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Enantiomerically Pure Isophorone Diamine [3-(Aminomethyl)-3,5,5-trimethylcyclohexylamine]: A Chiral 1,4-Diamine Building Block Made Available on Large Scale

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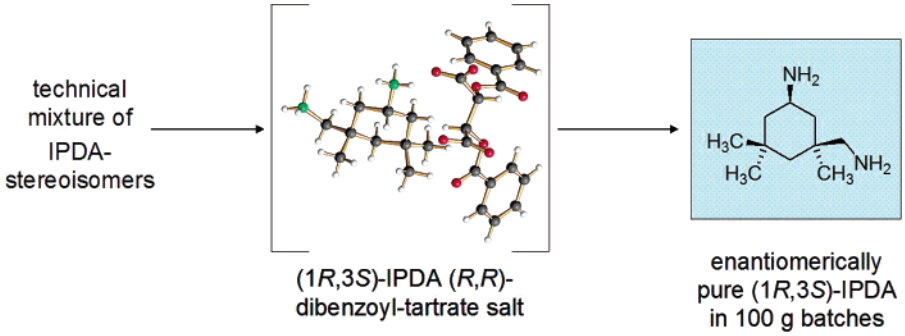

Isophorone diamine [IPDA, 3-(aminomethyl)-3,5,5-trimethylcyclohexylamine] is a chiral non-C_2-symmetric 1,4-diamine which is produced industrially on large scale as the mixture of all four stereoisomers (cis/trans ca. 3:1). Starting from this industrial bulk product, the preparation of the bis-tosyl, bis-Fmoc, bis-Boc and bis-*Z* derivatives of *cis*-IPDA, the preparation of the pure cis enantiomers by HPLC on chiral stationary phase, and the assignment of absolute configurations to the isolated enantiomers are described. We furthermore report an efficient method for the optical resolution of IPDA by salt formation with dibenzoyl tartaric acid. The latter method conveniently affords enantiomerically pure *cis*-IPDA in 100 g quantities. A number of salen ligands have been prepared from this enantiomerically pure 1,4-diamine and fully characterized. The nickel complex of one of the salen ligands was prepared and analyzed by X-ray crystallography. The crystal structure of the Ni_4L_4 complex illustrates the pronounced preference of *cis*-IPDA for adopting the chair conformation in which both the amino- and the aminomethyl substituents occupy equatorial positions. As a consequence, the two salicylidene imine moieties of one ligand molecule do not converge on one metal ion, but act as bridging ligands between two nickel ions.

Introduction

In recent years, chiral diamines have become ever more important as building blocks for chiral salen ligands[1] and metal complexes derived thereof, for the synthesis of chiral organocatalysts,[2] and for many other applications.[3] One of the most prominent chiral diamine building blocks is *trans*-1,2-diaminocyclohexane **1**.[4] The optical resolution of *rac*-**1** was reported by Galsbøl et al. in 1972 and later modified by Jacobsen and co-workers.[5] The *trans*-1,2-diamine **1** is readily obtained in enantiomerically pure form from the commercial mixture of all three stereoisomers by crystallization with tartaric acid. We have recently reported the successful application of chromium−salen complexes of *endo*,*endo*-2,5-diaminonorbornane (DIANANE) **2** in the asymmetric Nozaki−Hiyama−Kishi addition of allylic

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(2) (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (b) Dalko, P. I.; Moisan, L. *Angew. Chem.* **2004**, *116*, 5248−5286. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.

(3) (a) Collins, A. N., Sheldrake, G. N., Crosby, J., Eds. *Chirality in Industry*; John Wiley & Sons Ltd.: Chichester, U.K., 1992. (b) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, Heidelberg, Germany, 1999. (c) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem.* **1998**, *110*, 2724−2772. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. (d) Muñiz, K. *Angew. Chem.* **2005**, *117*, 6780−6785. *Angew. Chem., Int. Ed.* **2005**, *44*, 6622−6627.

(4) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161−3195.

(5) (a) Galsbøl, F.; Steenbøl, P.; Sørensen, B. S. *Acta Chem. Scand.* **1972**, *26*, 3605−3611. (b) Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 1939−1942. (c) Larrow, J. F; Jacobsen, E. N. *Org. Synth.* **1997**, *75*, 1−11.

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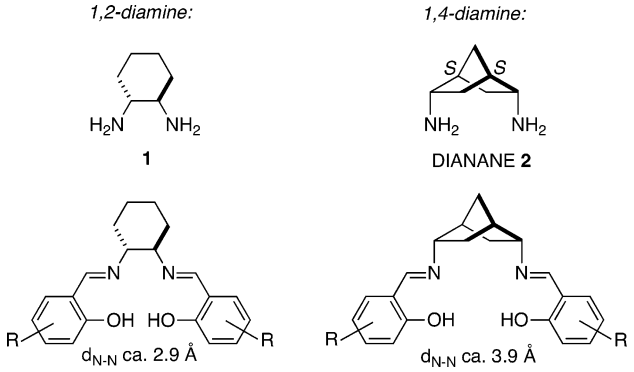


FIGURE 1. The C_2-symmetric diamines *trans*-1,2-diaminocyclohexane (DACH, **1**), *endo*,*endo*-2,5-diaminonorbornane (DIANANE, **2**), and salen ligands derived thereof.

and vinylic electrophiles to aldehydes.[6] DIANANE (**2**) is a C_2-symmetric 1,4-diamine. Compared to salen ligands prepared from *trans*-1,2-diaminocyclohexane (**1**), those derived from DIANANE (**2**) have a significantly larger N−N distance (Figure 1).[7]

Our positive results achieved with the 1,4-diamine DIANANE (**2**) raised the question whether other chiral 1,4-diamines might be available as building blocks for novel salen-type ligands. We realized that 3-aminomethyl-3,5,5-trimethylcyclohexylamine (isophorone diamine, IPDA; **3**, Figure 2) might be a suitable candidate: IPDA (**3**) is a chiral 1,4-diamine which is produced industrially on large scale as a ca. 3:1 mixture of the racemic cis- and trans-diastereomers (*rac*-**3**-*cis* + *rac*-**3**-*trans*). The bis-isocyanate derivative of IPDA (**3**) is produced on a ca. 10 000 t/a scale, and it is used for polyurethane synthesis.[8−10] We reasoned that IPDA (**3**) itself—as a cheap and readily available chiral diamine—could find use as a novel building block in asymmetric catalysis (e.g. for the synthesis of novel salen ligands, or as building block for chiral organocatalysts). A particularly interesting feature of *cis*-IPDA is the fact that this 1,4-diamine, as a cyclohexane derivate, largely prefers the bis-equatorial arrangement of its amino- and aminomethyl substituents (Figure 2b).[10b] In other words, organocatalysts derived from IPDA could be expected to have nonconvergent and thus independently acting functional groups. Similarly, the two binding sites of salen ligands derived from *cis*-IPDA could be anticipated to not bind simultaneously to one metal ion. Instead, the formation of metal complexes of higher nuclearity should result. In this article, we report a practical method for the preparation of enantiomerically pure *cis*-IPDA (**3**-*cis*, *ent*-**3**-*cis*)

