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Substituent effects on axial chirality in 1-aryl-3,4-dihydroisoquinolines: controlling the rate of bond rotation
Josep Mas Roselló, Samantha Staniland, Nicholas J. Turner and Jonathan Clayden*

3,4-Dihydroisoquinolines

X = Br, I: Marginally atropisomeric
X = OTf: Atropisomeric
X = P(O)Ph₂: Atropisomeric
Substituent effects on axial chirality in 1-aryl-3,4-dihydroisoquinolines: controlling the rate of bond rotation.

Josep Mas Roselló,a,b Samantha Staniland,a Nicholas J. Turnerc and Jonathan Clayden,a,b,*

*aSchool of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK
bSchool of Chemistry, University of Bristol, Cantock’s Close, Bristol BS8 1TS, UK
cSchool of Chemistry, University of Manchester, Manchester Institute of Biotechnology, 131 Princess Street, Manchester M1 7DN, UK

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ABSTRACT

A series of 1-aryl-3,4-dihydroisoquinolines (DHIQs) were synthesized and their barriers to bond rotation were determined by means of VT-NMR, dynamic HPLC or racemization studies. Although they all presented lower rotational stability than the related 1-arylsisoquinolines (such as QUINAP), certain 1-aryl-DHIQ structures had a sufficiently high barrier to bond rotation to show axial chirality. These compounds included 1-(2-triflyl-1-naphthyl)-4,5-dihydroisoquinoline 4h and 1-(2-diphenylphosphanyl-1-naphthyl)-4,5-dihydroisoquinoline 4i. This discovery opens the door to the development of a new group of axially chiral N,P ligands for asymmetric synthesis and also potentially to new strategies for the synthesis of axially chiral 1-arylsisoquinolines.

* Corresponding author. Tel.: +44-117-331-8054; fax: +44-117-927-7985; e-mail: j.clayden@bristol.ac.uk
1. Introduction

The majority of axially chiral compounds are biaryls, whether biphenyls or binaphthyls, or their heterocyclic counterparts. Particularly valuable are biaryls containing the isoquinoline ring, which function as atropisomeric chiral ligands because their basic nitrogen atom allows bideterminate coordination in P,N ligands such as QUINAP (Figure 1). QUINAP is the ligand of choice in many asymmetric reactions, including asymmetric hydrobrominations, diborations, dipolar cycloadditions, conjugate additions and additions to iminium ions.

Configurational stability about the biaryl axis in 1-naphthylisoquinolines depends on the substituent at the 2-position of the naphthyl ring. The 2-unsubstituted structure 1a is configurationally unstable at room temperature, with an estimated half-life for racemization of 13 min at –20 °C. In contrast, the amino-substituted structure 1b is configurationally stable, with a barrier to bond rotation of 125.4 kJ mol⁻¹. The more substituted compounds 1c and QUINAP 1d showed no sign of racemization on extended heating.

One report of a related partially saturated structure, 3,4-dihydroisoquinoline 2a, suggests that its barrier to rotation is too low to permit resolution, but the rate of bond rotation was not quantified. A chiral derivative 2b nonetheless displayed separable diastereoisomeric atropisomers, but again no barrier was reported. The diastereoisomers of the corresponding triflate 2c were not separable. Related 1-aryl-3,4-dihydroisoquinolines are of medicinal interest as potent neuroprotectors.

2. Results and discussion

2.1. Starting materials

A range of racemic 1-aryl-DHIQs halogenated at the 2-position of the 1-aryl ring (4a–g) were readily synthesized in high yields from the corresponding amides 3a–g by the modified Bischler-Napieralski cyclisation reported by Movassagh et al. Amidine starting materials for the cyclisation were made either by acylation of phenethylamine with available 2-halobenzoyl chloride or 1-naphthoyl chloride (giving 3a–d). The remaining amides 3e–f were made by halogenation of 3d by means of rhodium or palladium catalyzed C-H activation reactions, with the amide as a directing group for chemoselective halogenation at the ortho position of the 1-naphthyl ring.

