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Synthesis and Screening of Novel C₁ Substituted Tetrahydroisoquinoline Derivatives for Asymmetric Transfer Hydrogenation Reactions

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Tetrahydroisoquinoline (TIQ) derivatives exhibit good biological activity. However, utilization of TIQ compounds in asymmetric catalysis is limited. This paper presents a series of novel TIQ derivatives in asymmetric transfer hydrogenation (ATH) reactions. Chiral TIQ amino alcohol ligands were synthesized and screened for the ATH reaction of aromatic ketones. The effect of a *cis*- and *trans*-phenyl substitution at the C₁ position on the ligand backbone was investigated both experimentally and computationally. The results showed that the *trans* orientation on the TIQ scaffold yields higher turnover rates with a selectivity of 94 % *ee* obtained at room

temperature with a Ru complex where two TIQ ligands acts as the coordination species and isopropyl alcohol as the hydrogen donor. The *cis*-isomer results in a high turnover rate with no selectivity. The experiment with the *trans*-isomer was repeated at lower temperatures and a selectivity of 99 % *ee* was obtained. Furthermore, it was observed that substitution at the C₃- α position results in a drop of the enantioselectivity and the reactivity of the catalyst.

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Figure 1. Examples of chiral amino alcohol ligands reported with high selectivity in ATH reactions

Introduction

Chiral amino alcohol-containing ligands (Figure 1) are among the more successful classes of compounds in asymmetric transfer hydrogenation reactions (ATH).^[1-3] In these reactions transfer hydrogenation has been applied to ketones and imines.^[4, 5] In particular it has been very successful for the reduction of a range of unsymmetrical ketones. Nevertheless, there is still significant interest in the development of new varieties of chiral backbones as potential ligands in asymmetric catalysis.

Since the isolation of naphthyridinomycin in 1974, the biological activity of tetrahydroisoquinoline (TIQ) carboxylic acid derivatives have been widely investigated.^[6-8] Our interest in the development of novel chiral backbones prompted us to investigate the application of the TIQ scaffold as a source of chirality in ATH reactions. Previous reports on the use of TIQ derivatives as catalytic ligands have yielded limited success, with poor to moderate enantioselectivities in asymmetric catalysis such as allylic alkylation^[9] and borane mediated hydrogenation reactions.^[10, 11] Recently a related study of different TIQ ligands on the addition reaction of diethylzinc to benzaldehyde was reported with promising results.^[12]

Given the reports in literature thus far, we aimed to couple the catalytic success of the chiral amino alcohol-containing class of ligands, with the innovation of the TIQ scaffold towards the development of a novel series of efficient C₁ and C₃- α Phenyl substituted TIQ amino alcohol ligands for ATH reactions. The ligands were subsequently coordinated to Ru(arene), Rh(arene), Ir(arene) complexes and their efficiency as well as selectivity was investigated as ATH catalysts. The enantioselective reduction of unsymmetrical ketones is a reaction that has been widely examined with several ligands being reported in literature.^[13-15] As such, the TIQ-based catalysts were applied to the reduction of aryl-alkyl ketone substrates. To the best of our knowledge, this is the first successful application of a TIQ ligand to affect high enantioselective transfer hydrogenations yielding high turnover rates at reasonable catalyst loading.

Results and Discussion

From literature the nitrogen-oxygen classes of ligands in ATH reactions have been reported to be the most successful. Mechanistic studies on non-TIQ related ligands^[1, 3] developed by Noyori have demonstrated that typically two stereogenic centers, a cyclic secondary amine and a secondary alcohol is required for optimal chiral activity.^[16-18] For maximum activity these two metal

coordination sites are typically within three bonds of each other. In this paper, we introduce the tetrahydroisoquinoline (TIQ) ligands which have initially a single chiral centre, a secondary amine in a six membered ring with a primary alcohol as a side chain. Our first choice was ligand **4** which represents a simple TIQ backbone (Figure 2) from literature.^[19] To investigate the chiral activity of **4**, we examined this ligand for ATH reactions through coordination with a [Ru(*p*-cymene)Cl₂]₂ complex and by, using isopropyl alcohol as the hydride source.

Figure 2. Unsubstituted TIQ ligand for ATH reactions.

From our initial experiments to reduce acetophenone, it was observed that ligand **4** showed poor enantioselectivity in the ATH reaction (Table 1, entry 1).

To improve the ligand activity of our lead molecule, conversion of the primary alcohol **4** to a secondary alcohol could potentially improve the ligand activity. However, due to the difficulty in the synthesis as will be demonstrated later, we designed and synthesised the amino tertiary alcohol **8**, introducing phenyl moieties as bulky groups at the C₃ position. Ligand **8** was synthesised from the TIQ amino ester **5**^[19] and the benzyl protection of the secondary amine was carried out with benzyl bromide and K₂CO₃ in acetonitrile. Subsequently, a Grignard reaction was attempted on **6** affording **7** with low yields. Ultimately, deprotection of **7** resulted in the formation of ligand **8** as shown in scheme 1.

Scheme 1. Reagents for the synthesis of ligand **8**: (i) Benzyl Bromide, K₂CO₃, CH₃CN, reflux, 3hrs; (ii) PhMgBr, dry THF, reflux, 6 hrs; (iii) 10 wt% Pd/C, H₂ (1 atm), MeOH.

Disappointingly, phenyl substitution at the C₃-α position did not improve the catalytic system, in fact no reactivity was observed using this ligand (Table 1, entry 2). To further investigate the factors affecting the efficiency of our TIQ backbone, we returned to the primary alcohol system and substituted a chiral phenyl group at the C₁ position to increase the pK_a of the secondary nitrogen and the chiral steric bulk of the ligand. This proved difficult to achieve from the route employed before and to allow us to continue the study we chose to employ a different TIQ starting material. Therefore, ligands **14** (Scheme 3) and **17** (Scheme 4) were proposed.

