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Water enables transimination between hindered ketimines and β-aminoalcohols and selective protection of a vicinal diamine backbone

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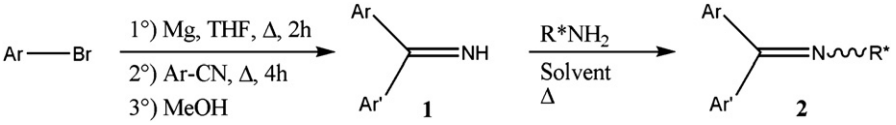
ABSTRACT

Water mediates synthesis of novel hindered Schiff bases via transmination protocol. The feature of the procedure is that it allows both tuning of steric and electronic factors of the substituents and mono-imination of vicinal diamines, which potentially facilitates one-pot approach to unsymmetrical metal ligands.

1. Introduction

Asymmetric aldimine ligands have played a significant role in the development of novel transition-metal catalyzed asymmetric reactions. The feature of these ligands is their ease of preparation. There are a variety of reactions in which good enantioselectivity has been achieved with transition-metal complexes of chiral aldimine ligands. Aldimine derivatives of simple chiral aminoalcohols and *N*-alkylamines have been demonstrated to be effective in asymmetric cyclopropanation,[1] Michael addition,[2] Mannich-type,[3] nitroaldol[4] desymmetrisation,[5] and kinetic resolution[6] reactions, to name a few. Transition-metal complexes of salen ligand have shown, among many other applications, high enantioselctivities in oxidation catalysis,[7] Diels/Alder cyclisation,[8,9] oxidative coupling of binaphthols[10] and have been used as chiral phase-transfer catalysts for the alkylation of α-alkyl imino esters.[11] Unsymmetrical chiral salen-type Schiff base ligands have also been synthesized via one-pot or stepwise approaches[12] and used in aerobic oxidation of cyclohexene.[13]

However, the number of investigation into the catalytic properties of the more stable chiral ketimines is relatively small probably due to preparation difficulties. Oguni et al.[14] have first reported hindered chiral ketimine ligands in 1995, transition-metal complexes of which have shown usefulness as catalysts for the enantioselective diketene ring opening reactions. We recently reported[15] the synthesis and structure determination of sterically crowded chiral biaryl ketimines **2** by means of transimination protocol between a methylenimine **1** and a primary amine[16] (Scheme 1). The atropisomerism due to restricted rotation about the C–C bond adjacent to C=N was evidenced by high field NMR and X-ray analysis. In some cases, physical separation of stereochemically stable ketimine atropisomers was accomplished.



Scheme 1.

The feasibility of the transimination process seemed of special interest to us in view of the ready availability of a variety of chiral primary amines. Nevertheless, the process showed limitations when electronic interactions and steric hindrance are combined.

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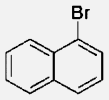
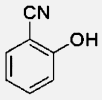
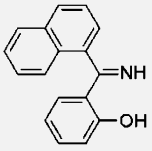
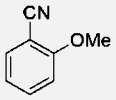
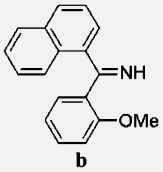
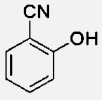
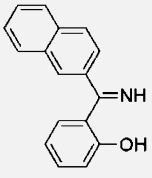
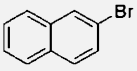
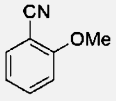
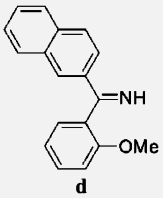
Table 1
Synthesis of hindered methylenimines **1**

Entry	Ar–Br	Ar′–CN	Imine **1**	Yield (%)
1			 **a**	90
2			 **b**	56
3			 **c**	60
4			 **d**	70

Similarly, the corresponding hindered ketones fail to react with primary amines under catalytic acidic conditions with azeotropic removal of water.

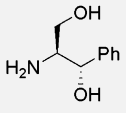
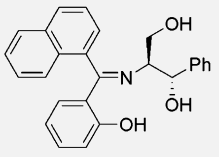
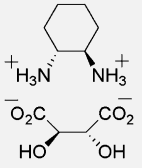
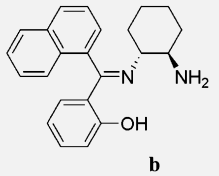
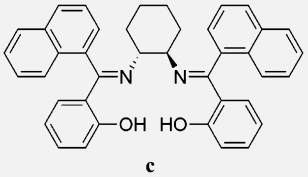
In continuing our endeavor to develop new multidentate imine ligands and sterically hindered iminium salts as chiral phase-transfer agents[17] with easily tunable steric and electronic properties, we report herein the rather unusual usefulness of water/ethanol solvent-system in the transimination protocol for the preparation of some challenging hindered ketimines and selective protection of vicinal diamines.

2. Results and discussion

When 1-naphthylmethylenimine derivative **1a** (Table 1) was heated to reflux with (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol in chlorinated or high boiling point solvents, no transimination occurred. Similarly, when the reaction was carried out in a protic solvent such as ethanol, only starting materials were recovered. Surprisingly, the addition of water to the ethanolic solution was found to be beneficial to transimination and produced imine **2a** with good yield (Table 2, entry 1) together with small amounts of the corresponding ketone due to hydrolysis of imine **1a**. The generally accepted mechanism of transimination is via a nucleophilic attack into the imino C=N bond by the primary amine as the first step, followed by the liberation of ammonia. The nucleophilic addition onto the imino bond becomes difficult when intramolecular dipole/dipole interaction is possible or/and when steric hindrance is important. We therefore reasoned that in the presence of water, solvatation of the starting methylenimine competes with the intramolecular hydrogen bonding and subsequently facilitate condensation of the primary amine. The steric hindrance brought by the naphthyl group stabilizes the imines toward hydrolysis in aqueous media.

