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Asymmetric conjugate addition of thioglycolate to a range of chalcones using tetrahydroisoquinoline (TIQ) *N,N′*-dioxide ligands

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ABSTRACT

A series of novel TIQ based *N,N′*-oxide ligands were synthesised and screened for their catalytic activity in the enantioselective conjugate addition of thioglycolate to chalcones. Bulky groups on the side chain of the TIQ backbone provided the highest enantioselectivity of up to 88% with 10 mol % catalyst loading. It was also observed that these reactions proceeded optimally in the presence of dichloromethane as a solvent. Screening of various metals emphasized $La(OTf)_3$ as the ideal pre-catalyst for this particular reaction.

1. Introduction

The need to synthesise enantiomerically pure compounds is a driving force for the huge interest in the field of asymmetric catalysis.[1–3] Reactions involving C–C bond formation provide methods by which larger molecules can be synthesised.[4–7] In this approach, important reactions, such as Suzuki couplings,[8,9] Heck reactions[10,11] and Michael additions[12,13] play a significant role in organic chemistry as well as in asymmetric catalysis.

The Michael addition is ubiquitous in organic chemistry and has been utilized to produce a diverse array of compounds for applications in various fields.[12–15] Furthermore, the use of this reaction in applications other than C–C bond formation opens up avenues by which molecules that possess unique properties can be prepared. One such deviation is the addition of sulphur as a nucleophile to α,β-unsaturated ketones. This type of conjugate addition has been widely reported on[16–19] and applications in total synthesis have already been proven.[20,21]

The use of *N*-oxide containing ligands in asymmetric catalysis is well documented with numerous examples of catalytic systems possessing this chemical moiety.[22] Some examples of these molecules are shown in Figure 1. Applications of *N*-oxide ligands include enantioselective reactions of allyltrichlorosilane with aldehydes (ligand **1**),[23] allylation of aldehydes (ligand **2**),[24,25] asymmetric aldol reactions (ligand **3**),[26–29] asymmetric opening of *meso*-epoxides,[30] cyanosilylation of ketones[31,32] and Michael additions.[33]

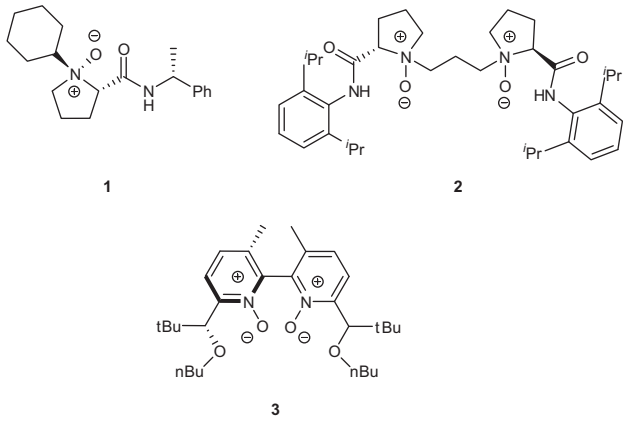

Figure 1. Examples of *N*-oxide ligands utilized in asymmetric catalysis.

The use of the TIQ scaffold in asymmetric catalysis is an ongoing interest in our research group. Its applications include catalytic asymmetric transfer hydrogenations (ATH),[34,35] high pressure hydrogenations of unsymmetrical olefins,[36] Henry type C–C bond formations[37,38] and an organocatalyst in Diels–Alder reactions.[39] Based on the seminal work of Feng et al., [40] we decided to examine the TIQ based catalyst system to see if it could also be utilized in similar reactions to Feng's ligands. We recently reported the use of TIQ based *N*-oxides as organocatalysts.[41] Herein, we report for the first time the synthesis and application of TIQ *N,N′*-dioxide derivatives for asymmetric catalysis. In this preliminary report

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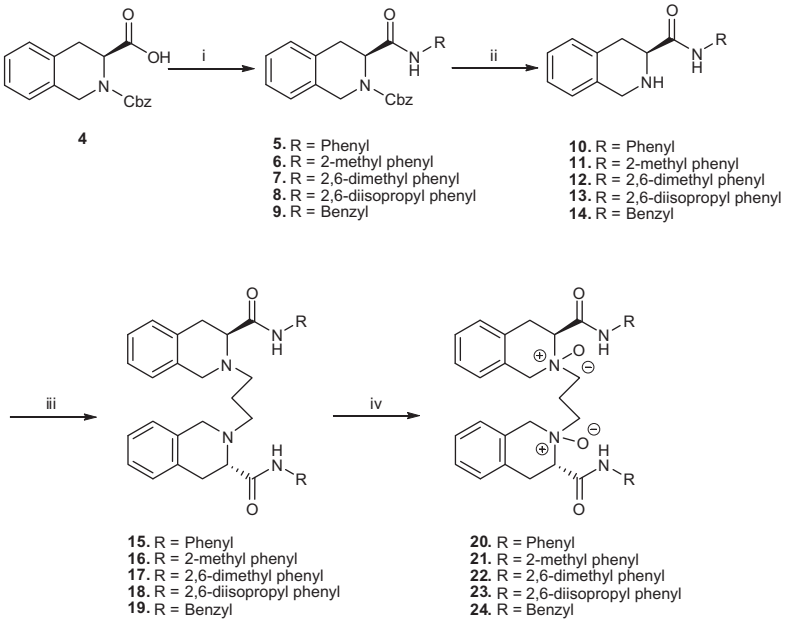


