A radical addition/cyclization of diverse ethers to 2-isocyanobiaryls under mildly basic aqueous conditions†

Cintia Anton-Torrecillas, Diego Felipe-Blanco and Jose C. Gonzalez-Gomez*

Mildly basic aqueous conditions facilitated the tert-butyl peroxybenzoate (TBPB) mediated dehydrogenative addition of a range of ethers, including acetals, to diverse substituted 2-isocyanobiaryls. Mechanistic studies suggest that this radical cascade is an example of base promoted homolytic aromatic substitution (BHAS).

Introduction

Phenanthridine is the scaffold of many naturally occurring products† that exhibit a wide range of bioactivities, such as antitumor,2 antituberculosis,3 antimicrobial,4 antiviral,5 acaricidal,6 and fungicidal activities.7 Some phenanthridine derivatives have also found application in biological chemistry as dyes for cytofluorometric assays8 or even in materials science due to their optoelectronic properties.9 Recently, the assembly of the phenanthridine framework has been elegantly achieved with a cascade that involves the addition of radicals to somophilic 2-isocyanobiphenyls, followed by intramolecular homolytic aromatic substitution.10,11 In this context, and given the progress made in the Cα–H oxidation of ethers with peroxides to form radicals,12 the oxidative addition of ethers to 2-isocyanobiphenyls has been successfully achieved using different conditions.13 This transformation requires a dual selective C–H bond functionalization, and constitutes a powerful tool to increase molecular complexity with high atom-economy, where only hydrogen is lost (Scheme 1). Moreover, ethers are very important raw materials and they are also common substructures of natural and synthetic bioactive products.14 Consequently, the development of methods that make use of relatively unreactive ethers to build complex molecules, is highly demanded by organic and medicinal chemists.

It is worth noting that 1,4-dioxane is the model substrate for C–H bond functionalization of ethers in most of the reported studies.13 This symmetric ether presents all eight C–H bonds adjacent to an oxygen atom, which stabilizes the radical by hyperconjugation with the non-bonding electrons. Moreover, theoretical studies suggest that the release of ring strain upon radical formation is greater in 1,4-dioxane than in other cyclic ethers such as tetrahydrofuran.15 As a matter of fact, when TBPB was used as the oxidant in the insertion of 2-isocyanobiaryls with ethers, only 1,4-dioxane was successful and THF failed.13b Notably, when benzoyl peroxide was used in the same transformation, another three ethers could be inserted with moderate results (40–45%).13a To the best of our knowledge, the greatest number of ethers tolerated in this reaction (seven examples) has been possible with the use of DTBP as the oxidant, FeCl3 as the catalyst and DBU as the co-catalyst.13a With these precedents we decided to develop a new protocol for this reaction aimed at accommodating a range of ethers, free of transition-metal catalysts and using economical and environmentally friendly conditions (Scheme 2).

Results and discussion

To explore new reaction conditions we selected 2-isocyanobiphenyl (1a) and THF (2a) as model substrates. In a control experiment we performed the reaction using BPO as the oxidant at 100 °C and we obtained 35% yield of the desired

†Electronic supplementary information (ESI) available: Experimental details for mechanistic studies and copies of NMR spectra. See DOI: 10.1039/c6ob02103d
product 3aa, a similar result to the one obtained by the Cheng group,\textsuperscript{13b} together with byproduct 4a (Table 1, entry 1). Surprisingly, the addition of K$_2$CO$_3$ and H$_2$O completely inhibited the formation of 3aa (entry 2). Prompted by the excellent results in oxidative transformations achieved with Bu$_4$NI as the catalyst and TBHP,\textsuperscript{16} we tried this combination, but 3aa was obtained in low yield (entry 3). The use of DTBP or (NH$_4$)$_2$S$_2$O$_8$ in combination with Bu$_4$NI was also unsuccessful in this transformation (entries 4–6). It is reported that TBPB fails to afford product 3aa in this reaction and that only compound 4a is obtained.\textsuperscript{13a} To our surprise, the inclusion of H$_2$O in this reaction mixture afforded product 3aa, although in low yield (entry 7). We were pleased to find that the same oxidant, but in the presence of K$_2$CO$_3$ and H$_2$O, allowed full conversion of 1a to obtain compound 3aa in good yield (entry 10). While the addition of Bu$_4$NI had no important impact on the reaction, the amount of base and the control of the reaction temperature were crucial to obtain good and reliable results (entries 8–11). Similar results were obtained with Na$_2$HPO$_4$, and lower yields were obtained for the desired product when non-nucleophilic organic bases were used in substoichiometric amounts (entries 12–14).

