Tetrahedron: *Asymmetry* 25 (2014) 1331–1339

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Effect of ligand N,N-substituents on the reactivity of chiral copper(II) salalen, salan, and salalan complexes toward asymmetric nitroaldol reactions

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ARTICLE INFO

Article history:
Received 18 July 2014
Accepted 31 July 2014
Available online 10 September 2014

ABSTRACT

The synthesis and effect of ligand N,N-substituents on the reactivity of chiral copper(II) salalen, salan, and salalan complexes toward nitroaldol reactions of nitromethane with various aldehydes have been described. The salan complexes exhibit superior results compared to the salalen and salalan complexes; the nature of the N,N-substituents is crucial for the enantioselectivity of the target nitroaldol products.

1. Introduction

Enantioenriched nitroaldols are versatile synthetic intermediates for the asymmetric synthesis of numerous pharmaceutically important compounds.[1,2] Furthermore, optically active β-nitro alcohols can be readily transformed into valuable chiral β-amino alcohols by reduction and into α-hydroxy acids by the Nef reaction.[3,4] The development of effective methods for their asymmetric synthesis has thus received much attention.[5]

Chiral salalen and salans have attracted significant recent interest as effective ligands for metal catalyzed asymmetric synthesis because they are more flexible and can be readily modified compared to a salen ligand.[6] In addition, metal salalen and salan complexes have a greater tendency to adopt the *cis*-β-configuration that might produce strong asymmetric induction in some reactions.[7] Herein we report the synthesis and the effect of ligand N,N-substituents on the reactivity of chiral copper(II) salalen **11a–b**, salan **12a–c**, and salalan **13** toward nitroaldol reaction of nitromethane with aldehydes at room temperature. Chiral salan complexes **12a–c** exhibited superior results compared to the salalen and salalan complexes, while the nature of the N,N-substituents plays a crucial role on the enantioselectivity of the nitroaldol products.

2. Results and discussion

The synthesis of the chiral salalen **8a–b** and salan **9a** ligands is shown in Scheme 1. The reaction of (*R*,*R*)-1,2-diaminocyclohexane **1** with phthalic anhydride **2** using hydrated *p*-toluenesulfonic acid gave imide **3** in 95% yield which could then be reacted with triethylamine (Et_3N) to afford **4** in 87% yield.[8] The condensation of **4** with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde **5** gave the Schiff base **6** in 85% yield that could be readily reduced utilizing $NaBH_4$ to furnish amine **7a** in high yield. The latter was reacted with formaldehyde followed by $NaCNBH_3$ to provide the *N*-methylated amine **7b** in 88% yield. Treatment of **7a** and **7b** with hydrazine hydrate afforded the respective amines, which could be reacted with **5** to produce salalens **8a** and **8b** in 60% and 64% yields, respectively. The reduction of salalen **8b** using $NaBH_4$ furnished salalen **9a** in high yield.

Chiral salen **10** was prepared by condensation of diamine **1** with aldehyde **5** in high yield.[9] Treatment of **10** with $NaBH_4$ in methanol furnished the salan **9b** in 96% yield. The latter was reacted with formaldehyde and acetaldehyde to afford the corresponding imines, which could be reduced using $NaBH_4$ to produce N,N-dialkylated salans **9c–d** in high yields (Scheme 2).[10]

The reaction of chiral ligands **8–10** with $Cu(OAc)_2{\cdot}H_2O$ in ethanol afforded the corresponding chiral copper(II) complexes **11–14** in high yields (Scheme 3).[11] Since the copper(II) complexes are effective Lewis acids for 1,2-addition reactions,[12] the catalytic activity of complexes **11–14** was studied toward the nitroaldol reaction.

First, the optimization of the reaction was performed using 4-nitrobenzaldehyde **15a** as a model substrate with nitromethane (Table 1). The reaction occurred readily to give the nitroaldol product with 21% ee when the substrates were stirred with 10 mol % of the salalen complex **11a** in toluene at room temperature (entry 1). Similar results were obtained using the N-methylated salalen complex **11b** as the catalyst. However, the use of the chiral salan

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http://dx.doi.org/10.1016/j.tetasy.2014.07.013
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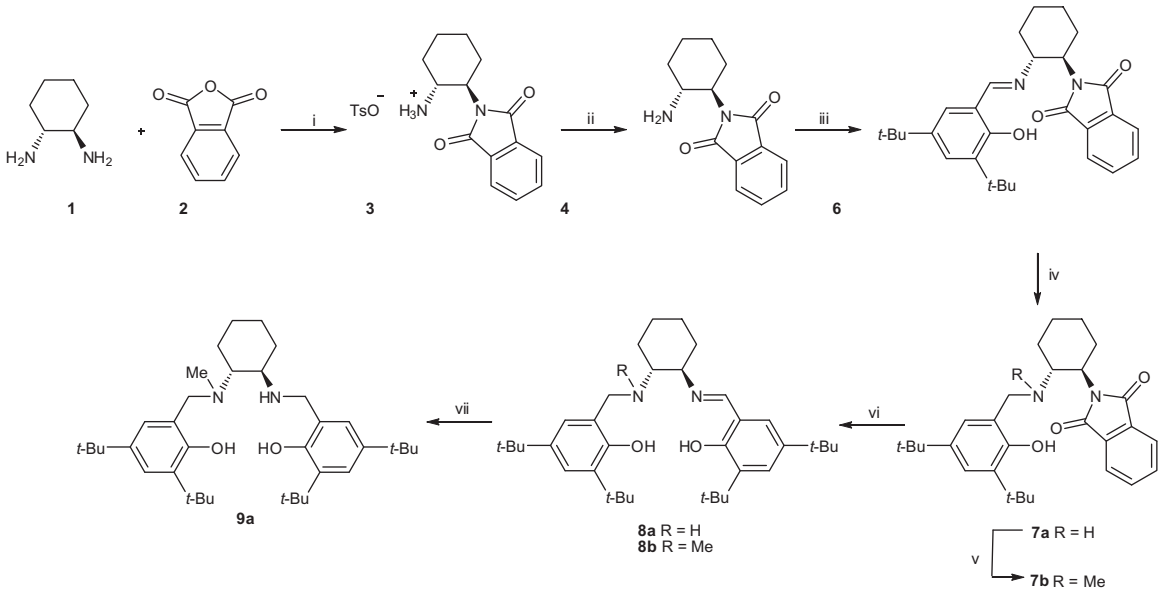
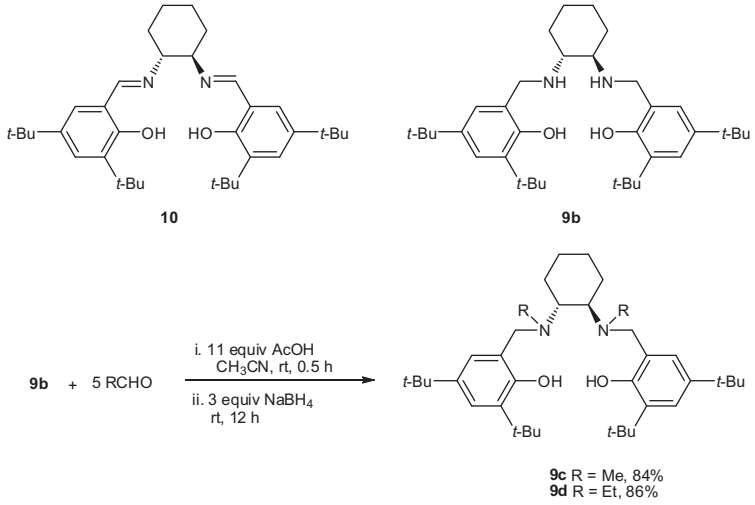


Scheme 1. Reagents and conditions: (i) *p*-TsOH·H_2O (1 equiv), xylene, reflux, 5 h, 95%; (ii) Et_3N (1.2 equiv), CH_2Cl_2/MeOH (1:1), rt, 3 h, 87%; (iii) 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde **5** (1 equiv), MeOH, 50 °C, 8 h, 85%; (iv) $NaCNBH_3$ (2.1 equiv), MeOH/CH_3CN (1:4), rt, 3 h, 97%; (v) HCHO solution (37–41% w/v) (5 equiv), AcOH (11 equiv), MeOH, rt, 0.5 h, $NaCNBH_3$ (3 equiv), rt, 12 h, 88%; (vi) N_2H_4·H_2O (10 equiv), THF, reflux, 4 h, **5** (1 equiv), MeOH, 50 °C, 8 h, (R = H, 60%; R = Me, 64%); (vii) $NaBH_4$ (1.2 equiv), MeOH/THF (3:1), rt, 3 h, 95%.