Scheme 1. Reagents for the synthesis of TIQ *N*-oxide ligands **20**–**24**: (i) ethyl chloroformate, triethylamine, anilines, DCM, 0 °C–rt, 18 h; (ii) 10% wt Pd/C, H_2 (1 atm), MeOH/THF, rt, 3 h; (iii) 1,3-dibromopropane, anhydrous K_2CO_3, ACN, 80 °C, 12 h; (iv) *m*-CPBA (70%), DCM, −20 °C to room temperature 1 h.

we chose the benchmark reaction of the conjugate addition of thioglycolate to chalcone to demonstrate the promising use of this class of ligand.

2. Results and discussion

The ligands were synthesised as described in Scheme 1. The Cbz protected TIQ acid **4**[42] underwent amide coupling, facilitated by active ester formation with ethyl chloroformate, with various substituted amines to afford intermediates **5–9**.[43] The cleavage of the Cbz group was accomplished with 10% wt palladium on carbon under a hydrogen atmosphere (1 atm) to afford the free amines **10**–**14**. Bridging of these free secondary amines was accomplished with K_2CO_3 and 1,3-dibromopropane in acetonitrile to yield compounds **15**–**19**, respectively. Finally, intermediates **15**–**19** were oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at −20 °C to ambient temperature to afford the final ligands **20**–**24** in good yields (65–75%).

Ligands **20**–**24** were evaluated for the conjugate addition of thioglycolate to chalcone (Table 1). The catalytic reaction conditions chosen were adapted from the literature.[33,43,44] Ligand **20**, derived from aniline, provided poor selectivity across all ranges of catalytic loadings (Table 1, entries 3–5). The employment of substituted anilines resulted in a marked increase in selectivity of the ligands. The 2-methyl aniline derivative **21** resulted in a selectivity of 50% (Table 1, entry 8) whilst that of 2,6-dimethyl aniline **22** afforded a selectivity of 71% (Table 1, entry 11). An increase in the steric bulk at the *ortho*-positions of the anilines resulted in the highest enantioselectivity of 83% (Table 1, entry 14). Reactions at lower temperatures did not affect the enantioselectivity (Table 1, entry 15). The use of a benzyl amide group resulted in a complete loss of selectivity (Table 1, entries 16–18). In order to determine if the conjugate addition could be organocatalysed, we performed the reaction with the addition of only the ligand (Table 1, entry 19). Taken together with the results obtained without the ligand or metal (Table 1, entry 1) and without the ligand but in the presence of metal (Table 1, entry 2), these results show that there are considerable background reactions taking place, which may be detrimental to the enantioselectivity.

Ligand **23**, which showed the best activity at a loading of 10 mol % was then used to screen a range of solvents under these reaction conditions (Table 2). Dicholoromethane provided the best selectivity whilst other chlorinated solvents such as chloroform and dichloroethane provided moderate to low selectivities (Table 2, entries 1, 3 and 5). Non-chlorinated solvents such as tetrahydrofuran and acetonitrile, gave poor selectivity and a racemic mixture, respectively (Table 2, entries 6, 7).

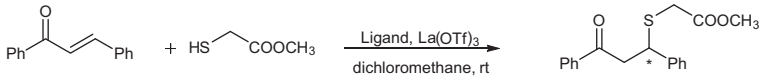
Having identified the most appropriate solvent, various other lanthanide group metals were screened to identify the best metal for our system (Table 3). The metal chosen initially was seen to be the best choice; although all the other metals showed good yields and drastically lower selectivities were obtained (Table 3, entries 2–5). This observation is in agreement with that made by Feng et al.[43]

The scope of the substrates was then extended using the results obtained from the optimized conditions (Table 4). Chalcones with both electron-donating and withdrawing groups had little influence on the yield or enantioselectivity (87–95% yield, 70–88% ee; Table 4, entries 1–4). Substrates with sterically bulky substituents were also tolerated in terms of activity and selectivity (89% yield, 78% ee; Table 4, entry 5).