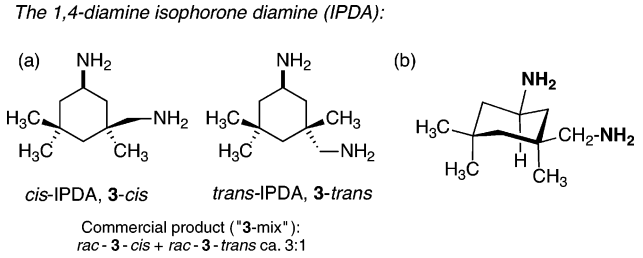


FIGURE 2. (a) Stereoisomers of isophorone diamine (IPDA, **3**); (b) preferred ee conformation of *cis*-IPDA **3**-*cis*.

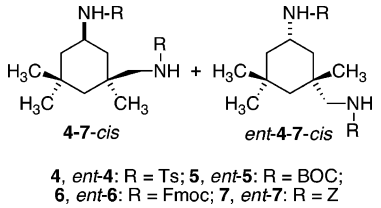
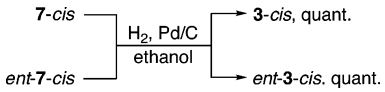


FIGURE 3. IPDA derivatives *rac*-**4**−**7**-*cis*.

SCHEME 1. Preparation of Enantiomerically Pure IPDA 3-*cis* and *ent*-3-*cis* by Hydrogenolytic Deprotection of Bis-*Z*-IPDA 7-*cis* and *ent*-7-*cis*



on large scale, the assignment of absolute configuration, the preparation of IPDA-salen ligands, and the structural features of a nickel complex derived from one of the novel *cis*-IPDA salen ligands.

Results and Discussion

The separation of the four stereoisomers of the industrial product ("**3**-*mix*") was first attempted by derivatization to the bis-tosylamide-, bis-Fmoc-, bis-Boc-, and bis-*Z*-derivative and subsequent preparative HPLC on chiral stationary phase.[11] In fact, recrystallization of the crude mixture of the tosylamide and the carbamates already furnished the diastereomerically pure cis-stereoisomers *rac*-**4**-*cis*, *rac*-**5**-*cis*, *rac*-**6**-*cis*, and *rac*-**7**-*cis* (see Figure 3). The separation of the cis-enantiomers of compounds *rac*-**4**-*cis* and *rac*-**7**-*cis* was readily achieved by preparative HPLC on Chiralpak AD. The separated enantiomers of the *cis*-bis-tosylamides (**4**-*cis* and *ent*-**4**-*cis*) were again crystallized and subjected to X-ray structural analysis. The absolute configurations for **4**-*cis* (1*S*,3*R*) and *ent*-**4**-*cis* (1*R*,3*S*) could be assigned by anomalous dispersion (see Supporting Information). By cleavage of the *Z*-protective group in **7**-*cis* (or *ent*-**7**-*cis*) with H_2/Pd−C, enantiomerically pure *cis*-IPDA **3**-*cis* (or *ent*-**3**-*cis*) was obtained for the first time, albeit in small quantities only, because of the limitations imposed by the HPLC separation (Scheme 1).

For the large scale preparation of enantiomerically pure IPDA, we performed a screening of chiral carboxylic acids that were hoped to form diastereomeric salts with IPDA (either cis or trans). Attempts in this direction using tartaric acid, mandelic acid, or amino acids such as glutamic or aspartic acid failed

(6) (a) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schröder, M.; Paterson, I. *Angew. Chem.* **2003**, *115*, 1062−1065; *Angew. Chem., Int. Ed.* **2003**, *42*, 1032−1035. (b) Paterson, I.; Bergmann, H.; Menche, D.; Berkessel, A. *Org. Lett.* **2004**, *6*, 1293−1295.

(7) Berkessel, A.; Schröder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudörfl, J. M. *J. Org. Chem.* **2004**, *69*, 3050−3056.

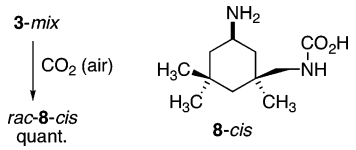
(8) For the preparation of IPDA with high cis/trans ratio, see (a) Funke, F.; Hill, T.; Melder, J.-P.; Schwab, E.; Himmel, W.; Henkes, E.; Petersen, H.; Körner, R. Int. Patent WO 2003020421 A1, 2003. (b) Haas, T.; Arntz, D.; Most, D. Eur. Patent EP 659733 A1, 1995. (c) Haas, T.; Arntz, D. *Chem. Eng. Technol.* **1996**, *68*, 161−165.

(9) For examples see (a) Hoenel, M.; Pfeil, A.; Budnick, T.; Schwan, H. German Patent DE 4344510 A1, 1995. (b) Tillack, J.; Schmalstieg, L.; Puetz, W.; Ruttmann, G. German Patent DE 19935329 A1, 2001. (c) Schmitt, K.; Disteldorf, J.; Hübel, W. U.S. Patent US 3352913, 1967.

(10) (a) Wendisch, D.; Reiff, H.; Dieterich, D. *Angew. Makromol. Chem.* **1986**, *141*, 173−183. (b) Auf der Heyde, W.; Hübel, W.; Boese, R. *Angew. Makromol. Chem.* **1987**, *153*, 1−13. (c) Born, L.; Wendisch, D.; Reiff, H.; Dieterich, D. *Angew. Makromol. Chem.* **1989**, *171*, 213−231.

(11) For the preparation of stereoisomeric mixtures of IPDA-carbamates see (a) Butler, D. C. D.; Alper, H. *Chem. Commun.* **1998**, 2575−2576. (b) Valli, V. L. K.; Alper, H. *J. Org. Chem.* **1995**, *60*, 257−258. (c) Afonso, C. A. M. *Synth. Commun.* **1998**, *28*, 261−276.

SCHEME 2. Reaction of IPDA 3-*Mix* to Afford the Crystalline Carbamic Acid *rac*-8-*cis*.



completely[12] and invariably led to the isolation of the crystalline carbamic acid *rac*-**8**-*cis* which is readily formed upon exposition of IPDA to air (Scheme 2).

