Synthesis of New C_2-Symmetric Chiral Bisamides from (1*S*,2*S*)-Cyclohexane-1,2-dicarboxylic Acid

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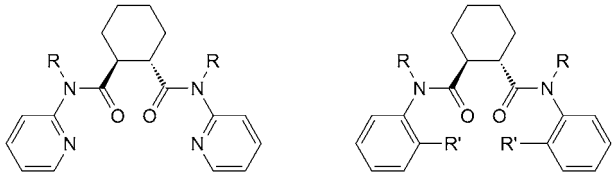
A series of new C_2-symmetric (1*S*,2*S*)-cyclohexane-1,2-dicarboxamides was synthesized from (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride and *N*-benzyl-substituted aromatic amines, which were prepared from 2-aminopyridine, 2-chloroaniline, and 2-aminophenol *via* imine formation with benzaldehyde and subsequent reduction with $NaBH_4$. (1*S*,2*S*)-*N*,*N*′-Dibenzyl-*N*,*N*′-bis[2-(benzyloxy)-phenyl]cyclohexane-1,2-dicarboxamide was converted to (1*S*,2*S*)-*N*,*N*′-dibenzyl-*N*,*N*′-bis(2-hydroxy-phenyl)cyclohexane-1,2-dicarboxamide *via* hydrogenolysis in the presence of $Pd(OH)_2$ on active carbon powder.

Introduction. – Chiral bisamide ligands have been widely and well developed because of their great enantiomer-discrimination ability with transition-metals in asymmetric catalysis in synthetic chemistry (for recent reviews and examples, see [1]). Most of the frequently applied chiral bisamides are synthesized by using chiral diamino compounds such as enantiomerically pure cyclohexane-1,2-diamines or 1,2-diphenyl-ethane-1,2-diamines, and carboxylic acids as starting materials [2]. Thus, these chiral bisamides have similar backbones with two N-atoms attached to the stereogenic centers. With diverse substituents and various substituted positions in pyridinyl and phenyl groups, there is a large number of derivatives of chiral bisamide ligands. *Trost et al*. have reported various applications of these chiral bisamide ligands in asymmetric syntheses [3]. The transition-metal-catalyzed asymmetric allylic alkylation (AAA) reactions in the presence of chiral bisamide ligands are major reactions and have been performed with different nucleophiles to afford alkylation adducts in good-to-excellent yields with good regio- and enantioselectivities [4]. New C–C and C–heteroatom bonds were achieved with various nucleophiles *via* catalysis with the complexes formed *in situ* from transition-metal sources and chiral bisamide ligands.

Trost's chiral bisamide ligands have the similar backbone with two N-atoms attached to the centers of chirality, because in most cases enantiomerically pure vicinal diamines were used as chiral sources. In 1964, *Overberger* and *Ishida* reported the synthesis of racemic bis(*N*-methylanilides) *via* the reaction of *cis*- and *trans*-cyclo-hexanedicarbonyl dichlorides with *N*-methylaniline [5]. Later in the 1970s, *Batzer et al.* [6], and *Richter* [7] synthesized *N*,*N*′-diglycidyl dianilide monomers by treating adipic acid dianilide with epichlorohydrin and Me_4NCl. In 2001, *Trost et al.* briefly referred to the synthesis and application of chiral bis(phosphine)-containing bisamide ligands with two CO groups directly attached to the centers of chirality from vicinal cycloalkane-

and bicycloalkanedicarboxylic acids with 2-(diphenylphosphino)aniline. However, most of these compounds showed low-to-moderate enantioselectivities in the desymmetrization of *meso*-diesters [8]. In 2005, our group utilized (1*S*,2*S*)-cyclohexane-1,2-dicarboxylic acid as starting material to prepare the bis-oxazoline ligand cHBOX and found that it showed excellent enantioselectivity in the asymmetric aziridination of chalcones [9]. To develop new C_2-symmetric bisamides from cycloalkane-1,2-dicarboxylic acids as chiral scaffolds, we designed and synthesized a series of new chiral bisamides from (1*S*,2*S*)-cyclohexane-1,2-dicarboxylic acid, and 2-aminopyridine, 2-aminophenol, and 2-chloroaniline as starting materials (*Fig. 1*).