3. Conclusion

A series of novel TIQ based *N*-oxide ligands have been synthesised and evaluated in the conjugate addition of thioglycolate to chalcones. Complexation of these novel ligands with various metals showed lanthanum to be the optimum choice for this particular reaction. These results show that bulkier substituents on the phenyl amide group afforded the highest enantioselectivity. The choice of solvent also played an important role in the selectivity of the reaction with chlorinated solvents, in particular dichloromethane, being the optimum solvent for the reaction. This conjugate addition is heavily dependent upon the catalytic loading, since high enantioselectivities were only achieved with loadings of 10 mol %. Further investigations into this new class of ligands are currently ongoing.

Table 1
Asymmetric conjugate addition of thioglycolate **26** to chalcone **25a** catalysed by ligands **20**–**24** with $La(OTf)_3$



25a **26** **27a**

Entry[a]	Ligand	Mol %	Yield[b] (%)	ee[c] (%)
1[d]	—	—	68	rac
2[e]	—	10	85	rac
3	**20**	1	75	rac
4	**20**	5	82	2
5	**20**	10	90	6
6	**21**	1	65	11
7	**21**	5	85	33
8	**21**	10	92	50
9	**22**	1	69	28
10	**22**	5	85	43
11	**22**	10	93	71
12	**23**	1	78	32
13	**23**	5	89	53
14	**23**	10	95	83
15[f]	**23**	10	64	80
16	**24**	1	69	rac
17	**24**	5	78	rac
18	**24**	10	93	rac
19[g]	**23**	10	75	rac

[a] All reactions were performed at 0 °C to room temperature for 12 h.
[b] Isolated by column chromatography.
[c] Determined by HPLC with a chiral column (Chiral Pak-IB).
[d] Neither a ligand nor a metal was used.
[e] With metal but without a ligand.
[f] Reaction performed at 0 °C for 18 h.
[g] With ligand but in the absence of metal.

Table 2
Asymmetric conjugative addition of thioglycolate **26** to chalcone **25a** using $La(OTf)_3$ with ligand **23** in different solvents

Entry[a]	Solvent	Yield[b] (%)	ee[c] (%)
1	$ClCH_2CH_2Cl$	92	76
2	$ClCH_2CH_2Cl$	64	56
3	CH_2Cl_2	95	83
4	$CHCl_3$	65	17
5	THF	45	9
6	CH_3CN	35	rac

[a] All reactions were performed at 0 °C to room temperature.
[b] All products were eluted from column chromatography.
[c] Determined by HPLC on a chiral column (IB-H).

Table 3
Asymmetric conjugative addition of thioglycolate **26** to chalcone **25a** catalysed by different metals with ligand **23**

Entry[a]	Metal	Mol %	Yield[b] (%)	ee[c] (%)
1	$La(OTf)_3$	10	95	83
2	$Yb(OTf)_3$	10	56	2
3	$Y(OTf)_3$	10	35	4
4	$In(OTf)_3$	10	43	1
5	$Sc(OTf)_3$	10	65	6

[a] All reactions were performed at 0 °C to room temperature.
[b] All products were eluted from column chromatography.
[c] Determined by HPLC with a chiral column (IB-H).

4. Experimental

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 at room temperature. Chemical shifts are expressed in ppm downfield from TMS as an internal standard, and coupling constants are reported in Hz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using Silica gel (60–200 mesh unless otherwise stated). 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 (Model 341). All melting points are uncorrected. High resolution mass spectrometric data were obtained using a Bruker micrOTOF-Q II instrument operating at ambient temperatures, and a sample concentration of approximately 1 ppm.

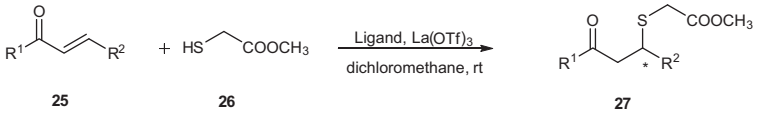
4.2. Typical procedure for the enantioselective conjugate addition of thioglycolate to chalcones

A solution of ligand **23** (7.44 mg, 0.001 mmol), $La(OTf)_3$ (5.86 mg, 0.001 mmol) and chalcone (20.8 mg, 0.1 mmol) in anhydrous dichloromethane (2 mL) was stirred under microwave irradiation at 35 °C for 30 min. The reaction mixture was cooled to 0 °C and the thioglycolate (15.92 mg, 0.15 mmol) was added. The reaction mixture was then stirred at 0 °C for 2 h, followed by 16 h at room temperature. Solvents were evaporated under reduced pressure and the residue was purified by column chromatography using hexane/ethyl acetate, (80:20) to afford the pure conjugate product. The enantioselectivity was determined by chiral HPLC using the IB column (hexane/2-propanol 90:10, λ = 254 nm); flow rate of 0.8 mL/min. IA column under similar conditions was used for the substrate R^1 = Ph, R^2 = 4-ClC_6H_4.

