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A method for the synthesis of pyridine-based C_2-symmetrical chiral nucleophilic organocatalysts via Pd-catalyzed coupling

Emre Y. Yazıcıoğlu, Cihangir Tanyeli *

Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey

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ABSTRACT

A one step Pd-catalyzed coupling methodology involving a reaction between a chiral diamine and a 2-bromo-4-(alkylamino)pyridine, was developed for the synthesis of novel C_2-symmmetrical chiral compounds with chemical yields of up to 87%. The organocatalytic performance was tested as an alternative to the enzymatic kinetic resolution of 1-phenylethanol and a promising result of 76% ee was obtained. We observed that the catalysts synthesized had their own characteristics in terms of enantioselectivity; for example, non-nucleophilic heterogeneous auxiliary bases and ether solvents proved to be more efficient.

1. Introduction

The demand for environmentally friendly procedures for the production of optically active materials has given rise to an important increase in work on asymmetric organocatalysis over the last few decades.[1] As a subgroup, chiral dialkylaminopyridines, which are used as acyl-transfer reagents and catalysts, have gained considerable attention[2] due to their acylase enzyme-mimicking function.[3] Intense work on this subject has resulted in catalysts such as those presented in the pioneering works of Fu and Fuji et al., and which provide high enantiomeric purity with reasonable reaction rates for a broad substrate range.[2,4] In the recent literature, studies have focused on lowering the amount of catalyst used while keeping the efficiency, by decreasing the number of steps required for the synthesis of such catalysts. An important contribution to the field was made by Yamada et al.[5]

Herein we attempt to solve this problem by exchanging the aforementioned multistep methodologies with a single step coupling approach for chiral catalyst synthesis, which should grant direct access to many different catalyst systems. The initial synthetic plan was to couple a 4-(dimethylamino)pyridine (DMAP) derivative with a C_2-symmetrical chiral diamine template at the 2-position of the pyridine ring to obtain a nucleophilic catalyst, where the DMAP rings are mounted onto each amino group. In the kinetic resolution of racemic secondary alcohols via esterification with an acid anhydride, such a design should have advantages such as: (i) protic hydrogen on the amine functionality of the catalyst would restrict the free rotation of the acyl group of the formed acyl pyridinium intermediate **1** over the course of the reaction; (ii) the pyridine rings are placed in proximity to each other thus providing chiral information by blocking one face of the acyl group of **1** toward nucleophilic attack of the alcohol by the other pyridine ring (iii) second amine functionality is substituted at C-2 on the pyridine ring and so might increase the nucleophilicity of the reactive pyridine nitrogen and thus increase turnover (Fig. 1). These advantages prompted us to develop a methodology for the synthesis of these catalyst systems and evaluate their efficiency.

2. Results and discussion

2.1. Pd-Catalyzed bis-DMAP coupling of C_2-symmetrical chiral diamines

A commercially available set of C_2-symmetrical chiral diamines[6] **3**–**6** were chosen as templates. For the synthesis of the designed organocatalysts, different retrosynthetic strategies were devised. Our first plan was to couple the C_2-symmetrical chiral diamine (9*R*,10*R*,11*S*,12*S*)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine **3** directly with a pyridine derivative such as a 4-hydroxypyridin-2-yl trifluoromethanesulfonate.[7] There are many examples in the literature where a primary amine is directly coupled with a trifluoromethanesulfonyl bearing pyridine derivative by heating.[8] In the next step, the phenolic hydroxyl group would be substituted with chlorine and then dimethyl amine moieties, respectively. The coupling of chiral diamine **3** and 4-hydroxypyridin-2-yl trifluoromethanesulfonate was performed under thermal conditions. For this purpose, two compounds were mixed in a high boiling solvent (mesitylene), after which the mixture was heated gradually starting from 45 °C to its boiling point, 150 °C. The molar ratio of pyridine derivative:chiral diamine **3** was 2:1. The reaction was monitored by TLC. However, no new product formation was observed.

* Corresponding author. Tel.: +90 312 210 3222; fax: +90 312 210 3200.
E-mail address: tanyeli@metu.edu.tr (C. Tanyeli).

