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Weinreb amide based synthetic equivalents for convenient access to 4-aryl-1,2,3,4-tetrahydroisoquinolines

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ABSTRACT

New synthetic equivalents, *N*-methoxy-*N*-methyl-*N*′-phenylsulfonyl glycinamide and *N*-methoxy-*N*-methyl-*N*′-benzyl-*N*′-*tert*-butyloxy carbonyl glycinamide based on WA functionality were developed for the convenient synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinoline framework. Two simple reactions, N-benzylation and addition of arylmagnesium halide on the WA functionality of the former afforded the key intermediate for convenient synthesis of *N*-phenylsulfonyl protected 4-aryl-1,2,3,4-tetrahydroisoquinoline, through reduction and acid promoted cyclization. With the latter, the addition of arylmagnesium halide on the WA functionality followed by the same protocol afforded the direct synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines in good yields. The acid promoted cyclization step enabled concomitant removal of *N*-Boc protection.

1. Introduction

The synthesis of isoquinoline alkaloids has been a field of increasing interest in synthetic organic chemistry both of natural and synthetic origin[1] because of their biological significance. Compared to 1-substituted tetrahydroisoquinolines, 4-substituted tetrahydroisoquinoline derivatives are less. The 4-aryl-tetrahydroisoquinolines **1**, in particular, have evoked considerable interest because of their biological activity and potential application for the treatment of depression,[2] oestrogen-related disorders,[3] Alzheimer's disease and Parkinson's disease.[4] Cherylline is a unique alkaloid that has produced long-standing interest, possesses basic 4-aryl-1,2,3,4-tetrahydroisoquinoline skeleton.[5] Recently, during molecular modelling studies, Prat et al.[6] observed close chemical analogies between 5-hydroxytryptamine (5-HT) and 4-(pyrid-4-yl)-1,2,3,4-tetrahydroisoquinoline. This initiated their efforts to synthesize tetrahydroisoquinolines bearing a pyridyl group at the 4-position. The 4-aryl-1,2,3,4-tetrahydroisoquinoline framework has been conveniently synthesized by three prominent approaches. The first approach[7,8] relies on acid promoted cyclization on to an aromatic ring in 2-benzylamino-1-arylethanol framework mimicking nature's approach and the second is based on Pictet–Spengler reaction.[9] The regioselectivity problem associated with the former approach is completely circumvented by an elegant use of an intramolecular Barbier reaction.[10] The use of *p*-quinone methides as a key intermediate for regioselective cyclization towards the targeted 4-aryl-1,2,3,4-tetrahydroisoquinoline skeleton has been particularly useful when the aryl group has a free hydroxy at the *para* position.[11a] Ring closure involving formation of either of the two C–N bonds present in tetrahydroisoquinoline, as a final step, has been rare.[11b] A recent report using an intramolecular Friedel–Crafts alkylation strategy for the construction of 4-aryl-1,2,3,4-tetrahydroisoquinolines moiety, summarizes all the distinct strategies most commonly employed in the literature towards this objective.[12]

2. Results and discussion

The importance of the target, our continued interest in developing synthetic equivalents based on the Weinreb amide (WA) functionality,[13,14] prompted these studies. Use of this functionality in the industry on kilogram scale further reflects the potentials associated with this functionality.[15] The absence of a strategy based on the proposed disconnection was the additional factor to undertake this study. The *N*-protected glycine derived Weinreb amides **2** and **3** were the envisaged WA-based building block towards the synthesis of target **1** (Fig. 1).The potency of these building blocks to quickly and conveniently assemble the benzyl and aryl residues on to it through N-benzylation and nucleophilic addition of ArMgX onto WA functionality renders themselves as valuable template for the synthesis of key intermediate **4** towards the synthesis of **1**. Since *N*-phenylsulfonyl group offers a robust protection and should also facilitate the desired N-benzylation, the synthesis of **2** and its use for the stated objective was undertaken

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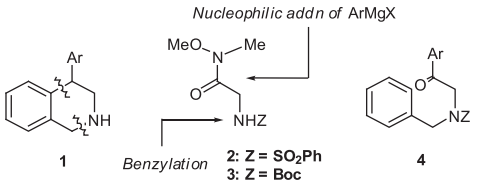
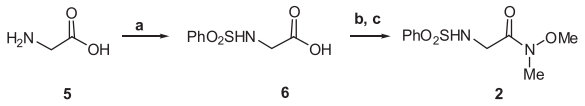


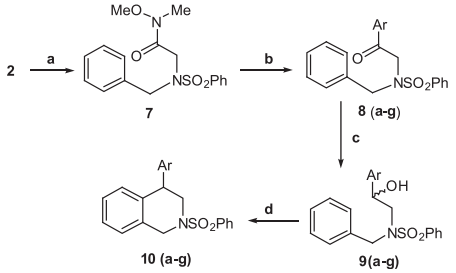
Figure 1.

first. The synthetic equivalent **2** was readily prepared in gram scale from commercially available glycine **5** (Scheme 1). Glycine **5** was converted to *N*-phenylsulfonyl glycine **6** by the literature[16] procedure using benzenesulfonylchloride and NaOH at 0 °C. The acid functionality in **6** was converted to corresponding WA **2** after several trials by in situ activation of the carboxyl group using oxalylchloride. The apparent difficulty in the formation of acid chloride was partly due to low solubility of **6** in dichloromethane. After exploring several solvents it was found that a combination of DMF and dichloromethane (1:5) was an appropriate medium for the facile formation of the acid chloride. The reaction of in situ generated acid chloride with *N*,*O*-dimethyl hydroxylamine (DMHA) released from the *N*,*O*-dimethyl hydroxylamine hydrochloride (DMHA·HCl) in presence of pyridine at 0 °C afforded the WA based synthetic equivalent **2** in 75% yield (Scheme 1), as stable crystalline solid with unlimited shelf life.



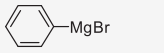
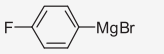
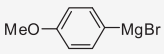
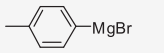
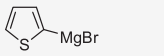
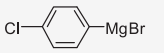
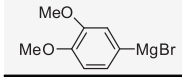
Scheme 1. Reagents and conditions: (a) $PhSO_2Cl$ (1.1 equiv), NaOH, Et_2O, 0 °C, 1.5 h, 93%; (b) $COCl_2$ (1.1 equiv), DMF: DCM (1:5), 0 °C to rt, 2 h; (c) DMHA·HCl (1.1 equiv), Pyridine (2.1 equiv), DCM, 0 °C, 1 h, 75% (two steps).

Facile N-benzylation on the WA **2** using benzyl bromide K_2CO_3 in DMF at 60 °C for 5 h yielded the *N*-benzylated compound **7** with 80% yield (Scheme 2). The addition of various aryl Grignard reagents on to the **7** at 0 °C in THF gave exclusively the corresponding aryl ketones **8a–g** in 70–80% yields (Table 1). No nucleophilic addition of the Grignard reagent on to the electrophilic sulfur atom was observed even at room temperature. The ketones **8a–g** were reduced using $NaBH_4$ in methanol to furnish the 2-(*N*-benzyl-*N*-phenylsulfonyl)-1-hydroxy-(1-aryl)-ethyl amino derivatives **9a–g** in quantitative yields. Using the literature precedence,[7b] the aminoalcohols **9a–g** were cyclized to tetrahydroisoquinoline derivative using a mixture of trifluoroacetic acid and concd sulfuric acid (Scheme 2). The resultant crude products were purified by silica-gel column chromatography to afford pure compounds **10a–g** in 65–95% isolated yields. This two-step protocol on aryl ketones **8a–g** led to the generalization and confirmation of the usefulness of the WA-based template **2** for the 4-aryl-*N*-phenylsulfonyl tetrahydroisoquinoline framework (Table 1).