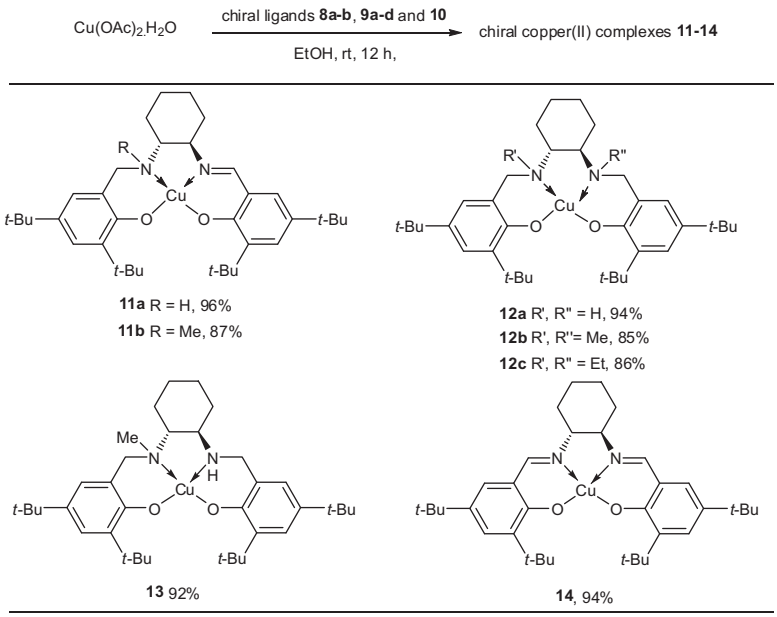


Scheme 2. Reagents and conditions: (i) RCHO (5 equiv), AcOH (11 equiv), CH_3CN, rt, 0.5 h; (ii) $NaBH_4$ (3 equiv), rt, 12 h.

complexes **12a–c** led to an improvement in the enantioselectivity of **16a**, and the best result was observed using the N,N-dimethylated **12b** with 69% ee, whereas **12a** afforded 41% ee. In contrast, complex **12c** with bulkier *N*,*N*-diethyl substituents yielded 54% ee. Furthermore, the *N*-methyl salalen complex **13** gave the product with 38% ee. In addition, the catalytic activity of the chiral salen complex **14** was examined; however, it was less effective and afforded inferior results.

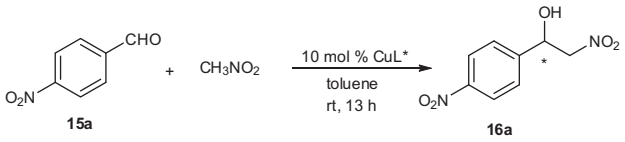
The effect of reaction temperature, solvent, and base was examined next (Table 2). Decreasing the reaction temperature to −40 °C led to an increase in the enantioselectivity to 76% (entry 1). Toluene was found to be the solvent of choice in affording the best results. In contrast, CH_2Cl_2, EtOAc, CH_3CN, EtOH, Et_2O, THF, xylene, and chlorobenzene were less effective and afforded **16a** with <67% ee (entries 2–9). The use of a base such as Et_3N, diisopropylethylamine (DIPEA), morpholine, *N*-methylmorpholine, *N*-methylimidazole, *N*,*N*-dimethylamino-pyriridine (DMAP), or 2,6-lutidine led to an acceleration of the reaction with high yield but led to a decrease in the enantioselectivity, which may be due to the base catalyzed reactions (entries 10–16).

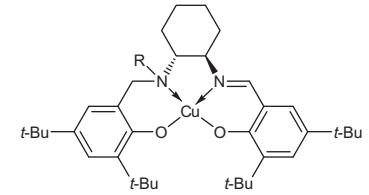
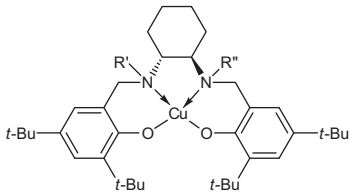
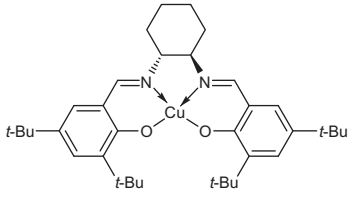
With the optimal conditions in hand, the substrate scope of this protocol was examined for the reaction of various aldehydes (Table 3). The substrates with electron withdrawing groups exhibited a greater reactivity compared to those bearing electron donating groups. For examples, benzaldehyde **15b** underwent reaction with 64% yield and 78% ee at room temperature, while the more reactive 2-nitrobenzaldehyde **15c** proceeded readily at −40 °C to give the product with 86% yield and 90% ee. Likewise, 3-bromobenzaldehyde **15d** proceeded with 61% yield and 80% ee at room temperature, whereas the highly reactive 3-nitrobenzaldehyde **15e** underwent reaction at −40 °C with 76% yield and 81% ee. Furthermore, 4-bromo-, 4-chloro-, 4-methoxy-, and 4-methylbenzaldehdyes **15f–i** underwent reaction with 54–89% yields and 65–82% ee. In addition, 2-naphthyl **15j**, 2-furyl **15k**, and 2-thiophene **15l**



Scheme 3. Synthesis of chiral copper(II) salalen **11a–b**, salan **12a–c**, salalan **13**, and salen **14** complexes.

Table 1
Screening of the chiral copper(II) complexes **11–14**[a]

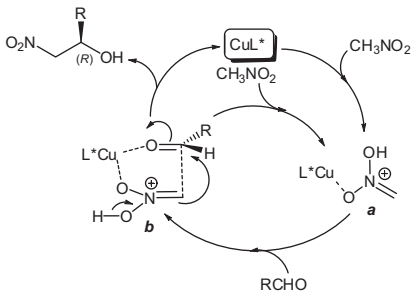


Entry	CuL*		Yield[b] (%)	ee[c] (%)
1		**11a** R = H	95	21
2		**11b** R = Me	99	21
3		**12a** R', R" = H	86 95	41 69
4		**12b** R', R" = Me	90	54
5		**12c** R', R"= Et	99	38
6		**13** R '= Me, R'' = H		
7		**14**	58	19

[b] Isolated yield.
[c] Determined by HPLC analysis with chiralcel OJ column using *n*-hexane/2-propanol (8:2).
[a] Reaction conditions: 4-nitrobenzaldehyde **15a** (0.25 mmol), nitromethane (2.5 mmol), catalyst (10 mol %), toluene (0.75 mL), 13 h, rt, N_2.

aldehydes proceeded with 34–71% yields and 71–77% ee, whereas *n*-heptyl aldehyde **15m** underwent reaction with 67% yield and 90% ee. These results suggest that the protocol is general and that reaction of aryl, heteroaryl, and alkyl aldehydes can be accomplished with good to high enantioselectivities at room temperature.

A proposed catalytic cycle is shown in Scheme 4. Coordination of nitromethane with a copper(II) salan complex may lead to the formation of the nitronate intermediate ***a*** that could undergo reaction with aldehyde to give intermediate ***b***. An intramolecular reaction of the nitronate to the chelated aldehyde can give the nitroaldol product and the catalyst to complete the catalytic cycle. Figure 1 shows the proposed transition state for the formation of the nitroaldol with an (*R*)-configuration.



Scheme 4. Proposed catalytic cycle.

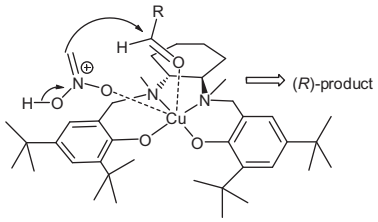


Figure 1. Proposed transition state.