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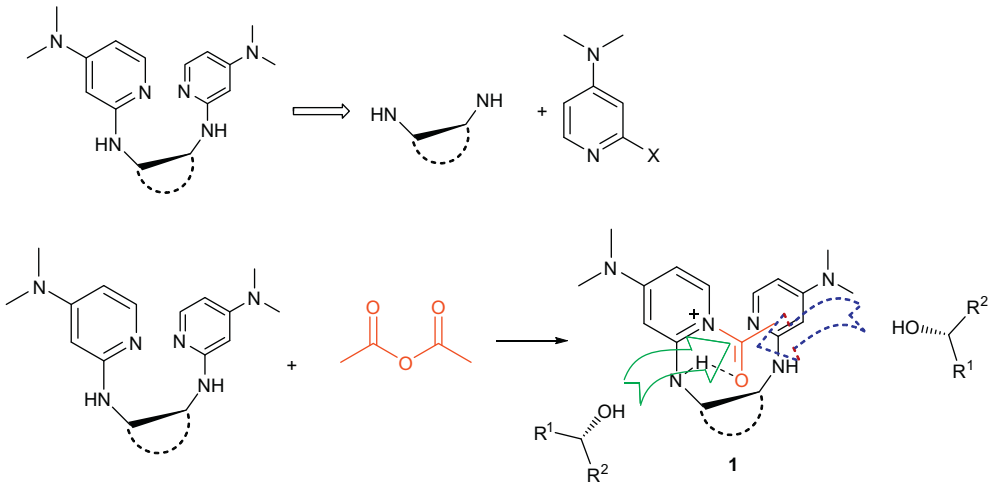
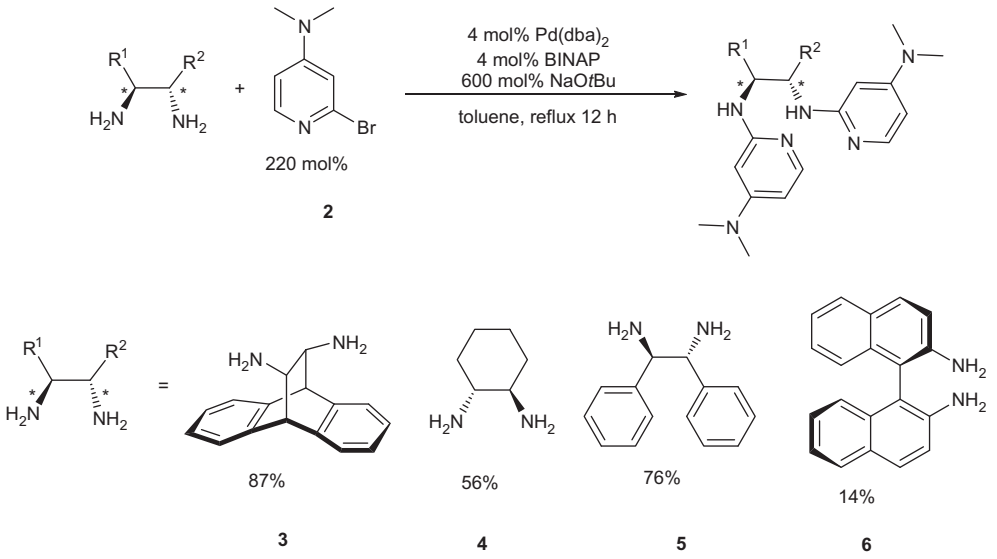


Figure 1. Retrosynthetic plan for novel catalyst systems and their presumed mode of function.

