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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.

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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.

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1. Introduction

The majority of axially chiral compounds are biaryl, whether biphenyls or binaphthyls or their heterocyclic counterparts. Particularly valuable are biaryl containing the isoquinoline ring, which function as atropisomeric chiral ligands because their basic nitrogen atom allows bidentate coordination in P,N ligands such as QUINAP (Figure 1). QUINAP is the ligand of choice in many asymmetric reactions, including asymmetric hydrobrominations, diberations, 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 diastereomeric 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 Movassaghi et al. Amide 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-aryl ring.

Figure 1. Bond rotations in 1-naphthylisoquinolines and their 3,4-dihydroisoquinolines analogues.

Although 1-aryl-DHIQs are more conformationally flexible than the related fully aromatic isoquinolines, and evidently display lower barriers to rotation, they do show potential for atropisomerism and could provide a new class of axially chiral compounds with potential applications as ligands or building blocks for asymmetric synthesis or chiral ligands. QUINAP is typically produced in enantiomerically pure form by classical resolution. Methods have also been reported for its asymmetric synthesis by dynamic resolution techniques, relying on the control of the kinetics and thermodynamics of bond rotation. Further interest arises from the possibility of using redox interconversions between QUINAP and its partially saturated analogues to control dynamic resolution processes. In this paper we describe our investigation into the control of rotational barriers in 1-aryl-3,4-dihydroisoquinolines as a potential new class of non-biaryl atropisomers.
Table 1. Line shape analysis in the VT NMR study of 4b

<table>
<thead>
<tr>
<th>T / ºC</th>
<th>Experimental line shape</th>
<th>Modeled line shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td><img src="image" alt="" /></td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="" /></td>
<td>20</td>
</tr>
<tr>
<td>0</td>
<td><img src="image" alt="" /></td>
<td>57</td>
</tr>
<tr>
<td>20</td>
<td><img src="image" alt="" /></td>
<td>220</td>
</tr>
<tr>
<td>30</td>
<td><img src="image" alt="" /></td>
<td>550</td>
</tr>
</tbody>
</table>

These rates were analyzed using the Eyring equation, allowing calculation of the barrier to bond rotation ($\Delta G^\ddagger$) and an estimation the half life for racemization ($t_{1/2}$) 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 ºC in 1,2-dichlorobenzene-d$_4$. 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 we explored showed a single peak, even on cooling the column to 0 ºC. 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 stationary phase, eluting with n-hexane/isopropanol (60:40). Peak profiles were monitored at 20, 30 and 40 ºC (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 atropisomeric$^{22}$ at 25 ºC ($\Delta G^\ddagger_{298} = 92.6$ kJ mol$^{-1}$; $t_{1/2} = 900$ 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 / ºC</th>
<th>Observed peak shape</th>
<th>k / 10$^3$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td><img src="image" alt="" /></td>
<td>4.5</td>
</tr>
<tr>
<td>30</td>
<td><img src="image" alt="" /></td>
<td>7.1</td>
</tr>
<tr>
<td>40</td>
<td><img src="image" alt="" /></td>
<td>9.9</td>
</tr>
</tbody>
</table>

