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Application of novel enantiopure hydroxymethyl-substituted pyridine derivatives in asymmetric catalysis

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ABSTRACT

The synthetic modification of enantiopure hydroxymethyl-substituted pyridine derivatives leading to novel chiral ligands is described. A set of these pyridine derivatives was examined as ligands in asymmetric transformations such as enantioselective alkylations or alkynylations of aldehydes, the asymmetric copper-catalyzed Henry reaction and the asymmetric allylation of benzaldehyde with allyl(trichloro)silane. This first screening revealed that several of the pyridine derivatives prepared are effective ligands affording high yields and good enantioselectivities. The asymmetric alkylation of aldehydes with diethylzinc provided yields of up to 93% with an enantiomeric excess of up to 88%. The asymmetric Henry reaction was also efficiently catalyzed by one of the prepared ligands affording (*S*)-2-nitro-1-phenylethanol in 68% yield and with 70% *ee*.

1. Introduction

Pyridine derivatives constitute an important class of nitrogen-containing heterocycles since compounds featuring this nucleus often possess distinct biological activities.[1] Moreover, their ability to coordinate metal ions makes them ideal ligands for metal-catalyzed processes. In particular, pyridines with stereogenic side chains at the 2- and/or 6-positions find many applications in asymmetric metal-catalyzed transformations, the most prominent example being compounds bearing a 2,6-bisoxazoline-substituted pyridine core.[2] A second common motif are ligands possessing pyridine moieties with hydroxymethyl substituents at the 2- and/or 6-positions. Examples in which such structures are employed as ligands include the enantioselective alkylation and alkynylation of aldehydes[3] and the nickel-catalyzed conjugate addition of organozincs to α,β-unsaturated carbonyl compounds.[4] Phosphinites derived from hydroxymethyl-substituted pyridines are effective ligands for the asymmetric iridium-catalyzed hydrogenation of unfunctionalized olefins.[5] Typically, hydroxymethyl-substituted pyridines are prepared by either enantioselective reduction of the respective ketone precursors, by the addition of lithiated pyridine derivatives to chiral ketones, or by traditional resolution.

We recently introduced a novel concept for the preparation of hydroxymethyl-substituted pyridine derivatives, which is based on a NEt_3/TMSOTf-promoted cyclocondensation of substituted β-ketoenamides **3** (Scheme 1).[6] We found that β-ketoenamides derived from readily available enantiopure α-hydroxy carboxylic acids **1** and simple enaminoketones **2** smoothly provide the respective 4-pyridone derivatives **4** in good yields and high enantiomeric purity. In addition, the 4-hydroxy and the 6-methyl substituents in compounds **4** allow for further derivatization reactions (e.g., alkylation or nonaflation of the 4-OH group or oxidation of the 2-alkyl group) thus providing access to a broad range of differently substituted pyridine derivatives with varying electronic and steric properties such as **5** and **6**.

Herein we report the expansion of our previously published methodology and the first applications of the prepared enantiopure pyridine derivatives as ligands in asymmetric transition metal-catalyzed transformations.

2. Results and discussion

2.1. Enantioselective alkylation of aldehydes

The enantioselective addition of diethylzinc to benzaldehyde is certainly one of the most intensively studied asymmetric transformations.[7] Initially, β-amino alcohols were identified as excellent ligands for this reaction,[8] but examples describing the use of chiral N-containing heterocycles such as aziridines,[9] pyrrolidines[10] and pyridines[3] have also been reported. On account of the deep understanding of the reaction mechanism and the numerous examples described in literature we decided to use the enantioselective addition of diethylzinc to benzaldehyde as a model reaction to test our prepared pyridine derivatives and to study the influence of different substituents at the 4-position on the reaction efficiency. We assumed a distinct impact on the reaction outcome by

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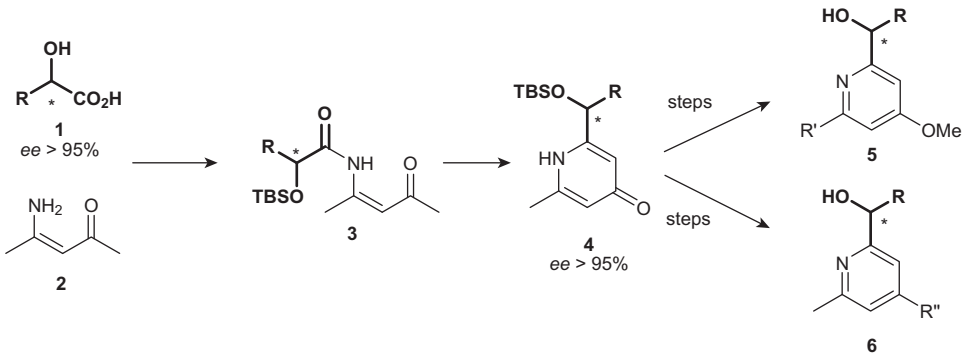


Scheme 1. Enantiopure pyridine derivatives **5** and **6** derived from α-hydroxy carboxylic acids **1** and enaminoketone **2**.

modifying the electronic properties of the pyridine ligands employed by attaching electron-donating or electron-withdrawing substituents to the 4-position. To test this hypothesis the set of previously prepared ligands[6a] as depicted in Figure 1 was used in the catalytic enantioselective addition of diethylzinc to aldehydes.

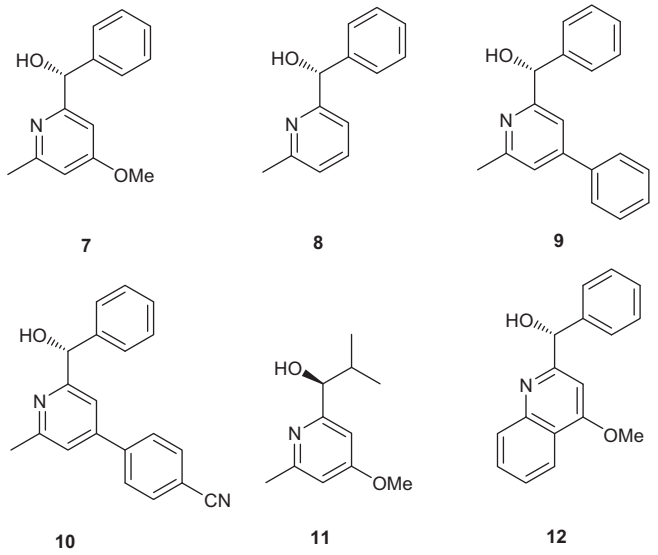
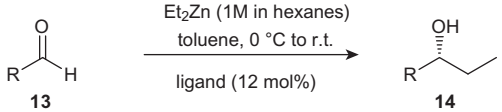


Figure 1. Pyridine ligands **7**–**12** for the asymmetric addition of diethyl zinc to aldehydes.

