

Comparison of Tetrahydroisoquinoline (TIQ) Thiazole and Oxazoline Ligands for Asymmetric Henry Reactions

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ABSTRACT

A series of novel C¹ symmetric thiazole ligands with a tetrahydroisoquinoline (TIQ) backbone were synthesized. Their application in the catalytic asymmetric Henry reaction was investigated with comparison to a corresponding TIQ oxazoline ligand. The Cu(II)-oxazoline complex was more reactive and furnished moderate enantioselectivities up to 61:36 (*syn:anti*) with 75:25 diastereomeric excess, while the Cu(II)-thiazole complexes had lower selectivity. This is the first example where a direct comparison between an *N, N*-type thiazole and oxazoline ligands has been studied.

KEYWORDS

Tetrahydroisoquinoline, thiazole, oxazoline, Henry reaction, enantioselectivity.

1. Introduction

Oxazolines are versatile ligands due to their ease of accessibility, modular nature and applications in catalytic asymmetric reactions.¹ These ligands however tend to be unstable.² This has prompted researchers to examine similar structures such as thiazoles and oxazoles as potential ligands (Fig. 1). Extensive studies on C₁-symmetric chiral thiazole moieties in various catalytic reactions have been performed. Teng *et al.* designed a series of bidentate pyridyl-thiazole ligands **1** for allylic oxidation of cyclohexene. The observed enantiomeric excess (*ee*) was up to 62%.³ The same group synthesized the bidentate pyridyl-thiazole **2** which was applied to the asymmetric cyclopropanation of styrene resulting in a best *ee* of 33%.⁴ Birkholz *et al.* evaluated an asymmetric allylic amination reaction using chiral phospholanes **3** up to 20% *ee*.⁵ Dong *et al.* designed a series of BINOL-based thiazole ligands **4** that catalyzed the stereoselective Henry reaction with *ees* up to 93%. The same ligands gave up to 33% *ee* in the conjugate addition reaction of Et₂Zn to enones.⁶ To date, the most successful class of thiazole ligands are the *P, N*-type systems **5–8** designed by Andersson and co-workers for asymmetric hydrogenation reactions. They predominantly gave high yields (up to 99) and selectivities of up to 99% *ee*.^{2,7–10} In addition, the phosphine-thiazole moiety **7** has been successfully utilized in Pd catalyzed allylic substitution¹¹ (*ee* up to 92%) and in allylic alkylation reactions¹¹ (92% *ee*). The phosphine-thiazole moiety **8** was applied to the Heck reaction giving excellent enantioselectivities of up to 90%.¹²

Andersson and co-workers, conducted a direct comparison of the thiazole and oxazoline in hydrogenation reactions, and concluded that oxazoline-phosphine superseded the thiazole counterpart in terms of reactivity and selectivity. A proposed explanation for these observations was attributed to the *pK_a* values of the unsubstituted thiazole (2.5) being lower than that of the oxazoline (5.6).¹³

Teng *et al.* have compared the activities of their *N, N*-type thiazole (pyridyl-thiazole **2**⁴) to the literature values obtained for pyridyl-oxazoline **9** type ligands.^{14–16} For a Pd catalyzed allylic substitution reaction, the oxazoline and thiazole analogues resulted in enantioselectivities of up to 90% and 85%, respectively.

In terms of importance, the Henry reaction is often used as an asymmetric benchmark reaction to test new chiral ligands.^{17–24} For example, Judeh and co-workers have used the Henry reaction for the synthesis of various isoquinoline derivatives.^{25–27}

We recently reported the enantioselective nitroaldol reaction between various aldehydes and nitromethane catalyzed by TIQ derived chiral oxazolines (Fig. 2).²⁸ Ligand **L4** gave the best yield (99%) and enantioselectivity (62%). Due to the lack of direct comparative studies between the two previously mentioned families of ligands (oxazolines and thiazoles) we decided to design and synthesize the thiazole analogues **L1–L3** and compare their activities and selectivities in the Henry reaction against that of the oxazoline **L4**.

2. Results and Discussion

2.1. Synthesis of TIQ Thiazole Ligands

Compound **11** was prepared from natural *L*-3,4-dihydroxy-phenylalanine as reported previously.²⁸ Amination of **11** with ammonium bicarbonate and di-*tert*-butyl dicarbonate yielded the *N*-Cbz protected amide **12**, which, upon reaction with Lawesson's reagent, was converted to the thioamide **13**. Thioamide **13** was cyclized with 2-bromoacetophenone and 1-bromopinacolone to give the corresponding *N*-protected thiazoles **14** and **15**, respectively. Ligands **L1** and **L2** were obtained by Cbz deprotection of **14** and **15**, respectively, using dipropylsulfide and boron trifluoride diethyl etherate (Scheme 1).

Compound **17** was prepared as previously reported from *L*-phenyl alanine.²⁹ It was converted to the *N*-Boc protected