Scheme 1. Synthesis of 1-aryl-3,4-dihydroisoquinolines. Reagents: (a) NCS, Pd(OAc)₂ (5 mol%), TfOH, NaS₂O₅, DCE, 80 °C, 32 h; (b) NBS/NIS, [RhCl₂P₅C₅] (2.5 mol%), AgSbF₆ (10 mol%), PivOH, DCE, 70 °C, 18 h.

In addition, triflyl-substituted DHIQ 4h was made by the method of Li et al. (Scheme 2) and converted into phosphine oxide 4i by palladium-catalyzed coupling with Pb₃P(O)H.

Scheme 2. Synthesis of substituted 1-naphthyl-3,4-dihydroisoquinolines.

2.2. Determination of the barriers to bond rotation in variously substituted DHIQs

Variable temperature NMR (VT-NMR) studies were carried out to estimate the rate of bond rotation about the Ar-DHIQ axis of the less hindered group of compounds 4a–d. The 1H NMR line shapes of the signals arising from the potentially diastereotropic protons in the –Ch₂–Ch₂– unit of the DHIQ were monitored in CDCl₃ at temperatures between –30 °C and +30 °C. The line shapes were modelled using the commercial program gNMR. Table 1 illustrates (for one example, bromo-substituted 4b) the modelled and observed line shapes of the two diastereotropic methylene protons (Hₐ, H₆) α to the nitrogen atom at a series of temperatures, and shows the estimated rate constant, k, for their exchange.
Table 1. Line shape analysis in the VT NMR study of 4b

<table>
<thead>
<tr>
<th>T / °C</th>
<th>Experimental line shape</th>
<th>Modelled line shape</th>
<th>k / s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

These rates are analysed using the Eyring equation, allowing calculation of the barrier to bond rotation (ΔG‡) and an estimation of the half-life for racemization (t₁/₂) of 4a–d in solution at a given temperature.

It was not possible to use VT-NMR to derive a barrier to rotation of the more sterically encumbered substrate 4e since no line broadening or coalescences were observed even at 120 °C in 1,2-dichlorobenzene-d₆. Rotationally restricted compounds with half-lives for racemization falling into the timescale of minutes at ambient temperature are typically difficult to analyse by VT-NMR for this reason, but this racemization profile is ideal for investigation by dynamic (variable temperature) HPLC (DHPLC) on a chiral stationary phase.¹³a,¹⁹–²¹

DHPLC studies were undertaken using DHIQs 4e–g. For 4e, all the chiral stationary phases and eluents explored showed a single peak, even on cooling the column to 0 °C. Although no numerical values for the barrier to rotation of 4e were obtained, we assume therefore that chloro-substituted 4e rotates freely (that is, on a time scale of seconds or less) at room temperature.

More information was obtained from 4f, which showed peak shapes characteristic of racemisation on the timescale of elution on a (R,R)-Whelk-O1 chiral stationary phase, eluting with n-hexane/isopropanol (60:40). Peak profiles were monitored at 20, 30 and 40 °C (Table 2) and the parameters obtained from the profiles were entered into the Unified Equation for Dynamic Chromatography.¹⁹,²⁰ From this equation, the rates of interconversion of the two enantiomers of 4f were calculated.

An Eyring plot of this data revealed that 4f was almost atropisomeric²² at 25 °C (ΔG‡₂₅ = 92.6 kJ mol⁻¹; t₁/₂ = 900 s).

Table 2. Dynamic HPLC profiles for 4f on the (R,R)-Whelk-O1 chiral stationary phase, eluting with n-hexane/isopropanol (60:40).