The results using uniformly 12 mol % of ligand are summarized in Table 1. Much to our surprise the electronic properties of the pyridine ligands had no significant influence on the chiral induction. The enantiomeric excesses for the addition product **14a** derived from benzaldehyde range from 69% to 74% employing ligands **7**–**10** (entries 1–4). The use of pyridine ligand **11** caused a slightly higher *ee* of the addition product (78%) as the isopropyl group apparently has a higher steric demand (entry 5) compared to the phenyl group. Surprisingly, the 4-methoxy-substituted quinoline derivative **12**[11] induces no enantiomeric excess at all and it provided **14a** in only moderate yield. The poor solubility of **12** might be the reason for this dramatic decrease in yield and *ee*. Although the 4-substituent has almost no influence on the efficacy of the process with respect to the *ee*s it does have a significant impact on the yields. Ligand **8** carrying no 4-substituent provided the addition product in 71% yield. In contrast, ligands **9** and **10** having 4-aryl substituents afforded the addition product in significantly higher yields (~90%), independent of the electronic nature of the substituent in position 4 (entries 3, 4). Ligand **7** carrying a 4-methoxy group was not as efficient as the 4-aryl-substituted pyridine derivatives **9** and **10** and the addition product **14a** was obtained

Table 1
Enantioselective addition of diethylzinc to aldehydes



Entry	Ligand	R	Product	Yield[a] (%)	*ee*[b] (%)
1	**7**	C_6H_5	**14a**	82	70
2	**8**	C_6H_5	**14a**	71	74
3	**9**	C_6H_5	**14a**	93	69
4	**10**	C_6H_5	**14a**	92	72
5	**11**	C_6H_5	**14a**	68	−78[c]
6	**12**	C_6H_5	**14a**	44	0
7	**7**	4-CH_3O–C_6H_4	**14b**	30	18
8	**7**	4-NC–C_6H_4	**14c**	69	58
9	**7**	C_6H_{11}	**14d**	68	52
10	**7**	2-$C_{10}H_7$	**14e**	83	72 (98)[d]

[a] Yields of purified products.
[b] Determined by HPLC (Chiralpak IA or IB) or GC analysis (Chiraldex-β-DM).
[c] *ent*-**14a** was obtained.
[d] After re-crystallization from hexane.

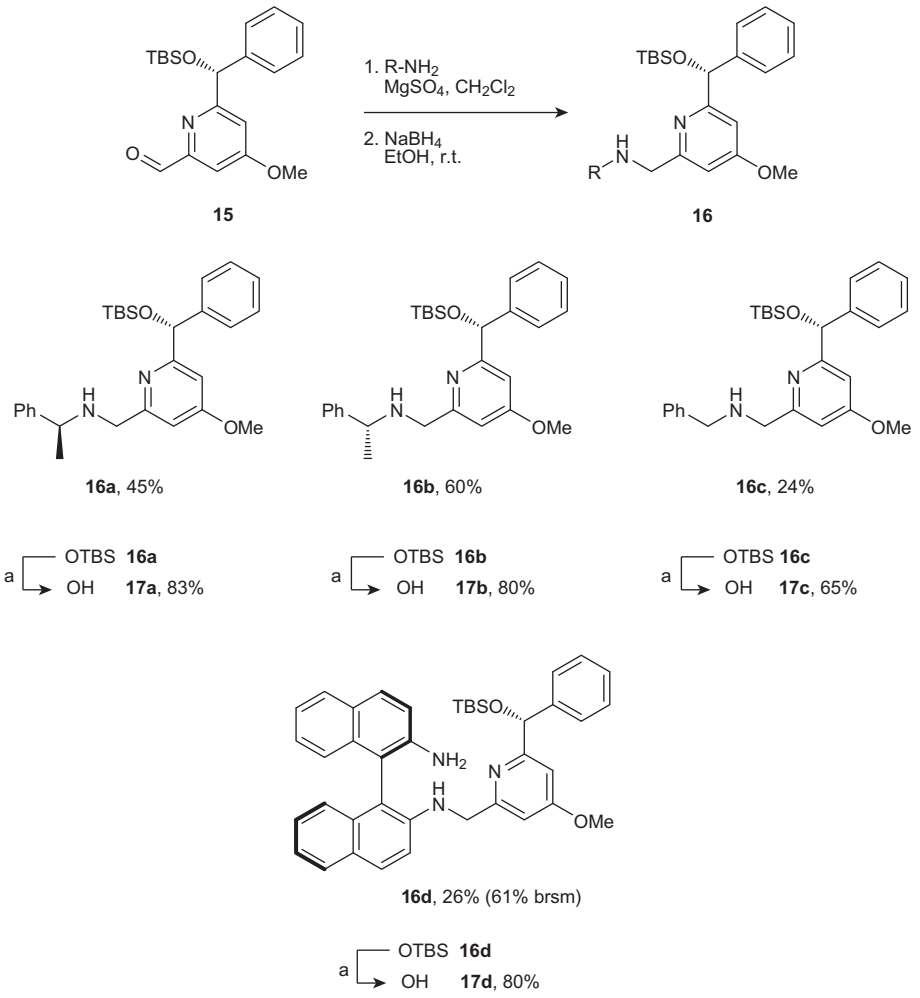
in 82% yield (entry 1). However, for these examples the *ee*s of the addition product **14a** were all in the range of 69–74%.

In addition, *p*-methoxybenzaldehyde, *p*-cyanobenzaldehyde, cyclohexanecarboxaldehyde, and 2-naphthaldehyde were tested as electrophiles. Hereby, the electronic nature of the aryl-substituent had a dramatic influence on the reaction efficiency as the addition product **14b** was obtained in moderate yield and with low *ee*. In contrast, product **14c** was obtained in a reasonable yield and *ee* (entries 7 and 8). Entry 9 demonstrates that not only aromatic aldehydes can be used but also related aliphatic aldehydes; however, yield and *ee* of addition product **14d** were only moderate. The addition of diethylzinc to 2-naphthaldehyde furnishing **14e** (entry 10) was efficient as that to benzaldehyde. Gratifyingly, the enantiomeric purity of the addition product **14e** could easily be improved to 98% *ee* by a single re-crystallization from hexane.

In accordance with established mechanistic models for asymmetric alkylations employing diethylzinc,[3a,b,8] all ligands with an (*R*)-configured side chain give the corresponding secondary alcohols with (*R*)-configuration and vice versa.

2.2. Preparation of aminomethyl-substituted pyridine derivatives

Wang et al. showed that aminomethyl-substituted pyridines are efficient catalysts for the asymmetric addition of organozincs to aldehydes.[12] They propose that the nucleophilicity is enhanced by an additional Lewis basic binding site by coordination to the zinc center. Similar structures can be accessed through reductive

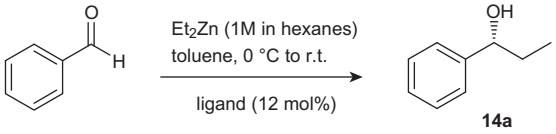


Scheme 2. Reductive amination of pyridyl aldehyde **15** with a series of primary amines. (a) TBAF (1 M in THF), THF, rt, 1–2 h. brsm = yield based on recovered starting material.

amination reactions of pyridyl aldehyde **15**[6a] (Scheme 2). Following this strategy the aminomethyl-substituted pyridine derivatives **17** were prepared by reductive amination followed by protodesilylation.

