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Synthesis of C_2-symmetric and unsymmetrically substituted 2,2′-dipyridylamines and crystal structure of a chiral 2,2′-dipyridylamine copper(II) complex

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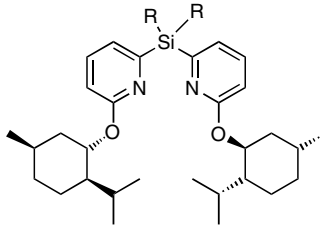
Abstract

C_2-symmetric and unsymmetrically substituted 2,2′-dipyridylamines have been synthesized by sequential Buchwald–Hartwig aminations of halo-pyridines. The X-ray crystal structure of a copper dichloride complex bearing a C_2-symmetric 2,2′-dipyridylamine reveals details of the binding properties of the ligand and the coordination geometry at the metal center. In preliminary experiments the use of the new nitrogen chelates in asymmetric catalysis has been demonstrated.

Keywords: Allylic oxidation; *N*-Arylation reactions; Catalysis; 2,2′-Dipyridylamines; Palladium

1. Introduction

In the field of enantioselective catalysis, nitrogen-containing compounds are regarded as privileged ligands [1]. Important representatives are chiral oxazolines and pyridines, which have found numerous applications in various asymmetric transformations. Among bidentate nitrogen-based ligands those with a bipyridine, phenanthroline, and terpyridine core have extensively been studied [2]. As recently pointed out by Chelucci, the chemistry of those compounds mostly relies on the efficient formation of five-membered chelates upon metal binding. Interestingly, only a few chiral pyridine-based ligands with the potential to form six-membered chelates with metals have been introduced. Wright's bis(pyridyl)silane **1** [3], Chelucci's dipyridylpropane **2** [4] and Kwong's dipyridylketone **3** [5] are rare examples of those compounds.



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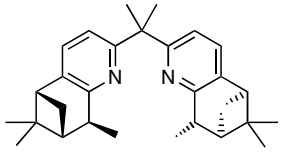

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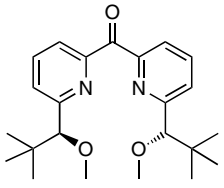

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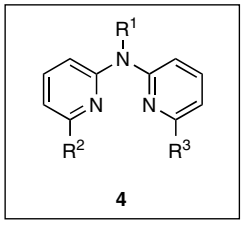

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Recently, Kempe showed the applicability of another class of dinitrogen ligands, 2,2′-dipyridylamines **4**, in transition metal-catalyzed transformations. Their nickel

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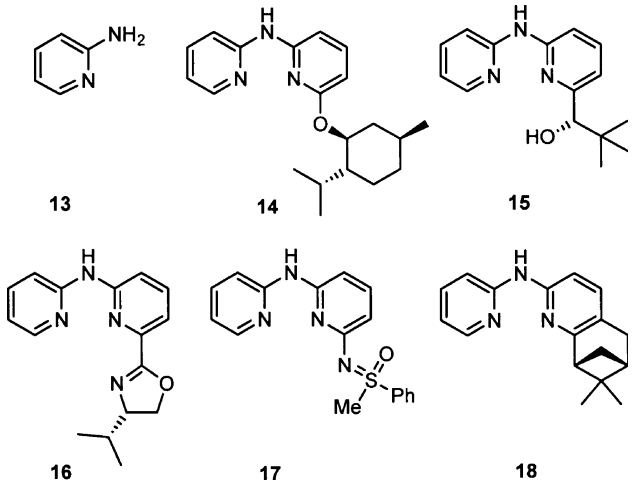
complexes are efficient catalysts in ethylene polymerization [6] and palladium complexes catalyze Heck reactions [7]. Despite these interesting examples, the chemistry of 2,2′-dipyridylamines has mainly been limited to the study of their coordination behaviour, and among the numerous dipyridylamine/metal complexes prepared for this purpose those of copper salts are the most dominant ones [8].



For the synthesis of 2,2′-dipyridylamines **4** palladium-catalyzed Buchwald–Hartwig amination reactions [9] starting from 2-halo-pyridines can be used (Scheme 1) [6,10]. With respect to the preparation of chiral compounds two general approaches are possible: First, the stereogenic center might be embedded in a substituent R^1 of the bridging amino unit. Alternatively, the pyridine rings can bear chiral groups (R^2 and R^3). If both of them are identical and homochiral, C_2-symmetric 2,2′ dipyridylamines result. The second approach appears more promising, since in this case the stereogenic elements are closer to the coordinating nitrogens, allowing a more direct control on the coordination sphere of the metal. Such influence could be the key for a successful asymmetric metal-catalyzed process.

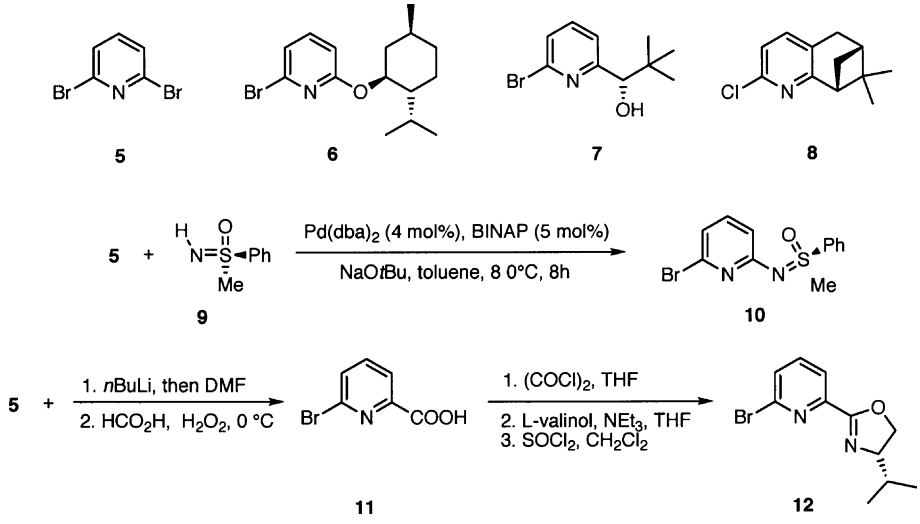
Recently, we reported the synthesis of simple 2,2′-dipyridylamines **4** with $R^1 = R^2 = H$ [11]. We now extended our synthetic program and prepared C_2-symmetric as well as unsymmetrically substituted derivatives with $R^2 = R^3$ and $R^2 \neq R^3 \neq H$, respectively. Furthermore, we investigated the use of those new 2,2′-dipyridylamines in copper-catalyzed asymmetric allylic oxidation reactions.

2. Results and discussions

2.1. Synthesis of the starting materials

In order to synthesize C_2-symmetric and unsymmetrically substituted 2,2′-dipyridylamines, chiral 2-halo-pyridines were required (Scheme 1). Those compounds have extensively been studied and their syntheses are well documented [2]. One of the most convenient methods is the desymmetrization of 2,6-dibromo-pyridine (**5**) [2,12]. In this manner, pyridines **6** [3] and **7** [12] were prepared according to literature protocols. Palladium-catalyzed *N*-arylation of **5** with one equivalent of NH-sulfoximine **9** following a method developed in our laboratories [13] afforded sulfoximidoyl-substituted pyridine **10** [14,15]. With a Pd(0)/BINAP catalyst, **10** was obtained in 84% yield.

