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Preparative Scale Synthesis of Vedejs Chiral DMAP Catalysts

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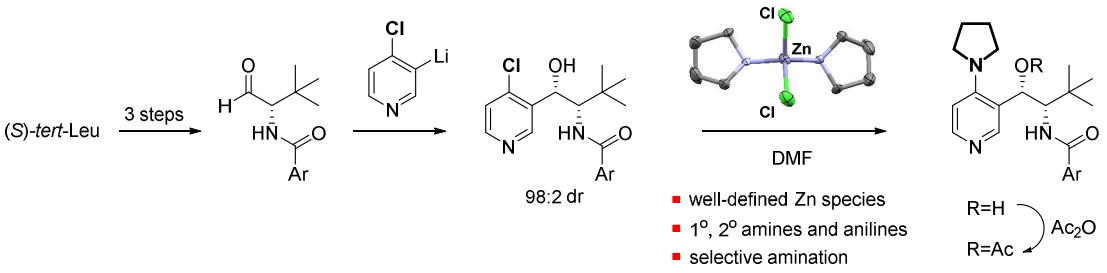
TOC Abstract.



Abstract. A scalable synthesis of chiral Vedejs-type DMAP catalysts is reported. The key step of the synthesis is amination of the enantiomerically pure 4-chloropyridine derivative using well-defined $ZnCl_2(amine)_2$ complexes. A series of Zn(II)-amine complexes have been synthesized to explore the scope of the $ZnCl_2$-mediated amination of 4-halopyridines. Mechanistic studies support a Zn(II)-facilitated nucleophilic aromatic substitution as a plausible mechanism for the chlorine-to-amine exchange.

Introduction

Chiral DMAP-catalyzed asymmetric acyl-transfer reactions are widely used in the synthesis of enantiomerically pure compounds.[1] A variety of chiral DMAP catalysts have been developed for a range of enantioselective acylation reactions.[2] Among them, a family of *tert*-leucine-derived chiral DMAP catalysts (*S*,*S*)–**1** developed by Vedejs (Figure 1, eq 1) have provided excellent enantiocontrol in the Steglich rearrangement of indolyl acetates and carbonates,[3a] in the kinetic resolution (KR) of secondary alcohols[3b] as well as in the dynamic KR of azole-derived hemiaminals.[3c] The efficiency of Vedejs catalysts in various asymmetric transformations is attributed to their modular design, which allows for a relatively simple fine-tuning of the chiral DMAP structure for a particular stereoselective reaction. Unfortunately, the challenges associated with the preparative scale synthesis of chiral DMAP (*S*,*S*)–**1** has hampered its wider application in enantioselective synthesis. The difficult step for the scale-up is attachment of the *tert*-leucine chiral subunit to the DMAP core, a reaction that requires lithiation of a DMAP derivative with excess *tert*-BuLi. Herein we report a new approach towards the family of chiral DMAP catalysts (*S*,*S*)–**1**, which is based on a highly diastereoselective addition of 3-lithio-4-chloropyridine intermediate to (*S*)–*tert*-leucine-derived aldehyde (*S*)–**2**, followed by $ZnCl_2$-mediated substitution of chlorine for amine as key steps (Figure 1, eq 2). The new approach is especially suitable for multi-gram scale syntheses of the chiral DMAP catalysts (*S*,*S*)–**1** since inexpensive starting 4-chloropyridine and easy-to-handle and safe LDA are used in the *ortho*-lithiation step. Furthermore, the $ZnCl_2$-promoted amination step allows for installation of a range of amines in the pyridine subunit, thus further increasing modularity of the chiral DMAP catalysts (*S*,*S*)–**1**. It should be also noted that halide-to-amine exchange is a frequently used transformation in the synthesis of chiral DMAP catalysts. For example, Connon and Spivey employed the amination of 4-chloropyridines under S_NAr conditions[2c-e] to obtain chiral DMAP species. Alternatively, 4-amino substituent was also introduced into pyridine core through 3,4-pyridyne intermediate.[2f] Finally, Mandai and Suga utilized Pd-catalyzed Buchwald-Hartwig amination of 4-bromopyridine[2b] in the synthesis of their C_2-symmetric chiral DMAP catalyst. Application of the $ZnCl_2$-promoted amination as inexpensive and relatively mild complementary methodology to access these catalysts is demonstrated below.

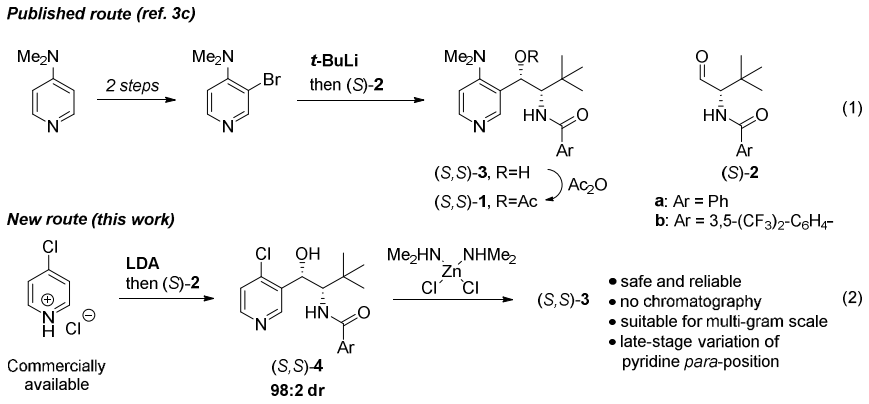


Figure 1. Synthesis of chiral DMAP catalysts.

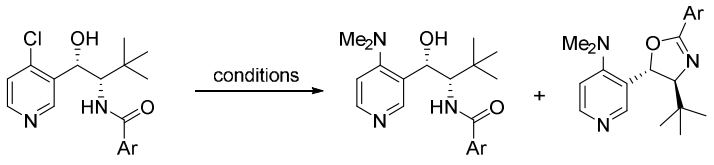
Results and Discussion

The requirement for an excess of the highly pyrophoric *t*-BuLi to generate 3-Li-DMAP from the corresponding bromide (Figure 1, eq 1)[3a,c] largely constrains multi-gram scale preparation of chiral DMAP (*S*,*S*)–**1** because of safety reasons. Attempts to replace *t*-BuLi with a less hazardous and easier-to-handle lithiation reagent such as *n*-BuLi was not successful and resulted in decreased yields of the addition product (*S*,*S*)–**3**. We realized that directed *ortho*-lithiation of a suitably substituted pyridine is the most straightforward approach for installation of the *tert*-leucine chiral subunit. Unfortunately, a directed *ortho*-lithiation[4] of DMAP at position 3 with LDA was not successful, apparently because of poor *ortho*-directing ability of the *N*,*N*-dimethylamino moiety. The search for a more efficient *ortho*-directing group that could be subsequently transformed into *N*,*N*-dimethylamino moiety led us to the choice of commercially available and inexpensive 4-chloropyridine as a substrate for the *ortho*-lithiation. Treatment of commercially available 4-chloropyridine hydrochloride[5] with two equivalents of LDA,[6] followed by a reaction with enantiomerically pure aldehyde (*S*)–**2b**[3c] afforded (*S*,*S*)–**4b** in 71% yield (Figure 1, eq 2). Gratifyingly, the addition of lithiated pyridine to (*S*)–**2b** proceeded with excellent diastereoselectivity (98:2 dr). The diastereomeric purity of the crystalline aldol product (*S*,*S*)–**4b** was increased to >99:1 dr by a single recrystallization of the crude material. Absolute configuration of the newly created stereogenic center was confirmed to be (*S*) by comparison of a downstream synthesis product (*S*,*S*)–**1b** with a batch of a previously synthesized catalyst.[3c] The lithiation-addition sequence was easily scaled-up to more than 5 g loading of 4-chloropyridine.

Next, substitution of the 4-chloro moiety by the dimethylamino group was investigated. Attempted reaction of 4-chloropyridine (*S*,*S*)–**4b** with 40% aqueous

dimethylamine (100 °C, 48 h)[7] afforded the desired (*S*,*S*)–**3b** in poor yields along with multiple decomposition products (entry 1, Table 1). Nucleophilic substitution of chlorine with liquid $HNMe_2$ in various anhydrous solvents such as methanol, DMSO and DMF (entries 2-4) was also unsuccessful. When a 1:1 (v/v) mixture of DMF and water was used as a solvent, the reaction with $HNMe_2$ resulted in formation of the desired (*S*,*S*)–**3b** without concomitant decomposition of the starting (*S*,*S*)–**4b**. Although the presence of water facilitated the formation of chiral DMAP (*S*,*S*)–**3b**, the reaction was very slow, and only 30% conversion after heating at 100 °C for 20 h could be achieved (entry 5). The use of DMF as a source of $HNMe_2$[8] led to complete decomposition of the starting (*S*,*S*)–**4b** (entry 6). Disappointingly, the reaction with liquid $HNMe_2$ in the presence of catalytic Cu/CuCl[9] did not afford the desired chiral DMAP (entry 7). In contrast, the reaction of (*S*,*S*)–**4b** with $ZnCl_2(NHMe_2)_2(HCl)_2$, prepared from $ZnCl_2$ and Me_2NH hydrochloride,[10] furnished the desired chiral DMAP (*S*,*S*)–**3b** in 71% yield (entry 8).[11] Unfortunately, the success of the $ZnCl_2$-mediated substitution was counterbalanced by experimental difficulties associated with handling the thick suspension of inorganic salts (ca. 1.8 g of solid in 1 mL of DMSO) and with generation of considerable amounts of inorganic waste. Furthermore, ca. 10% of a side-product oxazoline (*S*,*S*)–**5** was also formed, and its separation from the desired (*S*,*S*)–**3b** required chromatography. To address these shortcomings, the $ZnCl_2$-mediated substitution reaction was investigated in more detail.

Table 1. Optimization of the amination conditions.