Scheme 2. Reagents and conditions: (a) K_2CO_3 (3.0 equiv), BnBr (1.2 equiv), DMF, 60 °C, 5 h, 80%; (b) ArMgBr (4.0 equiv), THF, 0 °C to rt, 2 h, 70–80%; (c) $NaBH_4$ (1.0 equiv), MeOH, 0 °C to rt, 2 h, 95–100%; (d) TFA (1.1 equiv), H_2SO_4 (1.1 equiv), DCM, rt, 0.5 h, 65–95%.

Table 1
Preparation of various 4-aryl-*N*-phenylsulfonyl-1,2,3,4-tetrahydroisoquinolines

ArMgBr	Arylketones (Yield%)[a]	4-Aryl-*N*-phenylsulfonyl-1,2,3,4-tetrahydroisoquinoline (Yield%)[a]
	**8a** (74%)	**10a** (85%)
	**8b** (78%)	**10b** (94%)
	**8c** (72%)	**10c** (95%)
	**8d** (75%)	**10d** (92%)
	**8e** (83%)	**10e** (90%)
	**8f** (80%)	**10f** (86%)
	**8g** (62%)	**10g** (65%)

[a] Isolated yields after column chromatography. New compounds **8a–g**, **10a–g** exhibited satisfactory analytical and spectral data.

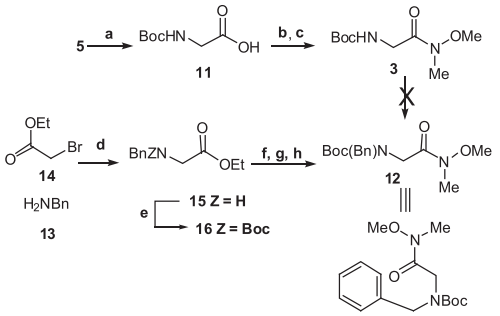
Although, *N*-phenylsulfonyl group offers a rugged protection, its removal has been difficult and requires strongly reductive conditions.[17] Replacing the sulfonyl group by an easily removable protecting group on nitrogen should, therefore, further enhance the significance and the potential of this glycine derived WA building block **2**. In order to have an easily removable during the last step in the synthetic scheme, we turned our attention to *N*-Boc protected building block **3**.

Although **3**[18] could be easily prepared by *N*-Boc protection on glycine **5** followed by conversion of the carboxyl group in **11** to its WA using the mixed anhydride approach,[19] its failure to undergo N-benzylation to afford the key intermediate **12** was a surprise and disappointment. In sharp contrast to the *N*-sulfonyl protected glycinamide **2**, which had undergone clean N-benzylation with the use of K_2CO_3 in DMF at 60 °C as a base, compound **3** was recovered under these conditions. Replacing K_2CO_3 with DBU also made no difference, whereas with the use of NaH as base, the starting material **3** underwent decomposition.

The key intermediate **12** was prepared alternatively using benzyl amine as the source of nitrogen and not glycine. Alkylating benzyl amine **13** with ethyl-2-bromo acetate **14** in the presence of triethylamine led to the formation of 2-aminoester **15**.[20] The Boc-protection on the amine **15** furnished **16**. Saponification of **16** followed by WA preparation using the mixed anhydride approach gave the required *N*-Boc protected WA building block **12** (Scheme 3). A similar reaction sequence was performed on **12** as discussed earlier for *N*-sulfonyl protected **8**, which included addition of ArMgBr onto **12** (Table 2), followed by sodium borohydride reduction of ketones **17a–e** and acid promoted cyclization to arrive at the 4-aryl-tetrahydroisoquinolines **18a–e**. The concomitant removal of the Boc-protection occurred with the use of excess equivalents of trifluoroacetic acid during the cyclization step. The aqueous basic work-up allowed isolation of the free amines **18a–e** for their quick structural characterization and confirmation. They were converted to corresponding hydrochloride salts **19a–e** using solution of dry HCl gas in dry ether for convenient storage (Table 3).

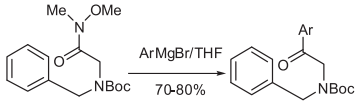
3. Conclusion

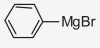
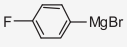
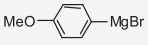
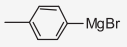
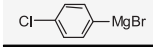
In summary, *N*-methoxy-*N*-methyl-*N*′-phenylsulfonyl glycinamide **2**, a crystalline solid with unlimited shelf life and



Scheme 3. Reagents and conditions: (a) $(Boc)_2O$ (1.1 equiv), 1 N NaOH, Dioxane/water (2:1), pH (9–10), 0 °C to rt, 12 h, 93%; (b) $(CH_3)_3CCOCl$ (1.1 equiv), TEA (1.5 equiv), DCM, 0 °C, 2.5 h; (c) DMHA·HCl (1.1 equiv), TEA (1.5 equiv), DCM, 0 °C to rt, 1.5 h, 75% (two steps); (d) TEA (1.1 equiv), THF, rt, 4 h, 90%; (e) $(Boc)_2O$ (1.2 equiv), TEA (2.2 equiv), DCM, 0 °C to rt, 7 h, 90%; (f) 2 N NaOH, MeOH, rt, 3 h; (g) $(CH_3)_3CCOCl$ (1.1 equiv), TEA (1.5 equiv), THF, 0 °C, 2.5 h; (h) DMHA·HCl (1.1 equiv), TEA (1.5 equiv), THF, 0 °C to rt, 1.5 h, 76% (three steps).

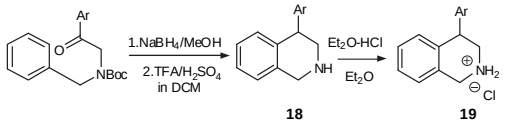
Table 2
Preparation of various *N*-benzyl-*N*-*tert*-butyloxy carbonyl (2-aryl)-aminoketones



ArMgBr	Arylketones (Yield%)[a]
	**17a** (76%)
	**17b** (80%)
	**17c** (76%)
	**17d** (74%)
	**17e** (78%)

[a] Isolated yields after column chromatography. New compound **17a**–**e** exhibited satisfactory analytical and spectral data.

Table 3
Preparation of various 4-aryl-1,2,3,4-tetrahydroisoquinolines and their amine hydrochlorides



Arylketones	4-Aryl-tetrahydrol-soquinoline (Yield%)[a]	4-Aryl-1,2,3,4-tetrahydroi-soquinoline amine hydrochlorides (Yield%)
17a	**18a** (92%)	**19a** (99%)
17b	**18b** (91%)	**19b** (97%)
17c	**18c** (90%)	**19c** (97%)
17d	**18d** (90%)	**19d** (97%)
17e	**18e** (92%)	**19e** (98%)

[a] Isolated yields after column chromatography.

N-methoxy-*N*-methyl-*N*′-benzyl-*N*′-*tert*-butyloxy carbonyl glycinamide **12**, based on the WA functionality serve as useful templates for the general synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinoline derivatives. The templates provide an efficient route for the preparation of various 4-aryl-1,2,3,4-tetrahydroisoquinolines.

