymmetric *oxo*-HDA reaction between keto-pyridines and activated dienes.

Results and Discussion

We have recently demonstrated that bidentate coordinating bisoxazoline[13] (box)−Cu(II) complexes are effective chiral Lewis acid catalysts for the Mukaiyama-aldol reaction between ketene silyl acetals and *N*-oxy-pyridine-2-carbaldehydes.[11] The "trick" in these reactions was to oxidize pyridine to the corresponding *N*-oxy-pyridine to facilitate an optimal bidentate coordination of the reagent to the chiral Lewis acid, as the non-oxidized pyridine derivatives gave low enantioselectivity. On the basis of these results, we thought that these catalytic systems might be suitable for the *oxo*-HDA reaction of *N*-oxy-pyridine-2-carbaldehyde derivatives **1** and *N*-oxy-pyridine-2-yl-ethanone **2** with electron-rich dienes **3** to synthesize six-membered oxygen-containing heterocycles **5** and **6** (eq 1).

The higher reactivity of aldehydes than ketones prompted us to perform the initial screening reactions with 5-bromo-*N*-oxy-pyridine-2-carbaldehyde **1a** and the commercially available 1-methoxy-3-(trimethylsiloxy)butadiene **3a** (Danishefsky's di-

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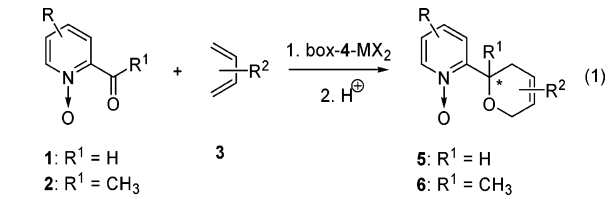
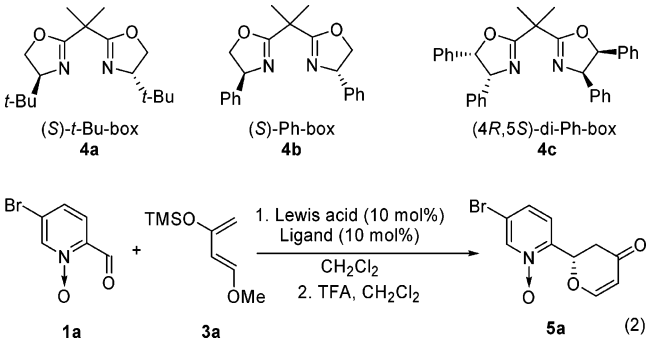


ene) (eq 2). Applying the same reaction conditions as used before in the Mukaiyama-aldol reaction between ketene silyl acetals and *N*-oxy-pyridine-2-carbaldehyde derivatives, CH_2Cl_2 as a solvent and (*S*)-**4a**-Cu(OTf)$_2$ complex as catalyst at −40 °C, gave the HDA-adduct **5a** in only 30% yield and moderate 80% ee (Table 1, entry 1). Other solvents were also tested with slightly better yields, and, as expected for the (*S*)-*t*-Bu-box ligand **4a**, similar enantiomeric excesses were obtained (entries 2, 3).[14] Different Lewis acids, in a combination with **4a**, also catalyzed the reaction, but gave the product **5a** with moderate yield and poor enantioselectivity (entries 4, 5). The use of (*S*)-**4b**−Cu(OTf)$_2$ complex gave, due to a changed geometrical arrangement at the copper center as compared to (*S*)-**4a**−Cu(OTf)$_2$, the opposite enantiomer of the *oxo*-HDA adduct with poor yield and 78% ee (entry 6).[15] Interestingly, the use of (4*R*,5*S*)-**4c**−Cu(OTf)$_2$ as the catalyst in toluene gave the product in 83% isolated yield and only 40% ee (entry 8). It appeared that the use of toluene gave highly improved yields (entry 8). Conversely, CH_2Cl_2 improved the enantioselectivity, but deteriorated the yield (entry 7). Subsequent experiments showed that the use of a toluene−CH_2Cl_2 mixture (4:1) gave the best overall result (47% yield and 93% ee) (entry 9). It should be noted that short exposure time (less than 3 h) of the reaction mixture to trifluoroacetic acid (TFA) gave a mixture of the unsaturated six-membered ring **5a** and the not-cyclized open-chain Mukaiyama-aldol adduct, when longer exposure time gave just the unsaturated six-membered rings.[16]