The resolution could eventually be achieved by reaction of IPDA with (*R*,*R*)-dibenzoyl tartaric acid (DBTA) to yield, after one recrystallization, the diastereomerically pure salt **9** in 56% yield (with respect to the amount of **3**-*cis* present in **3**-*mix*) and with a dr of >99:1 (Scheme 3). For the determination of the dr, the amine component was liberated from the salt **9**, and its enantiomeric purity was measured (as the bis-*Z*-derivative **7**-*cis*, *ent*-**7**-*cis*) by HPLC on chiral stationary phase. Furthermore, the DBTA salt **9** was subjected to X-ray analysis. As the configuration of the dibenzoyl tartrate (DBTA) employed in the separation was known, the relative and absolute configuration of the amine component (**3**-*cis*, 1*R*,3*S*) could be deduced from the X-ray structure. Clearly, the enantiomeric IPDA *ent*-**3**-*cis* is obtained when (*S*,*S*)-dibenzoyl tartaric acid is used in the crystallization. The enantiomerically pure IPDA **3**-*cis* is easily liberated from its DBTA-salt by addition of base (NaOH) and extraction with CH_2Cl_2. After Kugelrohr distillation, the enantiomerically pure diamine **3**-*cis* was routinely obtained in quantitative yield. By this procedure, the separation of crude IPDA **3**-*mix* can easily be carried out in 100 g batches. On the other hand, care has to be taken when handling small quantities of IPDA in air, because carbamate formation rapidly takes place (vide supra).

Upon combination with salicylic aldehydes, IPDA readily forms the corresponding diimines. As shown in Scheme 4, the bis-salicylidene imines **10a**−**g** can be prepared even more conveniently directly from the IPDA−DBTA salt **9** (or *ent*-**9**, respectively) in the presence of potassium carbonate as base. Scheme 4 also shows the X-ray crystal structure of a typical IPDA−salen, namely **10c**. As anticipated, the IPDA cyclohexane ring adopts a chair conformation, and both amine substitutents are oriented equatorially. In more commonly used salen ligands, for example, those incorporating DACH (**1**) as the diamine component, the salicylidene imine moieties can converge to bind a metal ion in a tetradentate fashion.[13] In the case of the IPDA salens, this converging of the two salicylidene units would require an energetically unfavorable bis-axial arrangement of the two amine substituents. As a consequence, coordination geometries different from "regular" salens may be expected for the metal complexes of the tetradentate ligands **10a**−**g**.

To test this assumption, we chose nickel(II) as a metal ion known to form square-planar complexes with various salen ligands. Indeed, the reaction of preformed nickel(II) bis-4-chlorosalicylic aldehyde complex with the mixture of IPDA stereoisomers (**3**-*mix*) did not afford a simple 1:1 salen complex. Instead, a crystalline material was obtained which by X-ray crystallography was identified as the [4× Ni + 4× **10c**]-aggregate *rac*-**11** (Figure 4). Inspection of the crystal structure reveals that two of the four nickel centers are coordinated in a (distorted) square-planar fashion, whereas the other two are octahedral. In the latter cases, the coordination spheres around the nickel ions are completed by water. As already observed for the *cis*-IPDA bis-salicylidene imines (such as **10c**, Scheme 4), the *cis*-IPDA core maintains the bis-equatorial orientation of the amine substituents, thus preventing the simultaneous binding of both salicylidene imine substituents to the same nickel ion. As a consequence, the four IPDA-derived salen ligands **10c** in the complex *rac*-**11**—without exception—coordinate *two different* nickel ions.

As the first application of enantiomerically pure IPDA in asymmetric organocatalysis, we recently described the IPDA-based bis(thio)ureas **12** (Figure 5) as highly efficient and enantioselective catalysts for the Morita−Baylis−Hillman reaction (up to quant. yield and 96% ee).[14]

Conclusions

The aim of the current study was to elaborate a method for the large-scale and practical preparation of IPDA **3**-*cis* (or *ent*-**3**-*cis*). We have shown that this goal can be achieved, starting from the industrial bulk product IPDA **3**-*mix* by salt formation with (*R*,*R*)- or (*S*,*S*)-dibenzoyl tartaric acid (DBTA). The absolute configurations of the resulting IPDA enantiomers **3**-*cis* and *ent*-**3**-*cis* were assigned. Seven bis-salicylidene imine ligands (**10a**−**g**) were prepared directly from the IPDA−DBTA salt **9** by treatment with salicylic aldehydes in the presence of base. The X-ray structural analyses of a number of *cis*-IPDA derivatives confirmed the pronounced preference of both amine substituents to occupy the equatorial positions at IPDA's cyclohexane core. As a consequence, and as expected, coordination of the ligand *rac*-**10c** to Ni(II) afforded the tetranuclear Ni complex *rac*-**11**, and not a mononuclear coordination compound typical, for example, for DACH-salens. Future work will address the synthesis of chiral and bifunctional IPDA-based catalysts, taking advantage of the different reactivity of the two amino moieties of IPDA **3**.[14]

Experimental Section

1-Toluenesulfonylamido-3-toluenesulfonylamidomethyl-3,5,5-trimethylcyclohexane *rac*-4-*cis*.[15] A solution of isophorone diamine **3**-*mix* (technical mixture of stereoisomers, ca. 70% *rac*-**3**-*cis*, 5.53 mL, 30.0 mmol) in CH_2Cl_2 (100 mL) was cooled to −78 °C, and toluenesulfonyl chloride (12.0 g, 63.0 mmol) in CH_2Cl_2 (50.0 mL) and NEt_3 (8.85 mL, 63.0 mmol) were added in a dropwise manner. After it was stirred at −78 °C for 3 h, the mixture was allowed to warm to room temperature overnight. The resulting suspension was extracted with 3 × 40.0 mL of 2 M aqueous HCl, 2 × 40.0 mL of H_2O, and 40.0 mL of brine and dried over $MgSO_4$. After the extract was concentrated in vacuo, a colorless semisolid was obtained. This crude product was washed several times with a Et_2O/pentane mixture (1/1, v/v) and crystallized from MeOH to yield 10.1 g (71%) of the bistosylamide *rac*-**4**-*cis* as a colorless solid, containing traces of the trans-isomer. Further purification was achieved by slow recrystallization from EtOH to give colorless crystals suitable for X-ray crystallography. HPLC (Daicel Chiralpak AD 4.60 mm