4. Experimental section

4.1. General

All reactions were carried out in an oven dried glasswares. Dry DMF was prepared by stirring with Calcium hydride, downward distilled and stored on 4 Å molecular sieves. Dry THF was distilled as needed from Na/benzophenone ketyl. Solvents used for column chromatography were LR grade. Magnesium metal was cleaned using 20% HCl (thrice) followed by washing with distilled water and acetone, which was dried by keeping it in hot air oven for 12 h at 100 °C. Grignard reagent prepared was estimated using menthol (dry) and 1, 10-phenanthroline as indicator in dry THF.[21] Thin-layer chromatography was performed on aluminium plates coated with silica gel 60. Visualization was observed by UV light or by dipping into a solution of cerium (IV) sulfate (2.5 g) and ammonium molybdate (6.25 g) in 10% sulfuric acid (250 mL) followed by charring on a hot plate. Melting points were determined in capillaries and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in chloroform-*d* ($CDCl_3$) and D_2O as the solvents and tetramethylsilane (TMS) as reference. HRMS were recorded on a MICRO-Q TOF mass spectrometer by using the ESI technique at 10 eV.

*4.1.1. N-Methoxy-N-methyl-2-(phenylsulfonamido)-acetamide (**2**).* To the solution of glycine (3 g, 40 mmol) in 2 N NaOH (20 mL), benzenesulfonylchloride (5.1 mL, 40 mmol) in ether (50 mL) was added at 0 °C and stirred for 1.5 h. The reaction mixture was washed with 2 N HCl (2×50 mL), followed by brine (50 mL), dried over Na_2SO_4 and the solvent was removed under vacuum to afford compound **7** as a colourless solid (8 g, 93%). Compound **7** (2 g, 9.3 mmol) was dissolved in the mixture of anhydrous DMF (3 mL) and anhydrous DCM (15 mL). The solution was cooled to 0 °C and oxalylchloride (1 mL, 9.6 mmol) was added drop-wise to it. The reaction mixture was stirred for 2 h at room temperature and cooled to 0 °C. *N*,*O*-Dimethyl hydroxylamine hydrochloride (1 g, 11 mmol) and solution of anhydrous pyridine (1.65 mL, 20 mmol) in anhydrous DCM (10 mL) were added to it, stirred for 1 h and allowed to attain room temperature. The reaction mixture was washed with 2 N HCl (2×25 mL), followed by saturated aqueous $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford crude product that was subjected to column chromatography to obtain pure *N*-methoxy-*N*-methyl-*N*′-phenylsulfonyl glycinamide (1.75 g, 75%) as a colourless solid. Mp: 66–68 °C; R_f (90% CH_2Cl_2/MeOH) 0.24; ν_{max}(liquid film) 3239, 1659, 1446, 1383, 1327, 1155, 1091, 988, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.86–7.90 (2H, m, SO_2Ph, Ar*H*-2,6), 7.45–7.62 (3H, m, SO_2Ph, Ar*H*-3,4,5), 5.6 (1H, br, N*H*), 3.9 (2H, s, NCH_2), 3.6 (3H, s, OCH_3), 3.1 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 168.2, 139.2, 132.7, 129.0, 127.1, 61.5, 43.1, 32.4; HRMS (ESI): MH$^+$, found 259.0746. $C_{10}H_{15}N_2O_4S$ requires 259.0753.

*4.1.2. 2-(N′-Benzylphenylsulfonamido)-N-methoxy-N-methyl-acetamide (**7**).* To a solution of compound **2** (2 g, 7.7 mmol) in anhydrous DMF (12 mL), benzyl bromide (1.1 mL, 9.3 mmol) and anhydrous potassium carbonate (3.2 g, 23.2 mmol) were added and heated at 60 °C for 5 h. The reaction mixture was cooled to room temperature and extracted into ethylacetate (2×50 mL). The combined ethylacetate extracts were washed with water (5×50 mL) and later with brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford crude product that was purified by column chromatography to give compound **7** (2.16 g, 80%) as a colourless solid. Mp: 110–112 °C; R_f (80% hexanes/EtOAc) 0.22; ν_{max}(liquid film) 1678, 1334, 1156, 1094, 743 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.82–7.84 (2H, m, SO_2Ph, Ar*H*-2,6), 7.37–7.49 (3H, m, SO_2Ph,

Ar*H*-3,4,5), 7.12–7.22 (5H, m, Ph, Ar*H*), 4.45 (2H, s, NCH_2CO), 4.02 (2H, s, CH_2Ph), 3.55 (3H, s, OCH_3), 2.93 (3H, s, NCH_3); δ_C ($CDCl_3$, 100 MHz) 160.1, 141.2, 136.2, 133.4, 129.9, 129.6, 129.5, 128.8, 125.4, 127.2, 62.0, 51.9, 46.4, 33.1; HRMS (ESI): MH^+, found 349.1218. $C_{17}H_{21}N_2O_4S$ requires 349.1222.

*4.1.3. N-Methoxy-N-methyl-N′-benzyl-N′-tert-butyloxy carbonyl glycinamide (**12**).* To a solution of *N*-benzyl-*N*-*tert*-butyloxy glycine (2 g, 7.5 mmol) in anhydrous THF (25 mL), triethylamine (1.5 mL, 11.3 mmol) was added, followed by drop wise addition of pivaloyl chloride (1.0 mL, 8.3 mmol) at 0 °C and stirred for 2.5 h at room temperature. To the reaction mixture, *N*,*O*-dimethyl hydroxylamine hydrochloride (0.817 g, 8.3 mmol), triethylamine (1.49 mL, 11.3 mmol) and anhydrous THF (10 mL) were added at 0 °C and stirred at room temperature for 1 h. TLC revealed the complete consumption of starting material. The solvent was evaporated under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethylacetate (2×50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (40 mL) and later with brine (40 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to obtain compound **12** (1.75 g, 76%) as a liquid. R_f (70% hexanes/EtOAc) 0.39; ν_{max}(liquid film) 2937, 1681, 1452, 1392, 1241, 1161, 765 cm^{-1}; δ_H ($CDCl_3$, 400 MHz). Mixture of two rotamers (60:40) 7.14–7.27 (5H, m, Ph, Ar*H*), 4.46, 4.49 (2H, s, NCH_2CO), 3.88, 4.02 (2H, s, CH_2Ph), 3.50, 3.55 (3H, s, OCH_3), 3.0 (3H, s, NCH_3), 1.39 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 100 MHz) 170.3, 170.1, 156.1, 156.0, 138.0, 137.8, 128.6, 128.4, 128.2, 127.4, 127.2, 80.3, 80.1, 61.1, 51.5, 50.8, 46.8, 46.7, 29.6; HRMS (ESI): MNa^+, found 331.1635. $C_{16}H_{24}N_2O_4$ requires 331.1634.

4.2. General procedure for the addition of Grignard reagents on to the Weinreb amide 7 and 12

To a solution of aryl or hetero arylmagnesium bromide (2.8 mmol) in dry THF (3 mL), a solution of alkane WA (0.7 mmol) in 3 mL of dry THF, was added under inert atmosphere at −10 °C and the mixture was stirred for 3 h between −10 and 10 °C. TLC revealed the complete consumption of starting material. Subsequent hydrolysis was achieved by the cautious addition of saturated ammonium chloride solution. Aqueous layer was extracted with ethylacetate, washed with water, dried over Na_2SO_4 and concentrated to get crude product. This was purified by column chromatography using hexanes/ethylacetate mixture, to get the desired ketones **8a**–**g** and **17a**–**e**.

*4.2.1. N-Benzyl-N-(2-oxo-2-phenylethyl) benzenesulfonamide (**8a**).* Mp: 66–68 °C; R_f (80% hexanes/EtOAc) 0.50; ν_{max}(liquid film) 1697, 1446, 1330, 1225, 1155 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77–7.81 (2H, m, SO_2Ph, Ar*H*-2,6), 7.59–7.64 (2H, m, SO_2Ph, Ar*H*-3,5), 7.44–7.50 (1H, m, SO_2Ph, Ar*H*-4), 7.36–7.43 (3H, m, Ar*H*), 7.25 (2H, t, *J*=7.6 Hz, Ar*H*), 7.07–7.15 (5H, m, CH_2Ph, Ar*H*), 4.52 (2H, s, NCH_2CO), 4.45 (2H, s, CH_2Ph); δ_C (100 MHz, $CDCl_3$) 193.9, 140.1, 135.1, 134.8, 133.7, 132.7, 129.0, 128.7, 128.2, 128.1, 127.8, 127.1, 51.5, 51.3; HRMS (ESI): MNa^+, found 388.0983. $C_{21}H_{19}NO_3S$ requires 388.0983.