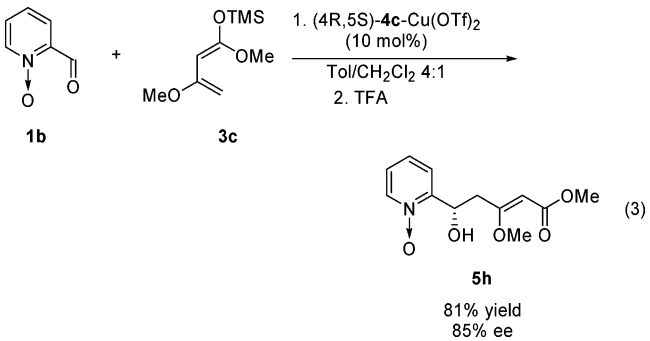
Under the optimized reaction conditions (Table 1, entry 9), the *oxo*-HDA reaction with a range of different pyridine-, isoquinoline-, and *N*-oxy-quinoline-2-carbaldehyde derivatives was performed (Table 2). The *oxo*-HDA adducts were obtained in moderate to good yields and high enantiomeric excesses. The presence of bromine in position five of the pyridine ring led to a high enantiomeric excess of the reaction product, while the bromine in position six of the pyridine gave lower enantioselectivity, probably due to steric reasons (entry 1 vs entry 3). Interestingly, the presence of the larger phenyl group in position six of the pyridine ring does not affect the enantioselectivity negatively; on the contrary, it improves the enantioselectivity. This might be due to an electronic interaction of the phenyl group in the substrate with the phenyl substituent(s) in the (4*R*,5*S*)-**4c**−Cu(OTf)$_2$ complex (entry 4). In accordance with these results, it is not surprising that the presence of the methyl group in position six of *N*-oxy-pyridine-2-carbaldehyde **1e** gave poorer results (entry 5). *N*-Oxy-quinoline and *N*-oxy-isoquinoline derivatives worked almost as efficiently as *N*-oxy-pyridines and provided the *oxo*-HDA adducts **5f**,**g** in good yields, but with lower enantiomeric excesses (entries 6, 7).

TABLE 1. Screening of Reaction Conditions for the Catalytic Enantioselective Addition of 1-Methoxy-3-(trimethylsiloxy)butadiene 3a to 5-Bromo-*N*-oxy-pyridine-2-carbaldehyde 1a Catalyzed by Chiral Lewis Acid Complexes[a,b]

entry	ligand	Lewis acid	solvent	temp. (°C)	yield (%)[c]	ee (%)[d]
1	**4a**	Cu(OTf)$_2$	CH_2Cl_2	−40	30	80
2	**4a**	Cu(OTf)$_2$	Tol	−40	49	76
3	**4a**	Cu(OTf)$_2$	THF	−40	41	79
4	**4a**	Zn(OTf)$_2$	CH_2Cl_2	−40	35	7
5	**4a**	Mg(OTf)$_2$	CH_2Cl_2	−40	44	10
6	**4b**	Cu(OTf)$_2$	CH_2Cl_2	−40	30	−78[e]
7	**4c**	Cu(OTf)$_2$	CH_2Cl_2	−40	32	87
8	**4c**	Cu(OTf)$_2$	Tol	−40	83	40
9[f]	**4c**	Cu(OTf)$_2$	Tol/CH_2Cl_2	−40	47	93

[a] Reaction conducted on a 0.25 mmol scale. [b] 100% conversion in all reactions after 16 h, estimated by ^{1}H NMR spectroscopy. [c] Yield of isolated product after purification by column chromatography. [d] Enantiomeric excess measured by chiral stationary phase HPLC. [e] Refers to the opposite enantiomer. [f] Tol/CH_2Cl_2 (4:1).

Next, we explored the possibility of using the electron-rich 1,3-dimethoxy-1-(trimethylsiloxy)butadiene (Brassard's diene)[17] **3c** in *oxo*-HDA reaction with *N*-oxy-pyridine-2-carbaldehyde **1b** as a reaction promoting agent. Interestingly, the reaction of Brassard's diene gave only the vinylogous[18] Mukaiyama-aldol adduct **5h** in 81% yield and 85% ee, and no trace of the cyclic HDA adduct was observed (eq 3).