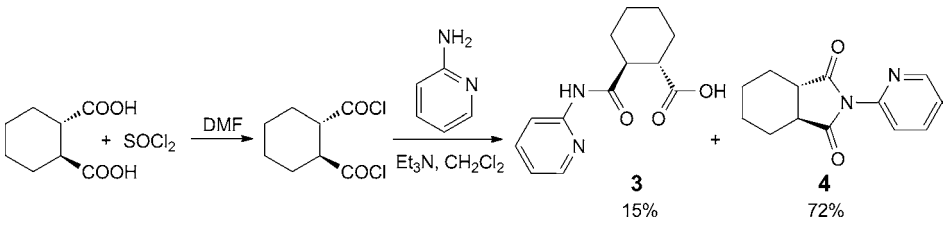


1a R = H; **1b** R = H, R' = Cl; **1c** R = H, R' = BnO; **1d** R = H, R' = OH
2a R = Bn; **2b** R = Bn, R' = Cl; **2c** R = Bn, R' = BnO; **2d** R = Bn, R' = OH

Fig. 1. *Envisaged chiral bisamide ligands*

Results and Discussion. – We initially planned to prepare a series of (1*S*,2*S*)-cyclohexane-1,2-dicarboxamides **1** from the reactions of (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride and aromatic amines, such as 2-aminopyridine, 2-chloroaniline, and 2-aminophenol. (1*S*,2*S*)-Cyclohexane-1,2-dicarboxylic acid was first obtained by resolution of *trans*-cyclohexane-1,2-dicarboxylic acid according to our previous procedure [9a]. (1*S*,2*S*)-Cyclohexane-1,2-dicarboxylic acid was treated with $SOCl_2$ to generate (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride and was further reacted with 2-aminopyridine in the presence of Et_3N in CH_2Cl_2. The results revealed that no bisamide was generated in the reaction. Instead, monoamido carboxylic acid **3** (15%) and the cyclic imide **4** (72%) were obtained, possibly due to favorable formation of the five-membered ring (*Scheme 1*). The structure of imide **4** was confirmed by a single-crystal X-ray diffraction analysis (*Fig. 2*)[1]).

Scheme 1. *Reaction of (1S,2S)-Cyclohexane-1,2-dicarbonyl Dichloride and 2-Aminopyridine*



[1]) The crystallographic data of compound **4** have been deposited with the *Cambridge Crystallographic Data Centre*. (CCDC-874970). These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

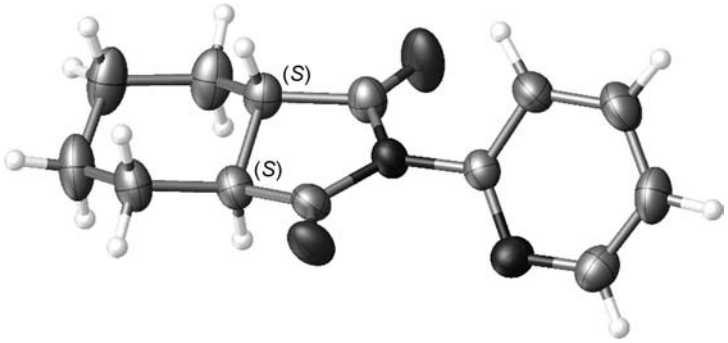
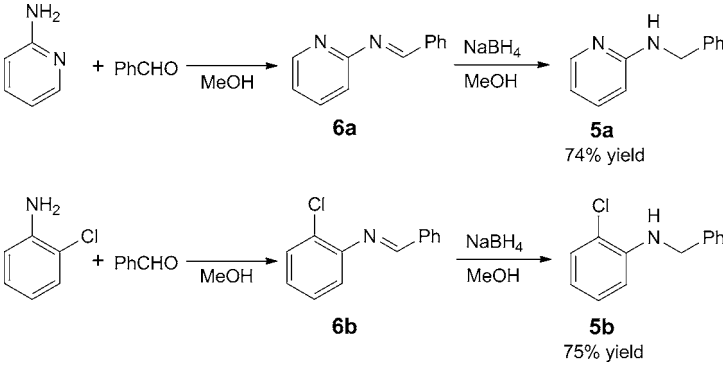


Fig. 2. *Single-crystal X-ray diffraction structure of (3a*S*,7a*S*)-hexahydro-2-(pyridin-2-yl)-1*H*-isoindole-1,3(2*H*)-dione* (**4**)

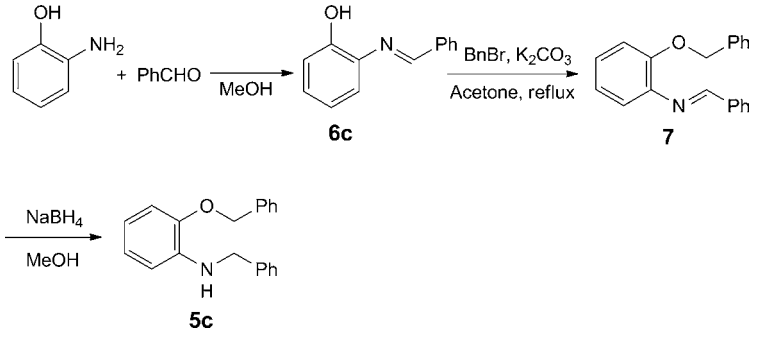
After failure of the direct synthesis of (1*S*,2*S*)-cyclohexane-1,2-dicarboxamide **1a** by reaction of (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride and 2-aminopyridine, we had to prepare **1** by an indirect method, in which the amino group of the aromatic amines, including 2-aminopyridine, 2-chloroaniline, and 2-aminophenol, was protected with a benzyl (Bn) group. Accordingly, (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride was reacted with 2-(benzylamino)pyridine (**5a**), *N*-benzyl-2-chloroaniline (**5b**), and *N*-benzyl-2-(benzyloxy)aniline (**5c**), respectively, to generate the corresponding tertiary (1*S*,2*S*)-cyclohexane-1,2-dicarboxamides **2**. We expected that the desired secondary (1*S*,2*S*)-cyclohexane-1,2-dicarboxamides **1** would be obtained after removal of the Bn group by Pd-catalyzed hydrogenolysis.

