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Synthesis and Screening of C^1-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 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 C^1 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 an Ru complex. The *cis* isomer results in a high turnover rate with no selectivity. The *trans* isomer gave 99 % *ee* at lower temperatures. Furthermore, it was observed that substitution at the C^3-α position results in a drop of the enantioselectivity and the reactivity of the catalyst.

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 chiral scaffolds as potential ligands in asymmetric catalysis.

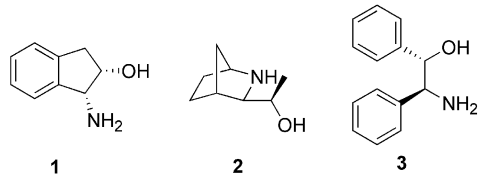

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Figure 1. Examples of chiral amino alcohol ligands reported with high selectivity in ATH reactions.

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 C^1-phenyl and C^3-α-phenyl substitutions. The ligands were coordinated to (arene)ruthenium, -rhodium, and -iridium precursors, and their efficiency was investigated as ATH catalysts for the reduction of prochiral ketones.[13–15] To the best of our knowledge, this is the first successful application of a TIQ ligand to effect high enantioselective transfer hydrogenations yielding high turnover rates at reasonable catalyst loading.

Results and Discussion

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 are 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,

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which have initially a single chiral center, 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] The ATH reduction of acetophenone proved to be inefficient with this ligand after coordination with a $[Ru(p\text{-cymene})Cl_2]_2$ complex and with isopropyl alcohol as the hydride source (Table 1, Entry 1).

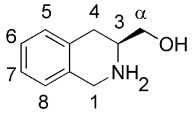

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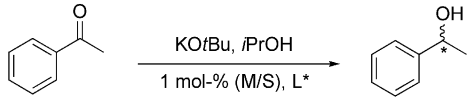
Figure 2. Unsubstituted TIQ ligand for ATH reactions.

Table 1. Asymmetric transfer hydrogenation of acetophenone using different ligands complexed with $[Ru(p\text{-cymene})Cl_2]_2$.

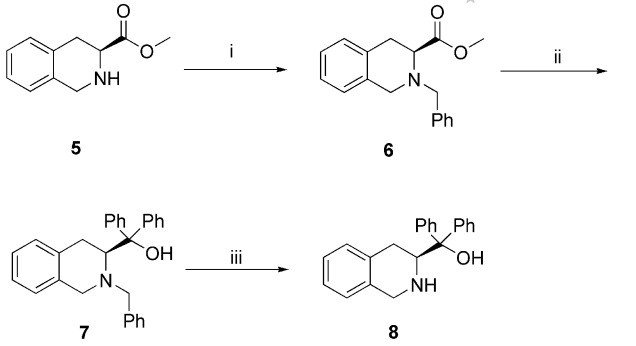


Entry	Ligand	Time [h]	Conversion [%][a]	*ee* [%] (*R*/*S*)[b]
1	**4**	24.0	28	35 (*S*)
2	**8**	24.0	n. r.[c]	n.r.[c]
3	**14**	0.75	94	94 (*R*)
4	**17**	0.75	80	racemic

[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.

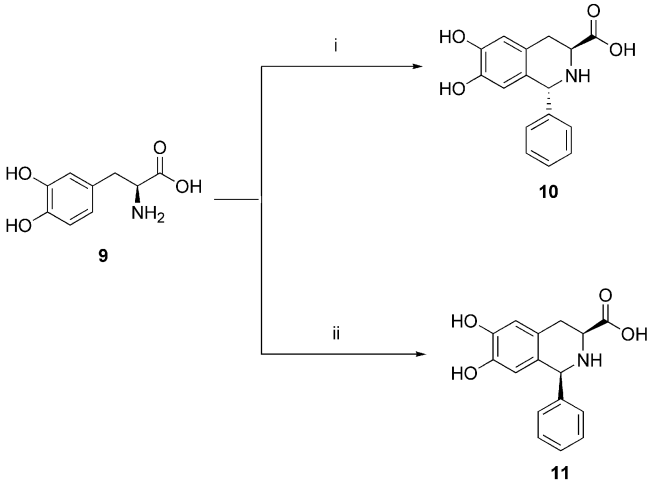
From our lead molecule we thought conversion of the primary alcohol **4** to a secondary alcohol could potentially improve the ligand activity. However, due to the difficulty in the synthesis as will be demonstrated later, we designed and synthesized the amino tertiary alcohol **8**, introducing phenyl moieties as bulky groups at the C^3 position. Ligand **8** was synthesized from the TIQ amino ester **5**,[19] and the benzyl protection of the secondary amine was carried out with benzyl bromide and K_2CO_3 in acetonitrile. Subsequently, a Grignard reaction was attempted on **6** affording **7** in less than 20% yields. Ultimately, deprotection of **7** resulted in the formation of ligand **8** as shown in Scheme 1.