The construction of quaternary stereocenters, due to the congestion imposed by the four attached substituents, is a

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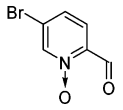
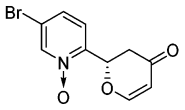
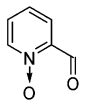
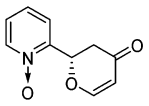
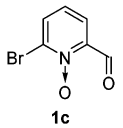
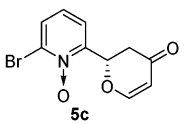
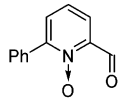
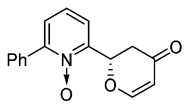
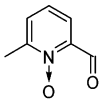
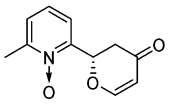
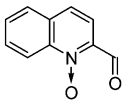
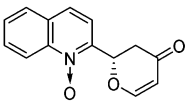
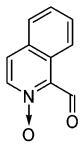
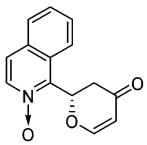
TABLE 2. ***oxo*-HDA Reaction between Danishefsky's Diene 3a and Different *N*-Oxy-pyridine-2-carbaldehyde Derivatives 1a−g Catalyzed by (4*R*,5*S*)-4c−Cu(OTf)$_2$[a]**

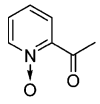
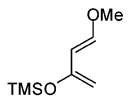
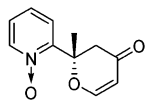
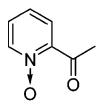
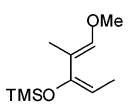
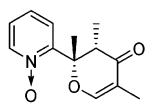
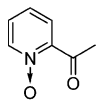
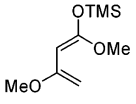
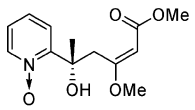
entry	substrate	product	yield (%)[b]	ee (%)[c]
1	 **1a**	 **5a**	47	93
2	 **1b**	 **5b**	42	90
3	 **1c**	 **5c**	70	79
4	 **1d**	 **5d**	49	95
5[d]	 **1e**	 **5e**	80	55
6	 **1f**	 **5f**	53	83
7	 **1g**	 **5g**	83	75

[a] Reactions performed in Tol/CH_2Cl_2 (4:1) at −40 °C, 16 h in the presence of 10 mol % (4*R*,5*S*)-**4c**−Cu(OTf)$_2$. All reactions gave full conversion. [b] Yield of isolated product. [c] Enantiomeric excess measured by chiral stationary phase HPLC. [d] With (*S*)-**4a**−Cu(OTf)$_2$ as catalyst, using (4*R*,5*S*)-**4c**−Cu(OTf)$_2$ complex, the enantioselectivity decreased to 47% ee.

challenge in organic chemistry. The Diels−Alder reaction is one of the most general approaches to form all-carbon quaternary stereocenters. Moreover, the *oxo*-HDA reaction of ketones as dienophiles and electron-rich dienes gives us the possibility to obtain the highly interesting *oxo*-substituted quaternary stereocenters. As mentioned above, very few examples of asymmetric HDA reactions of ketones have been reported, and almost all of them were with activated ketones.[9] However, recently, the group of Campagne achieved high yields and enantioselectivities by using unactivated ketones.[19]

In an attempt to extend the developed *oxo*-HDA reaction with aldehydes shown (Table 2 and eq 2), and because of the significant relevance of asymmetric quaternary stereogenic

TABLE 3. Catalytic Enantioselective Addition of Electron-Rich Dienes 3a−c to *N*-Oxy-pyridine-2-yl-ethanone 2a Catalyzed by (4*R*,5*S*)-4c−Cu(OTf)$_2$ Complex[a]

entry	substrate	enolate	product	yield (%)[b]	ee (%)[c]
1[d]	 **2a**	 **3a**	 **6a**	66	99
2[e]	 **2a**	 **3b**	 **6b**	67	97
3[f]	 **2a**	 **3c**	 **6c**	84	99

[a] Reactions performed in Tol/CH_2Cl_2 (4:1) at −30 °C, using 2 equiv of diene **3a**−**c**, 16 h in the presence of 10 mol % (4*R*,5*S*)-**4c**−Cu(OTf)$_2$; the absolute configuration of the products was based on analogy to the configuration of **5a**. [b] Yield of isolated product. [c] Enantiomeric excess measured by chiral stationary phase HPLC. [d] Compound **6a** was also prepared on a 7.5 mmol scale using 10 mol % (*S*)-**4a**−Cu(OTf)$_2$ with similar results (55% yield and 94% ee). [e] Diastereoselectivity 17:1. The relative configuration was assigned as anti by NOEDIF experiment. [f] The configuration of the double bond in the open-chain compound **6c** was established as *E* by NOEDIF experiment.