4.3. General procedure for the synthesis of amide coupling 5–9

This method was adapted from the literature.[43] To a stirred solution of TIQ Cbz acid **4** (2.0 g, 6.38 mmol) in dichloromethane

Table 4
Substrate scope for the asymmetric conjugate addition of thioglycolate to chalcones **25**



25 **26** **27**

Entry[a]	**25**	R^1, R^2	Yield[b] (%)	ee[c] (%)
1	**25b**	Ph, 4-MeC_6H_4	92	80
2	**25c**	4-MeC_6H_4, Ph	88	70
3	**25d**	Ph, 4-ClC_6H_4	87	88[d]
4	**25e**	Ph, 4-$MeOC_6H_4$	95	88
5	**25f**	Ph, 2-naphthyl	89	78

[a] All reactions were performed at 0 °C to room temperature.
[b] All products were eluted from column chromatography.
[c] Determined by HPLC on a chiral column (IB-H).
[d] Determined by HPLC on a chiral column (IA).

(20 mL), triethylamine (0.71 g, 7.07 mmol) and ethyl chloroformate (0.76 g, 7.07 mmol) were added at 0 °C. After 1 h, the substituted aniline (1.1 equiv) was added and stirred at ambient temperature for 18 h. Completion of the reaction was monitored by thin layer chromatography. The reaction mixture was washed with saturated sodium hydrogen carbonate (20 mL) followed by brine (10 mL). The organic layer was separated, dried over anhydrous magnesium sulphate and purified by column chromatography using hexane/ethyl acetate as the mobile phase and silica gel as the stationary phase.

4.4. General procedure for the deprotection of the Cbz group 10–14

A solution of Cbz-amide (1.0 g) in THF (20 mL) was added to a suspension of activated Pd/C (500 mg, 10 wt-%) in methanol under an inert atmosphere. The reaction mixture was connected to an H_2 source at 1 atm and stirred at room temperature for 3 h. Completion of the reaction was monitored by TLC using hexane/ethyl acetate (7:3). The Pd/C was filtered off on a pad of Celite and washed with ethyl acetate (10 mL) followed by dichloromethane (5 mL). The filtrate was concentrated under reduced pressure to afford the crude amide, which was purified by column chromatography using hexane/ethyl acetate as the mobile phase and silica gel as the stationary phase.

4.5. General procedure to form bridge compounds 15–19

This method was adapted from the literature.[43] To a solution of deprotected amine (0.20 g) in acetonitrile (10 mL), anhydrous K_2CO_3 (5.0 equiv) followed by 1,3-dibromopropane (1.1 equiv) was added and stirred under a microwave reactor at 100 °C for 12 h. Completion of the reaction was monitored by TLC using hexane/ethyl acetate. The solvent was evaporated and the crude product taken up in ethyl acetate (20 mL), and washed with water (2 × 10 mL) followed by brine (10 mL). The organic layer was separated, dried over anhydrous magnesium sulphate and concentrated under reduced pressure to afford the crude bridge compound, which was purified by column chromatography using hexane/ethyl acetate as the eluent to give the pure bridged amide compound.

4.6. General procedure to form *N*-oxide compounds 20–24

To a solution of bridge amide (0.2 g) in dichloromethane (10 mL) was added anhydrous K_2CO_3 (5.0 equiv) and the reaction mixture was cooled to −20 °C. Next, *m*-CPBA (2.2 equiv) was added in one portion and the temperature maintained for 3 h. The reaction mixture was allowed to warm to room temperature and stirred for 2 h whilst completion of the reaction was monitored by TLC. The reaction mixture was diluted with dichloromethane (5 mL), filtered through a pad of Celite and concentrated under reduced pressure to afford the crude *N,N′*-dioxide compound. The pure *N,N′*-dioxide compound was obtained after column chromatography using dichloromethane/methanol as the eluent.

4.7. (*S*)-Benzyl 3-(phenylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5

The synthesis of this compound has already been reported.[35]

4.8. (*S*)-Benzyl 3-(*o*-tolylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 6

R_f = 0.4 (Hexane/ethyl acetate, 7:3). Off white solid (1.7 g, yield 68%); mp: 108–110 °C (hexane/ethyl acetate); $[\alpha]_D^{20} = -19.2$ (*c* 0.78, $CHCl_3$); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–6.86 (m, 13H), 5.41–4.40 (m, 5H), 3.55–2.99 (m, 2H), 2.05–1.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 133.5, 130.3, 128.6, 128.4, 128.1, 127.7, 127.3, 126.8, 126.5, 126.3, 125.4, 123.4, 68.1, 57.1, 49.5, 45.2, 32.1, 16.8; IR ν_{max}/cm^{-1} (neat): 3259, 1701, 1661, 1533, 1412, 1202, 760, 698; HR ESI MS: m/z = 401.1864 $[M+H]^+$ (calcd for $C_{25}H_{25}N_2O_3$ 401.1860).

