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PAPER

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Stereoselective synthesis of 1,3-disubstituted dihydroisoquinolines *via* L-phenylalanine-derived dihydroisoquinoline *N*-oxides†

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The preparation of chiral pool-derived nitrone **3** and its use in the protecting-group free, stereoselective synthesis of a range of 1,3-disubstituted tetrahydroisoquinolines is described. Grignard reagent additions to nitrone **3** yielded *trans*-1,3-disubstituted *N*-hydroxytetrahydroisoquinolines **6** with good levels of selectivity, while 1,3-dipolar cycloadditions to this nitrone provided access to 3-(2-hydroxyalkyl)isoquinolines **12** as single diastereomers.

Introduction

Tetrahydroisoquinoline (THIQ) systems occur in a wide range of natural products and therapeutic drugs[1] and have been highlighted both as privileged scaffolds[2] and as useful moieties in fragment-based drug discovery.[3] Moreover, there is interest in the use of tetrahydroisoquinolines as ligands in asymmetric catalysis[4] and as chiral bases.[5] The methods for accessing 1,3-disubstituted THIQ's, can be broadly grouped into two strategies, based on either cyclisations of suitably substituted aromatic precursors[6] or functionalisation of isoquinoline-based scaffolds.[7] In an effort to develop a strategy towards enantiodefined tetrahydroisoquinolines, of general use, we became interested in an approach of the latter type utilizing a chiral pool-derived isoquinoline unit with a potentially broad reactivity profile. The only previous approaches with these criteria utilize either 1-lithiated derivative **1**[8] or imine **2**[5] – with reactivity restricted to additions to electrophiles or nucleophiles respectively (Fig. 1).

We envisaged that nitrone **3** would exhibit much utility in this regard. The core scaffold is readily accessible, in enantio-

enriched form from L-phenylalanine, and the reactivity of the nitrone group, functionalised *via* 1,3-dipolar cycloaddition,[9] nucleophilic addition[10] and reductive coupling with electrophiles,[11] confers wide scope to this system (Scheme 1). Furthermore, the hydroxymethyl group functions as a readily removable stereocontrol element.[12]

Results and discussion

Preparation of nitrone 3

Our approach to nitrone **3** centred on the oxidation of the known amine **5** (Scheme 2), accessed by Pictet–Spengler reaction of L-phenylalanine,[13] followed by borane-mediated reduction of the resulting acid.[5] Trialing a range of methods for the direct oxidative conversion of amines to nitrones, revealed that the corresponding isoquinoline *N*-oxide was a significant byproduct. Best results were achieved using Oxone as oxidant, providing dihydroisoquinoline derived nitrone **3** cleanly, in moderate yield (58%), with no evidence of overoxidation to the corresponding isoquinoline *N*-oxide.[14]
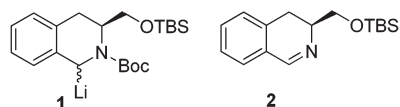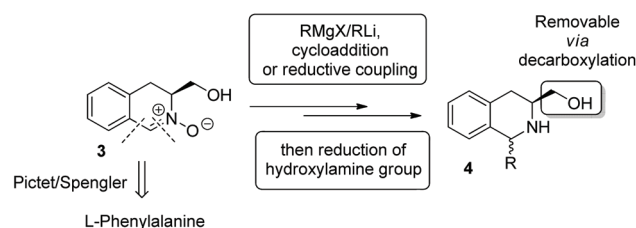

Fig. 1 Previous chiral pool-derived THIQ precursors.

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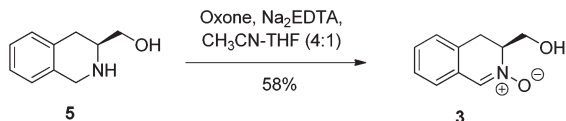*E-mail: b.macia-ruiz@mmu.ac.uk, v.caprio@mmu.ac.uk*
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ob02007h

Scheme 1 Synthetic approaches to 1,3-disubstituted tetrahydroisoquinolines utilising nitrone **3**.

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Paper

Scheme 2 Synthesis of nitrone **3**.

Table 1 Optimization of the addition of organometallic reagents to nitrone **3**[a]

Entry	RM	Solvent	T (°C)	**6a/7a**[b]	Conv.[c] (%)
1	MeMgBr	CH$_2$Cl$_2$	0	4.5/1	>99
2	MeMgBr	PhMe	0	7.1/1	>99
3	MeMgBr	Dioxane	0	3.0/1	>99
4	MeMgBr	^{t}BuOMe	0	3.5/1	>99
5	MeMgBr	Et$_2$O	0	5.5/1	>99
6	MeMgBr	THF	20	6.0/1	>99
7	MeMgBr	THF	0	7.5/1	>99
8	MeMgBr	THF	−20	7.5/1	>99
9	MeMgBr	THF	−40	7.5/1	>99
10	MeLi	THF	0	3.8/1	>99

[a] Reaction conditions: **3** (0.1 mmol), RM (3 eq.), T, solvent. [b] Ratio determined by analysis of ^{1}H-NMR spectra of crude products. Relative stereochemistry determined by 2D-NOESY studies; see ESI for further details. [c] Determined by ^{1}H-NMR analysis of crude products.

Addition of organometallic reagents to nitrone 3

With nitrone **3** in hand, the nucleophilic addition of organometallic reagents was initially investigated by screening of a range of solvents and temperatures, using methylmagnesium bromide and methyllithium as test reagents (Table 1). In all cases, full conversion was achieved using 3 equivalents of nucleophile, with the 1,3-*trans* isomer **6a** as the major product. THF provided the best diastereomeric ratios and no advantage was conferred by performing the reaction under cryogenic conditions see (entries 7–9). It is noteworthy that, while the addition of the more reactive methyllithium proceeded with full conversion, stereoselectivity was lower than that obtained with the corresponding Grignard reagent (entry 10 *vs.* entry 7). Consequently, subsequent studies were performed using Grignard species under the conditions outlined in entry 7.

The addition of different Grignard reagents to nitrone **3** provided, in all cases, the *trans*-isomer **6** as the major product (Table 2). No discernable trends are evident in Table 2, although the best levels of selectivity were obtained with the larger phenylmagnesium bromide (entry 5). *Cis/trans* stereochemistry of products **6** and **7** was assigned by 2D NOESY analysis (see Fig. 2 for an example). Strong correlations between the protons of the C1-substituent and H3 were observed in the *trans*-adduct, while the *trans*-diaxial correlations between H1 and H3 revealed the *cis*-diequatorial substitution pattern of the minor adduct, as illustrated on the ethyl-adduct **6b/7b**.

