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Iridium-catalyzed asymmetric hydrogenation of olefins using TIQ phosphine–oxazoline ligands

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ABSTRACT

A novel family of tetrahydroisoquinoline (TIQ) phosphine–oxazoline ligands and four corresponding iridium complexes have been developed and applied to the asymmetric hydrogenation of unfunctionalized olefins. The results showed that the best conversion rates were observed in up to 99% with an enantiomeric excess of 91%.

1. Introduction

The enantioselective hydrogenation of olefins represents an important process for obtaining enantiomerically pure biologically active compounds.[1–3] The discovery of the Wilkinson catalyst $\{RhCl[P(C_6H_5)_3]_3\}$ possessing chiral phosphine ligands for the hydrogenation of olefins sparked the development of other chiral ligands in this field.[4–6] Early ligands were coordinated with ruthenium and rhodium metals and applied to the asymmetric hydrogenation of olefins.[6] More recently there have been many reports describing the use of chiral N,P-ligands and Ir-catalyzed hydrogenations of olefins.[7,8] The first chiral mimic of the Crabtree complex[9] was reported by Pfaltz et al.[10] and was successfully used in the asymmetric hydrogenation of olefins. Among the nitrogen donor ligands, oxazoline has become one of the most popular moieties in the asymmetric catalysis (Fig. 1).[7,11–14] Andersson et al. have developed chiral iridium catalysts for a wide range of substrates.[15,16] In particular, the bicyclic phosphine–oxazolines **1** are among the most successful and have produced excellent results in the hydrogenation of acyclic aromatic *N*-arylamines,[17] enol phosphinates,[18] and vinyl boronates.[19] The asymmetric hydrogenation of unfunctionalized olefins remains a challenge due to substrate dependence, and the development of new catalysts targeting this class of substrate is imperative.[20]

Recently, we have reported on the synthesis and evaluation of several novel classes of chiral tetrahydroisoquinoline (TIQ) ligands.[21–23] Their metal complexes have been employed for asymmetric transfer hydrogenation[21,22] and Henry type reactions.[23] Previous reports have described the application of N,P-derived TIQ oxazoline ligands for asymmetric C–C bond-forming reactions.[24–26] Herein we report a new class of iridium phosphine–oxazoline catalysts for the asymmetric hydrogenation of olefins.

2. Results and discussions

For the first time an alternate route to that employed by Blanc et al. for the synthesis of the TIQ phosphine–oxazoline ligands is described herein, whereby the diphenyl phosphine is introduced after the formation of the oxazoline (Scheme 1). The TIQ carboxylic acid is easily available from a Pictet-Spengler reaction of L-phenylalanine.[27] The amine was protected with benzyl chloroformate (Cbz) to give TIQ-Cbz acid **4**[27] followed by amide coupling with the appropriate L- and D-amino alcohols, leading to hydroxylamides **5–8**.[17] The compounds were subsequently converted into five-membered oxazoline rings **9–12** with triphenylphosphine and diethyl azodicarboxylate (DEAD) by the Mitsunobu reaction in good yields.[28] The cleavage of the Cbz group was accomplished by hydrogenolysis using palladium on carbon as a catalyst to yield amines **13–16**. Ligands **17–20** were obtained by treating these amines with chlorodiphenylphosphine in the presence of di-isopropylethylamine.[17] Due to compound instability upon addition of the phosphine onto the sp^3 nitrogen of the TIQ oxazolines, the structures of these ligands were only confirmed by ^{31}P and ^{1}H NMR spectroscopy. Iridium complexes **21–24** were prepared by refluxing the appropriate phosphine–oxazoline ligands and $[Ir(COD)Cl]_2$ in CH_2Cl_2 followed by subsequent counter ion exchange with sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate ($NaBAr_F$) in a CH_2Cl_2/H_2O mixture with vigorous stirring. The crude complexes were purified by column chromatography on silica gel