(*S*,*S*)-**4b** (*S*,*S*)-**3b** (*S*,*S*)-**5**

Ar = 3,5-$(CF_3)_2$-C_6H_4-

entry	conditions	(*S*,*S*)–**3b**, %
1	40% $HNMe_2$ in water, 100 °C, 47 h	20[a]
2	$HNMe_2$ (liquid):methanol 1:1 (v/v), 100 °C, 13 h	<1[b]
3	$HNMe_2$ (liquid):DMF 1:1 (v/v), 100 °C, 13 h	<1[b]
4	$HNMe_2$ (liquid):DMSO 1:1 (v/v), 100 °C, 13 h	<1[b]
5	$HNMe_2$ (liquid):DMF:water 2:1:1 (v/v), 100 °C, 20 h	30[c]
6	K_2CO_3, DMF,[d] 80 °C, 60 h	<1[a]
7	$HNMe_2$ (liquid), Cu (0.25 equiv), CuI (0.25 equiv) 80 °C, 40 h	<1[a]

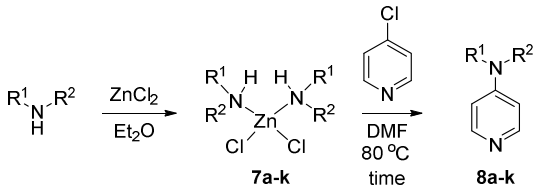
8	$ZnCl_2(NHMe_2)_2(HCl)_2$ (**6**; 5 equiv), K_2CO_3 (1.3 equiv), DMSO, 100 °C, 21 h	71[e]
9	$ZnCl_2(NHMe_2)_2$ (**7a**; 2 equiv), DMF, 80 °C, 63 h	80

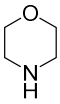
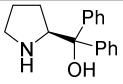
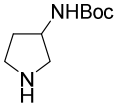
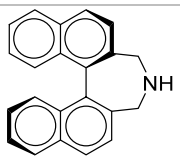
[a] Accompanied by multiple decomposition products [b] No conversion of (*S*,*S*)–**4b**. [c] At 30% conversion of (*S*,*S*)–**4b**. [d] DMF served both as a source of $HNMe_2$ and as a solvent. [e] Accompanied by ca. 10% of oxazoline (*S*,*S*)–**5**.

We hypothesized that a complex between $ZnCl_2$ and the *free base* $HNMe_2$ is the reactive species in the $ZnCl_2$-mediated substitution reaction, and that the role of K_2CO_3 is limited to the conversion of complex **6**[10b] into the reactive species. To verify this hypothesis, a new complex $ZnCl_2(NHMe_2)_2$ (**7a**) was prepared by mixing equimolar amounts of $HNMe_2$ (2M solution in THF) and $ZnCl_2$ in Et_2O.[12] Gratifyingly, addition of **7a** (2 equiv) to (*S*,*S*)–**4b** in DMF resulted in a smooth formation of the desired (*S*,*S*)–**3b** in 80% yield (entry 9, Table 1). Furthermore, the excellent solubility of the Zn(II)-amine complex **7a** in DMF completely circumvented difficulties with handling the previously encountered thick suspension of inorganic salts.

To examine the scope of amines in the Zn(II)–mediated chlorine substitution reaction, a series of Zn(II)-amine complexes **7b**–**j** have been synthesized (Table 2) from the corresponding amine and $ZnCl_2$ in Et_2O. Products **7a,c**–**j** precipitated from the reaction mixture and could be recrystallized from EtOH. Complex **7b** was obtained as an oil in moderate yield (entry 2). The structures of Zn complexes **7d**,**f**,**h**,**j** have been verified by X-ray crystallographic analysis. Interestingly, the alcohol moiety of 1,2-aminoalcohol **7h** is not involved in the complex formation with Zn(II) species as evidenced by the X-ray data (see Supporting Information). Secondary amine-derived complexes **7a,b,d**–**f** readily reacted with 4-chloropyridine and formed the corresponding 4-aminopyridines within 3 h (entries 1,2,4–6, Table 2). A slower reaction was observed for primary aliphatic and aromatic amine-containing Zn species **7c,g,j** (entries 3,7,10). as well as for sterically hindered secondary amine-derived Zn complexes **7h,k** (entries 8,11). It should be mentioned that Zn(II)-amine complexes could not be obtained in a pure form from sterically highly hindered *N*,*N*-diisopropylamine and 2,6-dimethylpiperidine. Hence, secondary amines possessing steric bulk next to the nitrogen atom are not suitable for the Zn(II)-mediated amination reaction. The Zn(II)-mediated amination reaction conditions are compatible with the alcohol (entry 8) and the carbamate N-H (entry 9) moieties in the amine. Finally, the reaction between 4-chloropyridine and Zn complex (*R,R*)–**7k** (entry 11, Table 2) is a less expensive alternative to the Pd-catalyzed Buchwald-Hartwig amination for the synthesis of axially chiral DMAP catalyst (*R*)–**8k**, developed by Mandai and Suga.[2b]

Table 2. The scope of amines.

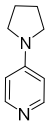
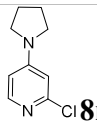
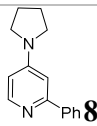
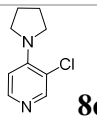
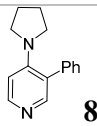
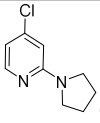
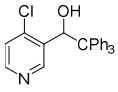
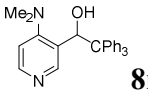
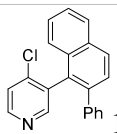
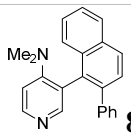


entry	R^1R^2NH	yield of **7**	yield of **8** (time)
1	Me_2NH	**7a**, 75%	**8a**, 82% (3 h)
2	Et_2NH	**7b**, 39%	**8b**, 68% (3 h)
3		**7c**, 64%	**8c**, 53% (18 h)
4		**7d**, 70%[a]	**8d**, 77% (3 h)
5		**7e**, 85%	**8e**, 64% (3 h)
6		**7f**, 80%[a]	**8f**, 73% (3 h)
7	$PhNH_2$	**7g**, 93%	**8g**, 86% (18 h)
8		(*S,S*)–**7h**, 76%[a]	(*S*)–**8h**, 79% (18 h)
9		**7i**, 86%	**8i**, 86% (18 h)
10		(*S,S*)–**7j**, 80%[a]	(*S*)–**8j**, 83% (32 h)
11		(*R,R*)–**7k**, 68%	(*R*)–**8k**, 75% (16 h)

[a] Structure confirmed by X-ray crystallographic analysis.

Next, the scope of pyridines was examined in the reaction with Zn(II)-amine complex **7d** (Table 3). The amination reaction of 4-halosubstituted pyridines with **7d** proceeded readily (entries 1–4) with 4-fluoropyridine being the most reactive among halides (entry 1). The reactivity of halides decreased in the order F>Cl>Br>I. In addition, 2-halosubstituted pyridines were less reactive than their 4-substituted congeners: only 2-fluoropyridine underwent amination with Zn complex **7d** (entry 5), whereas 2-Cl and 2-Br-pyridines did not react under standard conditions (entries 6,7). This allowed for selective substitution at the position 4 in 2,4-dichloropyridine (entry 8),[13] whereas 2-fluoro-4-chloropyridine underwent selective substitution of the more reactive fluoro-moiety (entry 12). Notably, the amination proceeded considerably faster for 2-unsubstituted pyridine (entry 2) as compared to its 2-Cl and 2-Ph substituted analogs (compare reaction half-lives in entries 2, 8 and 9, Table 3). The presence of a substituent in position 3 has a less pronounced influence on the reactivity with Zn complex **7d** (see reaction half-lives in entries 2, 10 and 11). These observations imply that the reactivity of the 4-chloro substituent in pyridines is influenced mostly by steric bulk in the remote *meta* position, and to a lesser extent by substitution of the proximal *ortho*-position. Finally, the Zn(II)–mediated amination of **9** and **10** with **7a** (entries 13 and 14, respectively) provides a convenient access to DMAP species such as *rac*–**8r** (precursor of TADMAP catalyst)[14] and the *N*,*N*-dimethylamino analogue of Spivey catalyst *rac*–**8s**.[2e,f]

Table 3. Substrate scope for the amination reaction.[a]

entry	substrate	product, yield	$t_{1/2}$, h
1	4-F-pyridine	 **8d**, 88-90%	<0.5
2	4-Cl-pyridine		3.6
3	4-Br-pyridine		4.7
4	4-I-pyridine		19.2
5	2-F-pyridine	 **8l**, 83%	4.2
6	2-Cl-pyridine	no reaction[b]	-
7	2-Br-pyridine	no reaction[b]	-
8		 **8m**, 78%	63.7
9[c]		 **8n**, 56%[d]	75.0
10		 **8o**, 73%	2.2
11		 **8p**, 67%	35.9
12		 **8q**, 95%	3
13[c]	 **9**	 **8r**, 83%	nd
14[e]	 **10**	 **8s**, 78%	nd

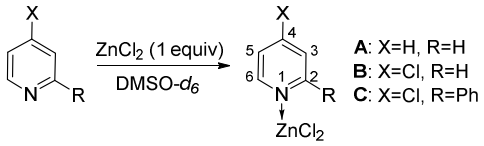
[a] Reaction conditions: pyridine (1 equiv), Zn complex **7** (2 equiv), DMF (1 mL per 1 mmol of pyridine), 40 °C. [b] 0% conversion after 24 h. [c] The reaction was performed at 80 °C; 0% conversion after 75h at 40 °C. [d] At 50% conversion. [e] The reaction was performed at 120 °C

The relative reactivity of 4-halopyridines (F>Cl>Br>I) is characteristic to that observed in nucleophilic aromatic substitution (S_NAr) reactions. Therefore we hypothesized

that the Zn complex–mediated amination of halopyridines proceeds through the S_NAr pathway. We propose that the Zn(II) species helps to stabilize a transient Meisenheimer-type anionic intermediate of the nucleophilic aromatic substitution reaction by forming a Lewis acid-Lewis base complex with pyridine under equilibrium conditions (Scheme 1). Experimental evidence for the complex formation between pyridine and $ZnCl_2$ was obtained from NMR studies. Thus, addition of $ZnCl_2$ (1 equiv) to 4-chloropyridine **B** resulted in an upfield shift of pyridine nitrogen (^{15}N-NMR)[15] and a downfield shift of carbon C4 resonances (Table 4). Less pronounced changes of ^{13}C signals were observed for other carbon atoms. Furthermore, substantial decrease of ^{13}C spin-lattice relaxation times T_1 for all carbon atoms was observed in pyridine **B** in the presence of $ZnCl_2$, with the largest decrease of 62% (from 12.6 to 4.8 sec) measured for carbon C4 (Table 4). Even larger shifts of ^{13}C and ^{15}N signals as well as more pronounced decrease of T_1 values were measured for the relatively more Lewis basic pyridine **A** in the presence of added $ZnCl_2$.[16] In sharp contrast, negligible changes of the chemical shifts and relaxation times were observed for 2-Ph substituted pyridine **C**. This suggests a small equilibrium concentration of the Lewis acid-Lewis base complex between $ZnCl_2$ and pyridine **C**, presumably because of a steric shielding of the nitrogen by 2-phenyl substituent. Such a hypothesis is in agreement with the considerably longer reaction times required for chlorine to amine exchange at position 4 of 2-Ph and 2-Cl pyridines (entries 8,9, Table 3) as opposed to their 3-substituted analogues (entries 10,11, Table 3) or 4-chloropyridine (entry 2, Table 3).