2-Aminopyridine and 2-chloroaniline were converted to their *N*-benzyl derivatives **5a** and **5b**, respectively, in satisfactory-to-good yields *via* imine formation with PhCHO [10], and subsequent *in situ* reduction with $NaBH_4$ in MeOH (*Scheme 2*) [11]. *N*-Benzyl-2-(benzyloxy)aniline (**5c**) was obtained from 2-aminophenol as starting material (*Scheme 3*). (Benzylideneamino)phenol **6c** was generated by the reaction of 2-aminophenol and PhCHO, and then underwent a reaction with BnBr in the presence of K_2CO_3 to protect the OH group. The benzyloxy derivative **7** was reduced with

Scheme 2. *Preparation of* N*-Benzylpyridin-2-amine* (**5a**) *and* N*-Benzyl-2-chloroaniline* (**5b**)



Scheme 3. *Preparation of* N-*Benzyl-2-(benzyloxy)aniline from 2-Aminophenol*

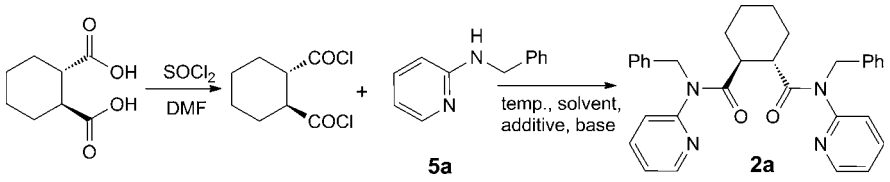


$NaBH_4$ to finally furnish the secondary *N*-benzyl-2-(benzyloxy)aniline (**5c**) in 50% yield.

Our next effort focused on the reaction of (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride with the *N*-benzyl amines **5**. We optimized the reaction conditions in the case of (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride and 2-(benzylamino)pyridine (**5a**) as model reaction. After optimization, it was found that the reaction of (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride (1.0 equiv.) and 2.2 equiv. of **5** afforded the desired bisamide **2a** in 75% yield in the presence of 3 equiv. of Et_3N in CH_2Cl_2 under reflux for 24 h (*Table 1*; *Entry 3*). However, the temperature and the additive 4-(dimethylamino)pyridine (DMAP) appeared to have no significant effect on the yield (*Table 1*; *Entries 1*, *2*, and *4*), but TLC monitoring indicated that the reaction system generated fewer by-products at reflux. Prolonging the reaction time did not lead to a significant increase in the yield (*Table 1*; *Entries 2* and *3*). Next, we attempted to employ NaH as a much stronger base than Et_3N in THF to perform this reaction. Unfortunately, the desired bisamide **2a** was not observed, possibly because NaH has a poor solubility in THF and the reaction was run in two phases.

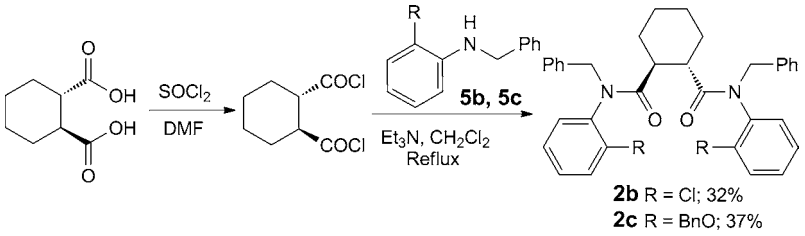
Under our optimized conditions, two other bisamides, (1*S*,2*S*)-*N*,*N*′-dibenzyl-*N*,*N*′-bis(2-chlorophenyl)cyclohexane-1,2-dicarboxamide (**2b**) and (1*S*,2*S*)-*N*,*N*′-dibenzyl-

Table 1. *Reaction of (1S,2S)-Cyclohexane-1,2-dicarbonyl Dichloride with 2-(Benzylamino)pyridine*



Entry	Temp. [°]	Time [h]	Additive	Base	Solvent	Yield [%]
1	r.t.	12	none	Et_3N	CH_2Cl_2	74
2	reflux	12	none	Et_3N	CH_2Cl_2	74
3	reflux	24	none	Et_3N	CH_2Cl_2	75
4	reflux	24	DMAP	Et_3N	CH_2Cl_2	75
5	r.t.	24	none	NaH	THF	0