3. Conclusions

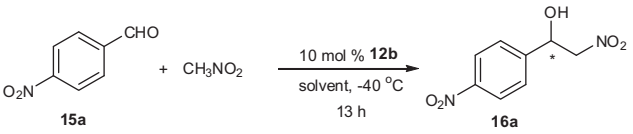
In conclusion, the synthesis and the effect of ligand N,N-substituents on the reactivity of chiral copper(II) salalen, salalan, and salan complexes toward the nitroaldol reaction have been described. The protocol is general and the reaction of aryl, heteroaryl, naphthyl, and alkyl aldehydes can be accomplished with nitromethane in high enantioselectivities at room temperature under additive free conditions. The salan complexes exhibit superior results, and the N,N-substituents play a crucial role on the enantioselectivity of the nitroaldol products.

4. Experimental section

4.1. General

All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in an oven-dried glassware under a nitrogen atmosphere. CH_3NO_2 (96%), aldehydes, and 2,4-di-*tert*-butyl phenol (99%) were purchased from Aldrich, $NaBH_4$ (95%), HCHO solution (37–41% w/v), phthalic anhydride (98%), $N_2H_4{\cdot}H_2O$ (99%), and $Cu(OAc)_2{\cdot}1H_2O$ (>98%) were purchased from Merck, and $NaCNBH_3$ (>96%) was purchased from Spectrochem and used as received. Solvents were purchased from Rankem and purified prior to use by standard procedure.[13a] Compounds **3**, **4**,[8] **9b**,[10] and **10**[13b] were prepared according to the literature procedure. Column chromatography was carried out with Rankem 60–120 mesh silica gel. Analytical TLC was performed with Rankem silica gel G and GF 254 plates. NMR spectra were recorded using a DRX-400 Varian spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) and a Bruker Avance III 600 MHz spectrometer (600 MHz for ^1H and 150 MHz for ^{13}C) using $CDCl_3$ as the solvent and Me_4Si as the internal standard. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were obtained using a Perkin–Elmer spectrum one spectrometer. Optical rotations were measured with a Rudolph Autpol II automatic polarimeter in the solvent indicated. HRMS mass was analyzed with an Agilent Q-TOF 6500. UV–vis spectra were recorded using Perkin–Elmer Lambda 25 UV/vis spectrometer. EPR spectra were measured on X-Band Microwave unit, JESFA200 ESR spectrometer. HPLC analysis was carried out using a Waters-2489 with Daicel Chiralcel OD-H, OJ-H, AD-H and OJ columns.

Table 2
Screening of solvents, temperature, and base[a]



Entry	Solvent	Base[b]	Yield[c] (%)	ee[d] (%)
1	Toluene	—	85[e], 72[f], **56**	70, 73, **76**
2	CH_2Cl_2	—	43	35
3	EtOAc	—	46	60
4	CH_3CN	—	15	32
5	EtOH	—	69[e]	12
6	Et_2O	—	34	67
7	THF	—	52	55
8	Xylene	—	72	53
9	Chlorobenzene	—	75	35
10	Toluene	Et_3N	87	47
11	Toluene	DIPEA	85	39
12	Toluene	Morpholine	91	09
13	Toluene	*N*-Methylmorpholine	79	21
14	Toluene	*N*-Methylimidazole	81	17
15	Toluene	DMAP	84	15
16	Toluene	2,6-Lutidine	14	64

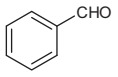
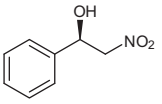
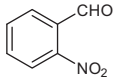
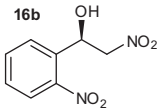
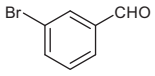
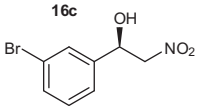
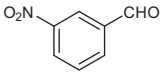
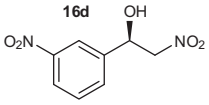
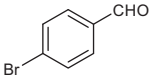
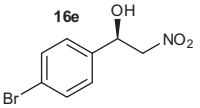
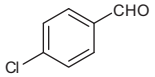
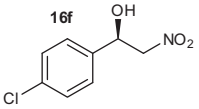
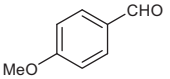
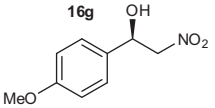
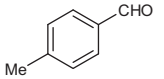
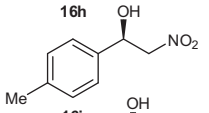
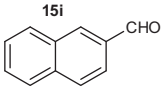
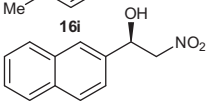
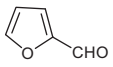
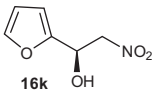
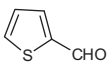
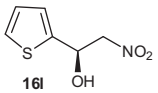
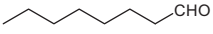
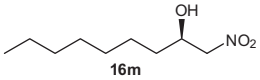
[a] Reaction conditions: 4-nitrobenzaldehyde **15a** (0.25 mmol), nitromethane (2.5 mmol), **12b** (10 mol %), solvent (0.75 mL), 13 h, −40 °C, N_2.
[b] Base (0.5 equiv) used.
[c] Isolated yield.
[d] Determined by HPLC analysis with Chiralcel OJ column using 80:20 *n*-hexane/2-propanol.
[e] Reaction temperature 0 °C.
[f] Reaction temperature at −20 °C.

4.2. Synthesis of ligands

4.2.1. 2-((1*R*,2*R*)-2-((*E*)-(3,5-Di-*tert*-butyl-2-hydroxybenzylidene)amino)cyclohexyl)isoindoline-1,3-dione 6

2-((1*R*,2*R*)-2-Aminocyclohexyl)isoindoline-1,3-dione **4** (4 mmol, 976 mg) and 3,5-di-*tert*-butylsalicylaldehyde **5** (4 mmol, 937 mg) were stirred in MeOH (15 mL) for 8 h at 50 °C. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the solvent was evaporated under reduced pressure and the residue was treated with water (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator gave a residue, which was purified on a silica gel column chromatography using ethyl acetate and hexane (3:17) as eluent to give **6** as a pale yellow solid; yield (1.566 g, 85%); mp 141.9–143.3 °C; $[\alpha]_D^{29} = -130.7$ (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 13.27$ (s, 1H), 8.30 (s, 1H), 7.75–7.73 (m,

Table 3
Chiral copper(II) salan **12b** catalyzed asymmetric nitroaldol reaction[a]

Entry	Substrate	Time (h)	Product	Yield (%)	ee (%)	Configuration
1	 **15b**	48	 **16b**	64	78	(*R*)
2	 **15c**	96	 **16c**	86	90	(*R*)
3	 **15d**	48	 **16d**	61	80	(*R*)
4	 **15e**	96	 **16e**	76	81	(*R*)
5	 **15f**	24	 **16f**	65	82	(*R*)
6	 **15g**	48	 **16g**	89	65	(*R*)
7	 **15h**	96	 **16h**	54	70	(*R*)
8	 **15i**	72	 **16i**	68	79	(*R*)
9	 **15j**	48	 **16j**	43	77	(*R*)
10	 **15k**	48	 **16k**	71	76	(*R*)
11	 **15l**	48	 **16l**	34	71	(*R*)
12	 **15m**	72	 **16m**	67	90	(*R*)

[b] Isolated yield.
[c] Determined by HPLC analysis with Chiralcel OD-H for **16d**, **16f**, **16g**, and **16l**, Chiralpak AD-H for **16c** and **16e**, Chiralcel OJ for **16a**, **16j**–**k**, and **16m** and Chiralcel OJ-H for **16b** and **16h**–**i** using *n*-hexane/2-propanol.
[d] Determined from the sign of the specific rotation.
[a] Reaction conditions: aldehyde **15** (0.25 mmol), nitromethane (2.5 mmol), and catalyst **12b** (10 mol %) were stirred in toluene (0.75 mL) for the appropriate time at room temperature (28 °C) under N_2 atmosphere.