Kinetic studies were also carried out to establish the kinetic order of Zn(II)-mediated amination of 4-chloropyridine in each reaction component. The reactions were monitored by NMR spectroscopy, and the reaction order in Zn(II) complex **7d** and 4-chloropyridine was determined by plotting the reaction half-time vs. natural logarithm of reactants concentration (Noyes plot). The amination of 4-chloropyridine in DMF at 40 ^{o}C was found to be second-order in Zn(II) complex **7d** (see SI, Figure S1) and first-order in 4-chloropyridine (see SI, Figure S2). These data indicate that two equivalents of Zn(II) complex **7d** are involved in a rate-determining step of the amination. In fact, a stoichiometry of a classical two-step base-catalyzed S_NAr reaction in polar aprotic solvents in the absence of added general base requires two equivalents of amine, with one acting as a nucleophile, and the other one serving as a base.[17]

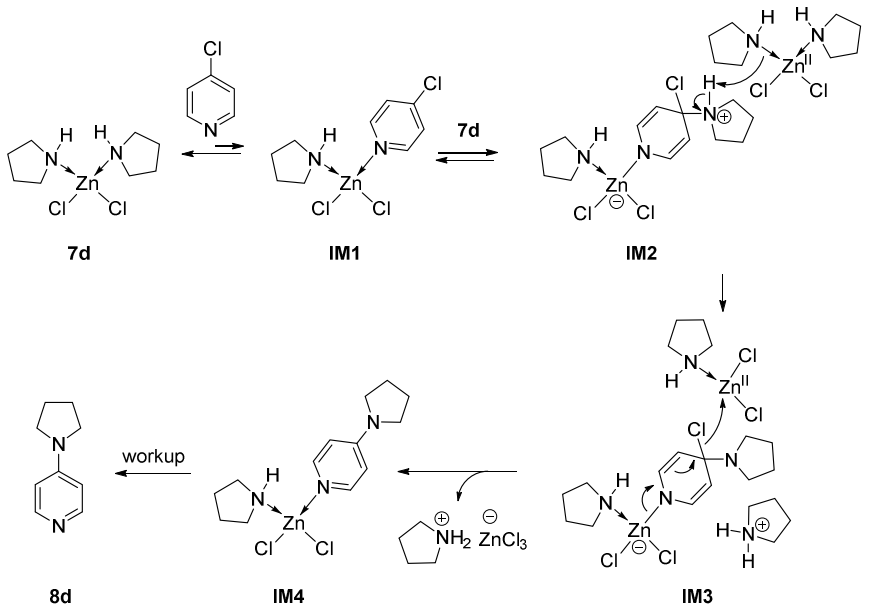
Table 4. Percent Change of ^{13}C and ^{15}N chemical shifts[a] and spin-lattice relaxation time T_1.[b]



Atom	A[c]		B		C[d]	
	Δδ (%)	ΔT1 (%)	Δδ (%)	ΔT1 (%)	Δδ (%)	ΔT1 (%)
C2	0.51	-74.2	0.30	-39.1	0.18	-15.7
C3	-1.03	-75.0	-0.38	-43.1	0.21	-15.0
C4	-2.06	-87.7	-0.72	-61.9	0.19	-10.6
C5	-1.03	-75.0	-0.38	-43.1	0.22	-11.6
C6	0.51	-74.2	0.30	-39.1	0.16	-13.4
N1	10.5	-	4.14	-	0.05	-

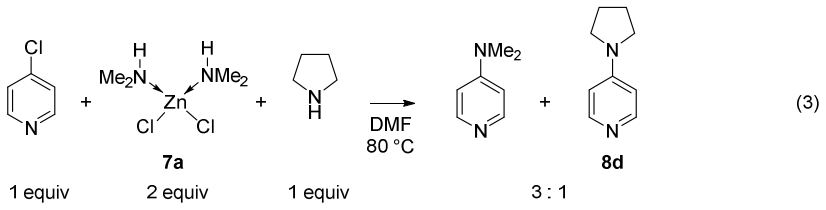
[a] For chemical shift values see SI. Negative values represent a downfield shift and positive values an upfield shift of NMR signals. [b] Negative ΔT1 values represent decrease of relaxation time. [c] A 1:1 mixture of 4-chloropyridine hydrochloride and DIPEA was used. [d] Determined in DMF–d_7.

Consistent with the data above is a plausible pathway for Zn(II)-mediated amination of 4-chloropyridines, which involves an initial reversible formation of Zn(II)-pyridine complex **IM1** and pyrrolidine (Scheme 1). Subsequent nucleophilic *ipso*-addition of pyrrolidine to the Zn(II)-coordinated 4-chloropyridine results in the formation of Meisenheimer-type intermediate **IM2**. Not only is the electrophilicity of pyridine increased, but also the intermediate zwitterionic complex **IM2** is stabilized by complexation with Lewis acidic Zn(II) species. Ion pair **IM3** is generated after proton transfer from intermediate **IM2** to the pyrrolidine ligand of the complex **7d.** Finally, departure of the chloride leaving group provides Zn complex **IM4** which hydrolyzes to pyridine **8d** during the workup (Scheme 1). It is conceivable that the departure of the chloride leaving group is facilitated by coordination to a Zn(II) species, however we do not have sufficient evidence to support this assumption.



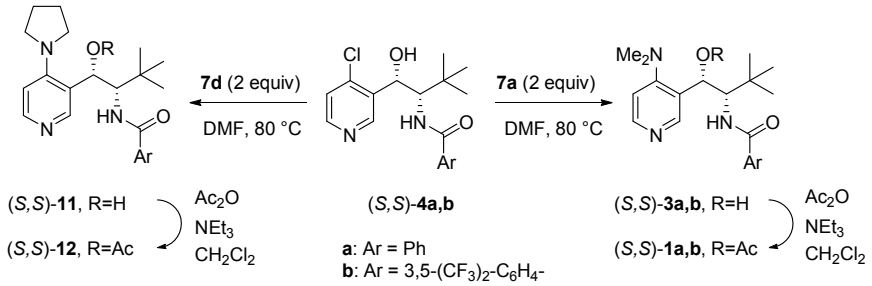
Scheme 1. Working mechanism for Zn(II)-mediated amination reaction.

The proposed mechanism implies that only 3 equivalents of pyrrolidine are available under equilibrium conditions for the nucleophilic substitution of chlorine, whereas one equivalent of the amine is involved in the Zn(II)-pyridine complex formation. This scenario was supported by a control experiment where 4-chloropyridine was reacted with a 2:1 mixture of Zn(II) complex **7a** and pyrrolidine under standard conditions (eq 3). In total 5 equivalents of amines of comparable Lewis basicity and nucleophilicity (nucleophilicity parameter *N* for Me_2NH in MeCN is *N*=17.96[18a] and for pyrrolidine *N*=18.64[18b]) were present in the reaction mixture under equlibrium conditions, however chlorine substitution products DMAP and PPY were formed in 3:1 ratio (^{1}H-NMR assay). Comparable reactivity of pyrrolidine and Zn-coordinated Me_2NH in the substitution of chlorine also supports exchange of amine ligands between different Zn(II) complexes.[19a] Finally, coordination of Zn(II) species by the solvent and formation of DMF-containg complexes such as $Zn(DMF)_2Cl_2$[19b] or mixed analogues such as $Zn(DMF)(amine)Cl_2$ under equilibrium conditions cannot be ruled out. Nevertheless, we regard the aromatic nucleophilic substitution mechanism *via* **IM1** (Scheme 1) to be sufficiently plausible and consistent with the available data for most experiments.[20]



(3)

Chiral DMAP derivatives (*S*,*S*)–**3a,b** and (*S*,*S*)–**11** were obtained in 76-80% yield from pyridines (*S*,*S*)–**4a,b** and Zn(II)-amine complexes **7a,d** under the optimized conditions for the aromatic nucleophilic substitution (Scheme 2). Because the amination proceeded without formation of side-products such as (*S*,*S*)–**5** (see Table 1), a simple extractive workup was sufficient to obtain targets (*S*,*S*)–**3a,b** and (*S*,*S*)–**11** in pure form and additional chromatographic purification was not required. Finally, *O*-acetylation with Ac_2O provided the corresponding chiral DMAP catalysts (*S*,*S*)–**1a,b** and (*S*,*S*)–**12** in excellent 91-95% yield (Scheme 2). Pure products were obtained by recrystallization of crude solid materials.



Scheme 2. Final stages of chiral DMAP synthesis.