For ligand **14**, L-DOPA (**9**) underwent the Pictet-Spengler reaction with benzaldehyde in the presence of K₂CO₃ and aqueous EtOH to afford the *trans*-substituted TIQ compound **10** in 20 %

yield (Scheme 2).^[20] The *cis*-substituted TIQ compound **11** was obtained from benzaldehyde and K₂CO₃ in water giving a 20 % yield.

Scheme 2. Reagents for the synthesis of TIQ acids **10** and **11**: (i) PhCHO, K₂CO₃, EtOH/H₂O, 0 °C – rt; (ii) PhCHO, K₂CO₃, H₂O, 0 °C – rt.

To obtain compound **12** C₁-substituted N-Cbz protected methyl ester, an *in situ* reaction was performed on **10**. Consequently, the secondary amine of **10** was protected (Scheme 3) with benzyl chloroformate. After the reaction went to completion, the solvent was evaporated under vacuum and the crude product was used directly and methylated at the phenolic and carboxylic acid positions. This was achieved by refluxing the compound in acetone in the presence of Me₂SO₄ and KHCO₃.^[21] The crude product was purified using column chromatography to obtain the desired compound **12** in a 80 % yield. Afterwards, deprotection of the Cbz group of **12** was accomplished and subsequent reduction to the amino alcohol afforded **14** (Scheme 3). It was observed that partial racemisation had occurred during the reduction of the ester at elevated temperatures (diastereomers were observed by HPLC and TLC). To afford maximum optical purity, the reduction of **13** was subsequently repeated at 0 °C yielding the pure ligand **14** (Scheme 3).

Scheme 3. Reagents for the synthesis of ligand **14**: (i) KHCO₃, Cbz-Cl, dioxane/water *in situ* solvent evaporation KHCO₃, Me₂SO₄, acetone, reflux, overnight; (ii) 10 wt% Pd/C, H₂ (1 atm), MeOH, rt; (iii) LiAlH₄, dry THF, 0 °C, 2 hrs.

A similar synthetic route was applied to produce the *cis* TIQ amino alcohol **17** starting from **11** (Scheme 4)

Scheme 4. Synthesis of ligand **17**.

Interesting results were observed for the ATH reduction reaction of acetophenone utilizing ligands **14** and **17**. Ligand **14** showed good catalytic activity giving 94 % conversion with 94 % *ee* (*R*) in 45 minutes. In the case of **17**, a racemic mixture was observed with an 80 % conversion (Table 1, entries 3 and 4).

Table 1. Asymmetric transfer hydrogenation of acetophenone using different ligands complexed with [Ru(*p*-cymene)Cl₂]₂.

Entry	Ligand	Time (h)	Conv. (%) ^[a]	<i>ee</i> (%) (<i>R/S</i>) ^[b]
1	4	24.0	28	35 (<i>S</i>)
2	8	24.0	NR ^[c]	NR ^[c]
3	14	0.75	94	94 (<i>R</i>)
4	17	0.75	80	Racemic

[a] Determined by chiral GC analysis. [b] Absolute configuration determined by comparison with reported retention times. Values reported are the average of three runs. [c] No reaction observed.

The reason for this difference in catalytic activity is not readily understood. With the encouraging results from ligand **14** however, we decided to modify the ligand by introducing phenyl groups at the C₃-α position to re-investigate the effect of steric bulk. To obtain this ligand, intermediate **13** could be converted to the *N*-benzyl methyl ester **18**. In order to introduce the phenyl groups, the secondary amine was first benzyl protected, after which a Grignard reaction with phenyl magnesium bromide afforded **19**. Deprotection of **19** (Scheme 5) resulted in the formation of ligand **20**. We attempted ATH reactions using the Ru(*p*-cymene) complex. Disappointing results were observed for this ligand. It showed a comparative activity with ligand **8** (Table 2, entry 1). It thus confirmed that bulky groups present on C₃-α position reduce the catalytic activity.

Scheme 5. Reagents for the synthesis of ligand **20**: (i) Benzyl Bromide, K₂CO₃, CH₃CN, reflux, 3hrs; (ii) PhMgBr, dry THF, reflux, 6 hrs; (iii) 10 wt% Pd/C H₂ (1 atm), MeOH.

From the results of ligand **14** and **20**, it was decided to investigate the effect of smaller substitution at the C₃-α position. There were two reasons for this, first from the literature it is known that amino alcohols with a secondary alcohol exhibit excellent reactivity and selectivity.^[22, 23] Second, this allows us to introduce another chiral centre into our catalytic design of ligand **24**. The synthesis of these ligands was not trivial. The reduction of ester **18** with LiAlH₄ followed by a Swern oxidation afforded the aldehyde **22** in 82 % yield. Subsequently, a Grignard reaction with methyl magnesium iodide under reflux conditions afforded two diastereomeric alcohols in a 1:1 mixture. To improve selectivity, the Grignard reaction was repeated at 0 °C giving the diastereomers in a 9:1 ratio and in good yields. These diastereomers were named major **23** and minor **23**. Separation of the two isomers and debenzylolation of the alcohols afforded major **24** and minor **24** ligands in 60 % yield (Scheme 4).

Scheme 4. Reagents for the synthesis of major **24** and minor **24** ligands: (i) LiAlH₄, dry THF, rt; (ii) DMSO, oxalyl chloride, TEA, CH₂Cl₂, -78 °C; (iii) CH₃MgI, dry THF, 0 °C; (iv) 10 wt% Pd/C, H₂ (1 atm), MeOH, rt (All experimental details are available in supporting information).

Major and minor **24** were tested for transfer hydrogenation activity under identical conditions. Ligand major **24** provided a selectivity of 94 % *ee* (*R*), minor **24** gave 70 % *ee* (*S*) albeit both with low conversions (Table 2, entries 2, 3).

Table 2. Asymmetric transfer hydrogenation of acetophenone using different ligands with [Ru(*p*-cymene)Cl₂]₂.

