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Bis(oxazoline) Lewis Acid Catalyzed Aldol Reactions of Pyridine *N*-Oxide Aldehydes—Synthesis of Optically Active 2-(1-Hydroxyalkyl)pyridine Derivatives: Development, Scope, and Total Synthesis of an Indolizine Alkaloid

Aitor Landa,[a] Anna Minkkilä,[a] Gonzalo Blay,[a, b] and Karl Anker Jørgensen*[a]

Abstract: A new, short, and simplified procedure for the synthesis of optically active pyridine derivatives from prochiral pyridine-*N*-oxides is presented. The catalytic and asymmetric Mukaiyama aldol reaction between ketene silyl acetals and 1-oxypyridine-2-carbaldehyde derivatives catalyzed by chiral copper(II)–bis(oxazoline) complexes gave optically active 2-(hydroxyalkyl)- and 2-(*anti*-1,2-dihydroxyalkyl)pyridine derivatives in good yields and diastereoselectivities, and in excellent enantioselectivities—up to 99% enantiomeric excess. As a synthetic application of the developed method, a full account for the asymmetric total synthesis of a nonnatural indolizine alkaloid is provided.

Keywords: aldol reaction · asymmetric catalysis · copper · nitrogen heterocycles

Introduction

In recent years, the search for more efficient and easily accessible procedures for the formation of chiral pyridine-containing compounds has been growing due to their proved utility in different chemical fields, for example, in supramolecular chemistry,[1] asymmetric catalysis,[2] and in natural product synthesis.[3] The great interest and importance in optically active pyridine units have resulted in the development of many methods to synthesize these compounds.[4] However, to the best of our knowledge, there are only a few general catalytic asymmetric methods for the preparation of optically active 2-(1-hydroxyalkyl)- and 2-(1,2-dihydroxyalkyl)pyridine units reported to date. These optically active molecules belong to a class of compounds of great importance as stated above, for example, for the synthesis of naturally occurring compounds such as hydroxylated indolizidine alkaloids.[5] Chiral 2-(hydroxyalkyl)pyridine derivatives have frequently been prepared by asymmetric reduction of 2-ketopyridines with (−)-chlorodiisopinocamphenyl borane [(−)-Ipc$_2$BCl)][6] and by lipase-catalyzed optical resolution.[7] The most used methods for the synthesis of 2-(1,2-dihydroxyalkyl)pyridine derivatives are probably the Sharpless asymmetric dihydroxylation of ethyl 3-(pyridine-2-yl)acrylate derivatives[8] or preparation from natural chiral pool sources.[9]

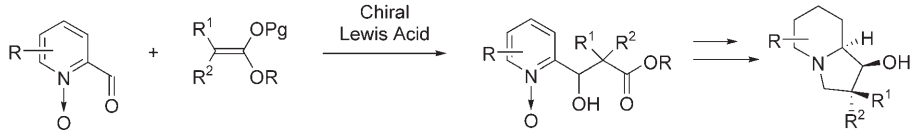
The considerable synthetic utility of chiral 2-(hydroxyalkyl)pyridine derivatives and β-hydroxyesters in many different fields of chemistry prompted us to find an alternative and general procedure to synthesize these compounds by asymmetric catalysis, and to demonstrate the potential of the procedure outlined by the total synthesis of a hydroxylated indolizine alkaloid derivative. For this purpose we have applied one of the most reliable C–C bond-forming reactions: the Lewis acid catalyzed reaction of silyl enolates with carbonyl compounds, the Mukaiyama aldol reaction (Scheme 1).[10]

Since the first successful catalytic enantioselective Mukaiyama aldol type reactions were reported in the early nineties,[11] intense efforts have been made to develop such reactions to be highly diastereo- and enantioselective by using sub-stoichiometric quantities of different Lewis acids and chiral ligands.[12]

The use of C_2 bis(oxazoline) Lewis acid complexes as catalysts has been established as an efficient strategy for the synthesis of optically active molecules.[13] One of the advantages of bis(oxazoline) compounds as chiral ligands is their

[a] Dr. A. Landa, A. Minkkilä, Dr. G. Blay, Prof. Dr. K. A. Jørgensen
The Danish National Research Foundation
Center for Catalysis, Department of Chemistry
Aarhus University, 8000 Aarhus C (Denmark)
Fax: (+45) 8919-6199
E-mail: kaj@chem.au.dk

[b] Dr. G. Blay
Departament de Química Orgánica
Facultat de Química, Universitat de Valéncia
C/Dr. Moliner, 50, 46100-Burjassot, Valéncia (Spain)



Scheme 1. Mukaiyama-type aldol reaction catalyzed by chiral Lewis acid complexes and its application in the total synthesis of hydroxylated indolizine alkaloid derivatives.

availability in both enantiomeric forms, which permits access to both enantiomeric forms of the target molecule.

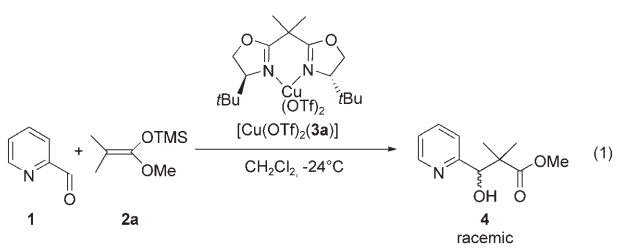
Despite the importance of this C–C bond forming aldol reaction, only a few examples of effective catalytic diastereo- and enantioselective Mukaiyama aldol reactions using bidentate-chelating C_2 bis(oxazoline) Lewis acid complexes have been reported so far. Evans et al. were the first to achieve enantio- and diastereoselectivities in the metal–bis(oxazoline)-catalyzed asymmetric Mukaiyama aldol reactions between benzyloxyacetaldehydes,[14] pyruvic esters,[15] or ethyl glyoxylates,[16] and enolsilanes. In these cases, the use of α-substituted carbonyl compounds capable of forming a five-membered chelate ring with the chiral Lewis acid catalyst seems to be essential for obtaining high enantiomeric excess. In 1999 Kobayashi et al. reported the interesting catalytic enantioselective Mukaiyama aldol reaction between aldehydes and enolsilanes in aqueous media using chiral Cu(OTf)$_2$/bis(oxazoline) complexes, albeit with moderate enantiomeric excess.[17]

Results and Discussion

We thought that the pyridine-2-carbaldehydes could be perfect substrates to be used as pro-chiral starting materials for synthesizing optically active pyridine units. We envisaged that the possibility of bidentate coordination between the lone-pair electrons of the nitrogen atom of the pyridine, the aldehyde oxygen atom, and an appropriate chiral metal–bis(oxazoline) complex could activate the aldehyde functionality for the subsequent asymmetric nucleophilic attack.

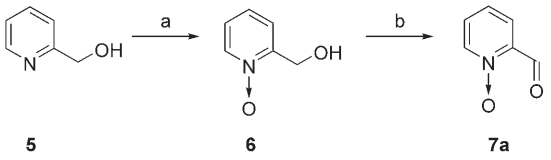
The Mukaiyama aldol reaction between the commercially available pyridine-2-carbaldehyde (**1**) and the ketene silyl acetal 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (**2a**) in the presence of the chiral [Cu(OTf)$_2$(**3a**)] complex [Eq. (1); **3a** = (*S*)-*t*Bu-BOX; BOX = bis(oxazoline)] was tested first. This reaction gave a full conversion at −24 °C, but to our surprise, the aldol product **4** was racemic.

This lack of selectivity was interpreted as a result of an inappropriate coordination between the substrate (**1**) and the catalyst. After this rather disappointing result, we thought that an oxidation of **1** to the 1-oxypyridine-2-carbaldehyde (**7a**) could provide a substrate with suitable electronic environment for a bidentate coordination to the chiral Lewis acid complex leading to a six-membered chiral metal chelate ring, which might improve the enantioselectivity of the reaction.



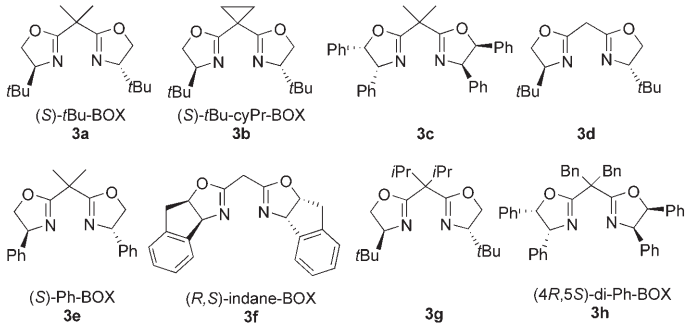
(1)

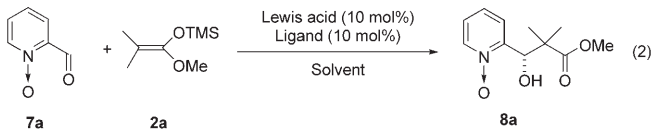
1-Oxypyridine-2-carbaldehyde (**7a**) was easily prepared by the two-step sequence shown in Scheme 2. Treatment of



Scheme 2. Synthesis of the 1-oxypyridine-2-carbaldehyde (**7a**): a) **5** and *m*-CPBA, $CHCl_3$, 65–70 °C, overnight (87 %); b) 9 equiv MnO_2, dioxane, 90 °C, 1 h (51 %).

the commercially available pyridin-2-ylmethanol (**5**) with 1.1 equivalents of *m*-CPBA (*m*-CPBA = *meta*-chloro peroxybenzoic acid) followed by the oxidation of the alcohol group in **6** by using MnO_2 afforded **7a** in a 44 % overall isolated yield.[18]





(2)

The initial screening showed that compound **7a** reacted smoothly at −24 °C with compound **2a** in CH_2Cl_2 catalyzed by 10 mol % [Cu(OTf)$_2$(**3a**)] affording the aldol adduct **8a** in a good yield and 84 % enantiomeric excess (*ee*; Table 1, entry 1), giving support to our hypothesis. Encouraged by this initial result, we decided to explore further this aldol reaction by using **7a** as test substrate in a series of reactions catalyzed by different C_2-symmetric bis(oxazoline)-type ligands (**3a**–**h**) in combination with various Lewis acids, varying temperature, and solvents [see Eq. (2) and Table 1].