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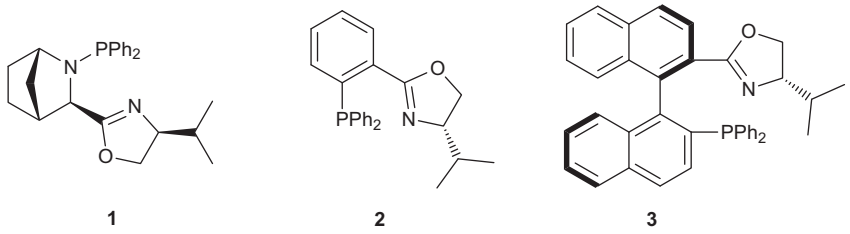
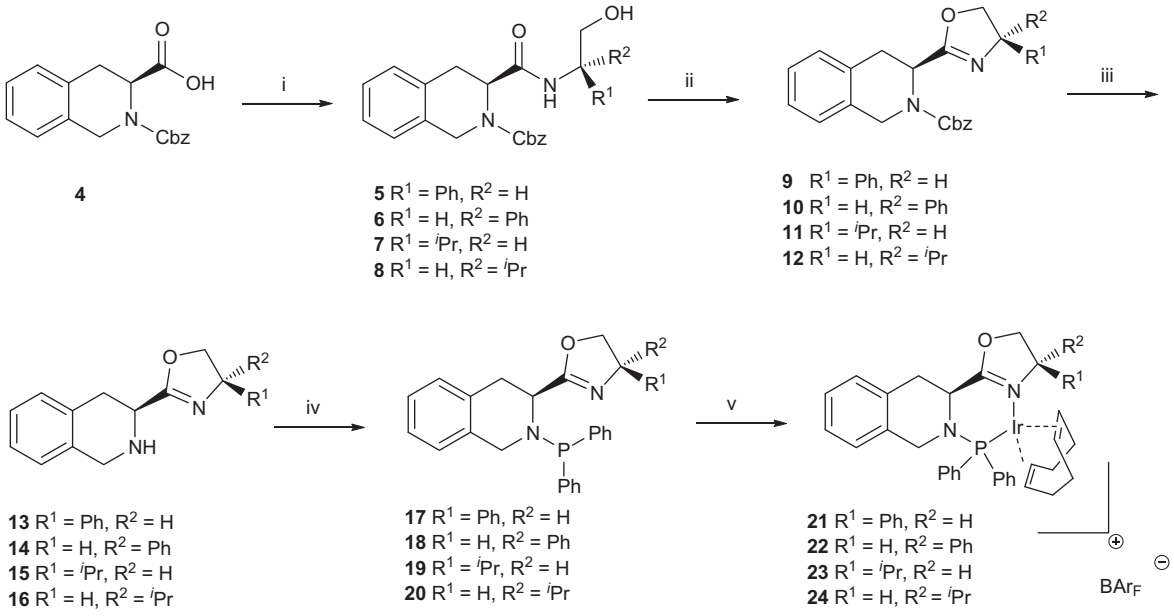


1 2 3

Figure 1. Previously reported P,N oxazoline ligands.



4

5 R^1 = Ph, R^2 = H
6 R^1 = H, R^2 = Ph
7 R^1 = ^{i}Pr, R^2 = H
8 R^1 = H, R^2 = ^{i}Pr

9 R^1 = Ph, R^2 = H
10 R^1 = H, R^2 = Ph
11 R^1 = ^{i}Pr, R^2 = H
12 R^1 = H, R^2 = ^{i}Pr

13 R^1 = Ph, R^2 = H
14 R^1 = H, R^2 = Ph
15 R^1 = ^{i}Pr, R^2 = H
16 R^1 = H, R^2 = ^{i}Pr

17 R^1 = Ph, R^2 = H
18 R^1 = H, R^2 = Ph
19 R^1 = ^{i}Pr, R^2 = H
20 R^1 = H, R^2 = ^{i}Pr

21 R^1 = Ph, R^2 = H
22 R^1 = H, R^2 = Ph
23 R^1 = ^{i}Pr, R^2 = H
24 R^1 = H, R^2 = ^{i}Pr

Scheme 1. Reagents for the synthesis of iridium complexes **21**–**24**. Reagents and conditions: (i) EDC·HCl, HOBt, triethylamine, amino alcohol, THF, H_2O, rt, 16 h; (ii) PPh_3, DEAD, dichloromethane, 0 °C–rt, 3 h; (iii) 10% Pd/C wt H_2 (1 atm), MeOH, rt, 1 h; (iv) PPh_2Cl, DIPEA, dichloromethane, rt, 16 h; (v) $[Ir(COD)Cl]_2$, dichloromethane, reflux 1 h then H_2O, $NaBAr_F \cdot 3H_2O$, rt, 2 h.

deactivated by triethylamine to afford the desired Ir-complexes **21**–**24** as crystalline compounds.

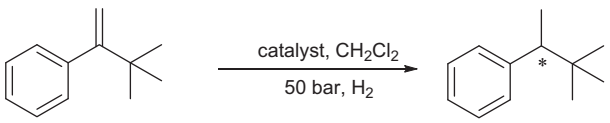
3. Ligand activity

In the first set of experiments, we used the Ir-catalyzed hydrogenation of (3,3-dimethylbut-1-en-2-yl) benzene **25** as the benchmark reaction for the catalysts **21**–**24**. The reaction was performed in dichloromethane with a catalyst loading of 0.5 mol % under a pressure of 50 bar of hydrogen gas. Good conversion rates were observed up to >99% using catalysts **21**–**24** for the benchmark reaction with variable enantioselectivities (Table 1). The best enantioselectivities were obtained with catalysts **22** and **23** with 88% for the (*S*)-isomer and 91% for the (*R*)-isomer, respectively (Table 1, entries 2 and 3). The enantioselectivity of the reaction was observed to be dependent on the configuration of the oxazoline ring.

The results obtained from the Ir-complexes **22** and **23** encouraged us to screen a wider range of olefins. Most substrates were hydrogenated with high conversions and moderate selectivities (Table 2).