Table 2 Addition of organometallic reagents to nitrone **3**[a]

Entry	RM	Products	**6 : 7**[a,b]	Yield[c] (%)
1	MeMgBr	**6a/7a**	7.5/1	75
2	EtMgBr	**6b/7b**	6.5/1	87
3	^{i}PrMgBr	**6c/7c**	5.9/1	85
4	AllylMgBr	**6d/7d**	2.8/1	90
5	PhMgBr	**6e/7e**	10/1	96

[a] Reaction conditions: **3** (0.3 mmol), RMgBr (3 eq.), THF, 0 °C to r.t. [b] Ratio determined by analysis of crude ^{1}H-NMR spectra. Relative stereochemistry determined by 2D-NOESY studies, see Fig. 2 and ESI for further details. [c] Isolated combined yield after column chromatography.
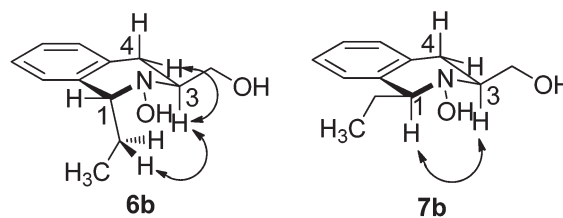
Fig. 2 Selected correlations observed in the 2D-NOESY spectra of tetrahydroisoquinolines **6b** and **7b**.

The effect of protection of the 3-hydroxymethyl group, in combination with increasing size of the 3-substituent, was investigated by studying the addition of different Grignard reagents to the TBS-protected nitrone **8** (Table 3), prepared by sodium tungstate-catalysed-oxidation of the known TBS-derivative of hydroxymethyl-THIQ **5**.[5,15] The addition of both ethyl- and phenylmagnesium bromide to **8** proceeded in favour of the *trans*-adducts **9**, but with much lower selectivities than those obtained with the unprotected nitrone **3** (compare Table 3, entries 1 and 2 with Table 2, entries 2 and 5, respectively).

These results indicate that, in addition to the metal, (see Table 1, entries 7 and 10, for the addition of MeMgBr and

Table 3 Addition of organometallic reagents to nitrone **8**[a]

Entry	RM	Product	**9/10**[b]	Yield[c] (%)
1	EtMgBr	**9a/10a**	2.5/1	56
2	PhMgBr	**9b/10b**	3/1	53

[a] Reaction conditions: **8** (0.3 mmol), RMgBr (3 eq.), THF, 0 °C to r.t. [b] Ratio determined by ^{1}H-NMR on the reaction crude. Relative stereochemistry determined by 2D-NOESY studies. [c] Isolated combined yield after column chromatography.
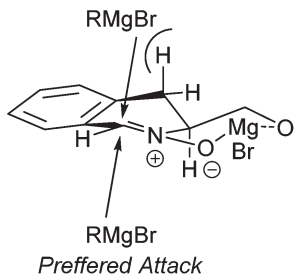
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Fig. 3 Proposed mode of addition of Grignard reagents to nitrone **3**.
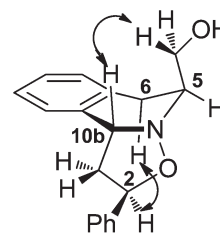

Fig. 4 Selected correlations observed in the 2D-NOESY spectrum of **11a**.

MeLi, respectively), the nitrone oxygen and the free hydroxyl group play an important role in determining the mode and level of diastereoselectivity in the addition to **3**. This hypothesis is supported by the results obtained with imine **2**, where the selectivities of the addition of organolithium species are generally lower than those reported in Table 2 for all but the largest nucleophiles.[5] We propose the model depicted in Fig. 3 to account for this selectivity, which involves a cyclic magnesium chelate similar to that hypothesized during additions to *N*-glycosyl nitrones.[16] In our model, the *syn* addition is hindered by the pseudo-axial proton at C4.

Cycloaddition reactions of nitrone 3

Next, the preparation of more functionalized, stereodefined 1,3-THIQ systems was investigated *via* 1,3-dipolar cycloaddition of **3** with a range of alkenes, followed by reduction of the resulting isoxazolidines **11** (Table 4). Styrene and hex-1-ene were chosen as the prototypical model dipolarophiles (entries 1 and 2), alongside functionalized butenes, selected to access products of subsequent synthetic utility (entries 3 and 4). Optimum yields/selectivity were obtained in toluene under reflux conditions. The stereochemistry of the cycloaddition was readily deduced by analysis of 2D-NOESY spectra of cycloadducts **11** (see an example in Fig. 4), which revealed strong correlations between H2/H6 and H10b/CH_2(OH). In all cases, the *exo*-1,3-*trans*-isoxazolidine was exclusively obtained in moderate to good yield and no traces of any other isomers

were detected in the ^{1}H NMR spectra of crude products. The cycloaddition reactions of nitrone **3** with a range of electron deficient systems, including acrylates, were trialed but, unfortunately, failed to provide the corresponding cycloadducts.

The subsequent reductive N–O bond cleavage of isoxazolidine **11**, with zinc powder in AcOH, proceeded with no stereochemical degradation,[17] providing the corresponding 1,3-THIQ **12a–d** in good to moderate yields (Table 2).

Conclusions

In conclusion, we have developed an approach to the synthesis of a range of optically active 1,3-disubstituted tetrahydroisoquinolines from (*S*)-3-(hydroxymethyl)-3,4-dihydroisoquinoline 2-oxide **3**. The addition of Grignard reagents to **3** proceeded with good yields and stereoselectivities, and unprecedented levels of stereoselection were found for the dipolar cycloaddition reaction of alkenes to nitrone **3**. This strategy allows the direct assembly of highly functionalized tetrahydroisoquinoline units with up to three stereogenic centres in a simple and effective manner, starting from a readily available chiral substrate.