2,6-Dibromopyridine (**5**) also served as starting material for the synthesis of oxazolinyl-substituted pyridine **12**. In the five-step reaction sequence, **5** was first converted into 6-bromo-pyridine-2-carboxylic acid **11** [16]. Chlorination of **11** with oxalyl chloride (in THF and in the presence of NEt_3) followed by amide formation with (*S*)-valinol and subsequent cyclization with thionyl



Scheme 1. 2-Halo-pyridines **6-12** used for the synthesis of chiral 2,2′-dipyridylamines [dba = dibenzylidene acetone; BINAP = 2,2′-bis-(dipenylphosphino)-1,1′-binaphthyl].

chloride furnished **12** in 45% overall yield (from **5**). The only 6-chloropyridine applied in this study was compound **8**. This β-pinene-derived halo pyridine attracted our attention since Kocovsky [17] reported on high enantioselectivities in the copper catalyzed allylic oxidation of cyclic alkenes with bipyridines prepared from **8**. Our initial attempts to prepare the 6-bromo analogue of **8** failed, and thus the subsequent 2,2′-dipyridylamine synthesis utilized Kocovsky's chloropyridine **8**.

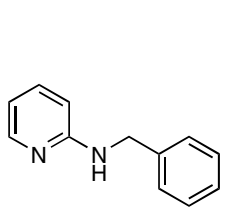
2.2. Synthesis of amino-bridged 2,2′-dipyridylamines 4 with $R^1 = H$

Our first targets were 2,2′-dipyridylamines possessing a bridging secondary amine (**4** with $R^1 = H$). An interesting feature of those products is the presence of an acidic NH function. The coordination properties of deprotonated 2,2′-dipyridylamine ligand in Ir(I), Rh(I) and Ru(II) complexes have already been investigated [18]. C_1-symmetric dipyridylamines with $R^1 = R^2 = H$ can easily be synthesized by *N*-arylation of 2-aminopyridine **13**. Applying a Pd(0)/BINAP catalyst system in the coupling of **13** with 6-halopyridines **6**, **7**, **8**, **10** and **12** led to 2,2′-dipyridylamines **14**-**18** in yields up to 86% [11].

For the synthesis of a C_2-symmetric 2,2′-dipyridylamine with a secondary amino group in the bridge (compound **21**), 6-chloropyridine **8** was converted into its 6-amino analogue **20** by palladium-catalyzed amination with a Pd(0)/BINAP catalyst and ammonia surrogates **19** [9,19] followed by acid hydrolysis of the intermediate benzophenone imine derivative (not shown; 91% yield over two steps). Palladium-catalyzed coupling of **8** and **20** afforded C_2-symmetric 2,2′-dipyridylamine **21** in 91% yield (Scheme 2).

2.3. Synthesis of amino-bridged 2-2′-dipyridylamines 4 with $R^1 \neq H$

In order to investigate the applicability of the palladium-catalyzed amination reaction in the formation of chiral 2,2′-dipyridylamines with tertiary amino bridges (**4** with $R^1 \neq H$), we first studied the coupling of **8** with commercially available *N*-benzyl-2-amino-pyridine (**22**). Using a catalyst prepared from 5 mol% of each $Pd(dba)_2$ and DPPP [1,3-bis(diphenylphosphino)propane] in combination with NaO*t*Bu and Bu_4NBr at 100 °C, 2,2′-dipyridylamine **23** was obtained in 81% yield after 24 h.



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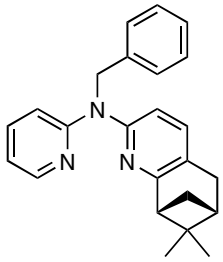

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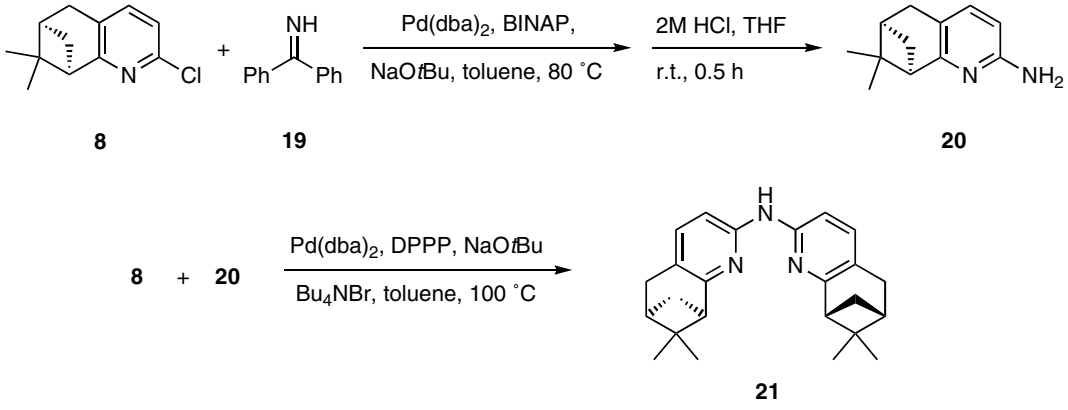
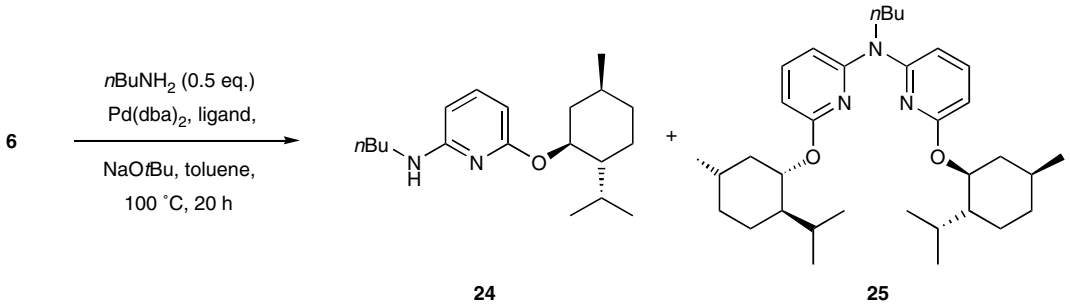
Next, we focused our attention on the preparation of C_2-symmetric derivatives by the palladium-catalyzed double *N*-arylation. Since previous studies [10] had shown that this transformation required long reaction times leading to low product yields, a screening of Pd(0) catalysts prepared from $Pd(dba)_2$ and various phosphine ligands was performed first. As coupling partners *N*-butylamine and readily available 6-bromopyridine **6** were chosen (Scheme 3).

From this initial catalyst screening a palladium catalyst with DPPP as ligand was identified as the most efficient one for the direct double *N*-arylation, giving mono- and diarylated amines **24** and **25**, respectively, in a ratio of 40:60. Since we had used a twofold excess with respect to the amine, the lack of remaining starting material indicated that **6** had either decomposed or that undesired side-reactions had occurred under these reaction conditions. Stimulated by Hartwig's [20] results, who described positive effects of bromide ions in aminations of aryl chlorides, and with the goal to maximize the yield of diarylated product **25** the catalysis was next performed



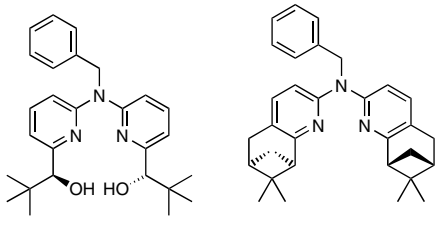
Scheme 2. Synthesis of C_2-symmetric dipyridylamine **21**.



ligand	**24** (%)	**25** (%)
BINAP	85	15
DPEphos	45	55
DPPP	40	60
DPPP + Bu_4NBr (1 eq.)	20	80

Scheme 3. Optimization of the conditions for the direct double *N*-arylation reaction.

in the presence of 1 equiv. of Bu_4NBr. To our delight we found that use of this additive increased the ratio of **24** and **25** to 20:80. Finally, with a slight excess of **6** (2.2 equiv.) the double arylation afforded **25** in 92% yield. Under these optimized conditions other C_2-symmetric 2,2′-dipyridylamines could also be obtained in high yield. Thus, use of benzyl amine and 6-halopyridines **7** and **8** led to **26** and **27** in 94% and 92% yield, respectively. 2,2′-Dipyridylamine **28** [21] was isolated in 96% yield starting from 2-picolylamine and 2-bromopyridine **6**. These results were very promising, as they showed that this strategy was also applicable to different substrates.