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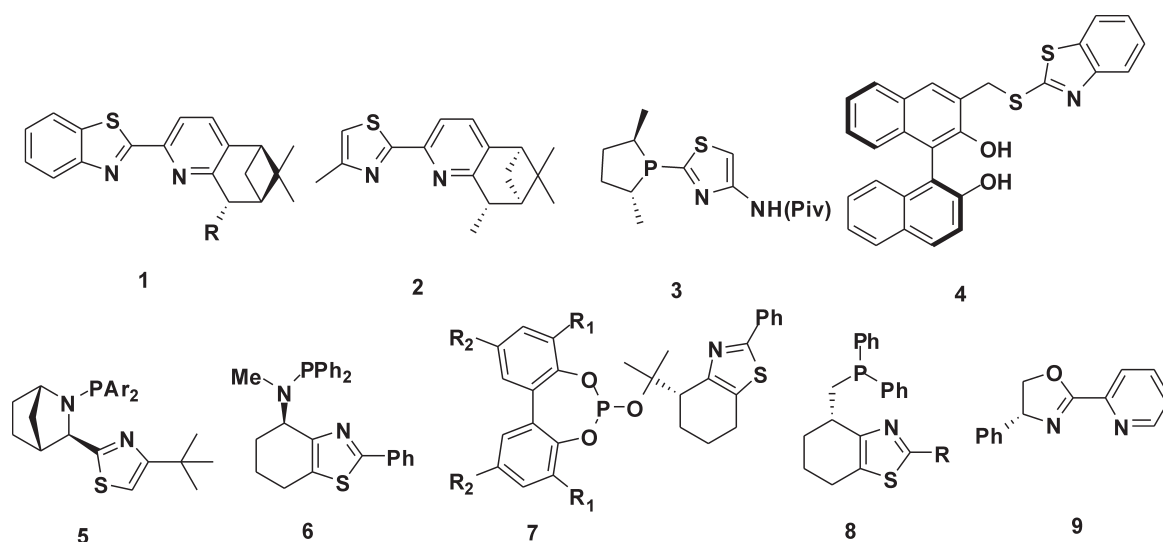


Figure 1 Thiazole catalysts evaluated for various asymmetric reactions.

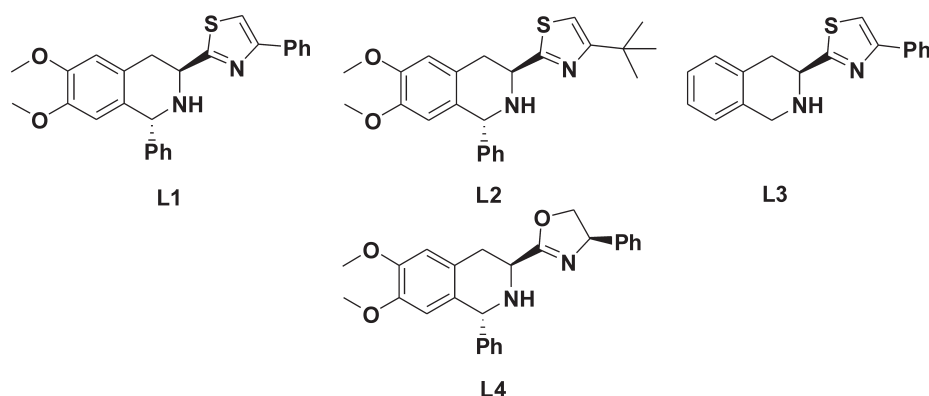


Figure 2 Catalysts evaluated for the Henry reaction.

thioamide **18** using Lawesson's reagent followed by cyclization with 2-bromoacetophenone to afford compound **19**. The protecting group was removed under acidic conditions to obtain the desired ligand **L3** (Scheme 2). It was observed that these chiral TIQ thiazole ligands were stable enough to be stored at ambient temperature with no special precautions against water or oxygen for several months.

Racemization of **19** is in principle possible under acidic conditions during deprotection. However, this appeared not to happen since the optical rotation values for **19** and **L3** are the essentially same.

Compound **11** was previously reported in our group^{28,30} and we noticed that some of the ¹³C NMR signals were split. This phenomenon can be attributed of conformational changes.³⁰ It is also possible that the rotamers due to rotation of the C=O and/or C=S groups can also lead to this observation.³¹ Interestingly, this effect is carried over to subsequent intermediates **12** and **13**, but is lost upon formation of the thiazole ring in **14** and **15**. The same is observed for the corresponding compounds in Scheme 2. We have performed a NMR study under elevated temperatures. The coalescence temperature for these conformations of compound **18** is about 45 °C.

2.2. Reaction Optimization

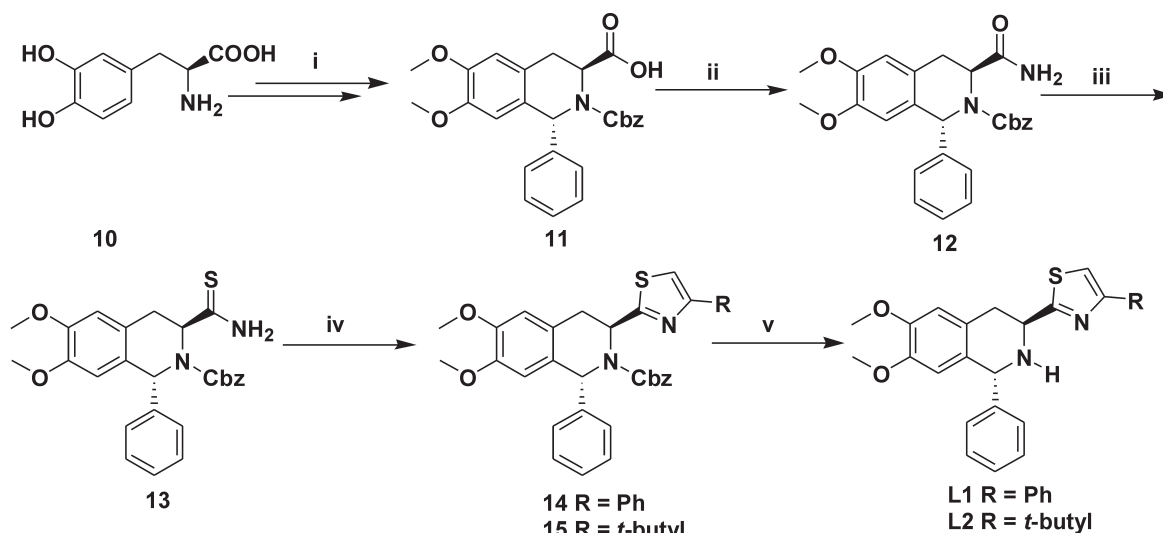
The metal-catalyzed Henry reaction between *p*-nitrobenzaldehyde and nitromethane was used as a benchmark reaction to evaluate the enantioselectivity of the thiazole ligands **L1–L3** (Table 1) and for comparison with oxazoline ligand **L4**.²⁸ All

reactions were completed within 24 hours with 1 mol % of the ligands **L1–L3** using Cu(OAc)₂·H₂O as the metal source in the presence of 2-propanol at room temperature.