Similar approximate analysis of the DHPLC trace of 4g around 0 ºC 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>$\Delta H^\ddagger$ / kJ mol$^{-1}$</th>
<th>$\Delta S^\ddagger$ / J mol$^{-1}$ K$^{-1}$</th>
<th>$\Delta G^\ddagger_{298}$ / kJ mol$^{-1}$</th>
<th>$t_{1/2}^{298}$ s</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Cl</td>
<td>56.6</td>
<td>-9</td>
<td>59.2</td>
<td>$\approx 10^3$ s</td>
</tr>
<tr>
<td>4b</td>
<td>Br</td>
<td>50.7</td>
<td>-26</td>
<td>58.4</td>
<td>$&lt; 10^2$ s</td>
</tr>
<tr>
<td>4c</td>
<td>I</td>
<td>64.0</td>
<td>+20</td>
<td>57.9</td>
<td>$&lt; 10^2$ s</td>
</tr>
<tr>
<td>4d</td>
<td>H</td>
<td>55.1</td>
<td>+1</td>
<td>54.7</td>
<td>$&lt; 10^3$ 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>10.7</td>
<td>+14.5</td>
<td>103.1</td>
<td>36 days</td>
</tr>
<tr>
<td>4g</td>
<td>I</td>
<td>10.7</td>
<td>+14.5</td>
<td>103.1</td>
<td>36 days</td>
</tr>
<tr>
<td>4j</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)Ph$_2$</td>
<td>-</td>
<td>-</td>
<td>$&gt; 100$</td>
<td>$&gt; 25$ days</td>
</tr>
</tbody>
</table>
In marked contrast, compound 4b 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 4b 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(εε) against time gave for the rate of racemisation at each temperature. Using the Eyring equation, 4εε at room temperature. Indeed, chiral HPLC traces 2a may be used to confirm the lack of racemization at this temperature of at least one month in solution.

We envisaged that a phosphine oxide substituent 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,N-dimethyl derivatives have been shown 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–CN bond were determined by means of VT-NMR, dynamic HPLC and racemization studies. Despite significantly greater molecular flexibility than the related 1-aryl-isoquinolines, two 1-naphthyl DHIQs showed stable axial chirality at ambient temperature. Notably, triflate, 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 Et₂N (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 Et₂N 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, 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. 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): 6 = 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 calced for C₂₀H₁₆ClNOnO [M+N⁺]: 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. [RhCp*Cl₂] (0.058 g, 0.09 mmol, 2.5 mol%), AgSbF₆ (0.127 g, 0.36 mmol, 10 mol%) and PivOH (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 without solvent 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 filtration and cooling to room temperature, the solution was 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): 6 = 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 calced for C₂₁H₁₃BrNO₂Na [M+N⁺Na⁺]: 376.0307, found: 376.0294.

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

Compound 3g was prepared according to the method of Glorius et al. [RhCp*Cl₂] (9.3 mg, 0.0014 mmol, 1 mol%), AgSbF₆ (20.4 mg, 0.058 mmol, 4 mol%), PivOH (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
The reaction mixture was refluxed for 2 h. The crude product was purified by flash column chromatography (70:30:1 Pent:EtOAc:Et(N) to afford the title compound as a white solid (0.752 g, 80%); Rf=70:30 Pet. Ether:EtOAc 0.3; IR (film, cm⁻¹)ν: max= 2934, 1576, 1411, 1367, 1278, 1173; 1H NMR (400 MHz, CDCl₃): δ= 7.86, 7.84 (2 H, m, ArH), 7.39 (1 H, d, ArH, J= 7.8 Hz, ArH). 7.27 (1 H, d, t, J= 7.8 Hz, ArH, 4.07 (1 H, m, ArH), 2.88 (2 H, m, NCH₂), 1.3 Hz, ArH), 4.01 (2 H, m, NCH₂), 2.98 ppm (2 H, t, J = 7.5 Hz, NCH₂CH₂Ar). IR (film, cm⁻¹)λ max= 1576, 1411, 1367, 1278, 1173; 1H NMR (400 MHz, CDCl₃): δ= 7.86, 7.84 (2 H, m, ArH), 7.39 (1 H, d, ArH, J= 7.8 Hz, ArH). 7.27 (1 H, d, t, J= 7.8 Hz, ArH, 4.07 (1 H, m, ArH), 2.88 (2 H, m, NCH₂), 1.3 Hz, ArH), 4.01 (2 H, m, NCH₂), 2.98 ppm (2 H, t, J = 7.5 Hz, NCH₂CH₂Ar). IR (film, cm⁻¹)λ max= 1576, 1411, 1367, 1278, 1173; 1H NMR (400 MHz, CDCl₃): δ= 7.86, 7.84 (2 H, m, ArH), 7.39 (1 H, d, ArH, J= 7.8 Hz, ArH). 7.27 (1 H, d, t, J= 7.8 Hz, ArH, 4.07 (1 H, m, ArH), 2.88 (2 H, m, NCH₂), 1.3 Hz, ArH), 4.01 (2 H, m, NCH₂), 2.98 ppm (2 H, t, J = 7.5 Hz, NCH₂CH₂Ar).
1420, 1200, 1140; 1H NMR (500 MHz, CDCl3); δH = 8.00 (1 H, d, J=9.0 Hz, ArH), 7.95 (1 H, d, J = 8.1 Hz, ArH), 7.70 (1 H, dd, J=8.4, 1.0 Hz, ArH), 7.56 (1 H, ddd, J = 8.2, 6.8, 1.2 Hz, ArH), 7.51 - 7.46 (2 H, m, 2xArH), 7.38 (1 H, td, J=7.5, 1.3 Hz, ArH), 7.31 (1 H, dd, J=7.5, 1.2 Hz, ArH), 7.09 (1 H, td, J=7.5, 1.2 Hz, ArH), 6.75 (1 H, dd, J=7.6, 1.2 Hz, ArH), 4.19 - 4.05 (2 H, m, NCH2HCNAr), 3.09 - 2.93 (2 H, m, NCH2CH2Ar) ppm; 13C [1H] NMR (125 MHz, CDCl3); δC = 162.7 (C-N), 144.6 (Ar), 137.3 (Ar), 132.6 (Ar), 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 (ArCSO2CF3), 48.1 (NCH2CH2Ar), 25.7 (NCH2CH2Ar); HRMS (ESI+) m/z calc'd for C2H21F2N5O6S Na+[M+Na+] = 482.0539, found: 482.0544.