*4.2.2. N-Benzyl-N-(2-(4-fluorophenyl)-2-oxoethyl) benzenesulfonamide (**8b**).* R_f (80% hexanes/EtOAc) 0.45; ν_{max}(liquid film) 1697, 1446, 1330, 1326, 1152 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80–7.83 (2H, m, SO_2Ph, Ar*H*-2,6), 7.66–7.72 (2H, m, SO_2Ph, Ar*H*-3,5), 7.51–7.56 (1H, m, Ar*H*-4), 7.42–7.48 (2H, m, Ar*H*), 7.10–7.19 (5H, m, CH_2Ph, Ar*H*), 6.95–7.01 (2H, m, Ar*H*), 4.50 (2H, s, NCH_2CO), 4.45 (2H, s, CH_2Ph); δ_C (100 MHz, $CDCl_3$) 192.4, 167.2, 164.7, 139.8, 134.9, 132.7, 131.2, 130.6, 130.5, 128.9, 128.8, 128.77, 128.70, 128.6, 128.1, 127.4, 116.0, 115.7, 51.6, 51.5; HRMS (ESI): MNa^+, found 406.0885. $C_{21}H_{18}NO_3FS$ requires 406.0889.

*4.2.3. N-Benzyl-N-(2-(4-methoxyphenyl)-2-oxoethyl)-benzenesulfonamide (**8c**).* Mp: 104–106 °C; R_f (80% hexanes/EtOAc) 0.38; ν_{max}(liquid film) 1688, 1600, 1331, 1262, 1160, 1093 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77–7.81 (2H, m, SO_2Ph, Ar*H*-2,6), 7.59–7.64 (2H, m, SO_2Ph, Ar*H*-3,5), 7.44–7.49 (1H, m, Ar*H*-4), 7.36–7.41 (2H, m, Ar*H*), 7.08–7.16 (5H, m, CH_2Ph, Ar*H*), 6.71–6.74 (2H, m, Ar*H*), 4.48 (2H, s, NCH_2CO), 4.45 (2H, s, CH_2Ph), 3.68 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 192.2, 171.1, 140.2, 135.2, 132.6, 130.2, 130.1, 129.0, 128.9, 128.75, 128.71, 128.6, 128.0, 127.9, 127.7, 127.5, 127.4, 113.9, 113.8, 55.5, 51.3, 51.1; HRMS (ESI): MNa^+, found 418.1092. $C_{22}H_{21}NO_4S$ requires 418.1089.

*4.2.4. N-Benzyl-N-(2-oxo-2-p-tolylethyl)benzenesulfonamide (**8d**).* Mp: 90–92 °C; R_f (80% hexanes/EtOAc) 0.42; ν_{max}(liquid film) 1694, 1446, 1413, 1332, 1238, 1160 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77–7.81 (2H, m, SO_2Ph, Ar*H*-2,6), 7.53 (2H, d, *J*=8.4 Hz, SO_2Ph, Ar*H*-3,5), 7.44–7.49 (1H, m, SO_2Ph, Ar*H*-4), 7.38 (2H, t, *J*=8.2 Hz, Ar*H*), 7.08–7.16 (5H, m, Ph. Ar*H*), 7.06 (2H, d, *J*=8.0 Hz, Ar*H*), 4.51 (2H, s, NCH_2CO), 4.45 (2H, s, CH_2Ph), 2.24 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 193.4, 144.7, 140.2, 135.2, 132.7, 132.3, 129.4, 128.93, 128.92, 128.76, 128.73, 128.6, 128.1, 127.97, 127.93, 127.9, 127.5, 127.4, 51.3, 21.7; HRMS (ESI): MNa^+, found 402.1144. $C_{22}H_{21}NO_3S$ requires 402.1140.

*4.2.5. N-Benzyl-N-(2-oxo-2-(thiophen-2-yl)ethyl)benzenesulfonamide (**8e**).* Mp: 60–62 °C; R_f (80% hexanes/EtOAc) 0.47; ν_{max}(liquid film) 1674, 1446, 1413, 1332, 1160, 1093 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J*=7.6 Hz, SO_2Ph, Ar*H*-2,6), 7.43–7.50 (3H, m, Ar*H*-3,4,5), 7.38 (2H, t, *J*=3.6 Hz, Ar*H*), 7.05–7.15 (5H, m, CH_2Ph, Ar*H*), 6.92 (1H, t, *J*=4.0 Hz, Ar*H*), 4.42 (4H, s, NCH_2CO, CH_2Ph); δ_C (100 MHz, $CDCl_3$) 186.6, 140.6, 139.5, 134.5, 134.0, 132.4, 132.0, 128.6, 128.5, 128.3, 128.2, 127.9, 127.7, 127.0, 51.2, 51.0; HRMS (ESI): MNa^+, found 394.0551. $C_{19}H_{17}NO_3S_2$ requires 394.0548.

*4.2.6. N-Benzyl-N-(2-(4-chlorophenyl)-2-oxoethyl)benzenesulfonamide (**8f**).* Mp: 60–62 °C; R_f (80% hexanes/EtOAc) 0.43; ν_{max}(liquid film) 1697, 1596, 1446, 1330, 1092 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80–7.83 (2H, m, SO_2Ph, Ar*H*-2,6), 7.66–7.72 (2H, m, SO_2Ph, Ar*H*-3,5), 7.51–7.56 (1H, m, SO_2Ph, Ar*H*-4), 7.42–7.48 (2H, m, Ar*H*), 7.10–7.19 (5H, m, CH_2Ph, Ar*H*), 6.95–7.01 (2H, m, C_6H_4Cl, Ar*H*), 4.49 (2H, s, NCH_2CO), 4.45 (2H, s, CH_2Ph); δ_C (100 MHz, $CDCl_3$) 193.0, 140.1, 139.8, 134.8, 132.7, 129.2, 129.0, 128.99, 128.96, 128.84, 128.80, 128.76, 128.71, 128.2, 127.44, 127.41, 51.7, 51.5; HRMS (ESI): MNa^+, found 422.0595. $C_{21}H_{18}NO_3ClS$ requires 422.0594.

*4.2.7. N-Benzyl-N-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)benzenesulfonamide (**8g**).* Mp: 96–98 °C; R_f (80% hexanes/EtOAc) 0.28; ν_{max}(liquid film) 2922, 1446, 1340, 1090, 753 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J*=7.6 Hz, SO_2Ph, Ar*H*-2,6), 7.49 (1H, t, *J*=7.2 Hz, SO_2Ph, Ar*H*-4), 7.41 (2H, t, *J*=7.2 Hz, SO_2Ph, Ar*H*-3,5), 7.27 (1H, d, *J*=8.4 Hz, Ar*H*), 7.21–7.24 (1H, s, Ar*H*), 7.08–7.17 (5H, m, CH_2Ph, Ar*H*), 6.69 (1H, d, *J*=8.4 Hz, Ar*H*), 4.50 (2H, s, NCH_2CO), 4.44 (2H, s, CH_2Ph), 3.80 (3H, s, OCH_3C$_6$H$_3$), 3.75 (3H, s, OCH_3C$_6$H$_3$); δ_C (100 MHz, $CDCl_3$) 192.4, 153.7, 149.0, 140.0, 135.1, 132.6, 128.6, 128.5, 127.9, 127.4, 122.5, 110.0, 60.3, 56.1, 56.0, 51.4; HRMS (ESI): MNa^+, found 448.1196. $C_{23}H_{23}NO_5S$ requires 448.1195.

