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Synthesis of tetrahydroisoquinoline-diamine ligands and their application in asymmetric transfer hydrogenation

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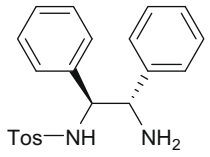
ABSTRACT

The use of the tetrahydroisoquinoline scaffold is well documented in biologically active compounds. However, reports of the utilisation of tetrahydroisoquinoline compounds in asymmetric catalysis are limited. The synthesis of novel diamine ligands possessing the tetrahydroisoquinoline (tetrahydroisoquinoline) backbone and evaluation of their activity in the asymmetric transfer hydrogenation of acetophenone are presented. The diamine ligands in conjunction with *i*-PrOH as the hydrogen source and $[RhCl_2(Cp^*)]_2$ as the metal precursor proved to be the most effective of the tetrahydroisoquinoline derivatives for this catalytic system. Water was found to have a profound influence on the enantioselectivity of the reaction. Optimisation of the amount water, *i*-PrOH and catalytic loading content rendered the best result of 70% enantioselectivity for the (*S*)-1-phenylethanol isomer product.

1. Introduction

Since the isolation of naphthyridinomycin in 1974, the biological activity of tetrahydroisoquinoline carboxylic acid derivatives has been widely investigated.[1–3] Previous reports on the use of tetrahydroisoquinoline derivatives as catalytic ligands have yielded limited success, with poor to moderate enantioselectivities in asymmetric catalysis such as allylic alkylation[4] and borane-mediated hydrogenation reactions.[5,6] However, in a related study the use of different tetrahydroisoquinoline ligands for the addition of diethylzinc to benzaldehyde gave promising results.[7] We have recently reported the use of tetrahydroisoquinoline amino alcohol derivatives to catalyse the asymmetric transfer hydrogenation of prochiral ketones with high reaction rates and moderate to good selectivities.[8]

It has been shown in the literature that amine and diamine-based ligands can be used for various asymmetric catalytic reactions.[9–13] Noyori et al. reported a variety of simple amino alcohols and diamines with a ruthenium precursor, an *i*-PrOH source and KOH as a co-catalyst for the reduction of acetophenone (see Fig. 1).[14,15] It was noted that a two carbon bridge between the donors formed the ideal chelator, and that unlike the amino alcohols, the diamines required one of the amines to be functionalised with an electron-withdrawing group. Inherently the *p*-toluene sulfonyl (tosyl) proved effective, which in turn spawned the (1*S*,2*S*)-*N*-(*p*-toluenesulfony1)-1,2-diphenylethylenediamin (Ts-DPEN) **1**.[15]



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Since this discovery there has been a surge of interest into asymmetric transfer hydrogenation, with the development of many successful catalysts.[16–20] Other studies have attempted to optimise the performance of these catalysts, by varying sterics, electronics and the solubility properties.[21,22] Development of the triethylamine: formic acid azeotrope (TEAF) and more recently formate salts in aqueous media have also broadened the scope for activity and selectivity.[23,20] The aqueous systems show promise and in many cases enhanced overall performance have been observed in the presence of water. A rigorous screening of these variables is necessary to discover the potential of any new ligand.

Herein we report a systematic study of novel diamine ligands possessing the tetrahydroisoquinoline as a rigid and tunable chiral backbone for pre-catalysts to the asymmetric reduction of acetophenone.

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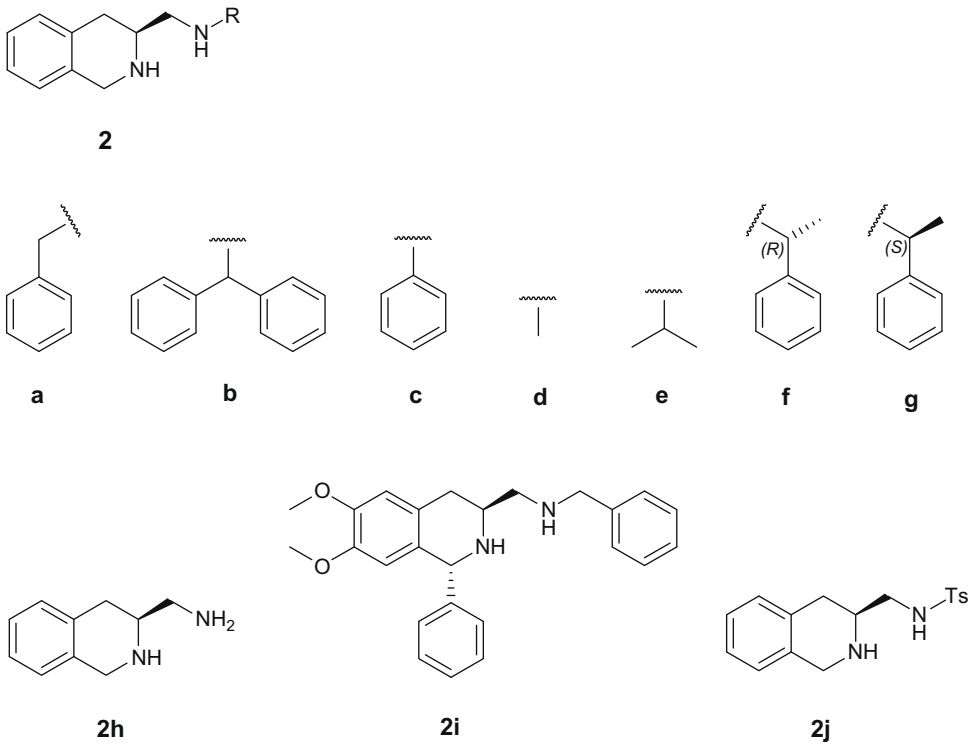


Figure 1. Diamine ligands studied for activity in asymmetric transfer hydrogenation.

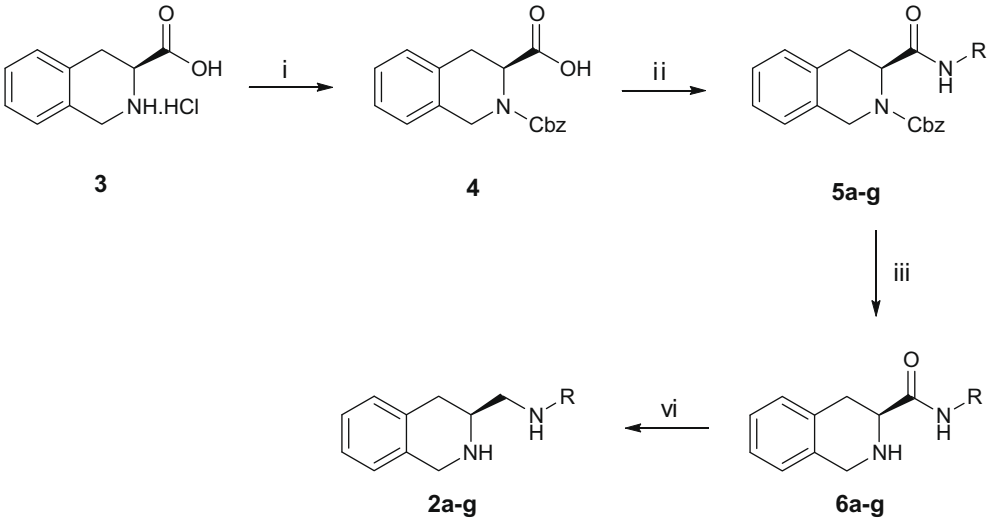
2. Results and discussion

2.1. Synthesis

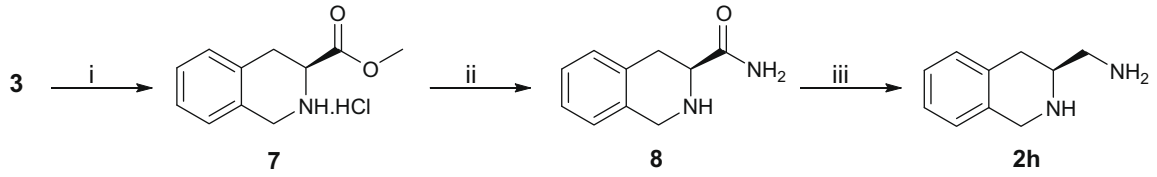
Ligands **2a–g** (Scheme 1) were synthesised from commercially available tetrahydroisoquinoline amino acid **3**. Benzyl carbamate (Cbz) protection of **3** allowed for subsequent coupling of the respective amines to yield **5a–g**. Thereafter, removal of the Cbz group with palladium on carbon (Pd/C) and one atmosphere of hydrogen (H_2) gas afforded the amides **6a–g**. The desired diamine products were obtained by lithium aluminium hydride ($LiAlH_4$) reduction of **6a–g**.