Disappointingly, phenyl substitution at the C^3-α position did not improve the catalytic system, in fact, no reactivity was observed with 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 phenyl group creating a stereogenic center at the C^1 position while increasing the pK_a of the secondary nitrogen atom and the steric bulk of the ligand. All attempts to achieve substitution at the C^1 position through a Pictet–Spengler reaction between phenylalanine and benzaldehyde were met with limited success. It was essential to employ the activated aromatic group of L-DOPA (**9**) to facilitate product formation.



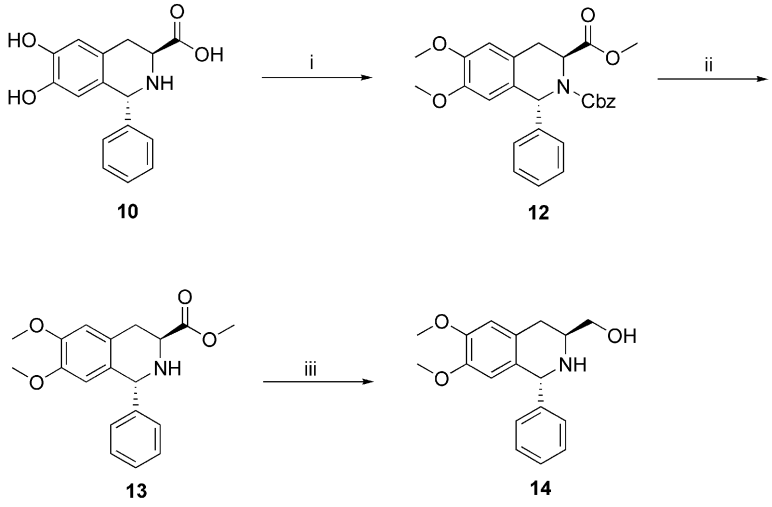
Scheme 1. Reagents for the synthesis of ligand **8**: (i) benzyl bromide, K_2CO_3, CH_3CN, reflux, 3 h; (ii) PhMgBr, dry THF, reflux, 6 h; (iii) 10 wt.-% Pd/C, H_2 (1 atm), MeOH.

Aubry et al. reported on the effect of solvent on the stereocontrol of Pictet–Spengler reactions.[20] For ligand **14**, L-DOPA (**9**) was treated with benzaldehyde in the presence of K_2CO_3 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 K_2CO_3 in water giving a 20% yield.



Scheme 2. Reagents for the synthesis of TIQ acids **10** and **11**: (i) PhCHO, K_2CO_3, EtOH/H_2O, 0 °C to room temp.; (ii) PhCHO, K_2CO_3, H_2O, 0 °C to room temp.

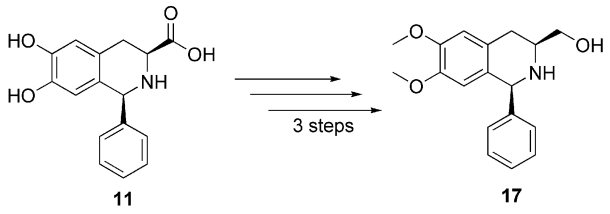
To obtain compound **12**, C^1-substituted *N*-Cbz-protected methyl ester, an in situ reaction was performed on **10** with benzyl chloroformate (Cbz) and monitored with LCMS. After completion of the reaction, the solvent was evaporated under vacuum and the crude product was used directly and methylated at the phenolic and carboxylic acid positions. This was achieved by refluxing the compound in acetone in the presence of Me_2SO_4 and $KHCO_3$.[21] The crude product was purified by column chromatography to obtain the desired compound **12** in 80% yield. Deprotection of the Cbz group gave **13**, which was reduced to the amino alcohol **14** (Scheme 3). It was observed that partial racemi-



Scheme 3. Reagents for the synthesis of ligand **14**: (i) $KHCO_3$, Cbz-Cl, dioxane/water, in situ solvent evaporation, $KHCO_3$, Me_2SO_4, acetone, reflux, overnight; (ii) 10 wt.-% Pd/C, H_2 (1 atm), MeOH, room temp.; (iii) $LiAlH_4$, dry THF, 0 °C, 2 h.

zation 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).