Considerable differences were observed for hydrogenations of the cyclic and acyclic olefins. No activity was observed for the propene substrate (Table 2, entry 1) but >99% conversion for the butene and pentene analogs was achieved (Table 2, entries 2–5). An increase in bulk did not result in a difference in conversion, but did give higher enantioselectivities. This effect was more profound for the butene derivatives and presumably this can be attributed to the increased steric crowding closer to the prochiral center. The external olefin cyclic alkanes (table 2, entries 6 and 7) and an internal cyclic olefin (Table 2, entry 8) gave quantitative conversions but essentially racemic mixtures. Poor conversions and selectivities were observed for activated branched olefins (Table 2, entries 9 and 10).

Table 1
Asymmetric hydrogenation of (3,3-dimethylbut-1-en-2-yl) benzene **25** using catalysts **21**–**24**[a]

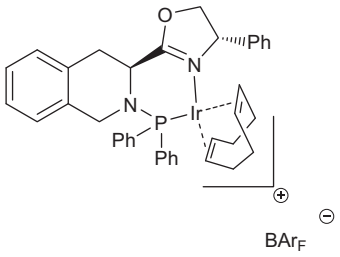


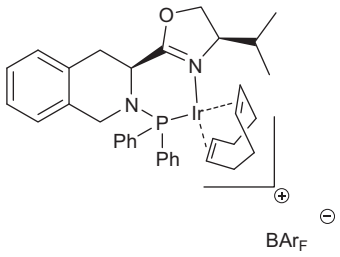
25

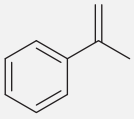
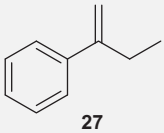
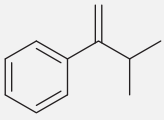
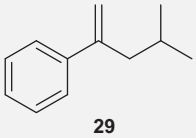
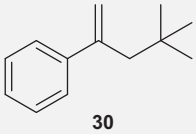
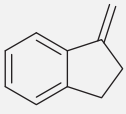
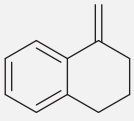
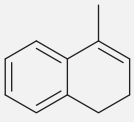
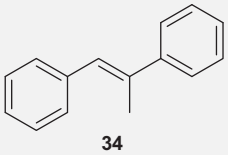
Entry	Catalyst	Conv.[b] (%)	ee[c] (%)
1	**21**	99	79 (*R*)
2	**22**	99	88 (*S*)
3	**23**	99	91 (*R*)
4	**24**	99	72 (*S*)

[a] All reactions were carried out at 50 bar H_2 in DCM at rt for 2 h with 0.5 mol % S/C loading.
[b] Conversions were determined by ^{1}H NMR.
[c] Enantiomeric excess was determined using HPLC with a chiral column and by GC using a β-dex chiral capillary column.

Table 2
Asymmetric hydrogenation of olefins using **22** and **23** as catalysts[a]

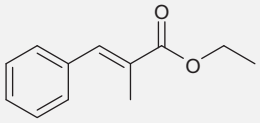




Entry	Substrate	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)
1	 **26**	0	—	0	—
2	 **27**	99	40 (*S*)	99	67 (*R*)
3	 **28**	99	63 (*S*)	99	48 (*R*)
4	 **29**	99	41 (*S*)	99	71 (*R*)
5	 **30**	99	46 (*S*)	99	73 (*R*)
6	 **31**	99	13 (*S*)	99	Racemic
7	 **32**	99	6 (*S*)	99	48 (*R*)
8	 **33**	99	16 (*S*)	99	51 (*R*)
9	 **34**	57	60 (*R*)	99	28 (*R*)

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)
10	 **35**	27	47 (*S*)	41	Racemic

[a] All reactions were carried out at 50 bar H_2 in DCM at rt for 2 h with 0.5 mol % S/C loading.
[b] Conversions were determined by ^{1}H NMR.
[c] Enantiomeric excess was determined using HPLC with a chiral column and by GC using a β-dex chiral capillary column.

4. Conclusion

We have developed TIQ phosphine–oxazoline iridium complexes for the asymmetric hydrogenation of olefins. The best results obtained in this study were with 99% conversions and enantiomeric excesses of up to 91% in 2 h with 0.5 mol % catalyst loading. The variation in the results clearly supports other reports on the substrate dependence for this important class of olefins and encourages further investigations.

5. Experimental

5.1. 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 hertz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using Silica gel (60–200 mesh except if stated different). All the 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.

5.2. General procedure for the preparation of hydroxylamides 5, 6, 7 and 8

This method was adapted from the literature.[14] To a round-bottomed flask were added Cbz-protected TIQ acid **4** (2.0 g, 0.044 mol), amino alcohol (1.1 equiv), and HOBt (2.0 equiv) in THF (60 mL). The mixture was cooled to 0 °C followed by the addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.0 equiv) and triethylamine (3.0 equiv) and allowed to react at ambient temperature for 16 h. Completion of the reaction was monitored by TLC using dichloromethane/methanol (98:2, R_f = 0.4). The solvent was evaporated and the residue was reconstituted in ethyl acetate (50 mL). The organic layer was washed with 10% HCl (10 mL) followed by saturated $NaHCO_3$ (10 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated to give a crude hydroxylamide, which was purified by column chromatography using 0–2% MeOH/CH_2Cl_2 as the eluent to yield pure compounds **5**, **6**, **7**, and **8**.