Ligand **2i** (Scheme 2) was prepared as previously reported.[24,25] Esterification of **3** via an in situ reaction to form the acyl chloride with thionyl chloride followed by condensation with methanol gave the methyl ester hydrochloride salt **7**. Conversion to the amide **8** was achieved by the treatment of this salt with a large excess of 25% ammonium hydroxide with stirring for several hours followed by reduction of the amide with $LiAlH_4$ in refluxing THF afforded the desired ligand **2h**.

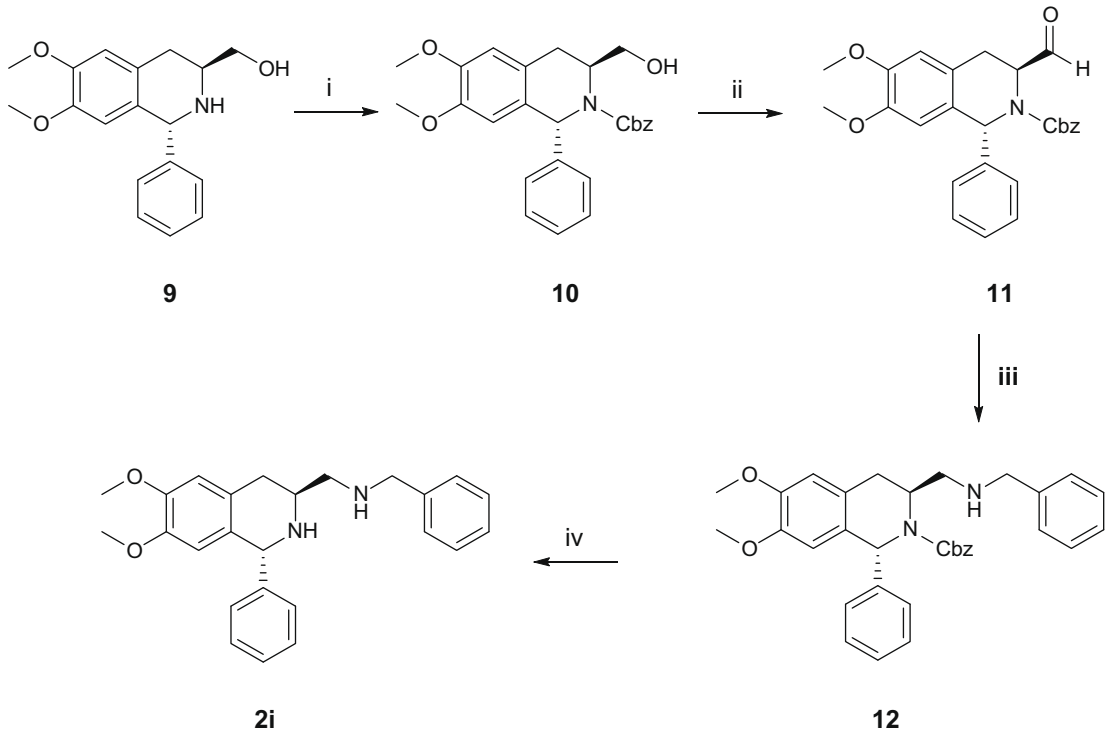
Ligand **2h** (Scheme 3) could not be prepared following the same approach as for **2a–g**, due to racemisation, which was observed under $LiAlH_4$ reduction conditions. Therefore an alternate procedure employing a milder reduction condition was sought.



Scheme 1. Synthetic route used to prepare **2a–g**. Reagents and conditions: (i) $KHCO_3$, dioxane, water, Cbz-Cl; (ii) EDC·HCl, HOBt, R-NH_2, DMAP, DMF; (iii) 10% wt. Pd/C, H_2, MeOH, THF; (iv) $LiAlH_4$, THF.



Scheme 2. Synthetic route used to prepare **2h**. Reagents and conditions: (i) $SOCl_2$, MeOH; (ii) 25% NH_4OH; (iii) $LiAlH_4$, THF.



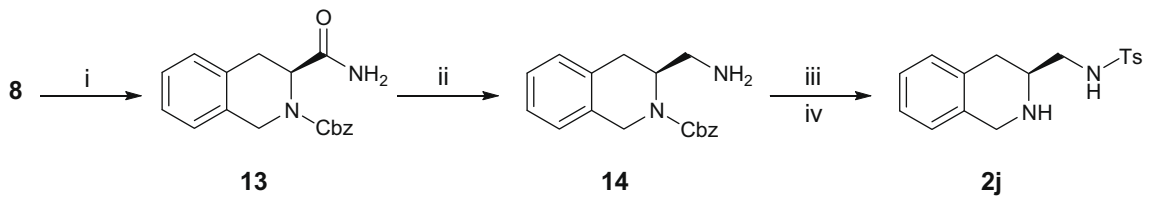
Scheme 3. Synthetic route used to prepare **2i**. Reagents and conditions: (i) $KHCO_3$, dioxane/water, Cbz-Cl; (ii) PCC, dry DCM; (iii) benzylamine, $NaCNBH_4$, MeOH/THF; (iv) 10% wt. Pd/C H_2 1 atm, MeOH/THF.

Cbz protection of the amino alcohol **9**[8] yielded **10** which was subsequently oxidised with pyridinium chlorochromate to obtain compound **11**. Reductive amination on **11** using benzyl amine and sodium cyanoborohydride afforded the desired product **12**. Selective deprotection of the *N*-Cbz group of **12** with Pd/C at one atm H_2 furnished **2i**.

Ligand **2j** (Scheme 4) was prepared from the amide **8**, which was Cbz protected to form **13**. Using $NaBH_4$ with acetic acid in dioxane,[26] the amide was reduced without cleavage of the Cbz group to yield **14**. Reaction of **14** with toluene sulfonyl with base followed by removal of Cbz with Pd/C at one atm H_2 rendered **2i**.

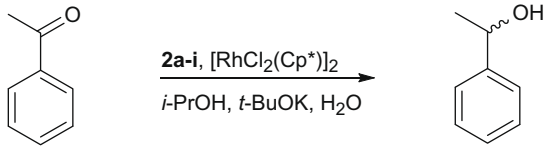
2.2. Structural modifications

Given the amines were designed to incorporate broad structural diversity to investigate the scope of tetrahydroisoquinoline-diamine ligands in asymmetric transfer hydrogenation, we proceeded to modify the backbone by changing the structural features of the substituent on the amine (see Fig. 1) and tested them for activity in asymmetric transfer hydrogenation of acetophenone (see Table 1). The groups were chosen to cover both steric and electronic character. Ligand **2a** was the first of the diamine derivatives to be prepared and tested for its catalytic activity in asymmetric transfer hydrogenation, producing reasonable results (81% conv., 70% ee,



Scheme 4. Synthetic route used to prepare **2j**. Reagents and conditions: (i) $KHCO_3$, dioxane/water, Cbz-Cl; (ii) $NaBH_4$, AcOH, dioxane, reflux; (iii) TsCl, DCM, TEA; (iv) 10% wt. Pd/C H_2 1 atm, MeOH/THF.