*4.2.8. tert-Butyl benzyl(2-oxo-2-phenylethyl)carbamate (**17a**).* R_f (70% hexanes/EtOAc) 0.54; ν_{max}(liquid film) 2973, 1692, 1598, 1226, 1156 cm^{-1}; δ_H (400 MHz, $CDCl_3$). Mixture of two rotamers (53:47) 7.77–7.83 (4H, dd, *J*=7.6, 16 Hz, Ar*H*), 7.47–7.50 (2H, m, Ar*H*), 7.32–7.35 (4H, m, Ar*H*), 7.13–7.28 (10H, m, Ar*H*), 4.53, 4.55 (2H, s, NCH_2CO), 4.38, 4.47 (2H, s, CH_2Ph), 1.33, 1.42 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 195.1, 194.8, 156.0, 155.9, 137.8, 137.6, 135.3, 135.2,

133.4, 129.5, 128.7, 128.67, 128.61, 128.5, 128.1, 127.9, 127.7, 127.5, 127.4, 120.1, 115.3, 80.6, 80.4, 52.4, 52.1, 51.4, 51.0, 28.3, 28.2; HRMS (ESI): MNa^+, found 348.1569. $C_{20}H_{23}NO_3$ requires 348.1576.

*4.2.9. tert-Butylbenzyl(2-(4-fluorophenyl)-2-oxoethyl)carbamate (**17b**).* R_f (70% hexanes/EtOAc) 0.61; ν_{max}(liquid film) 2796, 1700, 1589, 1366, 1162 cm^{-1}; δ_H (400 MHz, $CDCl_3$). Mixture of two rotamers (52:48) 7.87–7.98 (4H, m, Ar*H*), 7.22–7.41 (10H, m, Ar*H*), 7.05–7.18 (4H, m, Ar*H*), 6.81–6.89 (4H, m, Ar*H*), 6.72–6.81 (2H, m, Ar*H*), 4.57–4.66 (4H, m, NCH_2CO), 4.48 (4H, s, CH_2Ph), 1.44, 1.53 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 193.6, 193.3, 167.2, 164.7, 157.9, 156.2, 156.1, 155.5, 152.5, 137.5, 137.3, 131.5, 130.6, 130.5, 130.4, 130.3, 128.6, 128.0, 127.5, 116.2, 116.1, 115.9, 115.7, 81.1, 80.8, 52.3, 52.1, 51.6, 51.1, 28.3, 28.2; HRMS (ESI): MNa^+, found 366.1489. $C_{20}H_{22}NO_3F$ requires 366.1481.

*4.2.10. tert-Butyl benzyl(2-(4-methoxyphenyl)-2-oxoethyl)carbamate (**17c**).* R_f (70% hexanes/EtOAc) 0.25; ν_{max}(liquid film) 2974, 1690, 1452, 1365, 1228 cm^{-1}; δ_H (400 MHz, $CDCl_3$). Mixture of two rotamers (54:46) 7.76–7.82 (4H, m, Ar*H*), 7.76–7.82 (4H, m, Ar*H*), 7.10–7.30(11H, m, Ar*H*), 6.75–6.85 (5H, m, Ar*H*), 6.66–6.74 (2H, m, Ar*H*), 4.50–4.65 (5H, m), 4.34, 4.47 (2H, s, CH_2Ph), 3.65, 3.73 (3H, s, OCH_3), 1.32, 1.40 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 193.4, 193.2, 171.1, 163.7, 156.0, 153.0, 150.7, 137.9, 137.7, 130.1, 129.0, 128.6, 128.4, 128.3, 128.2, 128.0, 127.5, 127.3, 116.0, 114.6, 113.9, 113.8, 80.5, 80.2, 55.6, 55.3, 52.0, 51.8, 51.4, 51.0, 28.3, 28.1; HRMS (ESI): MNa^+, found 378.1685. $C_{21}H_{25}NO_4$ requires 378.1681.

*4.2.11. tert-Butyl benzyl(2-oxo-2-p-tolylethyl)carbamate (**17d**).* R_f (70% hexanes/EtOAc) 0.46; ν_{max} (liquid film) 2976, 1700, 1589, 1366, 1162 cm^{-1}; δ_H (400 MHz, $CDCl_3$). Mixture of two rotamers (52:48) 7.77–7.87 (4H, m, Ar*H*), 7.21–7.39 (14H, m, Ar*H*), 6.96–7.10 (1H, m, Ar*H*), 6.75–6.80 (1H, m, Ar*H*), 4.62–4.68 (4H, m, NCH_2CO), 4.49, 4.59 (4H, s, CH_2Ph), 2.26, 2.41 (3H, s, CH_3Ph), 1.45, 1.54 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 194.6, 194.4, 156.1, 156.0, 144.4, 144.3, 137.8, 137.6, 132.7, 129.8, 129.4, 129.3, 128.8, 128.6, 128.5, 128.1, 128.0, 127.8, 127.5, 127.4, 127.3, 115.2, 80.6, 80.4, 52.3, 52.1, 51.4, 51.0, 28.3, 28.2, 20.7, 20.5; HRMS (ESI): MNa^+, found 362. 1730. $C_{21}H_{25}NO_3$ requires 362.1732.

*4.2.12. tert-Butyl benzyl(2-(4-chlorophenyl)-2-oxoethyl)carbamate (**17e**).* R_f (70% hexanes/EtOAc) 0.47; ν_{max} (liquid film) 2943, 2686, 1570, 1451, 1184 cm^{-1}; δ_H (400 MHz, $CDCl_3$). Mixture of two rotamers (54:46) 7.70–7.60 (4H, m, Ar*H*), 7.25–7.36 (5H, m, Ar*H*), 7.12–7.25 (13H, m, Ar*H*), 7.04 (1H, d, *J*=8.4 Hz, Ar*H*), 6.66 (1H, *J*=8.4 Hz, d, Ar*H*), 4.40–4.52 (m, 7H), 4.34 (s, 2H, CH_2Ph), 1.32, 1.41 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 194.0, 193.7, 156.3, 156.1, 155.2, 140.08, 140.03, 137.4, 137.2, 133.4, 133.3, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 128.0, 127.5, 124.4, 116.7, 124.4, 116.7, 81.2, 80.9, 52.4, 52.2, 51.6, 51.2, 28.4, 28.2; HRMS (ESI): MNa^+, found 382.1192. $C_{20}H_{22}NO_3Cl$ requires 382.1186.

4.3. General procedure for the reduction of aryl ketones 8a–g and 17a–e and subsequent cyclization to 4-aryl-tetrahydroisoquinolines 10a–g and 18a–e, respectively

To the solution of aryl ketone (0.5 mmol) in MeOH (2 mL), sodium borohydride (1.0 mmol) was added at 0 °C. The mixture was stirred at room temperature for 1.5 h, the complete consumption of starting material as revealed by TLC. Excess sodium borohydride was quenched by cautious addition of acetic acid. Methanol was evaporated under reduced pressure and water was added to the residue. The aqueous suspension was extracted with ethylacetate (2×15 mL), the combined ethylacetate extracts were washed with water (2×15 mL) and later with brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford corresponding benzylic alcohol. The alcohol was subjected to cyclization without further purification.