Entry	Ligand	Time (h)	Conv. (%) ^[a]	<i>ee</i> (%) (<i>R/S</i>) ^[b]
1	20	1.0	NR ^[c]	NR ^[c]
2	Major 24	0.5	33	94 (<i>R</i>)
3	Minor 24	0.5	30	70 (<i>S</i>)

[a] Determined by chiral GC analysis. [b] Absolute configuration determined by comparison with reported retention times. Values reported are the average of three runs. [c] No reaction observed.

In total seven ligands were prepared and evaluated in the ruthenium catalysed asymmetric transfer hydrogenation of

acetophenone, the results are summarized in tables 1 and 2. Unsubstituted amino alcohol **4** reduced acetophenone with low conversion rates and enantiomeric excess (Table 1, entry 1). Phenyl substitution at the C₃-α position of ligands **8** (Table 1, entry 2) and **20** (Table 2, entry 1) reduced the activity of the catalyst. Similar phenyl substitution at the C₁ position gave *cis* and *trans* configurations which enhanced the turnover rates in ATH reactions. In this system, ligand **14** (*trans*) provided better selectivity than ligand **17** (*cis*) (Table 2, entry 3, 4). The TIQ amino alcohols with smaller substituents at the C₃-α position (major and minor **24** ligands) showed a decrease in activity compared to ligand **14**.

Having identified an efficient and selective ligand for catalytic purposes, the system was varied with the introduction of different metal complexes. Half-sandwich π-complexes such as ruthenium, rhodium or iridium complexes are the most important metal sources associated with amino alcohol ligands in ATH reactions.^[1, 3, 24] In this study, we measured the reactivity of **14** with various organometallic complexes *i.e.* [Ru(*p*-cymene)Cl₂]₂, [RhCl₂Cp*]₂ and [IrCl₂Cp*]₂.

All of the new complexes provided good conversions and selectivities, as shown in Table 3. Also the reactions at lower temperatures provided improved selectivities. We repeated the hydrogenation of acetophenone at 0 °C using [Ru(*p*-cymene)Cl₂]₂. Excellent selectivity was observed from the screening affording 99 % *ee* but with a low conversion of 33 %. [RhCl₂Cp*]₂ gave higher reactivity results (94 % conversion) with an excellent rate relative to the system using [Ru(*p*-cymene)Cl₂]₂, but with diminished optical purity of 90 % *ee* (Table 3, entry 4). The reaction was repeated at different temperatures affording respectable selectivities with moderate conversions (Table 3, entries 5, 6). Due to the higher rates when rhodium is used, we attempted the same reaction with a low catalyst loading of 0.5 mol % (M/S). The reaction rate was reduced providing good selectivity and conversion rates (Table 3, entry 7). Replacing rhodium with iridium gave poorer selectivity and conversion results.

Table 3. ATH of acetophenone of different metal complexes and **14** as the chiral ligand.

Entry	Metal	Temp.	Time (h)	Conv. (%) ^[a]	<i>ee</i> (%) (<i>R/S</i>) ^[b]
1	[Ru(<i>p</i> -cymene)Cl ₂] ₂	RT	0.75	94	94 (<i>R</i>)
2	[Ru(<i>p</i> -cymene)Cl ₂] ₂	0 °C	1.0	35	99 (<i>R</i>)
3 ^[c]	[Ru(<i>p</i> -cymene)Cl ₂] ₂	RT	1.25	85	94 (<i>R</i>)
4	[RhCl ₂ Cp*] ₂	RT	0.25	94	90 (<i>R</i>)
5	[RhCl ₂ Cp*] ₂	0 °C	0.5	86	94 (<i>R</i>)
6	[RhCl ₂ Cp*] ₂	−15 °C	0.5	42	99 (<i>R</i>)
7 ^[c]	[RhCl ₂ Cp*] ₂	RT	0.5	94	91 (<i>R</i>)
8	[IrCl ₂ Cp*] ₂	RT	0.5	35	75 (<i>R</i>)

[a] Determined by chiral GC analysis. [b] Absolute configuration determined by comparison with reported optical rotation. Values reported are the average of three runs. [c] Reaction was performed using 0.5 mol% of metal/substrate.

Having identified the most efficient metal complex in our system we then undertook studies on different substrates. The results are summarized in Table 4. In general, when compared to the reduction of acetophenone, all of the other substrates tested led to decreased conversions. The substrate can be grouped based on their electronic and steric properties. Placing electron donating (4-methylacetophenone) or electron withdrawing (4-nitroacetophenone) groups decreases the rate of conversion. Replacing the phenyl ring with a pyridyl species completely arrests any reactivity. This could be due to transient coordination of the sp² nitrogen to the metal centre thereby disrupting the active transition state. An increase in steric bulk (indanone and tetralone) renders a loss in selectivities and conversion rates.

Table 4. ATH of various aryl-alkyl ketones with [Ru(*p*-cymene)Cl₂]₂ and **14** as chiral ligand at ambient temperature.

Entry	Substrate	Time(h)	Conv. (%) ^[a]	<i>ee</i> (<i>R/S</i>) ^[b]
1	4-methyl acetophenone	1.0	80	92 (<i>R</i>)
2	4-nitroacetophenone	1.0	98	68 (<i>R</i>)
3	2-methoxy acetophenone	1.0	94	82 (<i>S</i>)
4	1-indanone	1.0	31	65 (<i>S</i>)
5	1-indanone	24.0	40	69 (<i>S</i>)
6	tetralone	1.0	40	racemic
7	2-acetylpyridine	1.0	NR ^c	NR ^c
8	2-acetylpyridine	24.0	NR ^c	NR ^c

[a] Determined by chiral GC analysis. [b] Absolute configuration determined by comparison with reported optical rotation. Values reported are the average of two runs. [c] No reaction observed.