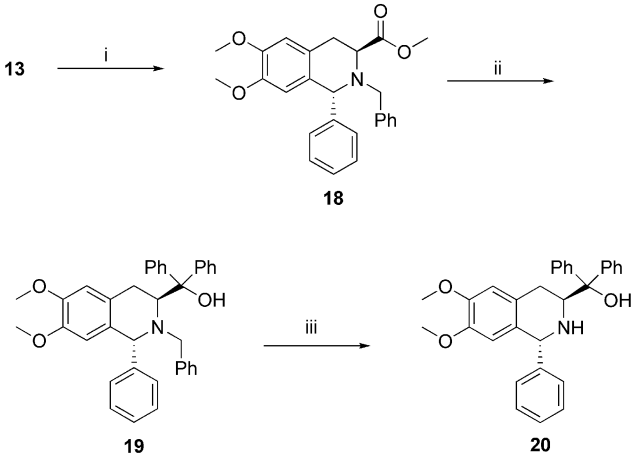
A similar synthetic route was applied to produce the *cis* TIQ amino alcohol **17** starting from **11** (Scheme 4).



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

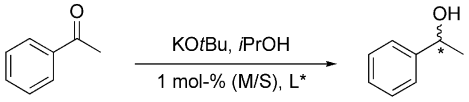
Interesting results were observed for the ATH reduction reaction of acetophenone utilizing ligands **14** and **17**. Ligand **14** showed good catalytic activity with 94% conversion and 94% *ee* (*R*) in 45 min. In the case of **17**, a racemic mixture was observed with an 80% conversion (Table 1, Entries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

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 C^3-α position to re-investigate the effect of steric bulk. To obtain this ligand, intermediate **13** could be converted into 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 phenylmagnesium bromide afforded **19**. Deprotection of **19** (Scheme 5) resulted in the formation of ligand **20**. It was comparative to ligand **8** (Table 2, Entry 1) and thus confirmed that bulky groups present on the C^3-α position hinder the catalytic activity.



Scheme 5. Reagents for the synthesis of ligand **20**: (i) benzyl bromide, K_2CO_3, CH_3CN, reflux, 3 h; (ii) PhMgBr, dry THF, reflux, 6 h; (iii) 10 wt.-% Pd/C H_2 (1 atm), MeOH.

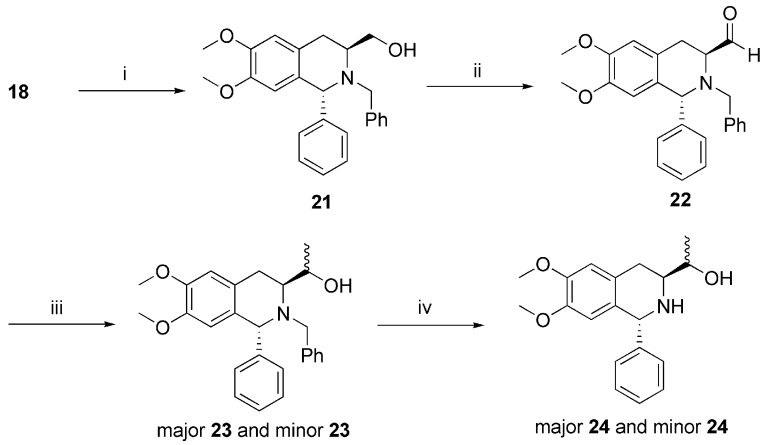
Table 2. Asymmetric transfer hydrogenation of acetophenone using different ligands with $[Ru(p\text{-cymene})Cl_2]_2$.



Entry	Ligand	Time [h]	Conversion [%][a]	*ee* [%] (*R*/*S*)[b]
1	**20**	1.0	n.r.[c]	n.r.[c]
2	major **24**	0.5	33	94 (*R*)
3	minor **24**	0.5	30	70 (*S*)

[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.

From the results of ligand **14** and **20**, it was decided to investigate the effect of less bulkier substitution at the C^3-α position. There were two reasons for this: (i) it is known



Scheme 6. Reagents for the synthesis of ligands major **24** and minor **24**: (i) $LiAlH_4$, dry THF, room temp.; (ii) DMSO, oxalyl chloride, TEA, CH_2Cl_2, –78 °C; (iii) CH_3MgI, dry THF, 0 °C; (iv) 10 wt.-% Pd/C, H_2 (1 atm), MeOH, room temp. All experimental details are available in the Supporting Information.

from the literature that amino alcohols with a secondary alcohol exhibit excellent reactivity and selectivity;[22,23] (ii) this allows us to introduce another chiral center into our catalytic ligand design. The reduction of ester **18** with $LiAlH_4$ followed by a Swern oxidation afforded the aldehyde **22** in 82% yield. Subsequently, a Grignard reaction with methylmagnesium iodide under reflux conditions afforded two diastereomeric alcohols in a 1:1 mixture. To improve the 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 isomers followed by deprotection afforded ligands major **24** and minor **24** in 60% yield (Scheme 6).

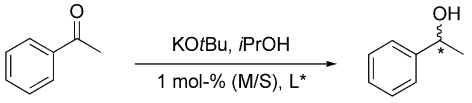
Ligands major **24** and minor **24** were tested for transfer hydrogenation activity under identical conditions. Ligand major **24** gave a 94% *ee* (*R*), and minor **24** gave 70% *ee* (*S*), albeit both with low conversions (Table 2, Entries 2, 3).