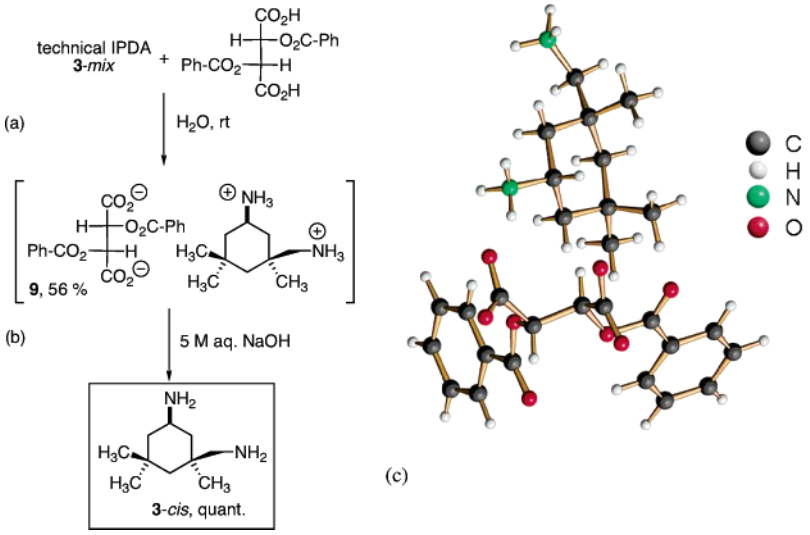
(12) Kozma, D., Ed. *Optical Resolutions via Diastereomeric Salt Formation*; CRC Press: Boca Raton, FL, 2002.

(13) For examples of tetradentate salen complexes see Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063−7064.

(14) Berkessel, A.; Roland, K.; Neudörfl, J. M. *Org. Lett.* **2006**, *8*, 4195−4198.

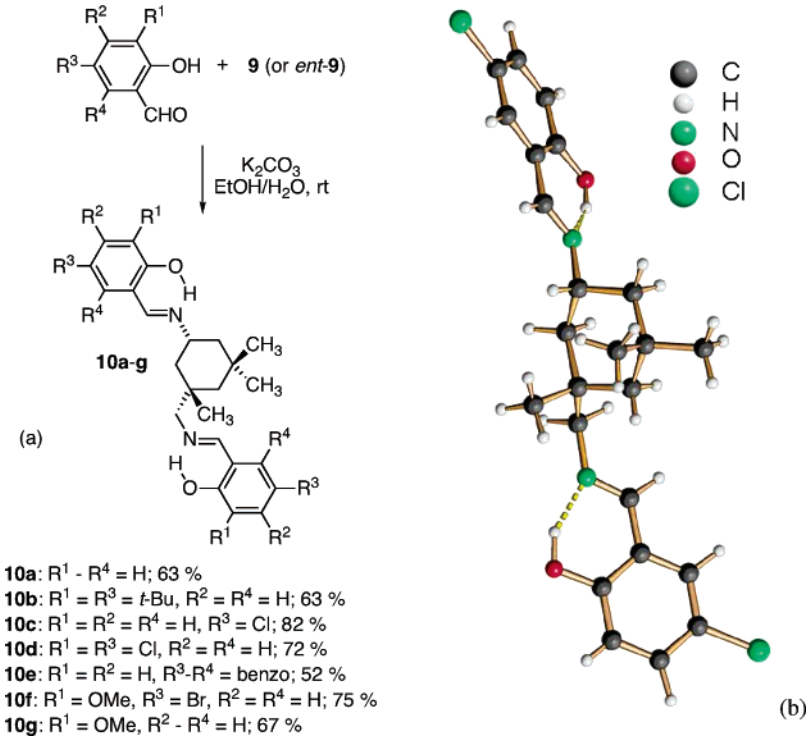
(15) Mixtures of the stereoisomers of **4** appear to be commercially available as components of screening libraries, e.g., Princeton Gold Collection I or Aurora Screening Library. No report on their preparation or assignment of configuration appears to exist.

SCHEME 3[a]



[a] Preparation of the (*R*,*R*)-dibenzoyl tartrate **9** of **3**-*cis* from the IPDA mixture of stereoisomers **3**-*mix* (a); conversion of **9** to enantiomerically pure (1*R*,3*S*)-IPDA **3**-*cis* (b); X-ray crystal structure of the tartrate salt **9** (c).

SCHEME 4[a]



[a] Preparation of the bissalicylidene imine ligands **10a**−**g** from the IPDA−DBTA Salt **9** (a); X-ray crystal structure of the ligand **10c** (b).

i.d. × 250 mm length; *n*-hexane/2-propanol 70/30, 0.5 mL/min; 80 min; UV, 220−400 nm) τ_R 44.0, 46.5 min (trans isomers), 57.3 min [**4**-*cis* (1*S*,3*R*)], 74.2 min [*ent*-**4**-*cis* (1*R*,3*S*)]; mp 201 °C. IR (CsI): 3448, 3272, 2957, 2361, 2358, 1598, 1348, 1323, 1157, 1153, 1096, 1072, 821, 668, 551 cm^{-1}. ^1H NMR (300 MHz, d^6-DMSO): δ 7.72−7.61 (m; 4H), 7.52−7.42 (m; 2H), 7.42−7.33 (m; 4H), 3.26−3.10 (m; 1H), 2.38 (s; 3H), 2.37 (s; 3H), 2.29 (d; J = 6.7 Hz, 2H), 1.32−1.13 (m; 2H), 1.03−0.82 (m; 4H), 0.81 (s; 3H), 0.79 (s; 3H), 0.75 (s; 3H). ^{13}C NMR (75 MHz, d^6-DMSO): δ 142.3 (s), 142.2 (s), 139.0 (s), 137.3 (s), 129.4 (d), 126.4 (d), 126.2 (d), 56.0 (t), 46.7 (d), 45.9 (t), 45.7 (t), 41.8 (t), 35.3 (s), 34.6 (q), 31.3 (s), 27.1 (q), 23.2 (q), 20.9 (q). Anal. Calcd for $C_{24}H_{34}N_2O_4S_2$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.16; H, 7.18; N, 5.86.