2H), 7.65 (dd, *J* = 12.4, 4.0 Hz, 2H), 7.30 (s, 1H), 6.95 (s, 2H), 4.42–4.37 (m, 1H), 4.16–4.109 (m, 1H), 2.23–2.18 (m, 1H), 1.94–1.83 (m, 3 H), 1.75–1.66 (m, 1H), 1.61–1.45 (m, 2H), 1.34 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 165.9, 158.0, 139.7, 136.6, 133.8, 131.7, 126.8, 125.9, 123.1, 117.6, 67.8, 55.6, 34.9, 34.8, 34.0, 31.4, 29.3, 29.0, 25.4, 24.2; FT-IR (KBr) 3464, 2952, 2864, 1769, 1713, 1627, 1595, 1468, 1440, 1390, 1362, 1330, 1273, 1255, 1244, 1202, 1173, 1156, 1133, 1099, 1066, 1052, 1016, 1000, 981, 948, 932, 906, 869, 860, 843, 868, 804, 773, 719, 698, 639, 531, 474 cm^{-1}; HRMS (ESI, pos.): Calcd for $C_{29}H_{37}N_2O_3$ $[M+H]^+$: 461.2799, found: 461.2812.

4.2.2. 2-((1*R*,2*R*)-2-((3,5-Di-*tert*-butyl-2-hydroxybenzyl)amino)-cyclohexyl)isoindoline-1,3-dione 7a

To a stirred solution of 2-((1*R*,2*R*)-2-((*E*)-(3,5-di-*tert*-butyl-2-hydroxybenzylidene)amino) cyclohexyl)isoindoline-1,3-dione **6**

(3.5 mmol, 1.612 g) in a 1:4 mixture of MeOH and CH_3CN (25 mL) was added $NaCNBH_3$ (7.35 mmol, 461 mg) at an ice-cool temperature. After complete consumption of the starting material, the solvents were evaporated under reduced pressure, and the residue was dissolved in water (10 mL), and extracted with CH_2Cl_2 (3×10 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator afforded a residue that was purified on a silica gel column chromatography using ethyl acetate and hexane (3:17) as eluent to give **7a** as a white solid; yield (1.570 g, 97%); mp 172.9–174.8 °C; $[\alpha]_D^{29} = -7.6$ (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.84$ (dd, $J = 5.2$, 3.2 Hz, 2H), 7.71 (dd, $J = 5.2$, 3.2 Hz, 2H), 7.10 (d, $J = 1.6$ Hz, 1H), 6.78 (d, $J = 1.2$ Hz, 1H), 4.04–3.96 (m, 2H), 3.77 (d, $J = 13.2$ Hz, 1H), 3.51 (td, $J = 11.1$, 3.6 Hz, 1H), 2.42–2.28 (m, 2H), 1.86 (br s, 3H), 1.22 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.9$, 154.9, 140.3, 135.9, 133.9, 132.1, 123.3, 122.9, 122.9, 121.9, 56.8, 50.6, 34.7, 34.2, 31.8, 29.6, 29.5, 25.6, 24.8; FT-IR (KBr) 3462, 3305, 2954, 1947, 1767, 1717, 1699, 1683, 1612, 1546, 1480, 1393 1331, 1330, 1236, 1155, 1116, 1084, 1047, 1017, 1002, 978, 955, 926, 903, 871, 859, 843, 823, 798, 719, 700, 677, 667, 648, 639, 530, 509, 454 cm^{-1}. HRMS (ESI, pos.): Calcd for $C_{29}H_{39}N_2O_3$ $[M+H]^+$: 463.2955, found: 463.2951.

4.2.3. 2-((1*R*,2R)-2-((3,5-Di-*tert*-butyl-2-hydroxybenzyl)(methyl)-amino)cyclohexyl)isoindo-line-1,3-dione 7b

To a stirred solution of 2-((1*R*,2*R*)-2-((3,5-di-*tert*-butyl-2-hydroxybenzyl)amino)cyclohexyl)iso-indoline-1,3-dione **7a** (1.5 mmol, 693.9 mg) in a 3:1 mixture of CH_3CN and MeOH (15 mL) was added dropwise CH_3COOH (3.5 mL) followed by HCHO solution (650 μL) at room temperature. The reaction mixture was stirred for 0.5 h, after which $NaCNBH_3$ (4.5 mmol, 282 mg) was added portionwise at 0 °C. The reaction mixture was then stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the solvent was evaporated under reduced pressure, and the residue was treated with saturated $NaHCO_3$ solution followed by water (5 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL), dried (Na_2SO_4), and evaporated on a rotary evaporator to give a residue, which was purified on a silica gel column chromatograph using ethyl acetate and hexane (3:17) as eluent to give **7b** as a colorless solid; yield (714 mg, 88%); mp 183.9–185.5 °C; $[\alpha]_D^{29} = -24.8$ (*c* 0.76, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.32$ (s, 1H), 7.82 (dd, $J = 4.5$, 2.4 Hz, 2H), 7.70 (dd, $J = 5.0$, 2.8 Hz, 2H), 7.02 (d, $J = 1.4$ Hz, 1H), 6.71 (d, $J = 2.2$ Hz, 1H), 4.32 (td, $J = 11.6$, 3.4 Hz, 1H), 3.76–3.66 (m, 3H), 2.36–2.28 (m, 1H), 2.15 (s, 3H), 2.06 (d, $J = 9.1$, 1H), 1.92–1.84 (m, 3H), 1.49–1.31 (m, 3H), 1.21 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.9$, 154.8, 139.9, 135.0, 133.7, 123.2, 123.0, 122.5, 120.2, 110.1, 63.2, 51.7, 34.5, 34.2, 31.8, 30.1, 29.2, 25.7, 24.9, 23.5; FT-IR (KBr) 3372, 2955, 2867, 1766, 1703, 1659, 1606, 1482, 1468, 1390, 1361, 1302, 1233, 1202, 1163, 1125, 1027, 1012, 937, 905, 876, 822, 797, 763, 720, 668, 648, 530, 510 cm^{-1}. HRMS (ESI, pos.): Calcd for $C_{30}H_{41}N_2O_3$ $[M+H]^+$: 477.3112, found: 477.3118.

4.2.4. General procedure for the synthesis of compounds 8a and 8b

To a stirred solution of **7** (1.5 mmol) in dry THF (10 mL), $N_2H_4 \cdot H_2O$ (2.25 mL) was added. After refluxing for 4 h, the reaction mixture was cooled to room temperature and diluted with Et_2O (20 mL) to precipitate out phthaloyl hydrazide. After filtering the solid, the filtrate was concentrated under reduced pressure to give a residue, which was dissolved in ethyl acetate (5 mL) and extracted with dilute HCl (2×5 mL). The solution was then neutralized using a saturated $NaHCO_3$ solution and extracted using dichloromethane (3×10 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator furnished a colorless solid, which was reacted with **5** in MeOH (15 mL) at 50 °C for 8 h to give a pale yellow solid, which was filtered and washed with cold methanol to yield analytically pure compounds **8a** and **8b**.

4.2.4.1. 2,4-Di-*tert*-butyl-6-((*E*)-((1*R*,2*R*)-2-(3,5-di-*tert*-butyl-2-hydroxybenzylamino)cyclohexylimino)methyl)phenol 8a. Pale yellow solid; yield (494 mg, 60%); mp 146.8–148.6 °C; $[\alpha]_D^{29} = -103.7$ (*c* 1.34, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 13.47$ (s, 1H), 11.63 (s, 1H), 8.40 (s, 1H), 7.37 (d, $J = 2.0$ Hz, 1H), 7.16 (d, $J = 2.0$ Hz, 1H), 7.05 (d, $J = 2.4$ Hz, 2H), 6.8 (d, $J = 2.0$ Hz, 1H), 4.04 (d, $J = 13.2$ Hz, 1H), 3.81 (d, $J = 13.44$ Hz, 1H), 3.06 (td, $J = 10.8$, 2.8 Hz, 1H), 2.83 (td, $J = 10.8$, 3.2 Hz, 1H), 2.25 (d, $J = 12.8$ Hz, 1H), 1.82–1.81 (m, 3H), 1.43 (s, 9H), 1.33 (s, 9H), 1.27 (s, 9H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.7$, 158.1, 154.7, 140.5, 140.3, 136.7, 136.0, 127.3, 126.3, 123.2, 123.0, 122.9, 117.9, 74.1, 61.2, 50.9, 35.2, 35.0, 34.2, 34.1, 31.8, 31.6, 29.8, 29.7, 24.7, 24.6. FT-IR (KBr) 3490, 2955, 2863, 1734, 1648, 1627, 1479, 1467, 1440, 1391, 1361, 1301, 1273, 1251, 1202, 1172, 1125, 1080, 1025, 981, 931, 877, 827, 801, 772, 738, 713, 645, 535, 510 cm^{-1}. HRMS (ESI, pos.): Calcd for $C_{36}H_{57}N_2O_2$ $[M+H]^+$: 549.4415, found: 549.4426.