Having found very simple optimized conditions for the model reaction, we evaluated its scope using different 2-isocyanobiaryls and THF (Scheme 3). We first examined substrates with substituents on the upper aromatic ring. Methyl-substituted products 3ba and 3ca were obtained in good to moderate yields. During the formation of 3ca, some compound 3aa was also observed (GC-MS), likely by ipso-homolytic aromatic substitution, and its isolated yield was affected due to difficulties in the chromatographic purification. A more electron-donating group such as methoxy was compatible with this protocol, affording compound 3da in reasonably good yield, as well as the corresponding byproduct 4d (detected by GC-MS and $^1$H-NMR).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Screening of reaction conditions</th>
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<tbody>
<tr>
<td>Entry</td>
<td>Oxidant (mol%)/additive (mol%)</td>
</tr>
<tr>
<td>1$^c$</td>
<td>BPO (120)</td>
</tr>
<tr>
<td>2</td>
<td>BPO (120)</td>
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<tr>
<td>3</td>
<td>TBHP (300)/Bu$_4$NI (20)</td>
</tr>
<tr>
<td>4</td>
<td>DTBP (300)/Bu$_4$NI (20)</td>
</tr>
<tr>
<td>5</td>
<td>DTBP (300)/Bu$_4$NI (20)</td>
</tr>
<tr>
<td>6</td>
<td>(NH$_4$)$_2$S$_2$O$_8$ (220)</td>
</tr>
<tr>
<td>7</td>
<td>TBHP (220)</td>
</tr>
<tr>
<td>8</td>
<td>TBHP (120)/Bu$_4$NI (20)</td>
</tr>
<tr>
<td>9</td>
<td>TBHP (220)</td>
</tr>
<tr>
<td>10$^c$</td>
<td>TBHP (220)</td>
</tr>
<tr>
<td>11</td>
<td>TBHP (220)/Bu$_4$NI (50)</td>
</tr>
<tr>
<td>12</td>
<td>TBHP (220)</td>
</tr>
<tr>
<td>13$^c$</td>
<td>TBHP (220)</td>
</tr>
<tr>
<td>14$^c$</td>
<td>TBHP (220)</td>
</tr>
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</table>

$^a$ By GC of the crude reaction mixture. $^b$ Yield calculated by $^1$H-NMR of the crude reaction mixture using durene as the internal standard. $^c$ Formation of other products is observed by GC. $^d$ The conversion was 90% at 80 °C and 0% at 60 °C. BPO = benzoyl peroxide. DTBP = di-tert-butylperoxide. TBHP = tert-butyl peroxybenzoate. DABCO = 1,4-diazabicyclo[2.2.2]octane. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.
When 2-(2-isocyanophenyl)-naphthalene was used, compound 3ea was the only regioisomer isolated in moderate yield, despite the steric hindrance between the ether moiety and the extra aromatic ring. Electron-withdrawing groups, such as acetyl, trifluoromethyl, chloro and fluoro, were suitable substituents in the upper aromatic ring, furnishing products (3fa, 3ga, 3ha and 3ia) in good isolated yields. Interestingly, when meta-substituted substrates 1j and 1k were used, both possible regioisomers were isolated after column chromatography. While the ratio of 3ja/3′ja was 1 : 1, for 1k the major product was the most crowded regioisomer (3ka).18 We also examined isocyanobiaryls substituted in the lower aromatic ring by electron-donating and electron-withdrawing groups, obtaining uniformly moderate yields in all cases (3la–3oa).

We further explore the performance of different ethers using the optimized procedure (Scheme 4). 1,4-Dioxane (2b) and THP (2c) were also suitable for this protocol, obtaining products 3ab and 3ac in moderate yields after purification, as well as compound 4a as the byproduct. With THP, minor amounts of regioisomers were formed (see the ESI† for GC-MS of isomers), complicating the isolation of 3ac in a pure form. Acyclic ethers such as i-Pr2O (2d), n-Bu2O (2e) and t-BuOMe (2g) afforded the corresponding products in good to excellent yields, with linear n-Bu2O providing the best yield. 2-MeTHF (2f) was also examined, affording the more substituted compound 3af as the major product and regioisomer 3′af as an inseparable trans/cis mixture. Surprisingly, when Bn2O (2h) was examined, the expected product (3ah) was obtained in only 17% yield and the addition of a benzyl radical took place preferentially (3′ah). It seems reasonable that after H-abstraction from Bn2O, a β-fragmentation gives rise to the benzyl radical, which is finally added to 1a. The addition of phthalan (2i) was also possible, but compound 3ai was obtained in lower yield. Importantly, acetals 2j and 2k led, respectively, to products 3aj and 3ak in synthetically useful yields. These compounds could be easily hydrolyzed to obtain the corresponding 6-formylphenanthridine and the acetal moiety has the potential to be transformed into other functionalities.19