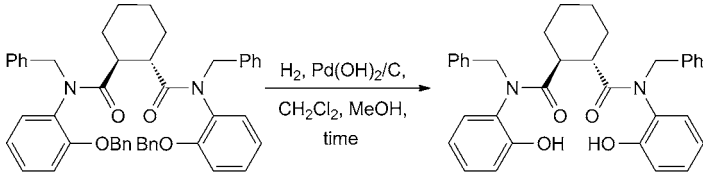
Scheme 4. *Reaction of (1S,2S)-Cyclohexane-1,2-dicarbonyl Dichloride with Secondary Amines* **5b** *and* **5c**



N,*N*′-bis[2-(benzyloxy)phenyl]cyclohexane-1,2-dicarboxamide (**2c**) were obtained in acceptable yields from the corresponding secondary amines **5b** and **5c**, respectively, and (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride (*Scheme 4*). The bisamides **2b** and **2c** were obtained in lower yields as compared to bisamide **2a**, probably because of the steric hindrance of the BnO group at C(2) of the benzene ring in **5c** and the Cl substituent in **5b** was much larger than that of the lone pair electrons at the N-atom of the pyridinyl group in **5a**.

Finally, we explored the removal of the *N*-Bn group of the synthesized chiral bisamides **2** *via* hydrogenolysis, with the aim to prepare the bisamides **1** without the Bn groups either on N- or on O-atom. We first attempted hydrogenolysis in the presence of Pd on active carbon powder as catalyst, widely used in hydrogenolysis, but to our disappointment, no hydrogenolysis product was generated under different reaction conditions (*Table 2*; *Entries 1–3*). We prolonged the reduction time from 12 h to 4 d. Neither the *N*-Bn nor the *O*-Bn group was removed. In our previous investigation, we found that $Pd(OH)_2$ on active carbon powder is an efficient catalyst for deprotection of *N*-Bn groups [12]. Therefore, $Pd(OH)_2$ on active carbon powder was employed as the hydrogenolytic catalyst for these bisamides as well. Strangely, no elimination of the *N*-

Table 2. *Hydrogenolysis of (1S,2S)-Bisamide* **2c**



Entry	Catalyst	Time [h]	Yield [%]
1	2% Pd/C	12	0
2	5% Pd/C	24	0
3	5% Pd/C	96	0
4	2% $Pd(OH)_2$/C	12	22
5	2% $Pd(OH)_2$/C	24	23
6	5% $Pd(OH)_2$/C	24	37
7	5% $Pd(OH)_2$/C	48	58
8	5% $Pd(OH)_2$/C	96	58
9	10% $Pd(OH)_2$/C	48	58

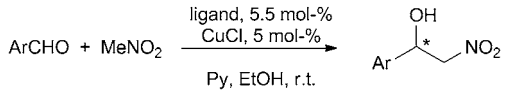
Bn group was observed with bisamides **2a**–**2c** as starting materials. However, the *O*-Bn group of (1*S*,2*S*)-*N*,*N*′-dibenzyl-*N*,*N*′-bis[2-(benzyloxy)phenyl]cyclohexane-1,2-dicarboxamide (**2c**) was removed in satisfactory yields. Three catalysts with different loading percentages of $Pd(OH)_2$ were screened. When the reaction was run in the presence of 2% $Pd(OH)_2$ on active carbon powder for 12 h or 24 h, the yield was only 23%, indicating that prolongation of the reaction time could not improve the yield. Employing 5% $Pd(OH)_2$ on active carbon powder led to a slight increase of the yield in 24 h (*Table 2*; *Entry 6*). The yield increased from 37% to 58% by prolonging the reaction time from 1 to 2 d. Continuously prolonging the reaction time to 4 d did not further improve the yield (*Table 2*; *Entry 8*). Further increase of $Pd(OH)_2$ (10%) on active carbon powder did not result in an improvement of the product yield either (*Table 2*; *Entry 9*). Thus, we accomplished the deprotection reaction in the presence of 5% $Pd(OH)_2$ on active carbon powder for 2 d to obtain product **2d** in 58% yield. The strong adsorbility of **2d** on the catalyst resulted in the relatively low yield.

Further, we also attempted to convert these chiral bisamides to C_2-symmetric chiral tertiary bisamines by reducing the C=O to CH_2 groups. Unfortunately, the attempts with both $LiAlH_4$ and a solution of borane in THF as reducing agents failed to provide the desired tertiary bisamines, possibly because of the steric hindrance around the C=O group. Even small reducing agents cannot reduce the C=O group due to steric hindrance. Thus, it is reasonable to state that the failure to remove the *N*-Bn group in the bisamides is caused by bulky steric hindrance around the amide group.