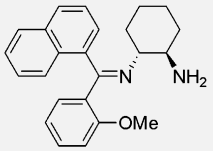
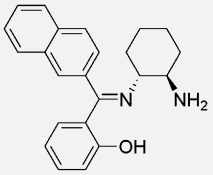
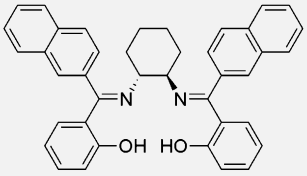
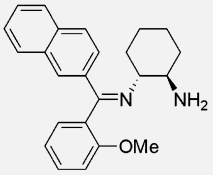
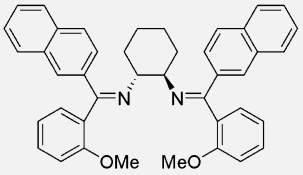
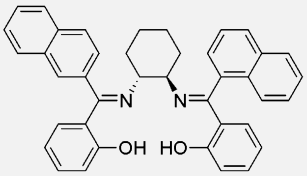
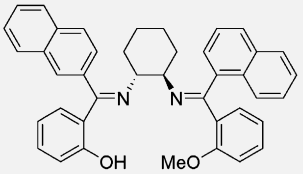
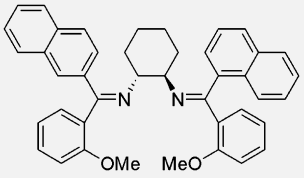
The ^{13}C NMR of a deuteriochloroform solution of pure **2a** showed two sets of imino ^{13}C=N signals at δ(176.8, 177.2 ppm) and 171.3 ppm with the proportion largely in favor of the two downfield shifted signals (ca. 95:5). The important chemical shift difference indicated the presence of both *anti* and *syn*-geometric configurations.[18] Thus, high field NMR spectroscopy (^1H, ^{13}C, HMQC, COSY, and NOESY) outlined an intense NOESY effect between the naphthyl group and the chiral hydroxyalkyl chain protons, which clearly evidenced the *anti*-geometric configuration for the major stereoisomer. Therefore, the pair of ^{13}C=N signals at δ(176.8, 177.2 ppm) indicated the presence of two inseparable conformers having the

Table 2
Preparation of hindered ketimines **2** by means of transimination between methylenimines **1** and chiral primary amines in ethanol/water mixture

Entry	Imine **1**	R*NH$_2$	Time (h)	Imine **2**	Yield (%)
1	**1a**		24	 **a**	60
2	**1a**		24	 **b**	41[a] 65[b]
3	**1a**		24	 **c**	10

(*continued on next page*)

Table 2 (*continued*)

Entry	Imine **1**	R^*NH_2	Time (h)	Imine **2**	Yield (%)
4	**1b**		24	 **d**	40[c]
5	**1c**		2	 **e**	50[d]
6	**1c**		2	 **f**	10
7	**1d**		24	 **g**	9
8	**1d**		24	 **h**	60
9	**1a**	**2e**	18	 **i**	68
10	**1b**	**2e**	18	 **j**	75
11	**1d**	**2d**	18		NR

NR=No reaction.
[a] Methylenimine **1a**: 1,2-DAC-Tr, 2:1 M ratio.
[b] Methylenimine **1a**: 1,2-DAC-Tr, 1:1 M ratio.
[c] Substantial amounts of hydrolysis of **1b** were observed.
[d] The medium became dark after 2 h heating.

same geometrical configuration further evidenced by the low chemical shift difference (Fig. 1).

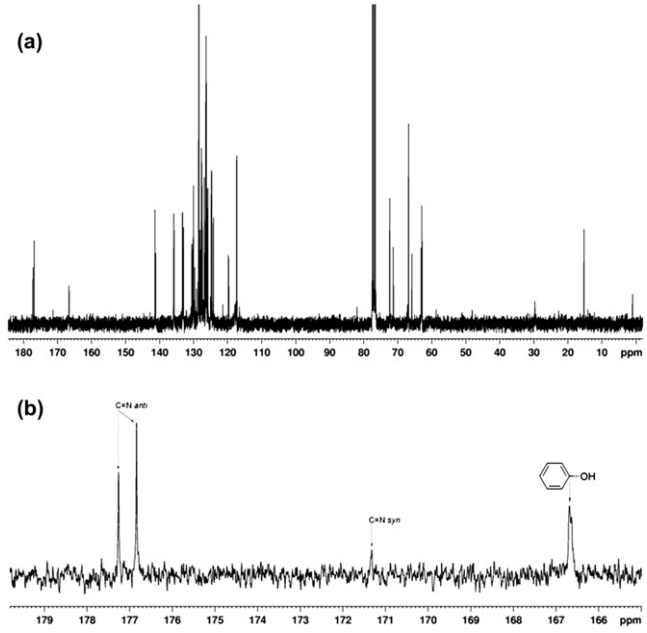


Figure 1. (a) ^{13}C NMR and (b) expansion for pure imine **2a** showing the presence of *anti* and *syn* stereoisomers and two conformers of the *anti*-geometric configuration.