Table 1. Screening of reaction conditions and catalysts for the enantioselective addition of **2a** to **7a** catalyzed by chiral Lewis acid complexes.[a–c]

	Ligand	Lewis acid	Solvent	T [°C]	Yield [%][d]	*ee* [%][e]
1	**3a**	$Cu(OTf)_2$	CH_2Cl_2	−24	82	84
2	**3a**	$Zn(OTf)_2$	CH_2Cl_2	−24	93	rac.
3[f]	**3a**	$Mg(OTf)_2$	CH_2Cl_2	−24	28	rac.
4	**3a**	$Cu(OTf)_2$	CH_2Cl_2	−40	79	93
5	**3a**	$Cu(OTf)_2$	CH_2Cl_2	−78	0	–
6	**3a**	$Cu(OTf)_2$	Et_2O	−40	86	87
7	**3a**	$Cu(OTf)_2$	THF	−40	72	93
8	**3b**	$Cu(OTf)_2$	CH_2Cl_2	−40	90	64
9	**3c**	$Cu(OTf)_2$	CH_2Cl_2	−40	88	89
10	**3d**	$Cu(OTf)_2$	CH_2Cl_2	−40	49	11
11	**3e**	$Cu(OTf)_2$	CH_2Cl_2	−40	80	−88[g]
12	**3f**	$Cu(OTf)_2$	CH_2Cl_2	−40	75	7
13	**3g**	$Cu(OTf)_2$	CH_2Cl_2	−40	69	46
14	**3h**	$Cu(OTf)_2$	CH_2Cl_2	−40	72	96

[a] Reaction conditions: $M(OTf)_2$ (25 μmol) and the corresponding C_2-bis(oxazoline) (**3a**–**h**) (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 (1 mL) was added, and the resulting solution was stirred for 30 min. The solution was cooled to −40 °C and then a solution of **7a** (0.25 mmol) in dry CH_2Cl_2 (1 mL) was added slowly. The resulting solution was stirred for 1 h at the same temperature and afterwards the solution of enolsilane **2a** (0.26 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise. The product **8a** was isolated by flash chromatography after 16 h. [b] Reaction conducted on a 0.25 mmol scale. [c] 100 % conversion in all reactions after 16 h, estimated by ^{1}H NMR spectroscopy. [d] Yield of isolated product after purification by column chromatography. [e] Enantiomeric excess measured by chiral stationary phase HPLC. [f] Conversion 45 %. [g] Refers to the opposite enantiomer.

Zinc(II)– and magnesium(II)–bis(oxazoline) complexes also catalyzed the reaction, but the aldol adduct **8a** was formed as a racemate (entries 2 and 3 vs. 1). With [Cu(OTf)$_2$(**3a**)], it was found that the enantioselectivity of **8a** increased from 84 to 93 % *ee* by lowering the reaction temperature from −24 °C to −40 °C (entry 4 vs. 1), whereas the reaction at −78 °C gave no conversion at all (entry 5). Various solvents were investigated for the aldol reaction catalyzed by the [Cu(OTf)$_2$(**3a**)] complex and, as it has been observed previously for the hetero-Diels–Alder reaction,[19] for example, no solvent dependence was found (entries 6, 7 vs. 4). The results in Table 1 show that the best catalytic systems in terms of enantioselectivity were obtained by using $Cu(OTf)_2$ as the Lewis-acid in combination with the (*S*)-*t*Bu-BOX (**3a**) or the (4*R*,5*S*)-di-Ph-BOX (**3h**) ligands. The reactions proceeded to completion affording the desired aldol adduct **8a** in good yield and excellent enantiomeric excess (entries 4, 14). It should be noted that we observed a change in absolute configuration of the final product (**8a**) when ligand (*S*)-*t*Bu-BOX (**3a**) was exchanged with the (*S*)-Ph-BOX (**3e**) ligand (entry 4 vs. 11). Similar observations have been made for a large number of catalytic asymmetric reactions with these catalytic systems.[20] The alteration on the bite angles of different chiral ligands has a considerable influence on the selectivity (entries 8, 10, 12, 13) and furthermore, when no substituents were present in the backbone of the bis(oxazoline) ligand, a significant decrease in enantioselectivity was observed (entries 10, 12).

After having established the optimal reaction conditions (Table 1, entries 4 and 14), the substrate scope of the Mukaiyama aldol reaction with a range of different pyridine-, isoquinoline-, and quinoline-*N*-oxide-2-carbaldehyde derivatives was performed (Table 2). Because the bis(oxazoline) ligands (4*R*,5*S*)-di-Ph-BOX (**3h**) and (*S*)-*t*Bu-BOX (**3a**) gave the aldol product with almost similar enantiomeric excess, we decided to use the more easily accessible (*S*)-*t*Bu-BOX (**3a**)[21] as the catalyst forming ligand.

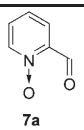
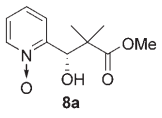
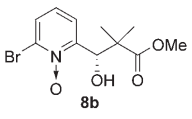
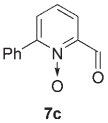
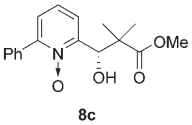
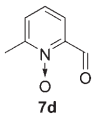
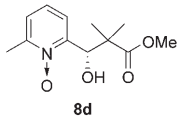
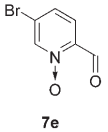
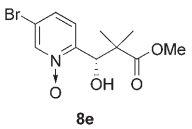
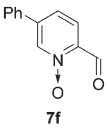
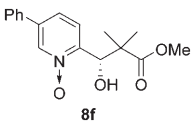
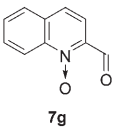
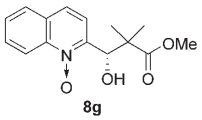
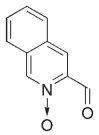
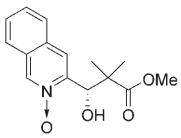
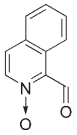
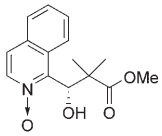
The reaction was found to be quite general with respect to the substrates tested; under the optimized reaction conditions the aldol products were obtained in good yields and excellent enantiomeric excesses. It appears from the results in Table 2 that the size of the substituent in position six of the pyridine ring has an influence on the enantioselectivity of the reaction. When the substrate had a substituent in this position such as phenyl (**7c**), methyl (**7d**), or in the case of 1-oxyquinoline-2-carbaldehyde (**7g**), the degree of the enantioinduction decreased slightly (Table 2, entries 3, 4, and 7). The use of the electron-withdrawing bromide atom in position six of 1-oxypyridine-2-carbaldehyde (**7b**) most likely made the chelate coordination to the [Cu(OTf)$_2$(**3a**)] complex more favorable, leading to the improvement in the enantiomeric excess of the aldol adduct (entry 2). Products with functional groups suitable for further manipulations, for example, bromide (compounds **8b** and **8e**) or ester functionalities were also obtained with excellent enantioselectivities (entries 2 and 5). The quinoline-*N*-oxide and isoquinoline-*N*-oxide derivatives worked as efficiently as pyridine-*N*-oxides and provided the aldol adducts in good to excellent yields and enantiomeric excesses. Even a significant enhancement in enantioselectivity arose when 2-oxyisoquinolinecarbaldehyde derivatives were used (entries 8 and 9). On the other hand, the reaction of **7g** catalyzed by [Cu(OTf)$_2$(**3a**)] gave the aldol product **8g** with only 35 % *ee*. However, the optical purity could be greatly enhanced to 85 % *ee* by using the [Zn(OTf)$_2$(**3h**)] instead of the [Cu(OTf)$_2$(**3a**)] complex (entry 7). Substrates with the substituent pointing away from the coordination site gave enantiomerically pure aldol adducts (entries 6, 8, and 9).

Due to the easy accessibility and high enantiomeric excess obtained, the importance of, for example, compound **8b** should be mentioned as these molecules, and their possible derivatives, are promising building blocks for construction of chiral C_2-symmetric 6,6′-bis(1-hydroxyalkyl)-2,2′-bipyridine-*N,N*-dioxide ligands with wide applications in asymmetric catalysis.[22]

After establishing the substrate scope of the reaction with compound **2a**, we studied the reaction of several 2-monosubstituted ketene silyl acetals **2b**–**d** with different pyridine- and isoquinoline-*N*-oxide-carbaldehyde derivatives (**7a**,**e**,**h**,**i**) using the optimized reaction conditions. The reaction with these enolates led to branched 2-(1-hydroxyalkyl)- and 2-(*anti*-1,2-dihydroxyalkyl)pyridine derivatives. The results are summarized in Table 3.

Interestingly, the reaction favored the formation of the *anti*-diol with good diastereoselectivity and excellent enan-

Table 2. Catalytic enantioselective Mukaiyama aldol reaction with different pyridine-2-carbaldehyde *N*-oxide derivatives **7a**–**i**.[a]

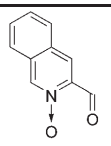
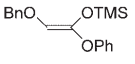
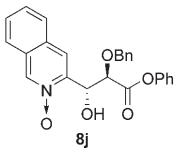
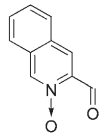
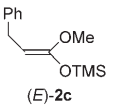
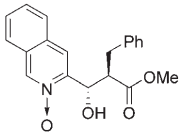
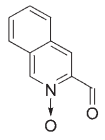
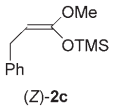
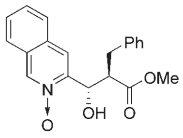
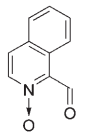
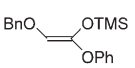
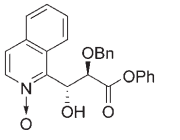
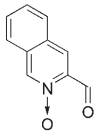
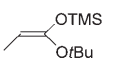
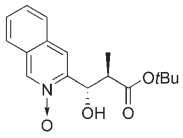
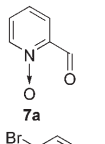
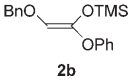
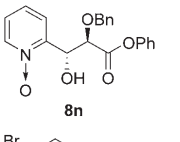
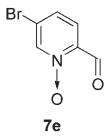
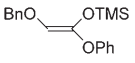
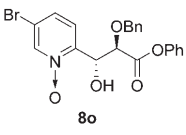
	Substrate	Product	Yield [%][b]	*ee* [%][c]
1	 **7a**	 **8a**	79	93
2[d]	 **7b**	 **8b**	92	96
3	 **7c**	 **8c**	64	77
4	 **7d**	 **8d**	78	81
5	 **7e**	 **8e**	72	93
6	 **7f**	 **8f**	84	>99
7[e]	 **7g**	 **8g**	90	85
8	 **7h**	 **8h**	89	>99
9	 **7i**	 **8i**	84	97

[a] Reactions performed in CH_2Cl_2 at −40 °C in the presence of 10 mol% [Cu(OTf)$_2$(**3a**)], all reactions gave full conversion. [b] Yield of isolated product. [c] Enantiomeric excess measured by chiral stationary phase HPLC. [d] Compound **8b** was also prepared on a 1 mmol scale under the optimized conditions with similar results (98% yield, 94% *ee*). [e] With (*S*)-**3h**-Zn(OTf)$_2$. With the [Cu(OTf)$_2$(**3a**)] complex the enantioselectivity decreased to 35% *ee*.