For N-sulfonyl protected substrates: To a solution of alcohol (0.2 mmol) in DCM (4 mL), a mixture of H_2SO_4 (0.02 mL, 0.3 mmol) and CF_3CO_2H (0.02 mL, 0.26 mmol) acids were added and stirred at room temperature for 0.5 h. TLC revealed the complete consumption of starting material. The solvent was evaporated under reduced pressure, ethylacetate was added to the residue, washed with 10% aqueous K_2CO_3 (10 mL), water (10 mL) and later with brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford crude product, which was purified by silica-gel flash column chromatography using ethylacetate/hexanes mixture, to get the cyclised products **10a**–**g** in good yields.

For N-Boc-protected substrates: To a solution of alcohol (0.2 mmol) in DCM (4 mL), a mixture of H_2SO_4 (0.02 mL, 0.3 mmol) and CF_3CO_2H (0.20 mL, 2.6 mmol) acids were added, excess TFA was used to remove the Boc-protection during cyclization. The mixture was stirred at room temperature for 6–7 h. TLC revealed the complete consumption of starting material. A similar work up procedure as mentioned for *N*-sulfonyl protected substrate was followed to get crude product. This was purified by silica-gel flash column chromatography using dichloro-methane/methanol mixture, to get the cyclised products **18a**–**e** in good yields. The obtained free amine was converted in to its hydrochloride salt by stirring the amine (0.18 mmol) with ether/HCl solution (3 ml) for 5–10 min. The precipitated salt was filtered, washed with ether and dried under high vacuum to get the pure amine hydrochlorides **19a**–**e** in very high yields.

*4.3.1. 4-Phenyl-2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (**10a**).* Mp: 66–68 °C; R_f (80% hexanes/EtOAc) 0.45; ν_{max}(liquid film) 2924, 1508, 1343, 1168, 1168, 1091 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.67–7.71 (2H, m, SO_2Ph, Ar*H*-2,6), 7.46–7.51 (1H, m, SO_2Ph, Ar*H*-4), 7.38–7.44 (2H, m, SO_2Ph, Ar*H*-3,5), 7.15–7.23 (4H, m, Ar*H*), 6.96–7.03 (4H, m, Ar*H*), 6.76 (1H, d, *J*=8.0 Hz, Ar*H*), 4.44 (1H, d, *J*=15.2 Hz, CH_aH$_b$C$_6$H$_4$), 4.20 (1H, dd, *J*=5.6, 8.0 Hz, NCH$_2$C*H*), 4.12 (1H, d, *J*=14.8 Hz, CH$_a$H$_b$C$_6$H$_4$), 3.72 (1H, dd, *J*=5.6, 12.0 Hz, NCH_aH$_b$CH), 3.01 (1H, dd, *J*=8.0, 12.0 Hz, NCH$_a$H$_b$CH); δ_C (100 MHz, $CDCl_3$) 142.3, 136.3, 136.2, 132.9, 131.8, 129.5, 129.1, 128.9, 128.8, 128.6, 127.7, 127.1, 127.0, 126.7, 126.2, 51.0, 48.0, 45.2; HRMS (ESI): MNa^+, found 350.1217. $C_{21}H_{20}NO_2S$ requires 350.1215.

*4.3.2. 4-(4-Fluorophenyl)-2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (**10b**).* R_f (80% hexanes/EtOAc) 0.42; ν_{max}(liquid film) 1508, 1446, 1354, 1168, 1091 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.69 (2H, d, *J*=7.6 Hz, SO_2Ph, Ar*H*-2,6), 7.47–7.52 (1H, m, SO_2Ph, Ar*H*-4), 7.41 (2H, t, *J*=7.2 Hz, SO_2Ph, Ar*H*-3,5), 7.09 (1H, t, *J*=7.2 Hz Ar*H*), 6.95–7.04 (4H, m, Ar*H*), 6.84–6.90 (2H, m, Ar*H*), 6.77 (1H, d, *J*=7.6 Hz, Ar*H*), 4.35 (1H, d, *J*=14.8 Hz, CH_2C$_6$H$_4$), 4.16–4.22 (2H, m), 3.60 (1H, dd, *J*=4.8, 12.0 Hz, NCH_aH$_b$CH), 3.08 (1H, dd, *J*=8.0, 12 Hz, NCH$_a$H$_b$CH); δ_C (100 MHz, $CDCl_3$) 162.0, 159.6, 137.2, 135.1, 134.9, 131.8, 130.7, 129.3, 129.2, 128.4, 128.0, 126.6, 126.0, 125.8, 125.2, 114.4, 114.2, 49.9, 46.7, 43.3; HRMS (ESI): MNa^+, found 390.0934. $C_{21}H_{18}NO_2SF$ requires 390.0940.

*4.3.3. 4-(4-Methoxyphenyl)-2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (**10c**).* Mp: 105–107 °C; R_f (80% hexanes/EtOAc) 0.32; ν_{max}(liquid film) 1508, 1446, 1348, 1160, 1089 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J*=7.2 Hz, SO_2Ph, Ar*H*-2,6), 7.45–7.52 (1H, m, SO_2Ph, Ar*H*-4), 7.41 (2H, t, *J*=7.6 Hz, SO_2Ph, Ar*H*-3,5), 7.05–7.11 (2H, m, Ar*H*), 6.97–7.03 (2H, m, Ar*H*), 6.91–6.96 (2H, m, Ar*H*), 6.77–6.81 (1H, m, Ar*H*), 6.72–6.76 (2H, m, C$_6$H$_4$OMe, Ar*H*-3,5), 4.43 (1H, d, *J*=14.8 Hz, CH_aH$_b$C$_6$H$_4$), 4.16 (1H, dd, *J*=5.6, 7.6 Hz, NCH$_2$C*H*), 4.14 (1H, d, *J*=14.8 Hz, CH$_a$H$_b$C$_6$H$_4$), 3.70 (3H, s, OCH_3), 3.66–3.72 (1H, m, NCH_aH$_b$CH), 2.97 (1H, dd, *J*=7.6, 12.0 Hz NCH$_a$H$_b$CH); δ_C

(100 MHz, $CDCl_3$) 158.6, 136.7, 136.2, 134.3, 132.8, 131.8, 129.9, 129.5, 129.1, 129.0, 128.8, 127.7, 127.6, 126.9, 126.6, 126.1, 114.0, 113.9, 55.2, 51.1, 47.9, 44.4; HRMS (ESI): MNa^+, found 402.1145. $C_{22}H_{21}NO_3S$ requires 402.1140.

*4.3.4. 2-(Phenylsulfonyl)-4-p-tolyl-1,2,3,4-tetrahydroisoquinoline (**10d**).* Mp: 66–68 °C; R_f (80% hexanes/EtOAc) 0.37; ν_{max}(liquid film) 2922, 1446, 1340, 1182, 1090 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.66–7.70 (2H, m, SO_2Ph, Ar*H*-2,6), 7.45–7.51 (1H, m, SO_2Ph, Ar*H*-4), 7.37–7.43 (2H, m, SO_2Ph, Ar*H*-3,5), 7.02–7.07 (1H, m, Ar*H*), 6.95–7.01 (4H, m, Ar*H*), 6.87–6.91 (2H, m, Ar*H*), 6.76 (1H, d, *J*=7.6 Hz, Ar*H*), 4.43 (1H, d, *J*=15.6 Hz, $CH_aH_bC_6H_4$), 4.17 (1H, dd, *J*=5.6, 8.0 Hz, NCH_2CH), 4.09 (1H, d, *J*=15.6 Hz, $CH_aH_bC_6H_4$), 3.71 (1H, dd, *J*=5.6, 11.6 Hz, NCH_aH_bCH), 2.95 (1H, dd, *J*=8.4, 11.6 Hz, NCH_aH_bCH), 2.23 (3H, s, $C_6H_4CH_3$); δ_C (100 MHz, $CDCl_3$) 139.2, 136.7, 136.6, 136.2, 132.8, 131.8, 129.3, 129.2, 128.8, 127.7, 127.0, 126.6, 126.1, 51.1, 48.8, 44.8, 21.1; HRMS (ESI): MNa^+, found 386.1191. $C_{22}H_{21}NO_2S$ requires 386.1191.