centers in synthetic chemistry,[10] we decided to implement the *oxo*-HDA reaction of the activated *N*-oxy-pyridine-2-yl-ethanone **2a** with electron-rich dienes (Table 3). The reaction of ketone **2a** with 2 equiv of Danishefsky's diene **3a** at −40 °C catalyzed by (4*R*,5*S*)-**4c**−Cu(OTf)$_2$ complex gave only 60% conversion. Warming the reaction mixture to −30 °C gave full conversion. To our delight, we found that the reaction with **2a** gave better yields and enantioselectivities than the reaction with aldehydes. Ketone **2a** reacted with the Danishefsky's type dienes **3a**,**b** smoothly in good yields and excellent enantioselectivities (Table 3, entries 1, 2). The reaction of **2a** with Brassard's diene **3c** gave enantiomerically pure vinylogous Mukaiyama-aldol adduct **6c** in very good yield (entry 3). As previously observed with aldehyde **1b** and **3c** (eq 3), no trace of the cyclic *oxo*-HDA adduct was detected. Furthermore, no decomposition of **3c** was observed in the presence of the Lewis acid.[20]

The absolute configurations of the newly formed stereogenic centers were established, assuming a uniform reaction mechanism, by a single-crystal X-ray crystallographic analysis of adduct **5a** (see Supporting Information). The relative configuration of major diastereomer **6b** was assigned to be anti by NOEDIF experiment.

In the reaction of carbonyl compounds with electron-rich conjugated dienes, two mechanistic pathways have generally been taken into account: (i) the concerted HDA-cycloaddition or (ii) the Mukaiyama-aldol pathway. The reaction course is

(19) For *oxo*-HDA reaction of unactivated ketones, see: Moreau, X.; Bazán-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 7288 and references therein.

(20) Du, H.; Zhao, D.; Ding, K. *Chem.-Eur. J.* **2004**, *10*, 5964.

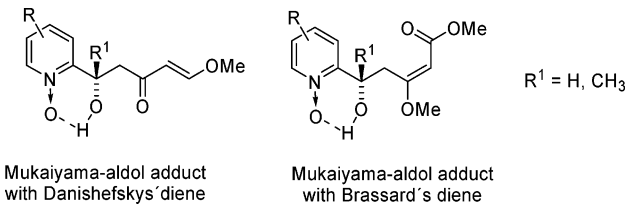


FIGURE 1. Possible stabilization of the open-chain methyl ester by intramolecular hydrogen bonding.

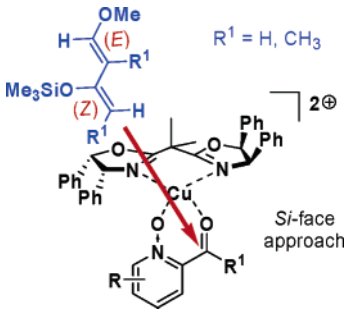


FIGURE 2. Proposed Mukaiyama-aldol intermediate and the diastereoselective approach of the diene to the *Si*-face of the carbonyl (from the top).

dependent on the Lewis acid employed.[21] ^{1}H NMR observations showed that in the reaction of the *N*-oxy-pyridine-2-carbaldehyde derivatives with Danishefsky's diene, a short exposure time (less than 3 h) to TFA gave the mixture of the unsaturated six-membered rings **5a**−**g** and the open-chain Mukaiyama-aldol adducts. Moreover, in the *oxo*-HDA reaction of 1-oxy-pyridine derivatives **1b** and **2a** with Brassard's diene **3c**, only the not-silylated vinylogous Mukaiyama-aldol adducts **5h** and **6c** were isolated, without a trace of the corresponding silylated open-chain adducts or the cycloadducts. A possible explanation for the isolation of the Mukaiyama-aldol adducts could be the stability of the formed open-chain methyl ester, due to hydrogen-bond stabilization between the *N*-oxide and the hydroxyl group (Figure 1). These observations indicated that the *oxo*-HDA reaction of *N*-oxy-pyridine-2-carbaldehyde and ketone derivatives with electron-rich dienes might proceed by a stepwise Mukaiyama-aldol mechanism.