As a result, we turned our attention to metal catalyzed coupling reactions carried out with CuBr[9] or various Pd complexes.[10] Our retrosynthetic approach involved a multistep transformation whereby a 2-halopyridine was coupled with C_2-symmetrical chiral diamine **3**. The optimal pyridine derivative was 2-bromo-4-nitropyridine since the 4-nitro group would decrease the electron density in the aromatic ring and thus make it easier for metal insertion and nucleophilic attack by the amine species. The last step of the synthesis was the replacement of the nitro group with a dimethyl amino unit. Three different conditions were screened. Throughout the reactions, the molar ratio of 3 and 2-bromo-4-nitropyridine was 1:2. The first screen was similar to a relevant literature procedure,[11] which involved conventional heating and adding 5% molar equivalent of CuBr, with the same stoichiometric amount of ligand *N*-benzyldinaphtho[2,1-d:1′,2′-*f*][1,3,2]dioxaphosphepin-4-amine in dry DMF. The best base was Cs_2CO_3 due to its high organic solubility compared with other bases. However, after 24 h, no product formation was observed. In the next trial, a microwave assisted coupling was carried out in ethanol under acidic conditions. It was presumed that the introduction of a catalytic amount of PTSA (1 mol %) may coordinate to the pyridine nitrogen and thus activate the ring for nucleophilic attack. In a sealed polytetrafluoroethylene (PTFE) of microwave, the compounds were mixed in ethanol and the mixture was heated to 160 °C for 10 min. Again, no trace of product formation was observed at the end of the reaction period. The last trial was carried out under similar conditions as the first, except that the solvent and reactor were changed; this time a microwave was used as the driving force for the reaction. Compounds were mixed in benzotrifluoride (BTF) and the mixture was heated up to 150 °C for 10 min. Again, no product formation was observed.

After screening various Pd-coupling conditions,[12] a Pd-catalyzed Buchwald-Hartwig amination method proved to be the most efficient (Scheme 1).[13] Initially, the bis-DMAP coupling of chiral diamine **3** was performed by using 2-bromo-4-(dimethylamino)pyridine[14] **2** as the DMAP source in the presence of catalytic amounts of $Pd(dba)_2$ and racemic BINAP ligand, with excess amounts of strong base (NaO*t*Bu) in toluene at reflux. The conversion was monitored by TLC and 87% conversion was achieved after 12 h. The ^1H and ^{13}C NMR spectra confirmed the presence of a C_2-symmetrical structure **7** (Fig. 2). We also decided to study the Pd-catalyzed bis-DMAP coupling condition with the most



Scheme 1. Synthesis of organocatalyst systems.

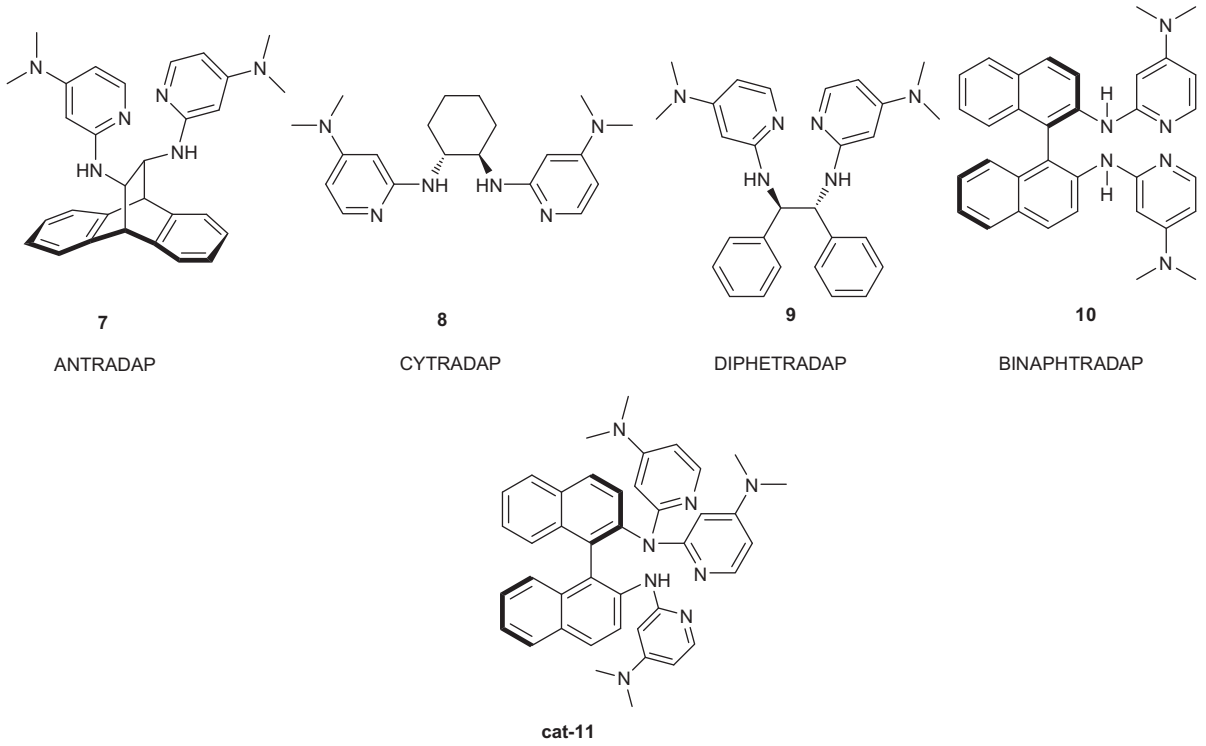
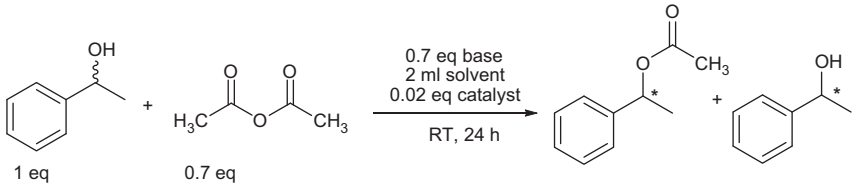