To summarize, a total of seven ligands were prepared and evaluated in the ruthenium-catalyzed ATH of acetophenone; the results are found 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 C^3-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 C^1 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 C^3-α position (ligands major **24** and minor **24**) 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. $[Ru(p\text{-cymene})Cl_2]_2$, $[RhCl_2Cp^*]_2$ and $[IrCl_2Cp^*]_2$.

All of the new complexes, catalytic conversions and selectivities are 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*-cy-

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



Entry	Metal complex	Temperature	Time [h]	Conversion [%][a]	*ee* [%] (*R*/*S*)[b]
1	$[Ru(p\text{-cymene})Cl_2]_2$	r.t.	0.75	94	94 (*R*)
2	$[Ru(p\text{-cymene})Cl_2]_2$	0 °C	1.0	35	99 (*R*)
3[c]	$[Ru(p\text{-cymene})Cl_2]_2$	r.t.	1.25	85	94 (*R*)
4	$[RhCl_2Cp^*]_2$	r.t.	0.25	94	90 (*R*)
5	$[RhCl_2Cp^*]_2$	0 °C	0.5	86	94 (*R*)
6	$[RhCl_2Cp^*]_2$	–15 °C	0.5	42	99 (*R*)
7[c]	$[RhCl_2Cp^*]_2$	r.t.	0.5	94	91 (*R*)
8	$[IrCl_2Cp^*]_2$	r.t.	0.5	35	75 (*R*)

[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.

Table 4. ATH of various alkyl aryl ketones with [Ru(*p*-cymene)Cl_2]$_2$ and **14** as chiral ligand at ambient temperature.

Entry	Substrate	Time [h]	Conversion (%)[a]	*ee* [%] (*R*/*S*)[b]
1	4-methylacetophenone	1.0	80	92 (*R*)
2	4-nitroacetophenone	1.0	98	68 (*R*)
3	2-methoxyacetophenone	1.0	94	82 (*S*)
4	1-indanone	1.0	31	65 (*S*)
5	1-indanone	24.0	40	69 (*S*)
6	tetralone	1.0	40	racemic
7	2-acetylpyridine	1.0	n.r.[c]	n.r.[c]
8	2-acetylpyridine	24.0	n.r.[c]	n.r.[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.

mene)Cl_2]$_2$, and an excellent selectivity was observed with 99% *ee* but with a low conversion of 35%. [$RhCl_2$Cp*]$_2$ gave a higher reactivity (94% conversion) than [Ru(*p*-cymene)Cl_2]$_2$, but with a diminished enantioselectivity 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 was used, we attempted the same reaction with a low catalyst loading of 0.5 mol-% (metal/substrate). 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.

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 substrates can be grouped based on their electronic and steric properties. Electron-donating (4-methylacetophenone) or electron-withdrawing (4-nitroacetophenone) groups decreased 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 sp^2 nitrogen atom to the metal center thereby disrupting the active transition state. An increase in steric bulk (indanone and tetralone) renders a loss in selectivities and conversion rates.

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 are 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 (Figure 3). LACVP in Jaguar defines a combination of the LANL2DZ basis set for ruthenium[27] 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.

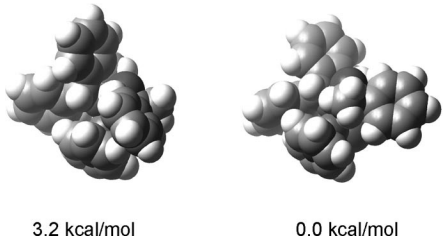


Figure 3. The calculated (*S*) (left) and (*R*) (right) transition states for the reduction of acetophenone using ligand **14**. The (*S*)-transition state showing a close-contact between the phenyl of the substrate and the arene ligand, making it less favorable. The Cartesian coordinates of the optimized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

The energy of the transition state leading to the (*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 Tables 1, 2, 3, and 4.

Conclusions

We have synthesized and evaluated seven ligands of a new class of N,O TIQ compounds. These ligands were coordinated with ruthenium, and they were evaluated in the asymmetric transfer hydrogenation of acetophenone. C^1-substituted TIQ amino primary alcohol **14** gave rise to a catalyst that induced good enantioselectivity, 94% *ee*. The reaction was repeated under various conditions, affording 99% *ee* at lower temperature as the best result. The rhodium complex with 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-% ratio of metal/substrate with a lower selectivity of 91% *ee*. Considering the good selectivity at ambient temperature, we screened different alkyl aryl ketone substrates, rendering moderate to reasonable results. Acetophenone as substrate gave the best results.