Investigation of the reaction mechanism
To gain insight into the reaction mechanism we performed some experiments. As shown in Scheme 5a, the use of TEMPO as a radical scavenger in our model reaction, under standard conditions, completely inhibited the formation of 3aa and the coupling product 5 was detected by MS. Since compounds 4 are consistent byproducts of the radical cyclization studied here, we were intrigued about their formation and we have not found any experimental evidence of this in the literature.20

When the reaction was conducted using D2O and D8-THF (Scheme 5b), the expected product D7-3aa was obtained,
accompanied by phenanthridine 4a. Importantly, the byproduct of this reaction is not deuterated, indicating that neither THF nor H$_2$O is the source of hydrogen for the formation of this phenanthridine. We also studied the intermolecular kinetic isotope effect (KIE) by competition experiments of equimolar amounts of THF and D$_2$THF with 1a at the initial stage of the reaction (Scheme 5c). The large KIE obtained ($k_d/k_s = 3.16$) suggests that the cleavage of the C(sp$^3$)-H bond is involved in the rate determining step of this reaction. In addition, we also performed competition experiments at the initial state of the reaction, using equimolar quantities of 1a and 2-isocyanobiphenyls substituted in position 4 with methyl or fluoro groups. The results shown in Scheme 4d suggested that electron-withdrawing substituents in the upper aromatic ring accelerate the reaction. Since this class of group stabilizes the LUMO of the upper aromatic ring, this result is also consistent with a radical cyclization pathway.

An important feature of this protocol is the crucial role of K$_2$CO$_3$ and H$_2$O in a successful transformation (Table 1, entries 6 and 9). Since the seminal contribution of Studer and Curran, several known reactions have been recognized as “base promoted homolytic substitutions” (BHAS) and many new transformations have been developed with this concept. Based on literature precedents and our own results, we believe that this reaction is an example of BHAS. A possible reaction mechanism is depicted in Scheme 6. Firstly, homolysis of TBPB takes place upon heating. From the two generated radicals, it is reported that $t$-BuO$^-$ abstracts a hydrogen atom from THF faster than Bz$^-$ to generate the α-furanyl radical. Addition of this intermediate to isonitrile 1a, followed by intramolecular addition to the upper aromatic ring, is well documented in a number of examples. DFT studies performed by the Studer group indicate that cyclohexadienyl radicals, such as I, are extremely strong acids ($pK_a \sim -15$ in H$_2$O). Therefore, this radical intermediate can be deprotonated under mild basic aqueous conditions (e.g. K$_2$CO$_3$ in H$_2$O) to generate a radical anion II. This species is a potent reductant that can easily transfer an electron to radical Bz$^-$ or to oxidant TBPB, while generating product 3aa. In addition, intermediate I can transfer a hydrogen atom to 1a, which after a similar BHAS process leads to the formation of byproduct 4a. This explanation is consistent with our observation that neither THF nor H$_2$O was the hydrogen source of 4a.

Conclusions

In conclusion, we have demonstrated that TBPB can be used under mildly basic aqueous conditions to promote the radical addition of a range of ethers to 2-isocyanobiaryls followed by cyclization. Mechanistic investigations suggest that this transformation is an example of BHAS and a plausible explanation is provided for the formation of byproduct 4. Some salient features of the developed methodology are: (a) neither transition metals nor any expensive additives are needed; (b) the wastes generated are harmless inorganic salts and can be easily removed by aqueous workup; (c) the reaction medium is constituted by the reactant ethers and water.

Experimental section

General remarks

All starting isonitrides were prepared according to a reported method. TLC was performed on silica gel 60 F$_{254}$ using aluminium plates and visualized by exposure to ultraviolet light. Flash chromatography was carried out on hand-packed columns of silica gel 60 (230–400 mesh). Infrared (IR) spectra were recorded with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm$^{-1}$. LRMS analyses were carried out using a mass spectrometer coupled with a gas chromatograph (GC); the mobile phase was helium (2 mL min$^{-1}$); HP-1 column of 12 m was used; temperature program starts at 80 °C for 3 min, then up to 270 °C at a rate of 20 °C min$^{-1}$, and 17.5 min at 270 °C. HRMS analyses were carried out using Electron Impact (EI) mode at 70 eV by Q-TOF. $^1$H NMR spectra were recorded at 300 or 400 MHz for $^1$H-NMR and 75 or 100 MHz for $^{13}$C-NMR, using CDCl$_3$ as the solvent and TMS as an internal standard (0.00 ppm). The data are being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration). $^{13}$C-NMR spectra were recorded with $^1$H-decoupling at 100 MHz and referenced to CDCl$_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH$_2$ and CH$_3$.