The observed enantioselectivity could be explained by the mechanism proposed for Ru-catalyzed transfer hydrogenations using amino alcohol ligands.^[16, 25] According to this mechanism, a ruthenium hydride and a proton from the ligand is simultaneously transferred from the catalyst to the prochiral carbonyl group. The structures of the two possible diastereomeric transition states were calculated using the Jaguar program.^[26] The transition state structures were located using the quadratic synchronous transit (QST) method and the B3LYP functional together with the LACVP ECP basis set. Normal mode analysis revealed one imaginary frequency for each structure. LACVP in Jaguar defines a combination of the LANL2DZ basis set for ruthenium^[27] **Error! Bookmark not defined.** and the 6-31G basis set for other atoms. LACVP implies the use of an effective core potential for 28 core electrons of ruthenium and a (5s, 6p, 4d) primitive basis contracted to [3s, 3p, 2d]. Final energies were retrieved from single point calculations at B3LYP/LACV3p+**. LACV3p+** differs from LACVP by using the 6-311+G** basis set in place of 6-31G.

Figure 3. The calculated (*S*) and (*R*)-transition states for the reduction of acetophenone using ligand **14**. The (*S*)-transition state showing a close-contact between the phenyl of the substrate and the arene ligand, making it less favorable. The Cartesian coordinates of the optimized structures are available as supplementary material.

The energy of the transition state leading to (*S*)-alcohol product is significantly higher in energy than that of the (*R*)-alcohol product. This theoretical result supports the observed experimental result for ligand **14** reported in Table 1-4.

Conclusions

We have synthesized and evaluated seven ligands of a new class of N,O TIQ compounds. These novel ligands were coordinated with ruthenium metal and they were evaluated in the asymmetric transfer hydrogenation of acetophenone. C₁ substituted TIQ amino primary alcohol **14** gave rise to a catalyst that induced good enantioselectivity, 94 % *ee*. The reaction was repeated in varying conditions affording 99 % *ee* at lower temperature as the best result. The rhodium-complex using amino alcohol ligand **14** showed the fastest rate of all complexes evaluated in this study, 94 % conversion in 0.5 h using a 0.5 mol % of metal to substrate with lower selectivity of 91 % *ee*. Considering the good selectivity at ambient temperature, we screened different substrates of aryl-alkyl ketone substrates rendering moderate to reasonable results. Acetophenone as substrate gave the best results.

Experimental Section

Reagents and solvents were purchased from Aldrich, Merck and Fluka. All NMR spectra were recorded on Bruker AVANCE III 400 MHz or 600 MHz instruments. Chemical shifts are expressed in ppm downfield from CDCl₃ as an internal standard, and coupling constants are reported in Hz. NMR Spectra were obtained at room temperature, except if stated different. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using Silica gel (60–200 mesh except if stated different). All solvents were dried using standard procedures. All IR spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded on a Perkin Elmer Polarimeter. All melting points are uncorrected. All testing reactions were carried out under dry UHP Argon gas. The results of all testing reactions were analyzed using GC analysis was performed on a Agilent capillary gas chromatograph with a CP-Chirasil-β-Dex column (25 m with 0.25 mm inner diameter), nitrogen as carrier gas, and a flame ionization detector. LC traces were recorded from Agilent 1100 HPLC with reverse phase using 0.1% formic acid in acetonitrile and Millipore water. High resolution mass spectrometric data was obtained using a Bruker micrOTOF-Q II instrument operating at ambient temperatures, using a sample concentration of approximately 1 ppm.

General procedure for transfer hydrogenation of aromatic ketones

To an oven dried Schlenk tube was added [Ru(*p*-cymene)Cl₂]₂ (3.0 mg, 4.8 μmol), ligand (4 eq) and was kept under vacuum for 10 min. Then, freshly distilled isopropyl alcohol was added under a dry argon atmosphere. The mixture was stirred for 15 min and freshly prepared 0.1 M KO^tBu solution was added to the complex, followed by the substrate. The reaction mixture was tested by taking samples at different intervals by quenching with 5 % acetic acid in isopropyl alcohol, passed through a pad of silica-gel and monitored by GC with chiral α-dex column. The percentage *ee* values were calculated from the integration values of the GC peaks for each enantiomer. The experiment was repeated two or three times and the average values are reported in the tables.

General procedure for compounds **11** and **15**

To a solution of C₁ substituted TIQ carboxylic acid (1.0 g, 3.5 mmol) in dioxane (20 mL) and water (10 mL) at 0 °C a solution of potassium hydrogen carbonate (2.1 g, 21.1 mmol) was added dropwise for 15 min followed by addition of Cbz-Cl (0.65 g, 3.8 mmol). The solution was stirred for 1.5 h at 0 °C and then at ambient temperature for a further 1.5 h. Completion of the reaction was monitored with LC-MS (by neutralizing the reaction mixture with 10 % HCl and extracted with ethyl acetate). The solvent was evaporated under reduced pressure and dried under high vacuum. The crude residue obtained was dissolved in acetone (40 mL) and potassium hydrogen carbonate (7.01 g, 70.17 mmol) was added followed by dimethylsulfate (4.45 g, 35.28 mmol) and stirred for 16 h (overnight) at reflux. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (60/40, *R_f* 0.6). The reaction solvent was evaporated under reduced pressure, ethyl acetate (60 mL) was added and washed with 20 mL (2 × 10) of water followed by 10 mL of brine. The organic layer was separated and dried over anhydrous MgSO₄ and the solvent was evaporated under reduced pressure to afford crude Cbz-ester, which was purified by column chromatography using 0–40 % ethyl acetate in hexane as the eluent to yield pure compounds **11** and **15**.

General deprotection procedure for preparation of amino esters **12** and **16**

A solution of the Cbz protected TIQ ester (1.0 g, 0.21 mmol) in THF (20 mL) was added to a suspension of activated 10 wt% Pd/C (500 mg) in dry MeOH (20 mL). The mixture was connected to a H₂ source under atmospheric pressure and stirred at room temperature for 1 h. Completion of the reaction was monitored with TLC in hexane/ethyl acetate (40/50, *R_f* 0.4). The Pd/C was filtered off through a celite pad and washed with methanol (20 mL). The filtrate was evaporated under reduced pressure affording the crude amino ester, which was purified by column chromatography using 0–50 % ethyl acetate in hexane as the eluent to yield pure compounds **12** and **16**.