<table>
<thead>
<tr>
<th>T / °C</th>
<th>Observed peak shape</th>
<th>k / 10³ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>7.1</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>9.9</td>
</tr>
</tbody>
</table>

Similar approximate analysis of the DHPLC trace of 4g around 0 °C indicated that 4g had a lower barrier to rotation than 4f. The replacement of a bromine atom by a bulkier iodine atom at the naphthyl ring's ortho position did not increase rotational stability at the Ar-DHIQ bond. Presumably the bigger atomic radius of iodine is countered by the longer bond length of C–I (a similar effect is well established in A values).²³

Table 3. Summary of kinetic parameters for bond rotations in 1-arylDHIQs

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>X</th>
<th>ΔH‡ / kJ mol⁻¹</th>
<th>ΔS‡ / J mol⁻¹ K⁻¹</th>
<th>ΔG‡₂₅ / kJ mol⁻¹</th>
<th>t₁/₂ in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Cl</td>
<td>56.6</td>
<td>-9</td>
<td>59.2</td>
<td>≈ 10³ s</td>
</tr>
<tr>
<td>4b</td>
<td>Br</td>
<td>50.7</td>
<td>-26</td>
<td>58.4</td>
<td>&lt; 10⁻³ s</td>
</tr>
<tr>
<td>4c</td>
<td>I</td>
<td>64.0</td>
<td>+20</td>
<td>57.9</td>
<td>&lt; 10⁻³ s</td>
</tr>
<tr>
<td>4d</td>
<td>H</td>
<td>55.1</td>
<td>+1</td>
<td>54.7</td>
<td>≈ 10⁻¹ s</td>
</tr>
<tr>
<td>4e</td>
<td>Cl</td>
<td>34.6</td>
<td>-195</td>
<td>92.6</td>
<td>15 min</td>
</tr>
<tr>
<td>4f</td>
<td>Br</td>
<td>4.6</td>
<td></td>
<td>81.9</td>
<td>&lt; 1 min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>X</th>
<th>ΔH‡ / kJ mol⁻¹</th>
<th>ΔS‡ / J mol⁻¹ K⁻¹</th>
<th>ΔG‡₂₅ / kJ mol⁻¹</th>
<th>t₁/₂ in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>4h</td>
<td>OTf</td>
<td>10.7</td>
<td>+14.5</td>
<td>103.1</td>
<td>36 days</td>
</tr>
<tr>
<td>4i</td>
<td>P(O)Ph₂</td>
<td></td>
<td></td>
<td>&gt;&gt;100</td>
<td>&gt;25 days</td>
</tr>
</tbody>
</table>
Estimated half life for racemization. 3Not determined (achiral by HPLC). 4Determined at 0 °C. Insufficient data to allow calculation of ΔHf and ΔSf. 5Assuming ΔSf = 0.

In marked contrast, compound 4h bearing an O-triflyl group at the ortho position of the naphthyl core showed no signs of racemization on the timescale of elution from a chiral stationary phase at room temperature. The enantiomers of 4h were therefore separated on a small scale by semi-preparative HPLC, and their interconversion was studied in isopropanol at three different temperatures: 43, 50 and 58 °C. The decrease in ee over time was monitored and plots of ln(ee) against time gave for the rate of racemisation at each temperature. Using the Eyring equation, values of ADG at room temperature could be derived along with ΔSf and ΔHf (Table 3). From these values we estimate 4h to have a half life for racemization of at least one month in solution.

We envisaged that a phosphine oxide substrate at the naphthyl 2-position might further increase the barrier to rotation, and possibly provide a valuable contrast to dihydro-QUINAP (2a, Figure 1), which was reported to be rotationally unstable at room temperature. Indeed, chiral HPLC traces of rac-4i showed no racemisation on-column at 50 °C, suggesting a half life for racemization at this temperature of at least 30 min, and hence a barrier to bond rotation of >100 kJ mol⁻¹. Phosphine oxide 4i is thus the first reported rotationally stable 1-aryl-3,4-dihydroisoquinoline. Interestingly, tertiary phosphine oxide N,P-ligands have been found to display higher catalytic activities in, for example, olefin hydroformylation reactions than their tertiary phosphine analogues, suggesting the possible use of 4i itself as a chiral ligand.