General procedure for the synthesis of compounds 3

Into a pressure tube were added K$_2$CO$_3$ (103 mg, 0.75 mmol) and H$_2$O (0.82 mL). Then, to it were added sequentially the 2-isocyanobiaryl derivative 1 (0.50 mmol), ether 2 (2.5 mL) and tert-butyl peroxibenzozate (TBPB) (213 µL, 1.10 mmol). The reaction mixture was stirred under an Ar atmosphere for 12–14 h at 110 °C (sand bath temperature). Upon full conver-
sion of the isonitrile (TLC or GC), a saturated solution of NaHCO₃ (5 mL) and EtOAc (10 mL) was added to the reaction mixture. After phase separation, the aqeous phase was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with brine (5 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the desired product.

6-(Tetrahydrofuran-2-yl)phenanthridine (3aa).

Following the general procedure, compound 3aa was obtained after column chromatography (hexane/EtOAc 9:1) as a yellow pale solid (91 mg, 0.36 mmol, 73%); Rf 0.23 (95:5 hexane/EtOAc); 1H-NMR (300 MHz, CDCl₃) δ 8.53 (d, J = 9.1 Hz, 1H), 8.47–8.41 (m, 1H), 8.17–8.12 (m, 1H), 7.82 (d, J = 2.6 Hz, 1H), 7.68–7.56 (m, 2H), 7.44 (dd, J = 9.1, 2.6 Hz, 1H), 5.69 (s, J = 6.9 Hz, 1H), 4.24–4.12 (m, 1H), 4.12–4.01 (m, 1H), 3.98 (s, 3H), 2.87–2.71 (m, 1H), 2.47–2.32 (m, 1H), 2.28–2.05 (m, 2H) ppm; 13C-NMR (101 MHz, CDCl₃) δ 158.6 (C), 158.4 (C), 142.5 (C), 130.5 (CH), 127.8 (CH), 127.6 (CH), 127.0 (CH), 126.3 (C), 124.3 (C), 124.1 (CH), 121.5 (CH), 120.8 (CH), 107.1 (CH), 80.1 (CH), 69.1 (CH₃), 55.6 (CH₂), 26.2 (CH₃) ppm; IR ν 3000, 2964, 2858, 1571, 1059, 754 cm⁻¹; LRMS (EI) m/z (%) = 279 (M⁺, 12), 236 (100), 223 (44), 207 (35); HRMS (EI) m/z calcd for C₁₁H₁₇NO₂ 279.1259, found 279.1261.

5-(Tetrahydrofuran-2-yl)benzo[i]phenanthridine (3ea).

Following the general procedure, compound 3ea was obtained after column chromatography (hexane/EtOAc 98:2–95:5) as a white solid (57 mg, 0.19 mmol, 38%); Rf 0.35 (96:4 hexane/EtOAc); 1H-NMR (400 MHz, CDCl₃) δ 9.19 (H-1, d, J = 8.5 Hz, 1H), 8.57 (H-12 + H-4, dd, J = 8.7, 5.2 Hz, 2H), 8.23 (H-7, dd, J = 8.2, 1.1 Hz, 1H), 8.10 (H-11, d, J = 8.9 Hz, 1H), 7.98 (H-10, d, J = 7.9 Hz, 1H), 7.78–7.71 (H-2 + H-8, 2H), 7.68–7.63 (H-3 + H-9, m, 2H), 5.91 (H-2', t, J = 6.4 Hz, 1H), 4.47–4.38 (H-5', m, 1H), 4.20–4.13 (H-5', m, 1H), 2.99–2.86 (H-3', m, 1H), 2.59–2.37 (H-4', m, 4H), 2.27–2.07 (H-3'+ H-4', m, 2H) ppm; 13C-NMR (101 MHz, CDCl₃) δ 157.7 (C), 144.0 (C), 133.8 (C), 133.2 (C), 131.9 (C), 130.1 (CH), 129.9 (C), 128.8 (CH), 128.4 (CH), 127.2 (CH), 126.9 (CH), 126.7 (CH), 126.3 (C), 123.0 (C), 122.5 (CH), 121.5 (CH), 120.8 (CH), 80.1 (CH), 69.4 (CH₃), 31.3 (CH₃), 26.8 (CH₃) ppm; IR ν 3019, 2961, 2937, 1561, 1465, 1350, 1051, 750 cm⁻¹; LRMS (EI) m/z (%) = 299 (M⁺, 14), 256 (100), 242 (28), 227 (19); HRMS (EI) m/z calcd for C₁₂H₁₂NO 299.1301, found 299.1304.

1-(6-(Tetrahydrofuran-2-yl)phenanthridin-8-yl)ethan-1-one (3fa).