General procedure for **14** and **17**

A solution of amino ester (0.5 g, 1.5 mmol) in dry THF (20 mL) was added dropwise to a suspension of LiAlH₄ (0.18, 4.5 mmol) in dry THF (20 mL) under N₂ atmosphere at 0 °C. The mixture was stirred at 0 °C for 2 h, completion of the reaction was monitored with TLC in hexane/ethyl acetate (50/50, *R_f* 0.5). Excess lithium aluminium hydride was quenched with saturated sodium sulphate solution at 0 °C. The reaction mixture was filtered and the solid was washed with THF (20 mL). The solvent was evaporated to dryness, ethyl acetate (20 mL) was added, washed with water (2 × 5 mL), the organic layer was separated and dried over anhydrous MgSO₄ to afford the crude amino alcohol, which was purified by column chromatography. The following solvent system was used: 10 % of a chloroform solution that was saturated with ammonia in dichloromethane. To this was added 0–2 % MeOH during the course of the separation to yield 70 % of pure amino alcohols **14** and **17**.

(*S*)-Diphenyl(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (**8**)

White solid; mp 104–106 °C (MeOH); Spectroscopic data identical to literature values.^[28]; [α]_D²⁰ – 130 (*c* 0.26 in CHCl₃); HRESIMS *m/z* 316.1774 [M + 1H]¹⁺ (calcd for C₂₂H₂₂NO, 316.1701).

Spectroscopic data of novel compounds

(1R,3S)-2-Benzyl 3-methyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (12)

R_f 0.6 (hexane/EtOAc 6:4); White solid; m.p. 127–129 °C (hexane–ethyl acetate); $[\alpha]_D^{20} = +9.54$ (c 0.26 in CHCl_3); ^1H NMR (400 MHz, DMSO, 100 °C): δ 7.36–7.15 (m, 9H), 7.09 (s, 1H), 6.76 (s, 1H), 5.16–5.05 (m, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.48 (s, 3H), 3.21 (dd, $J=15.69$, 5.97 Hz, 1H), 3.13–3.04 (m, 2H); ^{13}C NMR (100 MHz, DMSO, 100 °C): δ 172.1, 155.9, 149.0, 148.9, 137.0, 130.3, 128.6, 128.1, 127.7, 126.9, 126.4, 124.2, 113.4, 113.2, 67.2, 59.6, 56.8, 56.6, 55.9, 55.8, 52.1, 30.9; IR (neat): 2942, 1744, 1714, 1204, 735, 698 cm^{-1} ; HRESIMS m/z 462.1896 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{27}\text{H}_{28}\text{NO}_6$, 462.1916) and 484.1720 $[\text{M} + \text{Na}]^{2+}$ (calcd for $\text{C}_{27}\text{H}_{27}\text{NNaO}_6$, 484.1736).

(1R,3S)-Methyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13)

R_f 0.5 (hexane/EtOAc 6:4); Colorless oil; $[\alpha]_D^{20} = +15.38$ (c 0.26 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.35–7.24 (m, 3H), 7.23–7.16 (m, 2H), 6.65 (s, 1H), 6.34 (s, 1H), 5.25 (s, 1H), 3.88 (s, 3H), 3.80 (q, $J=8.58$, 5.06 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.15 (dd, $J=5.08$ Hz, 1H), 3.01 (dd, $J=8.68$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 173.8, 147.9, 147.4, 144.5, 128.6, 128.4, 127.9, 127.3, 125.6, 111.1, 110.8, 58.8, 55.8, 52.0, 51.3, 31.0; IR (neat): 2928, 2600, 1746, 1516, 1250, 1123, 727 cm^{-1} ; HRESIMS m/z 328.1547 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_4$, 328.1548).

[(1R,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl]-methanol (14)

R_f 0.4 ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{sat.NH}_3$ in CHCl_3 9.5:0.5:1); Pale yellow solid; m.p. 115–117 °C (CH_2Cl_2); $[\alpha]_D^{20} = +3.7$ (c 0.27 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.32–7.21 (m, 3H), 7.18–7.13 (m, 2H), 6.64 (s, 1H), 6.42 (s, 1H), 5.19 (s, 1H), 3.88 (s, 3H), 3.72 (s, 3H), 3.66–3.60 (dd, $J=10.76$, 2.96 Hz, 1H), 3.49–3.41 (dd, $J=10.64$, 7.81 Hz, 1H), 3.12–3.02 (m, 1H), 2.70 (dd, $J=4.56$ Hz, 1H), 2.57 (dd, $J=10.28$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 147.9, 147.2, 144.6, 128.7, 128.2, 127.1, 126.7, 111.5, 110.9, 65.7, 58.9, 55.9, 55.8, 48.8, 30.5; IR (neat): 3264, 2832, 1515, 1222, 1066, 981, 726, 694 cm^{-1} ; HRESIMS m/z 300.1622 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{28}\text{H}_{22}\text{NO}_3$, 300.1600).

(1S,3S)-2-Benzyl 3-methyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (15)

Colorless oil; $[\alpha]_D^{20} = -38.27$ (c 0.39 in CHCl_3); ^1H NMR (400 MHz, DMSO, 100 °C): δ 7.40–7.15 (m, 10H), 7.02 (s, 1H), 6.93 (s, 1H), 5.16 (s, 1H), 4.43 (dd, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.49 (s, 3H), 3.02 (dd, $J=15.09$, 5.67 Hz, 1H), 2.70 (dd, $J=14.73$, 11.13 Hz, 1H); ^{13}C NMR (100 MHz, DMSO, 100 °C): δ 172.1, 156.1, 149.4, 148.8, 142.0, 136.9, 129.6, 128.7, 128.2, 128.2, 127.9, 127.5, 127.1, 126.2, 113.5, 67.6, 67.6, 58.8, 56.9, 56.8, 56.7, 56.7, 56.5, 51.9, 30.2, 30.1; IR (neat): 1752, 1693, 1514, 1404, 1295, 1216, 1102, 697, 596 cm^{-1} ; HRESIMS m/z 462.1906 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{27}\text{H}_{28}\text{NO}_6$, 462.1916) and 484.1730 $[\text{M} + \text{Na}]^{2+}$ (calcd for $\text{C}_{27}\text{H}_{27}\text{NO}_6\text{Na}$, 484.1736).