Conclusions

A scalable synthesis of Vedejs-type chiral DMAP catalysts comprising two key steps has been described. The first key step is *ortho*-lithiation of readily available and inexpensive 4-chloropyridine hydrochloride with LDA, and subsequent highly diastereoselective (98:2 dr) addition of the lithiated intermediate to (*S*)–*tert*-leucine-derived aldehyde (*S*)–**2**. The diastereomeric purity of the crystalline aldol product (*S,S*)–**4** was increased to >99:1 dr by a single recrystallization. The second key step of the synthesis is the substitution of the 4-chloro moiety in the enantiomerically pure pyridine (*S,S*)–**4** with dimethylamine or pyrrolidine. The amination employs well-defined $Zn(amine)_2Cl_2$ complexes, which were prepared from $ZnCl_2$ and the respective amine. Only those amines which form relatively stable complexes with $ZnCl_2$ can be employed in the amination. Primary and secondary aliphatic amines as well as aniline readily formed crystalline complexes with $ZnCl_2$, and structures of $Zn(amine)_2Cl_2$ complexes **7d**,**f**,**h**,**j** were confirmed by X-ray crystallographic analysis. The reactivity of pyridyl halides with Zn(II)-amine species decreased in the order F>Cl>Br>I, and selective amination of the more reactive 4-chloro substituent in 2,4-dichloropyridine can be achieved. The reactivity of the 4-chloro substituent is reduced considerably if the heterocycle possesses a substituent next to the pyridine nitrogen. Mechanistic studies suggest that the pyridine nitrogen forms a complex with Zn(II) species

under equilibrium conditions. Lewis acid-Lewis base-type interactions between Zn(II) species and 4-halopyridine increases electrophilicity of the heterocycle and helps to stabilize the Meisenheimer-type intermediate of the aromatic nucleophilic substitution reaction. The developed synthetic approach is especially suitable for the multi-gram scale synthesis of chiral DMAP derivatives because it employs safe and inexpensive chemicals and avoids chromatographic purification. Late-stage introduction of the amine moiety in the pyridine core helps to fine-tune the nucleophilicity of Vedejs chiral DMAP catalysts for given asymmetric transformations. Efficiency of the Zn(II)–mediated chlorine substitution reaction in the synthesis of various DMAP catalysts is also demonstrated. Finally, the Zn(II)-mediated amination may be especially useful for the synthesis of pharmaceutically relevant aminopyridines in cases where the transition metal-catalyzed amination is not applicable.

Experimental Section

General Information. Unless otherwise noted, all chemicals were used as obtained from commercial sources and all reactions were performed under argon atmosphere. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F-254 plates. Nuclear magnetic resonance spectra were recorded on NMR spectrometers at the following frequencies: ^{1}H, 400 or 300 MHz; ^{13}C{^{1}H}, 101 or 75 MHz; HCNMBC, 800 MHz. Chemical shifts are reported in parts per million (ppm) relative to TMS or with the residual solvent peak as an internal reference. Infrared (IR) spectra were recorded with a KBr pellet, and wavenumbers are given in cm−1. High-resolution mass spectra (HRMS) were recorded on a TOF MS instrument using ESI or the APCI techniques.

General procedure A for synthesis of 4-chloropyridines (*S*,*S*)–4a,b. *n*-BuLi (2.5 M solution in hexane, 4.6 equiv) was added to a solution of diisopropylamine (4.6 equiv in anhydrous THF (1 mL of solvent / 1 mmol of diisopropylamine) at –75 °C (acetone/dry ice bath) under argon atmosphere. The light yellow solution was stirred at –75 °C for 2 h and then transferred via cannula to a suspension of 4-chloropyridine hydrochloride (2.2 equiv) in anhydrous THF (2.4 mL / 1 mmol of 4-chloropyridine hydrochloride) at –75 °C. The resulting light yellow solution was stirred at –75 °C for 2 h, whereupon a solution of aldehyde (*S*)-**2a**[3c] or (*S*)-**2b**[3c] (1 equiv) in anhydrous THF (0.7 mL/1 mmol of aldehyde) was added at a rate to maintain the reaction temperature below –73 °C. The light orange solution was stirred at –75 °C for 2 h, and then quenched with a saturated aqueous solution of NH_4Cl (0.5 mL/1 mmol of LDA). After warming to rt all volatiles were removed under reduced

pressure. The orange residue was diluted with EtOAc (15 mL/1 mmol of aldehyde) and washed twice with H_2O (15 mL/1 mmol of aldehyde), then with 0.5 M aqueous NaOH solution (15 mL/1 mmol of aldehyde) and brine (15 mL/1 mmol of aldehyde). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure.

***N*-((1*S*,2*S*)-1-(4-Chloropyridin-3-yl)-1-hydroxy-3,3-dimethylbutan-2-yl)benzamide ((*S*,*S*)–4a).** The title compound was obtained as fine sand-colored crystals (4.37 g, 63 %) from 4-chloropyridine hydrochloride (6.92 g, 46.2 mmol, 2.2 equiv) and aldehyde **(*S*)-2a**[3c] (4.6 g, 21.0 mmol, 1 equiv) by following general procedure A. Pure material was obtained by recrystallization from CH_2Cl_2 (50 mL) and hexane (200 mL); mp 181-182 °C. Analytical TLC on silica gel, 1:1 EtOAc/Hexanes, R_f= 0.12. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53 (1H, s), 8.24 (1H, d, J = 5.3 Hz), 7.66–7.60 (2H, m), 7.49–7.43 (1H, m), 7.41–7.34 (2H, m), 7.19 (1H, d, J = 5.3 Hz), 6.79 (1H, d, J = 10.2 Hz), 5.53 (1H, d, J = 3.5 Hz), 4.07 (1H, dd, J = 10.2, 0.9 Hz), 3.69 (1H, d, J = 3.5 Hz), 1.11 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.6, 149.1, 148.9, 141.3, 136.7, 134.7, 131.6, 128.8, 126.9, 124.4, 67.5, 59.4, 36.2, 27.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}N_2O_2Cl$ 333.1370; Found 333.1376. Optical rotation $[\alpha]^{20}_D$ +165.8 (*c* 0.41, CH_2Cl_2). HPLC/csp assay: Daicel CHIRALPAK IF, 25 cm × 4.6 mm i.d., mobile phase 15% IPA/85% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 13.2 min, major and 9.4 min, minor (99% ee).

***N*-((1*S*,2*S*)-1-(4-Chloropyridin-3-yl)-1-hydroxy-3,3-dimethylbutan-2-yl)-3,5-bis(trifluoromethyl)benzamide ((*S*,*S*)–4b).** The title compound was obtained as sand color crystals (5.32 g, 71 %) from 4-chloropyridine hydrochloride (5.3 g, 35.3 mmol, 2.2 equiv) and aldehyde (*S*)–**2b**[3c] (5.7 g, 16.0 mmol, 1.0 equiv) by following general procedure A. Pure material was obtained by recrystallization from Et_2O (30 mL) and hexane (100 mL); mp 127–129 °C. Analytical TLC on silica gel, 2:5 EtOAc/Hexanes, R_f= 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (1H, s), 8.31 (1H, d, J = 5.2 Hz), 8.09 (2H, s), 8.00 (1H, s), 7.39–7.18 (1H, m), 6.84 (1H, d, J = 10.1 Hz), 5.63 (1H, s), 4.17 (1H, d, J = 10.1 Hz), 3.12 (1H, s), 1.17 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 164.4, 149.6, 148.4, 141.5, 136.5, 136.2, 132.5 (q, J = 34.0 Hz), 127.1 (m), 125.3 (m), 124.7, 121.6 (q, J = 272.9 Hz), 67.6, 59.9, 36.2, 27.7. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ –62.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}N_2O_2F_6Cl$ 469.1117; Found 469.1122. Optical rotation $[\alpha]^{20}_D$ +116.6 (*c* 0.56, CH_2Cl_2). HPLC/csp assay: Daicel CHIRALPAK IE, 25 cm × 4.6 mm i.d., mobile phase 5% IPA/95% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 8.0 min, major and 6.1 min, minor (99% ee).

General procedure B for synthesis of 4-aminopyridines (*S*,*S*)–3a, b and (*S*,*S*)–9b. 4-Chloropyridine **(*S*,*S*)–4a** or **(*S*,*S*)–4b** (1.0 equiv) and $ZnCl_2(amine)_2$ complex **7a** or **7d** (2.0 equiv) were dissolved in anhydrous DMF (1 mL/1 mmol of 4-chloropyridine **(*S*,*S*)–4a,b**), and the resulting yellow-brown solution was stirred at 80 °C. Progress of the reaction was monitored by ^{1}H-NMR spectra. Upon complete conversion of the starting chloropyridine **(*S*,*S*)–4a,b**, all volatiles were removed under reduced pressure and the brown oil like residue was suspended in water (60 mL/1 mmol of the starting chloropyridine). The suspension was acidified to pH 6 using 1 M HCl solution and extracted three times with EtOAc (3x30 mL/1 mmol of the starting chloropyridine). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

***N*-((1*S*,2*S*)-1-(4-(Dimethylamino)pyridin-3-yl)-1-hydroxy-3,3-dimethylbutan-2-yl)benzamide ((*S*,*S*)–3a).** The title compound was obtained as a white powder (2.72 g, 78 %) from chloropyridine (*S*,*S*)-**4a** (3.4 g, 10.2 mmol, 1.0 equiv) and $ZnCl_2(NHMe_2)_2$ complex **7a** (4.6 g, 20.4 mmol, 2.0 equiv) by following general procedure B. After removal of EtOAc pale yellow solid was suspended in Et_2O (200 mL) and sonicated in ultrasound bath for 20 min. The resulting white suspension was centrifuged and the supernatant was decanted. The sonication/centrifugation cycle was repeated to afford (*S*,*S*)–**3a**; mp 225-226 °C. Analytical TLC on silica gel, EtOAc, R_f = 0.07. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 8.45 (1H, s), 8.01 (1H, d, J = 5.7 Hz), 7.70–7.62 (2H, m), 7.52–7.45 (2H, m), 7.45–7.38 (2H, m), 6.92 (1H, d, J = 5.7 Hz), 5.56 (1H, d, J = 6.0 Hz), 5.42 (1H, dd, J = 6.0, 1.8 Hz), 4.03 (1H, dd, J = 10.0, 1.8 Hz), 2.82 (6H, s), 1.03 (9H, s). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 166.5, 158.0, 147.8, 147.4, 134.9, 132.1, 130.8, 128.2, 127.1, 113.6, 65.5, 59.0, 43.4, 35.3, 27.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{28}N_3O_2$ 342.2182; Found 342.2175. Optical rotation $[\alpha]^{20}_D$ –31.5 (*c* 0.45, CH_2Cl_2).