Following the general procedure, compound 3fa was obtained after column chromatography (hexane/EtOAc 8:2) as a yellow pale solid (77 mg, 0.27 mmol, 53%); Rf 0.20 (8:2 hexane/EtOAc); 1H-NMR (300 MHz, CDCl₃) δ 9.10 (br s, 1H), 8.65 (d, J = 8.7 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.35 (dd, 2H), 8.19 (dd, J = 8.1, 1.2 Hz, 1H), 7.77 (dd, J = 8.3, 7.1, 1.4 Hz, 1H), 5.77 (t, J = 7.0 Hz, 1H), 4.22–4.13 (m, 1H), 4.13–4.04 (m, 1H), 2.88–2.79 (m, 1H), 2.77 (s, 3H), 2.52–2.37 (m, 1H), 2.31–2.10 (m, 2H) ppm; 13C-NMR (101 MHz, CDCl₃) δ 197.5 (C), 159.8 (C), 144.2 (C), 136.5 (C), 135.3 (C), 130.7 (C), 129.8 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 124.5 (C), 123.5 (C), 122.9 (CH), 122.6 (CH), 79.9 (CH), 69.2 (CH₃), 29.9 (CH₂), 26.2 (CH₃) ppm; IR ν 2977, 2921, 2856, 1683, 1615, 1521, 1052, 760 cm⁻¹; LRMS (EI) m/z (%) = 291 (M⁺, 5), 263 (20), 248 (100), 235 (65), 207 (17); HRMS (EI) m/z calcd for C₁₉H₁₇NO₂ 291.1259, found 291.1265.
Rf 0.25 (95:5 hexane/EtOAc); 1H-NMR (400 MHz, CDCl3) δ 8.81 (s, 1H), 8.72 (d, J = 8.6 Hz, 1H), 8.54 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.78 (t, J = 7.4 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 5.72 (t, J = 6.9 Hz, 1H), 4.14–4.12 (m, 1H), 2.88–2.75 (m, 1H), 2.48–2.35 (m, 1H), 2.30–2.08 (m, 2H); 13C-NMR (101 MHz, CDCl3) δ 159.2 (C), 144.0 (C), 135.6 (C), 130.7 (CH), 129.8 (CH), 129.1 (CH), 129.0 (C-8, 3JCF = 32.4 Hz), 127.6 (CH), 126.3 (CH), 126.2 (CH), 126.0 (CH), 124.7 (CH), 124.4 (CH), 124.0 (CH), 69.2 (CH2), 29.8 (CH2), 26.2 (CH2) ppm; IR ν 2921, 2881, 2742, 2732, 1673, 1670, 1220, 1038, 769 cm⁻¹; LRMS (EI) m/z (%) = 263 (M⁺, 8), 248 (6), 234 (13), 220 (100), 207 (13), 193 (19); HRMS (EI) m/z calc'd for C18H14FNO: 267.1059, found 267.1050.

9-Methyl-(tetrahydrofuran-2-yl)phenanthidine (3ja). From the same reaction where compound 3ja was obtained, and after column chromatography (hexane/EtOAc 95:5), isomer 3′ja was isolated as a yellow pale solid (37 mg, 0.14 mmol, 28%); Rf 0.19 (9:5 hexane/EtOAc); 1H-NMR (400 MHz, CDCl3) δ 8.52 (d, J = 8.1, 1.5 Hz, 1H), 8.40 (H-4, s, 1H), 8.31 (d, J = 8.4, 1.0 Hz, 1H), 7.68 (dd, J = 8.2, 7.1, 1.4 Hz, 1H), 7.60 (dd, J = 8.3, 7.1, 1.4 Hz, 1H), 7.50 (dd, J = 8.4, 1.4 Hz, 1H), 5.73 (t, J = 6.9 Hz, 1H), 4.23–4.16 (m, 1H), 4.11–4.00 (m, 1H), 2.67–2.65 (m, 1H), 2.62 (s, 3H), 2.46–2.32 (m, 1H), 2.27–2.04 (m, 2H) ppm; 13C-NMR (101 MHz, CDCl3) δ 159.3 (C), 143.6 (C), 140.7 (C), 133.5 (C), 130.5 (CH), 129.0 (CH), 128.4 (CH), 126.4 (CH), 124.1 (C), 122.1 (CH), 121.9 (CH), 79.8 (CH), 69.1 (CH2), 30.2 (CH2), 26.1 (CH2), 22.3 (CH3) ppm; HR ν 2875, 2868, 1618, 1460, 1053, 760; LRMS (EI) m/z (%) = 263 (M⁺, 5), 234 (13), 220 (100), 207 (51), 192 (23); HRMS (EI) m/z calc'd for C18H14N2O: 263.1310, found 263.1312.