5.3. General procedure for the preparation of protected oxazolines 9, 10, 11 and 12

This method was adapted from the literature.[28] To a stirred solution of Cbz-protected TIQ-hydroxylamide (1.0 g) in dry dichloromethane (60 mL) was added triphenyl phosphine (2.0 equiv) at room temperature under an N_2 atmosphere. The reaction mixture was cooled to 0 °C and to this was added a solution of diethylazodicarboxylate (2.2 equiv) in dry dichloromethane (20 mL) dropwise over a period of 20 min and stirred for 4 h under an N_2 atmosphere. After completion of the reaction, the mixture was diluted with dichloromethane (10 mL), washed with water (2 × 10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using (EtOAc/hexane, 50:50) as the eluent to yield pure compounds **9**, **10**, **11**, and **12**.

5.4. General deprotection procedure for the preparation of TIQ-oxazolines 13, 14, 15, and 16

This method was adapted from the literature.[14] A solution of Cbz-protected TIQ-oxazoline (1.0 g) in methanol (30 mL) was added to a suspension of 10 wt % Pd/C (0.5 g) in methanol (10 mL). The reaction mixture was connected to a hydrogen source at one atmospheric pressure and stirred at room temperature for 2 h. Completion of the reaction was monitored by TLC using hexane/ethyl acetate (50:50, R_f = 0.5). The Pd/C was filtered off on a Celite pad, and the filtrate was concentrated under reduced pressure to afford the crude TIQ-oxazoline ligand. The crude compounds were purified on a deactivated silica gel column. The deactivation was carried out as follows: the column was packed with a suspension of silica gel in 20% Et_3N/CH_2Cl_2 and the silica was washed with 1% Et_3N/CH_2Cl_2. The chromatography was performed using 0–2% MeOH: 1% Et_3N: 99–97% CH_2Cl_2 as the eluent to afford pure oxazoline compounds **13**, **14**, **15**, and **16**.

5.5. General procedures for preparation of ligands 17, 18, 19, and 20

This method was adapted from the literature.[20] The TIQ-oxazoline was co-evaporated with dry toluene (3 × 20 mL) and dissolved in dry THF (6 mL) under an N_2 atmosphere. Freshly distilled di-isopropylethylamine was added and the solution was cooled to 0 °C in an ice-bath. Freshly distilled chloro-diphenylphosphene was added dropwise and the reaction was kept at 4 °C (refrigerator) overnight. The reaction was quenched with saturated $NaHCO_3$ (20 mL) under an N_2 atmosphere at room temperature. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using deactivated silica gel with Et_3N/CH_2Cl_2: pentane as the eluent to afford ligands **17**, **18**, **19**, and **20**.

5.6. General procedure for preparation of iridium complexes 21–24

The ligand and $[Ir(COD)Cl]_2$ (0.5 equiv) were dissolved in CH_2Cl_2 (2 mL) under an N_2 atmosphere and the mixture was heated to reflux for 1 h. After the solution was allowed to reach room temperature, distilled water was added and while being vigorously stirring, $NaBAr_F{\cdot}3H_2O$ was added to the reaction mixture in one portion and reacted for 1 h at ambient temperature. The complex was extracted with CH_2Cl_2 (2×10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. Evaporation of the solvent produced the crude complex and purification by column chromatography on silica gel with CH_2Cl_2/pentane (1:1) as the eluent afforded the metal complexes **21**–**24**. All complexes were obtained as orange solids.

5.7. General procedure for iridium-catalyzed asymmetric hydrogenation of olefins

A vial was charged with substrate and iridium complex in dry CH_2Cl_2 (2 mL). The reaction vessel was placed in a high-pressure hydrogenation apparatus and it was flushed with hydrogen gas three times before being adjusted to 50 bar. The mixture was stirred for 2 h, after which the pressure released and the solvent was removed under vacuum. The conversion was determined by ^1H NMR of the crude product. The residue was filtered through a short pad of silica gel with pentane/diethyl ether (1:1) as the eluent. After the solvent was removed, the enantiomeric excess was determined by chiral HPLC or GC.

5.8. Literature preparations

Substrates **25**,[29] **27**,[30] **28**,[30] **29**,[31] **30**,[32] **32**,[33] **33**,[34] and **35**[34] were prepared according to the literature procedures.