Figure 2. Catalyst structures obtained.

demanding chiral backbones (1*R*,2*R*)-cyclohexane-1,2-diamine **4**, (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine **5**, and (*R*)-1,1′-binaphthyl-2,2′-diamine **6**. The C_2-symmetrical chiral diamines **4** and **5** afforded moderate chemical yields, 56 and 76%, respectively. When (*R*)-BINAM **6** was used as the starting material, the yield was significantly lower due to the formation of a side product whereby one of the BINAM amino groups was doubly substituted with DMAP and the other amino group was mono substituted with a DMAP unit (see **11**). The yield of this side product was 47% (Fig. 2).

Although Rabalakos and Wulff[15] (which was noticed during the course of this research) described a similar structure, which was referred to as a DMAP derivative, a different nomenclature was followed in our study. Due to hydrogen bonding and the presence of one more electron-donor amino group, the catalytic behavior of a 2-alkylamino-4-(dimethylamino)pyridine might have different properties than the other aforementioned DMAP derivatives, which bear only one amine functionality on the pyridine ring, in the kinetic resolution of secondary alcohols. The structures synthesized were named as 'trialkyldiaminopyridine' (TRADAP) in general and to distinguish the catalysts from each other, the initial letters of the diamine skeleton were taken to name the catalyst (e.g. CYTRADAP for 1,2-cyclohexanediamine) (Fig. 2).

Table 1
Kinetic resolution of 1-phenylethanol.

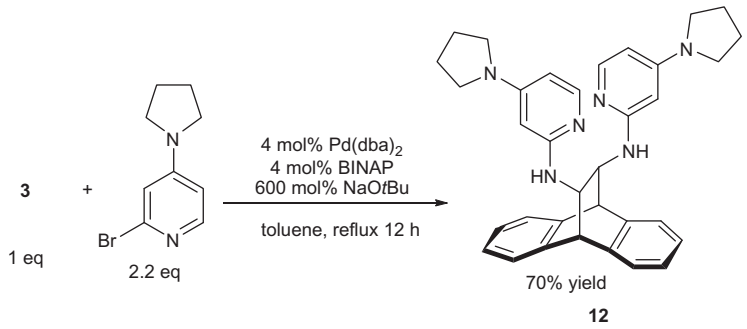


Entry	Cat.	Base	Solvent	ee (%) [a]	Conv. (%)[b]
1	**7**	NEt_3	CH_2Cl_2	4 (*R*)	<5
2	**8**	NEt_3	CH_2Cl_2	4 (*R*)	<5
3	**9**	NEt_3	CH_2Cl_2	0	<5
4	**10**	NEt_3	CH_2Cl_2	3 (*R*)	<5
5	**7**	DIEA	CH_2Cl_2	0	2
6	**7**	Cs_2CO_3	CH_2Cl_2	22 (*S*)	19
7	**7**	Cs_2CO_3	THF	40 (*S*)	40
8	**7**	—	THF	8 (*S*)	20
9	**8**	Cs_2CO_3	THF	8 (*R*)	25
10[c]	**7**	Cs_2CO_3	THF	76 (*S*)	26