The *N*-Bn bisamides **2** were submitted to the catalytic asymmetric allylic alkylation with 1,3-diphenylallyl acetate and diethyl malonate with $(\eta^3\text{-}C_3H_5PdCl)_2$ as transition metal source. Unfortunately, no reaction was observed, possibly due to the absence of the NH group in the bisamides, illustrating that the NH group plays a crucial role in the bisamide ligands.

The bisamides were also screened in organocatalytic asymmetric *Henry* reaction of PhCHO and $MeNO_2$. The addition of the amide ligands slightly improved the yield from 80 to 93% (*Table 3*). However, no obvious enantioselectivity was observed,

Table 3. *Catalytic* Henry *Reaction*



Entry	Ligand	Ar	Yield [%]	ee [%]
1	None	Ph	80	0
2	**4**	Ph	86	0
3	**2a**	Ph	92	0
4	**2b**	Ph	86	0
5	**2c**	Ph	93	2
6	**2d**	Ph	86	2
7	**2c**	4-O_2N–C_6H_4	97	2
8	**2c**	4-Cl–C_6H_4	95	2
9	**2c**	4-Me–C_6H_4	47	2
10	**2c**	4-MeO–C_6H_4	19	2

indicating that the NH group in the amide ligands plays a significant role in the asymmetric catalytic reactions. The electronic effects of different substituents of the phenyl group of the benzaldehydes were also screened by utilizing a series of *p*-substituted benzaldehydes under the catalysis of **2c**. The electron-withdrawing groups such as NO_2 and Cl efficiently enhanced the yield to 97% without enantioselectivity (2% ee).

3. Conclusions. – Some new chiral C_2-symmetric (1*S*,2*S*)-cyclohexane-1,2-dicarboxamides were synthesized *via* the reaction of (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride and *N*-benzylated aromatic amines, including *N*-benzyl 2-aminopyridine, 2-chloroaniline, and 2-aminophenol. To avoid the formation of cyclic imides of type **4**, *N*-benzylated aromatic amines, which were prepared from the corresponding aromatic amines *via* reaction with benzaldehyde and subsequent reduction, were used instead of the corresponding aromatic amines in the synthesis. However, the hydrogenolysis in the presence of Pd and $Pd(OH)_2$ on active carbon could not facilitate the removal the *N*-Bn group in the bisamides due to steric hindrance around the amide group.

Experimental Part

General. CH_2Cl_2 was refluxed over CaH_2 and freshly distilled prior to use. M.p.: *Yanaco MP-500* melting-point apparatus; uncorrected. Optical rotations: *PerkinElmer Model 341LC* polarimeter with a thermally jacketed 10-cm cell (*c* in g/100 ml). IR Spectra: *Nicolet Avatar 330* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian Mercury 200* at 200 or 50 MHz, resp., *Varian Mercury Plus 300* at 300 or 75 MHz, resp., or *Bruker AV 400* at 400 or 100 MHz, resp. in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-ESI-MS Spectra: *LC/MSD TOF* mass spectrometer, in *m*/*z*.

1. *Reaction of* (1*S*,2*S*)-*Cyclohexane-1,2-dicarboxylic Acid and 2-Aminopyridine.* A mixture of the acid (0.256 g, 1.49 mmol) with two drops of anh. DMF and $SOCl_2$ (1.0 ml, 1.679 g, 14.2 mmol) was stirred at r.t. for 5 h. The redundant $SOCl_2$ was removed under reduced pressure to give crude (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride as yellow oil, which was dissolved in anh. CH_2Cl_2 (8 ml). The soln. was added dropwise to a soln. of 2-aminopyridine (0.280 g, 2.98 mmol) in anh. CH_2Cl_2 (6 ml) with Et_3N (0.5 ml) in an ice H_2O bath. After stirring at r.t. overnight, the reaction was quenched with H_2O (10 ml). The org. phase was then dried (Na_2SO_4) and concentrated. The residue was purified through column chromotography (CC; SiO_2) to give the cyclic imide **4** (0.124 g) in 72% yield with R_f 0.5 and monoamide **3** (27.8 mg) in 15% yield with R_f 0.1 (SiO_2; petroleum ether (PE)/AcOEt 5 : 1 (*v*/*v*).

(1S,2S)-2-(Pyridin-2-ylcarbamoyl)cyclohexanecarboxylic Acid (**3**). Colorless crystals. M.p. 216–219°. $[\alpha]_D^{20} = +22.0$ ($c = 1.04$, $CHCl_3$). IR (CH_2Cl_2): 3209 (NH), 1703 (C=O), 1259 (C–N), 3761 (OH). ^1H-NMR ($CDCl_3$, 200 MHz): 1.39–2.07 (*m*, 4 CH_2); 2.66–2.72 (*m*, 2 CH); 6.94–8.37 (*m*, 4 arom. H); 10.94 (*s*, COOH). ^{13}C-NMR ($CDCl_3$, 50 MHz): 24.4; 24.5; 28.2; 28.6; 45.9; 48.2; 115.7; 119.3; 140.4; 144.4; 151.3; 174.7; 180.0. HR-MS-ESI: 249.1239 ($[M+H]^+$: $C_{13}H_{16}N_2O_3^+$; calc. 249.1234).