5.8.1. (*S*)-Benzyl 3-((*R*)-2-hydroxy-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2); Off white solid (2.2 g, yield 80%); mp: 133–135 °C (CH_2Cl_2); $[\alpha]_D^{20} = -26.2$ (*c* 0.42, CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^1H NMR (400 MHz, $CDCl_3$): δ 7.50–6.89 (m, 13H), 6.40 (m, 1H), 5.31–5.08 (m, 2H), 4.99–4.50 (m, 4H), 3.72–3.27 (m, 3H), 3.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.7, 128.6, 128.3, 128.0, 127.7, 127.2, 126.4, 126.0, 67.9, 65.9, 55.6, 45.2; IR ν_{max}/cm^{-1} (neat): 3230, 3063, 1702, 1647, 1336, 1308, 1231, 740, 691, 534; HR ESI MS: m/z = 431.1940 $[M+H]^+$ (calcd for $C_{26}H_{27}N_2O_4$ 431.1965).

5.8.2. (*S*)-Benzyl 3-((*S*)-2-hydroxy-1-phenylethylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carb-oxylate 6

R_f = 0.4 (CH_2Cl_2/MeOH, 9.8:0.2); Off white solid (2.0 g, yield 74%); mp: 120–122 °C; $[\alpha]_D^{20} = +10.7$ (*c* 0.70, CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.02 (m, 11H), 6.85–6.32 (m, 3H), 5.40–5.06 (m, 2H), 5.04–4.43 (m, 4H), 3.89–3.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 133.6, 133.3, 128.6, 128.5, 128.4, 128.2, 127.3, 126.0, 67.9, 65.5, 56.5, 55.9, 54.7, 45.3, 31.5; IR ν_{max}/cm^{-1} (neat): 3438, 3309, 2912, 1656, 1672, 1412, 1354, 1205, 1132, 749, 730, 691; HR ESI MS: m/z = 431.1985$[M+H]^+$ (calcd for $C_{26}H_{27}N_2O_4$ 431.1965).

5.8.3. (*S*)-Benzyl 3-((*R*)-1-hydroxy-3-methylbutan-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 7

R_f = 0.5 (CH_2Cl_2/MeOH, 9.8:0.2); Off white solid (2.2 g, yield 86%); mp: 110–112 °C (CH_2Cl_2); $[\alpha]_D^{20} = +4.4$ (*c* 0.80, CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers); ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.05 (m, 9H), 5.29–5.13 (m, 2H), 4.84–4.44 (m, 3H), 3.61–3.02 (m, 5H), 1.76 (m, 1H), 0.96–0.47 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 128.8, 128.6, 128.3, 128.2, 128.0, 128.0, 126.9, 67.9, 63.3, 57.0, 56.6, 45.3, 32.6, 31.3, 28.5, 19.2, 18.5; IR ν_{max}/cm^{-1} (neat): 3479, 3306, 2946, 1678, 1647, 1554, 1421, 1346, 1225, 1136, 1047, 756, 728, 692; HR ESI MS: m/z = 419.1941$[M+Na]^+$ (calcd for $C_{23}H_{28}N_2NaO_4$ 419.1941).

5.8.4. (*S*)-Benzyl 3-((*S*)-1-hydroxy-3-methylbutan-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 8

R_f = 0.5 (CH_2Cl_2/MeOH, 9.8:0.2); White solid (2.2 g, yield 86%); mp: 110–112 °C (CH_2Cl_2); $[\alpha]_D^{20} = -23.1$ (*c* 1.17, CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers); ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.07 (m, 9H), 5.86 (m, 1H), 5.41–4.99 (m, 2H), 4.89–4.40 (m, 3H), 3.64–2.99 (m, 5H), 0.79–0.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 128.6, 128.4, 127.9, 126.9, 126.1, 125.9, 67.9, 63.5, 56.7, 45.4, 28.6, 19.3, 17.8; IR ν_{max}/cm^{-1} (neat): 3407, 3333, 2955, 1678, 1662, 1538, 1411, 1347, 1228, 1124, 1094, 736; HR ESI MS: m/z = 419.1941$[M+Na]^+$ (calcd for $C_{23}H_{28}N_2NaO_4$ 419.1941).

5.8.5. (*S*)-Benzyl 3-((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 9

R_f = 0.6 (hexane/EtOAc, 65:35); Off white solid (0.86 g, yield 90%); mp: 96–98 °C (CH_2Cl_2); $[\alpha]_D^{20} = +2.7$ (*c* 0.37, CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.03 (m, 12H), 6.65–6.43 (m, 2H), 5.54–5.13 (m, 3H), 5.04 (m, 1H), 4.89–4.67 (m, 2H), 4.52 (m, 1H), 3.89 (m, 1H), 3.39–3.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 156.0, 142.1, 133.4, 132.9, 131.6, 128.9, 128.4, 128.0, 127.9, 127.2, 126.8, 126.6, 126.2, 69.5, 67.6, 67.4, 49.1, 48.9, 44.7, 32.1; IR ν_{max}/cm^{-1} (neat): 3324, 1702, 1665, 1411, 1326, 1304, 1184, 1114, 997, 744, 697; HR ESI MS: m/z = 413.1895 $[M+H]^+$ (calcd for $C_{26}H_{25}N_2O_3$ 413.1860).