4.9. (*S*)-Benzyl 3-(2,6-dimethylphenylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 7

R_f = 0.5 (Hexane/ethyl acetate, 70:30). Off white solid (1.6 g, yield 48%); mp: 143–145 °C (hexane/ethyl acetate); $[\alpha]_D^{20} = -32.0$ (*c* 0.50, $CHCl_3$); (NMR spectra are reported for a mixture of two rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–6.82 (m, 12H), 5.43–4.91 (m, 3H), 4.91–4.41 (m, 2H), 3.49 (m, 1H), 3.16 (m, 1H), 1.93–1.53 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 135.4, 133.8, 133.0, 128.8, 128.6, 128.1, 127.4, 126.6, 126.4, 68.3, 56.7, 45.9, 32.5, 17.8; IR ν_{max}/cm^{-1} (neat): 3275, 1697, 1650, 1526, 1417, 1207, 1123, 1093, 739; HR ESI MS: m/z = 415.2016 $[M+H]^+$ (calcd for $C_{26}H_{27}N_2O_3$ 415.2016).

4.10. (*S*)-Benzyl 3-(2,6-diisopropylphenylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 8

R_f = 0.4 (Hexane/ethyl acetate, 70:30). Off white solid (1.5 g, yield 51%); mp: 60–62 °C (hexane/ethyl acetate); $[\alpha]_D^{20} = -11.3$ (*c*

0.53, $CHCl_3$); (NMR spectra are reported for a mixture of two rotamers). ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–6.93 (m, 12H), 5.58–5.00 (m, 3H), 4.93–4.52 (m, 2H), 3.53 (m, 1H), 3.12 (m, 1H), 1.22 (m, 2H), 0.88 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 146.1, 132.6, 128.7, 128.4, 127.9, 123.2, 68.2, 56.6, 45.9, 32.2, 28.2, 23.6; IR ν_{max}/cm^{-1} (neat): 3280, 1643, 1547, 1453, 1222, 1029, 963, 755, 694; HR ESI MS: m/z = 471.2639 $[M+H]^+$ (calcd for $C_{30}H_{35}N_2O_3$ 471.2642).

4.11. (*S*)-Benzyl 3-(benzylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 9[35]

The synthesis of this compound has already been reported.[35]

4.12. (*S*)-*N*-Phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 10[35]

The synthesis of this compound has already been reported.[35]

4.13. (*S*)-*N*-*o*-Tolyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 11

R_f = 0.3 (Hexane/ethyl acetate, 7:3). Off white solid (0.6 g, yield 90%); mp: 124–126 °C (hexane/ethyl acetate); $[\alpha]_D^{20} = -60.0$ (*c* 0.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.08 (d, *J* = 7.96 Hz, 2H), 7.25–7.15 (m, 3H), 7.09 (m, 1H), 7.04 (m, 1H), 4.06 (d, *J* = 9.96 Hz, 2H), 3.74 (q, *J* = 9.98, 5.58 Hz, 1H), 3.35 (dd, *J* = 16.28, 5.56 Hz, 1H), 2.94 (dd, *J* = 16.28, 10.22 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 136.4, 135.9, 134.6, 130.4, 129.2, 127.8, 127.0, 126.9, 126.5, 125.6, 124.5, 121.4, 57.0, 47.4, 30.8, 17.8; IR ν_{max}/cm^{-1} (neat): 3280, 2905, 1659, 1587, 1531, 1455, 1125, 1042, 807, 724, 715; HR ESI MS: m/z = 267.1491 $[M+H]^+$ (calcd for $C_{17}H_{19}N_2O$ 267.1492).

4.14. (*S*)-*N*-(2,6-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 12

R_f = 0.4 (Hexane/ethyl acetate, 7:3). Off white solid (0.61 g, yield 91%); mp: 195–197 °C (hexane/ethyl acetate); $[\alpha]_D^{20} = -78.8$ (*c* 0.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.24–7.16 (m, 3H), 7.13–7.03 (m, 4H), 4.09 (d, *J* = 10.48 Hz, 2H), 3.80 (q, *J* = 9.38, 5.62 Hz, 1H), 3.33 (dd, *J* = 16.14, 5.58 Hz, 1H), 3.01 (dd, *J* = 16.08, 9.40 Hz, 1H), 2.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 136.3, 135.1, 134.6, 133.9, 129.1, 128.2, 127.1, 127.0, 126.5, 125.7, 56.5, 47.3, 31.3, 18.5; IR ν_{max}/cm^{-1} (neat): 3250, 2928, 1670, 1594, 1525, 1466, 1220, 761, 742, 713; HR ESI MS: m/z = 281.1648 $[M+H]^+$ (calcd for $C_{18}H_{21}N_2O$ 281.1649).