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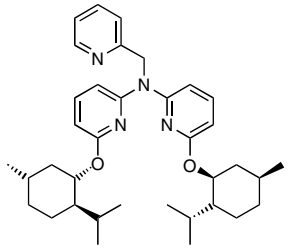

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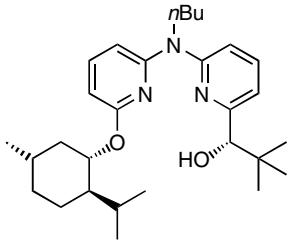
Another interesting point arose from this optimization study since it showed that the use of BINAP as ligand resulted in the predominant formation of mono-arylated (secondary) amines. As a consequence, we envisaged that highly unsymmetrical chiral 2,2′-dipyridylamines would become accessible by a subsequent second coupling [22] with a different 6-halopyridine. Such approach would allow the straightforward preparation of ligand libraries, which could prove useful in asymmetric catalysis. In order to test this hypothesis, amino pyridine **24** was first prepared using the Pd(0)/BINAP catalyst system as described in Scheme 3. On a 25 mmol scale, the product was obtained in 96% yield after 24 h at 100 °C, using only 1 mol% of catalyst. The arylation of **24** with 6-halopyridines **7** and **12** was then performed using 4 mol% of the DPPP-based palladium(0) catalyst (in toluene at 100 °C) with NaO*t*Bu as base and Bu_4NBr as additive. Under these reaction conditions, unsymmetrically substituted 2,2′-dipyridylamines **29** and **30** were obtained in 76 and 94% yield, respectively.



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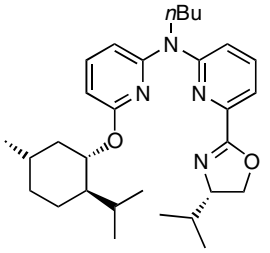

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In the light of these very positive results, it was surprising to note that the attempted coupling between **24** and sulfoximidoyl-substituted bromo-pyridine **10** did not proceed at all. Both reagents were recovered almost quantitatively. Also performing the reaction at higher temperature, longer reaction times and the use of *ent*-**10** did not lead to the desired coupling reaction.

2.4. X-ray crystal structure analysis of a copper(II) complex bearing a chiral dipyridylamine

Next, we wondered about the capability of the chiral 2,2′-dipyridylamines to coordinate to metals. In order to explore the limits we chose sterically crowded and rigid C_2-symmetric dipyridylamine **27** for this study and treated (in analogy to a literature protocol [23]) a solution of **27** in dichloromethane with a solution of anhydrous copper dichloride in ethanol. Crystals of 1:1 complex **31** (Fig. 1), which were suitable for X-ray crystal structure analysis, were then obtained by slow diffusion of diethyl ether into a CH_2Cl_2 solution of the **27**/$CuCl_2$ mixture.

The X-ray crystal structure of complex **31** differs significantly from that of known dichloro(di-2-pyridylamine-*N*,*N*′)copper(II) [24], prepared from unsubstituted 2,2′-dipyridylamine. Whereas the former complex is characterized by an almost planar ligand and a distorted tetrahedral coordination of the copper atom, the 2,2′-dipyridylamine segment is significantly bent in **31** with the Cu atom 1.39(1) Å above the N1–N2–N3 plane. Moreover, the angle between the N1–Cu–N2 and the Cl1–Cu–Cl2 planes is only 27.0(5)° in **31** but 61.3(1)° in dichloro(di-2-pyridylamine-*N*,*N*′)copper(II) [24]. In the former complex the N–Cu and Cl–Cu distances of 2.009(10)/2.078(12) and 2.209(8)/2.245(9) Å are slightly longer and shorter than those in the latter one [1.948(6) and 2.250(3) Å]. All of those data indicated that the steric crowding due to the annulated bicyclic ring systems on the two pyridines had a major effect on the coordination geometry at the metal. Furthermore, we realized that the originally C_2-symmetric 2,2′-dipyridylamine became part of a C_1-symmetric metal complex, which was most likely to be relevant for the use of such complexes in asymmetric catalysis.

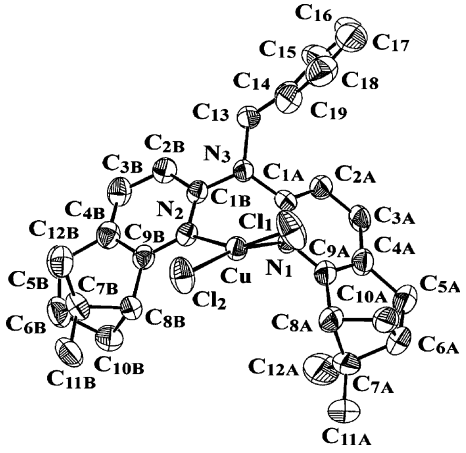
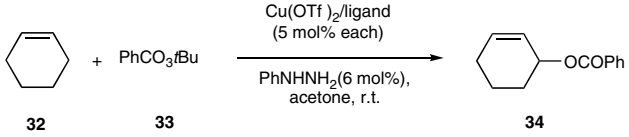


Fig. 1. ORTEP plot of complex **31**; H atoms omitted for clarity.

2.5. Applications of chiral 2,2′-dipyridylamines in asymmetric catalysis

After the development of the synthetic strategy and the investigation of the solid state structure of **31**, we wondered about the potential of the new 2,2′-dipyridylamines to serve as ligands in metal-catalyzed asymmetric processes. Bidentate pyridines are known to be effective in copper catalyzed transformations [2–4,17], and we therefore focussed our attention on the copper-catalyzed asymmetric allylic oxidation of olefins [25]. As test substrate cyclohexene (**32**) in combination with *tert*-butylperoxybenzoate (**33**) as oxidant was chosen. Following well-established routes, the catalytically active metal species was formed *in situ* by treatment of copper(II) triflate with phenylhydrazine in the presence of the ligand (Scheme 4).

The results of this study are summarized in Table 1. Unfortunately, use of 2,2′-dipyridylamines **15** and **16** as well as amino-pyridine **18** (with one or two equivalents relative to copper) led to inactive catalysts. On the other hand, 2,2-dipyridylamine **17** bearing a sulfoximidoyl substituent proved applicable leading to product **34** in good yield and with some enantioselectivity (15% ee; Table 1, entry 4). The most active catalysts were obtained with the various pinene-derived



Scheme 4. Copper-catalyzed allylic oxidation of cyclohexene (**32**).