tiomeric excess. The *anti*-diastereoselectivity obtained for the present reactions is in contrast to the *syn*-diastereoselectivity obtained by Evans et al.,[15b] for the aldol reaction of methyl pyruvate with enolsilanes catalyzed by [Cu(OTf)$_2$-(**3a**)], and by Kobayashi et al., for the aldol reaction between aldehydes and enolsilanes catalyzed by Cu(OTf)$_2$/bis(oxazoline) complexes in aqueous media,[17] while it is in agreement with the results obtained for the aldol reaction of benzyloxyacetaldehyde with enolsilanes catalyzed by the same chiral complex.[4b] The best result was obtained with the enolate derived from the benzyloxyacetic acid phenyl ester (**2b**)[23] and isoquinoline-*N*-oxide-2-carbaldehyde derivative **7h**. In this case, the *anti*-adduct **8j** was obtained in good yield and with a high level of stereocontrol (*anti*/*syn* 12:1, *anti* 99% *ee*, Table 3, entry 1). An exchange of the counterion from triflate to hexafluoroantimonate by using [Cu(SbF$_6$)$_2$(**3a**)] as the catalyst gave the *anti*-aldol adduct with slightly lower diastereoselectivity and the same enantioselectivity (*anti*/*syn* 5:1, *anti* 99% *ee*, 71% yield). The absolute configuration of the major diastereomer was found to be independent of the counterion of the chiral catalyst, indicating that the counterion is probably not coordinated to the catalyst during the enantioselective step. The enolate derived from methyl 3-phenylpropionate (**2c**) also underwent a highly enantioselective reaction; however, the diastereoselectivity decreased (*anti*/*syn* 5:1 for the enolate (*E*)-**2c** and *anti*/*syn* 3:1 for the enolate (*Z*)-**2c**, entries 2, 3 vs. 1). Furthermore, it was observed that the silyl enolates (*E*)- and (*Z*)-**2c** gave both the aldol adduct with *anti*-diastereoselectivity, irrespective of the geometry of the enolsilane (entries 2 and 3). The reaction between **7i** and **2b** proceeded also with excellent enantioselectivity (99% *ee*) for the major diastereomer, while the minor diastereomer was formed in 90% *ee* (entry 4). Finally, the reaction of the enolsilane **2b** with **7a** and **7e** gave the aldol adducts **8n** and **8o**, respectively, with good diastereo- and excellent enantioselectivities (entries 6 and 7). It should be mentioned that the diastereomeric mixtures were easily separated by column chromatography.

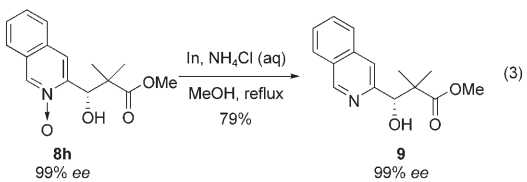
An important aspect of the present chemistry is that the optically active *N*-oxide adducts obtained can easily be deoxygenated to the corresponding amines without detectable

Table 3. Catalytic diastereo- and enantioselective Mukaiyama aldol reaction of pyridine-, isoquinoline-, and quinoline-*N*-oxide-2-carbaldehyde derivatives **7a**,**e**,**h**,**i** and enolsilanes **2b**–**d**.[a]

	Substrate	Enolate	Product	Yield [%][b]	*anti/syn*	*ee* [%][c]
1[d]	 **7h**	 **2b**	 **8j**	91	12:1	99:n.d.
2	 **7h**	 (*E*)-**2c**	 **8k**	96	5:1	99:98
3	 **7h**	 (*Z*)-**2c**	 **8k**	97	3:1	99:99
4	 **7i**	 **2b**	 **8l**	65	2.5:1	99:90
5	 **7h**	 **2d**	 **8m**	97	3:1	88:66
6	 **7a**	 **2b**	 **8n**	75	4:1	99:n.d.
7	 **7e**	 **2b**	 **8o**	88	5:1	99:n.d.

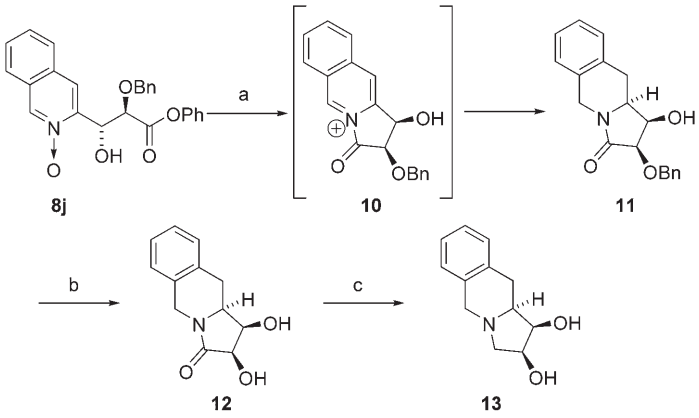
[a] Reactions performed in CH_2Cl_2 at −40 °C in the presence of 10 mol % [$Cu(OTf)_2$(**3a**)], all reactions give full conversion. [b] Yield of isolated product. [c] Enantiomeric excess measured by chiral stationary phase HPLC. [d] Compound **8j** was also prepared on a 2 mmol scale under the optimized conditions with similar results (82 % yield, *anti*/*syn* 10:1, *anti* 99 % *ee*).

loss of optical activity [Eq. (3)]. For instance, the optically active isoquinoline *N*-oxide adduct **8h** was deoxygenated by using 1.1 equivalents of indium metal in neutral aqueous media affording **9** in 79 % yield maintaining the *ee* of 99 %.[24]



8h 99% *ee* **9** 99% *ee*

Since polyhydroxylated indolizine alkaloids display interesting biological activity, intense efforts have been made very recently to synthesize these molecules, or their nonnatural analogues, in their optically active form.[25] By using the methodology developed for the synthesis of 2-(1-hydroxyalkyl)- and 2-(*anti*-1,2-dihydroxyalkyl)pyridine derivatives so far and due to the high diastereo- and enatioselectivities observed in the synthesis of, for example, compound **8j**, we decided to synthesize the nonnatural, but biologically interesting and optically active (1*R*,2*S*,10a*S*)-1,2-dihydroxy-1,2,3,5,10,10a-hexahydrobenzo[*f*]indolizine (**13**) in a stereocontrolled manner (Scheme 3). Starting from the Mukaiyama aldol adduct **8j**, compound **11** was obtained upon treatment with ammonium formate as reducing agent[26] in moderate 54 % yield and high diastereoselectivity (d.r. 7:1). To explain the formation of compound **11** and the high diastereoselectivity observed in the reduction of the pyridine ring



Scheme 3. Synthesis of **13**: a) 10% Pd/C, **8j**, NH_4CO_2H (5 equiv), *i*PrOH, RT, overnight (54%). b) **11**, CF_3CO_2H (cat.), 10% Pd/C, MeOH, RT, 16 h (98%). c) 1. **12**, $BH_3{\cdot}Me_2S$ (1.2 equiv), THF, 16 h; 2. EtOH, 5 h (71%).

compared with other examples reported in the literature for similar transformations, we propose a stepwise mechanism involving first the reduction of the *N*-oxide and subsequent intramolecular cyclization affording a rigid chiral pyridinium ring intermediate **10**, which is then activated toward hydrogenation by ammonium formate from the less hindered side of the molecule.[27] We were pleased to find that the major diastereoisomer was easily isolated as a white solid by washing the crude reaction mixture with EtOAc. The O-debenzylation of compound **11** with H_2 over Pd/C carried out in MeOH and CF_3CO_2H (cat.) gave **12** in quantitative yield. Finally, the reduction of **12** with $BH_3{\cdot}Me_2S$ in THF furnished **13** in 71% yield.

The absolute and relative configurations of the new formed stereogenic centers were established, assuming a uniform reaction mechanism, by a single-crystal X-ray crystallographic analysis of the adducts **8b**, **8n**, and **8o** (see Figure 1), as well as by chemical correlation with previously reported compound (*ent*)-**13**.[28]

Figure 1. X-ray crystallographic structure of **8o**.

For the mechanistic considerations, we propose that both the oxygen atoms of the aldehyde and *N*-oxide in the 1-oxypyridin-2-ylcarbaldehyde derivative coordinates to the Cu^{II} center in a bidentate fashion.[29] This leads to an square-planar distorted intermediate in which the *Si* face of the reacting carbonyl functionality is available for approach of the enolsilane, as the *Re* face is shielded by the *tert*-butyl group of the chiral bis(oxazoline) ligand (Figure 2, left). To account for the diastereoselectivity of the reaction, the R′

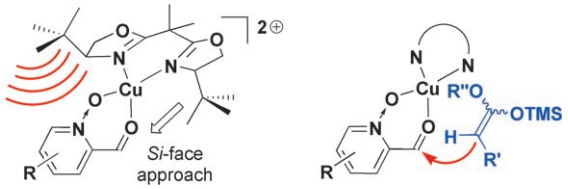


Figure 2. Proposed intermediate to the left and the diastereoselective approach of the enolsilane to the *Si*-face of the carbonyl (from the top) to the right.

group at the reacting carbon atom in the enolsilane has to point away from the *tert*-butyl group in the chiral bis(oxazoline) ligand in order to minimize steric repulsions, as outlined to the right in Figure 2.

In summary, we have developed a new catalytic asymmetric Mukaiyama aldol addition of enolsilanes to 1-oxypyridine-2-carbaldehyde derivatives catalyzed by a chiral [$Cu(OTf)_2$(**3a**)] complex affording optically active 2-(hydroxyalkyl)pyridine derivatives in good diastereo- and excellent enantioselectivities. The scope and potential of the reaction is demonstrated for a variety of different substrates and reagents. It was shown that a simple oxidation of the pyridine ring provides a suitable electronic environment for an optimal bidentate coordination with the chiral metal complex to give high diastereo- and enantioselectivities. The scope of the method was demonstrated by synthetic transformations: the deoxygenation of the *N*-oxide functionality without loss of optically activity and the total synthesis, in a stereocontrolled way, of a biologically important hydroxylated indolizine alkaloid derivative.

Experimental Section

General: The ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$ ppm) for ^1H NMR spectra and relative to the central $CDCl_3$ resonance ($\delta = 77.0$ ppm) for ^{13}C NMR spectra. Purification of reaction products was carried out by flash chromatography (FC) using silica gel 60 (230–400 mesh from Merck). The enantiomeric excess (*ee*) of the products was determined by HPLC using a Daicel Chiralpak AD and OD columns. Optical rotation was measured on a Perkin–Elmer 241 polarimeter.

Materials: Bis(oxazoline) ligands were prepared by the literature procedures.[13a] Commercially available starting materials were used without further purification. Solvents were distilled prior to use: CH_2Cl_2 was dried and distilled from CaH_2 and THF, *p*-dioxane, Et_2O, and toluene were distilled from sodium metal/benzophenone ketyl. Unless otherwise stated, all reactions were carried out in an inert atmosphere of Ar and in oven dried glassware.

General procedure for catalytic asymmetric Mukaiyama aldol reactions of aldehydes: $Cu(OTf)_2$ (25 μmol) and the 2,2′-isopropylidinenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (26 μmol) were stirred and heated under vacuum in a oven dried Schlenk tube for 1 h. The tube was filled with N_2 and dry

CH_2Cl_2 (1.5 mL) was added. The resulting mixture was stirred for 30 min and after this period the solution was cooled to −40 °C. A solution of *N*-oxide carbaldehyde **7** (0.25 mmol) in dry CH_2Cl_2 (1 mL) was added slowly. The resulting solution was stirred for 1 h at −40 °C and after this period the solution of silyl enolate **2** (0.25 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise. After 16–20 h the reaction mixture was filtered trough a plug of silica using EtOAc or EtOAc/EtOH 1:1 mixture as the eluent. The evaporation of solvents gave the crude product, which was treated with TBAF (1 equiv) in THF (10 mL) to remove the occasionally formed TMS protection of the alcohol group in the product. The pure compound was obtained after purification by FC in good to excellent yields.