The effect of solvent on this reaction was evaluated for these ligands as before.²⁸ All of the tested solvents (THF, ethanol, methanol, acetonitrile and dichloromethane) gave inferior results in comparison to 2-propanol. In order to improve the yield of the reaction for the thiazole ligands (**L1–L3**) various bases (diethylamine and DIPEA) were added to the solution in 1:1 ratio with the ligand. The yield of the Henry reaction was increased, but the enantioselectivity of the product decreased.

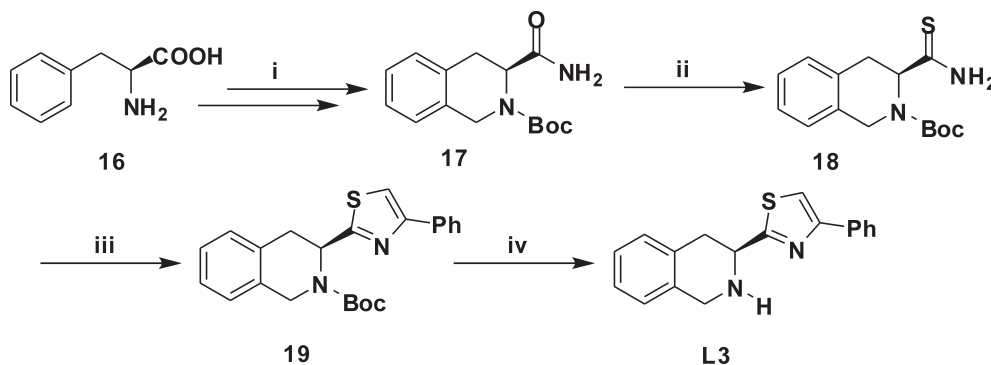
The reaction of *p*-nitrobenzaldehyde with nitromethane in the presence of the ligand **L1** gave 2-nitro-1-(4-nitrophenyl) ethanol in 87 % yield with a very low 2 % *ee* (Table 1, entry 1). The reactivity and selectivity obtained for ligand **L2** was comparable with **L1**. The TIQ-thiazole ligand **L3** was found to be the most reactive with 92 % yield and 22 % *ee*. By comparing literature data (chiral HPLC analysis)^{32,33} the absolute configuration of the product was determined to be *S*. Oxazoline ligand **L4** showed much better reactivity and enantioselectivity as compare to thiazole ligands **L1–L3**. With these preliminary results, we decided to use ligand **L3** for further investigations. A series of metals sources such as: Cu(OAc)₂·H₂O, Sc(OTf)₂, Zn(OAc)₂·H₂O, Et₂Zn and Cu(OTf)₂ with ligand **L3** in 2-propanol were screened (Table 2, entries 1–6). Cu(OAc)₂·H₂O still gave the best result.

It was decided not to reduce the temperature in order to see if better *ee* can be obtained, since it is likely that the yields will decrease too much. Previously, researchers investigated the



Scheme 1

Reagents for the synthesis of ligands **L1** and **L2** (i) See literature²⁸; (ii) $\text{NH}_4\text{CO}_3\text{H}$, $(\text{Boc})_2\text{O}$, pyridine, CH_3CN , rt, 18 h, 75 %; (iii) Lawesson's reagent, THF, rt, 16 h, 75 %; (iv) α -bromoketone, CaCO_3 , MeOH, reflux, 4 h, 78 % and 85 %, respectively; (v) dipropylsulfide, $\text{BF}_3(\text{OEt})_2$, DCM, rt, 4 h, 65 % and 45 %, respectively.



Scheme 2

Reagents for the synthesis of ligands **L3** (i) See literature²⁹; (ii) Lawesson's reagent, THF, rt, 16 h, 78 %; (iii) α -bromoketone, CaCO_3 , MeOH, reflux, 4 h, 89 %; (iv) 12 M HCl, THF, rt, 2 h, neutralization with base, 95 %.

effect of nitroethane in the Henry reaction.^{32,34–37} We decided to screen this nucleophile for the reaction with our optimized conditions (Table 3). From literature results we hoped to improve the reactivity and selectivity by introducing another prochiral centre.^{32,34–37}

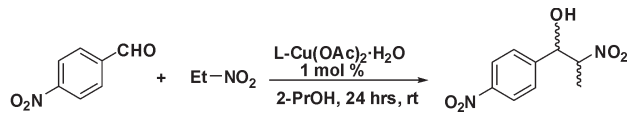
There was an insubstantial difference in reactivity and selectivity for the reaction with nitroethane. The observed trend was similar as previously for thiazoles **L1**, **L2**, **L3** and oxazoline **L4**. The TIQ-thiazole ligands **L1** and **L2** were nonselective (Table 3, entries 1–2). **L3** was found to be more reactive and selective than **L1** and **L2**, affording the product in moderate yield (75 %) with *ee* value 13:17 (*syn:anti*) and diastereoselectivity 60:40 (*syn:anti*) (Table 3, entry 3). The highest reactivity and selectivity was obtained using TIQ-oxazoline ligand **L4** (Table 3, entry 4). Ligand **L4** was slightly selective for the *anti* isomer giving an *ee* of 49:52 (*syn:anti*), and a diastereoselectivity of 45:55 (*syn:anti*). Having examined a change in nucleophile we decided to further study the catalytic system by employing a range of substituted aldehydes as the substrate under the optimized conditions. These results are summarized in Table 4.