9-Fluoro-(tetrahydrofuran-2-yl)phenanthidine (3ka). From the same reaction where compound 3ka was obtained, and after column chromatography (hexane/EtOAc 93:7) as a white solid (51 mg, 0.19 mmol, 38%); Rf 0.19 (9:1 hexane/EtOAc); 1H-NMR (300 MHz, CDCl3) δ 8.49 (d, J = 8.2 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.22 (dd, J = 8.2, 1.2 Hz, 1H), 7.82–7.70 (m, 2H), 7.64 (dd, J = 8.3, 7.4 Hz, 1H), 7.36 (dd, J = 12.5, 7.9, 1.0 Hz, 1H), 6.02 (dt, J = 8.2, 4.3 Hz, 1H), 4.43–4.32 (m, 1H), 4.17–4.05 (m, 1H), 2.60–2.45 (m, 1H), 2.40–2.23 (m, 1H), 2.13–1.96 (m, 1H) ppm; 13C-NMR (75 MHz, CDCl3) δ 160.2 (C-7, 3JCF = 255.2 Hz), 158.8 (C, 3JCF = 7.9 Hz), 143.3 (CH), 136.0 (C, 3JCF = 4.4 Hz), 131.0 (C-9, 3JCF = 9.8 Hz), 130.8 (CH), 129.3 (CH), 127.3 (CH), 122.7 (C, 3JCF = 2.7 Hz), 122.3 (CH), 118.7 (C-10, 3JCF = 4.0 Hz), 114.2 (CH), 114.1 (CH), 114.0 (C-6a, 3JCF = 24.6 Hz), 81.9 (C-2′, 3JCF = 14 Hz), 69.3 (CH3), 31.7 (CH3), 25.1 (CH3) ppm; IRν 2970, 2870, 1581, 1451, 1240, 757 cm⁻¹; LRMS (EI) m/z (%) = 267 (M⁺, 2), 224 (100), 211 (64), 197 (19), 169 (9); HRMS (EI) m/z calc'd for C19H14FNO: 267.1059, found 267.1050.
2.31 2.48 – 8.9, 2.6, 1.1 Hz, 1H), 5.77 (t, δC-F = 9.4 Hz, 1H), 129.8 (C, 7.7, 1.1 Hz, 1H), 129.3 (CH), 127.1 (CH), 123.8 (C6a, δC-F = 4.1 Hz, 1H), 122.2 (CH), 122.0 (C-6, δC-F = 2 Hz), 116.3 (C-10/C-8, δC-F = 23.7 Hz), 107.5 (C-8/C-10, δC-F = 22.0 Hz, 1H), 86.5 (CH2), 69.1 (CH2), 29.8 (CH2), 26.1 (CH2) ppm; IR ν 2967, 2872, 1619, 1496, 1195, 1052, 760 cm⁻¹; LRMS (EI) m/z (%) = 267 (M⁺, 3), 238 (13), 224 (100), 211 (55), 197 (17), 169 (9); HRMS (EI) m/z calc for C₁₃H₁₁ClNO 267.0591, found 267.0547.

3-Methyl-6-(tetrahydrofuran-2-yl)phenanthridine (3la).

Following the general procedure, but from 0.30 mmol of 1o, compound 3oa was obtained after column chromatography (hexane/EtOAc 96 : 4) as a brown oil (36 mg, 0.13 mmol, 45%): Rₚ 0.20 (93 : 7 hexane/EtOAc); ¹H-NMR (300 MHz, CDCl₃) δ 8.54 (d, δC-F = 8.2 Hz, 1H), 8.49 (H-1, dd, δC-F = 9.4, 5.0 Hz, 1H), 8.43 (d, δC-F = 8.2 Hz, 1H), 7.87–7.78 (m, 2H), 7.67 (dd, δC-F = 8.3, 7.0, 1.2 Hz, 1H), 7.38 (H-2, dd, δC-F = 8.9, 8.1, 2.7 Hz, 1H), 7.06 (t, δC-F = 6.9 Hz, 1H), 4.24–4.14 (m, 1H), 1.11–1.01 (m, 1H), 2.78–2.64 (m, 1H), 2.48–2.34 (m, 1H), 2.29–2.03 (m, 2H) ppm; ¹³C-NMR (101 MHz, CDCl₃) δ 158.7 (C), 148.1 (C), 131.9 (C), 130.7 (CH), 127.2 (CH), 126.7 (CH), 125.3 (C), 125.1 (C), 125.2 (CH), 121.7 (CH), 79.6 (CH2), 69.2 (CH2), 30.0 (CH2), 26.1(CH2) ppm; IR ν 2967, 2869, 1584, 1495, 1255, 1054, 822, 767 cm⁻¹; LRMS (EI) m/z (%) = 283 (M⁺, 4), 254 (16), 240 ([M – C₂H₂O₂]⁺, 100), 227 (51), 213 (13) 177 (29); HRMS (EI) m/z calc for C₁₆H₁₄ClNO 240.0580, found 240.0576.

3-Fluoro-6-(tetrahydrofuran-2-yl)phenanthridine (3oa).