[a] The enantiomeric excess of the major acetate ester enantiomer was determined by HPLC analysis by employing a Diacel Chiralcel OJ-H column. The absolute configurations denoted in parenthesis were determined according to the specific rotations reported in the literature.[16]

[b] Conversion calculated from the ee values of the acetate and the remaining alcohol, for ee values lower than the 5% conversion was calculated from the mass of the acetate.[17]

[c] Reaction conducted at −60 °C.



Scheme 2. Catalyst derived from 2-bromo-4-(pyrrolidin-1-yl)pyridine and **3**.

2.2. Performance of C_2-symmetrical chiral compounds 7–10 as organocatalysts in racemic alcohol resolutions

It is well-known that certain organic molecules can function as enzymes, and thus provide 'green' routes to many synthetic problems. Our novel DMAP based C_2-symmetrical chiral molecules **7–10** could serve as a versatile catalyst due to existence of two DMAP units in the context of nucleophilic organocatalysts. In order to evaluate the performance of compounds **7–10** as organocatalysts, *rac*-1-phenylethanol was resolved as a model secondary alcohol, using acetic anhydride. In addition to the catalyst, the solvent, auxiliary base and temperature were also screened as reaction parameters. Table 1 shows the catalysts' performance in some selected examples. The initial reaction conditions which employed NEt_3 as the base and dichloromethane as the solvent gave very poor results both in terms of ee and yield for all catalysts, as seen in entries 1–4. Due to the higher availability of the starting amine and higher synthetic yield, **7** was used for most of the later trials. After screening various bases, we observed that Cs_2CO_3 gave the best results. Homogeneous (soluble) bases such as diisopropylethylamine gave poor results while non-nucleophilic heterogeneous bases were relatively better. The reason for this may be the interference of these amine bases with the possible hydrogen bonding between the –NH proton of the catalyst and the carbonyl oxygen as a competing electron pair donor. The catalyst also works in the absence of the base as can be seen in entry 8. This may be the result of the formation of a bifunctional catalyst system whereby one of the pyridine units is functionalized as an acetate salt by the reaction of the acetic acid that is formed over the course of the reaction. Under identical conditions, ether solvents generally increased the efficiency of the catalyst. The overall catalytic inactivity of DIPHETRADAP **9** may be due to the insolubility of the compound in common organic solvents and/or lower the rigidity of the molecule due to less restricted rotation, which give rise to poor face discrimination and, as a result, no enantioselectivity.

The dimethylamino groups of the pyridine rings of ANTRADAP were exchanged with pyrrolidino groups in order to obtain structure **12** through a similar coupling reaction between 2-bromo-4-(pyrrolidin-1-yl)pyridine and **3**. When the same reaction conditions as shown in Table 1 were applied and **12** was used as the catalyst, 24 ee and 9% conversion were observed (Scheme 2).

3. Conclusion

In conclusion, we have described a novel and practical methodology for the synthesis of five TRADAP based chiral nucleophilic organocatalysts via Pd-catalyzed coupling reactions. Commercially available and demanding chiral diamines were chosen as templates. Although the chosen chiral diamines possess different backbones, all afforded the desired bis-DMAP coupling product with high chemical yields (56–87%) except BINAM (14%). The same coupling approach can be applied to many other diamine systems. The organocatalytic performance of all catalyst systems was evaluated in racemic alcohol resolutions and ANTRADAP-**7** showed a promising enantioselectivity (76% ee). Further applications of organocatalysts are currently under investigation.