Experimental

General

^{1}H NMR and ^{13}C NMR have been recorded on a JEOL® ECS-400 (400 and 100.6 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with TMS as internal standard ($CDCl_3$: δ 7.26 for ^{1}H-NMR, δ 77.0 for ^{13}C-NMR). Data are reported as follows: chemical shifts, multiplicity (s = singlet, quint = quintuplet, m = multiplet), coupling constants (Hz), and integration. IR spectra were recorded on Nicolet® 380 FT/IR – Fourier Transform Infrared Spectrometer. Only the most significant frequencies have been considered during the characterization, and have been reported in cm^{−1}. High resolution mass spectra were measured on an Agilent Technologies® 6540 Ultra-High-Definition (UHD) Accurate-Mass equipped with a time of flight (Q-TOF) analyzer and the samples were ionized by ESI techniques and introduced through a high pressure liquid chromatography (HPLC) model Agilent Technologies® 1260 Infinity Quaternary LC system. Optical rotations were measured on a Bellingham + Stanley®

Table 4 Cycloaddition of nitrone 3 and reduction of cycloadducts **11**[a]

Entry	R	Product	**11**[b] (% yield)	**12**[b] (% yield)
1	Ph	**11a/12a**	86	33
2	$(CH_2)_3CH_3$	**11b/12b**	74	90
3	$(CH_2)_2OBn$	**11c/12c**	61	51
4	$(CH_2)_2SPh$	**11d/12d**	64	47

[a] Reaction conditions: (i) CH_2=CH_2R (5 eq.), toluene, 110 °C; (ii) AcOH, Zn, reflux. [b] Isolated yield after flash chromatography. Relative stereochemistry determined by 2D-NOESY studies, see Fig. 4 and ESI for further details.

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ADP 440 + Polarimeter with a 0.5 cm cell (c given in g per 100 mL).

All reactions were monitored by thin-layer chromatography using precoated sheets of silica gel 60, 0.25 mm thick (F254 Merck KGaA®). The components were visualized by UV light (254 nm) and phosphomolybdic acid. Flash column chromatography was done using Geduran® Silica gel 60, 40–63 microns RE. The eluent used is mentioned in each particular case. All glassware employed during inert atmosphere experiments was flame-dried under a stream of dry argon. Alkenes reagents were purchased from Sigma-Aldrich or Fisher Scientific and used without further purification. Grignard and organolithium reagents were purchased from Sigma-Aldrich. Anhydrous THF was obtained from a Pure Solv™ Solvent Purification Systems.

(S)-3-(Hydroxymethyl)-3,4-dihydroisoquinoline-2-oxide (3). NaHCO$_3$ (6.72 g, 80.0 mmol) was added to a solution of tetra-hydroisoquinoline **5** (2.6 g, 16.0 mmol) in THF–CH$_3$CN 1 : 4 (28 mL) and 0.01 M aqueous EDTA solution (22.4 mL) at 5 °C. Oxone (10.3 g, 16.8 mmol) was then added portionwise over 2 h, and the mixture stirred for 20 min, at 5 °C. Ethyl acetate (80 mL) was added and the aqueous layer further extracted with ethyl acetate (2 × 80 mL). The combined organic extracts were dried over anhydrous MgSO$_4$ and concentrated under reduced pressure to give nitrone **3** (1.66 g, 59%) as a pale yellow solid; m.p. decomposes $T > 145$ °C; $[\alpha]_D^{25}$ 174 ($c = 3.3$, CHCl$_3$); IR (ATR): $\nu = 3242, 3054, 2945, 2897$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta_H = 7.80$ (s, 1H), 7.35–7.25 (m, 2H), 7.25–7.20 (m, 1H), 7.18–7.14 (m, 1H), 4.51 (br s, 1H), 4.26–4.16 (m, 1H), 4.04 (dd, $J = 12.0, 6.9$ Hz, 1H), 3.94 (dd, $J = 12.0$, 3.6 Hz, 1H), 3.22–3.07 (m, 2H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): $\delta_C = 135.4, 130.0, 129.8, 127.6, 127.5, 127.2, 125.6, 67.2, 62.7, 29.8$ ppm; MS (EI, 70 eV): m/z (%) = 177 (M$^+$, 8), 130 (100), 115 (34), 103 (22), 77 (26); HRMS (ESI-MeOH): m/z calcd for C$_{10}$H$_{12}$NO$_2$ [M + H]$^+$: 178.0863 found 178.0862.

General procedure for the diastereoselective addition of Grignard reagents

A solution of RMgBr (0.9 mmol, 3 eq.) was added to a solution of nitrone **3** (53.1 mg, 0.3 mmol) in THF (1.5 mL). The mixture was stirred at 0 °C for 1 h and then warmed to room temperature and quenched with water. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic phases dried over MgSO$_4$, and concentrated under reduced pressure. The crude product, was purified by flash column chromatography eluting with *n*-hexane/EtOAc (gradient from 10 to 60%) to give the corresponding 1,3-disubstituted tetrahydroisoquinoline-2-ol as a yellow oil.

(1R,3S)-3-(Hydroxymethyl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-ol (6a) and (1S,3S)-3-(hydroxymethyl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-ol (7a). Following the general procedure, the reaction of methylmagnesium bromide (3.0 M in Et$_2$O, 300 μL) with nitrone **3** gave the 1,3-disubstituted tetrahydroisoquinoline-2-ol **6a** (38 mg, 66% yield) as a yellow oil. $[\alpha]_D^{25}$ −15 ($c = 1$, CHCl$_3$); IR (ATR): $\nu = 3240, 3019, 2973, 2932$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta_H = 7.17–7.10$ (m, 2H), 7.10–7.01 (m, 2H), 4.32 (q, $J = 7.1$, 1H), 3.82 (dd, $J = 11.5, 7.6$ Hz, 1H), 3.72

(br s, 1H), 3.41–3.34 (m, 1H), 2.93 (dd, $J = 16.7, 11.5$ Hz, 1H), 2.53 (d, $J = 14.8$ Hz, 1H), 1.41 (d, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): $\delta_C = 137.6, 132.2, 128.7, 127.3, 126.4, 126.2, 63.2, 62.4, 56.5, 25.8, 21.0$ ppm; HRMS (ESI-MeOH): m/z calcd for C$_{11}$H$_{16}$NO$_2$ [M + H]$^+$: 194.1176 found 194.1778. **7a** (5 mg, 9% yield) as a yellow oil. $[\alpha]_D^{25}$ −27 ($c = 1$, CHCl$_3$); IR (ATR): $\nu = 3257, 2981, 2930, 2880$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta_H = 7.22–7.11$ (m, 3H), 7.10–7.04 (m, 1H), 4.06 (q, $J = 6.6$ Hz, 1H), 3.82–3.78 (m, 2H), 3.16 (brs, 1H), 3.03 (dd, $J = 16.2, 12.1$ Hz, 1H), 2.65 (d, $J = 14.8$ Hz, 1H), 1.61 (d, $J = 6.6$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): $\delta_C = 137.2, 133.0, 128.2, 126.6, 126.4, 126.0, 64.3, 64.0, 62.6, 29.7, 18.4$ ppm; HRMS (ESI-MeOH): m/z calcd for C$_{11}$H$_{16}$NO$_2$ [M + H]$^+$: 194.1176 found 194.1177.