(1*S*,3*R*)- and (1*R*,3*S*)-1-Toluenesulfonylamido-3-toluenesulfonylamidomethyl-3,5,5-trimethylcyclohexane 4-*cis* (1*S*,3*R*)- and *ent*-4-*cis* (1*R*,3*S*). The enantiomers of the bistosylamide *rac*-**4**-*cis* were separated by chiral preparative HPLC on a Daicel Chiralpak AD column (50 mm i.d. × 500 mm length) with *n*-hexane/*i*-PrOH (70/30), p 12 bar, flow 80 mL/min. τ_R 45.0−55.0 min [**4**-*cis*], 57.0−72.0 min [*ent*-**4**-*cis*]. A total of 100 mg of *rac*-**4**-*cis* in 10.0 mL of EtOH (dissolved by sonication) were injected per run. The fractions were concentrated in vacuo, and the residue was recrystallized from

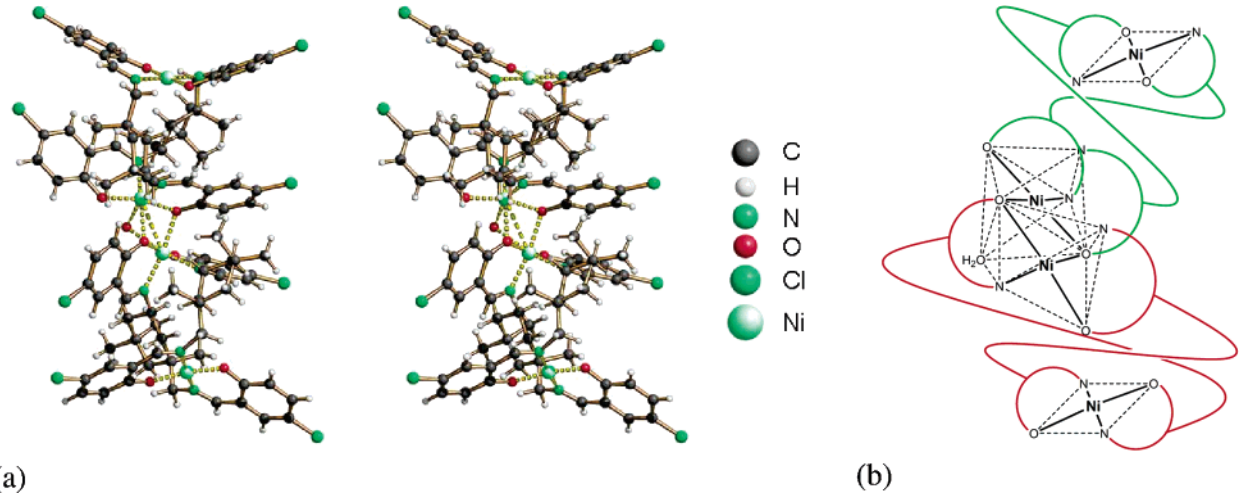


FIGURE 4. (a) X-ray crystal structure of the nickel(II)−IPDA salen complex *rac*-**11** (stereoscopic view); (b) schematic diagram of complex *rac*-**11**: green, (1*R*,3*S*)-configuration; red, (1*S*,3*R*)-configuration.

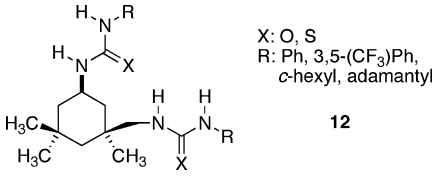


FIGURE 5. Organocatalysts **12** derived from enantiomerically pure IPDA **3**-*cis*.

EtOH. The products were obtained quantitatively as colorless crystals, suitable for X-ray crystallography. **4**-*cis*: mp 173 °C; $[\alpha]^{20}_D$ −36.0 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{24}H_{34}N_2O_4S_2$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.26; H, 7.13; N, 5.83. *ent*-**4**-*cis*: mp 173 °C; $[\alpha]^{20}_D$ +36.0 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{24}H_{34}N_2O_4S_2$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.13; H, 7.12; N, 5.80.

***cis-tert*-Butyl-*N*-{3-[(*tert*-butoxycarbonylamino)methyl]-3,5,5-trimethylcyclohexyl}carbamate *rac*-5-*cis*.** To a solution of di-*tert*-butyl-dicarbonate (5.45 g, 25.0 mmol) and K_2CO_3 (6.90 g, 50.0 mmol) in dioxane/water (2:1, 100 mL) was added at room temperature 3-aminomethyl-3,5,5-trimethylcyclohexylamine **3**-*mix* (1.85 mL, 10.0 mmol) and stirred for 12 h. The aqueous phase was brought to pH 7 by the addition of 10% hydrochloric acid and extracted with 3 × 20.0 mL of ethyl acetate. The organic phase was dried over $MgSO_4$, and the solvent evaporated under reduced pressure. Repeated crystallization of the resulting residue from ethanol yielded 1.70 g (46%) *cis-tert*-butyl-*N*-{3-[(*tert*-butoxycarbonylamino)methyl]-3,5,5-trimethylcyclohexyl}carbamate *rac*-**5**-*cis* as colorless crystals, suitable for X-ray crystallography: mp 127 °C. IR (CsI): 3386, 3326, 2979, 2957, 2924, 1692, 1678, 1525, 1456, 1392, 1367, 1308, 1288, 1276, 1173, 1047, 1023, 1008, 956, 648 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.66−4.47 (m; 1H), 4.38−4.19 (m; 1H), 3.84−3.55 (m; 1H), 2.91−2.67 (m; 2H), 1.76−1.57 (m; 2H), 1.41 (s; 18H), 1.19−1.07 (m; 1H), 1.05−0.67 (m; 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3 (s), 155.2 (s), 79.1 (s), 78.7 (s), 54.6 (t), 47.2 (t), 46.5 (t), 44.1 (d), 42.1 (t), 36.4 (s), 35.1 (q), 31.8 (s), 28.5 (q), 28.4 (q), 27.7 (q), 23.2 (q). HRMS (ESI): calcd for $C_{20}H_{38}N_2O_4$+Na^+, 393.2729; found, 393.2730. Anal. Calcd for $C_{20}H_{38}N_2O_4$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.82; H, 10.23; N, 7.59.