3. Conclusion

A series of rotationally restricted and axially chiral 1-aryl-3,4-dihydroisoquinolines (1-aryl-DHIQ) were readily synthesized using inter or intramolecular electrophilic aromatic substitution chemistry. Their barriers to rotation about their Ar=C-N bond were determined by means of VT-NMR, dynamic HPLC and racemisation studies. Despite significantly greater molecular flexibility than the related 1-aryl-isouquinolines, two 1-naphthyl DHIQs showed stable axial chirality at ambient temperature. Notably, trflate, as a pseudohalide, provided a much greater barrier to bond rotation than the equivalent halides (Br, I). This first report of atropisomeric 1-aryl-3,4-dihydroisoquinolines opens the door to the development of new axially chiral 3,4-dihydroisoquinoline-containing N,P ligands for asymmetric synthesis.

4. Experimental

4.1. General procedure for amide (3a-d) formation from 2-phenylethylamine and an acyl chloride.

2-Phenylethylamine (1 equiv) and Et3N (2 equiv) were added to a solution of the acyl chloride (1 equiv) in dichloromethane and the reaction mixture was stirred for 16 h at room temperature. The solvent and the excess Et3N were removed under reduced pressure. The residue was suspended in water and extracted twice in EtOAc. The combined organic layer was washed with brine and dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was used without any further purification. The experimental data for 2-chloro-N-phenethylbenzamide 3a, 2-bromo-N-phenethylbenzamide 3b, 2-iodo-N-phenethylbenzamide 3c and N-phenethyl-1-naphthamide 3d were consistent with the literature.

4.1.1. 2-Chloro-N-phenethyl-1-naphthamide (3e)

Compound 3e was prepared according to the method of Rao et al. 19 N-Phenethyl-1-naphthamide 3d (100 mg, 0.36 mmol), NCS (64 mg, 0.48 mmol), Pd(OAc)2 (6 mg, 0.018 mmol, 5 mol%) and sodium persulfate (174 mg, 0.72 mmol) were dissolved in dry 1,2-DCE (2 mL) in a flame-dried sealed vial under argon. The mixture was degassed under reduced pressure and the vessel was filled with argon. TIOH (110 mg, 0.72 mmol) was added dropwise. The reaction mixture was stirred for 32 h at 80 °C. After cooling to room temperature, the reaction was quenched by adding saturated aqueous NaHCO3. The reaction mixture was diluted with dichloromethane. The organic layer was dried over MgSO4, filtered, concentrated under reduced pressure and the crude product was purified by flash column chromatography (80:20 Pet. Ether:EtOAc) to afford the title compound as a yellow oil (62 mg, 55%); 3e: Rf (70:30 Pet. Ether:EtOAc) 0.45; IR (film, cm⁻¹): νmax = 3268, 1636 (C=O), 821; 1H NMR (400 MHz, CDCl3): δH = 7.90 (1 H, dd, J=6.2, 3.4 Hz, ArH), 7.80 (1 H, dd, J=8.2, 0.9 Hz, ArH), 7.63 (1 H, dd, J=7.6, 1.3 Hz, ArH), 7.51 - 7.47 (2 H, m, 2xArH), 7.45 - 7.42 (1 H, m, ArH), 7.34 - 7.29 (3 H, m, 3xArH), 7.23 (2 H, m, 2xArH), 5.81 (1 H, br, s, NH), 3.84 (2 H, dt, J=7.1, 6.3 Hz, NHCH2CH3Ph), 3.01 ppm (2 H, t, J=7.1 Hz, NHCH2CH3Ph); 13C [1H] NMR (100 MHz, CDCl3): δC = 171.0 (C=O), 138.8 (ArC), 135.4 (ArC), 134.3 (ArC), 130.4 (ArC), 130.2 (ArC), 130.1 (ArC), 129.0 (2xArC), 128.7 (ArC), 128.6 (ArC), 127.9 (ArC), 127.7 (ArC), 126.9 (ArC), 126.5 (ArC), 126.2 (ArC), 125.5 (ArC), 41.2 (NHCH2CH3Ph), 35.2 (NHCH2CH3Ph) ppm; HRMS (ESI+) m/z calculated for C20H17ClN2O Na⁺: 332.0813, found: 332.0820.