Experimental Section

General: Reagents and solvents were purchased from Aldrich, Merck and Fluka. All NMR spectra were recorded with Bruker AVANCE III 400 MHz or 600 MHz instruments. Chemical shifts are expressed in ppm relative to TMS, and coupling constants are reported in Hz. NMR spectra were obtained at room temperature, except where stated otherwise. Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F254. Crude compounds were purified by column chromatography with silica gel (60–200 mesh except if stated different). All solvents were dried according to standard procedures. IR spectra were recorded with a Perkin–Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded with a Perkin–Elmer Polarimeter. Melting points are uncorrected. Testing reactions were carried out under dry UHP argon gas. The results of all testing reactions that were analyzed using GC analysis was performed with an 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 with an Agilent 1100 HPLC with reverse phase using 0.1% formic acid in acetonitrile and Millipore water. High-resolution mass spectrometric data was obtained with a Bruker microTOF-Q II instrument operating at ambient temperatures, using a sample concentration of approximately 1 ppm.

General Procedure for the Transfer Hydrogenation of Aromatic Ketones: To an oven-dried Schlenk tube was added [Ru(*p*-cymene)-Cl_2]$_2$ (3.0 mg, 4.8 μmol), ligand (4 equiv.), and the tube was evacuated for 10 min. Thereafter, freshly distilled isopropyl alcohol was added under dry argon. The mixture was stirred for 15 min, and freshly prepared 0.1 M KO*t*Bu solution was added to the complex, followed by the substrate. An aliquot of the reaction mixture was tested at different intervals by quenching with 5% acetic acid in isopropyl alcohol, passed through a pad of silica gel and monitored by GC with a chiral β-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 12 and 15: To a solution of C^1-substituted TIQ carboxylic acid (1.0 g, 3.5 mmol) in dioxane (20 mL) and water (10 mL) at 0 °C was added dropwise a solution of potassium hydrogen carbonate (2.1 g, 21.1 mmol) over 15 min followed by addition of Cbz-Cl (0.65 g, 3.8 mmol). The solution was stirred at 0 °C for 1.5 h and then at ambient temperature for a further 1.5 h. The reaction was monitored by LC-MS (neutralizing the reaction mixture with 10% HCl and extracting with ethyl acetate). The solvent was evaporated under reduced pressure and the residue 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 dimethyl sulfate (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, and ethyl acetate (60 mL) was added and the mixture washed with 20 mL (2 × 10 mL) of water followed by 10 mL of brine. The organic layer was separated and dried with anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the crude Cbz-ester, which was purified by column chromatography using 0–40% ethyl acetate in hexane as the eluent to yield approximately 1.3 g (80% yield) of pure compounds **12** and **15**.

General Deprotection Procedure for the Preparation of Amino Esters 13 and 16: A solution of the Cbz-protected TIQ ester (1.0 g, 2.1 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 stirred at room temperature with H_2 under atmospheric pressure for 1 h. 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 then washed with methanol (20 mL). The filtrate was concentrated 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 approximately 0.65 g (95% yield) of pure compounds **12** and **16**.

General Procedure for the Preparation of 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 $LiAlH_4$ (0.18, 4.5 mmol) in dry THF (20 mL) under N_2 at 0 °C. The mixture was stirred at 0 °C for 2 h, and the reaction was monitored by TLC in hexane/ethyl acetate (50:50; R_f = 0.5). Excess lithium aluminum hydride was quenched with saturated sodium sulfate 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, the mixture washed with water (2 × 5 mL), the organic layer was separated and dried with anhydrous $MgSO_4$ to afford the crude amino alcohol. This was purified by gradient column chromatography [solvent A: saturated ammonia in DCM/DCM (10:90) and solvent B: MeOH/DCM (2:98)] to yield approximately 0.33 g (70% yield) of pure amino alcohols **14** and **17**.

(*S*)-Diphenyl(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (8): White solid, m.p. 104–106 °C (MeOH). Spectroscopic data identical to literature values.[28] $[\alpha]_D^{20}$ = –130 (*c* = 0.26, in $CHCl_3$). HR ESI MS: *m*/*z* = 316.1774 [M + H]$^+$ (calcd. for $C_{22}H_{22}NO$ 316.1701).

2-Benzyl 3-Methyl (1*R*,3*S*)-6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2,3(1*H*)-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 $CHCl_3$). ^{1}H NMR (400 MHz, DMSO, 100 °C): δ = 7.36–7.15 (m, 9 H), 7.09 (s, 1 H), 6.76 (s, 1 H), 5.16–5.05 (m, 3 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 3.48 (s, 3 H), 3.21 (dd, *J* = 15.69, 5.97 Hz, 1 H), 3.13–3.04 (m, 2 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 2942, 1744, 1714, 1204, 735, 698 cm^{-1}. HR ESI MS: *m*/*z* = 462.1896 [M + 1 H]$^+$ (calcd. for $C_{27}H_{28}NO_6$ 462.1916), 484.1720 [M + Na]$^+$ (calcd. for $C_{27}H_{27}NNaO_6$ 484.1736).