Table 1
Allylic oxidation of cyclohexene (**32**) to give **34** (Scheme 4) catalyzed by copper complexes bearing chiral 2,2-dipyridylamines

Entry	Ligand	Copper	Solvent	Time (h)	Yield (%)	ee (%)
1	**14**	$Cu(OTf)_2$	Acetone	8	76	0
2	**15**	$Cu(OTf)_2$	Acetone	160	n.r.[a]	–
3	**16**	$Cu(OTf)_2$	Acetone	160	n.r.[a]	–
4	**17**	$Cu(OTf)_2$	Acetone	8	89	15
5	**18**	$Cu(OTf)_2$	Acetone	3	91	17
6	**21**	$Cu(OTf)_2$	Acetone	8	84	11
7	**23**	$Cu(OTf)_2$	Acetone	6	76	9
8	**25**	$Cu(OTf)_2$	Acetone	8	65	0
9	**27**	$Cu(OTf)_2$	Acetone	3	92	0
10	**28**	$Cu(OTf)_2$	Acetone	36	45	0
11	**18**	$(CuOTf)_2 \cdot PhH$	Acetone	120	88	17
12	**18**	$CuPF_6$	Acetone	3	91	17
13	**18**	$Cu(OTf)_2$	CH_2Cl_2	2	87	11
14	**18**	$Cu(OTf)_2$	CH_3CN	150	56	15

[a] n.r. = no reaction.

2,2-dipyridylamines. Although in these cases high yields (84–91%) were reached, the enantioselectivities remained low (<20% ee). The best result was achieved with C_1-symmetric dipyridylamine **18** which led to **34** with 17% ee in 91% yield. The bridging amine was also found to influence the efficiency of the catalyst (Table 1, entries 5–7 and 9). Thus the ones derived from 2,2′-dipyridylamines possessing a secondary bridging amine gave higher enantioselectivities than their *N*-alkylated analogues. The solvent or the copper source did not significantly influence the enantioselectivity of the catalyst prepared from **18** and only the reaction times varied (Table 1, entry 5 versus entries 11–14).

The data presented in Table 1 also show that use of C_2-symmetric 2,2′-dipyridylamine **27** led to racemic **34** (entry 9). Taking into account the structural information of the X-ray crystal structure of **31** this result is not too surprising, since the catalysis appears to proceed rather remote from the stereogenic centers of the ligand system. Apparently, a better control of the stereochemical reaction path can be achieved with less crowded ligands in this particular case.

2.5.1. Conclusion and outlook

New chiral 2,2′-dipyridylamines have been synthesized by palladium-catalyzed cross coupling reactions and their applicability in copper-catalyzed allylic oxidations has been demonstrated. The information obtained by the X-ray crystal structure analysis of copper complex **31** proved useful for the understanding of the stereochemical requirements of the ligands. Our current efforts are devoted to the synthesis of other chiral 2,2′-dipyridylamines that will allow to improve the so far rather limited enantioselectivity in this synthetically highly useful oxidative C–O-bond formation.

3. Experimental

3.1. General

All reactions were performed under an inert atmosphere of argon using Schlenk techniques. All glasses were flame dried prior to use and then flushed with argon. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ using TMS as an internal standard on an Inova 400 spectrometer or Gemini 300. Chemical shifts are given in ppm relative to TMS. IR spectra were recorded on a Perkin–Elmer FTIR as KBr pellets. MS spectra were measured on a Varian MAT 212 and HRMS spectra on a Finnigan MAT 95 mass spectrometer. Optical rotation was measured on a polarimeter Perkin–Elmer PE-241 in $CHCl_3$ with $c=1$ unless otherwise stated. Melting points were measured on a Büchi B-540. Elemental analyses were measured on a *Heraeus* CHNO-Rapid.

3.2. Syntheses of the starting materials

3.2.1. (*S*)-2-Bromo-6-(*S*-methyl-*S*-phenyl)-sulfoximidoyl-pyridine (**10**)

In a Schlenk tube flushed with argon were successively added $Pd(dba)_2$ (0.08 mmol, 46 mg), *rac*-BINAP (0.1 mmol, 62 mg), (*S*)-(*S*-phenyl-*S*-methyl)-sulfoximine (2.0 mmol, 310 mg), 2,6-dibromo-pyridine (3.0 mmol, 711 mg) and sodium *tert*-butylate (3.0 mmol, 288 mg). Toluene (40 mL) was added and the solution was heated at 80 °C for 8 h. The reaction mixture was evaporated to dryness, and the oily residue redissolved in diethyl ether and filtered onto celite. The solvent was removed, and the yellow residue recrystallized from toluene/hexanes. White solid, 84% yield; m.p. 158–160 °C $[\alpha]_D=+77.4$. ^{1}H NMR (300 MHz): $\delta=8.08$ (m, 2H), 7.72–7.56 (m, 3H), 7.32 (d, $J=7.9$, 7.7 Hz, 1H), 6.95 (d, $J=7.7$ Hz, 1H), 6.79 (d, $J=7.9$ Hz, 1H), 3.46 (s, 3H). ^{13}C NMR (75 MHz): $\delta=158.9$, 139.6, 139.2, 133.3, 129.5, 127.8, 119.8, 114.9, 45.2. IR: 1426, 1389, 1302, 1201, 1154, 1123, 1123, 1095, 1068, 1021. MS (EI, 70 eV): $m/z=$ 312.0, 310.0 (M^+). Calc. for $C_{12}H_{11}BrN_2OS$: C, 46.31; H, 3.56; N, 9.00. Found: C, 46.35; H, 3.74; N, 8.93.

3.2.2. (4*S*)-2-Bromo-6-(4-isopropyl-4,5-dihydro-oxazol-2-yl)pyridine (**12**)

To a solution of oxalyl chloride (7.5 mmol, 635 μL) in THF (10 mL) were added 2-bromo-pyridine-6-carboxylic acid (5.0 mmol, 1.01 g), and the reaction mixture was stirred for 30 min at room temperature. The excess oxalyl chloride and the solvent were removed under reduced pressure, and the solid residue was dissolved in CH_2Cl_2 (20 mL). This solution was added dropwise to a cooled solution of (*S*)-valinol (6.0 mmol, 618 mg) and triethylamine (9.0 mmol, 1.2 mL) in CH_2Cl_2 (20 mL). The solution was stirred for 4 h, and then quenched with 1 M NaOH (50 mL). The organic layer was separated, washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. The resulting amido alcohol (with a purity of 95% as determined by NMR spectroscopy) was directly used for the next step. A solution of the amido alcohol in CH_2Cl_2 was cooled to 0 °C and $SOCl_2$ (6.0 mmol) was added. The mixture was stirred over night at room temperature and then quenched with 1 M NaOH. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic phases were dried with $MgSO_4$. The product was purified by column chromatography on silica gel. White solid, 74% yield; m.p. 105–107 °C. $[\alpha]_D=-67.1$. ^{1}H NMR (400 MHz): $\delta=8.05$ (dd, $J=7.4$, 1.4 Hz, 1H), 7.62 (dd, $J=7.9$, 7.4 Hz, 1H), 7.59 (dd, $J=7.9$ Hz, 1H), 4.51 (dd, $J=9.6$, 9.3 Hz, 1H), 4.19 (m, 2H), 1.89 (m, 1H), 1.04 (d, $J=6.9$ Hz, 3H), 0.94 (d, $J=6.9$ Hz, 3H). ^{13}C NMR (100 MHz): $\delta=161.1$, 147.6, 141.7, 138.5, 130.0, 122.7, 72.8, 70.9, 32.7, 19.0, 18.1. IR: 2984, 2961, 2870, 1640,

1550, 1442, 1357, 1120. MS (EI, 70 eV): *m/z* = 270.2, 268.2 (M^+). Calc. for $C_{11}H_{13}BrN_2O$: C, 49.09; H, 4.87; N, 10.41. Found: C, 48.76; H, 4.84; N, 10.31.