We demonstrated earlier that the steric environment imposed by the aromatic groups in similar hindered ketimines results in slow rotation of the substituents about the C–C bond adjacent to the imino C=N bond, which allows ambient temperature detection of atropisomeric structures.[15]

Interestingly, heating a solution of (*R*,*R*)-1,2-diaminocyclohexane-(+)-tartrate salt (1,2-DAC-Tr) and 2 M equiv of imine **1a** under basic conditions in ethanol/water (2/1, v/v) yielded mono-imine **2b** and bis-imine **2c** in the ratio of 4:1 (Table 2, entries 2 and 3). Both imines were purified by column chromatography and were isolated as oils.

More importantly, when a 1:1 M ratio of methylenimine **1a** to 1,2-DAC-Tr was used, the yield of mono-imine **2b** increased to 65%. The latter is stable and can be stored at room temperature without decomposition. It is worth emphasizing that the yield of the symmetrical bis-imine **2c**, which was the initially desired target compound, could not be optimized via a two-pot approach by means of a second transimination process between the mono-imine **2b** and methylenimine **1a**. Excessive heating and prolonged reaction time proved unsuccessful. The yield and stability of mono-imines such as **2b** makes possible a one-pot condensation procedure leading to unsymmetrical metal ligands. Classical homo- and hetero-nuclear experiments were undertaken in order to assign the naphthyl and phenol protons for mono-imine **2b**, which have been found to appear as two sets of well resolved multiplets at δ(7.23–8.06 ppm) and δ(6.33–7.22 ppm), respectively. Moreover, ^{13}C NMR showed two ^{13}C=N signals at δ(174.1 and 174.8 ppm) revealing detection of two stable conformers of mono-imine **2b** (9:1) on the NMR time scale. Of particular importance, the intense NOESY correlations observed between the naphthyl group protons H_2 and H_8 and the α-amino proton H_{16} and the α-imino proton H_{15}, respectively. This not only evidenced *anti*-geometric configuration for imine **2b**, but also more information about the naphthyl group orientation of the major conformer (Fig. 2, a).

In the same manner, the NOESY experiment allowed us to gain insight into the orientation of the aromatic groups of pure bis-imine **2c** since only two clear sets of correlations were observed between the naphthyl groups and the chiral auxiliary protons. This orientation is in favor of *anti anti*-geometric configurations.

In order to make feasible the isolation of stable hindered ketimine conformers, we used the more sterically crowded methylenimine **1b**, which was isolated with a moderate yield. Transimination with 1,2-DAC-Tr under the same conditions afforded exclusively mono-imine **2d** (Table 2, entry 4) isolated as a viscous yellow oil after chromatographic purification. As for mono-imine **2b**, two imino ^{13}C=N signals were observed at δ(174.5 and 173.9 ppm) evidencing the presence of more than one stereoisomer. TLC showed two spots with a different intensity, separation of which could not be achieved because of the very small difference in R_f. Again, 2D NMR experiments revealed absence of correlations between the phenol moiety and the chiral auxiliary for both isomers evidencing *anti*-geometric configuration and atropisomeric nature of the two stereoisomers (Fig. 2, b).

On the other hand, the 2-naphtylmethylenimino derivative **1c** was found to be more reactive toward 1,2-DAC-Tr and afforded about 50% of *anti* mono-imine **2e** (Fig. 3, a) and small amounts of bis-imine **2f** (Table 2, entries 5 and 6). Curiously, after two hours heating, the medium started to become darker with formation of an unidentified complex mixture of products. However, this phenomenon did not occur when methylenimine **1d** was subjected to transimination with 1,2-DAC-Tr under identical conditions (Table 2, entries 7 and 8). In opposition to all other methylenimines, **1d** double transiminated readily and in a better yield (Table 2, entry 8).

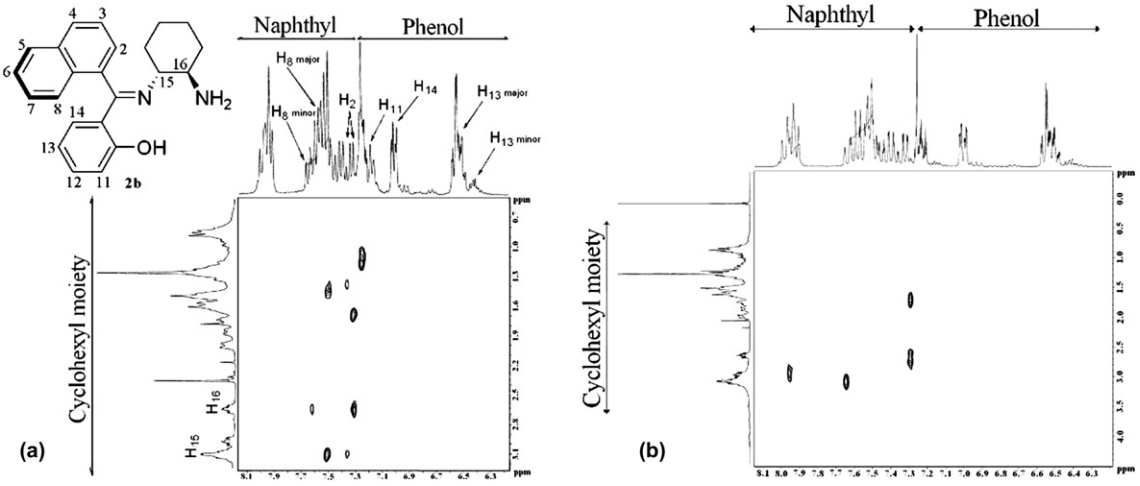


Figure 2. NOESY chart expansions for conformers of mono-imines **2b** (a) and **2d** (b) underlying correlations between the cyclohexyl moiety and the naphthyl group protons.