4.4. (1,3,4-Dihydroisooquinolin-1-yl)napthalen-2-yl)diphenylphosphine oxide (4i)

Compound 4i was prepared according to the method of Mikami et al.17 Dimethylsulfoxide (8 mL) and diisopropylphenylamine (1.29 mL, 7.4 mmol) were added to a mixture of 1-aryl-3,4-dihydroisooquinoline 4h (600 mg, 1.48 mmol), diphenylphosphine 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); δmax = 1629 (C=N), 1196; 1HM NMR (400 MHz, CDCl3); δH = 7.88 (2 H, dd, J=8.6, 1.3, 2xArH), 7.71 (1 H, d, J=8.8 Hz, ArH), 7.65 - 7.50 (6 H, m, 6xArH), 7.50 - 7.31 (7 H, m, 7xArH), 7.23 (1 H, td, J=7.3, 1.0 Hz, ArH), 7.17 (1 H, dd, J=7.3, 0.5 Hz, ArH), 6.88 (1 H, td, J=7.4, 1.3 Hz, ArH), 6.59 (1 H, d, J=7.1 Hz, ArH), 3.81 (2 H, m, NCH2CH2Ar), 3.01 (1 H, dt, J=16.0, 8.0 Hz, NCH2CH2Ar), 2.81 ppm (1 H, dt, J=16.0, 7.0 Hz, NCH2CH2Ar); 13C [1H] NMR (100 MHz, CDCl3); δC = 166.3 (ArC=O), δC, (J =13C,13P) = 4.0 Hz), 143.3 (Ar, δC, (J =13C,13P) = 8.0 Hz), 136.8, 134.6, 134.6, 133.5, 132.3, 132.1, 132.0, 131.9, 131.4, 131.4, 130.8, 130.4, 128.6, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.7, 127.5, 127.3, 127.2, 127.1, 126.7, 126.3, 47.5 (NCH2CH2Ar), 25.4 (NCH2CH2Ar) ppm; 31P [1H] NMR (162 MHz, CDCl3); δP = 29.6 ppm. HRMS (ESI+) m/z calc’d for C13H11F2N3O5P Na+[M+Na+] = 480.1488, found: 480.1475. HPLC: (R,R)-Whelk-O1, n-Hex:IPA = 60:40, T = 50 °C, flow = 1 mL/min, λ = 254 nm, tR,A = 6.8 min, tR,B = 10.2 min.

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References and notes


(continued)