In terms of reactivity and selectivity TIQ oxazoline **L4** was more reactive than TIQ thiazole **L3** (Table 4, entry 2/3, 5/6, 7/8). In the case of **L4**, piperonal undergoes 84 % conversion with 60:13 *ee* and 63:37 *dr*. For 2,5-dimethoxybenzaldehyde the *ee*

was 61:36, diastereomeric excess 75:25 and the *syn* isomer was the major product. In the case of *p*-anisaldehyde, the *ee* value decreased compared to 2,5-dimethoxybenzaldehyde and piperonal with ligand **L4**. The results obtained with substrates have substituents that are neutral in terms of electron donation/withdrawing characteristics (such as benzaldehyde and 2-naphthaldehyde) were poor with lower yields and enantioselectivity as compared to substrates having electron withdrawing groups. The substrates bearing electron-donating groups exhibited slightly greater reactivity and selectivity. It is noteworthy that not only the steric hindrance of the substitution at the aromatic ring, but also its electronic nature affected the reactivity and enantioselectivity (Table 4). In an attempt to increase the enantiomeric excess of the product, the temperature was decreased from room temperature to 0 °C. There was no observable conversion after 48 h, indicating that 0 °C is not providing sufficient activation energy required for the substrates to react.

3. Conclusion

A novel family of eight tetrahydroisoquinoline (TIQ)-thiazole intermediates and three ligands with corresponding Cu(II) catalysts has been developed. These ligands have been applied in the catalytic asymmetric Henry reaction. The TIQ thiazole

Table 1 The enantioselective Henry reaction of *p*-nitrobenzaldehyde with nitromethane in the presence of ligands L1–L4.^a


Entry	Ligands	Yield ^b /%	ee ^c /%
1	L1	87	2(-)
2	L2	70	rac
3	L3	92	22(-)
4	L4	99	62(-)

^a All reactions were carried out with 0.32 mmol of *p*-nitrobenzaldehyde, 3.2 mmol of nitroethane, 0.0032 mmol ligand, 0.0032 mmol Cu(OAc)₂·H₂O in 2 mL 2-propanol at room temperature.

^b Isolated product.

^c The enantiomeric excess was determined by HPLC using a Chiralcel AS-H column.

Table 2 Effect of Lewis acid type metal sources on the enantioselective Henry reaction of *p*-nitrobenzaldehyde with nitromethane using ligand L3.^a

Entry	Lewis acid	Yield ^b	ee ^c
1	–	47	rac
2	Cu(OTf) ₂	15	rac
3	Cu(OAc) ₂ ·H ₂ O	92	22 (S)
4	Sc(OTf) ₃	22	rac
5	Zn(OAc) ₂ ·H ₂ O	10	2 (S)
6	Et ₂ Zn	15	rac

^a All reactions were carried out with 0.32 mmol of *p*-nitrobenzaldehyde, 3.2 mmol of nitromethane, 0.0032 mmol ligand, 0.0032 mmol Cu(OAc)₂·H₂O in 2 mL 2-propanol at room temperature.

^b Isolated product.

^c The enantiomeric excess was determined by HPLC using a Chiralcel IB column.

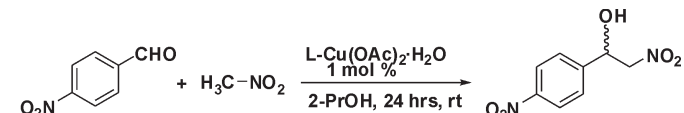
based chiral *N,N*-chelating ligands L1–L3 were synthesized in moderate to good yield. To the best of our knowledge, this is the first report describing the use of the TIQ-backbone in combination with a thiazole ring with a sp² and sp³ nitrogen system for the asymmetric Henry reaction. Comparing results with the two types of C₁ symmetric ligands in the catalytic asymmetric Henry reaction, it is clear that the thiazole ligand metal complexes were rather ineffective catalysts for the asymmetric Henry reaction. The Cu(II)-oxazoline complexes furnished moderate enantioselectivity with nucleophiles (MeNO₂, EtNO₂). The best result was the same than that previously observed in our laboratory.²⁸ For the thiazole ligands poor enantioselectivities were observed.

There are two possible reasons for that. First, the oxazoline has an additional chiral center that could contribute to the increased enantioselectivity. Second, it is possible that the bite angle of the oxazoline ligand is slightly different than that of the thiazoles since sulphur is considerably larger than oxygen (in the 5-membered heterocyclic ring). This study appears to be the first where a direct comparison of *N,N*-type thiazole and oxazoline ligands have been made. Further studies are currently in progress in our laboratory in order to expand the application of these chiral ligands to other asymmetric reactions.