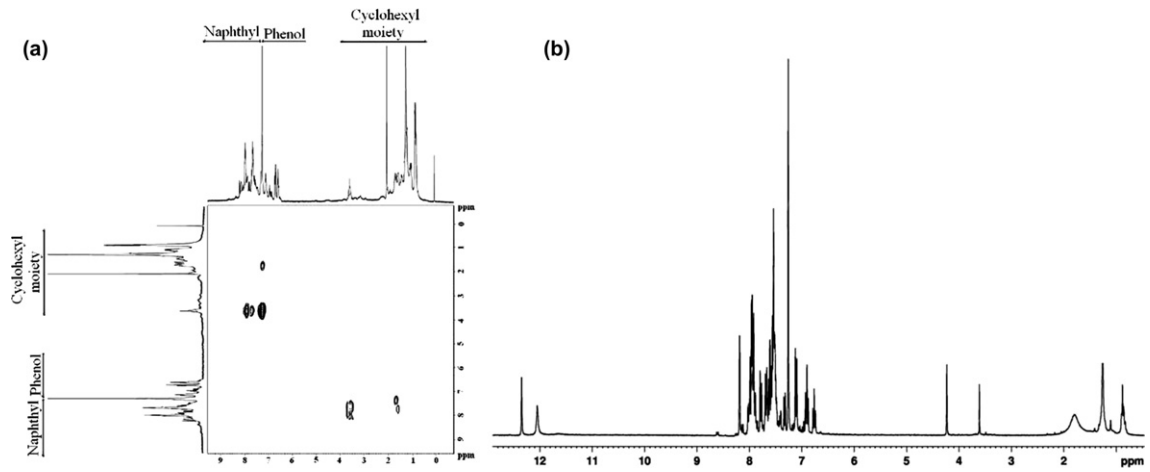


Figure 3. (a) NOESY spectrum of mono-imine **2e**; (b) ^{1}H NMR of the unsymmetrical bis-imine **2i**.

It is worth mentioning that bis-imine **2h** was isolated as the *anti anti* stereoisomer judging from the intense NOESY effect observed between the naphthyl group and the cyclohexyl moiety protons.

Finally, unsymmetrical bis-imines **2i** and **2j** could be prepared with good yield following the same protocol using mono-imine **2e** as the starting primary amine and either methylenimine **1a** or **1b** (Table 2, entries 9 and 10). Surprisingly, mono-imine **2e** remained chemically and stereochemically stable under these conditions, which allowed recovering the amount that did not react after 18 h. In the same way, structural information on the stereoisomeric nature of bis-imines **2i** and **2j** came from the NMR investigation. A particular point is the chemical shift observed for the two stereogenic centers protons and the hydroxy groups, which appeared for bis-imine **2i** as two pairs of singlets at δ(4.23, 3.61 ppm) and δ (12.34, 12.05 ppm), respectively (Fig. 3, b). The same chiral centers protons appeared at δ(4.22, and 3.97 ppm) for bis-imine **2j**. This helped to simultaneously assign each of these two protons and *anti*-geometric configuration for the newly created imino bonds. However, the more hindered mono-imine **2d** failed to transiminate with methylenimine **1d** under a variety of reaction conditions (Table 2, entry 11).

3. Conclusion

In conclusion, water/ethanol solvent-system was found to facilitate the synthesis of hindered schiff bases through a transimination process between hindered methylenimines and primary amines. In all cases, NMR spectroscopy evidenced the presence of an inseparable conformers possessing the same ketimine geometric configuration due to hindered rotation of the aryl groups about the C–C bond adjacent to C=N.

The transimination reaction between sterically crowded methylenimines and (*R*,*R*)-1,2-diaminocyclohexane under the optimized reaction conditions led to selective mono-imination with moderate to good yields. This procedure offers flexibility of substituents steric and electronic tuning, which opens up new perspectives in the rational design and one-pot approach to the synthesis of unsymmetrical metal ligands.

4. Experimental section

4.1. General

Uncorrected melting points were determined on a Büchi 510 instrument. Optical rotations were determined at 25 °C on Perkin/Elmer 240 polarimeter using the sodium D line and concentrations are given in g/100 mL. IR spectra were recorded on a Perkin/Elmer 16 PC FT instrument (in cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts are in parts per million referenced to TMS in $CDCl_3$. Mass spectra were determined on Thermo Finnigan SSQ 7000 GC/MS. High resolution mass spectra (HRMS) were recorded on a Micromass Zab Spectrometer at the University of Rennes (France). Elemental analyses were performed on Thermo Finnigan Elementary Analyser Flash EA 1112 at the UATRS, Rabat (Morocco). Analytical thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} glass plates (0.25 mm) and compounds were visualized by UV light (254 nm) or ninhydrine acid/ethanol (22.1 g–180 mL) spray. Column chromatography was carried out on Merck Kieselgel. Chemicals were purchased from either Sigma/Aldrich or Fluka and used as received. Solvents were distilled according to known procedures.