Methyl (1*R*,3*S*)-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 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 3 H), 7.23–7.16 (m, 2 H), 6.65 (s, 1 H), 6.34 (s, 1 H), 5.25 (s, 1 H), 3.88 (s, 3 H), 3.80 (q, *J* = 8.58, 5.06 Hz, 1 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.15 (dd, *J* = 5.08 Hz, 1 H) 3.01 (dd, *J* = 8.68 Hz, 1 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 2928, 2600, 1746, 1516, 1250, 1123, 727 cm^{-1}. HR ESI MS: *m*/*z* = 328.1547 [M + H]$^+$ (calcd. for $C_{19}H_{22}NO_4$ 328.1548).

[(1*R*,3*S*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl]-methanol (14): R_f = 0.4 (CH_2Cl_2/MeOH/satd. 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 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 3 H), 7.18–7.13 (m, 2 H), 6.64 (s, 1 H), 6.42 (s, 1 H), 5.19 (s, 1 H), 3.88 (s, 3 H), 3.72 (s, 3 H), 3.66–3.60 (dd, *J* = 10.76, 2.96 Hz, 1 H), 3.49–3.41 (dd, *J* = 10.64, 7.81 Hz, 1 H), 3.12–3.02 (m, 1 H), 2.70 (dd, *J* = 4.56 Hz, 1 H), 2.57 (dd, *J* = 10.28 Hz, 1 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 3264, 2832, 1515, 1222, 1066, 981, 726, 694 cm^{-1}. HR ESI MS: m/z = 300.1622 $[M + H]^+$ (calcd. for $C_{28}H_{22}NO_3$ 300.1600).

2-Benzyl 3-Methyl (1*S*,3*S*)-6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2,3(1*H*)-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, 10 H), 7.02 (s, 1 H), 6.93 (s, 1 H), 5.16 (s, 1 H), 4.43 (dd, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.49 (s, 3 H), 3.02 (dd, J = 15.09, 5.67 Hz, 1 H), 2.70 (dd, J = 14.73, 11.13 Hz, 1 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 1752, 1693, 1514, 1404, 1295, 1216, 1102, 697, 596 cm^{-1}. HR ESI MS: m/z = 462.1906 $[M + H]^+$ (calcd. for $C_{27}H_{28}NO_6$ 462.1916), and 484.1730 $[M + Na]^+$ (calcd. for $C_{27}H_{27}NNaO_6$ 484.1736).

Methyl (1*S*,3*S*)-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, 5 H), 6.64 (s, 1 H), 6.17 (s, 1 H), 5.09 (s, 1 H), 3.91–3.86 (m, 4 H), 3.85–3.74 (m, 4 H), 3.56–3.61 (s, 3 H), 3.41–3.05 (m, 2 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 3020, 1737, 1514, 1244, 1213, 749, 665 cm^{-1}. HR ESI MS: m/z = 328.1548 $[M + H]^+$ (calcd. for $C_{19}H_{22}NO_4$ 328.1548).

[(1*S*,3*S*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl]-methanol (17): R_f = 0.4 (CH_2Cl_2/MeOH/satd. 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, 5 H), 6.62 (s, 1 H), 6.14 (s, 1 H), 5.04 (s, 1 H), 3.85 (s, 1 H), 3.79–3.72 (m, 1 H), 3.62–3.53 (m, 4 H), 3.26–3.10 (m, 1 H), 3.00–2.52 (m, 2 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 3256, 2919, 1511, 1453, 1258, 1215, 1100, 1073, 822, 737, 700, 561 cm^{-1}. HR ESI MS: m/z = 300.1594 $[M + H]^+$ (calcd. for $C_{18}H_{22}NO_3$ 300.1600).

Methyl (1*R*,3*S*)-2-Benzyl-6,7-dimethoxy-1-*p*-tolyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (18): To a solution of compound **13** (500 mg, 1.52 mmol) in acetonitrile (20 mL) was added solid K_2CO_3 (635 mg, 4.58 mmol) 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 by TLC using hexane/ethyl acetate (60:40; R_f = 0.5). The solvent was evaporated, and ethyl acetate (30 mL) was added, the mixture washed with 2 × 10 mL of water, the organic layer was separated and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford a crude product, which was purified by column chromatography using 0–20% ethyl acetate/hexane as the eluent to yield approximately 0.44 g (90% yield) of pure product. 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, 2 H), 7.32–7.16 (m, 9 H), 6.54 (s, 1 H), 6.26 (s, 1 H), 5.19 (s, 1 H), 3.85–3.72 (m, 6 H), 3.61 (s, 6 H), 3.23 (dd, J = 5.10, 15.66 Hz, 1 H), 2.98 (dd, J = 3.00, 15.72, Hz, 1 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 2944, 1729, 1511, 1152, 753, 699 cm^{-1}. HR ESI MS: m/z = 418.2012 $[M + H]^+$ (calcd. for $C_{26}H_{28}NO_4$ 418.2018).