4.1.2. 2-Bromo-N-phenethyl-1-naphthamide (3f)

Compound 3f was prepared according to the method of Glorius et al. 15 [RhCp*Cl2]2 (0.058 g, 0.09 mmol, 2.5 mol%), AgSBF6 (0.127 g, 0.36 mmol, 10 mol%) and PirOH (0.5 ml, 4.00 mmol), 1,2-DCE (18 mL). N-phenethyl-1-naphthamide 3d (1.000 g, 3.63 mmol) and NBS (0.970 g, 5.45 mmol) were added under nitrogen to a flame-dried round-bottom flask. The reaction mixture was degassed under reduced pressure, the vessel filled with nitrogen, and the mixture heated at 65 °C for 18 h. After cooling to room temperature, diluted with EtOAc and filtered through a short pad of silica gel and eluted with EtOAc. After removal of solvent under reduced pressure, the crude product was purified by flash column chromatography (70:30 Pet. Ether:EtOAc) to afford the title compound as a white solid (1.184 g, 92%); 3f: Rf (50:50 Pet. Ether:EtOAc) 0.5; m.p. 135-137 °C; IR (film, cm⁻¹): νmax = 3264, 1639 (C=O), 1530, 760; 1H NMR (400 MHz, CDCl3): δH = 7.93 - 7.81 (3 H, m, 3xArH), 7.52 (1 H, dd, J = 7.1, 1.5 Hz, ArH), 7.50 - 7.42 (1 H, m, ArH), 7.38 - 7.28 (5 H, m, 5xArH), 7.26 - 7.20 (1 H, m, ArH), 5.84 (1 H, br, t, J = 4.8 Hz, NH), 4.07 - 3.64 (2 H, m, NHCH2CH3Ph), 3.03 ppm (2 H, t, J = 6.9 Hz, NHCH2CH3Ph); 13C [1H] NMR (125 MHz, CDCl3): δC = 170.7 (C=O), 138.8 (ArC), 135.7 (ArC), 135.6 (ArC), 133.3 (ArC), 131.7 (ArC), 130.7 (ArC), 130.5 (ArC), 128.8 (ArC), 128.7 (ArC), 128.6 (ArC), 128.1 (ArC), 128.1 (ArC), 126.6 (ArC), 126.5 (ArC), 125.4 (ArC), 119.3 (ArC), 41.4 (NHCH2CH3Ph), 35.1 (NHCH2CH3Ph) ppm; HRMS (ESI+) m/z calculated for C20H16BrN2O Na⁺: 376.0307, found: 376.0324.

4.1.3. 2-Iodo-N-phenethyl-1-naphthamide (3g)

Compound 3g was prepared according to the method of Glorius et al. 15 [RhCp*Cl2]2 (9.35 g, 0.0014 mmol, 1 mol%), AgSBF6 (20.4 mg, 0.058 mmol, 4 mol%), PirOH (165 mg, 1.598 mmol), 1,2-DCE (7.3 mL), N-phenethyl-1-naphthamide 3d (400 mg, 1.453 mmol) and NIS (0.360 g, 1.598 mmol). The reaction mixture was heated at 60 °C for 16 h. The crude product was purified by flash column chromatography (70:30 Pet. Ether:EtOAc) to afford the title compound as a yellow solid (199
mg, 34%); 3g: Rf (60-40 Pet. Ether:EtOAc) 0.4; m.p. 138-140 °C; IR (film, cm⁻¹): v max = 3297, 1632 (C=O), 1538, 532; ¹H NMR (300 MHz, CDCl₃): δH = 8.24 (1 H, dd, J = 7.3, 1.1 Hz, ArH), 7.89 - 7.90 (2 H, m, 2xArH), 7.56 - 7.59 (1 H, m, ArH), 7.47 - 7.47 (1 H, m, ArH), 7.36 - 7.20 (5 H, 5xArH), 7.15 (1 H, t, J = 7.7 Hz, ArH), 5.94 (1 H, br. t, J = 5.2 Hz, NH), 3.83 (2 H, br. m, NHCF₂CH₂Ph), 3.03 (2 H, t, J = 7.1 Hz, NHCH₂CH₂Ph) ppm; ¹³C [¹H] NMR (100 MHz, CDCl₃): δC = 169.8 (C=O), 141.9 (ArC), 139.7 (ArC), 138.8 (ArC), 137.7 (ArC), 137.4 (ArC), 135.3 (ArC), 131.3 (ArC), 130.5 (ArC), 129.7 (ArC), 128.8 (ArC), 128.7 (ArC), 128.3 (ArC), 127.1 (ArC), 126.6 (ArC), 125.2 (ArC), 92.0 (Ar-C), 41.6 (NHCH₂CH₂Ph), 35.0 (NHCH₂CH₂Ph) ppm; HRMS (ESI+) m/z calcd for C₉H₁₀NO₂N [M+Na⁺]: 424.0189, found: 424.0155.