(1-Oxypyridin-2-yl)methanol (6): Pyridin-2-ylmethanol (70.5 mmol, 6.8 mL) was dissolved in distilled $CHCl_3$ (30 mL). This solution was added dropwise to a solution of *m*-CPBA (14.6 g, 85 mmol) in $CHCl_3$ (60 mL) at RT. After the addition was complete the mixture was warmed to 65–70 °C and stirred for 20 h.[30] The reaction mixture was cooled to RT and the solvents were evaporated. The crude product was washed with Et_2O giving the pure product (7.68 g; 87 % yield) as white solid. ^{1}H NMR: $\delta = 8.25$ (d, $J = 6.4$ Hz, 1H), 7.38–7.27 (m, 2H), 4.81 ppm (s, 2H); ^{13}C NMR: $\delta = 150.1$, 139.3, 127.1, 124.6, 124.5, 61.0 ppm; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_6H_7NO_2Na$: 148.0375 $[M+Na]^+$; found: 148.0264.

1-Oxypyridine-2-carbaldehyde (7a): Activated MnO_2 (9 g, 103.5 mmol) was added to a solution of **6** (1.5 g, 12 mmol) in *p*-dioxane (100 mL) and the reaction mixture was heated at 90 °C for 1 h. The still hot mixture was filtrated trough Celite followed by washing with hot *p*-dioxane (100 mL) and hot EtOH (100 mL).[31] The combined filtrate and washings was evaporated under reduced pressure and the residue was purified by column chromatography (eluent EtOH/EtOAc 1:1). In the column some of the product reacted with EtOH forming corresponding acetal. The acetal groups were removed by treatment with Amberlyst®-15 in $CHCl_3$.[32] Filtration of Ambelyst®-15 and evaporation of solvent gave the pure product (0.75 g, 51 % yield) as pale yellow solid. ^{1}H NMR: $\delta = 10.63$ (s, 1H), 8.21 (d, $J = 6.4$, 1H), 7.82 (dd, $J = 2.0$, 7.8 Hz, 1H), 7.46 (ddd, $J =$ 2.0, 6.4, 7.8 Hz, 1H), 7.32 ppm (dd, $J = 7.8$, 7.8 Hz, 1H); ^{13}C NMR: $\delta =$ 185.5, 143.4, 140.1, 129.8, 125.2, 125.0 ppm; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_6H_5NO_2Na$: 146.0218 $[M+Na]^+$; found: 146.0145.

(6-Bromopyridin-2-yl)methanol:[33] 2,6-Dibromopyridine (10 g, 42.2 mmol) was dissolved in Et_2O (200 mL) and the resulting solution was cooled to −78 °C. A 1.6 M solution of *n*BuLi in hexane (42.2 mmol, 26.4 mL) was added dropwise to this cooled solution. After a period of 5 min, a mixture of DMF (4 mL) and Et_2O (20 mL) was slowly added to the solution of formed lithiate. The solution was allowed to warm to −10 °C, and the reaction was quenched with 10 % aqueous HCl until the mixture was acidic. The acidic mixture was stirred for 10 min at −10 °C and then basified with 10 % aqueous K_2CO_3. The aqueous layer was extracted three times with $CHCl_3$, and the organic layers were combined and dried with $MgSO_4$. Evaporation of solvent under reduced pressure gave a crude product that was dissolved without further purification in MeOH (150 mL). $NaBH_4$ (1.05 g, 27.8 mmol) was added to this stirred solution. The reaction mixture was stirred for 1 h at RT and then quenched with 10 % aqueous HCl and concentrated under reduced pressure. This concentrated solution was basified with 5 % aqueous K_2CO_3 and the aqueous layer was extracted three times with $CHCl_3$. The combined extractions were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (eluent EtOAc) gave 5.2 g (65 % overall yield) of pure alcohol as a white solid. ^{1}H NMR: $\delta =$ 7.46–7.15 (m, 3H), 4.63 (s, 2H), 3.20 ppm (s, 1H); ^{13}C NMR: $\delta = 161.4$, 141.2, 139.1, 126.5, 119.3, 64.1 ppm; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_6H_6BrNONa$: 209.9530 $[M+Na]^+$; found: 209.9537.

(6-Bromo-1-oxypyridin-2-yl)methanol: Oxidation procedure like for compound **6**. (6-Bromopyridin-2-yl)methanol (3.9 g, 20.36 mmol) was converted to the corresponding *N*-oxide with *m*-CPBA (4.3 g, 25 mmol) and purified by column chromatography (eluent EtOH/EtOAc 1:1) giving of the product (3.59 g, 85 % yield). ^{1}H NMR: $\delta = 7.66$ (dd, $J = 2.0$, 8.0 Hz, 1H), 7.36 (dd, $J = 2.0$, 7.6 Hz, 1H), 7.17 (dd, $J = 7.6$, 8.0 Hz, 1H), 4.82 ppm (s, 2H); ^{13}C NMR: $\delta = 151.6$, 133.4, 129.6, 126.5, 123.3, 61.8 ppm; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_6H_6BrNO_2Na$: 225.9480 $[M+Na]^+$; found: 225.9522.

6-Bromo-1-oxypyridine-2-carbaldehyde (7b): The same procedure above described for **7a** was employed. (6-Bromo-1-oxypyridin-2-yl)methanol (2.45 g, 12 mmol) was treated with MnO_2 (9 g, 103 mmol). Purification by column chromatography (eluent EtOAc) gave 1.48 g (61 % yield) of the pure product. ^{1}H NMR: $\delta = 10.60$ (s, 1H), 7.86 (dd, $J = 2.0$, 8.0 Hz, 1H), 7.79 (dd, $J = 2.0$, 8.0 Hz, 1H), 7.19 ppm (dd, $J = 8.0$, 8.0 Hz, 1H); ^{13}C NMR: $\delta = 185.4$, 144.7, 134.5, 134.0, 125.8, 124.3 ppm; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_6H_4BrNO_2Na$: 223.9323 $[M+Na]^+$; found: 223.9388.

2-Bromo-6-[1,3]dioxolan-2-ylpyridine: 6-Bromopyridine-2-carbaldehyde[33] (7.38 g, 39.7 mmol) and ethylene glycol (3.6 mL, 68 mmol) were dissolved in benzene (150 mL). *p*-TsOH (370 mg, 1.94 mmol) was added and the reaction mixture was refluxed under Dean–Stark conditions for 16 h and then quenched with 1 % aqueous Na_2CO_3 solution. The two phases were separated and the aqueous phase was extracted twice with $CHCl_3$. The combined organic phases were dried with anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by column chromatography (eluent EtOAc/hexane 1:1) giving the product (7.08 g, 78 % yield) as brown oil. ^{1}H NMR: $\delta = 7.58$ (dd, $J = 7.6$, 7.6 Hz), 7.47 (dd, $J = 2.0$, 7.4 Hz, 1H), 7.44 (dd, $J = 2.0$, 8.0 Hz, 1H), 5.77 (s, 1H), 4.12 (m, 2H), 4.02 ppm (m, 2H); ^{13}C NMR: $\delta = 158.4$, 141.5, 139.0, 128.4, 119.3, 102.6, 65.5 ppm; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_8H_8BrNO_2Na$: 251.9636 $[M+Na]^+$; found: 251.9644.

2-[1,3]Dioxolan-2-yl-6-phenylpyridine: 2-Bromo-6-[1,3]dioxolan-2-ylpyridine (3 g, 16.1 mmol), phenylboronic acid (2.95 g, 24.2 mmol, 1.5 equiv), aqueous Na_2CO_3 (2 M, 16 mL), THF (60 mL), and $[Pd(PPh_3)_4]$ (0.93 g, 0.805 mmol) were degassed at RT by N_2. Afterwards the resulting mixture was stirred at 60 °C for 72 h. The cooled solution was poured in H_2O (150 mL) and the product was extracted from the water phase three times with $CHCl_3$. The organic phase was then dried with anhydrous $MgSO_4$. Evaporation of solvents gave the crude product, which was purified by column chromatography (eluent EtOAc/hexane 1:7) giving 1.86 g (51 % yield) of product as viscous oil. ^{1}H NMR: $\delta = 8.03$ (dd, $J = 7.2$ Hz, 2H), 7.80 (dd, $J = 7.6$, 7.6 Hz, 2H), 7.50–7.39 (m, 4H), 5.95 (s, 1H), 4.25–4.10 ppm (m, 4H). The product was used directly to the preparation of 2-[1,3]dioxolan-2-yl-6-phenylpyridine 1-oxide, without further characterization.

2-[1,3]Dioxolan-2-yl-6-phenylpyridine 1-oxide: Oxidation procedure similar to that described for compound **6**. 2-[1,3]Dioxolan-2-yl-6-phenylpyridine (1.86 g, 8.18 mmol) was converted to the corresponding *N*-oxide by *m*-CPBA (2.89 g, 16.74 mmol) at RT for 16 h. Evaporation of the solvent under reduced pressure gave the product (1.55 g, 78 % yield) as yellow solid, which was used as such in the next step.

1-Oxy-6-phenylpyridine-2-carbaldehyde (7c): 2-[1,3]Dioxolan-2-yl-6-phenylpyridine 1-oxide (1.55 g, 6.38 mmol) was dissolved in 20 % HCl (60 mL) and the resulting solution was heated at 110 °C for 30 min. After this period the cooled reaction mixture was treated with solid $NaHCO_3$ until neutralized. The product was extracted from the aqueous phase with $CHCl_3$. The organic phase was dried with anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. Deprotection gave the pure product as yellow solid (1.05 g, 83 % yield). ^{1}H NMR: $\delta = 10.69$ (s, 1H), 7.82–7.76 (m, 3H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.54–7.49 (m, 3H), 7.38–7.34 ppm (m, 1H); ^{13}C NMR: $\delta = 186.5$, 150.3, 144.2, 131.4, 131.2, 129.2, 128.4, 124.8, 124.3 ppm; HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{12}H_9NO_2Na$: 222.0531 $[M+Na]^+$; found: 222.0529.

2-[1,3]Dioxolan-2-yl-6-methylpyridine: 6-Methylpyridine-2-carbaldehyde (3.37 g, 27.8 mmol) and ethylene glycol (2.5 mL, 41.7 mmol) were dissolved in benzene. *p*-TsOH (225 mg, 1.2 mmol) was added and the reaction mixture was refluxed under Dean–Stark conditions for 16 h and afterwards quenched with 1 % Na_2CO_3 aqueous solution. The two phases were separated and the aqueous phase was extracted twice with $CHCl_3$. The combined organic phases were dried with anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by column chromatography (eluent EtOAc/hexane 1:2). Yield 2.84 g (62 %); ^{1}H NMR: $\delta = 7.59$ (dd, $J = 7.6$, 7.6 Hz, 1H), 7.32 (d, $J = 7.6$ Hz, 1H), 7.11 (d, $J = 7.6$ Hz, 1H), 5.78 (s, 1H), 4.16–4.00 (m,

4H), 2.55 ppm (s, 3H); ^{13}C NMR: δ=158.1, 156.1, 136.9, 123.5, 117.2, 103.6, 65.4, 24.3 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_9H_{11}NO_2Na$: 188.0688 $[M+Na]^+$; found: 188.0686.