4. Experimental

The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Spectrospin Advance DPX 400 spectrometer and the chemical shifts are expressed in ppm relative to $CDCl_3$ (δ 7.26 and 77.0 for ^1H and ^{13}C NMR, respectively) as the internal standard. Standard COSY, HETCOR and DEPT experiments were performed to establish NMR assignments. Infrared spectra were obtained on Varian 1000 FT-IR spectrophotometer and are reported in cm^{-1}. HRMS data were obtained via LC–MS analysis performed with a Waters Synapt mass spectrometer at the central laboratory of Middle East Technical University. Optical rotations were measured a 1 dm cell using a Rudolph research analytical, Autopol III automatic polarimeter. HPLC measurements were performed with a Thermo Separation Products, Inc., P1500-SN-4000-UV2000 instrument using a Chiralcel OJ-H analytical column (250 × 4.60 mm). Flash column chromatography was performed on silica gel (60-mesh, Merck). The reactions were monitored by thin layer chromatography using Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected.

4.1. General procedure for the synthesis of organocatalysts via Pd-catalyzed coupling

Chiral diamine (2.67 mmol), 2-bromo-4-alkylaminopyridine (5.88 mmol), NaO*t*Bu (16 mmol), BINAP (0.11 mmol), and $Pd(dba)_2.CHCl_3$ (0.11 mmol) were mixed in 45 mL of toluene (which was distilled under Ar over Na-benzophenone) under an inert atmosphere. The mixture was heated to 110 °C for 12 h, brought to rt, and transferred to a separatory funnel. The toluene phase was washed with 50 mL of water, after which the two phases were separated. The remaining water phase was washed with CH_2Cl_2 and the combined organic phases were concentrated under vacuum. The mixture was purified by flash chromatography; the solvent polarity was gradually changed from pure EtOAc to 20:1 EtOAc:NEt_3 with each 100 mL mobile phase portion.

4.1.1. $N^2,N^{2\prime}$-((9*R*,10*R*,11*S*,12*S*)-9,10-Dihydro-9,10-ethanoanthracene-11,12-diyl) bis (N^4,N^4-dimethylpyridine-2,4-diamine) (9*R*,10*R*,11*S*,12*S*)-ANTRADAP-(−)-7

Compound (*S*,*S*)-**3** was used as the starting diamine. This compound was obtained as a yellow foam (87% yield). Mp: 143 °C.

$[\alpha]_D^{27} = -46$ (*c* 0.2, $CHCl_3$). ^1H NMR (400 MHz, 70:30 $CDCl_3$ + CCl_4): δ 7.59 (d, *J* = 6.2 Hz, 2H), 7.34–7.25 (m, 4H), 7.14–7.07 (m, 4H), 5.86 (dd, *J* = 6.2, 2.2 Hz, 2H), 5.52 (d, *J* = 2.0 Hz, 2H), 4.51 (s, 2H), 4.38 (d, *J* = 2.4 Hz, 2H), 3.62 (d, *J* = 7.5 Hz, 2H), 2.73 (s, 12H). ^{13}C NMR (101 MHz, 70:30 $CDCl_3$ + CCl_4): δ 168.2, 155.7, 154.1, 138.8, 137.0, 124.6, 124.5, 124.1, 122.2, 97.0, 86.0, 58.0, 47.3, 36.9. IR (neat) 3244, 2961 1600, 1526, 1486, 1446, 1370, 1288, 1260, 1164, 1107, 892, 808, 760 cm^{-1}. HRMS (APCI) calcd for $C_{30}H_{32}N_6$ 476.2688, found 477.2744 $[M+H]^+$.

4.1.2. N^2,$N^{2\prime}$-((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(N^4,N^4-dimethylpyridine-2,4-diamine) (1*R*,2*R*)-CYTRADAP-(−)-8

Compound (*R*,*R*)-**4** was used as the starting diamine. This compound was obtained as a yellowish-white solid (56% yield). Mp: 165 °C. $[\alpha]_D^{27} = -41$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 6.1 Hz, 2H), 5.84 (dd, *J* = 6.1, 2.3 Hz, 2H), 5.25 (d, *J* = 1.9 Hz, 2H), 4.70 (s, 2H), 3.69 (d, *J* = 3.3 Hz, 2H), 2.80 (s, 12H), 2.14 (d, *J* = 13.1 Hz, 2H), 1.71–1.65 (m, 2H), 1.41–1.32 (m, 2H), 1.28–1.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6, 154.7, 145.7, 98.0, 87.8, 54.6, 38.1, 32.4, 31.9, 23.7. IR (neat) 3244, 2932, 2849, 2360, 2343, 1601, 1526, 1490, 1447, 1364, 1338, 1288, 1263, 1220, 1162, 979, 770 cm^{-1}. HRMS (APCI) calcd for $C_{20}H_{30}N_6$ 354.2532, found 355.2624 $[M+H]^+$.