Table 1
Asymmetric transfer hydrogenation of acetophenone by ligand **2a**–**j** rhodium complexes



Entry	Ligand	Conv. (%)	ee (%)	Isomer
1	**2a**	81	70	*S*
2	**2b**	22	11	*S*
3	**2c**	—	—	—
4	**2d**	—	—	—
5	**2e**	67	71	*S*
6	**2f**	24	77	*R*
7	**2g**	5.5	51	*S*
8	**2h**	—	—	—
9	**2i**	—	—	—
10	**2j**	—	—	—

All reactions were carried out at 25 °C. In the case where the hydrogen source is HCO_2K the solvent used was water.
i-PrOH was used as the solvent when employed as the HS along with *t*-BuOK as the base. Testing was carried out using a S/C of 100.
[a]Measured by GC with chiral capillary column β-DEX™ 120.

entry 1). Derivatives **2b** and **2c** (entries 2 and 3) possessing a diphenyl and aniline groups, respectively, inherently make the nitrogen more acidic. Unfortunately **2b** demonstrated very poor reactivity and little selectivity (22% conv., 11% ee, entry 2) while **2c** showed no activity at all (entry 3). When the pK_a on the nitrogen was increased using derivatives **2d** (methyl) and **2e** (*iso*-propyl), **2d** also showed no activity (entry 4). However, **2e** was found to possess moderate reactivity with fair selectivity (67% conv., 71% ee, entry 5). It seemed apparent that the electronic effects of the substituent's on the nitrogen were not the issue, but rather a steric argument dictating the selectivity. To examine further, chiral amines possessing a benzyl and methyl group were employed. This would offer similar influence on the pK_a as that for the benzyl on **2a** and less steric crowding than the diphenyl group on **2b**. Promising results were obtained with the (*R*)-benzyl-methyl amine derivative **2f** (24% conv., 77% ee, entry 6) yielding the (*R*)-1-phenylethanol enantiomers, which then led us to try the (*S*) isomer. The (*S*)-benzyl-methyl amine derivative **2g** showed lower reactivity and selectivity than the (*R*) enatiomer (5.5% conv., 51% ee, entry 7), but had preference for the expected (*S*)-1-phenylethanol enantiomer. Compound **2h** was prepared to determine whether the primary amine could also be used as a ligand in asymmetric transfer hydrogenation reaction, but it was found to have no activity in this reaction (entry 8). Out of curiosity, and given our recent success with the amino alcohol derivative of the C1-substituted tetrahydroisoquinoline ligand **2i**, was prepared (Scheme 3). Disappointingly, this auxiliary showed no activity (entry 9). Based on the significant increase in rate an often selectivity observed upon tosylation of one of the amine donors we investigated **2j** for activity in asymmetric transfer hydrogenation of acetophenone. However the ligand was found to have no activity at all (entry 10).

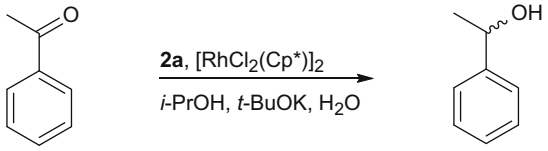
2.3. Effect of the water

As stated earlier it has been demonstrated in the literature that water has the potential to influence performance of a catalyst in asymmetric transfer hydrogenation reactions.[20,21,27–32] This prompted us to investigate how much water was necessary to obtain the highest enantiomeric excess using ligand **2a** (Table 2). Adding 1 equiv of water to the metal complex was found to increase activity (27%, entry 1). Progressively increasing the amount of water from 2 to 400 equiv showed the selectivity to improve even more (entries 2–6). Thereafter raising the amount of water to a 1000 and then further to 3000 equiv a maximum was reached with an optimum of 70% enantioselectivity (entries 7–9). Extending the amount to 50:50 *i*-PrOH/water (many times excess) destroyed the reactivity completely (entry 10). Since reactivity dropped significantly at 3000, 1500 equiv was taken as the best compromise between reactivity and selectivity for subsequent testing.

2.4. Metal and donor study

Compound **2a** was chosen as a representative of the di-secondary amine ligands for this study, the results of which are shown in Table 3. Entries 1 and 4 show that very little activity is observed

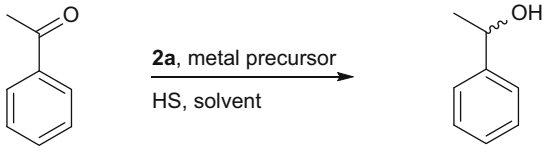
Table 2
Results of the effect in varying the water content on of acetophenone by rhodium complexes of ligands **2a**–**h**



Entry	Molar equiv H_2O to rhodium	Conv. (%)	ee (%)
1	1	64	27
2	2	81	43
3	10	88	45
4	100	92	54
5	200	88	62
6	400	92	66
7	1000	94	68
8	1500	81	70
9	3000	61	70
10[b]	50:50	—	—

All reactions were carried out at 25 °C. In the case where the hydrogen source is HCO_2K the solvent used was water.
i-PrOH was used as the solvent when employed as the hydrogen source along with *t*-BuOK as the base. Testing was carried out using a S/C of 100.
[a]Measured by GC with chiral capillary column β-DEX™ 120.
[b] A 50/50 mixture of water and *i*-PrOH was used.

Table 3
Asymmetric transfer hydrogenation of acetophenone by different hydrogen sources and ligand **2a** metal complexes



Entry	Metal complex	Hydrogen source	Conv.[a] (%)	ee[a] (%)	Isomer
1	$[Ru(p\text{-cymene})Cl_2]_2$	KCO_2H	2	10	*R*
2	$[IrCl_2(Cp^*)]_2$	KCO_2H	10	25	*R*
3	$[RhCl_2(Cp^*)]_2$	KCO_2H	43	50	*R*
4	$[Ru(p\text{-cymene})Cl_2]_2$	*i*-PrOH	—	—	—
5	$[IrCl_2(Cp^*)]_2$	*i*-PrOH	40	—	—
6	$[RhCl_2(Cp^*)]_2$	*i*-PrOH	90	—	*S*
7	$[RhCl_2(Cp^*)]_2$	TEAF	—	—	—
8	$RhPPh_3COH$	*i*-PrOH	10	48	*R*

All reactions were carried out at 25 °C. In the case where the hydrogen source is HCO_2K the solvent used was water.
i-PrOH was used as the solvent when employed as the hydrogen source along with *t*-BuOK as the base. Testing was carried out using a S/C of 100.
[a] Measured by GC with chiral capillary column β-DEX™ 120.

when the asymmetric transfer hydrogenation reaction is carried out in water using potassium formate on the hydrogen source (2%, entry 1), and no activity with the *i*-PrOH (entry 4) when [Ru(*p*-cymeme)Cl_2]$_2$ is employed as the metal precursor. The same held for the formate hydrogen source with [$IrCl_2$(Cp*)]$_2$ (10%, entry 2). However a marked increase in activity was observed when the hydrogen source was changed to *i*-PrOH (40%, entry 5). Implementing a [$RhCl_2$(Cp*)]$_2$ precursor rendered significant activity with the formate (43%, entry 3), but the greatest catalytic activity was seen when the *i*-PrOH was used instead (90%, entry 6). The results for the [$RhCl_2$(Cp*)]$_2$ prompted us to investigate whether using the TEAF hydrogen source could increase activity. Unfortunately this proved unsuccessful (entry 7). Changing from the [$RhCl_2$(Cp*)]$_2$ (arene) to the $RhPPh_3COH$ (hydride) did not improve on the [$RhCl_2$(Cp*)]$_2$ system (10%, entry 8). Therefore optimised conditions were found to be with the use of [$RhCl_2$(Cp*)]$_2$ precursor and *i*-PrOH.

3. Conclusions

We have prepared a series of diamine ligands possessing the tetrahydroisoquinoline backbone and tested them for activity in the asymmetric transfer hydrogenation of acetophenone. The amine donors were all secondary in nature, ligands **2a–g** and **i**, with the exception of **2h** which possessed both a primary and secondary amine. It was found that when using [$RhCl_2$(Cp*)]$_2$ in conjunction with an *i*-PrOH, the best conversion achieved was 92% in 1 h. Furthermore, it was determined that no selectivity was obtained under anhydrous conditions, and that an optimum of 1500 equiv of water to rhodium gave the best selectivity of 77% ee for ligand **2f**. However with regards to the best overall catalytic performance, ligands **2a** and **2d** bearing the benzyl and isopropyl substituents, respectively, shared both good reactivity and selectivity for the asymmetric reduction of acetophenone. We believe that these ligands could be successfully employed as catalysts for other asymmetric transformations.