Following the general procedure, but from 0.30 mmol of 1o, compound 3oa was obtained after column chromatography (hexane/EtOAc 96 : 4) as a brown oil (36 mg, 0.13 mmol, 45%): Rₚ 0.20 (93 : 7 hexane/EtOAc); ¹H-NMR (300 MHz, CDCl₃) δ 8.54 (d, δC-F = 8.2 Hz, 1H), 8.49 (H-1, dd, δC-F = 9.4, 5.0 Hz, 1H), 8.43 (d, δC-F = 8.2 Hz, 1H), 7.87–7.78 (m, 2H), 7.67 (dd, δC-F = 8.3, 7.0, 1.2 Hz, 1H), 7.38 (H-2, dd, δC-F = 8.9, 8.1, 2.7 Hz, 1H), 7.06 (t, δC-F = 6.9 Hz, 1H), 4.24–4.14 (m, 1H), 1.11–1.01 (m, 1H), 2.78–2.64 (m, 1H), 2.48–2.34 (m, 1H), 2.29–2.03 (m, 2H) ppm; ¹³C-NMR (101 MHz, CDCl₃) δ 158.7 (C), 148.1 (C), 131.9 (C), 130.7 (CH), 127.2 (CH), 126.7 (CH), 125.3 (C), 125.1 (C), 125.2 (CH), 121.7 (CH), 79.6 (CH2), 69.2 (CH2), 30.0 (CH2), 26.1(CH2) ppm; IR ν 2967, 2869, 1584, 1495, 1255, 1054, 822, 767 cm⁻¹; LRMS (EI) m/z (%) = 283 (M⁺, 4), 254 (16), 240 ([M – C₂H₂O₂]⁺, 100), 227 (51), 213 (13) 177 (29); HRMS (EI) m/z calc for C₁₆H₁₄ClNO 240.0580, found 240.0576.
6-(Isopropoxypyran-2-yl)phenanthridine (3ad).\textsuperscript{13c}

Following the general procedure, compound 3ad was obtained after column chromatography (100% hexane to hexane/EtOAc 98:2) as a brown pale oil (79 mg, 0.28 mmol, 57%): \( ^{1}H\)-NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.53 (dd, \( J = 7.8, 1.3 \) Hz, 1H), 7.87–7.64 (m, 3H), 4.98 (dd, \( J = 8.3, 1.3 \) Hz, 2H), 7.75–7.61 (m, 3H), 1.82 (s, 3H), 1.02 (d, \( J = 6.1 \) Hz, 6H) ppm; \( ^{13}C\)-NMR (101 MHz, CDCl\(_3\)) \( \delta \) 163.7 (CH), 142.9 (C), 133.9 (C), 130.6 (CH), 130.3 (CH), 129.9 (CH), 128.5 (CH), 127.0 (CH), 126.1 (CH), 124.5 (C), 124.1 (C), 122.3 (CH), 121.9 (CH), 81.8 (C), 67.0 (CH), 29.1 (CH\(_2\)), 24.8 (CH\(_3\)); IR \( \nu \) 2983, 2934, 2578, 1739, 1162, 1106, 990, 760, 730 cm\(^{-1}\); LRMS (EI) \( m/z \) (%) = 263 (M\(^{+}\), 100), 204 (34), 179 (54), 150 (18); HRMS (EI) \( m/z \) calced for C\(_{16}H_{12}N\): 263.1126, found 262.1128.

6-(1-Butoxybutyl)phenanthridine (3ae).\textsuperscript{13b}

Following the general procedure, compound 3ae was obtained after column chromatography (hexane/EtOAc 99:1–98:2) as a yellow oil (123 mg, 0.40 mmol, 80%): \( R_t \) 0.65 (9:1 hexane/EtOAc); \( ^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.94–8.89 (m, 1H), 8.69–8.64 (m, 1H), 8.57 (dd, \( J = 8.0, 1.6 \) Hz, 1H), 8.20–8.15 (m, 1H), 7.84 (dd, \( J = 8.3, 1.3 \) Hz, 1H), 7.77–7.72 (m, 3H), 4.98 (dd, \( J = 8.8, 5.4 \) Hz, 1H), 3.52–3.33 (m, 2H), 2.28–2.13 (m, 1H), 2.01–1.87 (m, 1H), 1.76–1.46 (m, 4H), 1.40–1.23 (m, 4H) ppm; \( ^{13}C\)-NMR (101 MHz, CDCl\(_3\)) \( \delta \) 161.9 (C), 143.4 (C), 133.5 (C), 130.5 (CH), 130.2 (CH), 128.7 (CH), 127.0 (CH), 124.5 (C), 124.1 (C), 122.4 (CH), 122.0 (CH), 86.5 (CH), 69.5 (CH\(_2\)), 33.8 (CH\(_3\)), 32.2 (CH\(_2\)), 20.0 (CH\(_2\)), 19.5 (CH\(_2\)), 14.1 (CH\(_3\)), 14.0 (CH\(_3\)) ppm; IR \( \nu \) 2957, 2932, 2870, 1759, 1459, 1092, 727 cm\(^{-1}\); LRMS (EI) \( m/z \) (%) = 265 (M\(^{+}\) – C\(_{2}\)H\(_5\)), 120 (29), 93 (20), 77 (18), 55 (15) ppm; HRMS (EI) \( m/z \) calced for C\(_{18}H\text{C}_{18}N\): 283.1310, found 263.1308.