(1S,3S)-Methyl 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (16)

R_f 0.6 (hexane/EtOAc 6:4); Colorless oil; $[\alpha]_D^{20} = -42.0$ (c 0.24 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.38–7.28 (m, 5H), 6.64 (s, 1H), 6.17 (s, 1H), 5.09 (s, 1H), 3.91–3.86 (m, 4H), 3.85–3.74 (m, 4H), 3.56–3.61 (s, 3H), 3.41–3.05 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.9, 147.7, 147.3, 143.8, 130.2, 129.0, 128.5, 127.8, 126.0, 111.2, 110.5, 62.8, 56.5, 55.8, 55.8, 52.1, 32.2; IR (neat): 3020, 1737, 1514, 1244, 1213, 749, 665 cm^{-1} ; HRESIMS m/z 328.1548 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_4$, 328.1548).

((1S,3S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (17)

R_f 0.4 ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{sat.NH}_3$ in CHCl_3 9.5/0.5/1); Off white solid; m.p. 175–177 °C (CH_2Cl_2); $[\alpha]_D^{20} = -24.0$ (c 0.25 in CHCl_3); ^1H NMR (600 MHz, CDCl_3): δ 7.39–7.27 (m, 5H), 6.62 (s, 1H), 6.14 (s, 1H), 5.04 (s, 1H), 3.85 (s, 1H), 3.79–3.72 (m, 1H), 3.62–3.53 (m, 4H), 3.26–3.10 (m, 1H),

3.00–2.52 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ 147.0, 143.7, 130.2, 128.9, 128.5, 127.7, 126.8, 111.4, 110.7, 65.5, 66.5, 62.8, 55.8, 55.7, 55.7, 31.2; IR (neat): 3256, 2919, 1511, 1453, 1258, 1215, 1100, 1073, 822, 737, 700, 561 cm^{-1} ; HRESIMS m/z 300.1594 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_3$, 300.1600).

(1R,3S)-Methyl 2-benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (18)

To a solution of compound **16** (500 mg, 1.52 mmol) in acetonitrile (20 mL), solid K_2CO_3 (635 mg, 4.58 mmol) was added followed by benzyl bromide (286 mg, 1.67 mmol) at ambient temperature. Thereafter the reaction mixture was refluxed for 3 h. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (60/40, R_f 0.5). The solvent was evaporated and 30 mL of ethyl acetate was added, washed with 2×10 mL of water, the organic layer was separated, and dried over anhydrous MgSO_4 . The solvent was evaporated under reduced pressure to afford crude product, which was purified by column chromatography using 0–20 % ethyl acetate/hexane as the eluent to yield 90 % pure benzyl ester (**18**): R_f 0.7 (hexane/EtOAc 6/4); White solid; m.p. 146–148 °C (hexane/EtOAc); $[\alpha]_D^{20} = -164.3$ (c 0.28 in CHCl_3); ^1H NMR (600 MHz, CDCl_3): δ 7.38 (d, $J=7.26$ Hz, 2H), 7.32–7.16 (m, 9H), 6.54 (s, 1H), 6.26 (s, 1H), 5.19 (s, 1H), 3.85–3.72 (m, 6H), 3.61 (s, 6H), 3.23 (dd, $J=5.10$, 15.66 Hz, 1H), 2.98 (dd, $J=3.00$, 15.72 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 173.5, 147.4, 147.3, 145.4, 139.3, 129.7, 128.7, 128.3, 128.2, 127.1, 127.0, 123.8, 111.5, 110.9, 64.7, 55.7, 55.7, 55.3, 54.6, 51.2, 31.5; IR (neat): 2944, 1729, 1511, 1152, 753, 699 cm^{-1} ; HRESIMS m/z 418.2012 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{26}\text{H}_{28}\text{NO}_4$, 418.2018).

[(1R,3S)-2-Benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinolin-3-yl]diphenylmethanol (19)

A solution of compound **18** (500 mg, 1.19 mmol) in THF (10 mL) was added to freshly prepared Grignard reagent of phenyl magnesium bromide (2.17 g, 11.9 mmol) under dry inert atmosphere at ambient temperature for 15 min. Completion of the reaction was monitored with TLC, by quenching the reaction mixture with saturated ammonium chloride solution at 0 °C, using 30/70 (ethyl acetate/hexane). The reaction mixture was filtered off and washed with 20 mL of ethyl acetate, evaporation of the filtrate yielded 80 % of crude C_3 - α diphenyl tert alcohol: R_f 0.5 (hexane/EtOAc 6/4); White solid; m.p. 205–207 °C (hexane/EtOAc); $[\alpha]_D^{20} = +20.37$ (c 0.27 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.44 (d, $J=1.16$ Hz, 2H), 7.32–7.10 (m, 14H), 7.0–6.88 (m, 6H), 6.69 (s, 1H), 6.38 (s, 1H), 4.74 (s, 1H), 4.21 (d, $J=13.60$ Hz, 1H), 4.14 (q, $J=3.70$, 12.74 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 3H), 3.57 (s, 1H), 3.30–3.18 (m, 2H), 2.60 (dd, $J=3.60$, 16.48 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 147.8, 147.5, 146.1, 145.5, 143.4, 140.2, 129.8, 129.1, 128.2, 128.1, 127.7, 127.6, 127.0, 126.7, 126.3, 126.1, 125.5, 112.1, 111.6, 79.4, 64.6, 56.8, 55.8, 55.8, 51.8, 23.4; IR (neat): 3589, 1509, 1240, 1093, 694 cm^{-1} ; HRESIMS m/z 542.2698 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{37}\text{H}_{36}\text{NO}_3$, 542.2695).