4.1.3. N^2,$N^{2\prime}$-((1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl)bis(N^4,N^4-dimethylpyridine-2,4-diamine) (1*R*,2*R*)-DIPHETRADAP-(+)-9

Compound (*R*,*R*)-**5** was used as the starting diamine. This compound was obtained as a yellow solid (76% yield). Mp: 201 °C. $[\alpha]_D^{27} = +35.6$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, 90:10 DMSO-d_6 + $CDCl_3$): δ 7.69 (d, *J* = 6.0 Hz, 2H), 7.13–7.01 (m, 10H), 5.82 (dd, *J* = 6.1, 2.2 Hz, 2H), 5.21 (d, *J* = 1.6 Hz, 2H), 4.88 (d, *J* = 2.6 Hz, 2H), 2.71 (s, 12H). ^{13}C NMR (101 MHz, 90:10 DMSO-d_6 + $CDCl_3$): δ 157.8, 155.5, 144.9, 141.6, 127.6, 127.5, 126.5, 99.2, 88.3, 60.2, 38.8. IR (neat): 3213, 2927, 2360, 2343, 1602, 1553, 1526, 1495, 1452, 1436, 1370, 1293, 1166, 980, 804, 783, 696 cm^{-1}. HRMS (APCI) calcd for $C_{28}H_{32}N_6$ 452.2688, found 453.2784 $[M+H]^+$.

4.1.4. (*R*)-N^2,$N^{2\prime}$-([1,1′-Binaphthalene]-2,2′-diyl)bis(N^4,N^4-dimethylpyridine-2,4-diamine) (*R*)-BINAPHTRADAP-(+)-10

Compound (*R*)-**6** was used as the starting diamine. This compound was obtained as a brown solid (14% yield). Mp: 146 °C. $[\alpha]_D^{22} = +232.8$ (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, 70:30 $CDCl_3$ + CCl_4): δ 7.93 (d, *J* = 9.0 Hz, 2H), 7.85 (d, *J* = 9.0 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 6.0 Hz, 2H), 7.33–7.23 (m, 2H), 7.16 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 5.83 (dd, *J* = 6.2, 2.3 Hz, 2H), 5.61 (d, *J* = 2.2 Hz, 2H), 2.73 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.9, 132.9, 129.6, 128.2, 127.1, 125.9, 124.2, 123.5, 120.9, 99.5, 88.8, 38.1. IR (neat): 3053, 2923, 1601, 1541, 1507, 1486, 1443, 1427, 1337, 1280, 1260, 1163, 804 cm^{-1}. HRMS (APCI) calcd for $C_{34}H_{32}N_6$ 524.2688, found 525.2755 $[M+H]^+$.

4.1.5. (*R*)-N^2-(4-(Dimethylamino)pyridin-2-yl)-N^2-(2′-((4-(dimethylamino)pyridin-2-yl)amino)-[1,1′-binaphthalen]-2-yl)-(N^4,N^4-dimethylpyridine-2,4-diamine (*R*)-(−)-11