4.2.4.2. 2,4-Di-*tert*-butyl-6-((*E*)-(((1*R*,2*R*)-2-((3,5-di-*tert*-butyl-2-hydroxybenzyl)(methyl)amino)cyclohexyl)imino)methyl)phenol 8b. Pale yellow solid; yield (540 mg, 64%); mp 114.3–116.4 °C; $[\alpha]_D^{29} = -97.0$ (*c* 0.88, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 13.57$ (s, 1H), 10.59 (s, 1H), 8.37 (s, 1H), 7.38 (d, $J = 2.0$ Hz, 1H), 7.10 (d, $J = 2.0$ Hz, 1H), 7.02 (d, $J = 2.0$ Hz, 1H), 6.79 (d, $J = 2.0$ Hz, 1H), 3.83–3.70 (m, 2H), 3.27–3.25 (m, 1H), 2.98–2.91 (m, 1H), 2.22 (s, 3H), 1.99–1.63 (m, 6H), 1.47 (s, 9H), 1.44–1.32 (m, 2H), 1.28 (s, 9H), 1.24 (s, 9H), 1.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.9$, 158.3, 154.9, 139.9, 139.9, 136.7, 135.5, 127.0, 125.9, 123.4, 122.6, 121.1, 118.3, 70.4, 66.8, 58.5, 35.4, 35.2, 34.8, 34.2, 31.9, 31.7, 31.5, 29.8, 29.6, 25.3, 24.8, 23.92; FT-IR (KBr) 3472, 2954, 2863, 1678, 1630, 1479, 1467, 1455, 1441, 1390, 1361, 1302, 1273, 1245, 1234, 1203, 1173, 1113, 1073, 1025, 982, 948, 938, 878, 825, 801, 772, 763, 738, 714, 695, 645, 566, 538, 509 cm^{-1}. HRMS (ESI, pos.): Calcd for $C_{37}H_{59}N_2O_2$ $[M+H]^+$: 563.4571, found: 563.4579.

4.2.5. 2,4-Di-*tert*-butyl-6-((((1*R*,2*R*)-2-((3,5-di-*tert*-butyl-2-hydroxybenzyl)(methyl)amino) cyclohexyl)amino)methyl)phenol 9a

To a stirred solution of 2,4-di-*tert*-butyl-6-((*E*)-(((1*R*,2*R*)-2-((3,5-di-*tert*-butyl-2-hydroxybenzyl)-(methyl)amino)cyclohexyl)-imino)methyl)phenol **8b** (0.75 mmol, 422 mg) in a 1:3 mixture of THF/MeOH at 0 °C, $NaBH_4$ (0.9 mmol, 30.2 mg) was added, and the resultant mixture was stirred for 12 h at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the solvent was evaporated under reduced pressure and the residue was neutralized with a saturated $NaHCO_3$ solution. The mixture was then treated with water (5 mL) and extracted with CH_2Cl_2 (3×10 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator provided a residue, which was purified by silica gel column chromatography using ethyl acetate and hexane (3:17) as eluent to give **9a** as a colorless viscous liquid; yield (382 mg, 95%); $[\alpha]_D^{29} = -5.0$ (*c* 1.38, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.22$ (d, $J = 2.4$ Hz, 2H), 6.88 (d, $J = 2.4$ Hz, 1H), 6.84 (d, $J = 2.4$ Hz, 1H), 4.08 (d, $J = 13.2$ Hz, 1H), 3.98 (d, $J = 13.2$ Hz, 1H), 3.90 (d, $J = 13.2$ Hz, 1H), 3.77 (d, $J = 13.2$ Hz, 1H), 2.67 (td, $J = 10.8$, 4.2 Hz, 1H), 2.52 (td, $J = 10.8$, 3 Hz), 2.28 (s, 3H), 1.98 (d, $J = 13.2$ Hz, 1H), 1.82–1.81 (m, 1H), 1.73–1.72 (m, 1H), 1.42 (s, 9H), 1.37 (s, 9H), 1.29 (s, 19H), 1.20–1.13 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 154.7$, 154.3, 140.8, 140.5, 135.9, 135.8, 123.6, 123.3, 123.1, 123.0, 122.6, 121.2, 65.3, 58.7, 56.8, 50.4, 35.7, 35.0, 34.3, 32.2,

31.9, 29.9, 29.9, 29.8, 25.2, 25.0, 22.5, 14.4; FT-IR (neat) 3503, 2954, 2860, 2071, 1634, 1480, 1390, 1361, 1302, 1235, 1202, 1165, 1124, 1096, 1018, 977, 878, 822, 799, 758, 724, 695, 667, 648, 509 cm^{-1}. HRMS (ESI, pos.): Calcd for $C_{37}H_{61}N_2O_2$ $[M+H]^+$: 565.4728, found: 565.4732.

4.2.6. General procedure for the synthesis of compounds 9c–d

To a solution of 6,6′-(1*R*,2*R*)-cyclohexane-1,2-diylbis(azanediyl)bis(methylene)bis(2,4-di-*tert*-butylphenol) **9b** (2 mmol, 1.101 g) in CH_3CN (25 mL) were added dropwise CH_3COOH (5 mL) and HCHO solution (2 mL) at room temperature. The resultant mixture was stirred for 0.5 h, and then treated with $NaBH_4$ (10 mmol, 378 mg) at 0 °C. After stirring at room temperature for 12 h, the solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL) and neutralized with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layer was washed with water, dried (Na_2SO_4), and evaporated on a rotary evaporator to give a residue, which was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to give compounds **9c–d**.

4.2.6.1. 6,6′-(((1*R*,2*R*)-Cyclohexane-1,2-diylbis(methylazanediyl))bis(methylene))bis(2,4-di-*tert*-butylphenol) 9c[10]. Colorless viscous liquid; yield (995 mg, 84%); $[\alpha]_D^{29}$ = +37.3 (*c* 0.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 2.0 Hz, 2H), 6.80 (d, *J* = 2.0 Hz, 2H), 7.73 (dd, *J* = 5.6, 2.8 Hz, 2H), 3.82–3.72 (m, 4H), 2.67 (m, 2H), 2.19 (s, 6H), 2.00–1.97 (m, 2H), 1.78–1.76 (m, 2H), 1.35 (s, 18H), 1.26 (s, 18H), 1.12–1.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 140.3, 135.7, 123.7, 122.9, 121.5, 61.5, 58.8, 35.0, 34.3, 31.9, 29.8, 27.1, 25.5, 22.7; FT-IR (neat): 3451, 2950, 2899, 2866, 1603, 1559, 1469, 1437, 1412, 1389, 1381, 1362, 1349, 1293, 1279, 1264, 1238, 1204, 1166, 1134, 1102, 1012, 994, 968, 879, 873, 831, 812, 777, 739, 668, 639, 538 cm^{-1}. HRMS (ESI, pos.): Calcd for $C_{38}H_{63}N_2O_2$ $[M+H]^+$: 579.4884, found: 579.4906.