We propose that both the oxygen atoms of the carbonyl group and *N*-oxide in the *N*-oxy-pyridine derivative coordinate to the copper(II) center in a bidentate fashion. This leads to a square-planar distorted intermediate in which the *Si*-face of the reacting carbonyl functionality is available for Mukaiyama-aldol approach of the diene. To account for the diastereoselectivity of the reaction (compound **6b**), the OTMS-group and R^1 (R^1 = CH_3) in the *Z*-alkene have to point away from the phenyl groups in the chiral bisoxazoline ligand to minimize steric repulsions (Figure 2). As the last step, treatment with TFA gave the six-membered heterocyclic compound.

Conclusions

In conclusion, we have demonstrated that the chiral bisoxazoline copper(II) Lewis-acid complex catalyzes the *oxo*-HDA reaction between *N*-oxy-pyridine-2-carbaldehydes and electron-rich dienes in moderated yields and good enantiomeric excesses. Furthermore, and most importantly, the *oxo*-HDA reactions with 1-pyridin-2-yl-ethanone gave better yields and excellent enantiomeric excesses. Finally, we have shown that the *oxo*-HDA reaction of the privileged bidentate *N*-oxy-pyridine-2-carbaldehyde and ketone derivatives with electron-rich dienes, catalyzed by bisoxazoline copper(II) Lewis acid complexes, proceeds by the Mukaiyama-aldol pathway.

Experimental Section

General Procedure for Aldehydes. $M(OTf)_2$ (25 μmol) and the corresponding C_2-bisoxazoline (**4a**−**c**) (26 μmol) were stirred under vacuum in a oven-dried Schlenk tube for 1 h. The tube was then filled with N_2, dry CH_2Cl_2 (0.5 mL) and toluene (0.5 mL) were added, and the resulting solution was stirred for 30 min. The solution was cooled to −40 °C, and then a solution of the aldehyde **1a**−**g** (0.25 mmol) in dry toluene (1 mL) was added slowly. The resulting solution was stirred for 1 h at the same temperature, and afterward the solution of diene **3** (0.28 mmol) in dry toluene (0.5 mL) was added dropwise. The reaction mixture was kept stirring at −40 °C for 16 h, and then trifluoroacetic acid (TFA) (0.1 mL in 20 mL of CH_2Cl_2) was added. The solution was stirred vigorously at room temperature for 3 h. The products **5a**−**g** were isolated directly, without aqueous workup by FC.

General Procedure for Ketones. $Cu(OTf)_2$ (25 μmol) and the corresponding C_2-bisoxazoline (**4c**) (26 μmol) were stirred under vacuum in a oven-dried Schlenk tube for 1 h. The tube was then filled with N_2, dry CH_2Cl_2 (0.5 mL) and toluene (0.5 mL) were added, and the resulting solution was stirred for 30 min. The solution was cooled to −30 °C, and then a solution of the ketone **2** (0.25 mmol) in dry toluene (1 mL) was added slowly. The resulting solution was stirred for 1 h at the same temperature, and afterward the solution of diene **3a**−**c** (2 equiv, 0.50 mmol) in dry toluene (0.5 mL) was added dropwise. The reaction was kept stirring at −30 °C for 16 h, and then TFA (0.1 mL in CH_2Cl_2 (20 mL)) was added. The solution was stirred at room temperature for 3 h. The products **6a**−**c** were isolated directly, without aqueous workup by FC.

2-(5-Bromo-*N*-oxy-pyridin-2-yl)-2,3-dihydro-pyran-4-one (5a). FC eluent EtOAc. ^{1}H NMR δ 8.59 (s, 1H), 7.81 (dd, J = 8.6, 1.8 Hz, 1H), 7.71 (m, 2H), 5.96 (dd, J = 14.0, 3.6 Hz, 1H), 5.56 (dd, J = 6.2, 1.2 Hz, 1H), 3.12 (ddd, J = 16.8, 3.6, 1.2 Hz, 1H), 2.72 (dd, J = 16.8, 14.0 Hz, 1H). ^{13}C NMR δ 193.3, 165.0, 149.0, 142.1, 132.7, 125.6, 121.2, 108.6, 76.1, 39.2. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{10}H_8BrNNaO_3$ 291.9585; found 291.9588. $[\alpha]^{23}_D$ = −150.4 (c = 1.00, $CHCl_3$, 93% ee (*S*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 30.4 min (major enantiomer); τ_2 = 52.1 min (minor enantiomer)).