4.2. General procedure for cyclodehydration of amides 3a-g to 1-aryl-3,4-dihydroisoquinolines 4a-g.

The cyclodehydration of amides 3a-g was performed according to the method of Movassaghi et al. [19]. The experimental data for 1-(2-chlorophenyl)-3,4-dihydroisoquinoline 4a, [20] 1-(2-bromophenyl)-3,4-dihydroisoquinoline 4b, [21] and 1-(2-bromophenyl)-3,4-dihydroisoquinoline 4c were in accordance with the literature.

4.2.1. 1-(Naphthalen-1-yl)-3,4-dihydroisoquinoline (4d).

General procedure for cyclodehydration of amides was followed: amide 3d (1.000 g, 3.63 mmol), trifluoromethanesulfonic anhydride (0.69 mL, 4.00 mmol), 2-chloropyridine (0.42 mL, 4.36 mmol) in dichloromethane (18 mL). The reaction mixture was refluxed for 2 h. The crude product was purified by flash column chromatography (70:30:1 Pentane:EtOAc:Et₃N) to afford the title compound as a white solid (0.752 g, 80%); Rf (70:30 Pet. Ether:EtOAc): 0.3; m.p. 135-136 °C; IR (film, cm⁻¹): v max = 1613 (C=O), 759; ¹H NMR (400 MHz, CDCl₃): δH = 7.87 - 7.87 (2 H, m, 2xArH), 7.73 (1 H, d, J = 8.4, 0.9 Hz, ArH), 7.58 – 7.52 (2 H, m, 2xArH), 7.47 (1 H, ddd, J = 8.2, 6.8, 1.3 Hz, ArH), 7.37 (2 H, tdd, J = 7.3, 4.7, 1.4 Hz, Ar₂H), 7.31 (1 H, dd, J = 7.5, 1.3 Hz, ArH), 7.09 (1 H, td, J = 7.5, 1.4 Hz, ArH), 6.87 (1 H, dd, J = 7.7, 1.3 Hz, ArH), 4.06 (2 H, br. m, J = 5.2 Hz, NCH₂CH₂Ar), 2.98 ppm (2 H, t, J = 7.5 Hz, NCH₂CH₂Ar); ¹³C [¹H] NMR (100 MHz, CDCl₃): δC = 165.8 (C=N), 137.3 (ArC), 136.7 (ArC), 135.8 (ArC), 133.1 (ArC), 131.7 (ArC), 130.4 (ArC), 130.3 (ArC), 129.9 (ArC), 129.8 (ArC), 128.7 (ArC), 127.5 (ArC), 127.2 (ArC), 126.2 (ArC), 126.1 (ArC), 126.5 (ArC), 119.7 (Ar-C), 47.8 (NCH₂CH₂Ar), 25.3 (NCH₂CH₂Ar) ppm; HRMS (ESI+) m/z calcd for C₁₃H₁₂NBrNa [M+Na⁺]: 358.0202, found: 358.0206.

4.2.4. 1-(2-Iodonaphthalen-1-yl)-3,4-dihydroisoquinoline (4g).