4.2.6.2. 6,6′-(((1*R*,2*R*)-Cyclohexane-1,2-diylbis(ethylazanediyl))bis(methylene))bis(2,4-di-*tert*-butyl phenol) 9d. Colorless solid; yield (1.068 g, 86%); mp 170.6–173.1 °C; $[\alpha]_D^{29}$ = +11.0 (*c* 0.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 2.4 Hz, 4H), 6.77 (s, 4H), 3.96 (s, 2H), 3.50 (q, *J* = 7.2 Hz, 4H), 3.29 (s, 2H), 2.43–2.35 (m, 4H), 2.04 (s, 4H), 1.76 (d = 7.2 Hz, 4H), 1.25 (s, 36H), 1.22 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.8, 140.4, 135.9, 124.2, 122.6, 122.2, 58.6, 52.7, 42.6, 34.9, 34.2, 31.9, 29.7, 25.9, 23.4, 13.0; FT-IR (KBr): 3387, 2952, 2863, 1739, 1605, 1481, 1470, 1390, 1361, 1285, 1262, 1240, 1216, 1201, 1164, 1123, 1109, 1069, 1055, 1033, 993, 971, 946, 928, 877, 865, 820, 800, 772, 759, 740, 726, 695, 672, 649, 605, 566, 540 cm^{-1}. HRMS (ESI, pos.): Calcd for $C_{40}H_{67}N_2O_2$ $[M+H]^+$: 607.5197, found: 607.5205.

4.3. General procedure for the synthesis of copper(II) complexes

To a stirred solution of ligand (0.5 mmol) in EtOH (5 mL) was added $Cu(OAc)_2{\cdot}1H_2O$ (0.5 mmol) in EtOH (2 mL). After stirring at room temperature under air for 12 h, the solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate (3 × 5 mL) and washed with water (1 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator gave a residue, which was purified on a silica gel column chromatography using hexane and ethyl acetate (2:3) as eluent to give the respective complex as a green solid.

4.3.1. Complex 11a

Green solid; yield (292 mg, 96%); $[\alpha]_D^{29}$ = −1471.4 (*c* 0.028, $CHCl_3$); FT-IR (KBr): 3505, 3226, 2950, 2865, 1728, 1658, 1622, 1526, 1467, 1435, 1409, 1383, 1360, 1349, 1301, 1286, 1254, 1236, 1201, 1167, 1134, 1092, 1025, 970, 927, 877, 858, 830, 807, 789, 741, 639, 624, 535, 503, 467 cm^{-1}; UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 586 (4655), 382 (37355), 275 (124897), 246 nm (186347 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; g_{II} = 2.333, $g_{\perp}$ = 2.019, A_{II} = 21.19 mT; HRMS (ESI, pos.): Calcd for $C_{36}H_{55}N_2O_2Cu$ $[M+H]^+$: 610.3554, Found: 610.3561.

4.3.2. Complex 11b

Green solid; yield (271 mg, 87%); $[\alpha]_D^{29}$ = −1828.6 (*c* 0.028, $CHCl_3$); FT-IR (KBr): 2950, 2905, 2866, 1726, 1674, 1617, 1527, 1474, 1433, 1412, 1386, 1360, 1333, 1303, 1254, 1235, 1202, 1167, 1133, 1090, 1004, 973, 931, 874, 831, 809, 790, 778, 742, 658, 639, 534, 480 cm^{-1}; UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 594 (5024), 402 (37346), 276 (133740), 251 nm (191144 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; g_{II} = 2.333, $g_{\perp}$ = 2.009, A_{II} = 21.71 mT; HRMS (ESI, pos.): Calcd for $C_{37}H_{57}N_2O_2Cu$ $[M+H]^+$: 624.3711, Found: 624.3715.

4.3.3. Complex 12a

Green solid; yield (287 mg, 94%); $[\alpha]_D^{29}$ = −558.8 (*c* 0.068, $CHCl_3$); FT-IR (KBr): 3428, 3188, 2950, 2865, 1773, 1665, 1623, 1527, 1469, 1439, 1411, 1388, 13,611, 1299, 1254, 1235, 1201, 1166, 1094, 1059, 876, 827, 805, 783, 738, 668, 536, 460 cm^{-1}; UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 623 (894), 423 (2406), 290 (13752), 246 nm (21776 mol^{-1} dm^3 cm^{-1}); HRMS (ESI, pos.): Calcd for $C_{36}H_{57}N_2O_2Cu$ $[M+H]^+$: 612.3711, Found: 612.3715.

4.3.4. Complex 12b

Green solid; yield (272 mg, 85%); $[\alpha]_D^{29}$ = −1981.4 (*c* 0.022, $CHCl_3$); FT-IR (KBr): 3418, 2948, 2899, 2866, 1761, 1604, 1539 1469, 1437, 1412, 1380, 1360, 1349, 1326, 1295, 1238, 1203, 1166, 1134, 1102, 1012, 994, 969, 876, 831, 812, 776, 739, 640, 538, 488 cm^{-1}; UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 641 (5396), 445 (8110), 299 (62478), 254 nm (80632 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; g_{II} = 2.341, $g_{\perp}$ = 2.016, A_{II} = 20.52 mT; HRMS (ESI, pos.): Calcd for $C_{38}H_{61}N_2O_2Cu$ $[M+H]^+$: 640.4024, Found: 640.4020.

4.3.5. Complex 12c

Green solid; yield (287 mg, 86%); $[\alpha]_D^{29}$ = −33.33 (*c* 0.024, $CHCl_3$); FT-IR (KBr): 3414, 2951, 2901, 2867, 1731, 1674, 1469, 1438, 1412, 1388, 1360, 1300, 1242, 1203, 1167, 1132, 1094, 969, 874, 831, 770, 741, 685, 669, 650, 538, 492 cm^{-1}; UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 669 (5968), 457 (8888), 300 (82100), 253 nm (104388 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; g_{II} = 2.345, $g_{\perp}$ = 2.026, A_{II} = 20.57 mT; HRMS (ESI, pos.): Calcd for $C_{40}H_{65}N_2O_2Cu$ $[M+H]^+$: 668.4337, Found: 668.4346.

4.3.6. Complex 13

Green solid; yield (288 mg, 92%); $[\alpha]_D^{29}$ = −3422.2 (*c* 0.090, $CHCl_3$); FT-IR (KBr): 2949, 2864, 1726, 1661, 1619, 1602, 1467, 1439, 1412, 1389, 1361, 1299, 1287, 1253, 1237, 1203, 1166, 1132, 998, 877, 828, 807, 778, 661, 642, 535 cm^{-1}; UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 622 (4933), 436 (8425), 298 (53208), 250 nm (71646 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; g_{II} = 2.329, $g_{\perp}$ = 2.010, A_{II} = 21.87 mT; HRMS (ESI, pos.): Calcd for $C_{37}H_{59}N_2O_2Cu$ $[M+H]^+$: 626.3867, Found: 626.3872.

4.3.7. Complex 14

Green solid; yield (285 mg, 94%); $[\alpha]_D^{29}$ = −331.2 (*c* 0.046, $CHCl_3$); FT-IR (KBr): 3313, 2954, 2905, 2867, 1726, 1621, 1527, 1463, 1431 1383, 1362, 1348, 1323, 1254, 1200, 1167, 1132, 1097, 968, 877, 832, 788, 743, 556, 537, 476 cm^{-1}; UV–vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 569 (940), 378 (14452), 281 (40276), 256 nm (43531 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; g_{II} = 2.333,

$g_{\perp}$ = 2.008, A_{II} = 22.24 mT; HRMS (ESI, pos.): Calcd for $C_{36}H_{53}N_2O_2Cu$ $[M+H]^+$: 608.3398, Found: 608.3394.

4.4. General procedure for enantioselective nitroaldol reactions

To a stirred solution of catalyst **12b** (16 mg, 0.025 mmol) and aldehyde (0.25 mmol) in dry toluene (0.75 mL), nitromethane (2.5 mmol) was added at the appropriate temperature. After the indicated time, the reaction mixture was treated with saturated NH_4Cl solution (1 mL) followed by water (3 mL). The mixture was extracted using ethyl acetate (3 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified on a silica gel column chromatography using hexane and ethyl acetate (4:1) as eluent to afford the analytically pure nitroaldol product.