2-(*N*-Oxy-pyridin-2-yl)-2,3-dihydro-pyran-4-one (5b). FC eluent EtOAc afterward EtOAc/EtOH 1:1). ^{1}H NMR δ 8.36 (d, J = 6.0, Hz, 1H), 7.83 (dd, J = 8.0, 2.0 Hz, 1H), 7.73 (d, J = 6.2 Hz, 1H), 7.64 (dt, J = 8.0, 2.0 Hz, 1H), 7.54 (dt, J = 8.0, 2.0 Hz, 1H), 6.04 (dd, J = 13.8, 3.6 Hz, 1H), 5.57 (dd, J = 6.0, 1.2 Hz, 1H), 3.15 (ddd, J = 16.8, 3.6, 1.2 Hz, 1H), 2.75 (dd, J = 16.8, 13.8 Hz, 1H). ^{13}C NMR δ 193.3, 165.0, 141.0, 130.5, 127.4, 125.3, 108.6, 76.3, 54.9, 39.5. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{10}H_9NNaO_3$ 214.0480; found 214.0480. $[\alpha]^{23}_D$ = −28.0 (c = 1.00, $CHCl_3$, 90% ee (*S*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min (τ_1 = 37.3 min (major enantiomer); τ_2 = 65.0 min (minor enantiomer)).

2-(6-Bromo-*N*-oxy-pyridin-2-yl)-2,3-dihydro-pyran-4-one (5c). FC eluent EtOAc afterward EtOAc/EtOH 1:1. ^{1}H NMR δ 7.78 (dd, J = 8.2, 2.0 Hz, 1H), 7.61 (dd, J = 8.2, 2.0 Hz, 1H), 7.59 (d, J = 6.0 Hz, 1H), 7.28 (t, J = 8.2 Hz, 1H), 5.96 (dd, J = 13.4, 3.6 Hz, 1H), 5.48 (dd, J = 6.0, 1.2 Hz, 1H), 3.02 (ddd, J = 16.8, 3.6, 1.2 Hz, 1H), 2.62 (dd, J = 16.8, 13.4 Hz, 1H). ^{13}C NMR δ 193.3, 165.0, 151.5, 134.8, 131.9, 129.4, 124.0, 108.6, 77.0, 39.3. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{10}H_8BrNNaO_3$ 291.9585; found

(21) Roberson, M.; Jepsen, A. S.; Jørgensen, K. A. *Tetrahedron* **2001**, *57*, 907.

291.9586. $[\alpha]^{23}_D = -112.0$ ($c = 1.00$, $CHCl_3$, 79% ee (*S*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min ($\tau_1 = 41.6$ min (minor enantiomer); $\tau_2 = 51.8$ min (major enantiomer)).

2-(*N*-Oxy-6-phenyl-pyridin-2-yl)-2,3-dihydro-pyran-4-one (5d). FC eluent EtOAc afterward EtOAc/EtOH 1:1. ^{1}H NMR δ 7.82−7.50 (m, 9H), 6.10 (dd, $J = 13.8$, 3.4 Hz, 1H), 5.58 (dd, $J = 6.2$, 1.2 Hz, 1H), 3.22 (ddd, $J = 16.8$, 3.6, 1.2 Hz, 1H), 2.77 (dd, $J = 16.8$, 13.8 Hz, 1H). ^{13}C NMR δ 193.6, 165.0, 151.3, 150.6, 133.7, 131.0, 130.7, 129.7, 129.5, 128.5, 123.9, 108.5, 76.8, 39.7. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{16}H_{13}NNaO_3$ 290.0793; found 290.0802. $[\alpha]^{23}_D = -164.3$ ($c = 1.00$, $CHCl_3$, 95% ee (*S*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min ($\tau_1 = 38.7$ min (major enantiomer); $\tau_2 = 51.4$ min (minor enantiomer)).