*(3aS,7aS)-Hexahydro-2-(pyridin-2-yl)-1*H*-isoindole-1,3(2*H*)-dione* (**4**). Colorless crystals. M.p. 184–187°. $[\alpha]_D^{20} = -81.5$ ($c = 1.05$, $CHCl_3$). IR (CH_2Cl_2): 1732 (C=O), 1225 (C–N). ^1H-NMR ($CDCl_3$, 400 MHz): 1.34–2.37 (*m*, 4 CH_2); 2.53–2.59 (*m*, 2 CH); 7.26–8.63 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 25.0; 25.4; 47.7; 121.8; 123.5; 138.2; 146.4; 149.5; 175.1. HR-MS-ESI: 231.1237 ($[M+H]^+$: $C_{13}H_{15}N_2O_2^+$; calc. 231.1128).

2. *Synthesis of* N-*Benzylated Aromatic Amines* **5a** *and* **5b**. *General Procedure.* A soln. of 2-aminopyridine (13.18 g, 140 mmol) in MeOH (200 ml) and PhCHO (14.3 ml, 14.86 g, 140 mmol) was stirred at r.t. for 5 h. Then, $NaBH_4$ (10.59 g, 280 mmol) was added portionwise to the mixture, which was cooled with cold H_2O, and another 250 ml of MeOH was added. After stirring for 5 h, colorless needle-like crystals were observed. The crystals were obtained through filtration. After addition of H_2O (100 ml) to the filtrate, the resulting mixture was stirred for 10 min. The soln. was concentrated under reduced pressure, and then was extracted with CH_2Cl_2 (50 ml × 2). The combined org. phase was dried (Na_2SO_4)

and concentrated under reduced pressure. The residue was purified by CC (SiO_2) to give **5a** (19.09 g; 74%).

N-*Benzylpyridin-2-amine* (**5a**). Colorless crystals. M.p. 95–96° ([13]: 100–105°). ^{1}H-NMR ($CDCl_3$, 200 MHz): 4.51 (*d*, *J* = 5.6, CH_2); 4.88 (*s*, NH); 6.35–8.13 (*m*, 9 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 46.3; 106.8; 113.2; 127.3; 127.4; 128.7; 137.5; 139.2; 148.3; 158.7.

N-*Benzyl-2-chloroaniline* (**5b**) [14][15]. White oil. Yield: 75%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.37 (*d*, *J* = 5.4, CH_2); 4.72 (*s*, NH); 6.59–7.35 (*m*, 9 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 47.8; 111.4; 117.3; 119.0; 127.2; 127.3; 127.7; 128.7; 129.0; 138.7; 143.8.

N-*Benzyl-2-(benzyloxy)aniline* (**5c**). A soln. of 2-aminophenol (3.27 g, 30 mmol) in MeOH (65 ml) and PhCHO (3 ml, 30 mmol) was stirred at r.t. for 2 h. MeOH was then removed under reduced pressure to give crude imine **6c** (5.112 g), which was then dissolved in acetone (70 ml). K_2CO_3 (6.9 g, 50 mmol) and BnBr (3.0 ml, 4.336 g, 25.35 mmol) were then added. The resulting mixture was refluxed overnight. After cooling, the mixture was filtered through *Celite*, which was then washed with acetone for several times. The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure to give **7** as dark-yellow oil. $NaBH_4$ (0.7566 g, 20 mmol) was added portionwise to a soln. of crude **7** (2.874 g, 10 mmol) in MeOH (100 ml), cooled with cold H_2O. After stirring for 10 h, H_2O (25 ml) was added to quench the reaction. After removal of MeOH under reduced pressure, the aq. soln. was extracted with Et_2O (3 × 25 ml) and CH_2Cl_2 (50 ml). The combined org. phase was dried (Na_2SO_4) and concentrated. The residue was purified by CC (SiO_2) to give **5c** (3.668 g, 50%). Colorless solid. M.p. 61–62°. IR (CH_2Cl_2): 3430 (NH), 1124 (C–O–C). ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.37 (*s*, NCH_2); 4.74 (*s*, NH); 5.10 (*s*, CH_2O); 6.57–7.44 (*m*, 14 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 54.9; 83.8; 84.1; 84.4; 85.3; 117.5; 118.3; 123.6; 128.8; 134.1; 134.3; 134.7; 135.1; 135.7; 144.3; 145.5; 146.8; 153.0. HR-MS-ESI: 290.1533 ($[M + H]^+$, $C_{20}H_{20}NO^+$; calc. 290.1539).