[(1R,3S)-6,7-Dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinolin-3-yl]diphenylmethanol (20)

A solution of compound **19** (400 mg, 0.73 mmol) in methanol (10 mL/mmol) was added to a suspension of activated Pd/C (200 mg, 10 wt%) in dry MeOH under inert atmosphere. The reaction mixture was connected to H_2 source at 1 atmosphere and stirred for 6 h at room temperature. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (40/60, R_f 0.5) The Pd/C was filtered off through a celite pad and washed with methanol (10 mL). The filtrate was evaporated under reduced pressure affording the crude amino ester, which was purified by column chromatography using 0–2 % methanol in dichloromethane as the eluent to yield pure compounds **20**. R_f 0.3 (hexane/EtOAc 5/5); Pale yellow solid; mp 77–79 °C (CH_2Cl_2); $[\alpha]_D^{20} = -119.5$ (c 0.26 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.42–7.34 (m, 5H), 7.29–7.24 (t, $J=15.20$ Hz, 1H), 7.05–7.21 (m, 6H), 7.02–6.96 (m, 2H), 6.56 (s, 1H), 6.43 (s, 1H), 5.23 (s, 1H), 3.89–3.85 (q, $J=10.94$, 3.86 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.03–2.92 (dd, $J=16.42$, 10.94 Hz, 1H), 2.24–2.16 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3):

δ 148.0, 147.2, 145.1, 144.6, 144.0, 128.4, 128.0, 127.7, 127.4, 126.9, 126.5, 126.2, 126.0, 125.4, 111.4, 110.6, 78.3, 60.0, 55.9, 55.8, 51.9, 28.5; IR (neat): 2926, 1512, 1447, 1243, 1063, 698 cm^{-1} ; HRESIMS m/z 452.2220 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{30}\text{H}_{30}\text{NO}_3$, 452.2226).

[(1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (21)

A solution of compound **18** (1.3 g, 3.11 mmol) in dry THF (20 mL) was added drop wise to a suspension of LiAlH_4 (0.35 g, 9.3 mmol) in 30 mL of dry THF under N_2 atmosphere at 0 $^\circ\text{C}$. The reaction mixture was stirred at 0 $^\circ\text{C}$ for 2 h. Completion of the reaction was monitored with TLC using hexane/ethyl acetate (80/20, R_f : 0.6). Excess lithium aluminium hydride was quenched with saturated sodium sulphate solution at 0 $^\circ\text{C}$. The reaction mixture was filtered and washed with 20 mL of THF. The solvent was evaporated to dryness. Ethyl acetate (20 mL) was added and washed with water (2×5 mL). The organic layer was separated and dried over anhydrous MgSO_4 to give crude amino alcohol. Crude product was purified with column chromatography using 0–40 % ethyl acetate in hexane as a mobile phase and silica gel as a stationary phase to yield 70 % of pure amino alcohol. R_f 0.3 (hexane/EtOAc 5/5); Yellow solid: m.p. 108–110 $^\circ\text{C}$; $[\alpha]_D^{20} = +66.0$ (c 0.25 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.43–7.28 (m, 5H), 7.24–7.12 (m, 3H), 6.98 (d, $J=6.88$ Hz, 2H), 6.70 (s, 1H), 6.41 (s, 1H), 4.85 (s, 1H), 3.98–3.89 (m, 4H), 3.77–3.69 (m, 4H), 3.58–3.49 (m, 1H), 3.41–3.29 (m, 2H), 2.69 (dd, $J=11.60$, 11.56 Hz, 1H), 2.53 (dd, $J=4.68$, 4.68 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 147.9, 147.5, 143.7, 139.2, 129.2, 129.0, 128.5, 127.9, 127.2, 126.9, 125.9, 112.3, 111.6, 62.6, 61.2, 55.8, 52.2, 49.0, 25.5; IR (neat): 3511, 2919, 1609, 1514, 1292, 1127, 1029, 697 cm^{-1} ; HRESIMS m/z 390.2060 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{25}\text{H}_{28}\text{NO}_3$, 390.2069).

(1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinoline-3-carbaldehyde (22)

To a solution of oxalyl chloride (0.34 g, 2.68 mmol) in dry CH_2Cl_2 (12 mL) at -78 $^\circ\text{C}$ was added a solution of DMSO (0.45 g, 5.85 mmol) in CH_2Cl_2 (1.2 mL) over 5 min, and the reaction mixture was stirred for 10 min at -78 $^\circ\text{C}$. Compound **21** (0.95 g, 2.43 mmol) was added as a solution in CH_2Cl_2 (1 mL) over 5 min. The reaction mixture was stirred for 15 min, and an excess of Et_3N (0.86 g, 8.53 mmol) was added over 5 min. The cooling bath was removed for the temperature to rise to room temperature. Water (30 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine and dried over MgSO_4 . Filtration and evaporation afforded a residue that was purified by column chromatography using 0–30 % ethyl acetate in hexane as a mobile phase and silica gel as a stationary phase yield 85 % as an yellow oil: R_f 0.8 (hexane/ethyl acetate 7/3); ^1H NMR (400 MHz, CDCl_3): δ 9.76 (s, 1H), 7.40–7.16 (m, 10H), 6.68 (s, 1H), 6.33 (s, 1H), 5.0 (s, 1H), 3.87 (s, 3H), 3.77–3.63 (m, 6H), 3.01–2.95 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 204.2, 147.9, 147.6, 144.1, 138.8, 129.1, 129.0, 127.4, 127.3, 127.2, 124.7, 111.9, 111.3, 63.8, 60.9, 55.8, 55.8, 54.1, 25.2; IR (neat): 2931, 2832, 1726, 1511, 1238, 1220, 697 cm^{-1} .