4.2. General procedure for the preparation of compounds 1a–d

In a 25-mL two-necked flask equipped with a dropping funnel and reflux condenser fitted with a calcium chloride drying tube, were introduced Magnesium turnings (120 mg, 4.94 mmol), anhydrous THF (2 mL), and 100 mg of either 1-bromonaphthalen (for the preparation of imines **1a** and **b**) or 2-bromonaphthalen (for the preparation of imines **1c** and **d**). When the reaction started, a moderate reflux began which was maintained by slow addition under vigorous stirring of a solution of the remaining amounts of the aryl bromide (total of 1 g, 4.829 mmol) in THF (4 mL). The resulting brown solution was heated under reflux for 2 h after which time it is cooled and a solution of either 2-cyanophenol (for the preparation of imines **1a** and **1c**) (287 mg, 2.41 mmol, 0.5 equiv) or 2-methoxybenzonirile (for the preparation of imines **1b** and **1d**) (578.5 mg, 4.34 mmol, 0.9 equiv) in THF (4 mL) was added. The dark solution was then heated to reflux for 4 h. The stirred mixture was cooled to room temperature before addition of absolute methanol (1.5 mL) and the stirring continued for 30 min. The solvents were removed in vacuo and the residual brown oil taken in ethyl acetate (20 mL). The solid, which separated was collected by filtration and the filtrate concentrated to dryness in vacuo. Column chromatography on silica gel afforded pure methylenimines **1a–d**.

*4.2.1. 1-(1-Naphtyl)-1-(2-hydroxyphenyl)methylenimine (**1a**).* Orange oil, (536 mg, 90%), R_f=0.21 (3:7 EtOAc/hexane), IR (KBr) ν_{max}:

3548, 1624 cm^{-1}; ^1H NMR δ=14.63 (s, 1H), 9.44 (s, 1H), 7.84–6.99 (m, 8H), 6.83 (m, 1H), 6.8 (m, 1H), 6.53 (m, 1H); ^{13}C NMR δ=181.7, 163.6, 137.0, 134.0, 133.8, 132.6, 130.4, 130.0, 128.8, 127.4, 126.9, 125.7, 125.5, 125.2, 119.8, 118.6, 118.3; *m/z* (EI) 247 (M^+), 230, 217, 128, 91, 69; HRMS (ES): M^+, found 247.0989. $C_{17}H_{13}NO$ requires 247.0997.

*4.2.2. 1-(1-Naphtyl)-1-(2-methoxyphenyl)methylenimine (**1b**).* Viscous yellow oil, (634 mg, 56%), R_f=0.10 (2:8 EtOAc/hexane), IR (KBr) ν_{max}: 2964, 1623 cm^{-1}; ^1H NMR δ=8.0–7.85 (m, 3H), 7.61–7.38 (m, 6H), 7.23–7.19 (m, 1H), 7.07–6.94 (m, 1H), 6.91–6.85 (m, 1H), 3.80 (s, 3H); ^{13}C NMR δ=176.2, 158.1, 132.2, 131.6, 131.1, 130.9, 130.8, 129.7, 129.2, 127.2, 126.2, 126.1, 125.9, 25.7, 124.9, 120.6, 120.5, 55.7; *m/z* (EI) 261 (M^+), 246; HRMS (ES): M^+, found 261.1149. $C_{18}H_{15}NO$ requires 261.1154.

*4.2.3. 1-(2-Naphtyl)-1-(2-hydroxyphenyl)methylenimine (**1c**).* Yellow oil, (357 mg, 60%), R_f=0.24 (3:7 EtOAc/hexane), IR (KBr) ν_{max}: 3168, 1623 cm^{-1}; ^1H NMR δ=12.05 (s, 1H), 8.21–8.18 (br s, 1H), 8.01–7.86 (m, 3H), 7.82–7.75 (m, 1H), 7.71–7.39 (m, 5H), 7.14–7.09 (m, 1H), 7.01–6.86 (m, 1H); ^{13}C NMR δ=163.2, 158.5, 136.3, 133.7, 132.8, 132.2, 130.4, 129.2, 128.3, 128.2, 127.8, 127.0, 125.3, 120.9, 119.4, 118.7, 118.4; *m/z* (EI) 247 (M^+), 171; HRMS (ES): M^+, found 247.0990. $C_{17}H_{13}NO$ requires 247.0997.

*4.2.4. 1-(2-Naphtyl)-1-(2-methoxyphenyl)methylenimine (**1d**).* Yellow solid, (793 mg, 70%), mp 76–78 °C, R_f=0.34 (2:8 EtOAc/hexane), IR (neat) ν_{max}: 3243, 1623 cm^{-1}; ^1H NMR δ=8.25 (s, 1H), 8.05–7.95 (m, 2H), 7.92–7.69 (m, 4H), 7.61–7.25 (m, 3H), 7.12–7.01 (m, 2H), 3.72 (s, 3H); ^{13}C NMR δ=175.9, 157.4, 136.2, 134.4, 132.1, 130.7, 129.6, 128.9, 128.3, 128.0, 127.6, 127.1, 126.5, 126.2, 125.1, 124.6, 120.6, 55.7; *m/z* (EI) 261 (M^+), 246; Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.53; H, 5.60; N, 5.16.

4.3. General procedure for transimination

Methylenimine **1** (1.0 mmol) and the primary amine (1 equiv), or the mixture consisting of (*R,R*)-1,2-diaminocyclohexane-(+)-tartrate salt (132 mg, 0.5 mmol) and K_2CO_3 (138 mg, 1 mmol), were dissolved in ethanol/water mixture (2/1, v/v) (6 mL) and the resulting solution heated to reflux for the period of time shown in Table 2 to complete the reaction (monitored by TLC). Then the crude product was subjected to column chromatography over silica gel using EtOAc/hexane to purify and separate the stereoisomers.