***N*-((1*S*,2*S*)-1-(4-(Dimethylamino)pyridin-3-yl)-1-hydroxy-3,3-dimethylbutan-2-yl)-3,5-bis(trifluoromethyl)benzamide ((*S*,*S*)–3b).** The title compound was obtained as a pale yellow powder (4.26 g, 80 %) from chloropyridine (*S*,*S*)–**4b** (5.2 g, 11.1 mmol, 1.0 equiv) and $ZnCl_2(NHMe_2)_2$ complex **7a** (5.0 g, 22.2 mmol, 2.0 equiv) by following general procedure B. Pure material was obtained by precipitation from CH_2Cl_2/heptane; mp 99-102 °C. Analytical TLC on silica gel, EtOAc, R_f = 0.17. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50 (1H, s), 8.25 (1H, d, J = 5.5 Hz), 8.09 (2H, s), 7.96 (1H, s), 6.93 (1H, d, J = 5.5 Hz), 6.90 (1H, d, J = 10.0 Hz), 5.53 (1H, s), 5.41 (1H, s), 4.29 (1H, d, J = 10.0 Hz), 2.74 (6H, s), 1.12 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 164.5, 158.8, 149.7, 148.2, 137.0, 132.3

(q, J = 33.7 Hz), 127.2 (m), 125.0 (m), 123.1 (q, J = 272.9 Hz), 115.0, 110.2, 67.5, 60.0, 44.3, 35.9, 27.6. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ –62.9. HRMS (ESI-TOF) m/z: Calcd for $C_{22}H_{26}N_3O_2F_6$ 478.1929; Found 478.1931. Optical rotation $[\alpha]^{20}_D$ +49.2 (*c* 0.95, CH_2Cl_2).

***N*-((1*S*,2*S*)-1-Hydroxy-3,3-dimethyl-1-(4-(pyrrolidin-1-yl)pyridin-3-yl)butan-2-yl)-3,5-bis(trifluoromethyl)benzamide ((*S*,*S*)–11).** The title compound was obtained as a pale yellow powder (1.09 g, 76 %) from chloropyridine (*S*,*S*)–**4b** (1.33 g, 2.84 mmol, 1.0 equiv) and $ZnCl_2$(pyrrolidine)$_2$ complex **7d** (1.58 g, 5.67 mmol, 2.0 equiv) by following general procedure B. Pure material was obtained by precipitation from CH_2Cl_2/heptane; mp 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.38 (1H, s), 8.04 (2H, s), 7.90–7.83 (2H, m), 7.43 (1H, d, J = 10.2 Hz), 6.57 (1H, d, J = 6.2 Hz), 5.57 (1H, d, J = 1.8 Hz), 4.18 (1H, dd, J = 10.2, 1.8 Hz), 3.52–3.34 (4H, m), 2.18–2.04 (2H, m), 2.03–1.90 (2H, m), 1.13 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 165.2, 153.8, 146.2, 144.3, 137.1, 131.9 (q, J = 33.7 Hz), 127.5, 126.1, 124.8, 123.2 (q, J = 273.0 Hz), 110.1, 68.3, 59.5, 51.3, 36.2, 28.1, 25.8. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ –62.84. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{28}N_3O_2F_6$ 504.2086; Found 504.2087. Optical rotation $[\alpha]^{20}_D$ +109.1 (*c* 0.59, CH_2Cl_2).

General procedure C for synthesis of chiral DMAP catalysts (*S*,*S*)–1a,b and (*S*,*S*)–12. Triethylamine (2.0 equiv) and acetic anhydride (1.1 equiv) were added to a solution of alcohol (*S*,*S*)–**3a**,**3b** or (*S*,*S*)–**11** (1.0 equiv) in anhydrous CH_2Cl_2 (1 mL/1 mmol of alcohol). The colorless solution was stirred at rt, and progress of the reaction was monitored by LC-MS assay. Full conversion of the starting alcohol was observed after 1 h. The colorless solution was diluted with CH_2Cl_2 (10 mL/1 mmol of alcohol) and washed sequentially with H_2O (2x15 mL/1 mmol of alcohol) and aqueous saturated $NaHCO_3$ solution (2x15 mL/1 mmol of alcohol). The organic layer was dried over Na_2SO_4, filtered and solvent was removed under reduced pressure.

(1*S*,2*S*)-2-Benzamido-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–1a). The title compound was obtained as white flakes (3.11 g, 92 %) from alcohol (*S*,*S*)–**3a** (3 g, 8.79 mmol, 1.0 equiv), acetic anhydride (0.91 mL, 9.67 mmol, 1.1 equiv) and triethylamine (2.45 mL, 17.57 mmol, 2.0 equiv) by following general procedure C. Pure material was obtained by recrystallization from Et_2O (50 mL) and hexane (250 mL); mp 171–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.32 (1H, d, J = 5.5 Hz), 8.25 (1H, s), 7.64–7.58 (2H, m), 7.51–7.45 (1H, m), 7.45–7.37 (2H, m), 6.92 (1H, d, J = 5.5 Hz), 6.57 (1H, d, J = 1.6 Hz), 6.35 (1H, d, J = 10.7 Hz), 4.34 (1H, dd, J = 10.7, 1.6 Hz), 2.87 (6H, s), 2.19 (3H, s), 1.07 (9H, s). The ^{1}H NMR spectra is in full agreement with that reported in the literature.[3a]

^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.8, 167.5, 158.4, 150.4, 147.4, 135.0, 131.4, 128.8, 128.6, 126.7, 114.6, 70.3, 58.7, 43.9, 35.4, 27.3, 21.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{30}N_3O_3$ 384.2287; Found 384.2288. Optical rotation $[\alpha]^{20}_D$ –1.0 (*c* 0.56, CH_2Cl_2). HPLC/csp assay: Daicel CHIRALPAK IF, 25 cm × 4.6 mm i.d., mobile phase 20% IPA/80% Hexanes, flow rate 1 mL/min, detector UV 297 nm, retention time 43.6 min, major and 18.7 min, minor (99% ee).

(1*S*,2*S*)-2-(3,5-Bis(trifluoromethyl)benzamido)-1-(4-(dimethylamino)pyridin-3-yl)-3,3-dimethylbutyl acetate ((*S*,*S*)–1b). The title compound was obtained as a white foam (3.7 g, 95 %) from alcohol (*S*,*S*)–**3b** (3.6 g, 7.54 mmol, 1.0 equiv), acetic anhydride (0.78 mL, 8.30 mmol, 1.1 equiv) and triethylamine (2.10 mL, 15.08 mmol, 2.0 equiv) by following general procedure C. Analytical TLC on silica gel, 95:5 MeOH/$CHCl_3$, R_f = 0.32. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.34 (1H, d, *J* = 5.4 Hz), 8.19–8.16 (1H, m), 8.03–7.96 (3H, m), 6.94 (1H, d, *J* = 5.4 Hz), 6.59 (1H, d, *J* = 1.6 Hz), 6.35 (1H, d, *J* = 10.6 Hz), 4.36 (1H, dd, *J* = 10.6, 1.6 Hz), 2.89 (6H, s), 2.22 (3H, s), 1.09 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.7, 164.5, 158.5, 150.6, 147.0, 136.8, 132.5 (q, *J* = 33.9 Hz), 128.2, 127.0, 125.3, 123.0 (q, *J* = 273.0 Hz), 114.7, 70.2, 59.3, 43.9, 35.3, 27.4, 21.4. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ –62.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{28}N_3O_3F_6$ 520.2035; Found 520.2032. Optical rotation $[\alpha]^{20}_D$ –5.0 (*c* 0.28, CH_2Cl_2). HPLC/csp assay: Daicel CHIRALPAK IC, 25 cm × 4.6 mm i.d., mobile phase 10% IPA/90% Hexanes, flow rate 1 mL/min, detector UV 254 nm, retention time 9.8 min, major and 7.6 min, minor (99% ee).

(1*S*,2*S*)-2-(3,5-Bis(trifluoromethyl)benzamido)-3,3-dimethyl-1-(4-(pyrrolidin-1-yl)pyridin-3-yl)butyl acetate ((*S*,*S*)–12). The title compound was obtained as a pale yellow amorphous solid (266 mg, 91 %) from alcohol (*S*,*S*)-**11** (270 mg, 0.54 mmol, 1.0 equiv), acetic anhydride (62 μL, 0.66 mmol, 1.2 equiv) and triethylamine (0.17 mL, 1.19 mmol, 2.2 equiv) by following general procedure C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.17 (1H, s), 8.11 (1H, d, *J* = 5.8 Hz), 8.03–7.95 (3H, m), 6.72 (1H, d, *J* = 2.4 Hz), 6.63 (1H, d, *J* = 5.8 Hz), 6.27 (1H, d, *J* = 10.5 Hz), 4.27 (1H, dd, *J* = 10.5, 2.4 Hz), 3.54 (2H, td, *J* = 8.9, 6.1 Hz), 3.41 (2H, td, *J* = 8.2, 7.7, 2.3 Hz), 2.19 (3H, s), 2.15–2.05 (2H, m), 1.99–1.89 (2H, m), 1.07 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.9, 164.7, 152.7, 149.3, 148.3, 136.8, 132.4 (q, *J* = 33.9 Hz), 127.1, 125.2, 123.0 (q, *J* = 273.1 Hz), 121.2, 110.4, 70.4, 59.1, 51.2, 35.7, 27.7, 25.9, 21.5. ^{19}F NMR (376.5 MHz, $CDCl_3$, ppm) δ –62.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{30}N_3O_3F_6$ 546.2191; Found 546.2195. Optical rotation $[\alpha]^{20}_D$ +80.7 (*c* 0.53, CH_2Cl_2).