1-[(1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinolin-3-yl]ethanol (23)

A solution of compound **22** (0.65 g, 1.67 mmol) in dry THF (10 mL) was added to the freshly prepared Grignard reagent of methyl magnesium iodide (1.4 g, 8.48 mmol) under inert atmosphere at 0 $^\circ\text{C}$ for 15 min. The reaction was stirred at 0 $^\circ\text{C}$ for 3 h and the completion of reaction was monitored with TLC by quenching the reaction mixture with saturated ammonium chloride solution at 0 $^\circ\text{C}$ for 15 min. using 30/70 ethyl acetate/hexane. The reaction mixture was filtered and washed with ethyl acetate (20 mL). Evaporation of the filtrate gives the crude C_3 - α methyl secondary alcohol yield 80 % obtained as a 9:1 mixture. Diastereomers were separated with column chromatography using 0–40 % ethyl acetate/hexane and silicagel (230–400 mesh) as a stationary phase.

Major 23:

R_f 0.6 (hexane/EtOAc 7/3); Yellow oil; $[\alpha]_D^{20} +64.15$ (c 0.26 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.46–7.05 (m, 12H), 6.74 (s, 1H), 6.39 (s, 1H), 4.74 (s, 1H), 3.92–3.98 (m, 1H), 3.91 (s, 3H), 3.84 (d, 1H), 3.73 (s, 3H), 3.48 (d, 1H), 2.95–2.76 (m, 3H), 2.34–2.15 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 147.8, 147.2, 144.1, 139.9, 129.0, 128.9, 128.4, 127.7, 127.0, 126.6, 125.9, 112.3, 111.7, 69.7, 63.1, 57.2, 55.8, 55.8, 50.7, 31.9, 29.6, 29.3, 25.7, 21.6; IR (neat): 2924, 2853, 1510, 1449, 1243, 1219, 1099, 1028, 749, 698 cm^{-1} ; HRESIMS m/z 404.2225 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{26}\text{H}_{30}\text{NO}_3$, 404.2226).

Minor 23:

R_f 0.65 (hexane/EtOAc 7/3); Yellow oil; $[\alpha]_D^{20} +57.69$ (c 0.28 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.42–7.37 (m, 4H), 7.21–7.14 (s, 3H), 6.92 (d, 2H), 6.73 (s, 1H), 6.42 (s, 1H), 4.86 (s, 1H), 4.0 (d, $J=12.92$ Hz, 1H), 3.92 (s, 3H), 3.91–3.82 (m, 2H), 3.75 (s, 3H), 3.33 (d, $J=12.88$ Hz, 1H), 2.89–2.54 (m, 3H), 2.37–2.13 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 148.0, 147.6, 143.3, 139.0, 129.4, 128.6, 127.3, 126.9, 125.2, 112.3, 111.6, 65.7, 62.3, 57.9, 55.9, 55.8, 49.3, 24.5, 19.3; IR (neat): 2931, 2850, 1510, 1493, 1450, 1222, 1102, 751, 699 cm^{-1} ; HRESIMS m/z 404.2220 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{26}\text{H}_{30}\text{NO}_3$, 404.2226).

(*S*)-1-[(1*R*,3*S*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl]ethanol (24)

A solution of benzyl protected TIQ *sec* alcohol (300 mg, 0.74 mmol) in methanol (10 mL) was added to a suspension of 10 % wt Pd/C (0.2 g) in methanol (10 mL). The reaction mixture was connected to a H_2 source at atmospheric pressure and stirred at room temperature for 6 h. Completion of the reaction was monitored with TLC. The Pd/C was filtered off on a celite pad and the filtrate was evaporated under reduced pressure to afford crude amino ester. Crude compound was purified with column chromatography using hexane/ethyl acetate as an eluent to yield major **24** and minor **24**.

Major 24:

R_f 0.3 (hexane/EtOAc 4/6); Brown oil; $[\alpha]_D^{20} -11.11$ (c 0.27 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.30–7.19 (m, 3H), 7.13–7.03 (m, 2H), 6.66 (s, 1H), 6.39 (s, 1H), 5.19 (s, 1H), 3.86 (s, 3H), 3.73–3.65 (m, 4H), 2.83–2.74 (m, 1H), 2.92–2.85 (m, 1H), 2.67–2.59 (dd, $J=4.20$, 4.21 Hz, 1H), 1.12 (d, $J=6.40$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 147.9, 147.1, 145.0, 128.5, 128.2, 127.7, 127.2, 127.1, 111.5, 110.8, 69.5, 59.6, 55.8, 51.5, 27.7, 18.2; IR (neat): 2930, 1589, 1520, 1454, 1346, 1226, 1124, 755, 702 cm^{-1} ; HRESIMS m/z 314.1761 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_3$, 314.1756).

Minor 24:

R_f 0.3 (hexane/EtOAc 4/6); Colorless oil; $[\alpha]_D^{20} -10.71$ (c 0.28 in CHCl_3); ^1H NMR (400 MHz, CDCl_3 , 25 $^\circ\text{C}$): δ 7.40–7.15 (m, 5H), 6.66 (s, 1H), 6.40 (s, 1H), 5.50 (s, 1H), 3.88 (s, 3H), 3.81–3.67 (m, 4H), 2.97–2.69 (m, 3H), 1.16 (d, $J=5.72$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 148.7, 147.9, 139.7, 129.3, 128.5, 125.0, 111.2, 110.5, 68.0, 57.9, 55.9, 55.8, 54.3, 29.4, 19.5; IR (neat): 2933, 1694, 1513, 1451, 1243, 1089, 751 cm^{-1} ; HRESIMS m/z 314.1756 $[\text{M} + 1\text{H}]^{1+}$ (calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_3$, 314.1756).

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Supporting Information (see footnote on the first page of this article)

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