5.8.6. (*S*)-Benzyl 3-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 10

R_f = 0.6 (hexane/EtOAc, 65:35); Off white solid (0.85 g, yield 89%); mp: 60–62 °C (CH_2Cl_2); $[\alpha]_D^{20} = +12.2$ (*c* 0.41, CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers).^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.04 (m, 12H), 6.77 (m, 2H), 5.55–4.99 (m, 4H), 4.97–4.38 (m, 3H), 3.94 (m, 1H), 3.44–3.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 156.3, 142.3, 136.4, 133.8, 132.2, 129.4, 129.0, 127.3, 127.0, 75.8, 68.0, 48.8, 44.8, 31.5; IR ν_{max}/cm^{-1} (neat): 3313, 3031, 2925, 1662, 1407, 1216, 1119, 744, 696; HR ESI MS: m/z = 413.1861$[M+H]^+$ (calcd for $C_{26}H_{25}N_2O_3$ 413.1860).

5.8.7. (*S*)-Benzyl 3-((*R*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 11

R_f = 0.6 (hexane/EtOAc, 60:40); Colorless oil (0.85 g, yield 89%); $[\alpha]_D^{20} = +3.4$ (*c* 0.89, CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers); ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–6.94 (m, 9H), 5.42–5.10 (m, 3H), 4.90–4.55 (m, 2H), 4.36–3.96 (m, 4H), 3.93–3.74 (m, 2H), 3.25–3.03 (m, 2H), 1.47 (m, 1H), 0.67–0.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 155.8, 136.5, 132.6, 128.3, 127.8, 127.6, 127.0, 126.7, 126.2, 71.6, 70.0, 67.4, 64.1, 62.5, 62.2, 48.5, 44.4, 31.8, 17.9, 17.1, 14.3; IR ν_{max}/cm^{-1} (neat): 3301, 2958, 1679, 1647, 1256, 1225, 1049, 756, 729; HR ESI MS: m/z = 379.2016$[M+H]^+$ (calcd for $C_{23}H_{27}N_2O_3$ 379.2016).

5.8.8. (*S*)-Benzyl 3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 12

R_f = 0.6 (hexane/EtOAc, 60:40); Colorless oil (0.85 g, yield 89%); $[\alpha]_D^{20} = -9.7$ (*c* 0.72, CH_2Cl_2); (NMR spectra are reported for a mixture of two rotamers). ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.07 (m, 9H), 6.65 (m, 1H), 5.39–5.07 (m, 2H), 4.91–4.44 (m, 3H), 3.64–3.01

(m, 4H), 1.90 (m, 1H), 0.91–0.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 132.1, 131.9, 128.6, 128.5, 128.3, 127.1, 126.5, 126.0, 67.7, 63.4, 62.2, 45.2, 28.4, 19.3, 17.9; IR ν_{max}/cm^{-1} (neat): 3334, 2956, 1662, 1679, 1412, 1220, 1121, 1095, 737, 694; HR ESI MS: m/z = 379.2016[M+H]$^+$ (calcd for $C_{23}H_{27}N_2O_3$ 379.2016).

5.8.9. (*R*)-4-Phenyl-2-((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dihydrooxazole 13

R_f = 0.3 (CH_2Cl_2/MeOH, 98:2); White solid (0.41 g, yield 59%); mp: 129–131 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = +46.15 (*c* 0.26, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.23 (m, 3H), 7.23–7.10 (m, 5H), 7.08–7.02 (m, 1H), 5.23 (t, *J* = 18.21 Hz, 1H), 4.68 (q, *J* = 10.10, 3.46 Hz, 1H), 4.16 (m, 3H), 3.92 (m, 1H), 3.19–3.06 (m, 2H), 1.93 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 142.0, 135.0, 133.3, 129.2, 128.7, 127.6, 126.5, 126.2, 126.1, 126.0, 75.0, 69.4, 51.5, 47.6, 32.4. IR ν_{max}/cm^{-1} (neat): 3225, 1663, 1493, 1454, 1366, 957, 916, 740, 697; HR ESI MS: m/z = 279.1500 [M+H]$^+$ (calcd for $C_{18}H_{19}N_2O$ 279.1492).

5.8.10. (*S*)-4-Phenyl-2-((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dihydrooxazole 14

R_f = 0.3 (CH_2Cl_2/MeOH, 98:2); Yellow oil (0.45, yield 65%); $[\alpha]_D^{20}$ = −7.4 (*c* 1.85, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.01 (m, 9H), 5.23 (t, *J* = 18.33 Hz, 1H), 4.68 (q, *J* = 10.04, 8.56 Hz, 1H), 4.20–4.13 (m, 3H), 3.92 (t, *J* = 5.84 Hz, 1H), 3.13 (d, *J* = 9.08 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 142.1, 135.0, 133.4, 129.4, 129.0, 127.8, 126.8, 126.4, 126.2, 75.2, 69.5, 51.6, 47.7, 32.5; IR ν_{max}/cm^{-1} (neat): 3227, 1663, 1493, 1109, 957, 916, 907, 749, 697; HR ESI MS: m/z = 279.1492[M+H]$^+$ (calcd for $C_{18}H_{19}N_2O$ 279.1492).