***cis*-(9*H*-Fluoren-9-ylmethyl)-*N*-(3-{[(9*H*-fluoren-9-ylmethoxycarbonyl)amino]methyl}3,5,5-trimethylcyclohexyl}carbamate *rac*-6-*cis*.** To a solution of 9-fluorenylmethyl-*N*-succinimidyl carbonate (1.00 g, 2.96 mmol) and $NaHCO_3$ (200 mg, 2.12 mmol) in dioxane/water (2:1, 50 mL) was added at room temperature 3-aminomethyl-3,5,5-trimethylcyclohexylamine **3**-*mix* (260 μl, 1.41 mmol), and the mixture was stirred for 10 h. The aqueous phase was brought to pH 5 by the addition of 10% hydrochloric acid and extracted with 3 × 20.0 mL of ethyl acetate. The organic phase was dried over $MgSO_4$, and the solvent evaporated under reduced pressure. Repeated crystallization of the resulting yellow residue from ethanol yielded 353 mg (41%) *cis*-(9*H*-fluoren-9-ylmethyl)-*N*-(3-{[(9*H*-fluoren-9-ylmethoxycarbonyl)amino]methyl}-3,5,5-trimethylcyclohexyl}carbamate *rac*-**6**-*cis* as pale yellow crystals, suitable for X-ray crystallography: mp 90 °C. IR (CsI): 3331, 3066, 3039, 2954, 2924, 1696, 1539, 1450, 1302, 1257, 1241, 1143, 1034, 1012, 996, 757, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (d; J = 7.3 Hz, 4H), 7.60 (d; J = 7.3 Hz, 4H), 7.39 (t; J = 7.3 Hz, 4H), 7.31 (t; J = 7.3 Hz, 4H), 4.92−4.79 (m; 1H), 4.67−4.52 (m; 1H), 4.51−4.34 (m; 4H), 4.28−4.14 (m; 2H), 3.93−3.76 (m; 1H), 3.02−2.82 (m; 2H), 1.84−1.58 (m; 2H), 1.26−0.66 (m; 13H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8 (s), 155.6 (s), 144.1 (s), 144.0 (s), 141.3 (s), 127.6 (d), 127.0 (d), 124.9 (d), 119.9 (d), 66.4 (t), 54.8 (t), 47.3 (d), 47.0 (t), 46.3 (t), 44.7 (d), 41.7 (t), 36.4 (s), 35.0 (q), 31.8 (s), 27.6 (q), 23.2 (q). HRMS (ESI): calcd for $C_{40}H_{42}N_2O_4$+Na^+, 637.3043; found, 637.3050. Anal. Calcd for $C_{40}H_{42}N_2O_4$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.97; H, 6.92; N, 4.60. HPLC (anal., Daicel Chiralpak AD (4.60 mm i.d. × 250 mm), *n*-hexane/ethanol (93/7, v/v), flow 1.10 mL/min) τ_R 45.5 min, 49.5 min [trans isomers], τ_R 81.4 min [**6**-*cis*], 101.9 min [*ent*-**6**-*cis*] (absolute configuration of the two cis-enantiomers was assigned arbitrarily).

***cis*-Benzyl-*N*-{3-[(benzyloxycarbonylamino)methyl]-3,5,5-trimethylcyclohexyl}carbamate *rac*-7-*cis*.[16]** To a suspension of benzyl chloroformate (4.50 mL, 31.5 mmol) and K_2CO_3 (6.20 g, 45.0 mmol) in water (100 mL) at 0 °C was added 3-aminomethyl-3,5,5-trimethylcyclohexylamin **3**-*mix* (2.80 mL, 15.0 mmol) and stirred at that temperature for 3 h. The aqueous phase was brought to pH 5 by the addition of 10% hydrochloric acid and extracted with 3 × 30.0 mL of ethyl acetate. The organic phase was dried over $MgSO_4$, and the solvent evaporated under reduced pressure. Repeated crystallization of the resulting residue from methanol yielded 2.93 g (44%) *cis*-benzyl-*N*-{3-[(benzyloxycarbonylamino)-methyl]-3,5,5-trimethylcyclohexyl}carbamate *rac*-**7**-*cis* as colorless crystals, suitable for X-ray crystallography: mp 103 °C. IR (CsI): 3346, 3034, 2985, 2953, 1707, 1686, 1536, 1457, 1307, 1246, 1128, 1033, 998, 752, 742, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48−7.27 (m; 10H), 5.07 (s; 2H), 5.06 (2s; 2H), 4.86−4.73 (m; 1H), 4.55−4.46 (m; 1H), 3.91−3.68 (m; 1H), 2.96−

(16) *rac*-**7**-*cis* was mentioned previously, but no procedure for its preparation was reported: Takata, M.; Hisamatsu, N. German Patent 19910363 A1, 1999.

2.85 (m; 2H), 1.78−1.61 (m; 2H), 1.27−0.78 (m; 4H), 0.90 (s; 3H), 1.04 (s; 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7 (s), 155.5 (s), 136.5 (s), 128.4 (d), 128.1 (d), 128.0 (d), 66.7 (t), 66.4 (t), 54.8 (t), 46.2 (t), 46.9 (t), 44.6 (d), 41.7 (t), 36.3 (s), 34.9 (q), 31.7 (s), 27.5 (q), 23.2 (q). HRMS (ESI): calcd for $C_{26}H_{34}N_2O_4$+Na^+, 461.2416; found, 461.2420. Anal. Calcd for $C_{26}H_{34}N_2O_4$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.13; H, 7.79; N, 6.44. HPLC (anal., Daicel Chiralpak AD (4.60 mm i.d. × 250 mm), *n*-hexane/2-propanol (80/20, v/v), flow 1.00 mL/min) τ_R 9.8 min, 11.1 min [trans isomers], τ_R 12.6 min [7-*cis* (1*R*,3*S*)], 18.2 min [*ent*-**7**-*cis* (1*S*,3*R*)]. The two enantiomers of carbamate *rac*-**7**-*cis* were separated by chiral preparative HPLC on a Daicel Chiralpak AD column (50 mm i.d. × 500 mm length) with *n*-hexane/2-propanol (60/40, v/v), flow 60 mL/min; τ_R 27 min [**7**-*cis*], 47 min [*ent*-**7**-*cis*] (strong tailing). A total of 250 mg of *rac*-**7**-*cis* dissolved in 10 mL of hot EtOH were injected per run. The fractions were concentrated in vacuo. **7**-*cis* $[\alpha]^{20}_D$ +10.7 ($CHCl_3$, *c* 0.98). *ent*-**7**-*cis* $[\alpha]^{20}_D$ −10.7 (*c* 1.14, $CHCl_3$).

(1*R*,3*S*)- and (1*S*,3*R*)-3-Aminomethyl-3,5,5-trimethylcyclohexylamine 3 [3-*cis* and *ent*-3-*cis*]. (1*R*,3*S*)- or (1*S*,3*R*)-*cis*-Benzyl-*N*-{3-[(benzyloxycarbonylamino)methyl]-3,5,5−trimethylcyclohexyl}-carbamate **7**-*cis* or *ent*-**7**-*cis* (120 mg, 274 μmol), obtained by preparative HPLC, were dissolved in 5.00 mL of absolute MeOH, and Pd−C (5%; 20.0 mg) was added. The mixture was stirred at room temperature under H_2 atmosphere (1 bar) for 12 h. The solid catalyst was filtered off over Celite, and the solvent was removed under reduced pressure to yield (1*R*,3*S*)- or (1*S*,3*R*)-3-aminomethyl-3,5,5-trimethylcyclohexylamine **3**-*cis* or *ent*-**3**-*cis* as clear liquids in quantitative yield. See below for the characterization of **3**-*cis*.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine carbamic acid *rac*-8-*cis*. Exposition of 3-aminomethyl-3,5,5-trimethylcyclohexylamine **3**-*mix* to air led to gradual precipitation of colorless crystals of the carbamic acid *rac*-**8**-*cis* which were subjected to X-ray crystallography: mp 142 °C dec. IR (CsI): 3385, 2948, 2738, 2617, 1597, 1473, 1465, 1455, 1376, 1326, 1213.