4.4.1. (*R*)-(−)-2-Nitro-1-(4-nitrophenyl)ethanol 16a[14]

Yellow oil, yield 56%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (dd, J = 6.4, 1.2 Hz, 2H), 7.63 (d, J = 9.2 Hz, 2H), 5.62–5.58 (m, 1H), 4.63–4.55 (m, 2H), 3.21 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 145.3, 127.1, 124.3, 80.8, 70.1; FT-IR (neat): 3528, 1557, 1520, 1350 cm^{-1}; ee: 76%, determined by HPLC (Daicel Chiralcel OJ, hexane/^{i}PrOH (4:1), flow rate 1.0 mL/min, λ = 215 nm): t_R = 11.5 min (minor), t_R = 14.9 min (major); $[\alpha]_D^{29}$ = −29.6 (*c* 0.52, $CHCl_3$).

4.4.2. (*R*)-(−)-2-Nitro-1-phenylethanol 16b[15]

Yellow oil, yield 64%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 5H), 5.49–5.45 (m, 1H), 4.64–4.49 (m, 2H), 2.84 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 129.0, 129.0, 126.0, 81.3, 71.0; FT-IR (neat): 3548, 1553, 1379 cm^{-1}; ee: 78%, determined by HPLC (Daicel Chiralcel OJ-H, hexane/^{i}PrOH (17:3), flow rate 0.8 mL/min, λ = 215 nm): t_R = 21.6 min (minor), t_R = 26.1 min (major); $[\alpha]_D^{29}$ = −33.1 (*c* 0.24, $CHCl_3$).

4.4.3. (*R*)-(+)-2-Nitro-1-(2-nitrophenyl)ethanol 16c[2a]

Yellow oil, yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, J = 8, 1.2 Hz, 1H), 7.96 (dd, J = 7.6, 0.8 Hz, 1H), 7.76 (td, J = 7.6, 0.8 Hz, 1H), 7.57 (td, J = 8.4, 0.8 Hz, 1H), 6.05–6.02 (m, 1H), 4.88–4.84 (m, 1H), 4.58–4.52 (m, 1H), 3.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 134.5, 134.3, 129.7, 128.8, 125.0, 80.2, 66.9; FT-IR (neat): 3529, 1555, 1525, 1346 cm^{-1}; ee: 90%, determined by HPLC (Daicel Chiralcel AD-H, hexane/^{i}PrOH 90/10, flow rate 1 mL/min, λ = 215 nm): t_R = 14.3 min (major), t_R = 15.7 min (minor); $[\alpha]_D^{20}$ = +185 (*c* 0.59, $CHCl_3$).

4.4.4. (*R*)-(−)-1-(3-Bromophenyl)-2-nitroethanol 16d[15]

Yellow oil, yield 61%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 5.47–5.43 (m, 1H), 4.61–4.49 (m, 2H), 2.91 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 132.0, 130.7, 129.2, 124.7, 123.1, 81.0, 70.2; FT-IR (neat): 3542, 1556, 1377 cm^{-1}; ee: 80%, determined by HPLC (Daicel Chiralcel OD-H, hexane/^{i}PrOH (17:3), flow rate 0.8 mL/min, λ = 215 nm): t_R = 11.7 min (minor), t_R = 14.5 min; $[\alpha]_D^{20}$ = −23.2 (*c* 1.50, $CHCl_3$).

4.4.5. (*R*)-(−)-2-Nitro-1-(3-nitrophenyl)ethanol 16e[15]

Yellow oil, yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 8.4 Hz, 1H), 5.63–5.59 (m, 1H), 4.66–4.56 (m, 2H), 3.23 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 140.4, 132.2, 130.3, 123.9, 121.3, 80.8. 70.0; FT-IR (neat): 3546, 1557, 1538, 1347 cm^{-1}; ee: 81%, determined by HPLC (Daicel Chiralcel AD-H, hexane/^{i}PrOH (9:1), flow rate 1 mL/min, λ = 215 nm): t_R = 16.1 min (major), t_R = 18.5 min (minor); $[\alpha]_D^{29}$ = −28.8 (*c* 0.13, $CHCl_3$).

4.4.6. (*R*)-(−)-1-(4-Bromophenyl)-2-nitroethanol 16f[15]

Yellow oil, yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, J = 9.0, 4.2 Hz, 2H), 7.28 (d, J = 10.2 Hz, 2H), 5.43–5.40 (m, 1H), 4.57–4.46 (m, 2H), 2.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2, 132.3, 127.8, 123.0, 81.0, 70.4; FT-IR (neat): 3404, 1553, 1381 cm^{-1}; ee: 82%, determined by HPLC (Daicel Chiralcel OD-H, hexane/^{i}PrOH (17:3), flow rate 0.9 mL/min, λ = 215 nm): t_R = 12.5 min (minor), t_R = 15.9 min (major); $[\alpha]_D^{29}$ = −22.1 (*c* 0.83, $CHCl_3$).

4.4.7. (*R*)-(−)-1-(4-Chlorophenyl)-2-nitroethanol 16g[15]

Yellow oil, yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.34 (m, 4H), 5.48–5.44 (m, 1H), 4.60–4.47 (m, 2H), 2.89 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.7, 134.7, 129.2, 127.4, 81.0, 70.3; FT-IR (neat): 3528, 1553, 1380 cm^{-1}; ee: 65%, determined by HPLC (Daicel Chiralcel OD-H, hexane/^{i}PrOH (17:3), flow rate 0.9 mL/min, λ = 215 nm): t_R = 11.3 min (minor), t_R = 12.5 min (major); $[\alpha]_D^{29}$ = −27.0 (*c* 0.61, $CHCl_3$).

4.4.8. (*R*)-(−)-1-(4-Methoxyphenyl)-2-nitroethanol 16h[15]

Yellow oil, yield 54%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 5.44–5.39 (m, 1H), 4.63–4.46 (m, 2H), 3.81 (s, 3H), 2.72 (t, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 130.0, 127.4, 126.1, 121.4, 110.7, 80.0, 68.0, 55.6; FT-IR (neat): 3472, 1553, 1379 cm^{-1}; ee: 70%, determined by HPLC (Daicel Chiralcel OJ-H, hexane/^{i}PrOH (9:1), flow rate 0.6 mL/min, λ = 215 nm): t_R = 42.4 min (minor), t_R = 50.1 min (major); $[\alpha]_D^{29}$ = −18 (*c* 1.80, $CHCl_3$).

4.4.9. (*R*)-(−)-2-Nitro-1-(*p*-tolyl)ethanol 16i[15]

Yellow oil, yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 5.45–5.41 (m, 1H), 4.63–4.47 (m, 2H), 2.75 (d, J = 4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 135.3, 129.7, 126.0, 81.3, 70.9, 21.2; FT-IR (neat): 3551, 1554, 1378 cm^{-1}; ee: 79%, determined by HPLC (Daicel Chiralcel OJ-H, hexane/^{i}PrOH (17:3), flow rate 0.8 mL/min, λ = 215 nm): t_R = 18.7 min (minor), t_R = 21.7 min (major); $[\alpha]_D^{29}$ = −24.3 (*c* 1.24, $CHCl_3$).

4.4.10. (*R*)-(−)-1-(Naphthalen-2-yl)-2-nitroethanol 16j[15]

Colorless solid, mp 80.9–81.8 °C, yield 43%, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.84 (m, 4H), 7.54–7.46 (m, 3H), 5.66–5.62 (m, 1H), 4.72–4.58 (m, 2H), 2.94 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 135.3, 129.7, 126.0, 81.3, 70.9; FT-IR (KBr): 3547, 1553, 1377 cm^{-1}; ee: 77%, determined by HPLC (Daicel Chiralcel OJ, hexane/^{i}PrOH (8:2), flow rate 1 mL/min, λ = 215 nm): t_R = 18.2 min (minor), t_R = 25.9 min (major); $[\alpha]_D^{29}$ = −35.6 (*c* 0.38, $CHCl_3$).

4.4.11. (*R*)-(−)-1-(Furan-2-yl)-2-nitroethanol 16k[14]

Yellow oil, yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 1H), 6.38 (d, J = 3.6 Hz, 1H), 6.36 (dd, J = 3.0, 1.8 Hz, 1H), 5.46–5.45 (m, 1H), 4.78–4.74 (m, 1H), 4.67–4.64 (m, 1H), 2.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8, 143.3, 110.8, 108.4, 78.5, 65.0; FT-IR (neat): 3418, 1555, 1380 cm^{-1}; ee: 76%, determined by HPLC (Daicel Chiralcel OJ, hexane/^{i}PrOH (17:3), flow rate 0.9 mL/min, λ = 215 nm): t_R = 15.9 min (minor), t_R = 18.6 min (major); $[\alpha]_D^{29}$ = −32.8 (*c* 0.22, $CHCl_3$).