*4.3.5. 2-(Phenylsulfonyl)-4-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline (**10e**).* Mp: 110–112 °C; R_f (80% hexanes/EtOAc) 0.40; ν_{max}(liquid film) 2921, 1446, 1340, 1166, 1090 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.71–7.75 (2H, m, SO_2Ph, Ar*H*-2,6), 7.49–7.51 (1H, m, SO_2Ph, Ar*H*-4), 7.42–7.7.47 (2H, m, SO_2Ph, Ar*H*-3,5), 7.02–7.14 (3H, m, Ar*H*), 6.99 (2H, t, *J*=7.2 Hz, Ar*H*), 6.86 (1H, m, Ar*H*), 6.81 (1H, d, *J*=3.2 Hz, Ar*H*), 4.50 (1H, t, *J*=5.6 Hz, NCH_2CH), 4.32 (1H, d, *J*=14.8 Hz, $CH_aH_bC_6H_4$), 4.22 (1H, d, *J*=14.8 Hz, $CH_aH_bC_6H_4$), 3.62 (1H, dd, *J*=4.8, 12.0 Hz, NCH_aH_bCH), 3.31 (1H, dd, *J*=7.2, 12.0 Hz, NCH_aH_bCH); δ_C (100 MHz, $CDCl_3$) 145.2, 136.3, 135.9, 132.9, 131.2, 129.1, 127.7, 127.1, 127.0, 126.6, 126.2, 126.0, 124.7, 60.4, 50.8, 47.7, 40.3; HRMS (ESI): MH^+, found 356.0776. $C_{19}H_{18}NO_2S_2$ requires 356.0779.

*4.3.6. 4-(4-Chlorophenyl)-2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (**10f**).* Mp: 80–82 °C; R_f (80% hexanes/EtOAc) 0.37; ν_{max}(liquid film) 2921, 1514, 1446, 1166, 1090 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.67–7.71 (m, 2H, SO_2Ph, Ar*H*-2,6), 7.48–7.54 (m, 1H, SO_2Ph, Ar*H*-4), 7.40–7.46 (m, 2H, SO_2Ph, Ar*H*-3,5), 7.09–7.19 (m, 3H, Ar*H*), 7.01–7.06 (m, 2H, C_6H_4Cl, Ar*H*-2,6), 6.93–6.97 (m, 2H C_6H_4Cl, Ar*H*-3,5), 6.78 (d, 1H, *J*=8.0 Hz, Ar*H*), 4.37 (d, 1H, *J*=14.4 Hz, $CH_2C_6H_4$), 4.16–4.24 (m, 2H), 3.61 (dd, 1H, *J*=4.8, 12 Hz, NCH_aH_bCH), 3.10 (dd, 1H, *J*=7.2, 12 Hz, NCH_aH_bCH); δ_C (100 MHz, $CDCl_3$) 140.0, 136.3, 135.6, 132.9, 131.8, 130.2, 129.5, 129.1, 128.7, 127.6, 127.1, 127.0, 126.3, 50.8, 47.8, 44.5; HRMS (ESI): MNa^+, found 406.0645. $C_{21}H_{18}NO_2ClS$ requires 406.0644.

*4.3.7. 4-(3,4-Dimethoxyphenyl)-2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (**10g**).* R_f (80% hexanes/EtOAc) 0.23; ν_{max}(liquid film) 2975, 1688, 1449, 1365, 1159 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.70–7.74 (2H, m, SO_2Ph, Ar*H*-2,6), 7.49–7.54 (1H, m, SO_2Ph, Ar*H*-4), 7.41–7.46 (2H, m, SO_2Ph, Ar*H*-3,5), 7.08–7.13 (1H, m, Ar*H*), 7.00–7.06 (2H, m, Ar*H*), 6.84 (1H, d,) Ar*H*, 6.71 (1H, d, Ar*H*), 6.55–6.60 (2H, m, Ar*H*), 4.43 (1H, d, *J*=14.8 Hz, $CH_2C_6H_4$), 4.12–4.20 (2H, m), 3.79 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.68–3.74 (1H, m, NCH_aH_bCH), 3.03 (1H, dd, *J*=8.0, 12 Hz, NCH_aH_bCH); δ_C (100 MHz, $CDCl_3$) 148.0, 147.1, 136.5, 134.8, 132.8, 131.7, 129.5, 129.1, 127.6, 127.0, 126.7, 126.1, 121.1, 112.0, 111.1, 55.8, 51.0, 47.9, 44.8; HRMS (ESI): MH^+, found 410.1423. $C_{23}H_{24}NO_4S$ requires 410.1426.

*4.3.8. 4-Phenyl-1,2,3,4-tetrahydroisoquinoline (**18a**).* R_f (90% CH_2Cl_2/MeOH) 0.21; ν_{max}(liquid film) 2755, 2650, 1589, 1508, 1222 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25–7.7.31 (2H, m, Ar*H*), 7.13–7.24 (3H, m, Ar*H*), 7.05–7.11 (4H, m, Ar*H*), 6.90 (1H, d, *J*=8.0 Hz, Ar*H*), 4.04–4.18 (3H, m), 3.39 (1H, dd, *J*=5.2, 12.8 Hz, NCH_aH_bCH), 3.09 (1H, dd, *J*=6.0, 12.8 Hz, NCH_aH_bCH), 2.49 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 144.8, 137.3, 136.1, 130.2, 128.8, 128.4, 126.4, 126.3, 125.8, 52.2, 48.4, 44.8; HRMS (ESI): MH^+, found 210.1283. $C_{15}H_{16}N$ requires 210.1283.

*4.3.9. 4-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**18b**).* R_f (90% CH_2Cl_2/MeOH) 0.21; ν_{max}(liquid film) 2633, 1589, 1197, 1080 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.18–7.22 (1H, m, Ar*H*), 7.06–7.15 (3H, m, Ar*H*), 6.96–7.04 (2H, m, Ar*H*), 6.91 (1H, d, *J*=6.0 Hz Ar*H*), 4.07–4.20 (3H, m), 3.40 (1H, dd, *J*=4.4, 10.4 Hz, NCH_aH_bCH), 3.08 (1H, dd, *J*=5.2, 10.4 Hz, NCH_aH_bCH), 2.2 (1H, br s,); δ_C (100 MHz, $CDCl_3$) 162.7, 160.3, 140.5, 137.0, 136.0, 130.1, 126.4, 126.0, 115.3, 115.1, 52.2, 48.3, 44.0; HRMS (ESI): MH^+, found 228.1185. $C_{15}H_{15}NF$ requires 228.1189.

*4.3.10. 4-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**18c**).* R_f (90% CH_2Cl_2/MeOH) 0.18; ν_{max}(liquid film) 2895, 2734, 1439, 1200, 1120, 1026 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.15 (1H, d, *J*=6.0 Hz, Ar*H*), 7.02–7.11 (3H, m, Ar*H*), 7.00 (1H, d, *J*=6.8 Hz, Ar*H*), 6.82 (1H, d, *J*=6.8 Hz, Ar*H*), 6.75 (1H, s, Ar*H*), 4.02–4.06 (3H, m), 3.76 (3H, s, OCH_3), 3.36 (1H, dd, *J*=4.0, 6.0 Hz, NCH_aH_bCH), 3.02–3.09 (1H, m, NCH_aH_bCH); δ_C (100 MHz, $CDCl_3$) 157.1, 138.1, 137.7, 135.9, 127.2, 126.8, 126.2, 125.7, 111.2, 55.0, 52.0, 48.2, 44.1; HRMS (ESI): MH^+, found 240.1385. $C_{16}H_{18}NO$ requires 240.1388.