2-(6-Methyl-*N*-oxy-pyridin-2-yl)-2,3-dihydro-pyran-4-one (5e). FC eluent EtOAc afterward EtOAc/EtOH 1:1. ^{1}H NMR δ 7.73 (d, $J = 6.0$ Hz, 1H), 7.68 (m, 1H), 7.55−7.54 (m, 2H), 6.05 (dd, $J = 13.8$, 3.6 Hz, 1H), 5.57 (dd, $J = 6.0$, 1.2 Hz, 1H), 3.18 (ddd, $J = 16.8$, 3.6, 1.2 Hz, 1H), 2.73 (dd, $J = 16.8$, 13.8 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR δ 193.6, 165.1, 151.1, 149.8, 129.5, 127.7, 122.8, 108.5, 76.7, 39.7, 17.8. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{11}H_{11}NNaO_3$ 228.0637; found 228.0637. $[\alpha]^{23}_D = +98.9$ ($c = 1.00$, $CHCl_3$, 55% ee). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min ($\tau_1 = 48.6$ min (minor enantiomer); $\tau_2 = 71.0$ min (major enantiomer)).

2-(*N*-Oxy-quinolin-2-yl)-2,3-dihydro-pyran-4-one (5f). FC Eluent EtOAc afterward EtOAc/EtOH 1:1. ^{1}H NMR δ 8.64 (d, $J = 8.80$ Hz, 1H), 8.17 (d, $J = 8.8$ Hz, 1H), 8.09 (d, $J = 8.8$ Hz, 1H), 7.85 (m, 4H), 6.28 (dd, $J = 14.0$, 3.4 Hz, 1H), 5.61 (dd, $J = 6.2$, 1.2 Hz, 1H), 3.24 (ddd, $J = 16.6$, 3.4, 1.2 Hz, 1H), 2.81 (dd, $J = 16.6$, 14.0 Hz, 1H). ^{13}C NMR δ 193.3, 165.0, 147.3, 142.2, 132.8, 131.3, 130.4, 129.9, 119.9, 119.7, 108.6, 77.0, 39.0. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{14}H_{11}NNaO_3$ 264.0637; found 264.0626. $[\alpha]^{23}_D = -250.0$ ($c = 1.00$, $CHCl_3$, 83% ee (*S*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min ($\tau_1 = 25.0$ min (major enantiomer); $\tau_2 = 55.4$ min (minor enantiomer)).

2-(*N*-Oxy-isoquinolin-1-yl)-2,3-dihydro-pyran-4-one (5g). FC eluent EtOAc afterward EtOAc/EtOH 1:1. ^{1}H NMR δ 8.52 (m, 1H), 8.25 (d, $J = 6.80$ Hz, 1H), 8.00 (m, 2H), 7.76 (m, 3H), 6.91 (dd, $J = 15.4$, 3.6 Hz, 1H), 5.65 (dd, $J = 6.0$, 1.2 Hz, 1H), 3.39 (dd, $J = 17.2$, 15.4 Hz, 1H), 2.77 (ddd, $J = 17.2$, 3.6, 1.2 Hz, 1H). ^{13}C NMR δ 193.1, 165.1, 144.6, 136.9, 132.1, 131.1, 131.0, 130.9, 129.2, 126.7, 125.5, 108.6, 76.4, 39.0. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{14}H_{11}NNaO_3$ 264.0637; found 264.0628. $[\alpha]^{23}_D = -227.0$ ($c = 0.5$, $CHCl_3$, 75% ee (*S*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min ($\tau_1 = 20.4$ min (major enantiomer); $\tau_2 = 25.0$ min (minor enantiomer)).

5-Hydroxy-3-methoxy-5-(*N*-oxy-pyridin-2-yl)-pent-2-enoic Acid Methyl Ester (5h). FC eluent EtOAc afterward EtOAc/EtOH 1:1. ^{1}H NMR δ 8.28 (dd, $J = 6.4$, 1.2 Hz, 1H), 7.70 (dd, $J = 7.8$, 2.2 Hz, 1H), 7.61 (dt, $J = 7.8$, 1.2 Hz, 1H), 7.44 (dt, $J = 7.6$, 2.2 Hz, 1H), 5.51 (dd, $J = 7.6$, 4.8 Hz, 1H), 5.19 (s, 1H), 3.61 (s, 3H), 3.59 (s, 3H), 3.50 (dd, $J = 13.6$, 7.6 Hz, 1H), 3.30 (dd, $J = 13.6$, 4.8 Hz, 1H). ^{13}C NMR δ 173.2, 170.3, 154.9, 140.8, 130.7, 126.3, 125.8, 93.7, 67.7, 56.3, 51.5, 37.2. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{12}H_{15}NaNO_5$ 276.0848; found 276.1844. $[\alpha]^{23}_D = -59.4$ ($c = 1.00$, MeOH, lamp: Hg 578, 85% ee (*S*)). HPLC: Daicel Chiralpak OD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min ($\tau_1 = 32.5$ min (minor enantiomer); $\tau_2 = 45.6$ min (major enantiomer)).