4. Experimental Procedures

4.1 General

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 relative to TMS, and coupling constants are reported in Hz. NMR Spectra were obtained at room temperature. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254 plates. Crude compounds were purified with column chromatography using silica gel (60–200 mesh). 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 instrument model 341 polarimeter. The values reported are the average of three readings. All melting points are uncorrected. All testing reactions were carried out under dry argon gas. The results of all testing

Table 3 The enantioselective Henry reaction of *p*-nitrobenzaldehyde with nitroethane in the presence of different ligands.^a


Entry	Ligands	Yield ^b /%	ee ^c /% (<i>syn:anti</i>)	dr ^d (<i>syn:anti</i>)
1	L1	68	17:1	55:45
2	L2	50	5:rac	57:43
3	L3	75	13:17	60:40
4	L4	79	49:52	45:55

^a All reactions were carried out with 0.32 mmol of *p*-nitrobenzaldehyde, 3.2 mmol of nitromethane, 0.0032 mmol ligand, 0.0032 mmol Cu(OAc)₂·H₂O in 2 mL 2-propanol at room temperature.

^b Isolated product.

^c The enantiomeric excess was determined by HPLC using a Chiralcel IB column.

^d The diastereomeric ratios were determined by ¹H NMR recorded at ambient temperature.

Table 4 Enantioselective Henry reaction of nitroethane with different aldehydes.^a

Entry	Ligand	Aldehyde	Yield ^b /%	ee ^c /% (<i>syn:anti</i>)	<i>dr</i> ^d (<i>syn:anti</i>)
1	L4	<i>p</i> -chlorobenzaldehyde	25	42:31	43:57
2	L4	benzaldehyde	45	45:38	63:37
3	L3	benzaldehyde	10	16:14	68:32
4	L4	2-naphthaldehyde	70	36:17	60:40
5	L4	piperonal	84	60:13	63:37
6	L3	piperonal	30	9:31	67:33
7	L4	2,5-dimethoxybenzaldehyde	65	61:36	75:25
8	L3	2,5-dimethoxybenzaldehyde	27	21:40	60:40
9	L4	anisaldehyde	33	55:30	72:28

^a All reactions were carried out with 0.32 mmol of aldehyde, 3.2 mmol of nitroethane, 0.0032 mmol ligand, 0.0032 mmol Cu(OAc)₂·H₂O in 2 mL 2-propanol at room temperature.

^b Isolated product.

^c The enantiomeric excess was determined by HPLC using a Chiralcel IA, AS-H column.

^d The diastereomeric ratios were determined by ¹H NMR recorded at ambient temperature.

reactions were analyzed using chiral HPLC analysis on a Shimadzu DGU-30A₃ instrument. The specific details and conditions are provided in the corresponding experimental section. High-resolution mass data was obtained using a Bruker microTOF-Q II ESI instrument operating at ambient temperatures, with a sample concentration of approximately 1 ppm.

4.2. Literature Preparations

The multistep conversion of **10** to **11** and **16** to **17** was performed as previously described.^{28,29,38}

4.3. General Procedure for the Enantioselective Henry Reaction

4.3.1. Henry Reaction of Aldehydes with Nitromethane

The method was modified from the literature procedure.³⁸ A solution of L3 (0.82 mg, 0.0032 mmol, 0.01 eq.) and Cu(OAc)₂·H₂O (0.6 mg, 0.0032 mmol, 0.01 eq.) in anhydrous 2-propanol (2 mL) was stirred room temperature under argon. It took up to 4 hours for the solution to become completely homogeneous. To the resulting green solution, nitromethane (0.18 mL, 3.2 mmol, 10 eq.) and *p*-nitrobenzaldehyde (50 mg, 0.32 mmol, 1 eq.) were added at room temperature. The reaction mixture was stirred for 24 h and the progress of the reaction was monitored by TLC (EtOAc/hexane, 15/85, R_f = 0.4). After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 10/90 and increased to 15/20) to afford the nitroaldol product up to 22% ee. Enantiomeric excess was determined by HPLC with a Chiralcel IB column (hexane/2-propanol 85:15, λ = 220 nm); flow rate 0.8 mL min⁻¹; R_f = 17.7 min (R), 20.7 min (S).

4.3.2. Henry Reaction of Aldehydes with Nitroethane

The method was modified from the literature procedure.³⁸ A solution of L4 (1.3 mg, 0.0032 mmol, 0.01 eq.) and Cu(OAc)₂·H₂O (0.6 mg, 0.0032 mmol, 0.01 eq.) in anhydrous 2-propanol (2 mL) was stirred for 4 h at room temperature under argon. To the resulting green solution, nitroethane (0.24 mL, 3.2 mmol, 10 eq.) and *p*-nitrobenzaldehyde (50 mg, 0.32 mmol, 1 eq.) were added at room temperature. The reaction mixture was stirred for 24 h and the progress of the reaction was monitored by TLC (EtOAc/hexane, 15/85, R_f = 0.4). After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 10/90 and increased to 15/20) to afford the

nitroaldol product as a mixture of *syn:anti* (45:55) *dr*, 49% and 52% ee, respectively. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (n-hexane/2-propanol 95/5, 0.8 mL min⁻¹, λ = 210 nm): R_f = 75.0 min (1R, 2S), 79.4 min (1S, 2R), 96.7 min (1R, 2R) and 106.8 min (1S, 2S) and diastereomeric excess was determined by NMR.