The compounds obtained were subsequently examined as ligands in the addition of diethylzinc to benzaldehyde. The results are summarized in Table 2. Pyridine derivative **17a** (entry 1) proved to be the most efficient ligand providing the addition product **14a** in 87% yield and with an *ee* of 88%. Interestingly, with diastereomeric ligand **17b** product **14a** was isolated in significantly lower yield and with modest enantioselectivity. The absolute configuration of the aminomethyl side chain apparently has a strong influence on the reaction efficacy. This assumption is supported by the results obtained with pyridine derivative **17c**. This ligand, lacking a stereocenter at the aminomethyl side chain, afforded the addition product **14a** in 70% yield and with 76% *ee*. These numbers are exactly in between those obtained with **17a** and **17b** showing that the amino group is not (solely) responsible for the observed enhancement in reactivity since with ligand **7** very similar results were obtained. The use of (*R*)-binaphthyl derived pyridine derivative **17d** as a ligand provided **14a** with similarly moderate results just as for ligand **17b** (entry 4).

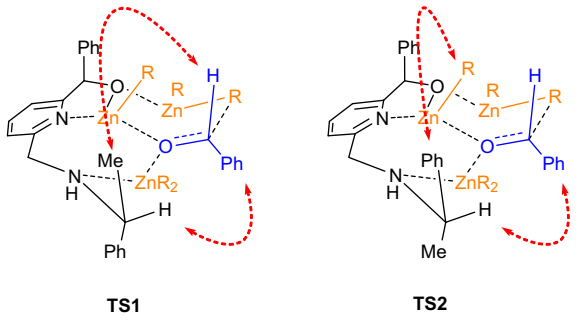
Table 2
Enantioselective addition of diethylzinc to benzaldehyde



Entry	Ligand	Yield[a] (%)	*ee*[b] (%)
1	**17a**	87	88
2	**17b**	48	62
3	**17c**	70	76
4	**17d**	52	58

[a] Yields of purified products.
[b] Determined by HPLC (Chiralpak IA or IB).

The predominating absolute configuration observed of our addition products **14** can be explained by the accepted transition states for the enantioselective addition of diethylzinc. However, the reactivity differences between the pyridine ligands **17a**, **17b,** and **17c** cannot be explained by these models. In order to provide an explanation we propose the transition states depicted in Scheme 3. In analogy to literature precedent[8a,3b] we postulate a 5/6 membered ring system formed by the pyridine ring chelating an alkyl zinc moiety that acts as Lewis acid and coordinates the reacting aldehyde. By this coordination the observed preferential re-face attack can be explained; however the influence of the C-6 aminomethyl side chain of the pyridine ligands **17** becomes unclear. Since the stereocenter at the aminomethyl side chain has remarkable influence on the asymmetric induction, a close proximity of this center



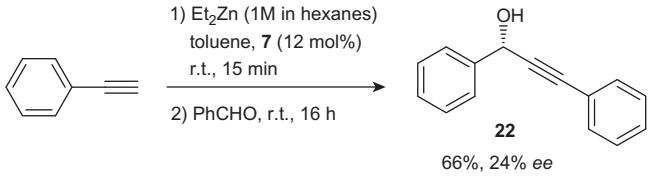
Scheme 3. Proposed transition states **TS1** and **TS2** for the enantioselective alkylation of benzaldehyde with pyridines **17a** and **17b** as ligands.

to the aldehyde carbonyl group in the transition state is likely. We suggest that a third molecule of diethylzinc is involved being coordinated between the amino group and the carbonyl oxygen. This brings the aminomethyl side chain close to the carbonyl center and leads to the preferred TS1 where the hydrogen points toward the coordinated aldehyde. In this conformation the bulky phenyl group of the aminomethyl group points away whereas the methyl group enhances the asymmetric induction as it points in the same direction as the C-2 phenyl group.[12] In TS2, that is the transition state for the alkylation with diastereomeric pyridine derivative **17b** as ligand, the phenyl group of the aminomethyl side chain probably points up generating a sterically more congested transition state TS2. This may result in a larger distance to this aminomethyl side chain and as a consequence a decreased activation of the carbonyl group and lower enantioselectivity.

Since pyridine derivative **17a** showed the best performance in the asymmetric alkylation of benzaldehyde we decided to investigate additional pyridines with functionalized C-6 side chains. Seyferth–Gilbert homologization of pyridyl aldehyde **15** leads to the C-6 alkynyl substituted pyridine derivative **18**[6a] which was subjected to copper-catalyzed [3+2] cycloaddition with acetylated α-glucose azide **19** (Scheme 4). The expected 1,2,3-triazole derivative **20** was obtained as a single diastereomer in high yield. Interestingly, although the reaction conditions were very mild, partial desilylation was observed and the free alcohol was acetylated either by transesterification or by reaction with the solvent (CH_3CN). However, after deprotection with TBAF both compounds could be easily separated by column chromatography. As carbohydrate-derived structures increasingly attract interest as ligands in asymmetric transformations[13] we also examined **21** in the asymmetric alkylation of benzaldehyde. The addition product **14a** was obtained in high yield (88%) but as a racemic mixture.

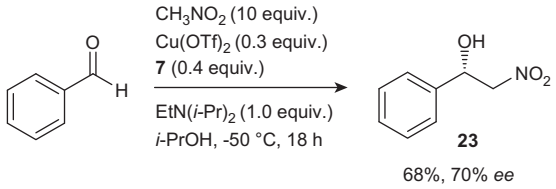
2.3. Applications in the asymmetric alkynylation and allylation of aldehydes and in the asymmetric Henry reaction

Encouraged by success in the asymmetric addition of diethylzinc to aldehydes we decided to briefly investigate the enantioselective alkynylation of aldehydes which provides synthetically valuable enantioenriched propargylic alcohols such as **22** (Scheme 5). The use of hydroxymethyl-substituted pyridine **7** as a ligand provided the respective propargylic alcohol in moderate yield, but only a low enantiomeric excess was achieved. Ligand **17a** did not lead to an improvement in yield and *ee* of this transformation.

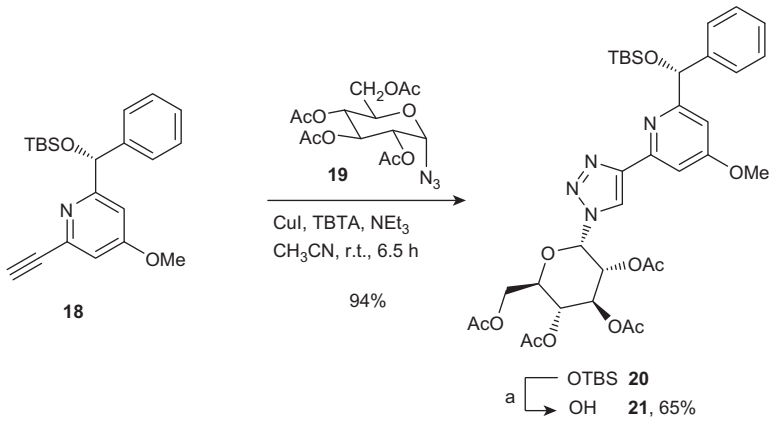


Scheme 5. Enantioselective alkynylation of benzaldehyde employing ligand **7**.