3.3. N-Arylation of primary amino pyridines (GP1)

In a Schlenk tube flushed with argon were successively added $Pd(dba)_2$ (0.04 mmol, 23 mg), *rac*-BINAP (0.05 mmol, 31 mg), 2-halo-6-substituted-pyridine (1.0 mmol), 2-amino-pyridine (13, 1.1 mmol, 103 mg) and sodium *tert*-butylate (1.5 mmol, 144 mg). The Schlenk tube was flushed with argon, toluene (20 mL) was added, and the reaction mixture was heated at 80 °C until the reaction was complete (monitored by TLC or GC). The mixture was cooled to room temperature, diluted with diethyl ether and filtered through celite. Solvents were removed on a rotary evaporator and the product purified by column chromatography on silica gel.

3.3.1. (1S,2R,5S)-(+)-[6-(2-Isopropyl-5-methyl-cyclohexyloxy)-pyridin-2-yl]-pyridin-2-yl-amine (**14**)

Synthesized according to GP1. White solid, 78% yield; m.p. 118–120 °C. $[\alpha]_D = +99.3$. ^1H NMR (400 MHz): $\delta = 8.27$ (d, $J = 4.1$ Hz, 1H), 7.83 (d, $J = 8.5$ Hz, 1H), 7.71 (br s, 1H), 7.57 (td, $J = 7.1$, 1.6 Hz, 1H), 7.45 (t, $J = 8.0$ Hz, 1H), 6.84 (dd, $J = 7.1$ Hz, 1H), 6.72 (d, $J = 7.7$ Hz, 1H), 6.25 (d, $J = 8.0$ Hz, 1H), 4.88 (ddd, $J = 10.7$, 10.7, 4.1 Hz, 1H), 2.31 (d, $J = 12.1$ Hz, 1H), 2.11 (m, 1H), 1.74 (m, 2H), 1.54 (m, 2H), 1.20–0.96 (m, 9H), 0.95 (m, 6H), 0.76 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (100 MHz): $\delta = 162.6$, 153.9, 152.0, 147.6, 140.0, 137.2, 116.0, 111.4, 102.1, 75.0, 47.5, 40.9, 34.6, 31.8, 26.3, 24.0, 22.2, 20.7, 16.7. IR: 3268, 3191, 2958, 1624, 1578, 1536, 1438, 1339, 1293, 1225, 1145, 1040. HRMS Calc. for $C_{20}H_{27}N_3O$: 325.21541. Found: 325.21549. Calc. for $C_{20}H_{27}N_3O$: C, 73.81; H, 8.36; N, 12.91. Found: C, 73.42; H, 8.35; N, 12.63.

3.3.2. (1S)-(+)-2,2-Dimethyl-1-[6-(pyridin-2-ylamino)-pyridin-2-yl]-propan-1-ol (**15**)

Synthesized according to GP1. Colorless viscous oil, 78% yield. $[\alpha]_D = +44.2$. ^1H NMR (400 MHz): $\delta = 8.37$ (br s, 1H), 8.26 (d, $J = 4.1$ Hz, 1H), 7.62–7.46 (m, 3H), 7.34 (d, $J = 8.2$ Hz, 1H), 6.83 (td, $J = 6.6$, 1.1 Hz, 1H), 6.72 (d, $J = 7.4$ Hz, 1H), 4.30 (s, 2H), 0.95 (s, 9H). ^{13}C NMR (100 MHz): $\delta = 158.3$, 154.2, 152.8, 138.0, 137.6, 116.6, 115.5, 112.0, 110.3, 80.7, 36.6, 26.4. IR: 3600–2820 (m), 1607, 1533, 1454, 1152, 1059, 1015. HRMS Calc. for $C_{15}H_{19}N_3O$: 257.15281. Found: 257.15263.

3.3.3. (4S)-(−)-[6-(4-Isopropyl-4, 5-dihydro-oxazol-2-yl)-pyridin-2-yl]-pyridin-2-yl-amine (**16**)

Synthesized according to GP1. White solid, 78% yield; m.p. 101–103 °C. $[\alpha]_D = -65.2$. ^1H NMR (400 MHz): $\delta = 8.20$ (dd, $J = 4.9$, 1.1 Hz, 1H), 8.09 (d, $J = 8.2$ Hz, 1H), 7.63 (dd, $J = 7.4$, 5.3 Hz, 1H), 7.56 (br s, 1H), 7.55–7.50 (m, 3H), 7.03 (d, $J = 8.2$ Hz, 1H), 6.78 (dd, $J = 7.2$, 5.8 Hz, 1H), 4.41 (dd, $J = 9.1$, 8.8 Hz, 1H), 4.11 (m, 2H), 1.92 (m, 1H), 1.06 (d, $J = 6.9$ Hz, 3H), 0.96 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (100 MHz): $\delta = 162.7$, 154.0, 153.7, 147.8, 144.9, 138.5, 138.0, 117.1, 116.7, 114.2, 111.8, 73.1, 70.9, 33.1, 19.6, 18.5. IR: 3201, 2865, 1646, 1576, 1533, 1459, 1331. MS (EI, 70 eV): *m/z* = 282.3 (M^+). Calc. for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84. Found: C, 68.02; H, 6.34; N, 19.48.

3.3.4. (S)-[6-(S-Methyl-S-phenyl)-sulfoximidoyl-pyridin-2-yl]-pyridin-2-yl-amine (**17**)

Synthesized according to GP1. White solid, 84% yield; m.p. 81–83 °C. $[\alpha]_D = +314.9$. ^1H NMR (300 MHz): $\delta = 8.11$ (d, $J = 4.9$ Hz, 1H), 7.99 (d, $J = 1.0$ Hz, 1H), 7.97 (d, $J = 1.5$ Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.53–7.43 (m, 4H), 7.35 (t, $J = 7.9$ Hz, 1H), 7.05 (br s, 1H), 6.72 (dd, $J = 5.9$, 1.0 Hz, 1H), 6.63 (d, $J = 8.2$ Hz, 1H), 6.41 (d, $J = 7.9$ Hz, 1H), 3.28 (s, 3H). ^{13}C NMR (75 MHz): $\delta = 158.6$, 153.8, 152.3, 147.6, 140.5, 139.4, 137.6, 133.1, 129.5, 128.0, 116.1, 111.9, 108.4, 103.3, 46.0. IR: 3191, 1601, 1433, 1336, 1151. MS (EI, 70 eV): 324.1 (M^+). Calc. for $C_{17}H_{16}N_4OS$: C, 62.94; H, 4.97; N, 17.27. Found: C, 63.32; H, 5.20; N, 16.86.

3.3.5. (6R,8R)-(−)-(5,6,7,8-Tetrahydro-7,7-dimethyl-6,8-methanoquinolin-2-yl)-pyridin-2-yl-amine (**18**)

Synthesized according to GP1. White solid, 86% yield; m.p. 72–74 °C. $[\alpha]_D = -49.4$. ^1H NMR (300 MHz): $\delta = 8.16$ (dq, $J = 4.9$, 1.0 Hz, 1H), 7.47 (td, $J = 8.6$, 2.0 Hz, 1H), 7.36 (d, $J = 8.2$ Hz, 1H), 7.30 (m, 2H), 6.70 (m, 1H), 2.76 (m, 3H), 2.61 (ddd, $J = 9.6$, 5.7, 5.7 Hz, 1H), 2.24 (sept, $J = 2.9$ Hz, 1H), 1.34 (s, 3H), 1.24 (d, $J = 9.4$ Hz), 0.64 (s, 3H). ^{13}C NMR (75 MHz): $\delta = 154.0$, 150.4, 147.6, 137.7, 137.3, 122.2, 115.8, 111.3, 108.8, 50.1, 40.4, 39.3, 30.9, 30.6, 29.6, 26.2, 21.3. IR: 3309, 2934, 1597, 1509, 1434, 1311. MS (EI, 70 eV): *m/z* = 265.2 (M^+). Calc. for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 77.16; H, 7.28; N, 15.52.