4.4. Benzyl (1R,3S)-3-carbamoyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**12**)

To a solution of Cbz-acid **11** (0.500 g, 1.120 mmol, 1 eq.) in acetonitrile (10 mL) in 25 mL two neck oven-dried round-bottomed flask, di-*tert*-butyl dicarbonate (0.378 g, 1.456 mmol, 1.3 eq.) and ammonium bicarbonate (0.125 g, 1.344 mmol, 1.2 eq.) was added under an argon atmosphere, a turbid white mixture formed, then pyridine (64.3 μL, 0.672 mmol, 0.6 eq.) was added and the resultant reaction mixture was stirred for 6 h at room temperature. The reaction was monitored by TLC using MeOH/DCM (5/95, R_f = 0.6), after completion of the reaction, the solvent was evaporated under reduced pressure, ethylacetate (30 mL) was added and washed with 20 mL of water followed by sodium bicarbonate (10 mL). The organic layer was separated and dried over anhydrous MgSO₄ and the solvent evaporated under reduced pressure to afford the Cbz amide **12** (0.37 g, 75% yield) as a pure white solid. m.p: 128–130 °C (MeOH/DCM); [α]_D²⁰ = +44.01 (c 0.1 in CHCl₃); (NMR spectra are reported for a mixture of two conformations). ¹H NMR (400 MHz, DMSO-d₆): δ 7.35–7.10 (m, 10H), 6.88 (d, J = 8.57 Hz, 1H), 6.68 (d, J = 9.16 Hz, 1H), 6.12 (d, J = 7.09 Hz, 1H), 5.07–4.88 (m, 3H), 3.75–3.67 (m, 6H), 3.16–3.03 (m, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 172.8, 172.7, 155.4, 155.3, 147.6, 147.0, 145.0, 143.9, 136.8, 136.5, 129.6, 129.5, 128.3, 128.1, 127.9, 127.6, 127.5, 127.3, 127.1, 126.8, 126.7, 125.9, 123.6, 123.4, 111.5, 111.4, 111.2, 66.3, 66.1, 59.0, 55.8, 55.6, 55.4, 33.3, 33.1, 28.1; IR ν_{max}/cm⁻¹ (neat): 2934, 1663, 1513, 1401, 1342, 1223, 1095, 737, 698; HR ESI MS: *m/z* = 469.1718 [M+ Na]⁺ (calcd. for C₂₆H₂₆N₂O₅Na 469.1734).

4.5. General Procedure for the Preparation of Thioamide (**13** and **18**)

To a solution of *N*-protected TIQ amide (0.4 g, 0.896 mmol, 1 eq.) in THF (4 mL) Lawesson's reagent (0.2 g, 0.448 mmol, 0.5 eq.) was added, the resultant solution was stirred overnight at room temperature. The reaction was monitored by TLC using MeOH/DCM (5/95, R_f = 0.4). The THF was evaporated under reduced pressure and diluted with ethylacetate (30 mL) and washed with 20 mL of water. The organic layer was separated

and dried over anhydrous MgSO_4 and the solvent evaporated under reduced pressure to afford crude Cbz-thioamide, which was purified by column chromatography using 0–1.5 % MeOH in DCM as the eluent to yield approximately 75 %, 78 % yield of pure thioamide compounds **13** and **18**, respectively.

4.5.1. Benzyl (1R,3S)-3-carbamothioyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**13**)

The compound **13** was prepared from **12**, according to general procedure, in 75 % yield as a yellow solid; m.p: 204–206 °C (MeOH/DCM, 5/95, $R_f = 0.4$); $[\alpha]_D^{20} = -4.03$ (c 0.1 in CHCl_3); (NMR spectra are reported for a mixture of two conformations) ^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ 7.33–7.11 (m, 10H), 6.90–6.88 (d, $J = 7.08$ Hz, 1H), 6.64–6.62 (d, $J = 13.34$ Hz, 1H), 6.22–6.20 (d, $J = 10.31$ Hz, 1H), 5.27–5.20 (dd, 1H), 5.07–4.90 (m, 2H), 3.77–3.75 (m, 2H), 3.67–3.66 (bs, 3H), 3.23–3.16 (m, 2H), 2.08 (s, 2H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 206.9, 206.3, 155.3, 154.8, 147.7, 147.6, 147.5, 147.4, 144.2, 143.2, 136.6, 136.4, 129.5, 129.4, 128.3, 127.8, 127.7, 127.5, 127.4, 127.3, 126.4, 126.2, 125.4, 123.4, 111.7, 111.6, 111.5, 111.4, 66.5, 66.4, 62.7, 62.4, 59.6, 59.3, 55.8, 55.6, 33.58, 33.4; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 2925, 1674, 1513, 1444, 1235, 1096, 997, 727, 693; HR ESI MS: $m/z = 463.1650$ $[\text{M} + \text{H}]^+$ (calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$ 463.1686).

4.5.2. tert-butyl (3S)-3-carbamothioyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**18**)

The compound **18** was prepared from **17**, according to general procedure, in 78 % yield as a white solid; m.p: 162–164 °C (MeOH/DCM, 5/95, $R_f = 0.4$); $[\alpha]_D^{20} = -38.01$ (c 0.1 in CHCl_3); (NMR spectra are reported for a mixture of two conformations. The carbon spectra at 45 °C is included with the Supplementary Material) ^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ 9.52 (s, 1H), 9.45 (s, 0.6H), 9.04 (s, 1H), 8.92 (s, 0.6H), 7.19 (bs, 6.8H), 4.78–4.58 (m, 3.4H), 4.48 (d, $J = 14.62$ Hz, 0.6H), 4.40 (d, $J = 15.06$ Hz, 1H), 3.16–3.15 (m, 2H), 3.10–3.07 (m, 1.1H), 1.44 (s, 5.8H), 1.36 (s, 9.7H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$); at rt: δ 207.8, 206.6, 154.4, 154.0, 135.4, 134.0, 133.3, 127.7, 127.2, 127.0, 126.7, 126.4, 125.8, 79.4, 61.8, 60.4, 45.0, 44.1, 34.4, 34.1, 27.9; at 45 °C: 207.8, 153.9, 135.2, 133.8, 127.4, 127.0, 126.7, 126.0, 79.2, 61.7, 44.0, 34.2, 27.9; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 3157, 2977, 1665, 1633, 1391, 1365, 1158, 1126, 871, 750, 698; HR ESI MS: $m/z = 315.1124$ $[\text{M} + \text{Na}]^+$ (calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2\text{SNa}$ 315.1138).