4.4.12. (*R*)-(−)-2-Nitro-1-(thiophen-2-yl)ethanol 16l[16a]

Yellow oil, yield 34%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.31 (m, 1H), 7.06–7.04 (m, 1H), 7.01–6.99 (m, 1H), 5.72–5.70 (m, 1H), 4.73–4.57 (m, 2H), 3.00 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 127.3, 126.2, 125.1, 81.0, 67.2; FT-IR (neat): 3416, 1618, 1557, 1380 cm^{-1}; ee: 71%, determined by HPLC (Daicel

Chiralcel OD-H, hexane/^{i}PrOH (17:3), flow rate 0.9 mL/min, λ = 215 nm): t_R = 10.1 min (minor), t_R = 11.5 min (major); $[\alpha]_D^{29}$ = −16 (*c* 0.25, $CHCl_3$).

4.4.13. (*R*)-(−)-1-Nitrononan-2-ol 16m[16b]

Yellow oil, yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 2H), 7.0–6.93 (m, 2H), 5.52 (d, *J* = 10.4 Hz, 1H), 4.2–4.14 (m, 2H), 3.63 (d, *J* = 9.2 Hz, 1H), 1.49 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.8, 68.8, 33.9, 31.8, 29.4, 29.2, 25.3, 22.7; FT-IR (neat): 3418, 1555, 1382 cm^{-1}; ee: 90%, determined by HPLC (Daicel Chiralcel OJ, hexane/^{i}PrOH (17:3), flow rate 0.8 mL/min, λ = 215 nm): t_R = 12.2 min (minor), t_R = 16.0 min (major); $[\alpha]_D^{29}$ = −15.1 (*c* 1.0, $CHCl_3$).

Acknowledgments

We thank the Council of Scientific and Industrial Research, New Delhi for financial support. M.K. thanks the Council of scientific and Industrial Research, New Delhi, for SRF fellowship. We thank the Central Instruments Facility, IIT Guwahati for the NMR and EPR analyses.

References

1. Henry, L. *Bull. Soc. Chim. Fr.* **1895**, *13*, 999.
2. For selected examples, see: (a) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. *Chem. Eur. J.* **2007**, *13*, 829; (b) Blay, G.; Domingo, L. R.; Hernandez-Olmos, V.; Pedro, J. R. *Chem.-Eur. J.* **2008**, *14*, 4725; (c) Kureshy, R. I.; Anjan Das, B. D.; Khan, N. H.; Abdi, S. H. R.; Bajaj, H. C. *Appl. Catal., A Gen.* **2012**, *439–440*, 74; (d) Niabaru, T.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 1644; (e) Lang, K.; Park, J.; Hong, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 1620; (f) White, J. D.; Shaw, S. *Org. Lett.* **2012**, *14*, 6270.
3. (a) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; ; Pergamon: New York, 1991; Vol. 2, p 321; (b) Shibasaki, M.; Groer, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; ; Springer: Berlin, 1991; Vol. III, p 1075; (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (d) Wolf, J. P. In *Name Reactions for Functional Group Transformations*; Li, J. J., Corey, E. J., Eds.; ; Wiley: New Jersey, 2007; Vol. III, p 645.
4. For examples, see: (a) Colvin, E. W.; Beck, A. K.; Seeback, D. *Helv. Chim. Acta* **1981**, *64*, 2264; (b) Seebach, D.; Beck, A. K.; Lehr, F.; Weller, T.; Colvin, E. W. *Angew. Chem., Int. Ed.* **1981**, *20*, 397; (c) Barrett, A. G. M.; Spiling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733; (d) Wehner, V.; Jager, V. *Angew. Chem., Int. Ed.* **1990**, *29*, 1169; (e) Kiess, F.-M.; Poggendorf, P.; Picasso, S.; Jager, V. *Chem. Commun.* **1998**, 119; (f) Ballini, R.; Palmieri, A.; Righi, P. *Tetrahedron* **2007**, *63*, 12099.
5. For some selected examples, see: (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418; (b) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *114*, 889; (c) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692; (d) Palmo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442; (e) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; Lopez, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117; (f) Park, J.; Lang, K.; Abboud, K. A.; Hong, S. *J. Am. Chem. Soc.* **2008**, *130*, 16484; (g) Sanjeevkumar, N.; Periasamy, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1842; (h) Zulauf, A.; Mellah, M.; Schulz, E. *J. Org. Chem.* **2009**, *74*, 2242; (i) Constable, E. C.; Zhang, G.; Housecroft, C. E.; Neuburger, M.; Schaffner, S.; Woggon, W. D. *New J. Chem.* **2009**, *33*, 1064; (j) Kureshy, R. I.; Das, A.; Khan, N. H.; Abdi, S. H. R.; Bajaj, H. C. *ACS Catal.* **2011**, *1*, 1529; (k) Dhahagani, K.; Rajesh, J.; Kannan, R.; Rajagopal, G. *Tetrahedron: Asymmetry* **2011**, *22*, 857; (l) Kanagaraj, K.; Suresh, P.; Pitchumani, K. *Org. Lett.* **2010**, *12*, 4070; (m) Ibrahim, F.; Jaber, N.; Guerineau, V.; Hachem, A.; Ibrahim, G.; Mellah, M.; Schulz, E. *Tetrahedron: Asymmetry* **2013**, *24*, 1395; (n) Didier, D.; Schulz, E. *Tetrahedron: Asymmetry* **2013**, *24*, 769; (o) Ni, B.; He, J. *Tetrahedron: Asymmetry* **2013**, *54*, 462; (p) Wolinska, E. *Tetrahedron* **2013**, *69*, 7269.
6. For selected examples, see: (a) Gao, J.; Reibenpies, J. H.; Martell, A. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 6008; (b) Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4600; (c) Yang, H.; Wang, J.; Zhu, C. *J. Org. Chem.* **2007**, *72*, 10029; (d) Suyama, K.; Sakai, Y.; Matsumoto, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 797; (e) Fujisaki, J.; Matsumoto, K.; Matsumoto, K.; Katsuki, T. *J. Am. Chem. Soc.* **2011**, *133*, 56; (f) Xuan, W.; Zhang, M.; Liu, Y.; Chen, Z.; Cui, Y. *J. Am. Chem. Soc.* **2012**, *134*, 6904; (g) North, M.; Stewart, E. L.; Young, C. *Tetrahedron: Asymmetry* **2012**, *23*, 1218.
7. Matsumoto, K.; Saito, B.; Katsuki, T. *Chem. Commun.* **2007**, 3619.
8. Kaik, M.; Gawronski, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1559.
9. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
10. (a) Balsells, J.; Carroll, P. J.; Walsh, J. *J. Inorg. Chem.* **2001**, *40*, 5568; (b) Sakthivel, S.; Jammi, S.; Punniyamurthy, T. *Tetrahedron: Asymmetry* **2012**, *23*, 101.
11. Velusamy, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2003**, 3919.
12. (a) Jammi, S.; Punniyamurthy, T. *Eur. J. Inorg. Chem.* **2009**, 2508; (b) Jammi, S.; Ali, M. A.; Sakthivel, S.; Rout, L.; Punniyamurthy, T. *Chem. Asian J.* **2009**, *4*, 314.
13. (a) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*; Pearson Education Pte Ltd: Indian Branch, Delhi, 2004; p 395; (b) Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 1939.
14. Jin, W.; Li, X.; Huang, Y.; Wu, F.; Wan, B. *Chem. Eur. J.* **2010**, *16*, 8259.
15. Jammi, S.; Saha, P.; Sanyashi, S.; Sakthivel, S.; Punniyamurthy, T. *Tetrahedron* **2008**, *64*, 11724.
16. (a) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616; (b) Boobalan, R.; Lee, G.-H.; Chen, C. *Adv. Synth. Catal.* **2012**, *354*, 2511.