*4.3.1. N-((1S,2S,anti)-1,3-Dihydroxy-1-phenylprop-2-yl)-1-naphthyl-1-(2′-hydroxyphenyl)methylenimine (**2a**).* Yellow oil, (238 mg, 60%), R_f=0.13 (3:7 EtOAc/hexane), $[\alpha]_D$ +68.1 (*c* 1, $CHCl_3$), IR (KBr) ν_{max}: 3412, 1605 cm^{-1}; ^1H NMR δ=10.02 (s, 1H), 7.99–7.92 (minor) and 7.91–7.85 (major) (m, 2H), 7.62–7.45 (m, 2H), 7.44–7.35 (m, 2H), 7.33–7.26 (m, 2H), 7.25–7.11 (m, 4H), 7.09–6.98 (minor) and 6.97–6.89 (major) (m, 1H), 6.69–6.41(m, 2H), 6.37–6.3 (m, 1H), 5.78 (dd, *J*=7.5 and 6 Hz, 1H), 5.26 (dd, *J*=7.5 and 6 Hz, 1H), 4.17–3.98 (major) and 3.97–3.87 (minor) (m, 1H), 3.84–3.65 (m, 1H), 3.52–3.39 (m, 2H); ^{13}C NMR δ=177.2, 176.8, 171.3, 166.7, 166.6, 141.4, 135.9, 133.4, 133.0, 132.9, 130.7, 129.9, 129.6, 128.7, 127.4, 127.1, 126.9, 125.8, 125.0, 124.7, 124.2, 121.4, 119.8, 117.3, 72.3, 63.1, 62.9; *m/z* (EI) 397 (M^+), 381, 153; HRMS (ES): M^+, found 397.1680. $C_{26}H_{23}NO_3$ requires 397.1678.

*4.3.2. (1R,2R,anti)-1-N-(2-Hydroxyphenyl-1-naphthylidene)-2-N′-aminocyclohexane (**2b**).* Brown oil, (141 mg, 41%), R_f=0.26 and 0.3 (two non-separated isomers) (0.5:9.5 MeOH/CH_2Cl_2), $[\alpha]_D$ +17.1 (*c* 0.8, $CHCl_3$), IR (KBr) ν_{max}: 3437, 1605 cm^{-1}; ^1H NMR δ=15.41 (s, 1H), 8.06–7.89 (m, 2H), 7.67 (minor) and 7.57 (major) (m, 1H), 7.55–7.46 (m, 2H), 7.42–7.23 (m, 2H), 7.22–7.15 (m, 1H), 7.04–6.98 (major) and 6.97–6.89 (minor) (m, 1H), 6.59–6.48 (major) and 6.45–6.33 (minor) (m, 2H), 3.18–3.05 (m, 1H), 3.02–2.91 (m, 0.5H), 2.69–2.58 (m, 0.5H), 2.03–1.71 (m, 2H), 1.7–1.29 (m, 4H), 1.28–1.20 (m, 2H); ^{13}C NMR δ=174.8, 174.1, 162.7, 162.5, 133.3, 132.6, 132.5, 131.8, 131.7, 131.4, 131.3, 130.5, 130.2, 129.4, 129.3, 129.0, 128.6, 128.5, 128.2, 127.3, 126.8, 126.7, 126.4, 126.3, 125.6, 125.4, 125.3, 125.0, 120.2, 120.1, 118.3, 117.9, 117.8, 117.7, 65.4, 55.8, 55.6, 33.4, 32.8, 32.3, 31.4, 29.7, 24.7, 24.2, 24.1, 23.7; *m/z* (EI) 344 (M^+), 308, 248, 154; HRMS (ES): M^+, found 344.1887. $C_{23}H_{24}N_2O$ requires 344.1889.

*4.3.3. (1R,2R,anti,anti)-1,2-N,N′-Bis(2-hydroxyphenyl-1-naphthylidene)cyclohexane (**2c**).* Yellow oil, (57 mg, 10%), R_f=0.45 (2:8 EtOAc/hexane), $[\alpha]_D$ +14.5 (*c* 0.8, $CHCl_3$), IR (KBr) ν_{max}: 3445, 1605 cm^{-1}; ^1H NMR δ=14.61 (br, 2H), 8.13–8.04 (m, 2H), 8.02–7.96 (m, 2H), 7.93–7.68 (m, 2H), 7.64–7.53 (m, 2H), 7.5–7.39 (m, 3H), 7.38–7.32 (m, 3H), 7.31–7.25 (m, 2H), 7.24–6.73 (m, 3H), 6.65–6.46 (m, 3H), 3.6–3.4 (m, 2H), 1.92–1.81 (m, 1H), 1.70–1.50 (m, 3H), 1.46–1.39 (m, 2H), 1.26–1.14 (m, 2H); ^{13}C NMR δ=176.8, 162.5, 134.6, 134.4, 134.1, 133.6, 133.4, 133.3, 133.1, 132.8, 132.6, 130.9, 130.4, 130.1, 130.0, 128.8, 128.7, 128.6, 128.1, 127.9, 127.8, 127.6, 127.1, 126.7, 126.5, 126.1, 125.9, 125.3, 125.0, 124.9, 124.7, 124.6, 123.1, 118.6, 118.2, 117.6, 117.1, 64.5, 29.4, 24.6; *m/z* (EI) 574 (M^+), 476, 341; HRMS (ES): M^+, found 574.2621. $C_{40}H_{34}N_2O_2$ requires 574.2620.