3. *Reaction of (1S,2S)-Cyclohexane-1,2-dicarbonyl Dichloride and Secondary Amines: General Procedure.* A mixture of (1*S*,2*S*)-cyclohexane-1,2-dicarboxylic acid (0.256 g, 1.49 mmol) with 2 drops of anh. DMF and $SOCl_2$ (1.0 ml, 1.679 g, 14.2 mmol) was stirred at r.t. for 5 h. Residual $SOCl_2$ was removed under reduced pressure to give crude (1*S*,2*S*)-cyclohexane-1,2-dicarbonyl dichloride as yellow oil, which was dissolved in anh. CH_2Cl_2 (8 ml). The soln. was added dropwise to a soln. of 2-(benzylamino)pyridine (0.549 g, 2.98 mmol) in anh. CH_2Cl_2 (6 ml) with Et_3N (0.5 ml) in ice-cold H_2O. The mixture was refluxed for 24 h, and then the reaction was quenched with H_2O (10 ml). The org. phase was then dried (Na_2SO_4) and concentrated. The residue was purified by CC (SiO_2) to give **2a** (0.564 g).

(1S,2S)-N,N′-*Dibenzyl*-N,N′-*di(pyridin-2-yl)cyclohexane-1,2-dicarboxamide* (**2a**). Colorless solid. Yield: 75%. M.p. 72–73°. $[\alpha]_D^{20} = -140.7$ (*c* = 1.0, acetone). IR (CH_2Cl_2): 1654 (C=O), 1266 (C–N). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.84–1.80 (*m*, 4 CH_2); 2.99 (*d*, *J* = 9.0, 2 CH); 4.72 (*d*, *J* = 15.6, 2 H of 2 CH_2N); 5.51 (*d*, *J* = 15.6, 2 H of 2 CH_2N); 7.20–7.04 (*m*, 12 arom. H); 7.57 (*d*, *J* = 5.7, 2 arom. H); 7.70 (*t*, *J* = 7.5, 2 arom. H); 8.52 (*d*, *J* = 4.5, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 25.4; 28.7; 44.3; 51.2; 122.3; 124.0; 126.8; 127.6; 128.3; 137.5; 138.2; 149.1; 155.0; 175.5. HR-MS-ESI: 505.2614 ($[M + H]^+$, $C_{32}H_{33}N_4O_2^+$; calc. 505.2598).

(1S,2S)-N,N′-*Dibenzyl*-N,N′-*bis(2-chlorophenyl)cyclohexane-1,2-dicarboxamide* (**2b**). White solid. Yield: 32%. M.p. 188–189°. $[\alpha]_D^{20} = +0.6$ (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2): 1662 (C=O), 1271 (C–N), 620 (C–Cl). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.76–1.77 (*m*, 4 CH_2); 2.74–7.08 (*m*, 2 CH); 4.16 (*d*, *J* = 11.1, 2 H of 2 CH_2N); 5.77 (*d*, *J* = 11.1, 2 H of 2 CH_2N); 6.62–7.54 (*m*, 18 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 25.4; 28.5; 45.0; 51.9; 127.0; 127.3; 127.7; 128.2; 128.5; 129.0; 129.3; 129.5; 130.0; 130.6; 132.0; 133.3; 174.3. HR-MS-ESI: 571.1917 ($[M + H]^+$, $C_{34}H_{33}Cl_2N_2O_2^+$; calc. 571.1914).

(1S,2S)-N,N′-*Dibenzyl*-N,N′-*bis[2-(benzyloxy)phenyl]cyclohexane-1,2-dicarboxamide* (**2c**). Colorless solid. Yield: 37%. M.p. 180–181°. $[\alpha]_D^{20} = -93.6$ (*c* = 1.0, acetone). IR (CH_2Cl_2): 1648 (C=O), 1261 (C–N), 1119 (C–O–C). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.76–1.72 (*m*, 4 CH_2); 2.87 (*d*, *J* = 10.8, 2 CH); 4.25 (*d*, *J* = 15.3, 2 H of 2 CH_2N); 5.04–5.07 (*m*, 2 CH_2O); 5.63 (*d*, *J* = 15.3, 2 H of 2 CH_2N); 6.89–7.48 (*m*, 28 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 25.4; 28.0; 43.9; 51.0; 69.6; 112.3; 121.2; 126.6; 126.7; 127.8; 128.1; 128.2; 128.6; 128.9; 130.3; 132.5; 136.6; 137.8; 153.9; 175.9. HR-MS-ESI: 715.3525 ($[M + H]^+$, $C_{48}H_{47}N_2O_4^+$; calc. 715.3530).

4. *Hydrogenolysis of* **2c***: General Procedure.* To a soln. of **2c** (0.1337 g, 0.187 mmol) in a mixture of anh. CH_2Cl_2 (5 ml) and anh. MeOH (10 ml) was added 5% $Pd(OH)_2$/C. The resulting mixture was stirred

under H_2 for 2 d. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by CC (SiO_2) to give **2d** (58.0 mg).