(1R,3S)-1-Ethyl-3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-ol (6b) and (1S,3S)-1-ethyl-3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-ol (7b). Following the general procedure, the reaction of ethylmagnesium bromide (3.0 M in Et$_2$O, 300 μL) with nitrone **3** gave the 1,3-disubstituted tetrahydroisoquinoline-2-ol **6b** (47 mg, 76% yield) as a yellow oil. $[\alpha]_D^{25}$ +3 ($c = 1$, CHCl$_3$); IR (ATR): $\nu = 3285, 3062, 2931, 2873$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta_H = 7.20–7.12$ (m, 2H), 7.10–7.07 (m, 2H), 4.07 (t, $J = 7.5$ Hz, 1H), 3.84 (dd, $J = 10.2, 9.0$ Hz, 1H), 3.68 (dd, $J = 11.0, 3.5$ Hz, 1H), 3.40–3.33 (m, 1H), 2.90 (dd, $J = 16.7, 11.7$ Hz, 1H), 2.52 (dd, $J = 16.7, 5.0$ Hz, 1H), 1.76–1.63 (m, 2H), 1.10 (t, $J = 7.5$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): $\delta_C = 136.7, 132.4, 128.8, 127.8, 126.4, 126.0, 68.9, 63.1, 56.2, 29.4, 24.6, 11.9$ ppm; HRMS (ESI-MeOH): m/z calcd for C$_{12}$H$_{18}$NO$_2$ [M + H]$^+$: 208.1332 found 208.1334. **7b** (7 mg, 11% yield) as a yellow oil. $[\alpha]_D^{25}$ −29 ($c = 1$, CHCl$_3$); IR (ATR): $\nu = 3279, 2961, 2931, 2873$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta_H = 7.22–7.11$ (m, 3H), 7.08 (d, $J = 7.1$ Hz, 1H), 4.00 (t, $J = 4.6$ Hz, 1H), 3.81 (d, $J = 4.9$ Hz, 2H), 3.17–3.09 (m, 1H), 2.96 (dd, $J = 16.1, 12.0$ Hz, 1H), 2.64 (dd, $J = 16.1, 4.0$ Hz, 1H), 2.29–2.17 (m, 1H), 2.01–1.89 (m, 1H), 0.92 (t, $J = 7.3$ Hz, 1H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): $\delta_C = 136.0, 133.9, 128.2, 126.3, 126.3, 125.9, 67.7, 64.9, 63.4, 29.7, 24.1, 9.2$ ppm; HRMS (ESI-MeOH): m/z calcd for C$_{12}$H$_{18}$NO$_2$ [M + H]$^+$: 208.1332 found 208.1334.

(1R,3S)-3-(Hydroxymethyl)-1-isopropyl-3,4-dihydroisoquinolin-2(1H)-ol (6c) and (1S,3S)-3-(hydroxymethyl)-1-isopropyl-3,4-dihydroisoquinolin-2(1H)-ol (7c). Following the general procedure, the reaction of isopropylmagnesium bromide (0.75 M in THF, 1.2 mL) with nitrone **3** gave the 1,3-disubstituted tetrahydroisoquinoline-2-ol **6c** (48 mg, 73% yield) as a yellow oil. $[\alpha]_D^{25}$ +15 ($c = 1$, CHCl$_3$); IR (ATR): $\nu = 3308, 3020, 2956, 2871$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta_H = 7.20–7.12$ (m, 2H), 7.12–7.05 (m, 2H), 3.85 (dd, $J = 11.3, 8.6$ Hz, 1H), 3.79 (d, $J = 8.7$ Hz, 1H), 3.64 (dd, $J = 11.3, 3.6$ Hz, 1H), 3.46–3.35 (m, 1H), 2.81 (dd, $J = 17.1, 11.3$ Hz, 1H), 2.57 (dd, $J = 17.1, 6.1$ Hz, 1H), 1.85–1.70 (m, 1H), 1.09 (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.7$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): $\delta_C = 135.0, 132.8, 129.3, 128.8, 126.5, 125.2, 73.3, 63.2, 56.2, 33.2, 24.5, 21.2, 20.8$ ppm; HRMS (ESI-MeOH): m/z calcd for C$_{13}$H$_{20}$NO$_2$ [M + H]$^+$: 222.1489 found 222.1483. **7c** (8 mg, 12% yield) as a yellow oil. $[\alpha]_D^{25}$ +88 ($c = 1$, CHCl$_3$); IR (ATR): $\nu = 3311, 3020, 2956, 2871$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta_H = 7.22–7.07$ (m, 4H), 4.12 (d, $J = 3.7$ Hz, 1H), 3.93 (dd, $J = 11.1, 3.0$ Hz, 1H), 3.72 (dd, $J = 11.1$,

4.5 Hz, 1H), 3.11–3.01 (m, 1H), 2.88 (dd, J = 15.6, 12.4 Hz, 1H), 2.59 (dd, J = 15.6, 3.2 Hz, 1H), 2.29–2.12 (m, 1H), 1.06 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 136.8, 134.9, 127.5, 126.8, 126.1, 126.0, 73.8, 64.9, 63.7, 34.6, 30.9, 20.6, 17.9 ppm; HRMS (ESI-MeOH): m/z calcd for C$_{13}$H$_{20}$NO$_2$ [M + H]$^+$: 222.1489 found 222.1482.