4. Experimental

4.1. General

All reagents and solvents were purchased from Aldrich, Merck and Fluka unless stated otherwise. All NMR analysis was carried out on either a Bruker AVANCE III 400 or 600 MHz instrument. Chemical shifts are expressed in parts per million (ppm) downfield from a TMS signal, and coupling constants are reported in Hertz. NMR spectra were obtained at room temperature, except if stated differently. Thin layer chromatography (TLC) was performed using Merck Kiesel gel 60 F254. Crude compounds were purified via column chromatography using Silica Gel (60–200 mesh except if stated otherwise). All solvents were dried using standard procedures for example, Vogel.[26] All IR spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were measured on a Perkin Elmer Polarimeter. All melting points are uncorrected. High resolution mass spectrometric data were obtained using a Bruker micrOTOF-Q II instrument, using a sample concentration of approximately 1 ppm. All gas chromatography was carried out on an Agilent 6820.

4.2. General procedure for transfer hydrogenation of acetophenone

4.2.1. *i*-PrOH hydrogen source

To an oven-dried Schlenk tube was added metal precursor (3.0 mg) followed by the ligand (4 mol equiv) and freshly distilled *i*-PrOH (5 mL) under a dry argon atmosphere. The mixture was heated to 60 °C and stirred for 20 min, after which the solution was allowed to cool to ambient temperature. The desired amount of acetophenone was then added (S/C = 100) followed by freshly prepared 0.1 M *t*-BuOK (2 equiv to metal) in *i*-PrOH. To monitor the reactions, small aliquots were drawn, diluted with *i*-PrOH and then run through a small plug of silica to remove any catalyst. The eluted sample was then injected into the GC.

4.2.2. *i*-PrOH hydrogen source in water

The reaction was carried out as reported above with the exception that the water was added after complexation and just before the addition of acetophenone. Monitoring of the progress of the reaction remained the same.

4.2.3. Formate hydrogen source

The metal precursor and ligand were complexed as describe above. Water was then added (2 mL), and the reaction mixture heated to 40 °C and stirred for 30 min. The mixture was then cooled and the acetophenone (S/C = 100) was added followed by the potassium formate. To monitor the reactions, small aliquots were drawn and extracted with hexane, which were then used for GC analysis.

4.2.4. TEAF hydrogen source

The TEAF was prepared as reported in the literature.[23] The metal precursor and ligand were stirred in DCM for 30 min, followed by the addition of acetophenone (S/C = 100) and TEAF (0.9 ml). The reaction was monitored similar to that when using the *i*-PrOH hydrogen source.

4.2.5. (*S*)-2-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid 4

To a suspension of **3** (5 g, 19.45 mmol) in dioxane (80 ml) and water (40 ml) was added $NaHCO_3$ (77.80 mmol) at 0 °C following Schotten–Baumann conditions. After addition of the base, Cbz-Cl was added and the reaction mixture was allowed to stir at 0 °C for 1.5 h and then at room temperature for a further 1.5 h. The product was extracted twice with ethyl acetate, the organic layer dried with anhydrous magnesium sulfate and concentrated to dryness affording **4** (5.56 g, 92% yield) that was carried forward without any purification.

4.3. General procedure for the preparation of 5a–g

(*S*)-2-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **4** (1.5 g, 4.8 mmol) was dissolved in DMF (15 mL) followed by addition of EDC·HCl (1.1 g, 5.8 mmol), HOBt (0.81 g, 5.3 mmol), a catalytic amount of DMAP and the appropriate amines (5.3 mmol). The reaction mixture was then stirred at room temperature until no more starting material could be detected by TLC analysis (approximately 1 h). The reaction mixture was poured into 30 volumes of chilled water; the mixture was then extracted twice with ethyl acetate. The extracts were combined, washed with 10% HCl (aq) to remove latent EDC urea, dried over anhydrous magnesium sulfate and then concentrated to dryness affording the crude product which was purified by column chromatography.

4.4. General procedure for the preparation of 6a–g

The precursors **5a–g** in 50/50 MeOH/THF with half an equivalent by mass of 10% palladium on carbon Pd/C was stirred under hydrogen (approximately 1 atm) for 2 h. The reaction was limited for this period as additional side products were observed. The crude product was obtained by filtering off the Pd/C through a plug of Celite, the filtrate was then concentrated to dryness and purified by column chromatography.

4.5. General procedure for the preparation of 2a–g

The amine amides **6a–g** were reduced with 4 equiv of $LiAlH_4$ in refluxing dry THF under a nitrogen atmosphere for 3–4 days or

alternatively the reductions could be carried out at 85 °C in a microwave reactor for 4–5 h. The reactions were quenched by slow addition of saturated sodium sulfate solution and the white aluminium sulfate precipitate was then filtered off. The filtrate was washed with water, dried over anhydrous magnesium sulfate and concentrated to dryness affording the crude product which was purified by column chromatography.

4.5.1. Synthesis of (*S*)-benzyl 3-(benzylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5a

The resultant product from reaction with benzyl amine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~0.45) to afford the benzyl-substituted tetrahydroisoquinoline derivative **5a** (1.44 g, 75%) as a white powder. $[\alpha]_D^{20} = -8.3$ (*c* 0.12, CH_2Cl_2). IR ν_{max}: 695, 729, 1118, 1216, 1302, 1322, 1400, 1650, 1680, 3029 and 3331 cm^{-1}. Melting point 105–107 °C. HRMS calculated for $C_{25}H_{24}N_2O_3$ (M+H$^+$) = 401.1867 *m*/*z*, found 401.1860 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^{1}H NMR (400 MHz, DMSO) δ = 8.42 (m, 1H), 7.51–7.07 (m, 12H), 6.91–6.76 (m, 2H), 5.27–5.07 (m, 2H), 4.87–4.42 (m, 3H), 4.28–4.05 (m, 2H), 3.26–3.06 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ = 170.6, 139.2–126.1, 66.4, 54.5, 44.7, 41.8 and 31.8.

4.5.2. Synthesis of (*S*)-*N*-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6a

Removal of Cbz and purification by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:3:10, R_f ~0.4) gave the benzyl amide tetrahydroisoquinoline **6a** (85%) as a white solid. $[\alpha]_D^{20} = -54.8$ (*c* 0.42, CH_2Cl_2). IR ν_{max}: 435, 467, 613, 694, 736, 797, 1029, 1222, 1453, 1546, 1643, 2925, 3033, 3057, 3279 and 3330 cm^{-1}. Melting point 83–85 °C. HRMS calculated for $C_{17}H_{18}N_2O$ (M+H$^+$) = 267.1492 *m*/*z*, found 267.1504 *m*/*z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (s, 1H), 7.42–7.12 (m, 9H), 4.48 (d, *J* = 5.6 Hz, 2H), 4.05–3.91 (d, *J* = 6.52 Hz, 2H), 3.61 (dd, *J* = 10.3 and 5.2 Hz, 1H), 3.28 (dd, *J* = 16.4 and 5.2 Hz, 1H), 2.88 (dd, *J* = 16.4 and 10.3 Hz, 1H), The NH proton was not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.0, 138.3, 135.9, 134.4, 129.2, 128.7, 127.7, 127.4, 126.6, 126.2, 125.5, 56.5, 47.5, 43.1 and 31.0.

4.5.3. Synthesis of (*S*)-*N*-benzyl-1-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine 2a

After reduction of **6a**, the crude compound was purified by column chromatography (DCM/MeOH/Et_2O/10% NH_3 in $CHCl_3$ = 66:4:20:10, R_f ~0.4) to afford the *N*-benzyl amine derivative **2a** (31%) as an off white/yellow solid. $[\alpha]_D^{20} = -70.9$ (*c* 0.43, CH_2Cl_2). IR ν_{max}: 695, 729, 1118, 1216, 1302, 1322, 1400, 1650, 1680, 3029 and 3331 cm^{-1}. Melting point 85–87 °C. HRMS calculated for $C_{17}H_{20}N_2$ (M+H$^+$) = 253.1699 *m*/*z*, found 253.1708 *m*/*z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.30 (m, 3H), 7.28–7.23 (m, 2H), 7.16–6.99 (m, 4H), 4.04 (s, 2H), 3.84 (d, *J* = 2.8 Hz, 2H), 3.05–2.96 (m, 1H), 2.86 (dd, *J* = 11.9 and 3.8 Hz, 1H), 2.73 (dd, *J* = 16.3 and 4.0 Hz, 1H), 2.64 (dd, *J* = 11.9 and 8.9 Hz, 1H), 2.59–2.51 (m, 1H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.3, 135.8, 134.4, 129.2, 128.4, 128.1, 127.0, 126.1, 126.0, 125.7, 54.4, 54.1, 53.4, 48.2 and 33.3.