2-Methyl-2-(*N*-oxy-pyridin-2-yl)-2,3-dihydro-pyran-4-one (6a). FC eluent EtOAc afterward EtOAc/EtOH 1:1. ^{1}H NMR δ 8.29 (dd, $J = 6.4$, 1.2 Hz, 1H), 7.76 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.64 (d, $J = 6.4$ Hz, 1H), 7.62 (dt, $J = 7.8$, 1.2 Hz, 1H), 7.49 (m, 1H), 5.46 (d, $J = 6.4$ Hz, 1H), 3.66 (d, $J = 16.8$ Hz, 1H), 3.35 (d, $J = 16.8$ Hz, 1H), 1.97 (s, 3H). ^{13}C NMR δ 193.5, 162.9, 151.4, 142.8, 130.2, 127.4, 125.7, 107.8, 85.1, 43.2, 22.2. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{11}H_{11}NNaO_3$ 228.0637; found 228.0627. $[\alpha]^{23}_D = -86.1$ ($c = 1.00$, EtOH, lamp: Hg 578, 99% ee (*S*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min ($\tau_1 = 38.0$ min (major enantiomer); $\tau_2 = 46.5$ min (minor enantiomer)).

2,3,5-Trimethyl-2-(*N*-oxy-pyridin-2-yl)-2,3-dihydro-pyran-4-one (6b). FC eluent EtOAc afterward EtOAc/EtOH 1:1. Major diastereomer: ^{1}H NMR δ 8.30 (d, $J = 6.4$ Hz, 1H), 7.97 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.65 (dt, $J = 8.4$, 1.2 Hz, 1H), 7.51 (dt, $J = 8.4$, 2.0 Hz, 1H), 7.43 (d, $J = 1.2$ Hz, 1H), 3.85 (q, $J = 7.4$ Hz, 1H), 1.87 (s, 3H), 1.71 (s, 3H), 0.79 (d, $J = 7.4$ Hz, 3H). ^{13}C NMR δ 198.8, 157.0, 152.2, 142.0, 130.3, 127.3, 126.1, 113.1, 87.0, 45.8, 19.1, 14.8, 10.4. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{13}H_{15}NaNO_3$ 256.0950; found 256.0958. HPLC: Daicel Chiralpak AD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min ($\tau_1 = 23.6$ min (major enantiomer); $\tau_2 = 35.5$ min (minor enantiomer)).

5-Hydroxy-3-methoxy-5-(*N*-oxy-pyridin-2-yl)-hex-2-enoic Acid Methyl Ester (6c). FC eluent EtOAc afterward EtOAc/EtOH 1:1. ^{1}H NMR δ 8.27 (dd, $J = 6.4$, 1.2 Hz, 1H), 7.65 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.58 (dt, $J = 8.0$, 1.2 Hz, 1H), 7.45 (dt, $J = 6.4$, 2.0 Hz, 1H), 5.11 (s, 1H), 3.72 (d, $J = 13.2$ Hz, 1H), 3.65 (d, $J = 13.2$ Hz, 1H), 3.60 (s, 3H), 3.34 (s, 3H), 1.69 (s, 3H). ^{13}C NMR δ 172.9, 170.1, 155.2, 141.6, 130.9, 126.5, 125.7, 94.2, 75.5, 55.9, 51.5, 41.1, 25.6. (TOF ES$^+$) $[M + Na]^+$ calcd for $C_{13}H_{17}NNaO_5$ 290.1004; found 290.1010. $[\alpha]^{23}_D = -4.1$ ($c = 1.00$, MeOH, lamp: Hg 578, 99% ee (*S*)). HPLC: Daicel Chiralpak OD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min ($\tau_1 = 35.6$ min (major enantiomer); $\tau_2 = 51.4$ min (minor enantiomer)).

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Supporting Information Available: Complete ^{1}H and ^{13}C NMR spectra of compounds **5a**−**h** and **6a**−**c**. X-ray structural data for **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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