2-[1,3]Dioxolan-2-yl-6-methylpyridine 1-oxide: The same procedure described above for **6** was employed. 2-[1,3]Dioxolan-2-yl-6-methylpyridine (2.84 g, 17.19 mmol) was converted to the corresponding *N*-oxide with *m*-CPBA (5.77 g, 33.48 mmol) and purified by column chromatography (eluent EtOAc) giving the product (0.94 g, 30% yield) as white solid. ^{1}H NMR: δ=7.44 (dd, J=2.0, 8.0 Hz, 1H), 7.26 (dd, J=2.0, 7.6 Hz, 1H), 7.17 (dd, J=7.6, 8.0 Hz, 1H), 6.42 (s, 1H), 4.10 (s, 4H), 2.53 ppm (s, 3H); ^{13}C NMR: δ=149.6, 147.3, 126.2, 124.5, 121.0, 97.7, 65.3, 17.6 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_9H_{11}NO_3Na$: 204.0637 $[M+Na]^+$; found: 204.0639.

6-Methyl-1-oxypyridine-2-carbaldehyde (7d): The same deprotection procedure was used as described for the preparation of **7c**. 2-[1,3]Dioxolan-2-yl-6-methylpyridine 1-oxide (0.94 g, 5.2 mmol) was converted to the corresponding aldehyde by treatment with 20% aqueous HCl (50 mL). Yield 0.7 g (98%); ^{1}H NMR: δ=10.67 (s, 1H), 7.70 (dd, J=2.0, 7.8 Hz, 1H), 7.45 (dd, J=2.0, 7.8 Hz, 1H), 7.22 (dd, J=7.8, 7.8 Hz, 1H), 2.53 ppm (s, 3H); ^{13}C NMR: δ=186.0, 149.7, 143.1, 130.1, 124.0, 122.8, 16.9 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_7H_7NO_2Na$: 160.0374 $[M+Na]^+$; found: 160.0373.

(5-Bromopyridin-2-yl)methanol:[34] A 1.6 M solution of *n*BuLi in hexane (25.1 mmol, 15.7 mL) was added dropwise to a solution of 2,5-dibromopyridine (5 g, 21.1 mmol) in toluene (200 mL) at −78 °C. After 2 h of stirring a mixture of DMF (2 mL) and toluene (5 mL) was added, and the solution was stirred for 1 h at −78 °C and then warmed to −10 °C. The reaction was quenched with saturated NH_4Cl solution and the mixture was allowed to reach RT. The two phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic phases were evaporated to dryness to give 5-bromo-pyridine-2-carbaldehyde (2.61 g, 5.52 mmol, yield 66%). The crude product obtained was dissolved in EtOH (50 mL) and $NaBH_4$ (0.21 g, 5.55 mmol) was added to this solution. The reaction mixture was stirred for 1 h at RT and then quenched with 10% aqueous HCl and concentrated under reduced pressure. This concentrated solution was basified with 5% aqueous K_2CO_3 and the aqueous layer was extracted three times with $CHCl_3$. The combined extractions were dried with anhydrous $MgSO_4$ and were evaporated under reduced pressure giving the product (1.01 g, 64% overall yield). ^{1}H NMR: δ=8.63 (s, 1H), 7.82 (d, J=8.2 Hz, 1H), 7.20 (d, J=8.4 Hz, 1H), 4.73 ppm (s, 2H). The product was used directly in the preparation of (5-bromo-1-oxypyridin-2-yl)methanol, without further purification.

(5-Bromo-1-oxypyridin-2-yl)methanol: An oxidation procedure similar to that used for compound **6** was used. (5-Bromo-pyridin-2-yl)methanol (1.01 g, 5.38 mmol) was converted to the corresponding *N*-oxide with *m*-CPBA (1.48 g, 8.60 mmol) and purified by washing with Et_2O giving the pure product (0.93 g, 85% yield) as a white solid. ^{1}H NMR: δ=8.39 (s, 1H), 7.47 (d, J=8.4 Hz, 1H), 7.27 (d, J=9.2 Hz, 1H), 4.76 ppm (s, 2H); ^{13}C NMR: δ=149.0, 140.7, 129.8, 124.7, 119.0, 60.7 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_6H_5BrNO_2Na$: 225.9480 $[M+Na]^+$; found: 225.9476.

5-Bromo-1-oxypyridine-2-carbaldehyde (7e): The same procedure described above for **7a** was employed. (5-Bromo-1-oxypyridin-2-yl)methanol (0.74 g, 3.64 mmol) was treated with MnO_2 (3.0 g, 34.5 mmol). Purification by column chromatography (eluent EtOAc) gave the product (0.49 g, 67% yield) as pale yellow solid. ^{1}H NMR: δ=10.43 (s, 1H), 8.27 (s, 1H), 7.58 (d, J=8.4 Hz, 1H), 7.36 ppm (d, J=8.4 Hz, 1H); ^{13}C NMR: δ=184.7, 141.6, 133.0, 128.6, 125.8, 125.5 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_6H_4BrNO_2Na$: 223.9323 $[M+Na]^+$; found: 223.9326.

2-[1,3]Dioxolan-2-yl-5-phenylpyridine: 5-Bromopyridine-2-carbaldehyde (0.81 g, 4.38 mmol) and ethylene glycol (0.39 mL, 7.4 mmol) were dissolved in toluene (50 mL). *p*-TsOH (41 mg, 0.21 mmol) was added and the reaction mixture was refluxed under Dean–Stark conditions for 16 h. Afterwards the reaction mixture was neutralized with 1% aqueous Na_2CO_3. Two phases were separated, and the aqueous phase was extracted twice with $CHCl_3$. Combined organic phases were dried with anhydrous $MgSO_4$ and the evaporation of solvents gave the crude product as dark oil. The crude product (1.0 g, 4.6 mmol), phenylboronic acid (1.11 g, 9.14 mmol, 1.5 equiv), Na_2CO_3 (2 M (aq.), 2.5 mL), TFH (20 mL) and [Pd-(PPh_3)$_4$] (0.26 g, 0.23 mmol) were degassed by N_2. The resulting mixture was stirred at 60 °C for 20 h. The cooled solution was poured in water (100 mL) and the product was extracted from the water phase three times with $CHCl_3$. The organic phases were dried with anhydrous $MgSO_4$. Evaporation of solvent gave the crude product, which was purified by column chromatography (eluent EtOAc/hexane 1:6). Overall yield 0.70 g (71%); ^{1}H NMR: δ=8.85 (s, 1H), 7.93 (d, J=8.0 Hz, 1H), 7.62–7.40 (m, 6H), 5.93 (s, 1H), 4.23–4.07 ppm (m, 4H); ^{13}C NMR: δ=155.3, 147.4, 137.0, 136.5, 134.7, 128.7, 127.8, 126.8, 120.3, 103.1, 65.2 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{14}H_{13}NO_2Na$: 250.0839 $[M+Na]^+$; found: 250.0829.

2-[1,3]Dioxolan-2-yl-5-phenylpyridine 1-oxide: The same procedure described above for **6** was employed. 2-[1,3]Dioxolan-2-yl-5-phenylpyridine (0.73 g, 3.23 mmol) was converted to the corresponding *N*-oxide with *m*-CPBA (1.11 g, 6.46 mmol) and purified by column chromatography (eluent EtOAc) giving the product (0.63 g, 80% yield), which was directly used for the preparation of compound **7f**.

1-Oxy-5-phenylpyridine-2-carbaldehyde (7f): A similar deprotection procedure to that described for the preparation of compound **7c** was used. 2-[1,3]Dioxolan-2-yl-5-phenylpyridine 1-oxide (0.63 g, 2.59 mmol) was converted to the corresponding aldehyde by treatment with 20% aqueous HCl (30 mL). The crude product was washed with Et_2O to give the pure product as yellow solid. Yield 0.25 g (48%); ^{1}H NMR: δ=10.67 (s, 1H), 8.47 (s, 1H), 7.89 (d, J=8.4 Hz, 1H), 7.60–7.52 ppm (m, 6H); ^{13}C NMR: δ=185.5, 144.0, 141.9, 138.2, 134.2, 130.2, 129.5, 127.0, 125.4, 123.8 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_9NO_2Na$: 222.0531 $[M+Na]^+$; found: 222.0529.

2-[1,3]Dioxolan-2-ylquinoline: A solution of quinoline-2-carbaldehyde (1.57 g, 10 mmol), ethylene glycol (1.2 mL, 22.5 mmol), and *p*-TsOH (100 mg) in benzene (50 mL) was refluxed overnight under Dean–Stark conditions. The solution was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by column chromatography (eluent EtOAc/hexane 1:4) gave the product (1.34 g, 67% yield). ^{1}H NMR: δ=8.22 (d, J=8.4 Hz, 1H), 8.15 (d, J=8.8 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.73 (dd, J=7.2, 8.4 Hz, 1H), 7.66 (d, J=8.4 Hz, 1H), 7.56 (dd, J=7.2, 8.0 Hz, 1H), 5.99 (s, 1H), 4.26–4.12 ppm (m, 4H); ^{13}C NMR: δ=151.1, 147.4, 137.1, 129.6, 129.6, 128.3, 127.5, 126.9, 118.0, 104.1, 65.7 ppm; HRMS: m/z calcd for $C_{12}H_{11}NO_2Na$: 224.0682 $[M+Na]^+$; found: 224.0684.

2-[1,3]Dioxolan-2-ylquinoline 1-oxide: 2-[1,3]Dioxolan-2-ylquinoline (0.71 g, 3.51 mmol) in CH_2Cl_2 (40 mL) was treated with *m*-CPBA (0.99 g, 11.4 mmol) at 0 °C for 6 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with 5% aqueous NaOH and brine (2×50 mL), and dried with anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by column chromatography (eluent EtOAc) giving the pure product (0.63 g, 83% yield). ^{1}H NMR: δ=8.77 (d, J=8.4 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.75–7.70 (m, 2H), 7.62 (dd, J=7.6, 8.0 Hz, 1H), 7.58 (d, J=8.4 Hz, 1H), 6.59 (s, 1H), 4.14 ppm (s, 4H); ^{13}C NMR: δ=143.9, 141.6, 130.1, 129.9, 128.6, 127.8, 124.9, 119.5, 118.5, 97.8, 65.4 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{11}NO_3Na$: 240.0631 $[M+Na]^+$; found: 240.0629.