4.5.4. Synthesis of (*S*)-benzyl 3-(benzhydrylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5b

The resultant product from the reaction with diphenylmethanime was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~0.4) to afford the diphenyl-substituted tetrahydroisoquinoline derivative **5b** (1.62 g, 71%) light yellow oil. $[\alpha]_D^{20} = -11.4$ (*c* 0.36, CH_2Cl_2). IR ν_{max}: 528, 546, 604, 616, 639, 695, 738, 909, 1001, 1028, 1094, 1120, 1215, 1303, 1346, 1403, 1453, 1494, 1658, 1696, 2851, 2925, 3029 and 3300 cm^{-1}. HRMS calculated for $C_{31}H_{28}N_2O_3$ (M+H$^+$) = 477.2137 *m*/*z*, found 477.2155 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^{1}H NMR (400 MHz, DMSO) δ = 8.95–8.69 (m, 1H), 7.64–6.88 (m, 19H), 6.11–5.85 (m, 1H), 5.30–4.37 (m, 5H), 3.02–3.27 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ = 170.2, 155.3–125.9, 86.6, 66.4, 54.8, 44.8 and 32.1.

4.5.5. Synthesis of (*S*)-*N*-benzhydryl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6b

Removal of Cbz and purification by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:3:10, R_f ~0.4) gave the diphenylmethamide tetrahydroisoquinoline **6b** (80%) as a light brown solid. $[\alpha]_D^{20} = -105.7$ (*c* 0.35 g/100 mL, CH_2Cl_2). IR ν_{max}: 402, 406, 619, 683, 734, 1159, 1219, 1365, 1451, 1493, 1544, 1640, 2929, 2973 and 3292 cm^{-1}. HRMS calculated for $C_{23}H_{22}N_2O$ (M+H$^+$) = 343.1795 *m*/*z*, found 343.1805 *m*/*z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97–8.10 (m, 1H), 7.42–6.95 (m, 14H), 7.09–7.02 (m, 1H), 4.08–3.95 (m, 2H), 3.58–3.40 (m, 1H), 3.31–3.19 (m, 1H), 2.99–2.87 (m, 1H), the NH proton of the amine was not observed in the spectra. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.0, 141.6, 141.5, 129.1–125.3, 56.4, 56.2, 47.1 and 30.3.

4.5.6. Synthesis of (*S*)-1,1-diphenyl-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)methanamine 2b

After the reduction of **6b**, the crude compound was purified by column chromatography (MeOH/Et_2O = 5:95, R_f ~0.6) to afford the *N*-diphenylmethanamine amine derivative **2b** (21%) as a yellow solid. $[\alpha]_D^{20} = -55.8$ (*c* 0.52, CH_2Cl_2). IR ν_{max}: 430, 696, 706, 743, 800, 1027, 1429, 1447, 1490, 1580, 1595, 2780, 2911, 3289, and 3324 cm^{-1}. Melting point 89–91 °C. HRMS calculated for $C_{23}H_{24}N_2$ (M+H$^+$) = 329.2012 *m*/*z*, found 329.2004 *m*/*z*. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.43–6.98 (m, 14H), 4.87 (s, 1H), 4.06 (s, 2H), 3.00 (m, 1H), 2.83 (dd, *J* = 11.8 and 3.8 Hz, 1H), 2.73 (dd, *J* = 16.2 and 3.9 Hz, 1H), 2.64 (dd, *J* = 11.8 and 8.7 Hz, 1H), 2.56 (dd, *J* = 16.2 and 10.8 Hz, 1H), the two NH protons were not observed. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 144.2, 143.9, 135.9, 134.5, 129.2, 128.5, 127.3, 127.3, 127.04, 127.02, 126.1, 126.0, 125.7, 67.7, 53.7, 53.6, 48.3 and 33.4.

4.5.7. Synthesis of (*S*)-benzyl 3-(phenylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5c

The resultant product from reaction with aniline was purified by column chromatography purified (EtOAc/Hex = 40:60, R_f ~0.5) to afford the aniline-substituted tetrahydroisoquinoline derivative **5c** (1.54 g, 83%) light yellow oil. $[\alpha]_D^{20} = -38.1$ (*c* 0.42, CH_2Cl_2). IR ν_{max}: 487, 693, 736, 749, 960, 1099, 1127, 1184, 1413, 1546, 1665, 1701, 3027 and 3301 cm^{-1}. Melting point 137–139 °C. HRMS calculated for $C_{24}H_{22}N_2O_3$ (M+H$^+$) = 387.1703 *m*/*z*, found 387.1689 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^{1}H NMR (400 MHz, DMSO) δ = 10.04 (d, *J* = 5.1 Hz, 1H), 7.62–6.85 (m, 14H), 5.22–5.02 (m, 3H), 4.90–4.51 (m, 2H), 3.33–3.02 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ = 169.9, 155.3–119.2, 66.5, 54.9, 44.8 and 31.8.

4.5.8. Synthesis of (*S*)-*N*-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6c

Removal of Cbz group the aniline amide tetrahydroisoquinoline **6c** (88%) formed as a white solid, which required no further purification. $[\alpha]_D^{20} = -144.7$ (*c* 0.38, CH_2Cl_2). IR ν_{max}: 440, 551, 695, 736, 1060, 1190, 1258, 1364, 1408, 1496, 1597, 1697, 2891, 2927, 2968, 3045 and 3299 cm^{-1}. Melting point 183–192 °C. HRMS calculated for $C_{16}H_{16}N_2O$ (M+H$^+$) = 253.1317 *m*/*z*, found 253.1335 *m*/*z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.39 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.01–7.25 (m, 5H), 4.05 (d, *J* = 5.4 Hz, 2H), 3.73 (dd, *J* = 10.3 and 5.3 Hz, 1H), 3.37 (dd, *J* = 16.4 and 5.2 Hz, 1H), 2.95 (dd, *J* = 16.3 and 10.3 Hz, 1H), the NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.1, 137.7,

135.8, 134.3, 129.2, 129.1, 126.9, 126.4, 125.5, 124.1, 119.4, 56.7, 47.3 and 30.5.

4.5.9. Synthesis of (*S*)-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl) methyl) aniline 2c

After reduction of **6c**, the crude compound was purified by column chromatography (100% diethyl ether, R_f ~0.5), yielding a white solid **2c** (57%). $[\alpha]_D^{20} = -64.3$ (*c* 0.14, CH_2Cl_2). IR ν_{max}: 435, 488, 513, 585, 690, 743, 805, 1258, 1346, 1494, 1600, 2792, 2929, 3218 and 3301 cm^{-1}. Melting point 90–92 °C. HRMS calculated for $C_{16}H_{18}N_2$ ($M+H^+$) = 239.1543 *m*/*z*, found 239.1543 *m*/*z*. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.23–6.99 (m, 6H), 6.76–6.62 (m, 3H), 4.07 (br s, 2H), 3.36 (d, *J* = 12.1 Hz, 1H), 3.26–3.17 (m, 1H), 3.14–3.06 (m, 1H), 2.85 (dd, *J* = 16.3 and 4.1 Hz, 1H), 2.66 (dd, *J* = 16.3 and 10.5 Hz, 1H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.4, 135.7, 134.0, 129.3, 129.3, 126.2, 126.0, 125.9, 117.5, 113.0, 53.0, 49.2, 48.1 and 33.1.

4.5.10. Synthesis of (*S*)-benzyl 3-(methylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5d

The resultant product from the reaction with methyl amine was purified by column chromatography purified by column chromatography (EtOAc/Hex = 50:50, R_f ~0.4) to afford the methyl-substituted tetrahydroisoquinoline derivative **5d** (1.06 g, 68%) light yellow oil. $[\alpha]_D^{20} = -6.4$ (*c* 0.62, CH_2Cl_2). IR ν_{max}: 495, 616, 696, 742, 908, 1011, 1120, 1215, 1302, 1323, 1406, 1536, 1655, 1695, 2939, 3031, 3065 and 3314 cm^{-1}. HRMS calculated for $C_{19}H_{20}N_2O_3$ ($M+H^+$) = 325.1547 *m*/*z*, found 325.1546 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^1H NMR (400 MHz, DMSO) δ = 7.85 (m, 1H), 7.58–7.08 (m, 9H), 5.36–4.98 (m, 2H), 4.86–4.28 (m, 2H), 3.22–2.89 (m, 2H), 2.60–2.52 (m, 1H), 2.47 (d, 4.66 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ = 170.8, 136.7–125.9, 66.4, 54.1, 44.4, 31.3 and 25.6.