4.15. (*S*)-*N*-(2,6-Diisopropylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 13

R_f = 0.4 (Hexane/ethyl acetate, 7:3). Off white solid (0.66 g, yield 93%); mp: 142–144 °C (hexane/ethyl acetate); $[\alpha]_D^{20} = -58.3$ (*c* 0.48, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.29–7.06 (m, 7H), 4.09 (d, *J* = 15.72 Hz, 2H), 3.85 (q, *J* = 8.84, 5.76 Hz, 1H), 3.31 (dd, *J* = 16.0, 5.72 Hz, 1H), 3.05 (dd, *J* = 15.98, 8.90 Hz, 1H), 2.88 (m, 2H), 1.15 (d, *J* = 6.88 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 145.9, 136.4, 134.8, 131.3, 129.0, 128.1, 127.0, 126.5, 125.7, 123.4, 56.3, 47.2, 31.2, 28.9, 23.7; IR ν_{max}/cm^{-1} (neat): 3234, 2958, 1671, 1494, 1454, 1471, 799, 742; HR ESI MS: m/z = 337.2274 $[M+H]^+$ (calcd for $C_{22}H_{29}N_2O$ 337.2273).

4.16. (*S*)-*N*-Benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 14[35]

The synthesis of this compound has already been reported.[35]

4.17. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(*N*-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) 15

R_f = 0.5 (Hexane/ethyl acetate, 1:1). Colourless oil (0.16 g, yield 68%); $[\alpha]_D^{20} = -28.6$ (*c* 0.35, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 2H), 7.43 (d, *J* = 7.84 Hz, 4H), 7.26 (t, *J* = 7.44 Hz, 4H), 7.22–7.12 (m, 6H), 7.11–7.01 (m, 4H), 3.92 (d, *J* = 15.00 Hz, 2H), 3.72 (d, *J* = 14.84 Hz, 2H), 3.47 (t, *J* = 6.78 Hz, 2H), 3.17–3.04 (m, 4H), 2.71–2.57 (m, 4H), 1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 137.6, 134.5, 134.2, 129.1, 128.2, 127.4, 126.6, 126.4, 124.2, 119.3, 63.3, 52.0, 28.3, 26.5; IR ν_{max}/cm^{-1} (neat): 3281, 2955, 2926, 1684, 1599, 1517, 1440, 1287, 1123, 1075, 743, 692; HR ESI MS: m/z = 545.2917 $[M+H]^+$ (calcd for $C_{35}H_{37}N_4O_2$ 545.2911).

4.18. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(*N*-*o*-tolyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) 16

R_f = 0.4 (Hexane/ethyl acetate, 1:1). Yellow oil (0.16 g, yield 69%); $[\alpha]_D^{20} = -15.15$ (*c* 0.33 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 9.14 (s, 2H), 7.92 (d, *J* = 7.96 Hz, 2H), 7.22–7.12 (m, 8H), 7.11–7.04 (m, 4H), 7.03–6.96 (m, 2H), 3.92 (d, *J* = 14.12 Hz, 2H), 3.71 (d, *J* = 14.12 Hz, 2H), 3.53 (t, *J* = 6.12 Hz, 2H), 3.13 (d, *J* = 6.12 Hz, 4H), 2.80–2.62 (m, 4H), 1.95–1.85 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 135.8, 135.2, 134.4, 130.4, 128.1, 127.6, 126.9, 126.7, 126.2, 124.5, 121.3, 63.5, 54.0, 51.9, 29.4, 26.7, 17.5; IR ν_{max}/cm^{-1} (neat): 3287, 2955, 2926, 1724, 1686, 1586, 1518, 1454, 1289, 1120, 745; HR ESI MS: m/z = 573.3228 $[M+H]^+$ (calcd for $C_{37}H_{41}N_4O_2$ 573.3224).