5.8.11. (*R*)-4-Isopropyl-2-((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dihydrooxazole (15)

R_f = 0.3 (CH_2Cl_2/MeOH, 9.8:0.2); Pale yellow oil (0.35 g, 54%); $[\alpha]_D^{20}$ = −12.7 (*c* 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.07 (m, 3H), 7.03 (m, 1H), 4.28 (q, *J* = 9.32, 8.12 Hz, 1H), 4.12 (s, 2H), 4.05–3.92 (m, 2H), 3.81–3.75 (m, 1H), 3.09–2.94 (m, 2H), 1.78 (m, 1H), 1.27 (t, *J* = 7.18 Hz, 1H), 0.96 (d, *J* = 6.88 Hz, 3H), 0.87 (t, *J* = 6.88 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 135.2, 133.6, 129.1, 126.2, 126.06, 126.04, 72.1, 70.4, 51.8, 48.0, 32.6, 18.9, 18.1; IR ν_{max}/cm^{-1} (neat): 3298, 2960, 1717, 1642, 1525, 1222, 1065, 741, 615; HR ESI MS: m/z = 245.1468[M+H]$^+$ (calcd for $C_{15}H_{21}N_2O$ 245.1462).

5.8.12. (*S*)-4-Isopropyl-2-((*S*)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dihydrooxazole 16

R_f = 0.3 (CH_2Cl_2/MeOH, 9.8:0.2); Pale yellow oil (0.38 g, yield 59%); $[\alpha]_D^{20}$ = −10.9 (*c* 0.69, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.08 (m, 3H), 7.02 (m, 1H), 4.33–4.14 (m, 2H), 4.11 (s, 2H), 4.05–3.91 (m, 2H), 3.79 (m, 1H), 3.02 (d, *J* = 7.58 Hz, 2H), 1.77 (m, 1H), 1.25 (t, *J* = 14.3 Hz, 1H), 0.96 (d, *J* = 6.79 Hz, 3H), 0.87 (d, *J* = 6.79 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 135.1, 133.6, 129.4, 126.4, 126.2, 72.1, 70.4, 51.7, 47.8, 32.6, 32.5, 18.9, 18.1; IR ν_{max}/cm^{-1} (neat): 3279, 2957, 1744, 1644, 1559, 1225, 1069, 880, 736; HR ESI MS: m/z = 245.1468[M+H]$^+$ (calcd for $C_{15}H_{21}N_2O$ 245.1462).

5.8.13. (*R*)-2-((*S*)-2-(Diphenylphosphino)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-phenyl-4,5-dihydrooxazole 17

Yield: quant.; ^{1}H NMR (400 MHz, C_6D_6): δ 7.85 (t, 2H), 7.54 (t, 2H), 7.21–6.84 (m, 13H), 6.71–6.61 (m, 2H), 4.82–4.56 (m, 3H), 4.20 (dd, *J* = 9.34, 2.99 Hz, 1H), 3.84 (m, 1H), 3.56 (m, 1H), 3.31 (m, 1H), 3.18 (m, 1H); ^{31}P NMR (162 MHz, C_6D_6): δ 65.81.

5.8.14. (*S*)-2-((*S*)-2-(Diphenylphosphino)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-phenyl-4,5-dihydrooxazole 18

Yield: quant.; ^{1}H NMR (400 MHz, C_6D_6): δ 7.83–7.45 (m, 4H), 7.23–6.90 (m, 13H), 6.78–6.58 (m, 3H), 4.82–4.58 (m, 3H), 4.20 (d, *J* = 8.64 Hz, 1H), 3.88 (m, 1H), 3.56 (m, 1H), 3.31 (m, 1H), 3.08 (m, 1H); ^{31}P NMR (162 MHz, C_6D_6): δ 65.38.

5.8.15. (*R*)-2-((*S*)-2-(Diphenylphosphino)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-isopropyl-4,5-dihydrooxazole 19

Yield: quant.; ^{1}H NMR (400 MHz, C_6D_6): δ 7.78 (m, 2H), 7.45 (m, 2H), 7.25–6.76 (m, 9H), 6.56 (m, 1H), 4.68–3.80 (m, 5H), 3.66–2.89 (m, 3H), 1.23 (m, 1H), 0.57 (d, *J* = 6.7 Hz, 3H), 0.50 (d, *J* = 6.7 Hz, 3H); ^{31}P NMR (162 MHz, C_6D_6): δ 67.99.

5.8.16. (*S*)-2-((*S*)-2-(Diphenylphosphino)-1,2,3,4-tetrahydroisoquinolin-3-yl)-4-isopropyl-4,5-dihydrooxazole 20

Yield: quant.; ^{1}H NMR (400 MHz, C_6D_6): δ 7.76 (m, 2H), 7.44 (m, 2H), 7.21–6.79 (m, 9H), 6.57 (m, 1H), 4.63 (m, 1H), 4.41 (d, 16.4 Hz, 1H), 4.10 (d, 16.1 Hz, 1H), 3.64–3.01 (m, 6H), 1.27 (m, 1H), 0.64 (d, *J* = 6.8 Hz, 3H), 0.54 (d, *J* = 6.8 Hz, 3H); ^{31}P NMR (162 MHz, C_6D_6): δ 68.39.