*(1S,2S)-*N,N′*-Dibenzyl-*N,N′*-bis(2-hydroxyphenyl)cyclohexane-1,2-dicarboxamide* (**2d**). White solid. Yield: 58%. M.p. 254–255°. $[\alpha]_D^{20} = +17.6$ ($c = 1.0$, $CHCl_3$). IR (CH_2Cl_2): 1630 (C=O), 1270 (C–N), 1346, 699 (OH). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.77–1.63 (*m*, 4 CH_2); 2.54–2.60 (*m*, 2 CH); 4.45 (*d*, $J =$ 14.1, 2 H of 2 CH_2N); 5.10 (*d*, $J = 14.1$, 2 H of 2 CH_2N); 6.72–7.28 (*m*, 18 arom. H); 8.57 (*s*, 2 OH). ^{13}C-NMR ($CDCl_3$, 100 MHz): 25.2; 28.1; 45.5; 53.0; 120.2; 120.8; 127.6; 128.4; 128.5; 129.1; 129.2; 129.2; 129.4; 130.1; 136.9; 152.8; 176.8. HR-MS-ESI: 535.2601 ($[M+H]^+$, $C_{34}H_{35}N_2O_4^+$; calc. 535.2591).

Henry *Reaction: General Procedure.* Ligand **2** (0.02 mmol) and CuCl (1.8 mg, 0.018 mmol) were dissolved in anh. CH_2Cl_2 (1.0 ml) under N_2. After stirring the soln. overnight at r.t., the solvent was removed under reduced pressure. The residue was dissolved in EtOH (1 ml). To the resulting clear green soln. was added $MeNO_2$ (0.2 ml, 0.222 g, 3.64 mmol), pyridine (0.05 ml, 47.5 mg, 0.6 mmol), and aromatic aldehyde (0.364 mmol) under N_2. After stirring the mixture for 16 h at r.t., the volatile components were removed under reduced pressure, and the residue was purified by CC (SiO_2; PE/AcOEt 10:1 (*v*/*v*) to afford the adduct. The ee value was determined by chiral HPLC analysis (*Phenomenex Lux Cellulose-1* chiral column).

2-Nitro-1-phenylethanol [16]. Yellow oil. Yield: 56.6 mg (93%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.83 (br. *s*, OH); 4.52 (*dd*, $J = 3.0$, 13.5, 1 H of CH_2); 4.62 (*dd*, $J = 9.6$, 13.5, 1 H of CH_2); 5.45–5.49 (*m*, CH); 7.37–7.43 (*m*, 5 arom. H).

2-Nitro-1-(4-nitrophenyl)ethanol [17]. Yellow oil. Yield: 74.9 mg (97%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 3.51 (br. *s*, OH); 4.59 (*dd*, $J = 4.8$, 13.6, 1 H of CH_2); 4.63 (*dd*, $J = 7.6$, 13.6, 1 H of CH_2); 5.62 (*dd*, $J = 4.8$, 7.6, CH); 7.63 (*d*, $J = 8.8$, 2 arom. H); 8.22 (*d*, $J = 8.8$, 2 arom. H).

1-(4-Chlorophenyl)-2-nitroethanol [17]. Yellow oil. Yield: 69.7 mg (95%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.89 (br. *s*, OH); 4.49 (*dd*, $J = 3.2$, 13.6, 1 H of CH_2); 4.58 (*dd*, $J = 9.6$, 13.6, 1 H of CH_2); 5.44–5.48 (*m*, CH); 7.35 (*d*, $J = 8.8$, 2 arom. H); 7.39 (*d*, $J = 8.8$, 2 arom. H).

1-(4-Methylphenyl)-2-nitroethanol [17]. Yellow oil: 31.0 mg (47%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.36 (*s*, Me); 2.72 (br. *s*, OH); 4.49 (*dd*, $J = 3.2$, 13.2, 1 H of CH_2); 4.60 (*dd*, $J = 9.6$, 13.2, 1 H of CH_2); 5.41–5.45 (*m*, CH); 7.21 (*d*, $J = 8.0$, 2 arom. H); 7.29 (*d*, $J = 8.0$, 2 arom. H).

1-(4-Methoxyphenyl)-2-nitroethanol [17]. Yellow oil: 13.6 mg (19%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 3.13 (br. *s*, OH); 3.78 (*s*, MeO); 4.43 (*dd*, $J = 3.2$, 13.2, 1 H of CH_2); 4.56 (*dd*, $J = 9.6$, 13.2, 1 H of CH_2); 5.43 (*dd*, $J = 3.2$, 9.6, CH); 6.89 (*d*, $J = 8.8$, 2 arom. H); 7.27 (*d*, $J = 8.8$, 2 arom. H).

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