4.19. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(*N*-(2,6-dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) 17

R_f = 0.4 (Hexane/ethyl acetate, 1:1). Pale yellow oil (.15 g, yield 65%); $[\alpha]_D^{20} = -35.7$ (*c* 0.14, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.7 (s, 2H), 7.24–7.11 (m, 8H), 7.08–6.89 (m, 6H), 3.98 (d, *J* = 13.12 Hz, 2H), 3.71 (d, *J* = 13.08 Hz, 2H), 3.60 (q, *J* = 7.16, 3.44 Hz, 2H), 3.26 (dd, *J* = 15.28, 3.44 Hz, 2H), 3.13 (dd, *J* = 15.16, 7.24 Hz, 2H), 2.91–2.75 (m, 4H), 2.04 (m, 2H), 1.90 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 135.6, 134.7, 133.7, 128.2, 128.0, 127.7, 127.1, 126.8, 126.1, 63.1, 54.7, 52.1, 30.4, 26.5, 18.4; IR ν_{max}/cm^{-1} (neat): 3205, 2955, 1725, 1646, 1520, 1263, 1135, 764, 728; HR ESI MS: m/z = 601.3538 $[M+H]^+$ (calcd for $C_{39}H_{45}N_4O_2$ 601.3537).

4.20. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(*N*-(2,6-diisopropylphenyl)-1,2,3,4-tetrahydroisoquinolin-e-3-carboxamide) 18

R_f = 0.4 (Hexane/ethyl acetate, 7:3); Colourless oil (0.17 g, yield 75%); $[\alpha]_D^{20} = -12.5$ (*c* 0.16, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 2H), 7.31–7.14 (m, 9H), 7.11–6.98 (m, 5H), 4.00 (d, *J* = 13.12 Hz, 2H), 3.69 (d, *J* = 13.12 Hz, 2H), 3.62 (q, *J* = 7.14, 2.42 Hz, 2H), 3.31 (dd, *J* = 15.05, 3.10 Hz, 2H), 3.1 (dd, *J* = 15.14, 7.22 Hz, 2H), 2.99–2.77 (m, 4H), 2.14–2.04 (m, 2H), 1.64 (m, 4H), 1.03 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 145.7, 136.0, 135.0, 131.2, 128.1, 127.87, 127.80, 126.8, 126.1, 123.4, 63.3, 55.4, 51.9, 30.6, 28.6, 26.8, 23.8, 23.7; IR ν_{max}/cm^{-1} (neat): 3269, 2958, 2925, 1664, 1486, 1472, 1256, 1129, 1098, 797, 738, 510; HR ESI MS: m/z = 713.4794 $[M+H]^+$ (calcd for $C_{47}H_{61}N_4O_2$ 713.4789).

4.21. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(N-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) 19

R_f = 0.4 (Hexane/ethyl acetate, 3:2). Yellow oil (0.16 g, yield 69%); $[\alpha]_D^{20} = -5.9$ (*c* 0.17, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ

7.50 (m, 2H), 7.25–7.15 (m, 13H), 7.05 (d, J = 6.52 Hz, 2H), 6.92 (m, 3H), 4.45 (dd, J = 15.04, 6.88 Hz, 2H), 4.18 (dd, J = 15.04, 5.28 Hz, 2H), 3.77 (d, J = 14.32 Hz, 2H), 3.54 (d, J = 14.53 Hz, 2H), 3.38 (t, J = 6.33 Hz, 2H), 3.11 (dd, J = 15.99, 6.08 Hz, 2H), 3.03 (dd, J = 15.82, 6.60 Hz, 2H), 2.48 (t, J = 7.26 Hz, 4H), 1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 138.3, 135.1, 134.4, 128.5, 128.0, 127.2, 126.4, 126.2, 62.6, 53.1, 52.0, 42.8, 29.3, 26.1; IR ν_{max}/cm^{-1} (neat): 3298, 2928, 1650, 1517, 1496, 1453, 1257, 1029, 742, 698; HR ESI MS: m/z = 573.3227 [M+H]$^+$ (calcd for $C_{37}H_{41}N_4O_2$ 573.3224).

4.22. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(3-(phenylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) 20

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). White solid (0.15 g, yield 71%); mp: 100–102 °C (DCM/MeOH); $[\alpha]_D^{20} = -27.3$ (c 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.62 (s, 2H), 7.67–7.46 (m, 4H), 7.36–6.92 (m, 14H), 4.82–4.37 (m, 4H), 4.35–4.01 (m, 2H), 3.99–3.47 (m, 4H), 3.48–3.11 (m, 4H), 2.78–2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 137.9, 129.9, 129.7, 129.0, 128.9, 128.5, 128.4, 128.2, 127.8, 127.6, 127.3, 126.7, 126.3, 124.5, 120.1, 73.0, 68.0, 66.1, 29.6, 29.3, 29.0, 25.7, 17.3; IR ν_{max}/cm^{-1} (neat): 2958, 1726, 1683, 1597, 1552, 1497, 1290, 1077, 906, 753, 692; HR ESI MS: m/z = 577.2808 [M+H]$^+$ (calcd for $C_{35}H_{37}N_4O_4$ 577.2809).