(2*R*,3*R*)-2,3-Bis(benzoyloxy)butanedioic Acid (1*S*,5*R*)−(5-Amino-1,3,3-trimethylcyclohexyl)-methaneamine Salt (1:1) 9. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine **3**-*mix* (200 mL, 1.08 mol) was added at room temperature to *R*,*R*-dibenzoyl tartaric acid (155 g, 432 mmol) suspended in distilled water (2.00 L) with vigorous stirring. During the exothermic reaction the solution cleared, and then the precipitation of the product started after about 5 min. The reaction mixture was cooled to 0 °C and left at this temperature for 1.5 h. The solid was filtered off, washed with 3 × 200 mL of 2-propanol, and dried under reduced pressure over phosphorus pentoxide. One recrystallization from 2-propanol/water (2:1, 1.00 L) yielded 120 g (21% corresponding to the amount of **3**-*mix* used, 56% based on the amount of (1*R*,3*S*)-**3**-*cis* present in **3**-*mix*) of (2*R*,3*R*)-2,3-bis(benzoyloxy)butanedioic acid (1*S*,5*R*)−(5-amino-1,3,3-trimethylcyclohexyl)-methaneamine salt (1:1) **9** as colorless crystals with dr > 99:1, suitable for X-ray crystallography: mp 205 °C. IR (CsI): 3428, 2954, 2713, 1723, 1607, 1407, 1333, 1280, 1122, 1025, 736, 716. ^{1}H NMR (300 MHz, d^6-DMSO): δ 8.04−7.96 (m; 4H), 7.66−7.57 (m; 2H), 7.56−7.46 (m; 4H), 5.53 (s; 2H), 4.31 (s(br); 6H), 3.25−3.03 (m; 1H), 2.16 (s; 2H), 1.60−1.41 (m; 2H), 1.08−0.98 (m; 2H), 0.96−0.87 (m; 2H), 0.84 (s; 3H), 0.82 (s; 3H), 0.81 (s; 3H). ^{13}C NMR (75 MHz, d^6-DMSO): δ 169.8 (s), 165.2 (s), 132.6 (d), 131.2 (s), 129.2 (d), 128.3 (d), 76.0 (d), 55.4 (t), 46.3 (t), 43.9 (d), 44.6 (t),41.1 (t), 34.6 (q), 35.4 (s), 34.6 (q), 31.1 (s), 22.8 (q). HRMS (ESI): calcd for $C_{10}H_{22}N_2$+H^+, 171.1861; found, 171.1860. Anal. Calcd for $C_{28}H_{36}N_2O_8$: C, 63.62; H, 6.86; N, 5.30. Found: C, 63.22; H, 6.98; N, 5.24. **9** $[\alpha]^{20}_D$ −74.1 (*c* 0.51, H_2O). Application of *S*,*S*-dibenzoyl tartaric acid gave the DBTA salt of the (1*S*,3*R*)-amine *ent*-**9**, respectively: *ent*-**9** $[\alpha]^{20}_D$ +74.1 (*c* 0.51, H_2O). To determine the enantiomeric composition of the diamine **3**-*cis* present in the salt **9**, a sample of the crystalline product and K_2CO_3 were dissolved in 1.00 mL of distilled water. An amount of 500 μl of benzyl chloroformate was added, and the suspension was heated thoroughly. After extraction with 500 μL of ethyl acetate and evaporation of the solvent, the sample was analyzed by HPLC on chiral stationary phase. HPLC (anal., Daicel Chiralpak AD (4.60 mm i.d. × 250 mm) column, *n*-hexane/2-propanol (80/20, v/v), flow 1.00 mL/min) τ_R 12.6 min [**7**-*cis* (1*R*,3*S*)], 18.2 min [*ent*-**7**-*cis* (1*S*,3*R*)].

(1*R*,3*S*)-3-Aminomethyl-3,5,5-trimethylcyclohexylamine 3-*cis*. (2*R*,3*R*)-2,3-Bis(benzoyloxy)butanedioic acid (1*S*,5*R*)−(5-amino-1,3,3-trimethylcyclohexyl)-methaneamine salt (1:1) **9** (5.28 g 10.0 mmol) was dissolved in 5 M sodium hydroxide solution (25.0 mL). The clear solution was extracted with 4 × 50.0 mL of dichloromethane, the organic phase was dried over Na_2SO_4, and the main part of the solvent evaporated. Vacuum distillation gave (1*R*,3*S*)-3-aminomethyl-3,5,5-trimethylcyclohexylamine **3**-*cis* as a clear liquid (to be stored under argon) in quantitative yield: bp 120 °C (0.5 mbar). HR-MS (EI): calcd for $C_{10}H_{22}N_2^+$, 170.1783; found, 171.1780. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.96 (tt; J = 11.7 Hz, J = 3.8 Hz, 1H), 2.30 (s; 2H), 1.65−1.40 (m; 2H), 1.19−1.09 (m; 1H), 1.07−0.66 (m; 16H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 58.0 (t), 50.9 (t), 47.6 (d), 46.2 (t), 44.5 (q), 36.9 (s), 35.6 (q), 32.4 (s), 28.4 (q), 23.8 (q). $[\alpha]^{20}_D$ +3.1 (*c* 1.51, $CHCl_3$).

General Procedure for the Preparation of IPDA Schiff-Base Ligands 10a, 10c, and 10g. To a solution of (2*R*,3*R*)-2,3-bis-(benzoyloxy)butanedioic acid (1*S*,5*R*)−(5-amino-1,3,3-trimethylcyclohexyl)-methaneamine salt (1:1) **9** (1.00 equiv) and K_2CO_3 (2.00 equiv) in water was added EtOH and a solution of the salicylic aldehyde (2.00 equiv) in EtOH. A yellow precipitation was formed immediately. The reaction mixture was allowed to stir at room temperature for an additional hour, then water was added, and the mixture was cooled to 5 °C for 1 h. The solid was filtered off, washed with EtOH and water, and then dissolved in CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure.