General procedure for cyclodehydration of amides was followed: amide 3g (0.195 g, 0.56 mmol), trifluoromethanesulfonic anhydride (0.13 mL, 0.62 mmol), 2-chloropyridine (78 µL, 0.68 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at 45 °C for 16 h. The crude product was purified by flash column chromatography (70:30:1 Pentane:EtOAc:Et₃N) to afford the title compound as a yellow oil (0.166 g, 90%); 4f: Rf (70:30 Pet. Ether:EtOAc): 0.3; IR (film, cm⁻¹): v max = 2928, 1298, 821, 764; ¹H NMR (500 MHz, CDCl₃): δH = 7.94 (1 H, dd, J = 7.0, 2.5 Hz, ArH), 7.89 (1 H, dd, J = 8.2, 1.3 Hz, ArH), 7.80 (1 H, dd, J = 7.4, 1.2 Hz, ArH), 7.58 - 7.50 (2 H, m, 2xArH), 7.35 (1 H, td, J = 7.4, 1.3 Hz, ArH), 7.28 (2 H, m, 2xArH), 7.09 (1 H, td, J = 7.6, 1.3 Hz, ArH), 6.81 (1 H, dd, J = 7.6, 1.2 Hz, ArH), 4.07 (2 H, m, NCH₂CH₂Ar), 2.99 (2 H, m, NCH₂CH₂Ar) ppm; ¹³C [¹H] NMR (125 MHz, CDCl₃): δC = 168.5(C=N), 137.3 (ArC), 136.7 (ArC), 135.8 (ArC), 133.1 (ArC), 131.7 (ArC), 130.4 (ArC), 130.3 (ArC), 129.9 (ArC), 129.8 (ArC), 128.7 (ArC), 127.5 (ArC), 127.2 (ArC), 126.2 (ArC), 126.1 (ArC), 126.5 (ArC), 119.7 (Ar-C), 47.8 (NCH₂CH₂Ar), 25.3 (NCH₂CH₂Ar) ppm; HRMS (ESI+) m/z calcd for C₁₃H₁₂NBrNa [M+Na⁺]: 358.0202, found: 358.0206.

4.3. 1-(3,4-Dihydroisoquinolin-1-yl)naphthalen-2-yl trifluoromethanesulfonate (4h).

Compound 4h was prepared from 2-naphthol (1.33 g, 9.10 mmol) and 3,4-dihydroisoquinoline (1.19 g, 9.10 mmol) according to the synthetic route reported by Li et al. [22]. The crude product was purified by flash column chromatography to afford the title compound as a clear oil (3.13 g, 85% overall yield); Rf (70:30:1 Pet. Ether:EtOAc:Et₃N) 0.6; IR (film, cm⁻¹): v max = 1618 (C=N),
4.4. (13,4-Dihydroisooquinolin-1-yl)naphthalen-2-yl)diphenylphosphine oxide (4i)