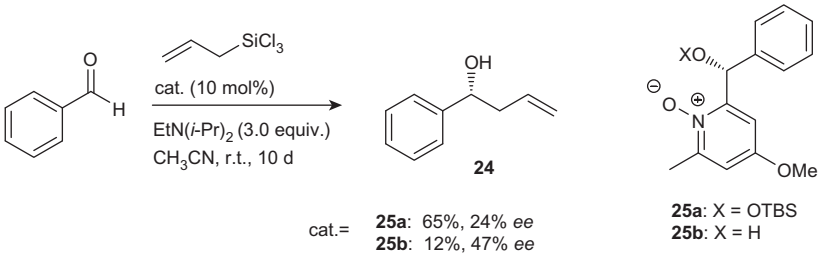
The nitroaldol reaction (Henry reaction) is a powerful method for the construction of β-hydroxy-substituted nitroalkanes.[14] Various methods have been disclosed in the literature, which describe the asymmetric addition of in-situ generated zinc nitronate species to aldehydes in high yields and with good enantiomeric excesses.[15] Reaction of nitromethane, diethylzinc and benzaldehyde using pyridine derivative **7** as a chiral ligand provided (*S*)-2-nitro-1-phenylethanol **23** in only moderate yield (41%) and very low *ee* (ca. 10%—as determined by comparison of the specific rotation values). However, a copper-catalyzed version[16] of the Henry reaction with pyridine derivative **7** immediately afforded addition product **23** in 68% yield and with a good *ee* of 70% after 18 h of reaction time at −50 °C[17] (Scheme 6). We are confident that our modular ligand design is suitable to achieve even better enantioselectivities in this important reaction.



Scheme 6. Enantioselective copper-catalyzed Henry reaction leading to (*S*)-2-nitro-1-phenylethanol **23**.



Scheme 4. [3+2] Cycloaddition of 6-alkynyl-substituted pyridine **18** and tetra-*O*-acetylated α-D-glucose azide. TBTA = Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine. (a) TBAF (1 M in THF), THF, rt, 2 h.



Scheme 7. Enantioselective allylation of benzaldehyde with allyl(trichloro)silane providing homoallylic alcohol **25**.

Finally, we also investigated the use of pyridine-*N*-oxides **25a** and **25b** (derived from an intermediate in the synthesis of **15**[6a]) as catalysts in the asymmetric allylation of benzaldehyde with allyl(trichloro)silane (Scheme 7).[18] In the presence of 5 mol % of **25a** the allylated product **24** was obtained in 65% and with an *ee* of 24% after 10 days reaction time at rt. When the corresponding desilylated compound **25b** was used the *ee* could be increased to 47%, but, unfortunately, the yield significantly decreased to 12%. Again further improvement of this asymmetric process should be possible since our ligand system can easily be modified.

3. Conclusion

We could demonstrate that hydroxymethyl-substituted pyridine derivatives prepared by our methods are versatile ligands for various asymmetric transformations. So far the best results were obtained in the asymmetric alkylation of benzaldehyde providing the respective addition products in yields of up to 93% and with an enantiomeric excess of up to 88%. Other transformations were only briefly examined for a first screen of the simplest ligands. The enantioselective alkynylation was not as efficient and only moderate results could be achieved. However, as demonstrated with one example, the asymmetric, copper-catalyzed Henry reaction was efficiently catalyzed by one of our prepared pyridine derivatives delivering the respective 2-nitro-1-phenylethanol in good yield and moderate enantiomeric purity. Based on these first results, further applications of our pyridine derivatives as ligands in asymmetric catalysis are obvious. They clearly have the potential to be modified and optimized in simple procedures.

4. Experimental section

4.1. General methods

Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were purified with a MB SPS-800-dry solvent system. NEt_3 was distilled from CaH_2 and stored over KOH under an atmosphere of argon. Pyridine was stored over KOH under an atmosphere of argon. Other reagents were purchased and used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Fluka). Unless otherwise stated, yields refer to analytically pure samples. NMR spectra were recorded with Bruker (AC 250, AC 500, AVIII 700) and JOEL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to solvent residual peaks or TMS (^{1}H: δ = 0.00 ppm [TMS], δ = 7.26 ppm [$CDCl_3$]; ^{13}C: δ = 77.0 ppm [$CDCl_3$]). Integrals are in accordance with the assignments and coupling constants are given in Hz. All ^{13}C NMR spectra are proton-decoupled. For detailed peak assignments 2D spectra were measured (COSY, HMQC, HMBC). IR spectra were measured with a Nicolet 5 SXC FT-IR spectrometer or with a Nexus FT-IR spectrometer fitted with a Nicolet Smart DuraSample IR ATR. HRMS analyses were measured on an Agilent 6210 ESI-TOF, Agilent Technologies, Santa Clara, CA, USA. The solvent flow rate was adjusted to 4 μL/min, the spray voltage was set to 4.000 V, the drying gas flow rate was set to 15 psi (1 bar). All other parameters were adjusted for a maximum abundance of the relative $[M+H]^+$. Elemental analyses were measured with a CHN-Analyzer 2400 (Perkin–Elmer) or a Vario EL III. Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at 22 °C. Compounds **7**, **8**, **9**, **10**, **11** were prepared as described in the literature.[6a] Compound **12** was prepared following the procedure described in the literature.[11]

4.2. Preparation of new pyridine derivatives

4.2.1. (*R*)-{4-Methoxy-6-[((*S*)-1-phenylethylamino)methyl]-pyridin-2-yl}(phenyl)methanol 17a

Typical procedure for the preparation of aminomethyl substituted pyridine derivatives ***17***: To a solution of pyridyl aldehyde **15** (97 mg, 0.27 mmol) in anhydrous CH_2Cl_2 (1 mL) was added (*S*)-methylbenzylamine (36 mg, 0.30 mmol) and $MgSO_4$. The resulting mixture was stirred at rt for 20 h until complete consumption of the starting material had been indicated by TLC. The mixture was then filtered and all volatile components were removed under reduced pressure to afford 120 mg of the respective crude imine as a pale yellow oil. The product was used in the next step without further purification. To a solution of the crude imine (74 mg, 0.16 mmol) in EtOH (1.5 mL) was added $NaBH_4$ (11 mg, 0.28 mmol) and the resulting mixture was stirred at rt for 4 h. The reaction mixture was concentrated under reduced pressure and the residue obtained was re-dissolved in CH_2Cl_2 (10 mL) and water (10 mL) was added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 7:3) to afford 37 mg (45% over two steps) of pure **16a** as a colorless oil. $[\alpha]_D = -15.6$ (*c* 0.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.00, 0.02, 0.95 (3s, 3H, 3H, 9H, OTBS), 1.33 (d, *J* = 6.4 Hz, 3H, CH*Me*), 2.22 (br s, 1H, NH), 3.59, 3.69 (AB system, J_{AB} = 14.3 Hz, 2H, CH_2Pyr), 3.66 (q, *J* = 6.4 Hz, 1H, C*H*Me), 3.78 (s, 3H, OMe), 5.83 (s, 1H, C*H*Ph), 6.52, 6.98 (2d, *J* = 2.1 Hz, 1H each, 3-H/5-H), 7.15–7.31 (m, 8H, Ph), 7.48 (d, *J* = 7.7 Hz, 2H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = −4.8, 18.3, 25.8 (q, s, q, OTBS), 24.4 (q, CH*Me*), 52.7 (t, CH_2Pyr), 55.0 (q, OMe), 57.4 (d, C*H*Me), 103.7, 106.6 (2d, C-3/C-5), 126.2, 126.8, 127.0, 127.9, 128.4 (5d, Ph)*, 144.0, 145.5 (2s, Ph), 160.4, 165.7, 166.7 (3s, C-2/C-4/C-6) ppm; *one signal (d, Ph) was not detected. IR (ATR): ν = 3005 (NH), 2960–2855 (=C–H, C–H), 1730–1595 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd for $C_{28}H_{39}N_2O_2Si$ $[M+H]^+$: 463.2781. Found: 463.2792. EA: Calcd for $C_{28}H_{38}N_2O_2Si$ (462.7): C, 72.68; H, 8.28; N, 6.05. Found: C, 73.12; H, 7.96; N, 6.13.