3-((4S,5S)-2-(3,5-Bis(trifluoromethyl)phenyl)-4-(tert-butyl)-4,5-dihydrooxazol-5-yl)-*N*,*N*-dimethylpyridin-4-amine ((*S*,*S*)–5). A sand colored suspension of finely ground and oven–dried (120 °C) K_2CO_3 (1.92 g, 13.86 mmol, 1.3 equiv), chloropyridine (*S*,*S*)–**4b** (5.00 g, 10.67 mmol, 1.0 equiv) and $ZnCl_2(Me_2NH)_2(HCl)_2$ complex **6** (15.96 g, 53.33 mmol, 5.0 equiv) in anhydrous DMF (11 mL) was stirred at 80 °C, and progress of the reaction was monitored by LC-MS assay. Complete conversion of (*S*,*S*)–**4b** was achieved after 63 h, whereupon a 9:1 mixture of (*S*,*S*)–**3b** and (*S*,*S*)–**5** was observed. DMF was removed under reduced pressure, the yellow oily residue was suspended in EtOAc (400 mL), washed with water (500 mL), saturated aqueous $NaHCO_3$ solution (430 mL) and brine (450 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The light brown oil like residue was split into three batches and each of the batches was subjected to column chromatography on silica gel (120 g of silica) using gradient elution from 50% EtOAc in hexanes to 100% EtOAc. In total 3.7 g (73%) of (*S*,*S*)–**3b** was obtained as a pale yellow amorphous solid together with 400 mg (8%) of (*S*,*S*)–**5** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.46 – 8.40 (3H, m), 8.38 (1H, d, *J* = 5.6 Hz), 7.98 (1H, s), 6.89 (1H, d, *J* = 5.6 Hz), 5.76 (1H, d, *J* = 7.4 Hz), 4.16 (1H, d, *J* = 7.4 Hz), 2.94 (6H, s), 0.96 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 159.8, 159.1, 151.1, 150.6, 132.1 (q, *J* = 33.7 Hz), 130.2, 128.6, 128.5, 124.8, 123.2 (q, *J* = 272.9 Hz), 113.2, 85.3, 77.9, 44.4, 35.0, 26.0. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}F_6N_3O$ 460.1824; Found 460.1825. Optical rotation $[\alpha]^{20}_D$ 213.9 (*c* 0.32, CH_2Cl_2).

Bis(dimethylammonium) zinc(II) chloride (6). The title compound was prepared according to the literature procedure.[10] Thus, a white suspension of anhydrous $ZnCl_2$ (15.00 g, 110.1 mmol, 1 equiv) and dimethylamine hydrochloride (17.95 g, 220.1 mmol, 2 equiv; dried by repeated vacuum evaporation of a suspension in anhydrous toluene) in EtOH (360 mL) was stirred at 82 °C. After 10 min the suspension turned to clear colorless solution. The solution was stirred at 82 °C for 1 h, then all volatiles were removed under reduced pressure to yield 32.16 g (98%) of title compound **6** as white crystals. Anal. Calcd for $C_4H_{16}Cl_4N_2Zn$: C, 16.05; H, 5.39; N, 9.36. Found: C, 16.26; H, 5.41; N, 9.25.

General procedure D for synthesis of zinc(II)-amine complexes 7a–k. Amine (2.0 equiv) was added to a well-stirred suspension of anhydrous $ZnCl_2$ (1.0 equiv) in anhydrous Et_2O (10 mL/1 mmol of $ZnCl_2$), and the resulting white suspension was stirred at rt for 12 h. The white precipitates were filtered and the filter-cake was washed with Et_2O.

Bis(dimethylamine) zinc(II) chloride (7a). The title compound was obtained as a white solid (310 mg, 75%) from dimethylamine (2M solution in THF, 1.83 mL, 3.67 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (250 mg, 1.83 mmol, 1.0 equiv) by following general procedure D. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 2.45 (12H, s). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 35.5. ^{1}H NMR spectrum was identical to that from the literature.[21]

Bis(diethylamine) zinc(II) chloride (7b). The title compound was obtained as a brown semi-solid (404 mg, 39%) from neat diethylamine (0.76 mL, 7.34 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (500 mg, 3.67 mmol, 1.0 equiv) by following general procedure D. *The material is highly hygroscopic!* ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 4.39–4.21 (2H, br s), 2.69 (8H, q, J = 7.2 Hz), 1.07 (12H, t, J = 7.2 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 42.4, 13.1. Anal. Calcd for $C_8H_{22}N_2Cl_2Znx4H_2O$: C, 27.10; H, 8.53; N, 7.90. Found: C, 26.74; H, 8.29; N, 7.77. HRMS (ESI-TOF) m/z: $[M + HCl + H]^+$ Calcd for $C_8H_{24}Cl_3N_2Zn$ 317.0297; Found 317.0307.

Bis(azetidine) zinc(II) chloride (7c). The title compound was obtained as a white powder (234 mg, 84%) from neat azetidine (0.16 mL, 2.42 mmol, 2.2 equiv) and anhydrous $ZnCl_2$ (150 mg, 1.10 mmol, 1.0 equiv) by following general procedure D. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 3.55 (8H, t, J = 7.7 Hz), 2.22 (4H, p, J = 7.7 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 47.0, 20.5. Anal. Calcd for $C_6H_{14}N_2Cl_2Zn$ + 2% $ZnCl_2$: C, 28.46; H, 5.57; N, 11.06. Found: C, 28.14; H, 5.45; N, 10.67.

Bis(pyrrolidine) zinc(II) chloride (7d). The title compound was obtained as a white crystalline material (7.16 g, 70%) from neat pyrrolidine (6.1 mL, 73.37 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (5 g, 36.69 mmol, 1.0 equiv) by following general procedure D. Pure material was obtained by recrystallization from EtOH (10 mL); mp 179–180 °C, elongated plates. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 4.89–4.15 (2H, br s), 2.90–2.75 (8H, m), 1.75–1.60 (8H, m). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 47.0, 24.3. Anal. Calcd for $C_8H_{18}N_2Cl_2Zn$: C, 34.50; H, 6.51; N, 10.06. Found: C, 34.65; H, 6.43; N, 9.90. HRMS (ESI-TOF) m/z: $[M + HCl + H]^+$ Calcd for $C_8H_{20}Cl_3N_2Zn$ 312.9984; Found 313.0002.

Bis(piperidine) zinc(II) chloride (7e). The title compound was obtained as an off-white powder (480 mg, 85%) from neat piperidine (0.36 mL, 3.67 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (250 mg, 1.83 mmol, 1.0 equiv) by following general procedure D. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 4.65–4.01 (2H, br s), 2.89–2.68 (8H, m), 1.59–1.43 (12H, m).

^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 46.2, 24.8, 23.5. Anal. Calcd for $C_{10}H_{22}N_2Cl_2Zn$: C, 39.18; H, 7.23; N, 9.14. Found: C, 39.18; H, 7.19; N, 8.98.

Bis(morpholine) zinc(II) chloride (7f). The title compound was obtained as sand color crystals (458 mg, 80%) from neat morpholine (0.32 mL, 3.67 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (250 mg, 1.83 mmol, 1.0 equiv) by following general procedure D. Pure material was obtained by recrystallization from EtOH (1.5 mL); mp 234–236 °C, block clusters. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 4.07–3.69 (2H, br s), 3.64–3.51 (8H, m), 2.81–2.70 (8H, m). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 66.2, 45.8. Anal. Calcd for $C_8H_{18}N_2O_2Cl_2Zn$: C, 30.94; H, 5.84; N, 9.02. Found: C, 31.16; H, 5.82; N, 8.87.

Bis(aniline) zinc(II) chloride (7g). The title compound was obtained as a white solid (1.32 g, 93%) from neat aniline (0.8 mL, 8.8 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (600 mg, 4.4 mmol, 1.0 equiv) by following general procedure D. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 7.05–6.95 (4H, m), 6.60–6.52 (4H, m), 6.51–6.43 (2H, m), 5.23–4.80 (4H, br s). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 148.5, 128.8, 115.7, 113.9. Anal. Calcd for $C_{12}H_{14}N_2Cl_2Zn$: C, 44.69; H, 4.37; N, 8.69. Found: C, 44.72; H, 4.31; N, 8.57.

Bis((*S*)-diphenyl(pyrrolidin-2-yl)methanol) zinc(II) chloride ((*S,S*)–7h). The title compound was obtained as a white powder (193 mg, 76%) from (*S*)-diphenyl(pyrrolidin-2-yl)methanol (201 mg, 0.79 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (54 mg, 0.40 mmol, 1.0 equiv) by following general procedure D. Pure material was obtained by recrystallization from EtOH (7 mL); mp 205–207 °C, block clusters. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 7.61–7.55 (4H, m), 7.51–7.44 (4H, m), 7.32–7.23 (8H, m), 7.20–7.11 (4H, m), 4.44 (2H, t, J = 7.7 Hz), 3.43–3.26 (4H, br s), 3.01–2.86 (4H, m), 1.74–1.60 (4H, m), 1.60–1.48 (4H, m). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 147.1, 146.3, 127.9, 127.9, 126.3, 126.2, 126.2, 125.4, 77.5, 64.2, 47.0, 26.5, 25.3. Anal. Calcd for $C_{34}H_{38}N_2O_2Cl_2Zn$: C, 63.51; H, 5.96; N, 4.36. Found: C, 63.59; H, 5.95; N, 4.18. Optical rotation $[\alpha]^{20}_D$ –70.2 (*c* 1.94, DMSO).

Bis(*tert*-butyl pyrrolidin-3-ylcarbamate) zinc(II) chloride (7i). The title compound was obtained as a white powder (1.175 g, 86%) from *tert*-butyl pyrrolidin-3-ylcarbamate (1.0 g, 5.37 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (366 mg, 2.69 mmol, 1.0 equiv) by following general procedure D. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 7.22–6.76 (2H, m), 4.78–4.29 (2H, br s), 4.01–3.83 (2H, m), 3.03–2.89 (4H, m), 2.89–2.77 (2H, m), 2.62 (2H, dd, J = 11.7, 5.1 Hz), 2.04–1.89 (2H, m), 1.68–1.52 (2H, m), 1.38 (18H, s). ^{13}C NMR (100.6 MHz,

DMSO-d_6, ppm) δ 155.1, 77.8, 53.0, 50.4, 45.7, 31.4, 28.2. Anal. Calcd for $C_{18}H_{36}N_4O_4Cl_2Zn$: C, 42.49; H, 7.13; N, 11.01. Found: C, 42.59; H, 7.09; N, 10.89.