1-Oxyquinoline-2-carbaldehyde (7g): A suspension of 2-[1,3]dioxolan-2-ylquinoline 1-oxide (0.58 g, 2.67 mmol) in 20% aqueous HCl (25 mL) was stirred at 110 °C for 1 h. After this time, the reaction mixture was cooled to 0 °C and treated with $NaHCO_3$ until neutralized. The mixture was extracted with CH_2Cl_2 (6×15 mL) and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the product (0.43 g, 93% yield) as yellow solid. ^{1}H NMR: δ=10.83 (s, 1H), 8.75 (d, J=8.8 Hz, 1H), 7.88 (dd, J=1.0, 8.0 Hz, 1H), 7.82–7.72 (m, 3H), 7.70 ppm (d, J=8.0 Hz, 1H); ^{13}C NMR: δ=186.4, 132.0, 131.0, 130.9, 130.9, 128.4, 124.6, 119.9, 118.9 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{10}H_7NO_2Na$: 196.0369 $[M+Na]^+$; found: 196.0366.

3-[1,3]Dioxolan-2-ylisoquinoline:[35] This compound was prepared by the same procedure used as for the synthesis of 2-[1,3]dioxolan-2-ylquinoline. The mixture of 3-[1,2]dioxan-3-ylisoquinoline (5.0 g, 31.9 mmol), ethylene glycol (4.4 mL, 78.0 mmol), and *p*-TsOH (200 mg) in benzene (200 mL) was refluxed overnight under Dean–Stark conditions giving the product (5.0 g, 80% yield). ^{1}H NMR: δ=9.28 (s, 1H), 7.98 (d, J=8.0 Hz, 1H),

7.88 (s, 1H), 7.85 (d, $J=8.0$ Hz, 1H), 7.70 (dd, $J=7.0$, 8.0 Hz, 1H), 7.62 (dd, $J=7.0$, 8.0 Hz, 1H), 6.07 (s, 1H), 4.26–4.12 ppm (m, 4H); ^{13}C NMR: $\delta=152.4$, 149.9, 135.6, 130.3, 128.4, 127.4, 127.3, 126.7, 117.3, 65.3; HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{11}NO_3Na$: 240.0631 $[M+Na]^+$; found: 224.0676.

3-[1,3]Dioxolan-2-ylisoquinoline 2-oxide: This compound was prepared by the same procedure used as for the synthesis of 2-[1,3]dioxolan-2-yl-quinoline 1-oxide. 3-[1,3]Dioxan-2-ylisoquinoline (4.3 g, 21.5 mmol) was treated with *m*-CPBA (5.56 g, 32.2 mmol) giving the corresponding *N*-oxide (4.3 g, 93% yield). ^{1}H NMR: $\delta=8.84$ (s, 1H), 7.99 (s, 1H), 7.82 (d, $J=7.2$ Hz, 1H), 7.72 (d, $J=8.4$ Hz, 1H), 7.65–7.55 (m, 2H), 6.53 (s, 1H), 4.17 ppm (s, 4H); ^{13}C NMR: $\delta=144.0$, 136.9, 129.5, 129.4, 128.9, 128.5, 127.1, 124.5, 121.8, 97.7, 65.5 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{11}NO_3Na$: 240.0631 $[M+Na]^+$; found: 240.0524.

2-Oxyisoquinoline-3-carbaldehyde (7h): A similar deprotection procedure as for 1-oxyquinoline-2-carbaldehyde was used. 3-[1,3]Dioxan-2-yl-isoquinoline 2-oxide (4.21 g, 19.3 mmol) was treated with 20% aqueous HCl (200 mL). Recrystallization from CH_2Cl_2 gave the product (2.21 g, 66% yield). ^{1}H NMR: $\delta=10.80$ (s, 1H), 8.75 (s, 1H), 8.30 (s, 1H), 6.93 (d, $J=8.0$ Hz, 1H), 7.94–7.63 ppm (m, 3H); ^{13}C NMR: $\delta=186.4$, 136.9, 131.9, 131.6, 129.7, 129.0, 127.9, 125.7, 124.9 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{10}H_7NO_2Na$: 196.0369 $[M+Na]^+$; found: 196.0366.

1-[1,3,5]Trioxan-2-ylisoquinoline 2-oxide: This compound was prepared by the same procedure used for the synthesis of 2-[1,3]dioxolan-2-yl-quinoline 1-oxide. 1-[1,3,5]Trioxan-2-ylisoquinoline[36] (0.93 g, 4.25 mmol) gave the corresponding *N*-oxide (1.0 g, 100% yield). ^{1}H NMR: $\delta=8.95$ (d, $J=8.8$ Hz, 1H), 8.12 (d, $J=7.2$ Hz, 1H), 7.74 (d, $J=8.0$ Hz, 1H), 7.70–7.57 (m, 3H), 7.47 (s, 1H), 5.48–5.44 ppm (m, 4H); ^{13}C NMR: $\delta=$ 136.1, 129.3, 129.2, 128.8, 128.0, 126.8, 125.5, 125.2, 96.4, 94.3 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{11}NO_4Na$: 256.0580 $[M+Na]^+$; found: 256.0579.

2-Oxyisoquinoline-1-carbaldehyde (7i): Compound **7i** (0.79 g, 88% yield) was obtained by the same procedure used for the synthesis of 1-oxy-quinoline-2-carbaldehyde, from 1-[1,3,5]trioxan-2-ylisoquinoline 2-oxide (1.2 g, 5.2 mmol). ^{1}H NMR: $\delta=10.81$ (s, 1H), 8.90 (d, $J=8.8$ Hz, 1H), 8.11 (d, $J=7.2$ Hz, 1H), 7.82 (d, $J=7.2$ Hz, 1H), 7.77 (d, $J=8.4$ Hz, 1H), 7.71 (dd, $J=8.4$, 8.8 Hz, 1H), 7.61 ppm (dd, $J=8.4$, 8.4 Hz, 1H); ^{13}C NMR: $\delta=188.5$, 137.0, 131.7, 129.0, 128.43, 128.36, 127.7, 127.1, 123.5 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{10}H_7NO_2Na$: 196.0369 $[M+Na]^+$; found: 196.0367.

Methyl (*S*)-3-hydroxy-2,2-dimethyl-3-(1-oxypyridin-2-yl)propionate (8a): This compound was prepared according to the general procedure described above. It was obtained after purification by flash chromatography (eluent EtOH/EtOAc 1:1) in 79% yield. ^{1}H NMR: $\delta=8.18$ (d, $J=6.4$ Hz, 1H), 7.35–7.23 (m, 3H), 5.09 (s, 1H), 3.69 (s, 3H), 1.29 (s, 3H), 1.30 ppm (s, 3H); ^{13}C NMR: $\delta=176.4$, 148.7, 140.2, 126.8, 126.8, 124.6, 76.7, 52.2, 48.9, 21.7, 21.7 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{11}H_{15}NO_4Na$: 248.0899 $[M+Na]^+$; found: 248.0901. The *ee* was determined by HPLC on a Daicel Chiralpack OD, hexane/*i*PrOH (90:10) as eluent, flow rate = 1.0 mL min^{-1}. $t_R=15.5$ (minor enantiomer), 18.9 min (major enantiomer). $[\alpha]_D^{25}=+61.6$ ($c=0.57$ in $CHCl_3$).

Methyl (*S*)-3-(6-bromo-1-oxypyridin-2-yl)-3-hydroxy-2,2-dimethylpropionate (8b): This compound was prepared according to the general procedure described above. It was obtained after purification by flash chromatography (eluent EtOAc) in 92% yield. ^{1}H NMR: $\delta=7.65$ (dd, $J=2.0$, 8.0 Hz, 1H), 7.26 (dd, $J=2.0$, 8.0 Hz, 1H), 7.15 (dd, $J=8.0$, 8.0 Hz, 1H), 6.39 (d, $J=8.8$ Hz, 1H), 5.13 (d, $J=8.8$ Hz, 1H), 3.69 (s, 3H), 1.31 (s, 3H), 1.29 ppm (s, 3H); ^{13}C NMR: $\delta=176.1$, 151.4, 133.8, 129.3, 125.9, 125.3, 76.0, 52.2, 48.6, 21.7, 21.6 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{11}H_{14}BrNO_4Na$: 326.0004 $[M+Na]^+$; found: 326.0007. The *ee* was determined by HPLC on a Daicel Chiralpack OD, hexane/*i*PrOH (90:10) as eluent, flow rate = 1.0 mL min^{-1}. $t_R=9.7$ (minor enantiomer), 12.8 min (major enantiomer); $[\alpha]_D^{25}=+37.02$ ($c=5.00$ in $CHCl_3$).

Methyl (*S*)-3-hydroxy-2,2-dimethyl-3-(1-oxy-6-phenylpyridin-2-yl)propionate (8c): This compound was prepared according to the general procedure described above. It was obtained after purification by flash chromatography (eluent EtOAc) in 64% yield. ^{1}H NMR: $\delta=7.71$–7.69 (m, 2H), 7.51–7.31 (m, 5H), 7.20 (d, $J=7.6$ Hz, 1H), 5.04 (s, 1H), 3.68 (s, 3H), 1.33 (s, 3H), 1.31 ppm (s, 3H); ^{13}C NMR: $\delta=176.3$, 150.3, 148.3, 132.3, 129.7, 129.3, 128.3, 126.2, 125.5, 79.0, 52.2, 49.0, 22.6, 21.9 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{17}H_{19}NO_4Na$: 324.1212 $[M+Na]^+$; found: 324.1215. The *ee* was determined by HPLC on a Daicel Chiralpack OD, hexane/*i*PrOH (90:10) as eluent, flow rate = 1.0 mL min^{-1}. $t_R=9.1$ (minor enantiomer), 12.9 min (major enantiomer). $[\alpha]_D^{25}=+32.1$ ($c=2.37$ in $CHCl_3$).

Methyl (*S*)-3-hydroxy-2,2-dimethyl-3-(6-methyl-1-oxypyridin-2-yl)propionate (8d): This compound was prepared according to the general procedure described above. It was obtained after purification by flash chromatography (eluent EtOAc) in 78% yield. ^{1}H NMR: $\delta=7.61$ (d, $J=9.2$ Hz, 1H), 7.25–7.18 (m, 2H), 7.09 (dd, $J=2.4$, 7.2 Hz, 1H), 4.99 (d, $J=9.2$ Hz, 1H), 3.67 (s, 3H), 2.49 (s, 3H), 1.30 (s, 3H), 1.28 ppm (s, 3H); ^{13}C NMR: $\delta=176.3$, 150.1, 147.6, 125.8, 125.2, 124.4, 79.0, 52.2, 49.2, 22.4, 21.8, 18.0 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{17}NO_4Na$: 262.1055 $[M+Na]^+$; found: 262.1055. The *ee* was determined by HPLC on a Daicel Chiralpack OD, hexane/*i*PrOH (90:10), flow rate = 1.0 mL min^{-1}. $t_R=8.6$ (minor enantiomer), 10.6 min (major enantiomer); $[\alpha]_D^{25}=+55.9$ ($c=0.69$ in $CHCl_3$).