To a solution of **16a** (35 mg, 0.08 mmol) in THF (1 mL) was added TBAF (1 M in THF, 0.09 mL, 0.09 mmol) and the resulting

mixture was stirred at rt for 2 h. Then water and EtOAc were added (15 mL each) and the resulting phases were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by flash column chromatography on silica gel (5% MeOH in CH_2Cl_2 + approx. 1 vol % NEt_3) to afford 23 mg (83%) of pure **17a** as a colorless oil. $[\alpha]_D = -26.2$ (*c* 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$ (d, $J = 6.6$ Hz, 3H, CH*Me*), 3.63, 3.68 (AB system, $J_{AB} = 14.0$ Hz, 1H each, PyrCH_2), 3.65 (s, 3H, OMe), 3.73 (q, $J = 6.6$ Hz, 1H, C*H*Me), 5.56 (s, 1H, PhC*H*), 6.37, 6.56 (2 d, $J = 2.2$ Hz, 1H each, 3-H/5-H), 7.16–7.32 (m, 10H, Ph) ppm; the OH signal was not detected. ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 24.1$ (q, CH*Me*), 52.4 (t, PyrCH_2), 55.2 (q, OMe), 57.7 (d, C*H*Me), 74.5 (d, PhCH), 105.4, 107.3 (2d, C-3/C-5), 126.8, 127.1, 127.2, 127.8, 128.50, 128.53 (6d, Ph), 159.5, 162.1, 166.8 (3s, C-2/C-4/C-6) ppm. IR (ATR): $\nu = 3245$ (OH), 3060–2870 (=C–H, C–H), 1710–1550 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): Calcd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$: 349.1916. Found: 349.1897.

4.2.2. (*R*)-{4-Methoxy-6-[((*R*)-1-phenylethylamino)methyl]-pyridin-2-yl}(phenyl)methanol 17b

Following the typical procedure, reaction of pyridyl aldehyde **15** (75 mg, 0.21 mmol) and (*R*)-methylbenzylamine (28 mg, 0.23 mmol) in the presence of $MgSO_4$ in CH_2Cl_2 (1.5 mL) afforded 70 mg of the respective crude imine as a yellow oil. Reduction of the crude imine (64 mg, 0.14 mmol) with $NaBH_4$ (19 mg, 0.50 mmol) in EtOH (1.5 mL) afforded 55 mg (60% over two steps) of pure **16b** as a yellow oil which was used in the next step without further purification. Proto-desilylation of **16b** (55 mg, 0.12 mmol) with TBAF (1 M in THF, 0.12 mL, 0.12 mmol) in THF (1 mL) provided after flash column chromatography on silica gel (4% MeOH in CH_2Cl_2 + approx. 1 vol % NEt_3) 33 mg (80%) of pure **17b** as a yellow oil. $[\alpha]_D = -50.3$ (*c* 2.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.41$ (d, $J = 6.7$ Hz, 3H, CH*Me*), 3.73 (m, 5H, OMe, PyrCH_2), 3.81 (q, $J = 6.7$ Hz, 1H, C*H*Me), 5.65 (s, 1H, C*H*Ph), 6.47, 6.66 (2d, $J = 2.4$ Hz, 1H each, 3-H/5-H), 7.32–7.34 (m, 10H, Ph) ppm; the OH signal was not detected. ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 24.3$ (q, CH*Me*), 52.7 (t, PyrCH_2), 55.2 (q, OMe), 57.6 (d, *C*HMe), 76.7 (d, *C*HPh), 105.2, 107.2 (2d, C-3/C-5), 126.7, 126.9, 127.0, 127.7, 128.5 (5d, Ph)*, 143.3, 145.2 (2s, Ph), 159.9, 162.2, 166.8 (3s, C-2/C-4/C-6) ppm; *one signal (d, Ph) was not detected. IR (ATR): $\nu = 3305$ (O–H), 3080–2850 (=C–H, C–H), 1570–1500 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$: 349.1916. Found: 349.1915.

4.2.3. (*R*)-{6-[(Benzylamino)methyl]-4-methoxypyridin-2-yl}(phenyl)methanol 17c

Following the typical procedure, reaction of pyridyl aldehyde **15** (240 mg, 0.68 mmol) and benzylamine (73 mg, 0.68 mmol) in the presence of $MgSO_4$ in CH_2Cl_2 (3.5 mL) afforded 302 mg of the respective crude imine as a pale yellow oil. Reduction of the crude imine (302 mg, 0.67 mmol) with $NaBH_4$ (76 mg, 2.00 mmol) in EtOH (7 mL) afforded after flash column chromatography on silica gel (hexane/EtOAc = 7:3 to 3:2) 73 mg (24% over two steps) of pure **16c** as yellow oil. $[\alpha]_D = +55.4$ (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$, 0.96 (2s, 6H, 9 H, OTBS), 3.76–3.85 (m, 7H, OMe, PhCH_2, PyrCH_2), 5.85 (s, 1H, C*H*Ph), 6.67, 7.02 (2d, $J = 2.3$Hz, 1H each, 3-H/5-H), 7.49–7.51 (m, 10H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = -4.89$ 18.3, 25.8 (q, s, q, OTBS), 53.2, 54.3 (2t, PhCH_2, PyrCH_2), 55.0 (q, OMe), 77.5 (d, *C*HPh), 103.9, 106.7 (2d, C-3/C-5), 126.1, 126.8, 127.0, 128.0, 128.1, 128.2 (6d, Ph), 140.3, 143.9 (2s, Ph), 160.2, 165.8, 166.8 (3s, C-2/C-4/C-6) ppm. IR (ATR): $\nu = 3050–2850$ (=C–H, C–H), 1595–1500 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd for $C_{27}H_{37}N_2O_2Si$ $[M+H]^+$: 449.2624. Found 449.2625.

Proto-desilylation of **16c** (70 mg, 0.16 mmol) with TBAF (1 M in THF, 0.16 mL, 0.16 mmol) in THF (1.5 mL) provided after flash column chromatography on silica gel (5% MeOH in CH_2Cl_2 + approx. 1 vol % NEt_3) 33 mg (65%) of pure **17c** as a yellow oil. $[\alpha]_D = -108$ (*c* 1.50, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.75$ (s, 3H, OMe), 3.83, 8.90 (2s, 2H each, PhCH_2, PyrCH_2), 5.66 (s, 1H, C*H*Ph), 6.49, 6.76 (2d, $J = 2.1$ Hz, 1H each, 3-H/5-H), 7.33–7.35 (m, 10H, Ph) ppm; the OH signal was not detected. ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 53.3$, 54.1 (2t, PhCH_2, PyrCH_2), 55.2 (q, OMe), 75.0 (d, *C*HPh), 105.3, 107.2 (2d, C-3/C-5), 127.0, 127.7, 128.2, 128.4, 128.5 (5d, Ph)*, 139.9, 143.2 (2s, Ph), 159.8, 162.2, 166.9 (3s, C-2/C-4/C-6) ppm; *one signal (d, Ph) was not detected. IR (ATR): $\nu = 3315$ (OH), 3060–2850 (=C–H, C–H), 1560 (C=C) cm^{-1}. HRMS (ESI-TOF): Calcd for $C_{21}H_{23}N_2O_2$ $[M+H]^+$: 335.1760. Found: 335.1758.