Bis((*S*)-1-phenylethan-1-amine) zinc(II) chloride complex ((*S,S*)–7j). The title compound was obtained as a white powder (668 mg, 80%) from (*S*)-phenylethylamine (534 mg, 4.4 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (300 mg, 2.2 mmol, 1.0 equiv) by following general procedure D. Pure material was obtained by recrystallization from EtOH (5 mL); mp 165–166 °C, colorless needles. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 7.41–7.36 (4H, m), 7.35–7.28 (4H, m), 7.25–7.19 (2H, m), 4.03 (2H, q, J = 6.7 Hz), 3.69–3.58 (4H, m), 1.37 (6H, d, J = 6.7 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 146.2, 128.3, 126.9, 126.0, 51.2, 24.3. Anal. Calcd for $C_{16}H_{22}N_2Cl_2Zn$: C, 50.75; H, 5.86; N, 7.40. Found: C, 50.66; H, 5.90; N, 7.37. Optical rotation $[\alpha]^{20}_D$ –22.9 (*c* 0.23, DMSO).

Bis((*R*)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepine) zinc(II) chloride ((*R,R*–7k). The title compound was obtained as a white solid (152 mg, 68%) from (*R*)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepine[22] (182 mg, 0.62 mmol, 2.0 equiv) and anhydrous $ZnCl_2$ (42 mg, 0.31 mmol, 1.0 equiv) by following general procedure D. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 8.07 (8H, dd, J = 8.4 Hz), 7.69 (4H, d, J = 8.4 Hz), 7.56 – 7.46 (4H, m), 7.38 – 7.19 (8H, m), 4.02 – 3.87 (4H, m), 3.33 – 3.25 (4H, m). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 134.3, 133.6, 132.9, 130.6, 128.7, 128.5, 127.9, 126.6, 126.1, 125.8, 47.6. Anal. Calcd for $C_{44}H_{34}N_2Cl_2Zn$: C, 72.69; H, 4.71; N, 3.85. Found: C, 72.83; H, 4.79; N, 3.74. Optical rotation $[\alpha]^{20}_D$ –305.9 (*c* 0.68, DMSO).

General procedure E for synthesis of 4-aminopyridines 8a–k. To a suspension of 4-chloropyridine hydrochloride (1 equiv) and zinc-amine complex **7a–k** (2 equiv) in anhydrous DMF (1 mL/1 mmol of 4-chloropyridine) was added neat DIPEA (1 equiv), and the resulting yellow-brown solution was stirred at 40 °C. Progress of the reaction was monitored by ^{1}H-NMR spectra. Upon complete conversion of 4-chloropyridine hydrochloride, the reaction mixture was diluted with Et_2O (50 mL) and washed with saturated aqueous $NaHCO_3$ (75 mL), followed by brine (75 mL). The organic layer was dried over Na_2SO_4 and filtered. Anhydrous HCl (2M solution in Et_2O, 1 equiv) was added to a solution of 4-aminopyridines **8a–k** in Et_2O. The precipitate that formed was filtered and dried under reduced pressure.

General procedure F for synthesis of 4-aminopyridines 8l–s. A yellow-brown solution of a halogen-substituted pyridine (1 equiv) and zinc-amine complex **7** (2 equiv) in anhydrous DMF (1 mL/1 mmol of halopyridine) was stirred at 40 °C, and the progress of the reaction

was monitored by ^{1}H-NMR spectra. Upon complete conversion of the pyridine the reaction mixture was diluted with Et_2O (50 mL) and washed with saturated aqueous $NaHCO_3$ (75 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (10 g of silica) using gradient elution from 0% EtOAc in hexanes to 100% EtOAc afforded 4-aminopyridines.

***N*,*N*-Dimethylpyridin-4-amine hydrochloride (8a).** The title compound was obtained as a white powder (48 mg, 82%) from bis(dimethylamine) zinc(II) chloride **8a** (166 mg, 0.73 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (55 mg, 0.37 mmol, 1.0 equiv) and DIPEA (63 μL, 0.37 mmol, 1.0 equiv) by following general procedure E. ^{1}H NMR spectrum was identical to that from the literature.[23]

***N*,*N*-Diethylpyridin-4-amine hydrochloride (8b).** The title compound was obtained as a white powder (93 mg, 68%) from bis(diethylamine) zinc chloride **7b** (414 mg, 1.47 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (110 mg, 0.73 mmol, 1.0 equiv) and DIPEA (127 μL, 0.73 mmol, 1.0 equiv) by following general procedure E. ^{1}H NMR spectrum was identical to that from the literature.[24]

4-(Azetidin-1-yl)pyridine hydrochloride (8c). The title compound was obtained as an off-white powder (30 mg, 53%) from bis(azetidine) zinc chloride **7c** (167 mg, 0.67 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (50 mg, 0.33 mmol, 1.0 equiv) and DIPEA (58 μL, 0.33 mmol, 1.0 equiv) by following general procedure E. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 15.88–14.98 (1H, br s), 8.27–7.88 (2H, m), 6.53–6.19 (2H, m), 4.26 (4H, t, J = 7.7 Hz), 2.61 (2H, p, J = 7.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 155.9, 138.9, 105.2, 51.2, 15.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_{11}N_2$ 135.0922; Found 135.0919.

4-(Pyrrolidin-1-yl)pyridine hydrochloride (8d). The title compound was obtained as a white powder (48 mg, 77%) from bis(pyrrolidine) zinc chloride **7d** (186 mg, 0.67 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (50 mg, 0.33 mmol, 1.0 equiv) and DIPEA (58 μL, 0.33 mmol, 1.0 equiv) by following general procedure E. ^{1}H NMR spectrum was identical to that from the literature.[25]

4-(Piperidin-1-yl)pyridine hydrochloride (8e). The title compound was obtained as an off-white powder (94 mg, 64%) from bis(piperidine) zinc chloride **7e** (450 mg, 1.47 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (110 mg, 0.73 mmol, 1.0 equiv) and DIPEA (127

μL, 0.73 mmol, 1.0 equiv) by following general procedure E. ^{1}H NMR spectrum was identical to that from the literature.[26]

4-(Pyridin-4-yl)morpholine hydrochloride (8f). The title compound was obtained as a white powder (98 mg, 73%) from bis(morpholine) zinc chloride **8f** (414 mg, 1.33 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (100 mg, 0.66 mmol, 1.0 equiv) and DIPEA (115 μL, 0.66 mmol, 1.0 equiv) by following general procedure E. ^{1}H NMR spectrum was identical to that from the literature.[27]

***N*-Phenylpyridin-4-amine (8g).** The title compound was obtained as a pale yellow solid (117 mg, 86%) from bis(aniline) zinc chloride **7g** (516 mg, 1.60 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (120 mg, 0.80 mmol, 1.0 equiv) and DIPEA (138 μL, 0.80 mmol, 1.0 equiv) by following general procedure E. Pure pyridine **8g** was obtained by purification on silica gel (10 g) using gradient elution from 10% EtOAc in hexanes to 100% EtOAc. Analytical TLC on silica gel, EtOAc, R_f = 0.7. ^{1}H NMR spectrum was identical to that from the literature.[28]

(*S*)-Diphenyl(1-(pyridin-4-yl)pyrrolidin-2-yl)methanol ((*S*)–8h). The title compound was obtained as an off-white amorphous solid (33 mg, 79%) from bis((*S*)-diphenyl(pyrrolidin-2-yl)methanol) zinc chloride **7h** (163 mg, 0.25 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (19 mg, 0.13 mmol, 1.0 equiv) and DIPEA (21 μL, 0.13 mmol, 1.0 equiv) by following general procedure E. Pure pyridine **8h** was obtained by purification on silica gel (5 g) using gradient eluent from 0% MeOH in chloroform to 90% MeOH in chloroform. Analytical TLC on silica gel, 3:7 MeOH/$CHCl_3$, R_f = 0.17; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.95 (2H, s), 7.45–7.40 (2H, m), 7.40–7.29 (5H, m), 7.24–7.16 (3H, m), 6.36–6.26 (2H, m), 4.88–4.80 (1H, m), 3.48 (1H, td, J = 9.4, 2.7 Hz), 3.24 (1H, q, J = 8.9 Hz), 2.11–2.01 (2H, m), 1.80–1.66 (1H, m), 1.57–1.38 (1H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 154.3, 149.1, 145.3, 144.8, 128.3, 128.1, 127.8, 127.5, 127.5, 108.5, 82.1, 65.6, 50.7, 29.4, 23.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}N_2O$ 331.1810; Found 331.1816. Optical rotation $[\alpha]^{20}_D$ +60.0 (*c* 0.10, CH_2Cl_2).

***tert*-Butyl (1-(pyridin-4-yl)pyrrolidin-3-yl)carbamate (8i)**. The title compound was obtained as a white foam (443 mg, 86%) from bis(*tert*-butyl pyrrolidin-3-ylcarbamate) zinc chloride **7i** (1.99 g, 3.92 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (294 mg, 1.96 mmol, 1.0 equiv) and DIPEA (339 μL, 1.96 mmol, 1.0 equiv) by following general procedure E. Pure pyridine **8i** was obtained by purification on silica gel (120 g of RP-18

silica gel) using gradient eluent from 0% MeCN in water to 100% MeCN in water. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.09–7.94 (2H, m), 6.73–6.51 (2H, m), 5.65 (1H, s), 4.38 (1H, s), 3.84–3.68 (2H, m), 3.63–3.50 (2H, m), 2.42–2.26 (1H, m), 2.26–2.14 (1H, m), 1.41 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 155.6, 155.0, 138.9, 107.6, 80.2, 54.0, 50.3, 47.0, 31.1, 28.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{22}N_3O_2$ 264.1712; Found 264.1712.