4.5.11. Synthesis of (*S*)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6d

Removal of Cbz and purification by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:3:10, R_f ~0.4) afforded methyl amide tetrahydroisoquinoline **6d** (77%) as a white solid. $[\alpha]_D^{20} = -222.5$ (*c* 0.20, CH_2Cl_2). IR ν_{max}: 399, 435, 515, 609, 674, 738, 797, 963, 1129, 1225, 1413, 1562, 1643, 2835, 2877, 2940 and 3302 cm^{-1}. Melting point 84–86 °C. HRMS calculated for $C_{11}H_{14}N_2O$ ($M+H^+$) = 191.1179 *m*/*z*, found 191.1183 *m*/*z*. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.24 (br s, 1H), 7.19–7.11 (m, 3H), 7.03 (m, 1H), 3.99 (d, *J* = 3.6 Hz, 2H), 3.52 (dd, *J* = 10.8 and 5.1 Hz, 1H), 3.24 (dd, *J* = 16.5 and 5.1 Hz, 1H), 2.85 (d, *J* = 5.0 Hz, 3H), 2.80 (dd, *J* = 16.5 and 10.8 Hz, 1H), the NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.7, 135.9, 134.4, 129.2, 126.6, 126.2, 125.5, 56.6, 47.6, 31.0 and 25.8.

4.5.12. Synthesis of (*S*)-*N*-methyl-1-(1,2,3,4-tetrahydroisoquinolin- 3-yl)methanamine 2d

After reduction the crude product **2d** was purified by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:3:10, R_f ~0.4). However this purification was not sufficient, therefore further refinement was achieved by precipitating the compound out as the dihydrochloride salt using a solution of HCl gas bubbled in ether, which generated a precipitate when added to the compound in DCM. The precipitated salt was filtered and washed with a 90:10 mixture of ether/DCM affording **2d** (15%) a light brown solid. $[\alpha]_D^{20} = -1.3$ (*c* 0.1, MeOH). IR ν_{max}: 428, 448, 763, 1025, 1451, 2598, 2717, 2941 and 3395 cm^{-1}. HRMS calculated for $C_{11}H_{16}N_2$ ($M+H^+$) = 177.1386 *m*/*z*, found 177.1389 *m*/*z*. ^1H NMR (400 MHz, MeOD) δ = 7.13–7.26 (m, 4H), 4.42 (s, 2H), 3.98–3.89 (m, 1H), 3.46 (dd, *J* = 13.6 and 6.5 Hz, 1H), 3.37 (dd, *J* = 13.7 and 5.6 Hz, 1H), 3.24 (d, *J* = 4.7 Hz, 1H), 3.03 (dd, *J* = 17.1 and 11.0 Hz, 1H) and 2.76 (s, 3H), the two NH protons were not observed in the spectra. ^{13}C NMR (101 MHz, MeOD) δ = 130.9, 130.2, 129.5, 128.7, 128.4, 127.7, 51.8, 51.2, 46.0, 34.4, 30.4.

4.5.13. Synthesis of (*S*)-benzyl 3-(isopropylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5e

The resultant product from the reaction with isopropyl amine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~0.45) to afford the **5e** (1.43 g, 85%) as a beige powder. $[\alpha]_D^{20} = -3.5$ (*c* 0.58, THF). IR ν_{max}: 695, 733, 749, 1124, 1212, 1311, 1408, 1546, 1644, 1701, 2970 and 3299 cm^{-1}. Melting point 95–97 °C. HRMS calculated for $C_{21}H_{24}N_2O_3$ ($M+H^+$) = 353.1860 *m*/*z*, found 353.1860 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^1H NMR (400 MHz, DMSO) δ = 7.69 (m, 1H), 7.53–7.01 (m, 9H), 5.33–4.84 (m, 2H), 4.78–4.35 (m, 3H), 3.72 (m, 1H), 3.21–2.81 (m, 2H), 0.99–0.82 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ = 169.6, 155.2–125.8, 67.0, 55.2, 44.6, 40.5, 31.8 and 22.1.

4.5.14. Synthesis of (*S*)-*N*-isopropyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6e

Removal of Cbz and purification by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:3:10, R_f ~0.5) afforded the isopropyl amide tetrahydroisoquinoline **6e** (92%) as a white solid. $[\alpha]_D^{20} = -105.7$ (*c* 0.35, CH_2Cl_2). IR ν_{max}: 402, 406, 619, 683, 734, 1159, 1219, 1365, 1451, 1493, 1544, 1640, 2929, 2973 and 3292 cm^{-1}. Melting point 87–89 °C. HRMS calculated for $C_{13}H_{18}N_2O$ ($M+H^+$) = 219.1492 *m*/*z*, found 219.1501 *m*/*z*. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.12–7.19 (m, 3H), 7.08–6.93 (m, 2H), 4.10 (m, 1H), 4.00 (d, *J* = 4.1 Hz, 2H), 3.50 (dd, *J* = 10.7 and 5.0 Hz, 1H), 3.24 (dd, *J* = 16.5 and 5.0 Hz, 1H), 2.80 (dd, *J* = 16.5 and 10.7 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), the NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 135.8, 134.4, 129.2, 126.6, 126.1, 125.5, 56.6, 47.7, 40.8, 31.1, 22.8, 22.7.

4.5.15. Synthesis of (*S*)-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)propan-2-amine 2e

After reduction of **6e**, the crude compound was purified by column chromatography (EtOAc/MeOH = 95:5, R_f ~0.5), yielding an off white solid **2e** (46%). $[\alpha]_D^{20} = -8.3$ (*c* 0.12, CH_2Cl_2). IR ν_{max}: 695, 729, 1118, 1216, 1302, 1322, 1400, 1650, 1680, 3029 and 3331 cm^{-1}. Melting point 39–41 °C. HRMS calculated for $C_{13}H_{20}N_2$ ($M+H^+$) = 205.1699 *m*/*z*, found 205.1708 *m*/*z*. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.15–6.99 (m, 4H), 4.05 (s, 2H), 3.02–2.90 (m, 1H), 2.71–2.87 (m, 3H), 2.60–2.52 (m, 2H), 1.09 (overlapping-d, *J* = 6.5 Hz, 6H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.0, 134.5, 129.2, 126.0, 126.0, 25.7, 53.9, 52.9, 49.0, 48.3, 33.5, 23.1 and 23.0.

4.5.16. Synthesis of (*S*)-benzyl 3-((*R*)-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5f

The resultant product from the reaction with (*R*)-1-phenylethanamine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~0.4) to afford the (*R*)-1-phenylethanamine-substituted tetrahydroisoquinoline derivative **5f** (1.55 g, 78%) as a light yellow oil. $[\alpha]_D^{20} = +10.7$ (*c* 1.03, CH_2Cl_2). IR ν_{max}: 491, 599, 696, 740, 905, 1001, 1093, 1119, 1214, 1302, 1322, 1347, 1400, 1448, 1522, 1638, 1697, 2932, 3029, 3062 and 3315 cm^{-1}. HRMS calculated for $C_{26}H_{26}N_2O_3$ ($M+H^+$) = 415.2016 *m*/*z*, found 415.1998 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^1H NMR = (400 MHz, DMSO) δ = 8.24 (m, 1H), 7.53–6.91 (m, 14H), 5.32–4.96 (m, 2H), 4.93–4.41 (m, 4H), 3.20–3.02 (m, 2H), 1.25 (d, *J* = 7.07 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ = 170.1, 144.1–125.6, 66.4, 54.4, 47.5, 44.7, 32.0 and 22.0.