[(1*R*,3*S*)-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 phenylmagnesium bromide (2.17 g, 11.9 mmol) under a dry inert gas at ambient temperature for 15 min. Completion of the reaction was monitored by TLC, and the reaction was quenched by adding a saturated ammonium chloride solution to the mixture at 0 °C. The reaction mixture was filtered off and washed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure to yield approximately 0.52 g (80% yield) of the crude product. 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, 2 H), 7.32–7.10 (m, 14 H), 7.0–6.88 (m, 6 H), 6.69 (s, 1 H), 6.38 (s, 1 H), 4.74 (s, 1 H), 4.21 (d, J = 13.60 Hz, 1 H), 4.14 (q, J = 3.70, 12.74 Hz, 1 H), 3.89 (s, 3 H), 3.72 (s, 3 H), 3.57 (s, 1 H), 3.30–3.18 (m, 2 H), 2.60 (dd, J = 3.60, 16.48 Hz, 1 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 3589, 1509, 1240, 1093, 694 cm^{-1}. HR ESI MS: m/z = 542.2698 $[M + H]^+$ (calcd. for $C_{37}H_{36}NO_3$ 542.2695).

[(1*R*,3*S*)-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 an inert gas. The reaction mixture was connected to an H_2 source at 1 atm and stirred at room temperature for 6 h. Completion of the reaction was monitored by 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 concentrated 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 approximately 0.30 g (92% yield) of pure product. R_f = 0.3 (hexane/EtOAc, 5:5). Pale yellow solid, m.p. 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, 5 H), 7.29–7.24 (t, J = 15.20 Hz, 1 H), 7.05–7.21 (m, 6 H), 7.02–6.96 (m, 2 H), 6.56 (s, 1 H), 6.43 (s, 1 H), 5.23 (s, 1 H), 3.89–3.85 (q, J = 10.94, 3.86 Hz, 1 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 3.03–2.92 (dd, J = 16.42, 10.94 Hz, 1 H), 2.24–2.16 (m, 1 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 2926, 1512, 1447, 1243, 1063, 698 cm^{-1}. HR ESI MS: m/z = 452.2220 $[M + H]^+$ (calcd. for $C_{30}H_{30}NO_3$ 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 dropwise to a suspension of $LiAlH_4$ (0.35 g, 9.3 mmol) in dry THF (30 mL) under N_2 at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Completion of the reaction was monitored by TLC using hexane/ethyl acetate (80:20; R_f= 0.6). Excess lithium aluminum hydride was quenched with a saturated sodium sulfate solution at 0 °C. The reaction mixture was filtered and washed with THF (20 mL). The solvent was evaporated to dryness under reduced pressure. Ethyl acetate (20 mL) was added and washed with water (2 × 5 mL). The organic layer was separated and dried with anhydrous $MgSO_4$ to give the crude amino alcohol. The crude product was purified by column chromatography using silica gel as a stationary phase and 0–40% ethyl acetate in hexane as a mobile phase to yield 0.85 g (70% yield) of pure amino alcohol. R_f = 0.3 (hexane/EtOAc, 5:5). Yellow solid, m.p. 108–110 °C. $[\alpha]_D^{20}$ = +66.0 (c = 0.25, in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.28 (m, 5 H), 7.24–7.12 (m, 3 H), 6.98 (d, J = 6.88 Hz, 2 H), 6.70 (s, 1 H), 6.41 (s, 1 H), 4.85 (s, 1 H), 3.98–3.89 (m, 4 H), 3.77–3.69 (m, 4 H), 3.58–3.49 (m, 1 H), 3.41–3.29 (m, 2 H), 2.69 (dd, J = 11.60, 11.56 Hz, 1 H), 2.53 (dd, J = 4.68, 4.68 Hz, 1 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 3511, 2919, 1609, 1514, 1292, 1127, 1029, 697 cm^{-1}. HR ESI MS: m/z = 390.2060 [M + H]$^+$ (calcd. for $C_{25}H_{28}NO_3$ 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 °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 at –78 °C for 10 min. 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), and the combined organic extracts were washed with brine and dried with $MgSO_4$. Filtration and concentration afforded a residue that was purified by column chromatography using silica gel as a stationary phase and 0–30% ethyl acetate in hexane as a mobile phase to yield approximately 0.80 g (85% yield) of the product as a yellow oil. R_f = 0.8 (hexane/ethyl acetate, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H), 7.40–7.16 (m, 10 H), 6.68 (s, 1 H), 6.33 (s, 1 H), 5.0 (s, 1 H), 3.87 (s, 3 H), 3.77–3.63 (m, 6 H), 3.01–2.95 (m, 2 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 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 a freshly prepared Grignard reagent of methylmagnesium iodide (1.4 g, 8.48 mmol) under an inert gas at 0 °C for 15 min. The reaction mixture was stirred at 0 °C for 3 h and the progress monitored by TLC using ethyl acetate/hexane (30:70); the reaction was quenched by adding a saturated ammonium chloride solution at 0 °C for 15 min. The reaction mixture was filtered and washed with ethyl acetate (20 mL). Concentration of the filtrate gave 0.54 g (80% yield) of the crude product as a 9:1 mixture. The diastereomers were separated by column chromatography using silica gel (230–400 mesh) as a stationary phase and 0–40% ethyl acetate/hexane as a mobile phase.