(1R,3S)-1-Allyl-3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-ol (6d) and (1S,3S)-1-allyl-3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-ol (7d). Following the general procedure, the reaction of allylmagnesium bromide (1.0 M in Et$_2$O, 900 μL) with nitrone **3** gave the 1,3-disubstituted tetrahydroisoquinoline-2-ol **6d** (44 mg, 67% yield) as a yellow oil. $[\alpha]_D^{25}$ −51 (c = 1, CHCl$_3$); IR (ATR): ν = 3302, 3076, 3021, 2928, 2044 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.21–7.13 (m, 2H), 7.13–7.04 (m, 2H), 6.01–5.85 (m, 1H), 5.09–5.05 (m, 2H), 4.26 (t, J = 7.4 Hz, 1H), 3.83 (dd, J = 11.2, 8.4 Hz, 1H), 3.68 (dd, J = 11.2, 3.4 Hz, 1H), 3.44–3.35 (m, 1H), 2.92 (dd, J = 16.7, 11.7 Hz, 1H), 2.53 (dd, J = 16.7, 4.7 Hz, 1H), 2.49–2.39 (m, 2H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 135.8, 135.5, 132.5, 128.8, 127.7, 126.6, 126.0, 117.1, 66.8, 63.1, 56.3, 40.6, 24.7 ppm; HRMS (ESI-MeOH): m/z calcd for C$_{13}$H$_{18}$NO$_2$ [M + H]$^+$: 220.1332 found 220.1325. **7d** (15 mg, 23% yield) as a yellow oil. $[\alpha]_D^{25}$ −41 (c = 1, CHCl$_3$); IR (ATR): ν = 3280, 3075, 3021, 2927, 2042 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.26–7.14 (m, 3H), 7.14–7.06 (m, 1H), 6.02–5.87 (m, 1H), 5.16 (dd, J = 17.2, 1.6 Hz, 1H), 5.06 (d, J = 10.3 Hz, 1H), 4.15 (t, J = 5.7 Hz, 1H), 3.85–3.74 (m, 2H), 3.21–3.12 (m, 1H), 3.02–2.95 (m, 2H), 2.78–2.69 (m, 1H), 2.63 (dd, J = 16.3, 3.8 Hz, 1H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 136.3, 135.8, 133.8, 128.4, 126.5, 126.4, 126.1, 116.4, 66.1, 64.6, 63.3, 36.8, 28.9 ppm; HRMS (ESI-MeOH): m/z calcd for C$_{13}$H$_{18}$NO$_2$ [M + H]$^+$: 220.1332 found 220.1326.

(1R,3S)-3-(Hydroxymethyl)-1-phenyl-3,4-dihydroisoquinolin-2(1H)-ol (6e) and (1S,3S)-3-(hydroxymethyl)-1-phenyl-3,4-dihydroisoquinolin-2(1H)-ol (7e). Following the general procedure, reaction of phenylmagnesium bromide (3.0 M in Et$_2$O, 300 μL) with nitrone **3** gave the 1,3-disubstituted tetrahydroisoquinoline-2-ol **6e** (67 mg, 87% yield) as a yellow oil. $[\alpha]_D^{25}$ −84 (c = 1, CHCl$_3$); IR (ATR): ν = 3240, 3061, 3026, 2889 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.29–7.24 (m, 3H), 7.23–7.18 (m, 2H), 7.18–7.12 (m, 1H), 7.12–7.06 (m, 2H), 6.91 (d, J = 7.6 Hz, 1H), 5.33 (s, 1H), 3.77 (dd, J = 11.4, 7.6 Hz, 1H), 3.55 (d, J = 9.2 Hz, 1H), 3.36–3.26 (m, 1H), 2.96 (dd, J = 16.9, 10.1 Hz, 1H), 2.70 (dd, J = 16.9, 5.1 Hz, 1H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 140.6, 134.0, 133.3, 130.2, 129.0, 128.6, 128.2, 127.7, 127.0, 126.2, 70.3, 62.8, 56.7, 26.2 ppm; HRMS (ESI-MeOH): m/z calcd for C$_{16}$H$_{18}$NO$_2$ [M + H]$^+$: 256.1332 found 256.1336. **7e** (6 mg, 9% yield) as a yellow oil. $[\alpha]_D^{25}$ +4.5 (c = 1, CHCl$_3$); IR (ATR): ν = 3238, 3061, 3025, 2890 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.35–7.30 (m, 2H), 7.29–7.23 (m, 2H), 7.15–7.08 (m, 2H), 7.03–6.95 (m, 1H), 6.54 (d, J = 7.8 Hz, 1H), 5.35 (br s, 1H), 4.88 (s, 1H), 3.95–3.82 (m, 1H), 3.77 (dd, J = 11.8, 5.3 Hz, 1H), 3.21 (d, J = 11.8 Hz, 1H), 3.14 (dd, J = 27.5, 11.8 Hz, 2H), 2.82 (d, J = 15.6 Hz, 1H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 141.9, 136.6, 133.2, 130.3, 128.3, 128.2, 127.8, 127.7, 126.7, 125.9, 75.1, 64.8, 64.6, 31.6 ppm; HRMS (CI-CH$_4$): m/z calcd for C$_{16}$H$_{18}$NO$_2$ [M + H]$^+$: 256.1332 found 256.1337.

(S)-3-(((tert-Butyldimethylsilyl)oxy)methyl)-3,4-dihydroisoquinoline 2-oxide (8). A solution of (S)-3-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dihydroisoquinoline[5,15] (0.76 g, 2.77 mmol) was added to a solution of sodium tungstate (0.14 g, 0.046 mmol) in methanol (1 mL). A 30% aqueous solution of H$_2$O$_2$ (1.0 mL, 8.31 mmol) was added at 0 °C over a period of 30 min and the reaction mixture was warmed to room temperature and stirred overnight. The mixture was concentrated under reduced pressure, diluted with brine and extracted with CH$_2$Cl$_2$ (2 × 15 mL). The combined organic layers were dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography, using CHCl$_3$–CH$_3$OH (10 : 1) as eluent, to give nitrone **10** (0.46 g, 57%) as a viscous oil. $[\alpha]_D^{25}$ −36 (c = 1, CHCl$_3$); IR (ATR): ν = 2952, 2927, 2883, 2855 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.73 (s, 1H), 7.28–7.18 (m, 3H), 7.08 (d, J = 6.9 Hz, 1H), 4.16–4.08 (m, 1H), 3.96 (dd, J = 9.9, 3.8 Hz, 1H), 3.84 (dd, J = 9.9, 7.7 Hz, 1H), 3.42 (dd, J = 16.7, 7.3 Hz, 1H), 3.25 (dd, J = 16.8, 3.2 Hz, 1H), 0.79 (s, 9H), −0.01 (s, 3H), −0.03 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 134.8, 129.6, 129.2, 127.7, 127.6, 127.2, 125.1, 68.8, 61.8, 29.2, 25.5, 18.0, −5.7, −5.78 ppm; HRMS (ESI-MeOH): m/z calcd for C$_{16}$H$_{26}$NO$_2$Si [M + H]$^+$: 292.1727 found 292.1734.