3.3.6. (6R,6′R,8R,8′R)-(+)-bis-(5,6,7,8-Tetrahydro-7,7-dimethyl-6,8-methanoquinolin-2-yl)-amine (**21**)

Synthesized according to GP1 using **20** instead of 2-amino-pyridine (**13**). White solid, 84% yield; m.p. 179–181 °C. $[\alpha]_D = +120.4$ ($c = 0.735$). ^1H NMR (400 MHz): $\delta = 7.23$ (m, 4H), 7.02 (br.s, 1H), 2.84-2.72 (m, 6H), 2.61 (m, 2H), 2.24 (sept, $J = 3.2$ Hz, 2H) 1.33 (s, 6H), 1.25 (d, $J = 9.6$ Hz, 2H), 0.63 (s, 6H). ^{13}C NMR (100 MHz): $\delta = 164.3$, 150.8, 137.0, 121.4, 108.1, 50.2, 40.5, 39.4, 31.0, 30.7, 26.3, 21.4. IR: 3406, 2937, 1582, 1510, 1444, 1344, 1265. MS (EI 70 eV): *m/z* = 359.3 (M^+). Calc. for $C_{24}H_{29}N_3$: C, 80.18; H, 8.13; N, 11.68. Found: C, 80.23; H, 7.83; N, 11.85.

3.4. Direct bis-N-arylation reaction (GP2)

In a Schlenk tube flushed with argon were successively added $Pd(dba)_2$ (0.04 mmol, 46 mg), DPPP (0.05 mmol, 42 mg) in toluene (2 mL) and the solution was stirred 15 min at room temperature. Then, the 2-halo-6-substituted-pyridine (2.2 mmol), tetrabutylammonium bromide (2.0 mmol, 644 mg), amine (1.0 mmol) and sodium *tert*-butylate (3.0 mmol, 288 mg) were added under inert atmosphere. The reaction mixture was treated with toluene (18 mL), and then heated at 100 °C until the reaction was complete (monitored by TLC or GC). The mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite. Solvents were removed on a rotary evaporator and the product was purified by column chromatography on silica gel.

3.4.1. (1S,1′S,2R,2′R,5S,5′S)-(+)-Butyl-bis-[6-(2-isopropyl-5-ethyl-cyclohexyloxy)-pyridin-2-yl]-amine (**25**)

Synthesized according to GP2. Colorless oil, 92% yield. $[\alpha]_D = +207.8$. ^{1}H NMR (400 MHz): $\delta = 7.35$ (t, $J = 8.0$ Hz, 2H), 6.70 (d, $J = 8.0$ Hz, 2H), 6.20 (d, $J = 8.0$ Hz, 2H), 4.96 (ddd, $J = 10.7$, 10.7, 4.1 Hz, 2H), 4.12 (m, 2H), 2.22 (m, 2H), 2.10 (septd, $J = 4.4$, 7.1 Hz, 2H), 1.71 (m, 4H), 1.58–1.31 (m, 6H), 1.16-0.88 (m, 20H), 0.77 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (100 MHz): $\delta = 163.0$, 155.5, 139.5, 105.8, 102.7, 74.6, 48.0, 47.4, 41.0, 34.6, 31.6, 30.7, 26.3, 23.9, 22.2, 20.7, 20.6, 16.6, 14.1. IR: 2956, 2868, 1592, 1454, 1372, 1329, 1251, 1215, 1155, 1049, 1013. HRMS Calc. for $C_{34}H_{53}N_3O_2$: 535.41377. Found: 535.41384.

3.4.2. (1S)-(+)1-(6-{Benzyl-[6-(1-hydroxy-2,2-dimethyl-propyl)-pyridin-2-yl]-amino}-pyridin-2-yl)-2,2-dimethyl-propan-1-ol (**26**)

Synthesized according to GP2. White solid, 94% yield; m.p. 96–98 °C. $[\alpha]_D = +99.6$. ^{1}H NMR (300 MHz): $\delta = 7.39$ (dd, $J = 8.2$, 7.6 Hz, 2H), 7.24–7.03 (m, 7H), 7.00 (d, $J = 8.2$ Hz, 2H), 6.66 (d, $J = 7.6$ Hz, 2H), 5.47 (d, $J = 16.3$ Hz, 1H), 5.20 (d, $J = 16.3$ Hz, 1H), 4.15 (d, $J = 6.9$ Hz, 2H), 3.94 (d, $J = 6.9$ Hz, 2H), 0.77 (s, 18H). ^{13}C NMR (75 MHz): $\delta = 158.6$, 155.5, 139.5, 137.1, 128.5, 126.7, 126.5, 116.3, 112.8, 80.2, 52.0, 36.3, 26.0. IR: 3433, 2956, 2865, 1595, 1574, 1464, 1399, 1231, 1060. MS (EI, 70 eV): $m/z = 433.3$ (M^+). Calc. for $C_{27}H_{35}N_3O_2$: C, 74.79; H, 8.14; N, 9.69. Found: C, 74.47; H, 7.89; N, 9.57.

3.4.3. (6R,6′R,8R,8′R)-(+)-Benzyl-bis-(5,6,7,8-tetrahydro-7,7-dimethyl-6,8-methanoquinolin-2-yl)-amine (**27**)

Synthesized according to GP2. White solid, 92% yield; m.p. 94–96 °C. $[\alpha]_D = +45.9$. ^{1}H NMR (300 MHz): $\delta = 7.28$ (d, $J = 8.3$ Hz, 2H), 7.16–7.02 (m, 5H), 6.78 (d, $J = 8.3$ Hz, 2H), 5.39 (dt, $J = 15.6$, 8.3 Hz, 2H), 2.84–2.71 (m, 6H), 2.57 (ddd, $J = 9.4$, 6.9, 6.9 Hz, 2H), 2.20 (m, 2H), 1.31 (s, 6H), 1.23 (d, $J = 9.4$ Hz, 2H), 0.59 (s, 6H). ^{13}C NMR (75 MHz): $\delta = 164.6$, 154.1, 140.4, 136.4, 128.1, 128.0, 126.3, 122.2, 111.7, 51.2, 50.2, 40.4, 39.2, 30.9, 30.7, 26.2, 21.3. IR: 2911, 1582, 1448, 1244, 1222. MS (EI, 70 eV): $m/z = 449.5$ (M^+). Calc. for $C_{31}H_{35}N_3$: C, 82.81; H, 7.85; N, 9.35. Found: C, 82.53; H, 7.69; N, 9.23.

3.4.4. (1S,1′S,2R,2′R,5S,5′S)-(+)-Bis-[6-(2-isopropyl-5-methyl-cyclohexyloxy)-pyridin-2-yl]-pyridin-2-ylmethyl-amine (**28**)

Synthesized according to GP2. White solid, 96% yield; m.p. 93–95 °C. $[\alpha]_D = +160.0$. ^{1}H NMR (300 MHz): $\delta = 8.45$ (dq, $J = 4.0$, 1.0 Hz, 1H), 7.41 (td, $J = 7.9$, 2.0 Hz, 1H), 7.34 (t, $J = 7.9$ Hz, 2H), 7.15 (d, $J = 7.9$ Hz, 1H), 6.99 (m, 1H), 6.82 (d, $J = 7.7$ Hz, 2H), 6.16 (d, $J = 7.7$ Hz, 2H), 5.53 (d, $J = 17.3$ Hz, 1H), 5.33 (d, $J = 17.3$ Hz, 1H), 4.60 (ddd, $J = 10.6$, 10.6, 4.2 Hz, 2H), 1.98–1.78 (m, 4H), 1.59–1.49 (m, 6H), 1.19–1.0 (m, 2H), 0.98 (m, 18H), 0.52 (d, $J = 6.9$ Hz, 6H). ^{13}C NMR (75 MHz): $\delta = 162.8$, 160.7, 154.7, 148.8, 139.6, 136.1, 121.1, 120.7, 105.0, 103.3, 74.5, 53.7, 47.4, 40.9, 34.5, 31.2, 26.3, 23.8, 22.2, 20.7, 16.6. IR: 2953, 2922, 1572, 1434, 1328, 1263, 1216, 1151. MS (EI, 70 eV): $m/z = 570.6$ (100). Calc. for $C_{36}H_{50}N_4O_2$: C, 75.75; H, 8.83; N, 9.82. Found: C, 75.59; H, 9.05; N, 9.75