2-((*E*)-(((1*S*,5*R*)-5-((*E*)-2-Hydroxybenzylideneamino)-1,3,3-trimethylcyclohexyl)methylimino)methyl)phenol 10a. The bis-Schiff base was crystallized from EtOH/CH_2Cl_2 to yield 90.0 mg (63%) of the product **10a** as bright yellow needles, which were subjected to X-ray crystallography: mp 145 °C. IR (CsI): 3406, 2964, 1630, 1605, 1501, 1476, 1378, 1347, 1280, 892, 769 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.58 (s(br); 2H), 8.41 (s; 1H), 8.31 (s; 1H), 7.36−7.19 (m; 4H), 7.00−6.81 (m; 4H), 3.59 (tt; J = 11.6 Hz, J = 3.9 Hz, 1H), 3.43−3.28 (m; 2H), 1.70−1.56 (m; 2H), 1.48−1.34 (m; 2H), 1.24−1.26 (m; 2H), 1.21 (s; 3H), 1.12, (s; 3H), 1.00 (s; 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3 (d), 163.0 (d), 161.2 (s), 161.1 (s), 132.2 (d), 132.0 (d), 131.3 (d), 131.1 (d), 118.7 (s), 118.5 (d), 118.4 (d), 117.0 (d), 75.1 (t), 62.0 (d), 48.0 (t), 47.3 (t), 43.8 (t), 36.0 (s), 31.5 (s), 35.0 (q), 28.0 (q), 24.4 (q). HRMS (EI): calcd for $C_{24}H_{30}N_2O_2^+$, 378.2307: found, 378.2305. Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.06; H, 8.01; N, 7.38. $[\alpha]^{20}_D$ −42.5 (*c* 1.05, $CHCl_3$).

2-((*E*)−(((1*S*,5*R*)-5-((*E*)-5-Chloro-2-hydroxybenzylideneamino)-1,3,3-trimethylcyclohexyl)methylimino)methyl-4-chlorophenol 10c. The bis-Schiff base was crystallized from EtOH/CH_2Cl_2 to yield 138 mg (82%) of the product **10c** as yellow needles, which were subjected to X-ray crystallography: mp 220 °C. IR (CsI): 3423, 2959, 1633, 1605, 1481, 1382, 1346, 1279 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.52 (s(br); 2H), 8.34 (s; 1H), 8.24 (s; 1H), 7.30−7.18 (m; 2H), 6.95−6.82 (m; 4H), 3.60 (tt; J = 11.6 Hz, J = 3.8 Hz, 1H), 3.43−3.29 (m; 2H), 1.68−1.56 (m; 2H), 1.48−1.34 (m; 2H), 1.29−1.23 (m; 2H), 1.20 (s; 3H), 1.12, (s; 3H), 1.00 (s; 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3 (d), 161.9 (d), 159.9 (s), 132.2 (d), 132.0 (d), 130.5 (d), 130.3 (d), 123.1 (s), 123.0 (d), 119.4 (d), 118.6 (d), 74.9 (t), 62.0 (d), 47.9 (t), 47.1 (t), 43.6 (t),-36.0 (s), 35.1 (q), 31.5 (s), 28.0 (q), 24.5 (q). HRMS (EI): calcd for $C_{24}H_{28}Cl_2N_2O_2^+$, 446.1528; found, 446.1523. Anal. Calcd for $C_{24}H_{28}Cl_2N_2O_2$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.06; H, 6.33; N, 6.17. $[\alpha]^{20}_D$ −6.3 (*c* 1.10, $CHCl_3$).

2-((*E*)−(((1*S*,5*R*)-5-((*E*)-2-Hydroxy-3-methoxybenzylideneamino)-1,3,3-trimethylcyclohexyl)methylimino)methyl-6-methoxyphenol 10g. The bis-Schiff base was crystallized from EtOH/

CH_2Cl_2 to yield 1.00 g (67%) of the product **10g** as yellow crystals: mp 62 °C. IR (ATR): 2949, 2910, 2835, 1625, 1461, 1439, 1416, 1248, 1168, 1079, 1047, 974, 838, 777, 732, 664 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 14.22 (s(br); 1H), 14.06 (s(br); 1H), 8.44−8.35 (m; 1H), 8.35−8.25 (m; 1H), 6.98−6.73 (m; 6H), 3.96−3.85 (m; 6H), 3.69−3.53 (m; 1H), 3.45−3.27 (m; 2H), 1.72−1.58 (m; 2H), 1.54−1.31 (m; 3H), 1.30−0.92 (m; 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4 (d), 163.0 (d), 152.3 (s), 148.6 (s), 122.9 (d), 118.6 (s), 118.4 (s), 117.7 (d), 117.6 (d), 114.0 (d), 113.7 (d), 74.5 (t), 61.4 (d), 56.2 (q), 56.0 (q), 47.9 (t), 47.2 (t), 43.8 (t), 36.0 (s), 35.1 (q), 31.5 (s), 28.0 (q), 24.4 (q). HRMS (EI): calcd for $C_{26}H_{34}N_2O_4^+$, 438.2518; found, 438.2515.

Nickel Complex *rac*-11. Nickel acetate (378 mg, 1.52 mmol) was dissolved in water (5.00 mL) and heated to 50 °C with 5-chloro-2-hydroxybenzaldehyde (238 mg, 1.52 mmol) in ethanol (5.00 mL).[17] A green solid precipitated which was filtered off, dried, and then suspended in ethanol (5.00 mL), and IPDA **3**-*mix* (140 μl, 758 μmol) was added. The mixture was heated to 80 °C for 1 h, then water (20.0 mL) was added, and the dark green precipitation was isolated by filtration. A crystal suitable for X-ray crystallography was obtained by recrystallization from $CHCl_3$/EtOH/H_2O.

(17) Pfeiffer, P.; Breith, E.; Lübbe, E.; Tsumaki, T. *Liebigs Ann. Chem.* **1933**, *503*, 84−130.

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Supporting Information Available: Preparation of the IPDA−salen ligands **10b**,**d**−**f**; ^1H and ^{13}C NMR spectra for all new compounds, Crystallographic information files (CIF) for compounds *rac*-**4**-*cis*, **4**-*cis*, *ent*-**4**-*cis*, *rac*-**5**-*cis*, *rac*-**6**-*cis*, *rac*-**7**-*cis*, *rac*-**8**-*cis*, **9**, **10a**,**c** and *rac*-**11**; X-ray crystallographic data and crystal structures for compounds *rac*-**4**-*cis*, **4**-*cis*, *ent*-**4**-*cis*, *rac*-**5**-*cis*, *rac*-**6**-*cis*, *rac*-**7**-*cis*, *rac*-**8**-*cis*, **9**, **10**a,c and *rac*-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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