4.6. General Procedure for the Preparation of Thiazole (**14**, **15** and **19**)

The N-protected thioamide (2.3 g, 5 mmol, 1 eq.), α -bromoketone (1 g, 5 mmol, 1 eq.), and CaCO_3 (2.5 g, 25 mmol, 5 eq.) were mixed in dry MeOH (25 mL). The reaction mixture was refluxed for 3–4 h. The reaction was monitored by TLC using EtOAc/Hexane (40/60, $R_f = 0.4$), after completion of reaction the mixture was filtered through celite to remove CaCO_3 . The crude filtrate was evaporated and purified by column chromatography in EtOAc/Hexane (40:60) to afford pure Cbz thiazole compounds.

4.6.1. Benzyl (1R,3S)-6,7-dimethoxy-1-phenyl-3-(4-phenyl-1,3-thiazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**14**)

The compound **14** was prepared from **13**, according to general procedure, in 78 % yield as a yellow solid; m.p: 162–164 °C (EtOAc/Hexane, 40/60, $R_f = 0.4$); $[\alpha]_D^{20} = -82.04$ (c 0.1 in CHCl_3); ^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ 7.99 (d, $J = 6.63$ Hz, 2H), 7.88 (s, 1H), 7.57–7.12 (m, 13H), 7.03 (d, $J = 6.90$ Hz, 1H), 6.75 (d, $J = 14.10$ Hz, 1H), 6.37 (s, 1H), 6.15 (d, $J = 16.39$ Hz, 1H), 5.17–5.12 (m, 2H), 3.86 (m, 3H), 3.67 (m, 3H), 3.59–3.47 (m, 1H), 3.25 (dd, $J =$

15.63 Hz, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 174.4, 155.2, 148.2, 147.6, 144.7, 134.7, 128.9, 128.8, 128.5, 128.1, 127.5, 126.4, 126.3, 112.6, 111.4, 111.0, 59.5, 56.0, 51.2, 35.4; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 2925, 1711, 1606, 1514, 1324, 1225, 1094, 732, 698; HR ESI MS: $m/z = 563.1992$ $[\text{M} + \text{H}]^+$ (calcd. for $\text{C}_{34}\text{H}_{31}\text{N}_2\text{O}_4\text{S}$ 562.1999).

4.6.2. Benzyl (1R,3S)-3-(4-tert-butyl-1,3-thiazol-2-yl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**15**)

The compound **15** was prepared from **13**, according to general procedure, in 85 % yield as a yellow solid; m.p: 86–88 °C (EtOAc/Hexane, 40/60, $R_f = 0.4$); $[\alpha]_D^{20} = -20.02$ (c 0.1 in CHCl_3); (NMR spectra are reported for a mixture of two conformations) ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.42–7.39 (m, 2H), 7.28–7.19 (m, 8H), 7.03 (s, 1H), 6.90 (2H, bs), 6.58–5.54 (d, $J = 14.72$ Hz, 1H) 6.19 (s, 1H), 5.95–5.93 (m, 1H), 5.07–4.99 (m, 2H), 3.78–3.71 (m, 3H), 3.58–3.57 (m, 3H), 3.25–3.02 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 172.9, 172.6, 165.0, 164.6, 155.2, 154.9, 148.2, 147.8, 147.6, 147.5, 144.4, 143.3, 136.4, 129.5, 129.1, 128.4, 128.3, 126.0, 125.4, 123.6, 123.5, 112.1, 112.0, 111.7, 111.2, 111.0, 110.5, 110.3, 66.5, 59.2, 58.8, 55.4, 54.9, 54.7, 34.3, 34.0, 33.8, 29.8; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 3406, 2956, 1698, 1573, 1395, 1224, 1092, 697; HR ESI MS: $m/z = 543.2342$ $[\text{M} + \text{H}]^+$ (calcd. for $\text{C}_{32}\text{H}_{35}\text{N}_2\text{O}_4\text{S}$ 542.2312).

4.6.3. tert-butyl (3S)-3-(4-phenyl-1,3-thiazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**19**)

The compound **19** was prepared from **18**, according to general procedure, in 89 % yield as a yellow solid; m.p: 82–84 °C (EtOAc/Hexane, 40/60, $R_f = 0.4$); $[\alpha]_D^{20} = -71.75$ (c 0.1 in CHCl_3); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.87–7.84 (m, 3H), 7.42–7.38 (m, 2H), 7.32–7.30 (m, 1H), 7.17–7.15 (m, 4H), 5.76–5.63 (m, 1H), 4.80–4.46 (m, 2H), 3.39 (s, 2H), 1.50–1.34 (s, 9H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): 172.7, 172.1, 154.5, 154.0, 153.8, 153.7, 134.0, 132.6, 132.3, 128.6, 127.9, 126.8, 126.4, 126.1, 125.8, 113.9, 80.0, 79.8, 53.3, 51.9, 44.0, 43.5, 33.8, 33.3, 28.0, 27.8; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 2925, 1693, 1402, 1305, 1292, 1156, 745, 688; HR ESI MS: $m/z = 393.1640$ $[\text{M} + \text{H}]^+$ (calcd. for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_2\text{S}$ 393.1631).