Methyl (*S*)-3-(5-bromo-1-oxypyridin-2-yl)-3-hydroxy-2,2-dimethylpropionate (8e): This compound was prepared according to the general procedure described above. It was obtained after purification by flash chromatography (eluent EtOH/EtOAc 1:1) in 72% yield. ^{1}H NMR: $\delta=8.27$ (s, 1H), 7.41 (d, $J=8.6$ Hz, 1H), 7.18 (d, $J=8.8$ Hz, 1H), 6.23 (d, $J=8.4$ Hz, 1H), 5.15 (d, $J=8.4$ Hz, 1H), 3.69 (s, 3H), 1.27 (s, 3H), 1.26 ppm (s, 3H); ^{13}C NMR: $\delta=176.3$, 148.5, 141.2, 129.2, 126.8, 119.0, 75.5, 52.3, 48.7, 21.7, 21.5 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{11}H_{14}BrNO_4Na$: 326.0004 $[M+Na]^+$; found: 326.0007. The *ee* was determined by HPLC on a Daicel Chiralpack OD, hexane/*i*PrOH (90:10), flow rate = 1.0 mL min^{-1}. $t_R=8.9$ (minor enantiomer), 14.9 min (major enantiomer); $[\alpha]_D^{25}=+36.7$ ($c=2.30$ in $CHCl_3$).

Methyl (*S*)-3-hydroxy-2,2-dimethyl-3-(1-oxy-5-phenylpyridin-2-yl)propionate (8f): This compound was prepared according to the general procedure described above. It was obtained after purification by flash chromatography (eluent EtOH/EtOAc 1:1) in 84% yield. ^{1}H NMR: $\delta=8.41$ (s, 1H), 7.54–7.46 (m, 6H), 7.30 (d, $J=8.4$ Hz, 1H), 5.13 (s, 1H), 3.72 (s, 3H), 1.34 (s, 3H), 1.33 ppm (s, 3H); ^{13}C NMR: $\delta=176.4$, 146.5, 138.8, 138.4, 134.6, 129.4, 126.8, 125.3, 77.7, 52.3, 49.3, 22.0, 21.8 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{17}H_{19}NO_4Na$: 324.1212 $[M+Na]^+$; found: 324.1216. The *ee* was determined by HPLC on a Daicel Chiralpack AD, hexane/*i*PrOH (90:10), flow rate = 1.0 mL min^{-1}. $t_R=28.5$ (major enantiomer), 39.0 min (minor enantiomer); $[\alpha]_D^{25}=+46.3$ ($c=2.05$ in $CHCl_3$).

Methyl (*S*)-3-hydroxy-2,2-dimethyl-3-(1-oxyquinolin-2-yl)propionate (8g): This compound was prepared according to the general procedure described above. It was obtained after purification by flash chromatography (eluent hexane/EtOAc 1:2) in 90% yield. ^{1}H NMR: $\delta=8.66$ (d, $J=$ 8.8 Hz, 1H), 7.80–7.70 (m, 2H), 7.64 (dd, $J=7.6$, 7.6 Hz, 1H), 7.55 (d, $J=$ 8.8 Hz, 1H), 7.28 (d, $J=7.6$ Hz, 1H), 7.21 (d, $J=8.8$ Hz, 1H), 5.39 (d, $J=$ 7.2 Hz, 1H), 3.66 (s, 3H), 1.31 (s, 3H), 1.29 ppm (s, 3H); ^{13}C NMR: $\delta=$ 176.3, 146.5, 141.3, 130.8, 129.0, 128.7, 127.9, 126.0, 122.1, 119.4, 77.0, 52.2, 49.5, 22.0, 21.6 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{15}H_{17}NO_4Na$: 298.1050 $[M+Na]^+$; found: 298.1049. The *ee* was determined by HPLC on a Daicel Chiralpack OD, hexane/*i*PrOH (90:10) as eluent, flow rate = 1.0 mL min^{-1}. $t_R=10.8$ (minor enantiomer), 15.6 min (major enantiomer); $[\alpha]_D^{25}=+81$ ($c=0.47$ in $CHCl_3$).

Methyl (*S*)-3-hydroxy-2,2-dimethyl-3-(2-oxyisoquinolin-3-yl)propionate (8h): This compound was prepared according to the general procedure described above. It was obtained after purification by flash chromatography (eluent hexane/EtOAc 1:9) in 89% yield. ^{1}H NMR: $\delta=8.70$ (s, 1H), 7.73–7.67 (m, 2H), 7.62–7.55 (m, 3H), 7.10 (d, $J=8.8$ Hz, 1H), 5.28 (d, $J=8.8$ Hz, 1H), 3.69 (s, 3H), 1.32 (s, 3H), 1.31 ppm (s, 3H); ^{13}C NMR: $\delta=176.3$, 144.4, 137.2, 129.4, 129.2, 128.9, 127.9, 126.4, 124.5, 124.1, 76.8, 51.9, 48.7, 21.72, 21.66 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{15}H_{17}NO_4Na$: 298.1050 $[M+Na]^+$; found: 298.1063. The *ee* was determined by HPLC on a Daicel Chiralpack AD, hexane/*i*PrOH (80:20) as eluent, flow rate = 1.0 mL min^{-1}. $t_R=14.5$ (major enantiomer), 29.0 min (minor enantiomer); $[\alpha]_D^{25}=-8.3$ ($c=0.48$ in $CHCl_3$).

Methyl (*S*)-3-hydroxy-2,2-dimethyl-3-(2-oxyisoquinolin-1-yl)propionate (8i): This compound was prepared according to the general procedure described above. It was obtained after purification by flash chromatography using (eluent hexane/EtOAc 1:9) in 84% yield .^{1}H NMR: δ=8.46 (brs, 1H), 8.03 (d, J=7.5 Hz, 2H), 7.80 (d, J=7.5 Hz, 1H), 7.70–7.61 (m, 2H), 5.70 (d, J=10.8 Hz, 1H), 3.61 (s, 3H), 1.37 (s, 3H), 1.30 ppm (s, 3H); ^{13}C NMR: δ=175.9, 144.6, 136.8, 129.5, 129.4, 129.2, 128.4, 127.5, 123.8, 123.7, 75.2, 52.3, 49.8, 23.4, 22.8 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{15}H_{17}NO_4Na$: 298.1050 $[M+Na]^+$; found: 298.1064. The *ee* was determined by HPLC on a Daicel Chiralpack AD, hexane/*i*PrOH (90:10) as eluent, flow rate=1.0 mL min^{-1}. t_R=31.1 (major enantiomer), 85.9 min (minor enantiomer); $[\alpha]_D^{25}$=+101 (c=0.65 in $CHCl_3$).

Phenyl (*R*,*R*)-2-benzyloxy-3-hydroxy-3-(2-oxyisoquinolin-3-yl)propionate (8j): This compound was prepared according to the general procedure described above. It was obtained in 91% yield as a 12:1 d.r. mixture. The major diastereomer could be isolated pure in 80% yield with flash chromatography (eluent hexane/EtOAc 2:3). Major diastereomer: ^{1}H NMR: δ=8.71 (s, 1H), 7.75 (s, 1H), 7.65–7.57 (m, 2H), 7.50–7.47 (m, 2H), 7.23 (dd, J=8.0, 8.0 Hz, 2H), 7.12–7.10 (m, 6H), 6.96 (d, J=7.6 Hz, 2H), 6.38 (brs, 1H), 5.34 (d, J=6.6, 1H), 4.99 (d, J=6.6 Hz, 1H), 4.63 (d, J=11.5 Hz, 1H), 4.48 ppm (d, J=11.5 Hz, 1H); ^{13}C NMR: δ=169.1, 150.3, 143.6, 137.2, 136.6, 129.6, 129.3, 128.4, 128.2, 128.0, 127.8, 126.7, 125.8, 124.8, 124.2, 121.4, 78.7, 72.9, 72.6 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{25}H_{21}NO_5Na$: 438.1312 $[M+Na]^+$; found: 438.1322. The *ee* was determined by HPLC on a Daicel Chiralpack OD, hexane/*i*PrOH (95:5) as eluent, flow rate=1.0 mL min^{-1}. t_R=60.0 (minor enantiomer), 75.5 (major enantiomer); $[\alpha]_D^{25}$=−17.7 (c=0.52 in $CHCl_3$).

Methyl (*R*,*R*)-2-benzyl-3-hydroxy-3-(2-oxyisoquinolin-3-yl)-propionate (8k): This compound was prepared according to the general procedure described above. Obtained in 96% yield as a 5:1 d.r. mixture. The major diastereomer could be separated as a pure form by column chromatography (eluent hexane/EtOAc 1:4). Major diastereomer: ^{1}H NMR: δ=8.80 (s, 1H), 7.80–7.70 (m, 2H), 7.68 (s, 1H), 7.64–7.61 (m, 2H), 7.27–7.15 (m, 5H), 5.09 (d, J=8.8 Hz, 1H), 3.84 (ddd, J=4.0, 8.8, 10.2 Hz, 1H), 3.35 (dd, J=4.0, 13.6 Hz, 1H), 3.29 (s, 3H), 3.11 ppm (dd, J=10.2, 13.6 Hz, 1H); ^{13}C NMR: δ=174.1, 144.7, 138.6, 137.6, 129.8, 129.4, 128.9, 128.3, 126.8, 126.3, 124.9, 123.4, 73.0, 51.4, 50.9, 34.6 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{19}NO_4Na$: 360.120 $[M+Na]^+$; found: 360.1219. The *ee* was determined by HPLC on a Daicel Chiralpack AD, hexane/*i*PrOH (90:10) as eluent, flow rate=1.0 mL min^{-1}. t_R=54.5 (major enantiomer), 66.5 (minor enantiomer); $[\alpha]_D^{25}$=−71.1 (c=0.36 in $CHCl_3$).

Phenyl (*R*,*R*)-2-Benzyloxy-3-hydroxy-3-(2-oxyisoquinolin-1-yl)propionate (8l): This compound was prepared according to the general procedure described above. The major diastereomer could be separated as a pure form by column chromatography (eluent hexane/EtOAc 1:2). Major diastereomer: ^{1}H NMR: δ=8.26 (m, 1H), 8.05 (d, J=7.2 Hz, 1H), 7.83 (m, 1H), 7.68 (m, 3H), 7.41 (dd, J=7.6, 7.6 Hz, 2H), 7.16 (m, 6H), 6.78 (d, J=7.6 Hz, 2H), 5.92 (d, J=9.2 Hz, 1H), 5.02 (d, J=9.2 Hz, 1H), 4.55 (d, J=12.0 Hz, 1H), 4.31 ppm (d, J=12.0 Hz, 1H); ^{13}C NMR: δ=169.6, 150.6, 144.6, 136.3, 136.3, 129.6, 129.5, 129.4, 128.1, 127.7, 127.5, 127.0, 126.0, 124.5, 124.1, 121.6, 78.4, 72.8, 69.6 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{25}H_{21}NO_5Na$: 438.1217 $[M+Na]^+$; found: 438.1311. The *ee* was determined by HPLC on a Daicel Chiralpack AD, hexane/*i*PrOH (80:20) as eluent, flow rate=1.0 mL min^{-1}. t_R=72.1 (major enantiomer); $[\alpha]_D^{25}$=+73.5 (c=1.8 in $CHCl_3$).