3.5. Syntheses of 2-aminopyridines

3.5.1. (6R,8R)-(−)-(5,6,7,8-Tetrahydro-7,7-dimethyl-6,8-methaquinolin-2-yl)-amine (**20**)

In a Schlenk tube flushed with argon were successively added $Pd(dba)_2$ (0.04 mmol, 23 mg), DPPP (0.05 mmol, 21 mg), 2-chloro-6-pinenyl-pyridine (**8**, 1.0 mmol), benzophenone imine (**19**, 1.2 mmol, 217 mg) and sodium *tert*-butylate (1.5 mmol, 144 mg). The Schlenk tube was again degassed (three times) and flushed with argon. Toluene (20 mL) was added, and the reaction mixture heated at 80 °C until the reaction was complete (monitored by TLC or GC). The mixture was cooled to room temperature, diluted with diethyl ether and filtered through celite. Solvents were removed using a rotary evaporator and the crude product redissolved in THF (5 mL). A 2 M HCl solution (5 mL) was added, and the solution stirred 30 min at room temperature. The solution was diluted with 0.5 M HCl (5 mL), the aqueous phase extracted twice with ether and finally rendered alkaline. The aqueous layer was extracted with diethyl ether, the combined organic phases dried on Na_2SO_4 and the solvent evaporated. The brown solid was recrystallized from ether/pentane to give a white solid, 91% yield; m.p. 101–103 °C. $[\alpha]_D = -6.7$. ^{1}H NMR (400 MHz): $\delta = 7.11$ (d, $J = 8.0$ Hz, 1H), 6.24 (d, $J = 8.0$ Hz, 1H), 4.2 (br s, 2H), 2.71 (dd, $J = 3.6$, 3.3 Hz, 2H), 2.66 (dd, $J = 5.8$, 5.4 Hz, 1H), 2.56 (m, 1H), 2.21 (sept, $J = 3.0$ Hz, 1H), 1.31 (s, 3H), 1.21 (d, $J = 13.4$ Hz, 1H), 0.61 (s, 3H). ^{13}C NMR (100 MHz): $\delta = 164.4$, 155.2,

137.2, 119.2, 105.5, 53.2, 50.1, 40.5, 39.3, 30.9, 30.5, 26.3, 21.3, 20.7, 14.0. IR: 3291, 3173, 2921, 1631, 1599, 1473, 1421.MS (EI, 70 eV): 188.1 (M^+). Calc. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.77; H, 8.90; N, 14.48.

3.5.2. *(1S,2R,5S)-(+)-Butyl-[6-(2-isopropyl-5-methyl-cyclohexyloxy)-pyridin-2-yl]-amine (**24**)*

In a Schlenk tube flushed with argon were successively added $Pd(dba)_2$ (0.2 mmol, 115 mg), BINAP (0.2 mmol, 125 mg), 6-bromopyridine **6** (20.0 mmol, 6.22 g), *N*-butylamine (30.0 mmol, 2.19 g) and sodium *tert*-butylate (30.0 mmol, 2.88 g). Toluene (100 mL) was added, and the reaction mixture was heated for 24 h at 80 °C. After the reaction was complete, the mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite. Solvents were removed using a rotary evaporator, and the product purified by column chromatography on silica gel using pentane/ether (100:1) as eluent. Colorless oil, 96% yield. $[\alpha]_D = +72.8$. ^{1}H NMR (300 MHz): $\delta = 7.30$ (dd, $J = 7.9$, 7.7 Hz, 1H), 5.95 (d, $J = 7.9$ Hz, 1H), 5.87 (d, $J = 7.7$ Hz, 1H), 4.83 (td, $J = 10.6$, 4.8 Hz, 1H), 3.21(m, 1H), 2.36 (m, 2H), 2.2–2.04 (m, 2H), 1.77–1.35 (m, 8H), 1.15–0.86 (m, 12 H), 0.77 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz): $\delta = 163.2$, 157.9, 139.9, 97.8, 96.9, 74.1, 47.7, 42.1, 41.0, 34.6, 31.8, 31.6, 26.2, 23.7, 22.2, 20.8, 20.3, 16.6, 13.9. IR: 3420, 2955, 2868, 1592, 1499, 1371, 1328, 1314, 1255, 1144. HRMS Calc. for $C_{19}H_{32}N_2O$: 304.25124. Found: 304.25146

3.6. *N*-Arylation of secondary amino pyridines (GP3)

In a Schlenk tube flushed with argon were successively added $Pd(dba)_2$ (0.04 mmol, 23 mg) and DPPP (0.05 mmol, 21 mg) in toluene (2 mL) and the solution was stirred 15 min at room temperature. The 2-bromo-6-substituted-pyridine (1.2 mmol), tetrabutylammonium bromide (1.0 mmol, 322 mg), amino pyridine **24** (1 mmol) and sodium *tert*-butylate (1.5 mmol, 144 mg) were then added under argon. The reaction mixture was then treated with toluene (18 mL) and subsequently heated at 100 °C until the reaction was complete (monitored by TLC or GC). The mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite. The solvents were removed using a rotary evaporator, and the product purified by column chromatography on silica gel.

3.6.1. *(+)-1-(6-{Butyl-[6-(2-isopropyl-5-methyl-cyclohexyloxy)-pyridin-2-yl]-amino}-pyridin-2-yl)-2,2-dimethyl-propan-1-ol (**29**)*

Synthesized according to GP3. Colorless viscous oil, 94% yield. $[\alpha]_D = +139.6$. ^{1}H NMR (300 MHz): $\delta = 7.41$ (m, 2H), 7.08 (d, $J = 8.4$ Hz, 1H), 6.68 (d, $J = 7.4$ Hz, 1H), 6.61 (d, $J = 7.9$ Hz, 1H), 6.26 (d, $J = 7.9$ Hz, 1H), 4.90 (ddd, $J = 10.6$, 10.6, 4.2 Hz, 1H), 4.31 (dd, $J = 7.4$, 4.6 Hz, 2H), 4.26–4.0 (m, 2H), 2.26–2.0 (m, 2H), 1.80-1.65 (m, 4H), 1.60-1.25 (m, 4H), 1.20–0.80 (m, 21H), 0.76 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz): $\delta = 162.9$, 158.0, 155.9, 155.2, 139.6, 136.3, 115.2, 113.2, 105.3, 103.4, 80.0, 74.6, 48.2, 47.4, 41.0, 36.3, 34.6, 31.6, 30.7, 26.4, 26.0, 23.9, 22.2, 20.7, 20.5, 16.7, 14.1. IR: 3464, 2956, 2927, 2864, 1572, 1439, 1249, 1214, 1152. HRMS Calc. for $C_{29}H_{45}N_3O_2$: 467.351178. Found: 467.351115.