*4.3.11. 4-p-Tolyl-1,2,3,4-tetrahydroisoquinoline (**18d**).* R_f (90% CH_2Cl_2/MeOH) 0.20; ν_{max}(liquid film) 2918, 1491, 1103, 812, 737 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.12–7.18 (1H, m, Ar*H*), 7.04–7.12 (4H, m, Ar*H*), 6.95–7.01 (2H, m, Ar*H*), 6.90 (1H, d, *J*=7.2 Hz, Ar*H*), 4.03–4.17 (3H, m), 3.38 (1H, dd, *J*=4.8, 12.8 Hz, NCH_aH_bCH), 3.07 (1H, dd, *J*=6.4, 13.2 Hz, NCH_aH_bCH), 2.31 (3H, s, $C_6H_4CH_3$), 2.18 (1H, N*H*); δ_C (100 MHz, $CDCl_3$) 141.8, 137.5, 136.0, 135.9, 130.2, 129.1, 128.2, 126.2, 125.7, 52.2, 48.4, 44.4, 20.9; HRMS (ESI): MH^+, found 224.1443. $C_{16}H_{18}N$ requires 224.1439.

*4.3.12. 4-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (**18e**).* R_f (90% CH_2Cl_2/MeOH) 0.20; ν_{max}(liquid film) 2924, 1488, 1449, 1089, 1013, 826 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23 (2H, d, *J*=8.0 Hz, C_6H_4Cl, H-2,6), 7.16 (1H, t, *J*=7.6 Hz, Ar*H*), 7.07 (2H, t, *J*=8.0 Hz, Ar*H*), 7.02 (2H, d, *J*=8.4 Hz, Ar*H*), 6.86 (1H, d, *J*=7.2 Hz, C_6H_4Cl, H-3,5), 4.02–4.17 (3H, m), 3.37 (1H, dd, *J*=5.2, 12.8 Hz, NCH_aH_bCH), 3.04 (1H, dd, *J*=6.4, 13.2 Hz, NCH_aH_bCH), 2.63 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 143.3, 136.8, 136.1, 132.1, 130.1, 130.0, 128.5, 126.4, 125.9, 60.3, 52.1, 48.3, 44.2; HRMS (ESI): MH^+, found 244.0896. $C_{15}H_{15}NCl$ requires 244.0893.

*4.3.13. 4-Phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**19a**).* ν_{max}(liquid film) 2943, 2686, 1570, 1451, 1184 cm^{-1}; δ_H (400 MHz, D_2O) 7.26–7.35 (3H, m, Ar*H*), 7.19–7.26 (2H, m, Ar*H*), 7.11–7.18 (3H, m, Ar*H*), 6.86 (1H, d, *J*=8.0 Hz, Ar*H*), 4.44–4.52 (2H, m), 4.38 (1H, d, *J*=15.2 Hz, $CH_2C_6H_4$), 3.71 (1H, dd, *J*=6.0, 12.0 Hz, NCH_aH_bCH), 3.39 (1H, dd, *J*=10.0, 12.0 Hz, NCH_aH_bCH); δ_C (100 MHz, D_2O) 143.4, 137.2, 131.9, 131.5, 130.7, 130.3, 130.0, 129.1, 50.0, 47.0, 43.7.

*4.3.14. 4-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (**19b**).* ν_{max}(liquid film) 2755, 2650, 1589, 1508, 1222 cm^{-1}; δ_H (400 MHz, D_2O) 7.19–7.30 (3H, m, Ar*H*), 7.13–7.18 (2H, m, Ar*H*), 7.02–7.08 (2H, m, Ar*H*), 6.90 (1H, d, *J*=8.0 Hz, Ar*H*), 4.46–4.55 (2H, m), 4.39 (1H, d, *J*=16.0 Hz, $CH_2C_6H_4$), 3.74 (1H, dd, *J*=5.6, 12.4 Hz, NCH_aH_bCH), 3.40 (1H, dd, *J*=10.0, 12.4 Hz, NCH_aH_bCH); δ_C (100 MHz, D_2O) 162.2, 134.7, 130.9, 130.8, 129.4, 128.3, 128.2, 127.6, 126.7, 115.8, 115.6, 47.9, 44.9, 40.5.

*4.3.15. 4-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (**19c**).* ν_{max}(liquid film) 2633, 1589, 1197, 1080, 856 cm^{-1}; δ_H (400 MHz, D_2O) 7.33 (2H, d, *J*=8.0 Hz, Ar*H*), 7.23 (3H, m, Ar*H*), 7.12 (2H, d, *J*=8.0 Hz, Ar*H*), 6.89 (1H, d, *J*=7.6 Hz, Ar*H*), 4.46–4.55 (2H,

m), 4.38 (1H, d, J=16.0 Hz, CH_2C$_6$H$_4$), 3.74 (1H, dd, J=5.6,12.0 Hz, NCH_aH$_b$CH), 3.38 (1H, dd, J=10.0, 12.0 Hz, NCH$_a$$H_b$CH); δ_C (100 MHz, D$_2$O) 158.2, 135.0, 133.4, 130.2, 129.3, 128.2, 128.0, 127.4, 127.4, 126.6, 114.4, 55.4, 47.9, 44.8, 40.4.

*4.3.16. 4-p-Tolyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**19d**).* ν_{max}(liquid film) 2895, 2734, 1439, 1200, 1120, 1026 cm^{-1}; δ_H (400 MHz, D$_2$O) 7.18–7.28 (3H, m, ArH), 7.16 (2H, d, J=8.0 Hz, C$_6H_4$CH$_3$, H-2,6), 7.05 (2H, d, J=8.0 Hz, C$_6H_4$CH$_3$, H-3,5), 6.87 (1H, d, J=7.6 Hz, ArH), 4.43–4.51 (2H, m), 4.37 (1H, d, J=16.0 Hz, CH_2C$_6$H$_4$), 3.70 (1H, dd, J=6.0, 12.4 Hz, NCH_aH$_b$CH), 3.38 (1H, dd, J=10.0, 12.4 Hz, NCH$_a$$H_b$CH), 2.23 (3H, s, C$H_3$); δ_C (100 MHz, D$_2$O) 139.3, 136.6, 132.8, 129.5, 129.3, 129.1, 128.8, 127.7, 126.9, 126.1, 51.1, 48.0, 44.8, 21.0.

*4.3.17. 4-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (**19e**).* ν_{max}(liquid film) 2761, 2644, 1513, 1440, 1421 cm^{-1}; δ_H (400 MHz, D$_2$O) 7.34 (2H, d, J=8.4 Hz, C$_6H_4$Cl, H-2,6), 7.19–7.26 (3H, m, ArH), 7.13 (2H, d, J=8.4 Hz, C$_6H_4$Cl, H-3,5), 6.88 (1H, d, J=8.0 Hz, ArH), 4.46–4.55 (2H, m), 4.39 (1H, J=16.0 Hz, CH_2C$_6$H$_4$), 3.74 (1H, dd, J=6.0, 12.4 Hz, NCH_aH$_b$CH), 3.40 (1H, dd, J=10.0, 12.4 Hz, NCH$_a$$H_b$CH); δ_C (100 MHz, D$_2$O) 142.0, 133.1, 131.9, 131.4, 130.8, 130.1, 129.5, 129.2, 50.2, 47.4, 43.1.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.03.074.

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