4.2.4. (*R*)-{6-[((*R*)-2′-Amino-1,1′-binaphthyl-2-ylamino)-methyl]-4-methoxypyridin-2-yl}(phenyl)methanol 17d

Following the typical procedure, reaction of pyridyl aldehyde **15** (240 mg, 0.68 mmol) and (*R*)-1,1′-binaphthyl-2,2′-diamine (96 mg, 0.34 mmol) in the presence of $MgSO_4$ in anhydrous $ClCH_2CH_2Cl$ (3.5 mL) at 50 °C provided 414 mg of the respective crude product as a yellow oil. Reduction of the crude imine with $NaBH_4$ (114 mg, 3.01 mmol) in EtOH (4.5 mL) afforded after flash column chromatography on silica gel (hexane/EtOAc = 8:2) 55 mg (26%, 85 mg of **15** were re-isolated; yield brsm: 61%) of pure **16d** as a colorless solid; mp 167 °C. $[\alpha]_D = +73.3$ (*c* 2.6, $CHCl_3$). Due to the presence of rotamers only characteristic signals are given: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.00$, 0.92 (2s, 6H, 9H, OTBS), 3.67 (s, 3H, OMe), 4.44 (s, 2H, PyrCH_2), 5.60 (br s, 1H, C*H*Ph), 6.56, 7.09 (2s, 1H each, 3-H/5-H), 7.15–7.24, 7.76–7.81 (2m, 17H, BINAM, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = -4.95$, 18.2, 25.8 (q, s, q, OTBS), 55.1 (q, OMe), 104.0, 105.9 (2d, C-3/C-5), 112.3, 112.5 (2s, BINAM), 114.1, 118.4 (2s, BINAM), 121.9, 122.4, 124.0, 126.0, 126.7, 126.8, 127.1, 127.7, 128.0, 128.1, 129.5 (11d, Ph, BINAM), 133.5, 134.0 (2s, BINAM), 142.6, 143.0 (2s, Ph, BINAM) ppm. IR (ATR): $\nu = 3050–2850$ (=C–H, C–H), 1600–1550 (C=C) cm^{-1}. HRMS (ESI-TOF): Calcd for $C_{40}H_{44}N_3O_2Si$ $[M+H]^+$: 626.3203. Found: 626.3189.

Proto-desilylation of **16d** (52 mg, 0.08 mmol) with TBAF (1 M in THF, 0.08 mL, 0.08 mmol) in THF (0.2 mL) provided after flash column chromatography on silica gel (hexane/EtOAc = 1:1) 33 mg (80%) of pure **17d** as a colorless oil. $[\alpha]_D = -17.6$ (*c* 1.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.64$ (s, 3H, OMe), 4.46, 4.51 (AB system, $J_{AB} = 16.8$ Hz, 2H, PyrCH_2), 5.56 (s, 1H, C*H*Ph), 6.41, 6.64 (2d, $J = 2.3$Hz, 1H each, 3-H/5-H), 7.05–7.27, 7.77–7.85 (2 m, 17H, BINAM, Ph) ppm; the OH signal was not detected. ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 48.2$ (t, PyrCH$_2$), 55.4 (q, OMe), 74.3 (d, *C*HPh), 105.9, 106.3 (2d, C-3/C-5), 112.2, 112.7, 113.9, 118.4 (4s, BINAM), 122.1, 122.7, 123.7, 123.9, 126.8, 126.9, 127.8, 128.1, 128.2, 128.5, 129.7 (11d, Ph, BINAM)*, 133.6, 133.9 (2s, BINAM), 142.5, 142.9, 143.3 (3s, Ph, BINAM), 159.1, 161.9, 167.6 (3s, C-2/C-4/C-6) ppm; *four signals (d, Ph/BINAM) were not detected. IR (ATR): $\nu = 3365$ (O–H), 3050–2850 (=C–H, C–H), 1600–1550 (C=C) cm^{-1}. HRMS (ESI-TOF): Calcd for $C_{34}H_{30}N_3O_2$ $[M+H]^+$: 512.2333. Found: 512.2357.

4.2.5. (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-{4-(6-[(*R*)-(*tert*-butyldimethylsiloxy)(phenyl)methyl]-4-methoxypyridin-2-yl)-1*H*-1,2,3-triazol-1-yl}tetrahydro-2*H*-pyran-3,4,5-triyl triacetate 20

To a solution of alkynyl pyridine **18** (84 mg, 0.24 mmol) in CH_3CN (5 mL) was added 1-azido-2,3,4,6-tetra-*O*-acetyl-α-D-glucose **19** (89 mg, 0.24 mmol), CuI (9 mg, 0.05 mmol), TBTA (25 mg, 0.05 mmol), and NEt_3 (7 μL, 0.05 mmol). The resulting mixture was stirred at rt under an atmosphere of argon for 6.5 h. Then water (20 mL) and EtOAc (20 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic layers were dried with Na_2SO_4,

filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 3:2) to provide 163 mg (94%) of **20** as a colorless oil. $[\alpha]_D$ = +40.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01, 0.96 (2s, 6H, 9H, OTBS), 1.86, 2.03, 2.06, 2.09 (4s, 3H each, OCOCH_3), 3.86 (s, 3H, OMe), 4.03 (ddd, *J* = 1.9, 5.0, 9.9 Hz, 1H, 2′-H), 4.16 (dd, *J* = 1.9, 12.7 Hz, 1H, CH_2OAc), 4.32 (dd, *J* = 5.0, 12.7 Hz, 1H, CH_2OAc), 5.28 (t, *J* = 9.9 Hz, 1H, 3′-H), 5.43, 5.56 (2 t, *J* = 9.5 Hz, 1H each, 4′-H/5′-H), 5.92 (d, *J* = 9.5 Hz, 1H, 6′-H), 5.83 (s, 1H, C*H*Ph), 7.05, 7.50 (2d, *J* = 2.4 Hz, 1H each, 3-H/5-H), 7.17–7.20, 7.25–7.30, 7.51–7.52 (3m, 1H, 2H, 2H, Ph), 8.31 (s, 1H, 5″-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = −4.93, 18.2, 25.8 (q, s, q, OTBS), 20.2, 20.47, 20.49, 20.7 (4q, OCO*C*H$_3$), 55.3 (q, OMe), 61.5 (t, *C*H$_2$OAc), 67.6, 70.2, 72.8, 75.0 (4d, C-2′/C-3′/C-4′/C-5′), 77.3 (d, *C*HPh), 85.7 (d, C-6′), 104.1, 105.8 (2d, C-3/C-5), 120.8 (d, C-5″), 126.2, 127.2, 128.2, 143.8 (3d, s, Ph), 149.2, 149.8, 166.1, 167.1 (4s, C-2/C-4/C-6/C-4″), 168.9, 169.4, 170.1, 170.6 (4s, O*C*OCH$_3$) ppm. IR (ATR): ν = 3155–2850 (=C–H), 1750–1560 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): Calcd for $C_{35}H_{46}N_4NaO_{11}Si$ $[M+Na]^+$: 749.2825. Found: 749.2839.