Compound (*R*)-**6** was used as the starting diamine. This compound was obtained as a white solid (47% yield). Mp: 179 °C. $[\alpha]_D^{22} = -35.5$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$ + CCl_4) δ ppm 8.02 (d, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 6.0 Hz, 1H), 7.63 (s, 1H), 7.54 (d, *J* = 6.0 Hz, 1H), 7.52 (d, *J* = 5.8 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.32–7.24 (m, 1H), 7.20 (d, *J* = 7.3 Hz, 2H), 7.12–7.03 (m, 1H), 7.00–6.91 (m, 1H), 6.77–6.68 (m, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 5.89 (dd, *J* = 6.1, 2.3 Hz, 1H), 5.76 (s, 1H), 5.73 (d, *J* = 2.2 Hz, 1H), 5.62 (s, 2H), 2.81 (s, 6H), 2.63 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$ + CCl_4) δ 155.3, 153.7, 153.3, 146.1, 145.6, 141.8, 136.6, 132.2, 131.4, 130.2, 129.5, 127.6, 127.5, 127.1, 126.9, 126.7, 125.8, 125.5, 125.0, 124.6, 124.3, 124.12, 123.4, 122.7, 120.5, 100.5, 98.5, 90.1, 37.4, 37.1. IR (neat) 2924, 2360, 1602, 1540, 1486, 1443, 1427, 1373, 1337, 1279, 1163, 1125, 1063, 1011, 984, 807, 774, 746 HRMS (APCI) calcd for $C_{41}H_{40}N_8$ 644.3376, found 645.3469 $[M+H]^+$.

4.1.6. (9*R*,10*R*,11*S*,12*S*)-N^{11},N12-Bis(4-(pyrrolidin-1-yl)pyridin-2-yl)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine, (9*R*,10*R*,11*S*,12*S*)-(−)-12

Compound (*S*,*S*)-**3** was used as the starting diamine. This compound was obtained as a yellow foam (70% yield). Mp: 159 °C. $[\alpha]_D^{23} = -93.9$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$ + CCl_4): δ ppm 7.59 (d, *J* = 5.9 Hz, 2H), 7.37–7.21 (m, 4H), 7.16–7.02 (m, 4H), 5.70 (dd, *J* = 5.9, 1.8 Hz, 2H), 5.31 (d, *J* = 1.9 Hz, 2H), 4.34 (d, *J* = 2.5 Hz, 2H), 4.09–4.02 (m, 2H), 3.58 (d, *J* = 9.8 Hz, 2H), 3.08–2.99 (m, 4H), 2.99–2.86 (m, 4H), 1.89–1.66 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$ + CCl_4): δ 156.1, 151.3, 145.9, 139.1, 137.3, 124.6, 124.5, 124.0, 122.4, 97.3, 86.2, 58.2, 47.7, 44.7, 23.2. IR (neat): 2964, 2840, 2360, 2342, 1601, 1541, 1521, 1480, 1457, 1380, 1353, 1280, 1248, 1220, 772 cm^{-1}. HRMS (APCI) calcd for $C_{34}H_{36}N_6$ 528.6898, found 529.3080 $[M+H]^+$.

4.2. General procedure for the resolution of secondary alcohols

Representative procedure for reactions with **7**. In a 10 mL Schlenk flask, 0.02 equiv of organocatalyst (10 mg) and if solid, 0.7 equiv of base were added and the flask then sealed with a rubber septum. The flask was kept under vacuum with a Teflon plug and flushed with Ar with a cannula through the septum several times. Next, 1 mL of solvent and 1 equiv of *rac*-methylbenzyl alcohol were added. If the base was liquid at room temperature, it was also added in this step. Finally 0.7 equiv of anhydride was added and the walls of the flask were washed with 1 mL of solvent, after which the rubber septum was exchanged with a glass stopper and the mixture was stirred for 24 h with a magnetic stirrer. The reaction was monitored by TLC using *p*-anisaldehyde as the stain. After 24 h, methanol was added to quench the reaction, and the mixture was purified by column chromatography.

4.2.1. (*S*)-1-Phenyethyl acetate

$[\alpha]_D^{26} = -59.2$ (*c* 0.5, $CHCl_3$) for 76% ee, in lit. $[\alpha]_D^{23} = +108.7$ (*c* 1.0, $CHCl_3$) for the (*R*)-enantiomer with 99% ee.[16] The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H column, hexane/*i*-PrOH 99:1, flow rate = 1.0 mL min^{-1}, λ = 254 nm), t_R = 11.35 min [(*R*)-isomer], t_R = 13.15 min [(*S*)-isomer] in comparison with a racemic sample.

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