*4.3.4. (1R,2R,anti)-1-N-(2-Methoxyphenyl-1-naphthylidene)-2-N′-aminocyclohexane (**2d**).* Viscous yellow oil, (143 mg, 40%), R_f=0.29 and 0.31 (two non-separated isomers) (0.5:9.5 MeOH/CH_2Cl_2), $[\alpha]_D$ −19.2 (*c* 0.6, $CHCl_3$), IR (KBr) ν_{max}: 2925, 1605 cm^{-1}; ^1H NMR δ=8.03–7.89 (m, 3H), 7.66–7.55 (m, 2H), 7.54–7.5 (m, 2H), 7.49–7.3 (m, 2H), 7.27–7.19 (m, 1H), 7.03–6.98 (m, 1H), 6.58–6.49 (m, 2H), 3.15–3.02 (m, 3H), 3.0–2.9 (m, 1H), 2.67–2.58 (m, 1H), 2.0–1.7 (m, 2H), 1.68–1.56 (m, 2H), 1.55–1.45 (m, 2H), 1.40–1.27 (m, 2H); ^{13}C NMR δ=174.5, 173.9, 162.8, 162.6, 133.3, 132.5, 131.8, 131.6, 131.4, 130.5, 130.2, 129.4, 129.2, 128.6, 128.5, 127.8, 127.2, 126.8, 126.7, 126.4, 126.3, 125.6, 125.5, 125.4, 125.3, 125.0, 124.2, 121.6, 120.2, 120.1, 117.9, 117.8, 117.7, 117.3, 68.0, 65.8, 55.8, 55.6, 53.4, 33.4, 33.1, 32.2, 31.8, 29.7, 24.8, 24.3, 24.2, 23.8; *m/z* (EI) 358 (M^+); HRMS (ES): M^+, found 358.2061. $C_{24}H_{26}N_2O$ requires 358.2045.

*4.3.5. (1R,2R,anti)-1-N-(2-Hydroxyphenyl-2-naphthylidene)-2-N′-aminocyclohexane (**2e**).* Brown oil, (172 mg, 50%), R_f=0.28 and 0.34 (two non-separated isomers) (0.5:9.5 MeOH/CH_2Cl_2), $[\alpha]_D$ +15.1 (*c* 1, $CHCl_3$), IR (KBr) ν_{max}: 3429, 1606 cm^{-1}; ^1H NMR δ=12.05 (s, 1H), 8.55–8.10 (m, 1H), 8.08–7.71 (m, 4H), 7.69–7.59 (m, 2H), 7.35–7.2 (m, 2H), 7.13–7.1 (m, 1H), 6.95–6.8 (m, 1H), 6.73–6.59 (m, 2H), 3.7–3.5 (m, 1H), 3.3–2.83 (m, 1H), 2.07–1.8 (m, 2H), 1.75–1.42 (m, 4H), 1.4–1.26 (m, 2H); ^{13}C NMR δ=175.3, 175.2, 163.0, 162.9, 136.3, 136.1, 135.1, 134.9, 133.7, 133.1, 132.4, 132.1, 130.4, 129.2, 128.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.0, 126.9, 126.4, 125.8, 125.3, 124.9, 124.3, 121.6, 121.1, 118.7, 118.4, 117.9, 117.4, 64.9, 37.1, 32.7, 32.5, 29.7, 29.3, 31.9, 30.0, 27.1, 23.7, 22.7, 20.6; *m/z* (EI) 344 (M^+), 246; HRMS (ES): M^+, found 344.1877. $C_{23}H_{24}N_2O$ requires 344.1889.

*4.3.6. (1R,2R,anti,anti)-1,2-N,N′-Bis(2-hydroxyphenyl-2-naphthylidene)cyclohexane (**2f**).* Greenish oil, (57 mg, 10%), R_f=0.46 (2:8 EtOAc/hexane), $[\alpha]_D$ +11.1 (*c* 0.7, $CHCl_3$), IR (KBr) ν_{max}: 3436, 1606 cm^{-1}; ^1H NMR δ=14.32 (br, 1H), 12.04 (s, 1H), 8.81–7.92 (m, 7H), 7.90–7.7 (m, 7H), 7.2–6.98 (m, 4H), 6.9–6.5 (m, 4H), 4.19–3.5 (m, 2H), 2.40–1.54 (m, 6H), 1.53–1.39 (m, 2H); ^{13}C NMR δ=177.8, 177.6, 163.2, 162.7, 136.2, 135.0, 134.1, 133.7, 133.5, 133.3, 132.9, 132.7, 132.2, 130.4, 130.3, 129.3, 129.2, 128.9, 128.5, 128.4, 128.2, 128.1, 127.9, 127.4, 127.0, 126.7, 125.7, 125.3, 124.7, 124.0, 119.9, 118.7, 118.4, 115.6, 58.5, 32.3, 29.7, 24.7, 23.9, 23.5; *m/z* (EI) 574 (M^+), 447, 345, 290; HRMS (ES): M^+, found 574.2619. $C_{40}H_{34}N_2O_2$ requires 574.2620.

*4.3.7. (1R,2R,anti)-1-N-(2-Methoxyphenyl-2-naphthylidene)-2-N′-aminocyclohexane (**2g**).* Brown oil, (32 mg, 9%), R_f=0.29 (0.5:9.5 MeOH/CH_2Cl_2), $[\alpha]_D$ +12.5 (*c* 0.7, $CHCl_3$), IR (KBr) ν_{max}: 2925, 2854,

1615 cm^{-1}; ^1H NMR δ=8.10–8.05 (m, 1H), 7.96–7.71 (m, 4H), 7.64–7.35 (m, 3H), 7.18–6.99 (m, 3H), 3.71 (s, 3H), 3.4–3.16 (m, 2H), 3.15–2.82 (m, 2H), 2.10–1.85 (m, 1H), 1.81–1.5 (m, 4H), 1.4–1.25 (m, 3H); ^{13}C NMR δ=166.8, 166.0, 156.3, 155.4, 137.2, 136.7, 134.3, 134.2, 132.9, 132.4, 132.1, 131.8, 130.1, 129.8, 129.6, 128.9, 128.7, 128.6, 128.3, 127.7, 127.6, 126.8, 126.0, 125.5, 125.1, 124.7, 124.5, 120.9, 120.7, 118.1, 117.4, 111.5, 111.3, 110.9, 68.9, 68.4, 55.8, 55.2, 37.1, 32.3, 31.7, 29.7, 27.4, 27.0, 26.7, 24.9, 24.1, 20.1; *m*/*z* (EI) 358 (M^+), 328, 239, 219, 135; HRMS (ES): M^+, found 358.2050. $C_{24}H_{26}N_2O$ requires 358.2045.