4.7. General Procedure for Cbz Deprotection (**L1** and **L2**)

A solution of Cbz protected thiazole compound (0.100 g, 0.177 mmol, 1 eq.) in dry DCM (4 mL) under argon atmosphere was treated with dipropylsulfide (0.788 mL, 5.338 mmol, 30 eq.), boron trifluoride diethyl etherate (0.230 mL, 10 eq.) and stirred at room temperature for 1.5 h, then dipropylsulfide (0.499 mL, 2.336 mmol, 20 eq.) was added, the reaction was allowed to proceed for another 2 h. The reaction was monitored by TLC using EtOAc/Hexane (20/80, $R_f = 0.5$). The mixture was then poured into water (5 mL) and 10 % aqueous NH_4OH (10 mL) was added and extracted with ethylacetate (30 mL) followed by washing with water (2×10 mL). The organic layer was separated and dried over anhydrous MgSO_4 and the solvent evaporated under reduced pressure to afford crude thiazole, which was purified by column chromatography using silica gel (deactivated with 5 % Et_3N) using 100:5 hexane/ Et_3N – 10:90:5 % EtOAc/hexane/ Et_3N as the eluent to 65 %, 45 % yield, respectively, of pure thiazole compounds **L1** and **L2**.

4.7.1. 2-((1R,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-phenyl thiazol (**L1**)

The compound **L1** was prepared from **14**, according to general procedure, in 65 % yield as a yellow solid; m.p: 115–117 °C (EtOAc/Hexane, 20/80, $R_f = 0.5$); $[\alpha]_D^{20} = -48.04$ (c 0.1 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.86 (d, $J = 7.56$ Hz, 2H), 7.41–7.24 (m, 9H), 6.72 (s, 1H), 6.41 (s, 1H), 5.30 (s, 1H), 4.56–4.53 (q, 1H), 3.90

(s, 3H), 3.71(s, 3H), 3.43–3.38 (dd, $J = 4.6$ Hz, 1H), 3.14–3.08 (dd, $J = 9.27$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 174.3, 155.1, 154.8, 148.0, 147.4, 144.6, 134.5, 129.1, 128.7, 128.7, 128.4, 128.0, 127.3, 127.9, 126.3, 126.2, 123.2, 113.8, 113.6, 112.5, 111.2, 110.9, 59.4, 55.9, 51.0, 35.2; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 3281, 2926, 1704, 1608, 1513, 1236, 1251, 1106, 1025, 737, 694; HR ESI MS: $m/z = 429.1682$ [$\text{M} + \text{H}$] $^+$ (calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_2\text{S}$ 429.1631).

4.7.2. 4-tert-butyl-2-((1R,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl) thiazole (L2)

The compound L2 was prepared from 15, according to general procedure, in 45 % yield as a yellow solid; m.p: 120–121 °C (EtOAc/Hexane, 20/80, $R_f = 0.5$); $[\alpha]_{\text{D}}^{20} = -44.04$ (c 0.1 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.31–7.26 (m, 3H), 7.25–7.22 (m, 2H), 6.77 (s, 1H), 6.69 (s, 1H), 6.39 (s, 1H), 5.26 (s, 1H), 4.48–4.45 (q, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.35–3.30 (dd, $J = 4.68$ Hz, 1H), 3.05–2.99 (dd, $J = 9.36$ Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): 173.3, 166.4, 148.1, 144.9, 128.8, 128.5, 128.0, 127.4, 126.5, 111.3, 111.0, 109.8, 59.5, 56.0, 51.0, 35.6, 34.8, 30.5; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 3277, 2968, 2928, 1726, 1607, 1510, 1460, 1355, 1252, 1221, 1103, 1076, 856, 813, 702; HR ESI MS: $m/z = 409.2021$ [$\text{M} + \text{H}$] $^+$ (calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$ 409.1944).

4.8. (S)-4-phenyl-2-(1,2,3,4-tetrahydroisoquinolin-3-yl) thiazole (L3)

The N-protected thiazole 19 (3 mmol) was dissolved in THF (15 mL), to this 12 M HCl (15 mL) was added slowly and the reaction mixture was stirred at room temperature for 2 h. THF was evaporated under vacuum. The reaction was monitored by TLC using EtOAc/Hexane (20:80, R_f 0.5). The reaction mixture was slowly poured into aqueous saturated NaHCO_3 solution, the mixture was then extracted with CH_2Cl_2 (3 \times 30 mL). The combined organic layer was dried over MgSO_4 . And the solvent evaporated under reduced pressure, the residue was purified by column chromatography on silica gel (deactivated with 5 % Et_3N) with $\text{Et}_3\text{N}/\text{EtOAc}/\text{Hexane}$ (5/8/100) as the eluent to afford thiazole L3 as a yellow solid (0.27 g, yield 95 %). m.p: 84–86 °C (EtOAc/Hexane); $[\alpha]_{\text{D}}^{20} = -71.55$ (c 0.1 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.93–7.91 (d, $J = 7.39$ Hz, 2H), 7.44–7.33 (m, 4H), 7.25–7.19 (m, 3H), 7.08 (s, 1H), 4.50–4.47 (m, 1H), 4.31–4.17 (q, 2H), 3.46–3.42 (m, 1H), 3.18–3.12 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): 173.8, 155.5, 135.1, 134.7, 133.6, 129.3, 128.8, 128.2, 126.6, 126.5, 126.3, 126.1, 112.8, 56.0, 48.2, 35.4; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 3288, 3064, 2926, 1601, 1503, 1427, 1071, 1026, 738, 687; HR ESI MS: $m/z = 293.1113$ [$\text{M} + \text{H}$] $^+$ (calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{S}$ 293.1107).

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