***(S)-N*-(1-Phenylethyl)pyridin-4-amine ((*S*)–8j).** The title compound was obtained as a 87:13 mixture of tautomers (54 mg, 83%, colorless oil) from bis((*S*)-1-phenylethylamine) zinc chloride 7**j** (252 mg, 3.92 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (50 mg, 0.33 mmol, 1.0 equiv) and DIPEA (58 μL, 0.33 mmol, 1.0 equiv) by following general procedure E. Pure material was obtained by purification on a silica gel (5 g) using gradient eluent from 0% MeOH in chloroform to 100% MeOH. Analytical TLC on silica gel, MeOH, R_f = 0.36; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.09–7.98 (2H, m), 7.36–7.30 (4.2 H, m), 7.31–7.20 (1.36H, m), 6.50–6.44 (2H, m), 5.67–5.53 (1H, m), 4.60–4.50 (1H, p, *J* = 6.6 Hz), 4.12 (0.15H, q, *J* = 6.6 Hz), 3.93 (1H, s), 1.58 (3H, d, *J* = 6.6 Hz), 1.40 (1.4H, d, *J* = 6.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 153.7, 147.5, 143.4, 129.1, 128.6, 127.6, 127.0, 125.8, 108.4, 53.0, 24.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{15}N_2$ 199.1235; Found 199.1241. Optical rotation $[\alpha]^{20}_D$ –152.5 (*c* 1.09, DMSO).

(*R*)-4-(Pyridin-4-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepine ((*R*)–8k).

The title compound was obtained as a white solid (15 mg, 75%) from bis((*R*)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepine) zinc(II) chloride ((*R,R*)–**7k**) (75 mg, 0.11 mmol, 2.0 equiv), 4-chloropyridine hydrochloride (8 mg, 0.05 mmol, 1.0 equiv) and DIPEA (9 μL, 0.05 mmol, 1.0 equiv) by following general procedure E. The reaction was stirred at 80 °C for 16 h. ^{1}H NMR spectrum was identical to that from the literature.[2d] Optical rotation $[\alpha]^{20}_D$ +306.6 (*c* 0.60, DMSO).

2-(Pyrrolidin-1-yl)pyridine (8l). The title compound was obtained as a colorless oil (25 mg, 83%) from bis(pyrrolidine) zinc chloride **7d** (113 mg, 0.40 mmol, 2.0 equiv) and 2-fluoropyridine (17 μL, 0.20 mmol, 1.0 equiv) by following general procedure F. ^{1}H NMR spectrum was identical to that from the literature.[29]

2-Chloro-4-(pyrrolidin-1-yl)pyridine (8m). The title compound was obtained as a white solid (29 mg, 78%) from bis(pyrrolidine) zinc chloride **7d** (113 mg, 0.40 mmol, 2.0 equiv)

and 2,4-dichloropyridine (30 mg, 0.20 mmol, 1.0 equiv) by following general procedure F. ^{1}H NMR spectrum was identical to that from the literature.[30]

2-Phenyl-4-(pyrrolidin-1-yl)pyridine (8n). The title compound was obtained as a light yellow oil (66 mg, 56%) from bis(pyrrolidine) zinc chloride **7d** (293 mg, 1.05 mmol, 2.0 equiv) and 4-chloro-2-phenylpyridine (100 mg, 0.53 mmol, 1.0 equiv) by following general procedure F. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.30 (1H, d, J = 5.8 Hz), 8.01–7.88 (2H, m), 7.52–7.33 (3H, m), 6.79 (1H, d, J = 2.4 Hz), 6.36 (1H, dd, J = 5.8, 2.4 Hz), 3.44–3.28 (4H, m), 2.12–1.96 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 157.9, 152.6, 149.7, 140.9, 128.6, 128.5, 127.1, 105.9, 104.0, 47.2, 25.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2$ 225.1392; Found 225.1388.

3-Chloro-4-(pyrrolidin-1-yl)pyridine (8o). The title compound was obtained as a white amorphous solid (27 mg, 73%) from bis(pyrrolidine) zinc chloride **7d** (113 mg, 0.40 mmol, 2.0 equiv) and 3,4-dichloropyridine (30 mg, 0.20 mmol, 1.0 equiv) by following general procedure F. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.20 (1H, s), 8.05 (1H, d, J = 5.8 Hz), 6.46 (1H, d, J = 5.8 Hz), 3.63–3.53 (4H, m), 2.00–1.89 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 151.1, 150.2, 147.8, 116.4, 110.0, 50.4, 25.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{12}N_2Cl$ 183.0689; Found 183.0692.

3-Phenyl-4-(pyrrolidin-1-yl)pyridine (8p). The title compound was obtained as a light yellow oil (13 mg, 67%) from bis(pyrrolidine) zinc chloride **7d** (49 mg, 0.18 mmol, 2.0 equiv) and 3-phenyl-4-chloropyridine (17 mg, 0.09 mmol, 1.0 equiv) by following general procedure F. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.19 (1H, d, J = 6.0 Hz), 8.09 (1H, s), 7.43–7.27 (5H, m), 6.59 (1H, d, J = 6.0 Hz), 3.05–2.95 (4H, m), 1.87–1.73 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 151.9, 150.7, 147.1, 139.7, 130.0, 128.0, 127.2, 123.4, 108.4, 50.8, 25.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2$ 225.1392; Found 225.1393.

4-Chloro-2-(pyrrolidin-1-yl)pyridine (8q). The title compound was obtained as a colorless oil (105 mg, 95%) from bis(pyrrolidine) zinc chloride **7d** (334 mg, 1.20 mmol, 2.0 equiv) and 4-chloro-2-fluoropyridine (59 μL, 0.60 mmol, 1.0 equiv) by following general procedure F. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.02 (1H, d, J = 5.5 Hz), 6.50 (1H, dd, J = 5.5, 1.8 Hz), 6.33 (1H, d, J = 1.8 Hz), 3.52–3.33 (4H, m), 2.08–1.90 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 158.1, 149.2, 144.3, 111.6, 106.1, 46.9, 25.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{12}N_2Cl$ 183,0689; Found 183,0691.

1-(4-(Dimethylamino)pyridin-3-yl)-2,2,2-triphenylethan-1-ol (8r). The title compound was obtained as a white solid (51 mg, 83%) from bis(dimethylamine) zinc chloride **7a** (70 mg, 0.31 mmol, 2.0 equiv) and 1-(4-chloropyridin-3-yl)-2,2,2-triphenylethan-1-ol (**9**) (60 mg, 0.16 mmol, 1.0 equiv) by following general procedure F. The reaction was stirred at 80 °C for 48 h. ^{1}H NMR spectrum was identical to that from the literature.[3d]

***N*,*N*-Dimethyl-3-(2-phenylnaphthalen-1-yl)pyridin-4-amine (8s).** The title compound was obtained as a yellow oil (17 mg, 78%) from bis(dimethylamine) zinc(II) chloride (**7a**) (86 mg, 0.38 mmol, 6.0 equiv) and 4-chloro-3-(2-phenylnaphthalen-1-yl)pyridine (**10**) (20 mg, 0.06 mmol, 1.0 equiv) by following general procedure F. The reaction was stirred at 120 °C for 170 h. ^{1}H NMR spectrum was identical to that from the literature.[31]

1-(4-Chloropyridin-3-yl)-2,2,2-triphenylethan-1-ol (9). *n*-BuLi (2.4 M solution in hexane, 0.42 mL, 1.0 mmol, 2.3 equiv) was added to a solution of diisopropylamine (0.14 mL, 1.0 mmol, 2.3 equiv) in anhydrous THF (1 mL) at –75 °C (acetone/dry ice bath) under argon atmosphere. The light yellow solution was stirred at –75 °C for 2 h and then transferred via cannula to a suspension of 4-chloropyridine hydrochloride (72 mg, 0.48 mmol, 1.1 equiv) in anhydrous THF (1.15 mL) at –75 °C. The resulting light yellow solution was stirred at –75 °C for 2 h, whereupon a solution of 2,2,2 triphenylacetaldehyde (118 mg, 0.43 mmol, 1 equiv) in anhydrous THF (0.3 mL) was added at a rate to maintain the reaction temperature below –73 °C. The light orange solution was stirred at –75 °C for 2 h, and then quenched with saturated aqueous solution of NH_4Cl (0.5 mL). After warming to room temperature all volatiles were removed under reduced pressure. The orange residue was diluted with EtOAc (10 mL) and extracted twice with water (15 mL), then with aqueous 0.5 M NaOH solution (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The light orange oily residue was purified by column chromatography on silica gel (12 g silica gel) using gradient elution from 20% EtOAc in hexanes to 100% EtOAc to afford **9** as a pale yellow solid (60 mg, 49% yield). Analytical TLC on silica gel, 1:1 EtOAc/Hexanes, R_f = 0.27. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.34 – 8.21 (2H, m), 7.31 – 7.22 (15H, m), 7.16 (1H, d, J = 5.3 Hz), 6.45 (1H, s), 2.86 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 152.3, 149.2, 145.6, 143.4, 134.9, 131.0, 128.1, 127.1, 124.0, 73.9, 63.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{21}ClNO$ 386.1312; Found 386.1325.

4-Chloro-3-(2-phenylnaphthalen-1-yl)pyridine (10). White suspension of 4-chloro-3-iodopyridine (62 mg, 0.26 mmol, 1.0 equiv), 4,4,5,5-tetramethyl-2-(2-phenylnaphthalen-1-yl)[1,3,2]dioxaborolane[2k] (85 mg, 0.26 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol, 0.04

equiv) and K_2CO_3 (107 mg, 0.77 mmol, 3.0 equiv) were stirred in anhydrous toluene (1 mL) under argon atmosphere at 80 °C for 72 h. The resulting brown suspension was diluted with EtOAc (50 mL) and washed with water (50 mL) and brine (50 mL). Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography (12 g of RP-18 silica gel) using gradient elution from 10% MeCN in water containing 0.1% HCOOH to 100% MeCN afforded **10** as a white solid (59 mg, 72% yield). ^{1}H NMR spectrum was identical to that from the literature.[31]

Associated Content

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXXX.

Details of the kinetic experiments, ^{1}H and ^{13}C NMR spectra, X-ray crystallographic data for Zn complexes **6,7d**,7**f**,7**h**,7**j** (CIF).

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Notes

The authors declare no competing financial interest.

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