(1R,3S)-3-(((tert-Butyldimethylsilyl)oxy)methyl)-1-ethyl-3,4-dihydroisoquinolin-2(1H)-ol (9a) and (1S,3S)-3-(((tert-butyldimethylsilyl)oxy)methyl)-1-ethyl-3,4-dihydroisoquinolin-2(1H)-ol (10a). Following the general procedure, the reaction of ethylmagnesium bromide (3.0 M in Et$_2$O, 300 μL) with nitrone **8** gave the 1,3-disubstituted tetrahydroisoquinoline-2-ol **9a** (38 mg, 40% yield) as a yellow solid; m.p. 50–51 °C; $[\alpha]_D^{25}$ −12 (c = 1.2, CHCl$_3$); IR (ATR): ν = 3229, 3063, 2954, 2928, 2856, 1462, 1252, 1100, 834, 774, 748 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.18–7.09 (m, 4H), 6.42 (br s, 1H), 4.05 (dd, J = 8.3, 6.3 Hz, 1H), 3.99 (dd, J = 10.0, 5.6 Hz, 1H), 3.79 (dd, J = 10.0, 6.1 Hz, 1H), 3.31 (td, J = 11.1, 5.6 Hz, 1H), 2.98 (dd, J = 16.7, 11.0 Hz, 1H), 2.66 (dd, J = 16.7, 5.2 Hz, 1H), 1.76–1.67 (m, 2H), 1.09 (t, J = 7.4Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 137.4, 133.3, 128.9, 127.8, 126.3, 126.0, 68.7, 65.5, 56.6, 29.7, 26.1, 25.6, 18.5, 11.9, −5.1, −5.2 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{18}$H$_{31}$NO$_2$Si [M + H]$^+$ 322.2202 found 322.2197. **10a** (16 mg, 16% yield) as a yellow oil. $[\alpha]_D^{25}$ −7 (c = 1.5, CHCl$_3$); IR (ATR): ν = 3263, 3066, 2954, 2928, 2855, 1462, 1252, 1103, 834, 775, 739 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.19–7.11 (m, 4H), 5.05 (br s, 1H), 4.03 (dd, J = 10.0, 4.9 Hz, 1H), 3.96 (t, J = 4.6 Hz, 1H), 3.77 (dd, J = 10.0, 6.2 Hz, 1H), 3.09 (m, 1H), 2.93–2.86 (m 1H), 2.79 (dd, J = 16.2, 4.2 Hz, 1H), 2.28–2.17 (m, 1H), 1.98–187 (m, 1H), 0.92 (s, 9H), 0.89 (t, J = 7.2 Hz, 1H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 136.6, 134.6, 128.3, 126.3, 126.2, 126.0, 68.1, 66.1, 63.6, 29.9, 26.1, 24.6, 18.5, 9.2, −5.1, −5.2 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{18}$H$_{31}$NO$_2$Si [M + H]$^+$ 322.2202 found 322.2197.

(1R,3S)-3-(((tert-Butyldimethylsilyl)oxy)methyl)-1-phenyl-3,4-dihydroisoquinolin-2(1H)-ol (9b) and (1S,3S)-3-(((tert-butyldimethylsilyl)oxy)methyl)-1-phenyl-3,4-dihydroisoquinolin-2(1H)-(10b). Following the general procedure, the reaction of phenyl-

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magnesium bromide (3.0 M in Et$_2$O, 300 μL) with nitrone **8** gave the 1,3-disubstituted tetrahydroisoquinoline-2-ol **9b** (44 mg, 40% yield) as a yellow oil. $[\alpha]_D^{25}$ −4 (c = 1, CHCl$_3$); IR (ATR): ν = 3213, 3062, 2927, 2855 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ = 7.39–7.31 (m, 3H), 7.29–7.28 (m, 2H), 7.25–7.17 (m, 3H), 6.96 (d, J = 7.7 Hz, 1H), 6.92 (s, 1H), 5.28 (s, 1H), 4.06 (dd, J = 10.0, 5.2 Hz, 1H), 3.82 (dd, J = 10.0, 6.7 Hz, 1H), 3.48–3.40 (m, 1H), 3.14 (dd, J = 16.8, 8.3 Hz, 1H), 2.98 (dd, J = 16.8, 5.3 Hz, 1H), 0.92 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ$_C$ = 141.8, 134.9, 133.7, 130.0, 128.9, 128.7, 128.1, 127.4, 126.7, 125.9, 70.0, 63.4, 57.5, 27.2, 25.8, 18.2, −5.4, −5.5 ppm; HRMS (ESI-MeOH): m/z calcd for C$_{22}$H$_{32}$NO$_2$Si [M + H]$^+$ 370.2197 found 370.2205. **10b** (15 mg, 13% yield) as a yellow oil. $[\alpha]_D^{25}$ −55 (c = 1, CHCl$_3$); IR (ATR): ν = 3306, 3028, 2927, 2854 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ = 7.39–7.34 (m, 5H), 7.16–7.11 (m, 2H), 7.04–6.97 (m, 1H), 6.59 (d, J = 7.8 Hz, 1H), 4.89 (s, 2H), 4.16 (dd, J = 9.9, 4.4 Hz, 1H), 3.79 (dd, J = 9.9, 6.9 Hz, 1H), 3.29–3.18 (m, 1H), 3.09 (s, 1H), 3.07 (s, 1H), 0.93 (s, 9H), 0.10 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ$_C$ = 142.9, 137.3, 133.5, 129.9, 128.4, 128.1, 127.8, 127.5, 126.5, 125.8, 74.7, 65.3, 64.1, 25.9, 22.7, 18.3, −5.2, −5.3 ppm; HRMS (ESI-MeOH): m/z calcd for C$_{22}$H$_{32}$NO$_2$Si [M + H]$^+$ 370.2197 found 370.2203.

General procedure for the cycloaddition reactions of nitrone 3

A solution of nitrone **3** (0.1 g, 0.56 mmol) in dry toluene (5 mL) was heated to 80 °C. A solution of the corresponding alkene (5 eq.) in dry toluene (5 mL) was added dropwise and the reaction was heated at 110 °C overnight. Removal of the solvent under reduced pressure yielded the crude product as a dark brown oil. Purification by flash chromatography eluting with EtOAc/cyclohexane (1 : 1) gave the corresponding products **11**.