5.8.17. Complex 21

Yield: 64%; $[\alpha]_D^{20}$ = −3.1 (*c* 0.32, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81–7.58 (m, 10H), 7.56–7.41 (m, 7H), 7.40–7.11 (m, 11H), 6.82 (m, 2H), 6.71 (m, 1H), 5.21–4.72 (m, 2H), 4.38 (m, 1H), 4.11 (m, 2H), 3.76 (m, 2H), 3.36–3.18 (m, 3H), 2.76 (m, 1H), 2.31–2.06 (m, 2H), 1.98–1.78 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 163.1–160.7, 138.9, 135.0, 133.0–131.4 (m), 130.5–127.4 (m), 126.31, 125.6, 125.2, 123.8, 122.0, 117.6 (d, *J* = 3.89 Hz), 42.4, 36.2, 29.2, 20.1, 8.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 66.13; IR ν_{max}/cm^{-1} (neat): 2928, 2034, 1610, 1353, 1273, 1115, 885, 838, 744, 711; HR ESI MS: m/z = 763.2418 [M−BAr_F]$^+$ (calcd for $C_{38}H_{39}IrN_2OP$ 763.2424).

5.8.18. Complex 22

Yield: 62%; $[\alpha]_D^{20}$ = +40.9 (*c* 1.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02–6.82 (m, 30H), 6.67 (m, 1H), 5.16–4.77 (m, 2H), 4.62 (m, 1H), 4.55–4.28 (m, 4H), 3.66 (m, 1H), 3.44–3.28 (m, 2H), 3.10–2.88 (m, 2H), 2.51–1.85 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 162.2 (q), 138.3, 135.2, 133.6–131.9 (m), 130.6–127.6 (m), 126.5, 126.4, 123.6, 120.9, 117.9 (t), 94.7, 69.1, 65.9, 63.9, 57.6, 53.9, 52.3, 36.5, 34.6, 30.1, 27.5, 22.8, 14.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 65.83; IR ν_{max}/cm^{-1} (neat): 2924, 2024, 1610, 1353, 1272, 1114, 885, 734, 711, 681; HR ESI MS: m/z = 763.2424 [M−BAr_F]$^+$ (calcd for $C_{38}H_{39}IrN_2OP$ 763.2424).

5.8.19. Complex 23

Yield: 68%; $[\alpha]_D^{20}$ = +1.6 (*c* 0.64, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.83 (m, 3H), 7.78–7.45 (m, 15H), 7.43–7.07 (m, 7H), 6.63 (d, 1H), 5.02–4.66 (m, 5H), 3.48–3.01 (m, 4H), 2.74 (m, 1H), 2.44–1.16 (m, 8H), 0.94–0.73 (m, 6H), 0.32 (d, *J* = 6.79 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 162.1 (q, *J* = 96.43, 44.72 Hz), 135.0–131.9 (m), 129.9–129.0 (m), 127.7–125.7 (m), 123.4, 120.7, 117.6, 94.7 (d), 92.8 (d), 73.3, 65.6 (t), 57.2, 53.6, 51.8, 42.4, 36.1, 35.4, 32.5, 29.1, 26.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 65.5; IR ν_{max}/cm^{-1} (neat): 2924, 2036, 1610, 1353, 1272, 1114, 885, 744; HR ESI MS: m/z = 729.2580 [M−BAr_F]$^+$ (calcd. for $C_{35}H_{41}IrN_2OP$ 729.2580).

5.8.20. Complex 24

Yield: 65%; $[\alpha]_D^{20}$ = +30.2 (*c* 0.86, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.64 (m, 5H), 7.64–7.47 (m, 9H), 7.40–7.09 (m, 9H), 6.87–6.77 (m, 2H), 6.67 (d, *J* = 7.6 Hz, 1H), 5.04–4.62 (m, 5H), 3.46–3.19 (m, 4H), 2.80 (m, 1H), 2.01–1.62 (m, 8H), 1.61–1.41 (m, 3H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.17 (d, *J* = 6.7 Hz, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 172.9 (m), 162.1 (q, J = 99.58, 49.81 Hz), 135.3, 133.0–132.6 (m, 132.3 (m), 130.3–127.6 (m), 126.0 (m), 125.4, 124.1, 122.3, 117.9, 95.4, 70.1, 65.8, 64.1, 57.1, 52.4, 36.7, 36.0, 32.7, 32.4, 30.2, 29.2, 26.8, 18.8, 14.6, 13.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 65.94; IR ν_{max}/cm^{-1} (neat): 2990, 2791, 2029, 1641, 1353, 1272, 1114, 885, 744; HR ESI MS: m/z = 729.2580 $[M-BAr_F]^+$ (calcd for $C_{35}H_{41}IrN_2OP$ 729.2580).

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