4.23. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(3-(o-tolylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) 21

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). White solid (0.14 g, yield 66%); mp: 112–114 °C (DCM/MeOH); $[\alpha]_D^{20} = -20.0$ (c 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.63 (s, 2H), 8.05 (d, J = 8.04 Hz, 2H), 7.34–6.93 (m, 14H), 4.67 (d, J = 15.16 Hz, 2H), 4.48 (d, J = 15.16 Hz, 2H), 3.95 (dd, J = 17.16, 8.56 Hz, 2H), 3.78–3.62 (m, 4H), 3.24 (dd, J = 16.90, 4.58 Hz, 2H), 2.99–2.86 (m, 2H), 2.28–2.15 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 136.1, 130.4, 129.9, 128.9, 128.4, 128.3, 128.2, 128.0, 127.5, 127.4, 127.2, 126.7, 126.5, 124.4, 120.9, 72.7, 66.2, 66.0, 50.6, 29.7, 29.4, 29.0, 18.3, 17.3; IR ν_{max}/cm^{-1} (neat): 2918, 1677, 1588, 1547, 1458, 1290, 753; HR ESI MS: m/z = 605.3118 [M+H]$^+$ (calcd for $C_{37}H_{41}N_4O_4$ 605.3122).

4.24. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(3-(2,6-dimethylphenylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) 22

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Off white solid (0.13 g, yield 62%); mp: 106–108 °C (DCM/MeOH); $[\alpha]_D^{20} = -26.7$ (c 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.82 (s, 2H), 7.34–7.19 (m, 5H), 7.14–6.95 (m, 9H), 4.82 (d, J = 15.20 Hz, 2H), 4.54 (d, J = 15.24 Hz, 2H), 4.03 (dd, J = 17.10, 8.30 Hz, 2H), 3.95–3.68 (m, 4H), 3.31 (dd, J = 17.08, 4.88 Hz, 2H), 3.00 (m, 2H), 2.21 (s, 12H), 2.30–2.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ165.1, 134.1, 133.5, 130.9, 129.8, 128.8, 128.3, 128.2, 128.1, 127.4, 127.2, 27.1, 126.9, 126.6, 72.9, 66.0, 65.6, 29.9, 19.0, 18.4; IR ν_{max}/cm^{-1} (neat): 2958, 2926, 1728, 1682, 1522, 1470, 1377, 1285, 1123, 1073, 767, 741; HR ESI MS: m/z = 633.3435 [M+H]$^+$ (calcd for $C_{39}H_{45}N_4O_4$ 633.3435).

4.25. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(3-(2,6-diisopropylphenylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) 23

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Off white solid (0.16 g, yield 77%); mp: 78–80 °C (DCM/MeOH); $[\alpha]_D^{20} = -38.5$ (c 0.13, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.96 (s, 2H), 7.33–7.13 (m, 9H), 7.04 (m, 5H), 4.81 (d, J = 15.40 Hz, 2H), 4.56 (d, J = 15.40 Hz, 2H), 4.18–4.02 (m, 2H), 3.90 (m, 2H), 3.65 (m, 2H), 3.46 (m, 2H), 3.31 (dd, J = 17.06, 4.74 Hz, 2H), 3.19–3.02 (m, 4H), 2.31 (m, 2H), 1.31–1.11 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 166.5, 164.7, 145.9, 145.2, 136.0, 133.0, 131.0, 129.9, 128.9, 128.3, 128.0, 127.4, 126.5, 123.5, 72.6, 66.5, 60.7, 45.3, 31.8, 29.8, 29.1, 23.8, 23.6, 22.5; IR ν_{max}/cm^{-1} (neat): 3248, 2960, 2927, 2868, 1724, 1681, 1500, 1458, 1383, 1272, 1122, 797, 740; HR ESI MS: m/z = 745.4686 [M+H]$^+$ (calcd for $C_{47}H_{61}N_4O_4$ 745.4686).

4.26. (3*S*,3′*S*)-2,2′-(Propane-1,3-diyl)bis(3-(benzylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide) 24

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2). Off white solid (0.17 g, yield 81%); mp: 72–74 °C (DCM/MeOH); $[\alpha]_D^{20} = -22.2$ (c 0.18, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.46 (s, 2H), 7.83–6.68 (m, 18H), 4.80–4.14 (m, 8H), 3.68–2.84 (m, 6H), 2.80–1.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 138.2, 130.9, 130.1, 128.7, 128.6, 128.4, 128.2, 128.0, 127.9, 127.6, 127.4, 127.1, 126.5, 72.8, 66.1, 65.2, 43.0, 29.6, 16.5; IR ν_{max}/cm^{-1} (neat): 3230, 2927, 1727, 1670, 1542, 1497, 1454, 1271, 1120, 1029, 919, 740, 699; HR ESI MS: m/z = 605.3129 [M+H]$^+$ (calcd for $C_{37}H_{41}N_4O_4$ 605.3122).

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