major 23: R_f = 0.6 (hexane/EtOAc, 7:3). Yellow oil. $[\alpha]_D^{20}$ = +64.15 (c = 0.26, in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.05 (m, 12 H), 6.74 (s, 1 H), 6.39 (s, 1 H), 4.74 (s, 1 H), 3.92–3.98 (m, 1 H), 3.91 (s, 3 H), 3.84 (d, 1 H), 3.73 (s, 3 H), 3.48 (d, 1 H), 2.95–2.76 (m, 3 H), 2.34–2.15 (m, 2 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 2924, 2853, 1510, 1449, 1243, 1219, 1099, 1028, 749, 698 cm^{-1}. HR ESI MS: m/z = 404.2225 [M + H]$^+$ (calcd. for $C_{26}H_{30}NO_3$ 404.2226).

minor 23: R_f = 0.65 (hexane/EtOAc, 7:3). Yellow oil. $[\alpha]_D^{20}$ = +57.69 (c = 0.28, in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 4 H), 7.21–7.14 (s, 3 H), 6.92 (d, 2 H), 6.73 (s, 1 H), 6.42 (s, 1 H), 4.86 (s, 1 H), 4.0 (d, J = 12.92 Hz, 1 H), 3.92 (s, 3 H), 3.91–3.82 (m, 2 H), 3.75 (s, 3 H), 3.33 (d, J = 12.88 Hz, 1 H), 2.89–2.54 (m, 3 H), 2.37–2.13 (m, 2 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 2931, 2850, 1510, 1493, 1450, 1222, 1102, 751, 699 cm^{-1}. HR ESI MS: m/z = 404.2220 [M + H]$^+$ (calcd. for $C_{26}H_{30}NO_3$ 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 an H_2 source at atmospheric pressure and stirred at room temperature for 6 h. The Pd/C was filtered off on a Celite pad, and the filtrate was concentrated under reduced pressure to afford the crude amino ester. The products were purified by column chromatography using hexane/ethyl acetate as an eluent to yield a combined mass of 0.14 g (60% yield) for 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 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.19 (m, 3 H), 7.13–7.03 (m, 2 H), 6.66 (s, 1 H), 6.39 (s, 1 H), 5.19 (s, 1 H), 3.86 (s, 3 H), 3.73–3.65 (m, 4 H), 2.83–2.74 (m, 1 H), 2.92–2.85 (m, 1 H), 2.67–2.59 (dd, J = 4.20, 4.21 Hz, 1 H), 1.12 (d, J = 6.40 Hz, 3 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 2930, 1589, 1520, 1454, 1346, 1226, 1124, 755, 702 cm^{-1}. HR ESI MS: m/z = 314.1761 [M + H]$^+$ (calcd. for $C_{19}H_{24}NO_3$ 314.1756).

minor 24: R_f = 0.3 (hexane/EtOAc, 4:6). Colorless oil. $[\alpha]_D^{20}$ = –10.71 (c = 0.28, in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.15 (m, 5 H), 6.66 (s, 1 H), 6.40 (s, 1 H), 5.50 (s, 1 H), 3.88 (s, 3 H), 3.81–3.67 (m, 4 H), 2.97–2.69 (m, 3 H), 1.16 (d, J = 5.72 Hz, 3 H) ppm. ^{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 ppm. IR (neat): $\tilde{\nu}$ = 2933, 1694, 1513, 1451, 1243, 1089, 751 cm^{-1}. HR ESI MS: m/z = 314.1756 [M + H]$^+$ (calcd. for $C_{19}H_{24}NO_3$ 314.1756).

Supporting Information (see footnote on the first page of this article): NMR, LC traces, HRMS and Cartesian coordinates for DFT calculations.

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