***tert*-Butyl (*S*,*R*)-3-Hydroxy-2-methyl-3-(2-oxyisoquinolin-3-yl)propionate (8m)**: This compound was prepared according to the general procedure described above. It was obtained in 97% yield as a 3:1 d.r mixture. The major diastereomer could be separated as a pure form by column chromatography (eluent hexane/EtOAc 1:4). Major diastereomer: ^{1}H NMR: δ=8.78 (s, 1H), 7.78–7.71 (m, 3H), 7.62–7.58 (m, 2H), 5.73 (brs, 1H, OH), 5.14 (d, J=7.2 Hz, 1H), 3.40 (m, J=7.2 Hz, 1H), 1.27 (d, J=7.2 Hz, 3H), 1.26 ppm (s, 9H); ^{13}C NMR: δ=174.8, 145.9, 137.2, 129.6, 129.3, 129.2, 128.2, 126.7, 124.7, 123.2, 80.8, 72.5, 43.1, 27.8, 13.0 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{13}H_{21}NO_4Na$: 326.1363 $[M+Na]^+$; found: 326.1367. The *ee* was determined by HPLC on a Daicel Chiralpack AD, hexane/*i*PrOH (90:10) as eluent, flow rate=1.0 mL min^{-1}. t_R=24.9 (major enantiomer), 37.2 (minor enantiomer); $[\alpha]_D^{25}$=−19.0 (c=0.51 in $CHCl_3$).

Phenyl (*R*,*R*)-2-benzyloxy-3-hydroxy-3-(1-oxypyridin-2-yl)propionate (8n): This compound was prepared according to the general procedure described above. The major diastereomer could be separated as a pure form by column chromatography (eluent hexane/EtOAc 1:4). Major diastereomer: ^{1}H NMR: δ=8.22 (d, J=6.4 Hz, 1H), 7.50 (d, J=2.0 Hz, 1H), 7.48–7.20 (m, 10H), 7.06 (d, J=7.6 Hz, 2H), 5.23 (d, J=7.6 Hz, 1H), 4.98 (d, J=7.2 Hz, 1H), 4.72 (d, J=11.6 Hz, 1H), 4.56 ppm (d, J=11.6 Hz, 1H); ^{13}C NMR: δ=169.0, 150.4, 147.8, 139.7, 136.6, 129.4, 128.4, 128.1, 127.0, 126.6, 126.0, 125.0, 121.4, 77.9, 73.0, 72.9 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{19}NO_5Na$: 388.1161 $[M+Na]^+$; found: 388.1167. The *ee* was determined by HPLC on a Daicel Chiralpack AD, hexane/*i*PrOH (90:10) as eluent, flow rate=1.0 mL min^{-1}. t_R=49.3 (minor enantiomer), 70.4 min (major enantiomer); $[\alpha]_D^{25}$=+6.9 (c=1.90 in $CHCl_3$).

Phenyl (*R*,*R*)-2-benzyloxy-3-(5-bromo-1-oxypyridin-2-yl)-3-hydroxypropionate (8o): This compound was prepared according to the general procedure described above. The major diastereomer could be separated as a pure form by column chromatography (eluent hexane/EtOAc 1:4). Major diastereomer: ^{1}H NMR: δ=8.29 (s, 1H), 7.45–7.24 (m, 10H), 7.05 (d, J=8.8 Hz, 2H), 5.37 (d, J=8.0 Hz, 1H), 5.20 (dd, J=6.4, 8.0 Hz, 1H), 4.95 (d, J=6.4 Hz, 1H), 4.75 (d, J=11.6 Hz, 1H), 4.57 ppm (d, J=11.6 Hz, 1H); ^{13}C NMR: δ=168.7, 150.2, 147.1, 140.8, 136.5, 129.6, 129.4, 128.5, 128.3, 128.1, 126.3, 126.1, 121.3, 119.3, 77.5, 73.1, 72.0 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{18}BrNO_5Na$: 466.0266 $[M+Na]^+$; found: 466.0272. The *ee* was determined by HPLC on a Daicel Chiralpack OD, hexane/*i*PrOH (90:10) as eluent, flow rate=1.0 mL min^{-1}. t_R=16.2 (major enantiomer), 19.8 min (minor enantiomer); $[\alpha]_D^{25}$=−5.7 (c=2.40 in $CHCl_3$).

Methyl (*S*)-3-hydroxy-2,2-dimethyl-3-(isoquinolin-3-yl)propionate (9):[24] A mixture of compound **8h** (27 mg, 0.1 mmol), indium powder (14 mg, 0.11 mmol), and saturated NH_4Cl solution (0.3 mL) in MeOH (0.4 mL) was refluxed for 9 h. The reaction mixture was filtered through Celite with EtOAc (30 mL), washed with brine (2×5 mL), and dried with anhydrous Na_2SO_4. Purification by column chromatography (eluent hexane/EtOAc 1:1) gave 21 mg (79% yield) of the product. ^{1}H NMR: δ=9.19 (s, 1H), 7.97 (d, J=8.0 Hz, 1H), 7.80 (d, J=8.0 Hz, 1H), 7.70 (dd, J=7.2, 8.0 Hz, 1H), 7.60 (dd, J=7.2, 8.0 Hz, 1H), 7.55 (s, 1H), 5.07 (d, J=7.8 Hz, 1H), 4.58 (d, J=7.8 Hz, 1H), 3.74 (s, 3H), 1.19 (s, 3H), 1.17 ppm (s, 3H); ^{13}C NMR: δ=177.3, 151.6, 151.1, 135.8, 130.7, 128.1, 127.6, 127.3, 126.7, 118.5, 77.6, 51.9, 48.6, 21.4, 20.7 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{15}H_{17}NO_3Na$: 282.1101 $[M+Na]^+$; found: 282.1105. The *ee* was determined by HPLC on a Daicel Chiralpack AD, hexane/*i*PrOH (90:10) as eluent, flow rate=1.0 mL min^{-1}. t_R=19.4 (major enantiomer), 28.3 min (minor enantiomer); $[\alpha]_D^{25}$=−25.1 (c=0.39 in $CHCl_3$).

(1*S*,2*R*,10a*S*)-2-Benzyloxy-1-hydroxy-1,5,10,10a-tetrahydro-2*H*-pyrrolo-[1,2-*b*]isoquinolin-3-one (11):[26] Dry ammonium formate (80 mg) was added to a solution of substrate **8j** (50 mg, 0.12 mmol) and Pd/C 10% (20 mg) in anhydrous *i*PrOH (1.2 mL). The mixture was stirred overnight under N_2 atmosphere and the solution was filtered through Celite. The solvent was removed under reduced pressure and the resulting solid was washed with EtOAc (2 mL) to give compound **11** (20 mg, 54% yield). ^{1}H NMR: δ=7.44–7.33 (m, 5H), 7.22–7.15 (m, 4H), 5.08 (d, J=11.6 Hz, 1H), 4.87 (d, J=11.6 Hz, 1H), 4.79 (d, J=17.6 Hz, 1H), 4.40–4.34 (m, 2H),4.17 (d, J=5.2 Hz, 1H), 3.65 (ddd, J=4.0, 4.0, 11.6 Hz, 1H), 3.19 (dd, J=15.6 Hz, 1H), 2.81 ppm (dd, J=4.0, 15.6 Hz, 2H); ^{13}C NMR: δ=170.2, 136.8, 133.8, 130.9, 129.1, 128.6, 128.3, 126.9, 126.7, 77.3, 73.2, 67.2, 55.4, 42.5, 29.2 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{19}NO_3Na$: 332.1257 $[M+Na]^+$; found: 332.1262; $[\alpha]_D^{25}$=−27.0 (c=0.27 in $CHCl_3$).

(1*S*,2*R*,10a*S*)-1,2-Dihydroxy-1,5,10,10a-tetrahydro-2*H*-pyrrolo[1,2-*b*]isoquinolin-3-one (12): A solution containing substrate **11** (26.8 mg, 0.086 mmol), two drops of CF_3CO_2H, and 10% Pd/C (3 mg) in MeOH (4 mL) was stirred under H_2 atmosphere at 15 bar overnight. After this time, the reaction mixture was filtered through Celite, the solvent was removed under reduced pressure and the residue purified by column chromatography (eluent hexane/EtOAc 1:9) to give the product (15.1 mg, 98% yield). ^{1}H NMR ([D$_4$]MeOH): δ=7.20–7.10 (m, 4H), 4.55 (d, J=17.4 Hz, 1H), 4.37–4.31 (m, 2H), 4.31 (d, J=17.4 Hz, 1H), 3.65 (ddd, J=

3.3, 4.0, 11.6 Hz, 1H), 3.07 (dd, J=11.6, 15.4 Hz, 1H), 2.75 ppm (dd, J=4.0, 15.4 Hz, 1H); ^{13}C NMR ([D$_4$]MeOH): δ=175.3, 135.5, 132.1, 130.1, 128.1, 127.8, 127.8, 73.5, 70.5, 57.0, 43.6, 29.9 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{13}NO_3Na$: 242.0788 $[M+Na]^+$; found: 242.0786; $[\alpha]_D^{25}$=−86.2 (c=0.38 in MeOH).

(1*R*,2*S*,10a*S*)-1,2-Dihydroxy-1,2,3,5,10,10a-hexahydrobenzo[*f*]indolizine (13): $BH_3{\cdot}Me_2S$ (0.08 mL, 0.8 mmol) was added to a solution of **12** (13 mg, 0.059 mmol) in THF (2 mL) at 0 °C. The mixture was stirred overnight, then EtOH (5 mL) was added slowly and the solution was refluxed for 5 h. After removal of the solvents, the crude mixture was treated with EtOH (3×5 mL). After evaporation of solvent under reduced pressure, the mixture was purified by column chromatography (eluent EtOH/EtOAc 1:9) to give the product (9.2 mg, 71 % yield). ^{1}H NMR: δ=7.25–7.13 (m, 3H), 7.04 (d, J=6.8 Hz), 4.34 (unresolved dd, 1H), 4.20 (unresolved dd, 1H), 4.08 (d, J=14.4 Hz, 1H), 3.39 (d, J=14.4 Hz, 1H), 3.18 (*t*, J=10.4 Hz, 1H), 3.13 (d, J=16.4 Hz, 1H), 2.80 (d, J=16.4 Hz, 1H), 2.50 (m, 1H), 2.43 ppm (m, 1H); ^{1}H NMR ([D$_6$]DMSO): δ=7.20–7.06 (m, 4H), 4.81 (br d, J=4.8 Hz, 1H), 4.50 (br s, 1H), 4.19 (unresolved q, 1H), 3.99 (*t*, J=5.2 Hz, 1H), 3.94 (d, J=14.6 Hz), 3.35 (br s, 1H), 3.27 (d, J=14.6 Hz, 1H), 3.04 (dd, J=11.6, 16.0 Hz, 1H), 2.97 (dd, J=0.8, 9.6 Hz, 1H), 2.63 (dd, J=3.6, 16.0 Hz, 1H), 2.40 (*t*, J=8.4 Hz, 1H), 2.33 ppm (br s, 1H); ^{13}C NMR ([D$_6$]DMSO): δ=134.8, 134.4, 128.9, 126.2, 126.0, 125.3, 70.6, 68.8, 63.4, 61.2, 55.0, 28.3 ppm; HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{15}NO_2Na$: 228.0995 $[M+Na]^+$; found: 228.0993; $[\alpha]_D^{25}$=−27.1 (c=0.25 in acetone).

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