4.5.17. Synthesis of (*S*)-*N*-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6f

Removal of Cbz and purification by column chromatography (Et_2O/Acetone = 80:20, R_f ~0.5) gave the (*R*)-1-phenylethanamide

tetrahydroisoquinoline **6f** (72%) as a white solid. $[\alpha]_D^{20} = -33.82$ (*c* 0.34 g/100 mL, CH_2Cl_2). IR ν_{max}: 430, 583, 617, 695, 733, 748, 790, 803, 1180, 1221, 1446, 1492, 1544, 1643, 2838, 2926 and 3284 cm^{-1}. Melting point 119–121 °C. HRMS calculated for $C_{18}H_{20}N_2O$ ($M+H^+$) = 281.1648 *m*/*z*, found 281.1645 *m*/*z*. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 8.0 Hz, 1H), 7.34–7.27 (m, 2H), 7.26–7.20 (m, 3H), 7.20–7.12 (m, 3H), 7.04 (m, 1H), 5.14 (m, 1H), 3.99 (d, *J* = 11.82 Hz, 2H), 3.59 (dd, *J* = 10.2 and 5.2 Hz, 1H), 3.23 (dd, *J* = 16.4 and 5.2 Hz, 1H), 2.82 (dd, *J* = 16.4 and 10.2 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), the NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.2, 143.3, 135.9, 134.4, 129.2, 128.6, 127.2, 126.6, 126.2, 126.0, 125.5, 56.4, 48.1, 47.6, 31.0 and 22.0.

4.5.18. Synthesis of (*R*)-1-phenyl-*N*-(((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)ethanamine 2f

After reduction of **6f**, the crude compound was purified by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:4:10, R_f ~0.5) to yield **2f** (30%), a light yellow oil. $[\alpha]_D^{20} = -43.55$ (*c* 0.93, CH_2Cl_2). IR ν_{max}: 431, 543, 695, 783, 1118, 1451, 1492, 2789, 2918, 2960, 3026 and 3240 cm^{-1}. HRMS calculated for $C_{18}H_{22}N_2$ ($M+H^+$) = 267.1856 *m*/*z*, found 267.1846 *m*/*z*. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.29 (m, 4H), 7.21 (m, 1H), 7.10–7.05 (m, 2H), 7.03–6.96 (m, 2H), 3.96 (d, *J* = 16.78 Hz, 2H), 3.74 (m, 1H), 2.82 (m, 1H), 2.66–2.61 (m, 2H), 2.51–2.42 (m, 2H), 1.37 (d, *J* = 6.7, 3H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.6, 135.9, 134.5, 129.2, 128.4, 126.9, 126.5, 126.0, 126.0, 125.6, 58.2, 53.7, 52.8, 48.3, 33.3 and 24.6.

4.5.19. Synthesis of (*S*)-benzyl 3-((*S*)-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5g

The resultant product from reaction with (*S*)-1-phenylethanamine was purified by column chromatography (EtOAc/Hex = 50:50, R_f ~0.4) to afford the (*S*)-1-phenylethanamine-substituted tetrahydroisoquinoline derivative **5g** (1.77 g, 89%) light yellow oil. $[\alpha]_D^{20} = -21.43$ (*c* 0.70, CH_2Cl_2). IR ν_{max}: 696, 738, 1059, 1119, 1213, 1303, 1329, 1407, 1449, 1495, 1534, 1656, 1697, 2972, 3029, 3062 and 3299 cm^{-1}. HRMS calculated for $C_{26}H_{26}N_2O_3$ ($M+H^+$) = 415.2016 *m*/*z*, found 415.2009 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^1H NMR (400 MHz, DMSO) δ = 8.29 (m, 1H), 7.49–6.91 (m, 14H), 5.22–4.99 (m, 2H), 4.86–4.41 (m, 4H), 3.23–2.97 (m, 2H), 1.30–1.13 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ = 169.9, 154.9–125.5, 66.3, 54.1, 47.5, 44.7, 31.8, 22.1.

4.5.20. Synthesis of (*S*)-*N*-((*S*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 6g

Removal of Cbz and purification by column chromatography (Et_2O/Acetone = 80:20, R_f ~0.5) afforded the (*S*)-1-phenylethanamide tetrahydroisoquinoline **6g** (76%) as a cream/beige solid. $[\alpha]_D^{20} = -100.7$ (*c* 0.36, CH_2Cl_2). IR ν_{max}: 428, 449, 525, 551, 609, 643, 697, 734, 750, 780, 1077, 1137, 1225, 1248, 1493, 1533, 1646, 2926, 2966 and 3333 cm^{-1}. Melting point 119–121 °C. HRMS calculated for $C_{18}H_{20}N_2O$ ($M+H^+$) = 281.1648 *m*/*z*, found 281.1644 *m*/*z*. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.48 (m, 1H), 7.38–7.11 (m, 8H), 7.04 (m, 1H), 5.13 (m, 1H), 3.99 (s, 2H), 3.53 (dd, *J* = 10.5 and 5.1 Hz, 1H), 3.23 (dd, *J* = 16.5 and 5.1 Hz, 1H), 2.85 (dd, *J* = 16.4 and 10.5 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 143.3, 135.7, 134.3, 129.2, 128.7, 128.5, 127.3, 126.6, 126.2, 125.5, 56.5, 48.3, 47.5, 31.0 and 22.0.

4.5.21. Synthesis of (*S*)-1-phenyl-*N*-(((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)ethanamine 2g

After reduction of **6g**, the crude compound was purified by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:4:10, R_f ~0.5) to yield **2g** (35%), a light yellow oil, which was then also stored as the dihydrochloride salt. $[\alpha]_D^{20} = -43.55$ (*c* 0.93, CH_2Cl_2). IR ν_{max}: 431, 543, 695, 783, 1118, 1451, 1492, 2789, 2918, 2960, 3026 and 3240 cm^{-1}. HRMS calculated for $C_{18}H_{22}N_2$ ($M+H^+$) = 267.1856 *m*/*z*, found 267.1846 *m*/*z*. ^1H NMR (400 MHz, MeOD) δ = 7.58–7.10 (m, 9H), 4.52–4.31 (m, 3H), 3.87 (m, 1H), 3.49 (m, 1H), 3.19–3.01 (m, 3H), 1.71 (d, *J* = 6.7, 3H). ^{13}C NMR (101 MHz, MeOD) δ = 137.1, 131.0, 130.6, 130.1, 129.4, 129.0, 128.7, 128.6, 128.3, 127.7, 61.3, 52.5, 48.5, 46.0, 30.6 and 19.5.

4.5.22. Synthesis of (1*R*,3*S*)-benzyl 3-(hydroxymethyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 10

Compound **9**[8] (1 g, 3.34 mmol) was protected with a Cbz group, under the conditions described in the general procedure to afford **10** (1.31 g, 91%), a light yellow oil after column chromatography (EtOAc/Hex = 60:40, R_f ~0.5). $[\alpha]_D^{20} = +40.38$ (*c* 0.26 g/100 mL, CH_2Cl_2). IR ν_{max}: 697, 1088, 1220, 1285, 1337, 1404, 1516, 1638, 1688, 2247, 3301 and 3553 cm^{-1}. HRMS calculated for $C_{26}H_{27}NO_5$ ($M+H^+$) = 434.1928 *m*/*z*, found 434.1962 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.43–6.92 (m, 10H), 6.78 (s, 1H), 6.66 (s, 1H), 6.01 (s, 1H), 5.38–4.87 (m, 2H), 4.47 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.63 (m, 1H), 3.34 (m, 1H), 3.02–2.89 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.4–125.3, 112.0, 110.7, 67.5, 64.4, 59.8, 56.1, 55.9, 54.7 and 29.4.

4.5.23. Synthesis of (1*R*,3*S*)-benzyl 3-formyl-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 11

Oxidation of **10** (0.8 g, 1.84 mmol) with PCC (3 equiv) and $MgSO_4$ (3 equiv) in dry DCM[34] gave **11** (0.45 g, 57%) as a yellow oil after treatment with wet diethylether and filtration through a small plug of silica to remove excess PCC and other metal species. $[\alpha]_D^{20} = +41.5$ (*c* 0.41, CH_2Cl_2). IR ν_{max}: 594, 697, 737, 994, 1028, 1092, 1221, 1264, 1339, 1397, 1513, 1692, 2838 and 2924 cm^{-1}. HRMS calculated for $C_{26}H_{25}NO_5$ ($M+Na^+$) = 454.1625 *m*/*z*, found 454.1606 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^1H NMR (400 MHz, $CDCl_3$) δ = 9.38 (m, 1H), 7.65–7.02 (m, 10H), 6.96–5.90 (m, 3H), 5.38–4.84 (m, 2H), 4.59 (m, 1H), 3.95–3.75 (m, 6H), 3.24–2.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.5–126.0, 110.7, 67.5, 60.6, 56.0, 55.9 and 29.7.