*4.3.8. (1R,2R,anti,anti)-1,2-N,N′-Bis(2-methoxyphenyl-2-naphthylidene)cyclohexane (**2h**).* Yellowish oil, (361 mg, 60%), R_f=0.37 (2:8 EtOAc/hexane), $[\alpha]_D$ +18 (*c* 0.9, $CHCl_3$), IR (KBr) ν_{max}: 2964, 1660, 1625 cm^{-1}; ^1H NMR δ=8.40–7.93 (m, 3H), 7.91–7.60 (m, 8H), 7.59–7.34 (m, 6H), 7.20–6.70 (m, 5H), 3.75 (s, 6H), 3.49–3.46 (m, 1H), 3.35–3.3 (m, 1H), 1.9–1.50 (m, 6H), 1.34–1.15 (m, 2H); ^{13}C NMR δ=175.1, 161.6, 157.6, 145.5, 144.8, 134.1, 133.3, 132.9, 132.1, 131.9, 129.6, 129.4, 129.1, 128.8, 128.3, 128.0, 127.9, 127.7, 127.5, 126.5, 125.8, 125.1, 123.5, 123.0, 122.4, 121.5, 120.5, 120.1, 119.1, 118.8, 118.1, 111.8, 111.5, 110.5, 65.8, 64.1, 55.6, 55.3, 29.8, 29.7, 26.9, 24.3; *m*/*z* (EI) 602 (M^+), 503, 477, 265; HRMS (ES): M^+, found 602.2938. $C_{42}H_{38}N_2O_2$ requires 602.2933.

*4.3.9. (1R,2R,anti,anti)-1-N-(2-Hydroxyphenyl-2-naphthylidene)-2-N′-(2-hydroxyphenyl-1-naphthylidene)cyclohexane (**2i**).* Yellow oil, (390 mg, 68%), R_f=0.45 (2:8 EtOAc/hexane), $[\alpha]_D$ −16.4 (*c* 0.5, $CHCl_3$), IR (KBr) ν_{max}: 3057, 1624 cm^{-1}; ^1H NMR δ=12.34 (s, 1H), 12.05 (s, 1H), 8.25–8.15 (m, 2H), 8.03–7.85 (m, 9H), 7.8–7.5 (m, 3H), 7.45–7.3 (m, 2H), 7.22–7.05 (m, 2H), 6.98–6.84 (m, 2H), 6.8–6.6 (m, 2H), 4.23 (s, 1H), 3.61 (s, 1H), 2.1–1.6 (m, 6H), 1.40–1.20 (m, 2H); ^{13}C NMR δ=176.6, 176.5, 163.4, 163.2, 136.9, 136.7, 136.3, 134.8, 134.0, 133.0, 133.7, 132.5, 130.9, 130.4, 129.2, 129.0, 128.5, 128.4, 128.2, 127.8, 127.5, 127.3, 127.0, 126.6, 126.4, 125.4, 125.3, 124.4, 120.2, 119.3, 118.8, 118.7, 118.4, 118.3, 57.0, 56.4, 31.9, 29.7, 29.3, 22.7; *m*/*z* (EI) 574 (M^+), 445, 335, 158; HRMS (ES): M^+, found 574.2618. $C_{40}H_{34}N_2O_2$ requires 574.2620.

*4.3.10. (1R,2R,anti,anti)-1-N-(2-Hydroxyphenyl-2-naphthylidene)-2-N′-(2-methoxyphenyl-1-naphthylidene)cyclohexane (**2j**).* Orange oil, (441 mg, 75%), R_f=0.82 (2:8 EtOAc/hexane), $[\alpha]_D$ −21.1 (*c* 0.6, $CHCl_3$), IR (KBr) ν_{max}: 3054, 2959, 1602 cm^{-1}; ^1H NMR δ=10.21 (br, 1H), 8.60 (dd, *J*=13.3 Hz, 1H), 8.26–8.16 (m, 1H), 8.10–7.88 (m, 5H), 7.8–7.40 (m, 8H), 7.38–7.18 (m, 2H), 7.16–6.72 (m, 4H), 6.72–6.40 (m, 1H), 4.22 (s, 1H), 3.97 (s, 1H), 3.6 (s, 3H), 1.98–1.49 (m, 6H), 1.48–1.34 (m, 2H); ^{13}C NMR δ=178.6, 163.3, 162.4, 154.0, 149.5, 148.3, 136.2, 135.3, 135.0, 134.3, 133.7, 132.7, 132.1, 130.9, 130.4, 129.7, 128.5, 128.4, 128.3, 127.7, 127.5, 127.4, 126.2, 125.7, 125.3, 124.3, 122.2, 121.4, 120.4, 118.7, 118.2, 117.6, 111.9, 111.2, 55.6, 54.1, 53.7, 29.6, 29.3, 22.6, 22.3; *m*/*z* (EI) 588 (M^+), 524, 507, 473, 363, 324; HRMS (ES): M^+, found 588.2770. $C_{41}H_{36}N_2O_2$ requires 588.2777.

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