4.2.6. (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-{4-(6-[(*R*)-hydroxy(phenyl)methyl]-4-methoxypyridin-2-yl)-1*H*-1,2,3-triazol-1-yl}tetrahydro-2*H*-pyran-3,4,5-triyl triacetate 21

To a solution of **20** (144 mg, 0.20 mmol) in THF (2 mL) was added TBAF (1 M in THF, 0.22 mL, 0.22 mmol) and the resulting mixture was stirred at rt for 2 h. Then water (15 mL) and EtOAc (15 mL) were added and the resulting phases were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 1:1) to afford 73 mg (65%) of pure **21** as a colorless oil. $[\alpha]_D$ = −106.4 (*c* 0.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.89, 2.03, 2.06, 2.09 (4s, 3H each, OCOCH_3), 3.83 (s, 3H, OMe), 4.04 (ddd, *J* = 2.0, 5.0, 10.1 Hz, 1H, 2′-H), 4.17 (dd, *J* = 2.0, 12.7 Hz, 1H, CH_2OAc), 4.34 (dd, *J* = 5.0, 12.7 Hz, 1H, CH_2OAc), 5.31 (t, *J* = 10.1 Hz, 1H, 3′-H), 5.45, 5.54 (2t, *J* = 9.4 Hz, 1H each, 4′-H/5′-H), 5.68 (s, 1H, C*H*Ph), 5.93 (d, *J* = 9.4 Hz, 1H, 6′-H), 6.54, 7.61 (2d, *J* = 2.4 Hz, 1H each, 3-H/5-H), 7.25–7.39 (m, 5H, Ph), 8.43 (s, 1H, 5″-H) ppm; the OH signal was not detected. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.2, 20.5*, 20.7 (3q, OCO*C*H$_3$), 55.5 (q, OMe), 61.5 (t, *C*H$_2$OAc), 67.6, 70.4, 72.6, 75.2 (4d, C-2′/C-3′/C-4′/C-5′), 74.7 (d, *C*HPh), 85.9 (d, C-6′), 104.6, 107.4 (2d, C-3/C-5), 120.9 (d, C-5″), 127.1, 127.9, 128.5, 142.9 (3d, s, Ph), 148.5, 149.2, 151.7, 167.2 (4s, C-2/C-4/C-6/C-4″), 168.8, 169.2, 170.0, 170.5 (4s, O*C*OCH$_3$) ppm; * signal with higher intensity. IR (ATR): ν = 3400 (OH), 3030–2855 (=C–H), 1750–1570 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): Calcd for $C_{29}H_{32}N_4NaO_{11}$ $[M+Na]^+$: 635.1960. Found: 635.1980.

4.2.7. (*R*)-2-[Hydroxy(phenyl)methyl]-4-methoxy-6-methylpyridine 1-oxide 25b

To a stirred solution of (*R*)-2-[(*tert*-butyldimethylsiloxy)-(phenyl)methyl]-4-methoxy-6-methylpyridine 1-oxide[6a] (40 mg, 0.11 mmol) in THF (1.0 mL) was added TBAF (1 M in THF, 0.12 mL, 0.12 mmol) and the resulting mixture was stirred at rt for 2 h. The mixture was then diluted with EtOAc (10 mL) and water (10 mL) was added. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (10% MeOH in CH_2Cl_2) to provide 18 mg (67%) of **25b** as a colorless solid; mp 165 °C. $[\alpha]_D$ = −23.6 (*c* 0.85, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3H, Me), 3.72 (s, 3H, OMe), 6.08 (s, 1H, C*H*Ph), 6.35, 6.73 (2d, *J* = 3.4 Hz, 1H each, 3-H/5-H), 7.28–7.41, 7.43–7.51 (2 m, 2H, 3H, Ph) ppm; the OH signal was not detected. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.3 (q, Me), 55.8 (q, OMe), 72.6 (d, *C*HPh), 109.1, 110.3 (2d, C-3/C-5), 127.1, 128.2, 128.5, 138.9 (3d, s, Ph), 150.6, 153.2, 158.1 (3s, C-2/C-4/C-6) ppm. IR (ATR): ν = 3295 (OH), 3065–2825 (=C–H, C–H), 1630-1565 (C=C) cm^{-1}. HRMS (ESI-TOF): Calcd for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125. Found: 246.1111.

4.3. Applications of the ligands in catalysis

4.3.1. (*R*)-1-Phenylpropan-1-ol 14a

A flame-dried Schlenk flask was charged with **7** (27 mg, 0.12 mmol) evacuated and purged with argon. Toluene (1.0 mL) was added followed by diethylzinc (1 M in hexanes, 2.00 mL, 2.00 mmol), the resulting mixture was stirred at rt for 20 min and benzaldehyde (0.10 mL, 1.0 mmol) was added at 0 °C. The mixture was allowed to warm to rt and stirring was continued for 16 h. The reaction was quenched by the addition of aq 1 M HCl (10 mL) followed by EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford 112 mg (82%) of **14a** as colorless oil. $[\alpha]_D$ = +37.8 (*c* 1.0, $CHCl_3$); lit.: $[\alpha]_D$ = +45.4 (*c* 0.5, $CHCl_3$) for 98% *ee*.[19] ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.63–1.89 (m, 2H, CH_2CH$_3$), 2.24 (br s, 1H, OH), 4.54 (t, *J* = 6.6 Hz, 1H, C*H*OH), 7.25–7.39 (m, 5H, Ph) ppm. 70% *ee* determined by HPLC analysis: Daicel Chiralpak IA column, 254 nm UV detector, 2% *i*-PrOH in hexane, flow rate: 0.5 mL/min, retention time (*R*)-enantiomer: 39 min, (*S*)-enantiomer: 42 min.

4.3.2. (*R*)-1-(4-Methoxyphenyl)propan-1-ol 14b

According to the typical procedure, 4-methoxybenzaldehyde (136 mg, 1.00 mmol) was reacted with diethylzinc (1 M in hexane, 2.00 mL, 2.00 mmol) in the presence of **7** (28 mg, 0.12 mmol) in toluene (0.8 mL). Flash column chromatography on silica gel (hexane/EtOAc = 7:3) afforded 50 mg (30%) of **14b** as a colorless oil. $[\alpha]_D$ = +7.0 (*c* 1.0, $CHCl_3$); lit.: $[\alpha]_D$ = +34.0 (*c* 2.6, $CHCl_3$) for 90% *ee*.[20] ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.55–1.95 (m, 2H, CH_2CH$_3$), 3.81 (s, 3H, OMe), 4.55 (t, *J* = 6.7 Hz, 1H, C*H*OH), 6.84–7.00, 7.16–7.39 (2 m, 2H each, Ar) ppm; the OH signal was not detected. 18% *ee* determined by HPLC analysis: Daicel Chiralpak IA column, 254 nm UV detector, 5% *i*-PrOH in hexane, flow rate: 0.7 mL/min, retention time (*R*)-enantiomer: 18 min, (*S*)-enantiomer: 20 min.