4.5.24. Synthesis of (1*R*,3*S*)-benzyl 3-((benzylamino)methyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 12

To a 50% mixture of dry THF in MeOH (6 ml) was added compound **11** (0.3 g, 0.69 mmol), followed by benzyl amine (0.23 g, 2 mmol) and the mixture was allowed to stir at room temperature for 3 h. The reaction mixture was then cooled to 0 °C with an ice bath, followed by slow addition of $NaCNBH_4$ (~0.3 g) and stirred for 30 min at 0 °C, and a further 30 min at rt. Water was added to the reaction and the resultant mixture was extracted three times with DCM. The crude product was purified by column chromatography (EtOAc/Hex = 70:30, R_f ~0.7) to afford **12** (0.21 g, 60%) yellow oil. $[\alpha]_D^{20} = +27.3$ (*c* 0.44, CH_2Cl_2). IR ν_{max}: 593, 697, 736, 999, 1028, 1092, 1219, 1338, 1397, 1452, 1514, 1689, 2931 and 3028 cm^{-1}. HRMS calculated for $C_{33}H_{34}N_2O_4$ ($M+H^+$) = 523.2591 *m*/*z*, found 523.2579 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.10 (m, 15H), 6.78 (s, 1H), 6.59 (s, 1H), 5.99 (s, 1H), 5.26–4.91 (m, 2H), 4.46 (m, 1H), 3.97–3.56 (m, 9H), 3.08–2.68 (m, 3H), NH proton of the amine was not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.3–126.0, 112.2, 110.8, 77.3–77.0, 76.6, 67.5, 60.3, 56.1–55.9, 53.5, 30.1 and 29.6.

4.5.25. Synthesis of *N*-benzyl-1-((1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine 2i

Compound **12** (0.1 g, 0.19 mmol) was treated with palladium on carbon as mentioned in the general procedure to remove the Cbz group. The reaction was monitored carefully to avoid removal of the benzyl group. Purification by column chromatography (DCM/MeOH/10% NH_3 in $CHCl_3$ = 87:3:10, R_f ~0.5) yielded **2i** (0.038 g, 52%) as a white oil. $[\alpha]_D^{20} = -26.8$ (*c* 0.41, CH_2Cl_2). IR ν_{max}: 573, 699, 753, 819, 1057, 1127, 1224, 1293, 1449, 1519, 1609, 2832, 2920, 2994 and 3060 cm^{-1}. HRMS calculated for $C_{25}H_{28}N_2O_2$ ($M+H^+$) = 389.2224 *m*/*z*, found 389.2224 *m*/*z*. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.13 (m, 10H), 6.63 (s, 1H), 6.41 (s, 1H), 5.10 (s, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 3.50 (s, 2H), 3.02 (m, 1H), 2.74–2.67 (m, 2H), 2.59–2.47 (m, 2H), the two NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.8, 147.1, 145.3, 140.3, 128.5, 128.33, 128.34, 128.32, 128.17, 128.10, 126.95, 126.86, 111.41, 111.09, 59.3, 55.89, 55.83, 53.87, 53.45, 46.2 and 33.1.

4.5.26. (*S*)-Benzyl 3-carbamoyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 13

Compound **8** (0.4 g, 2.27 mmol) was protected with a Cbz group, under the conditions described in the general procedure to afford **13** (0.63 g, 89%), a colourless oil after column chromatography (EtOAc/Hex = 20:80, R_f ~0.5). $[\alpha]_D^{20} = -2.2$ (*c* 0.59, CH_2Cl_2). IR ν_{max}: 427, 593, 675, 697, 740, 908, 983, 1027, 1038, 1091, 1119, 1216, 1348, 1403, 1496, 1605, 1661, 2158, 2586, 2882 and 3179 cm^{-1}. HRMS calculated for $C_{18}H_{18}N_2O_3$ ($M+Na^+$) = 333.1210 *m*/*z*, found 333.1211 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.50–7.00 (m, 9H), 5.29–4.86 (m, 3H), 4.84–4.50 (m, 2H), 3.37–3.02 (m, 2H), the amide protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.1, 136.6, 132.5, 129.0, 128.5, 128.5, 128.0, 127.9, 126.7, 126.3, 126.0, 67.3, 52.5, 43.3, 43.1 and 30.7.

4.5.27. (*S*)-Benzyl 3-(aminomethyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 14

To a solution of **13** (0.5 g, 1.5 mmol) in dioxane (3 mL) was added $NaBH_4$ (0.17 g, 4.5 mmol). The mixture was then cooled to 0 °C and acetic acid (0.18 g, 4.5 mmol) was added dropwise, after addition the reaction was set to reflux for 48 h to yield **14** as yellow oil.[26] Due to problems with stability the crude product **14** (0.07 g, 15% in ~90% purity) was carried forward without further purification. $[\alpha]_D^{20} = -15.0$ (*c* 0.16, CH_2Cl_2). IR ν_{max}: 426, 495, 548, 565, 658, 705, 746, 810, 850, 880, 1071, 1093, 1154, 1314, 1450, 1494, 1598, 1722, 2853, 2922, 3031 and 3288 cm^{-1}. HRMS calculated for $C_{18}H_{20}N_2O_2$ ($M+H^+$) = 297.1595 *m*/*z*, found 297.1598 *m*/*z*. NMR spectra are reported for a mixture of two rotamers.[33] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.46–7.24 (m, 5H), 7.23–6.98 (m, 4H), 5.26–5.10 (m, 2H), 4.89 (m, 1H), 4.59–4.25 (m, 2H), 3.06 (m, 1H), 2.77 (m, 1H), 2.70 (dd, *J* = 7.94 and 13.24 Hz, 1H), 2.59 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.1, 136.6, 132.5, 129.0, 128.5, 128.5, 128.0, 127.9, 126.7, 126.3, 126.0, 67.3, 52.5, 43.3, 43.1 and 30.7.

4.5.28. (*S*)-4-Methyl-*N*-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzenesulfonamide 2j

Compound **14** (0.06 g, 0.2 mmol) was first treated with TsCl (0.042 g, 0.22 mmol) and TEA (0.045 g, 0.45 mmol) in CH_2Cl_2 (1.5 mL) for 12 h at room temperature. Water was then added, and the organic layer washed with diluted HCl and then saturated sodium carbonate. The resulting oil was dried and the deprotection of the Cbz group was carried out as described in the general procedure. The crude oil was purified by column chromatography (EtOH/Toluene, 20:80 R_f ~0.7) to yield **2j** (0.038 g, 60%) as a pale yellow oil: $[\alpha]_D^{20} = -13.8$ (*c* 0.17, CH_2Cl_2). HRMS calculated for $C_{17}H_{20}N_2O_2S$ ($M+H^+$) = 317.1339 *m*/*z*, found 317.1318 *m*/*z*. IR ν_{max}: 430, 457, 594, 696, 735, 808, 912, 1020, 1095, 1117, 1217, 1249, 1320, 1418, 1495, 1678, 2927, 3030, 3315 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.13 Hz, 2H), 7.30 (d, *J* = 8.75 Hz, 2H), 7.14–6.96 (m, 4H), 3.94 (d, *J* = 4.66 Hz, 2H), 3.19 (dd, *J* = 3.86 and 12.66 Hz, 1H), 3.00 (m, 1H), 2.84 (dd, *J* = 8.99 and 12.65 Hz, 1H), 2.71 (dd, *J* = 4.43 and 16.27 Hz, 1H), 2.49 (dd, *J* = 10.86 and 16.83 Hz, 1H), 2.41 (s, 3H), The NH protons were not observed. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.4, 136.8, 135.1, 133.3, 129.8, 129.2, 127.2, 126.4, 126.1, 125.1, 68.3, 52.7, 47.4, 32.2 and 21.5.

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