((2R,5S,10bR)-2-Phenyl-1,5,6,10b-tetrahydro-2H-isoxazolo[3,2-a]isoquinolin-5-yl)methanol (11a). Following the general procedure, reaction of styrene (2.8 mmol, 322 μL) with nitrone **3** gave the cycloadduct **11a** (26 mg, 86% yield) as a yellow oil; $[\alpha]_D^{25}$ −29 (c = 3.6, CHCl$_3$); IR (ATR): ν = 3372, 3027, 2937, 2886, 1733, 1241, 1047, 927, 794, 699 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ = 7.46–7.43 (m, 2H), 7.42–7.37 (m, 2H), 7.36–7.31 (m, 1H), 7.21–7.14 (m, 3H), 7.09–7.07 (m, 1H), 5.44 (dd, J = 9.5, 4.5 Hz, 1H), 4.88 (dd, J = 10.3, 8.2 Hz, 1H), 3.94–3.93 (m, 2H), 3.35–3.30 (m, 1H), 2.97 (dd, J = 16.4, 11.5 Hz, 1H), 2.82–2.72 (m, 2H), 2.68–2.62 (m, 1H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ$_C$ = 141.1, 134.7, 132.2, 128.6, 128.2, 128.0, 127.0, 126.9, 126.4, 79.1, 66.2, 64.1, 56.9, 45.5, 31.5 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{18}$H$_{19}$NO$_2$ [M + H]$^+$: 282.1494 found 282.1489.

((2S,5S,10bR)-2-Butyl-1,5,6,10b-tetrahydro-2H-isoxazolo[3,2-a]isoquinolin-5-yl)methanol (11b). Following the general procedure reaction of 1-hexene (2.8 mmol, 350 μL) with nitrone **3** gave the cycloadduct **11b** (17 mg, 74% yield) as a yellow oil; $[\alpha]_D^{25}$ −6 (c = 1, CHCl$_3$); IR (ATR): ν = 3405, 2953, 2858, 1454, 1050, 944, 748, 713 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ = 7.20–7.14 (m, 2H), 7.10–7.09 (m, 2H), 4.60 (t, J = 9.2, 1H), 4.41 (dq, J = 12.6, 6.1 Hz, 1H), 3.86–3.85 (m, 2H), 3.29 (br s, 1H),

3.20–3.14 (m, 1H), 2.85 (dd, J = 16.3, 11.6 Hz, 1H), 2.70 (dd, J = 16.4, 3.6 Hz, 1H), 2.40–2.31 (m, 2H), 1.72–1.66 (m, 1H), 1.64 (m, 1H), 1.44–1.30 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ$_C$ = 135.3, 132.2, 128.3, 127.1, 126.8, 126.4, 77.6, 66.7, 63.9, 56.5, 42.4, 35.0, 31.6, 28.2, 22.8, 14.1 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{16}$H$_{23}$NO$_2$ [M + H]$^+$: 262.1807 found 262.1802.

((2R,5S,10bR)-2-(2-(Benzyloxy)ethyl)-1,5,6,10b-tetrahydro-2H-isoxazolo[3,2-a]isoquinolin-5-yl)methanol (11c). Following the general procedure, reaction of 4-benzyloxybut-1-ene[18] (2.8 mmol, 454 mg) with nitrone **3** gave the cycloadduct **11c** (42 mg, 61% yield) as a yellow oil. $[\alpha]_D^{25}$ −1.21 (c = 9.9, CHCl$_3$); IR (ATR): ν = 3421, 3027, 2916, 2882, 1454, 1361, 1096, 910, 733, 697 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ = 7.38–7.27 (m, 5H), 7.21–7.15 (m, 2H), 7.12–7.07 (m, 2H), 4.64–4.55 (m, 2H), 4.52 (s, 2H), 3.86 (d, 4.2 Hz, 2H), 3.65–3.60 (m, 2H), 3.24 (br s, 1H), 3.17 (ddd, J = 11.7, 7.9, 4.0 Hz, 1H), 2.88 (dd, J = 16.3, 11.6 Hz, 1H), 2.72 (dd, J = 16.4, 3.6 Hz, 1H), 2.48–2.36 (m, 2H), 2.05–1.92 (m, 2H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ$_C$ = 138.1, 135.0, 132.1, 128.3, 128.1, 127.6, 127.5, 126.9, 126.7, 126.2, 77.2, 74.8, 73.1, 66.9, 66.1, 63.6, 56.5, 42.2, 35.2, 31.4 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{21}$H$_{25}$NO$_3$ [M + H]$^+$: 340.1913 found 340.1907.

((2R,5S,10bR)-2-(2-(Phenylthio)ethyl)-1,5,6,10b-tetrahydro-2H-isoxazolo[3,2-a]isoquinolin-5-yl)methanol (11d). Following the general procedure, reaction of but-3-en-1-yl(phenyl)sulfane[19] (2.8 mmol, 459 mg) with nitrone **3** gave the cycloadduct **11d** (50 mg, 64% yield) as a yellow oil. $[\alpha]_D^{25}$ −91 (c = 1, CHCl$_3$); IR (ATR): ν = 3408, 3058, 2930, 2884, 1582, 1438, 1051, 1024, 944, 736, 690 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ = 7.37–7.35 (m, 2H), 7.32–7.28 (m, 2H), 7.21–7.06 (m, 5H), 4.63–4.54 (m, 2H), 3.86 (s, 2H), 3.19–3.07 (m, 3H), 2.99 (ddd, J = 13.1, 8.3, 7.2 Hz, 1H), 2.88 (dd, J = 16.2, 11.6 Hz, 1H), 2.72 (dd, J = 16.4, 3.6 Hz, 1H), 2.45–2.30 (m, 2H), 2.08–1.91 (m, 2H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ$_C$ = 135.8, 134.8, 132.1, 129.2, 128.9, 128.1, 126.9, 126.8, 126.3, 126.1, 75.7, 66.1, 63.7, 56.7, 42.1, 34.7, 31.4, 29.9 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{20}$H$_{23}$NO$_2$S [M + H]$^+$: 342.1528 found 342.1522.

General procedure for the reduction of cycloadducts 11[16]

Zinc dust (5.0 eq.) was added to a solution of cycloadduct **11** (1 eq.) in 50% acetic acid : water at room temperature. The mixture was stirred under reflux for 3 h. After cooling, the mixture was neutralized with saturated aqueous NaHCO$_3$ and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic phases were dried over MgSO$_4$, concentrated under reduced and the residue purified by column chromatography.

