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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-oxy-pyridine 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-oxy-pyridines 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 bisoxazoline¹³ (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, CH₂Cl₂ 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, CH₂Cl₂ improved the enantioselectivity, but deteriorated the yield (entry 7). Subsequent experiments showed that the use of a toluene-CH₂Cl₂ 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

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 ₂ Cl 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 ₂ Cl ₂	-40	35	7
5	4a	Mg(OTf) ₂	CH ₂ Cl ₂	-40	44	10
6	4b	Cu(OTf) ₂	CH ₂ Cl ₂	-40	30	-78 ^e
7	4c	Cu(OTf) ₂	CH ₂ Cl ₂	-40	32	87
8	4c	Cu(OTf) ₂	Tol	-40	83	40
9 ^f	4c	Cu(OTf) ₂	Tol/CH ₂ Cl ₂	-40	47	93

^a Reaction conducted on a 0.25 mmol scale. ^b 100% conversion in all reactions after 16 h, estimated by ¹H 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/CH₂Cl₂ (4:1).

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).

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 vinylogous¹⁸ 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			47	93
2			42	90
3			70	79
4			49	95
5 ^d			80	55
6			53	83
7			83	75

^a Reactions performed in Tol/CH₂Cl₂ (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				66	99
2 ^e				67	97
3 ^f				84	99

^a Reactions performed in Tol/CH₂Cl₂ (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 ¹H 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 ($R^1 = \text{CH}_3$) 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 moderate 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. $\text{M}(\text{OTf})_2$ (25 μmol) and the corresponding C_2 -bisoxazoline (**4a–c**) (26 μmol) were stirred under vacuum in an 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. $\text{Cu}(\text{OTf})_2$ (25 μmol) and the corresponding C_2 -bisoxazoline (**4c**) (26 μmol) were stirred under vacuum in an 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. ¹H 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). ¹³C NMR δ 193.3, 165.0, 149.0, 142.1, 132.7, 125.6, 121.2, 108.6, 76.1, 39.2. (TOF ES⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{BrNNaO}_3$ 291.9585; found 291.9588. $[\alpha]_D^{25} = -150.4$ ($c = 1.00$, CHCl_3 , 93% ee (S)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min ($\tau_1 = 30.4$ min (major enantiomer); $\tau_2 = 52.1$ min (minor enantiomer)).

2-(*N*-Oxy-pyridin-2-yl)-2,3-dihydro-pyran-4-one (5b). FC eluent EtOAc afterward EtOAc/EtOH 1:1. ¹H 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). ¹³C NMR δ 193.3, 165.0, 141.0, 130.5, 127.4, 125.3, 108.6, 76.3, 54.9, 39.5. (TOF ES⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{NNaO}_3$ 214.0480; found 214.0480. $[\alpha]_D^{25} = -28.0$ ($c = 1.00$, CHCl_3 , 90% ee (S)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (80/20), flow rate = 1.0 mL/min ($\tau_1 = 37.3$ min (major enantiomer); $\tau_2 = 65.0$ 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. ¹H 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). ¹³C NMR δ 193.3, 165.0, 151.5, 134.8, 131.9, 129.4, 124.0, 108.6, 77.0, 39.3. (TOF ES⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{BrNNaO}_3$ 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. ^1H 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⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{13}\text{NNaO}_3$ 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. ^1H 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⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{11}\text{NNaO}_3$ 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. ^1H 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⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{NNaO}_3$ 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. ^1H 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⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{NNaO}_3$ 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. ^1H 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⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{15}\text{NNaO}_5$ 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. ^1H 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⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{11}\text{NNaO}_3$ 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: ^1H 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⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{NNaO}_3$ 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. ^1H 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⁺) $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{NNaO}_5$ 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 ^1H 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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