Compound 4i was prepared according to the method of Miakami et al.17 Dimethylsulfide (8 mL) and diisopropylphtylylene (1.29 mL, 7.4 mmol) were added to a mixture of 1-aryl-3,4-
dihydroisooquinoline 4h (600 mg, 1.48 mmol), diphenylphosphate oxide (617 mg, 2.96 mmol), palladium diacetate (33 mg, 0.15 mmol), and 1,3-bis(diphenylphosphino)propane (dppp; 94 mg, 0.22 mmol, 15 mol%), and the mixture was heated with stirring at 100 °C for 22 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with water, dried over MgSO4, and concentrated again under reduced pressure. The crude product was purified by flash column chromatography (EtOAc:MeOH 95:5) to afford the title compound as a yellow solid (0.508 g, 75%); 4i: Rf (95.5% EtOAc:MeOH) 0.6; m.p. 97-98 °C; IR (film, cm⁻¹): vmax = 1629 (C=O), 1196; 1H NMR (400 MHz, CDCl3): δ = 8.78 (2 H, dd, 6=8.6, 1.3 Hz, 2xArH), 7.17 (1 H, d, 6=7.7 Hz, ArH). 6.8 (1 H, t, 6=7.4, 1.3 Hz, ArH) and 6.59 (1 H, d, 6=7.1 Hz, ArH). 3.81 (2 H, m, NCH2CH2Ar); 2.08 ppm (1 H, d, 6=16.0, 7.0 Hz, NCH2CH2Ar); 1H NMR (100 MHz, CDCl3): δc = 166.3 (Ar-C=O), 143.3 (Ar, d, J=1.5, 10.14). 1H NMR (500 MHz, CDCl3): δ = 8.80 (1 H, d, 6=7.0 Hz, ArH) and 7.75 (1 H, d, 6=8.1 Hz, ArH), 7.56 (1 H, ddd, 6=8.2, 6.8, 1.2 Hz, ArH), 7.51 - 7.46 (2 H, 2xArH), 7.38 (1 H, td, 6=7.5, 1.3 Hz, ArH), 7.31 (1 H, dd, 6=7.5, 1.2 Hz, ArH), 7.09 (1 H, td, 6=7.5, 1.2 Hz, ArH), 6.75 (1 H, dd, 6=7.6, 1.2 Hz, ArH), 4.19 - 4.05 (2 H, m, NCH2CH2Ar); ppm; 13C NMR (125 MHz, CDCl3); δ = 162.7 (C=N), 144.6 (ArC), 137.3 (ArC), 132.6 (ArC), 131.6 (ArC), 131.1 (ArC), 129.7 (ArC), 129.3 (ArC), 128.4 (ArC), 128.0 (ArC), 127.8 (ArC), 127.3 (ArC), 127.3 (ArC), 127.1 (ArC), 126.3 (ArC), 119.8 (ArC), 119.4 (ArC), 117.3 (ArCOSO2CF3); 1H NMR (500 MHz, CDCl3): δc = 8.80 (1 H, d, 6=7.0 Hz, ArH) and 7.75 (1 H, d, 6=8.1 Hz, ArH), 7.56 (1 H, ddd, 6=8.2, 6.8, 1.2 Hz, ArH), 7.51 - 7.46 (2 H, 2xArH), 7.38 (1 H, td, 6=7.5, 1.3 Hz, ArH), 7.31 (1 H, dd, 6=7.5, 1.2 Hz, ArH), 7.09 (1 H, td, 6=7.5, 1.2 Hz, ArH), 6.75 (1 H, dd, 6=7.6, 1.2 Hz, ArH), 4.19 - 4.05 (2 H, m, NCH2CH2Ar); ppm; 13C NMR (125 MHz, CDCl3); δ = 162.7 (C=N), 144.6 (ArC), 137.3 (ArC), 132.6 (ArC), 131.6 (ArC), 131.1 (ArC), 129.7 (ArC), 129.3 (ArC), 128.4 (ArC), 128.0 (ArC), 127.8 (ArC), 127.3 (ArC), 127.3 (ArC), 127.1 (ArC), 126.3 (ArC), 119.8 (ArC), 119.4 (ArC), 117.3 (ArCOSO2CF3); 1H NMR (500 MHz, CDCl3): δc = 8.80 (1 H, d, 6=7.0 Hz, ArH) and 7.75 (1 H, d, 6=8.1 Hz, ArH), 7.56 (1 H, ddd, 6=8.2, 6.8, 1.2 Hz, ArH), 7.51 - 7.46 (2 H, 2xArH), 7.38 (1 H, td, 6=7.5, 1.3 Hz, ArH), 7.31 (1 H, dd, 6=7.5, 1.2 Hz, ArH), 7.09 (1 H, td, 6=7.5, 1.2 Hz, ArH), 6.75 (1 H, dd, 6=7.6, 1.2 Hz, ArH), 4.19 - 4.05 (2 H, m, NCH2CH2Ar); ppm; HRMS (ESI+) m/z calc'd for C67H51F3N4O5P [M+Na]+: 1120.3428, found: 1120.3394. HPLC: Chiralpak® AD-H, n-Hex:IPA = 80:20, T = 25 °C; flow = 1 mL/min, λ = 254 nm, tR,A = 4.8 min, tR,B = 8.2 min.

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References and notes