(R)-2-((1R,3S)-3-(Hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanol (12a). Following the general procedure, reduction of cycloadduct **11a** (50 mg, 0.18 mmol) gave 1,3-disubstituted THIQ **12a** (17 mg, 33% yield) as a yellow oil. $[\alpha]_D^{25}$ −0.42 (c = 2.4, CHCl$_3$); IR (ATR): ν = 3300, 3060, 3024, 2918, 1655, 1450, 1057, 1028, 743, 700 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ = 7.45 (d, J = 7.4 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.27–7.23 (m, 1H), 7.12–7.03 (m, 3H), 6.82–6.80

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(m, 1H), 5.09 (t, J = 4.3 Hz, 1H), 4.4 (br s, 2H), 4.17 (dd, J = 11.2, 2.2 Hz, 1H), 3.76 (dd, J = 11.1, 3.8 Hz, 1H), 3.59 (dd, J = 11.2, 6.3 Hz, 1H), 3.30–3.24 (m, 1H), 2.69 (dd, J = 16.5, 4.2 Hz, 1H), 2.56 (dd, J = 16.4, 10.7 Hz, 1H), 2.44 (ddd, J = 14.8, 11.4, 3.6 Hz, 1H), 1.98 (ddd, J = 14.7, 5.2, 2.8 Hz, 1H), ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 144.7, 138.0, 134.0, 129.4, 128.2, 126.7, 126.2, 125.9, 125.4, 72.3, 65.1, 51.5, 48.6, 41.8, 30.4 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{18}$H$_{21}$NO$_2$ [M + H]$^+$: 284.1651 found 284.1645.

(S)-1-((1R,3S)-3-(Hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)hexan-2-ol (12b). Following the general procedure, reduction of cycloadduct **11b** (17 mg, 0.07 mmol) gave 1,3-disubstituted THIQ **12b** (16 mg, 90% yield) as a yellow oil. $[\alpha]_D^{25}$ −0.21 (c = 4.7, CHCl$_3$); IR (ATR): ν = 3310, 3062, 2926, 2857, 1452, 1123, 1035, 743 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.14–7.01 (m, 4H), 4.43 (dd, J = 10.8, 2.4 Hz, 1H), 3.82 (br s, 3H), 3.70 (dd, J = 11.1, 3.7 Hz, 1H), 3.54 (dd, J = 11.0, 7.3 Hz, 1H), 3.26–3.20 (m, 1H), 2.73 (dd, J = 16.4, 4.1 Hz, 1H), 2.56 (dd, J = 16.4, 10.2 Hz, 1H), 2.10 (ddd, J = 14.2, 11.3, 3.0 Hz, 1H), 1.73–1.61 (m, 2H), 1.56–1.1.25 (m, 6H), 0.91 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 138.3, 133.8, 129.4, 126.3, 126.2, 126.0, 69.4, 64.8, 51.3, 48.9, 40.3, 36.8, 30.5, 28.3, 22.8, 14.1 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{16}$H$_{25}$NO$_2$ [M + H]$^+$: 264.1964 found 264.1958.

(R)-4-(Benzyloxy)-1-((1R,3S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-ol (12c). Following the general procedure, reduction of cycloadduct **11c** (27 mg, 0.08 mmol) gave 1,3-disubstituted THIQ **12c** (14 mg, 51% yield) as a yellow oil. $[\alpha]_D^{25}$ −0.31 (c = 3.2, CHCl$_3$); IR (ATR): ν = 3298, 3061, 3028, 2916, 2857, 1452, 1362, 1090, 1027, 740, 697 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.28–7.18 (m, 5H), 7.06–6.89 (m, 4H), 4.43 (s, 2H), 4.36 (dd, J = 10.9, 2.5 Hz, 1H), 4.01–3.92 (m, 4H), 3.64 (dd, J = 11.2, 3.8 Hz, 1H), 3.53 (t, J = 6.1 Hz, 2H), 3.45 (dd, J = 11.1, 7.4 Hz, 1H), 3.20–3.14 (m, 1H), 2.64 (dd, J = 16.5, 4.3 Hz, 1H), 2.49 (dd, J = 16.5, 10.4 Hz, 1H), 2.02–1.95 (m, 1H), 1.88–1.81 (m, 1H), 1.78–1.64 (m, 2H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 138.4, 138.2, 133.7, 129.5, 128.5, 127.9, 127.8, 126.6, 126.5, 126.2, 73.4, 68.5, 67.8, 64.9, 51.4, 49.1, 41.1, 36.8, 30.6 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{21}$H$_{27}$NO$_3$ [M + H]$^+$: 342.2069 found 342.2064.

(R)-1-((1R,3S)-3-(Hydroxymethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-4-(phenylthio)butan-2-ol (12d). Following the general procedure, reduction of cycloadduct **11d** (47 mg, 0.13 mmol) gave 1,3-disubstituted THIQ **12d** (22 mg, 47% yield) as a white solid; m.p. 60–62 °C; $[\alpha]_D^{25}$ −6 (c = 2, CHCl$_3$); IR (ATR): ν = 3369, 3070, 2919, 1581, 1479, 1437, 1090, 1027, 735, 689 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H = 7.25 (d, J = 7.4 Hz, 2H), 7.18 (t, J = 7.6 Hz, 2H), 7.09–7.02 (m, 31H), 7.00–6.97 (m, 1H), 6.92–6.90 (m, 1H), 4.31 (dd, J = 10.8, 2.6 Hz, 1H), 3.94–3.88 (m, 1H), 3.71 (br s, 3H), 3.61 (dd, J = 11.1, 3.8 Hz, 1H), 3.44 (dd, J = 11.1, 7.2 Hz, 1H), 3.16–3.03 (m, 2H), 2.95–2.88 (m, 1H), 2.64 (dd, J = 16.5, 4.3 Hz, 1H), 2.46 (d, J = 16.4, 101 Hz, 1H), 2.02 (ddd, J = 14.2, 11.2, 3.1), 1.96–1.87 (m, 1H), 1.75–1.67 (m, 1H), 1.62 (ddd, J = 14.7, 6.6, 3.1 Hz, 1H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$): δ_C = 128.3, 136.6, 133.9, 129.7, 129.0, 128.9, 126.5, 126.4, 126.2, 125.9, 68.6, 65.1, 51.6, 49.0, 40.4, 36.5, 30.7

30.3 ppm; HRMS (ESI-EtOAc): m/z calcd for C$_{20}$H$_{25}$NO$_2$S [M + H]$^+$: 344.1684 found 344.1679.

Conflicts of interest

There are no conflicts to declare.

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