3.6.2. *Butyl-[6-(4-isopropyl-4,5-dihydro-oxazol-2-yl)-pyridin-2-yl]-[6-(2-isopropyl-5-methyl-cyclohexyloxy)-pyridin-2-yl]-amine (**30**)*

Synthesized according to GP3. Colorless viscous oil, 76% yield. $[\alpha]_D = +42.5$. ^{1}H NMR (400 MHz): $\delta = 7.63$ (d, $J = 6.9$ Hz, 1H), 7.54 (t, $J = 8.2$, 6.9 Hz, 1H), 7.38 (t, $J = 8.0$, 7.7 Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 6.58 (d, $J = 8.0$ Hz, 1H), 6.21 (d, $J = 7.7$ Hz, 1H), 4.91 (ddd, $J = 10.7$, 10.7, 4.1 Hz, 1H), 4.49 (dd, $J = 9.3$, 8.0 Hz, 1H), 4.19 (m, 4H), 2.21–2.05 (m, 2H), 1.89 (sext, $J = 6.6$ Hz, 1H), 1.77–1.64 (m, 4H), 1.55–1.32 (m, 4H), 1.07 (d, $J = 6.9$ Hz, 3H), 0.97–0.87 (m, 12H), 0.74 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (100 MHz): $\delta = 162.4$, 156.9, 155.0, 145.3, 139.5, 136.7, 118.2, 117.1, 103.8, 102.7, 74.2, 72.7, 70.6, 48.2, 47.3, 40.9, 34.5, 32.9, 31.6, 30.6, 26.3, 23.9, 22.2, 20.6, 20.4, 19.1, 18.2, 16.6, 14.0. IR: 2956, 1645, 1569, 1439, 1253. MS (EI, 70 eV): $m/z = 492.6$ (M^+). Calc. for $C_{30}H_{44}N_4O_2$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.03; H, 9.40; N, 11.65.

3.6.3. *(6R,8R)-(+)-Benzyl-(5,6,7,8-tetrahydro-7,7-dimethyl-6,8-methanoquinolin-2-yl)-pyridin-2-yl-amine (**23**)*

In a Schlenk tube flushed with argon were successively added $Pd(dba)_2$ (0.04 mmol, 23 mg) and DPPP (0.05 mmol, 21 mg) in toluene (2 mL), and the solution was stirred 15 min at room temperature. Benzyl-2-pyridinyl amine **9** (1.2 mmol), tetrabutylammonium bromide (1.0 mmol, 322 mg), *N*-benzyl-2-amino-pyridine (1.0 mmol) and sodium *tert*-butylate (1.5 mmol, 144 mg) were then added under argon. The reaction mixture was then treated with toluene (18 mL) and subsequently heated at 100 °C until the reaction was complete (monitored by TLC or GC). The mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite. Solvents were removed using a rotary evaporator and the product purified by column chromatography on silica gel. White solid, 81% yield; m.p. 70–72 °C. $[\alpha]_D = +23.8$. ^{1}H NMR (400 MHz): $\delta = 8.23$ (dd, $J = 4.9$, 1.1 Hz, 1H), 7.40 (dt, $J = 4.9$, 1.1 Hz, 1H), 7.33 (d, $J = 7.4$ Hz, 1H), 7.29–7.20 (m, 4H), 7.18–7.12 (m, 1H), 7.02 (d, $J = 8.5$ Hz, 1H), 6.95 (d, $J = 7.9$ Hz, 1H), 6.72 (ddd, $J = 7.1$, 4.9, 0.8 Hz, 1H), 5.46 (dd, $J = 16.2$, 14.2 Hz, 2H), 2.91–2.83 (m, 3H), 2.67 (ddd, $J = 9.7$, 5.8, 5.8 Hz, 1H), 2.30 (sept, $J = 2.8$ Hz, 1H), 1.40 (s, 3H), 1.31 (d, $J = 9.6$ Hz, 1H), 0.67 (s, 3H). ^{13}C NMR

(100 MHz): δ = 165.2, 157.4, 153.6, 147.9, 139.8, 136.7, 136.7, 128.2, 127.4, 126.4, 124.3, 115.4, 114.1, 112.3, 51.4, 50.3, 40.4, 39.3, 30.9, 26.2, 21.4. IR: 2921, 2864, 1589, 1434, 1244, 1222, 1101, 1088. MS (EI, 70 eV): m/z = 355.6 (M^+). Calc. for $C_{24}H_{25}N_3$: C, 81.09; H, 7.09; N, 11.82. Found: C, 81.47; H, 6.91; N, 11.85.

3.7. Synthesis of the copper(II) complex

3.7.1. (6R,6′R,8R,8′R)-(+)-Benzyl-bis-(5,6,7,8-tetrahydro-7,7-dimethyl-6,8-methanoquinolin-2-yl)-amine copper dichloride (31)

To a solution of anhydrous $CuCl_2$ (0.5 mmol, 67 mg) in absolute ethanol (10 mL) was added under vigorous stirring 2,2′-dipridylamine **27** (0.5 mmol, 225 mg) in CH_2Cl_2 (2 mL). Immediately, a green solid precipitated and stirring was continued for 15 min. The solvent was partially evaporated under reduced pressure, and the solution let to stand at 4 °C over night. The green solid was collected by filtration to afford **31** in 93% yield. Crystals suitable for X-ray analysis were grown by slow diffusion of diethyl ether into a CH_2Cl_2 solution of the complex, which was obtained as the CH_2Cl_2 adduct. M.p. >250 °C. Calc. for $C_{31}H_{35}Cl_2CuN_3O\cdot CH_2Cl_2$: C, 57.45; H, 5.57; N, 6.28. Found: C, 57.60; H, 5.78; N, 6.25.

Crystal data for complex **31**: $C_{31}H_{35}N_3Cl_2Cu\cdot CH_2Cl_2$, M = 669.03 g mol^{-1}, green crystal (plate), 0.07×0.31×0.38 mm, monoclinic, space group $P2_1$ (No. 4), Z = 2, a = 8.318(3), b = 16.125(5), c = 12.609(4) Å, β = 107.216(6)°, V = 1615.4(8) Å^3, $\rho_{calc.}$ = 1.375 g cm^{-3}, T = 298 K, Mo Kα, μ = 1.033 mm^{-1}, 37,620 reflections measured, 5528 observed reflections ($I > 2\sigma I$, R_{int} = 0.05), 361 parameters, R (R_w) = 0.056(0.054, $w = [\sigma(F)^2 + 0.0004F^2]^{-1}$), X_{abs} = 0.008(23), S = 1.317, residual electron density −0.51/+0.71 e Å^{-3}.

3.8. Asymmetric allylic oxidation of cyclohexene

To a solution of $Cu(OTf)_2$ (0.05 mmol, 18.1 mg, 5 mol%) in acetone (5 mL) was added under argon 0.05 mmol of the ligand (5 mol%) and the solution was stirred 30 min at room temperature. The mixture was then treated with phenylhydrazine (0.06 mmol, 6.5 mg) and further stirred for 15 min. Subsequently, cyclohexene (**32**, 10 mmol, 1 mL) followed by *tert*-butylperoxybenzoate (**33**, 1.0 mmol) were added, and the solution stirred at room temperature until the oxidant was consumed. The solvent was removed in a vacuum, the residue was dissolved in CH_2Cl_2 (15 mL), washed with saturated $KHCO_3$, brine, and dried over $MgSO_4$. Removal of the solvent followed by chromatography column afforded pure **34**. The enantiomeric excesses were determined by HPLC using a Chiralpak AD column [hexane–isopropanol (250:1), flow rate 0.5 mL/min. tR = 10.6 min, tS = 12.8 min, UV detection at 254 nm].

4. Supplementary material

The crystallographic data for the structural analysis have been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 230412. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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