4.3.3. (*R*)-4-(1-Hydroxypropyl)benzonitrile 14c

According to the typical procedure, 4-cyanobenzaldehyde (131 mg, 1.00 mmol) was reacted with diethylzinc (1 M in hexane, 2.00 mL, 2.00 mmol) in the presence of **7** (28 mg, 0.12 mmol) in toluene (0.8 mL). Flash column chromatography on silica gel (hexane/EtOAc = 4:1) afforded 112 mg (69%) of **14c** as a colorless oil. $[\alpha]_D$ = +19.4 (*c* 1.0, $CHCl_3$); lit.: $[\alpha]_D$ = +31.6 (*c* 0.5, $CHCl_3$) for 93% *ee*.[20] ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.55-1.89 (m, 2H, CH_2CH$_3$), 2.75 (br s, 1H, OH), 4.60 (t, *J* = 6.4 Hz, 1H, C*H*OH), 7.39, 7.55 (2d, *J* = 8.4 Hz, 2H each, Ar) ppm. 58% *ee* determined by HPLC analysis: Daicel Chiralpak IA column, 254 nm UV detector, 5% *i*-PrOH in hexane, flow rate: 0.5 mL/min, retention time (*R*)-enantiomer: 45 min, (*S*)-enantiomer 48 min.

4.3.4. (*R*)-1-Cyclohexylpropan-1-ol 14d

According to the typical procedure, cyclohexylcarboxaldehyde (112 mg, 1.00 mmol) was reacted with diethylzinc (1 M in hexane, 2.00 mL, 2.00 mmol) in the presence of **7** (28 mg, 0.12 mmol) in

toluene (0.8 mL). Flash column chromatography on silica gel (hexane/EtOAc = 4:1) afforded 96 mg (68%) of **14d** as a colorless oil. $[\alpha]_D$ = +8.22 (*c* 1.0, $CHCl_3$); lit. $[\alpha]_D$ = +30.6 (*c* 0.47, $CHCl_3$) for 99% *ee*.[21] ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.01–1.81 (m, 13H, C_5H_{11}/CH_2CH_3), 3.20–3.31 (m, 1H, CHOH) ppm; the OH signal was not detected. 52% *ee* determined by GC analysis: Chiraldex β-DM column, 85 °C (isotherm), N_2 flow rate: 0.7 mL/min, retention time (*S*)-enantiomer: 38 min, (*R*)-enantiomer 39 min.

4.3.5. (*R*)-1-(Naphth-2-yl)propan-1-ol 14e

According to the typical procedure, 2-naphthaldehyde (156 mg, 1.00 mmol) was reacted with diethylzinc (1 M in hexane, 2.00 mL, 2.00 mmol) in the presence of **7** (28 mg, 0.12 mmol) in toluene (0.8 mL). Flash column chromatography on silica gel (hexane/EtOAc = 4:1) afforded 154 mg (83%) of **14e** as a colorless solid; m.p. 50–51 °C (recrystallized from hexane). $[\alpha]_D$ = +30.3 (*c* 1.1, $CHCl_3$); lit.: $[\alpha]_D$ = +41.9 (*c* 1.1, $CHCl_3$) for 96% *ee*.[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.71–2.04 (m, 2H, CH_2CH_3), 2.54 (br s, 1H, OH), 4.73 (t, *J* = 6.6 Hz, 1H, CHOH), 7.39–7.64, 7.68–8.02 (2 m, 3H, 4H, Ar) ppm; the OH signal was not detected. 72% *ee* determined by HPLC analysis: Daicel Chiralpak IA column, 254 nm UV detector, 7.5% EtOAc in hexane, flow rate: 0.7 mL/min, retention time (*R*)-enantiomer: 21 min, (*S*)-enantiomer 23 min.

4.3.6. (*S*)-1,3-Diphenylprop-2-yn-1-ol 22

To a solution of **7** (28 mg, 0.12 mmol) in THF (0.8 mL) was added phenylacetylene (204 mg, 2.00 mmol) followed by diethylzinc (1 M in hexane, 2.00 mL, 2.00 mmol) and the resulting mixture was stirred under an atmosphere of argon for 15 min. Then benzaldehyde (106 mg, 1.00 mmol) was added and the resulting yellow solution was stirred for 16 h at rt. The reaction was quenched by the addition of aq 1 M HCl and diluted with EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to provide 168 mg of an inseparable 3:1 mixture of **22** and **14a** (calculated yield for **22**: 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (br s, 1H, OH), 5.70 (s, 1H, CHOH), 7.32–7.49 (m, 8 H, Ph), 7.62–7.64 (m, 2H, Ph) ppm. 24% *ee* determined by HPLC: Daicel chiralpak IA column, RI detector, 5% *i*-PrOH in hexane, flow rate: 0.7 mL/min, retention time (*R*)-enantiomer: 36 min, (*S*)-enantiomer 39 min.

4.3.7. (*S*)-2-Nitro-1-phenylethanol 23

To a solution of **7** (23 mg, 0.10 mmol) in *i*-PrOH (1.5 mL) was added $Cu(OTf)_2$ (27 mg, 0.08 mmol) and the resulting green solution was stirred under an atmosphere of argon at rt for 1 h before benzaldehyde (27 mg, 0.25 mmol), $(i\text{-Pr})_2$NEt (0.4 mL, 0.25 mmol) and nitromethane (0.13 mL, 2.50 mmol) were added. The resulting mixture was stirred under an atmosphere of argon at -50 °C for 18 h until complete consumption of the starting materials had been indicated by TLC. The reaction was quenched by the addition of aq 1 M HCl (5 mL) and CH_2Cl_2 (15 mL) was added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford 23 mg (68%) of **23** as a colorless oil. $[\alpha]_D$ = +33.7 (*c* 0.9, $CHCl_3$); lit.: $[\alpha]_D$ = +44.5 (*c* 0.5, $CHCl_3$) for 92% *ee*.[23] ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.47–4.66 (m, 2H, CH_2NO_2), 5.43–5.50 (m, 1H, PhCHOH), 7.35–7.41 (m, 5H, Ph) ppm; the OH signal was not detected. 70% *ee* determined by HPLC analysis: Daicel Chiralpak IB column, 254 nm UV detector, 15% *i*-PrOH in hexane, flow rate: 0.5 mL/min, retention time (*R*)-enantiomer: 16 min, (*S*)-enantiomer: 18 min.

4.3.8. (*R*)-1-Phenylbut-3-en-1-ol 24

To a solution of **25a** (34 mg, 0.10 mmol) in CH_3CN (4 mL) was added $(i\text{-Pr})_2$NEt (0.5 mL, 3.0 mmol) and benzaldehyde (106 mg, 1.00 mmol) followed by allyl(trichloro)silane (210 mg, 1.20 mmol) and the resulting mixture was stirred at rt for 10 days. After complete consumption of the starting materials the reaction was diluted with EtOAc and sat. aq $NaHCO_3$ (10 mL) was added. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 9:1) to provide 97 mg (65%) of **24** as colorless oil. $[\alpha]_D$ = +15.3 (*c* 0.85, $CHCl_3$); lit.: $[\alpha]_D$ = +51.8 (*c* 1.5, $CHCl_3$) for 87% *ee*.[24] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (br s, 1H, OH), 2.37–2.70 (m, 2H, $CH_2CH{=}CH_2$), 4.75 (t, *J* = 5.7 Hz, 1H, CHOH), 5.14–5.20 (m, 2H, $CH{=}CH_2$), 5.74–5.91 (m, 1H, $CH{=}CH_2$), 7.26–7.56 (m, 5H, Ph) ppm. 24% *ee* determined by comparison of the specific rotation values.

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