6-(2-Methyltetrahydrofuran-2-yl)phenanthridine (3af).\textsuperscript{26}

From the same reaction where compound 3af was obtained, and after column chromatography (hexane/EtOAc 99:1–98:2) as a colorless oil (43 mg, 0.16 mmol, 33%): \( R_t \) 0.75 (9:1 hexane/EtOAc); \( ^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.14 (d, \( J = 8.4 \) Hz, 1H), 8.63 (dd, \( J = 8.3 \) Hz, 1H), 8.53 (dd, \( J = 8.1, 1.5 \) Hz, 1H), 8.12 (d, \( J = 8.0 \) Hz, 1H), 1.87 (m, 1H), 1.78 (dd, \( J = 8.1, 6.6, 1.2 \) Hz, 1H), 7.72–7.58 (m, 3H), 4.14–4.03 (m, 3H), 3.80–3.69 (m, 1H), 3.66–3.56 (m, 1H), 2.10–1.88 (m, 3H), 1.83 (s, 3H) ppm; \( ^{13}C\)-NMR (75 MHz, CDCl\(_3\)) \( \delta \) 161.1, 142.9, 134.0, 130.4, 130.0, 129.3, 128.4, 126.9, 126.6, 124.4, 124.1, 122.4, 121.9, 88.7, 68.1, 37.4, 28.2, 25.2 ppm; IR \( \nu \) 3065, 2970, 2930, 2872, 1570, 1597, 758 cm\(^{-1}\); LRMS (EI) \( m/z \) (%) = 263 (M\(^{+}\), 18), 235 (48), 207 (86), 179 (55), 85 (100); HRMS (EI) calced for C\(_{16}H_{12}NO\): 263.1310, found 263.1308.

6-Benzylphenanthridine (3ah).\textsuperscript{26}

From the same reaction where compound 3ah was obtained, and after column chromatography (hexane/EtOAc 99:1–98:2) as a yellow solid (32 mg, 0.08 mmol, 17%): \( R_t \) 0.5 (9:1 hexane/EtOAc); \( ^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.65–8.55 (m, 3H), 8.30–8.25 (m, 1H), 7.81–7.66 (m, 3H), 7.57–7.43 (m, 3H), 7.39–7.25 (m, 7H), 7.24–7.19 (m, 1H), 6.27 (s, 1H), 4.73 (d, \( J = 11.7 \) Hz, 1H), 4.64 (d, \( J = 11.7 \) Hz, 1H) ppm; \( ^{13}C\)-NMR (101 MHz, CDCl\(_3\)) \( \delta \) 159.9 (C), 143.4 (C), 140.8 (C), 138.3 (C), 133.9 (C), 130.5 (CH), 130.5 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 127.7 (CH), 127.4 (CH), 127.1 (CH), 126.3 (CH), 124.5 (C), 124.3 (C), 122.3 (CH), 122.1 (CH), 86.5 (CH), 71.7 (CH\(_2\)) ppm; IR \( \nu \) 3060, 3029, 2915, 2850, 1572, 1449, 1067, 722 cm\(^{-1}\); LRMS (EI-DIP) \( m/z \) (%) = 284 (M\(^{+}\) – C\(_{2}\)H\(_5\)), 269 (100), 268 (52), 178 (16), 91 (32); HRMS (EI) calced for C\(_{22}H\text{C}_{29}N\): 375.1623, found 375.1605.

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1.2 Hz, 1H), 7.41 (ddd, 8.0, 1.2 Hz, 1H), 7.30 (m, 1H), 7.28 (m, 2H), 7.26 (m, 2H), 7.13 (m, 4H), 4.74 (s, 2H) ppm; 13C-NMR (75 MHz, CDCl 3) δ 152.5 (C), 147.5 (2C), 142.9 (C), 133.9 (C), 130.9 (2CH), 129.0 (CH), 128.4 (CH), 127.7 (CH), 125.9 (CH), 125.0 (C), 123.8 (C), 122.6 (CH), 122.3 (CH), 122.1 (CH), 112.2 (CH), 109.4 (2CH) ppm; IR ν 3078, 2909, 1479, 1338, 1229, 724 cm−1; LRMS (EI) m/z (%) = 267 (M+ , 2), 268 (100), 251 (3), 119 (12); HRMS (EI) calcd for C16H13NO3 267.0895, found 267.0879.

Phenanthridine (4a). This compound was obtained as the by-product of 3aa and of all compounds represented in Scheme 3. After purification by column chromatography (hexane/EtOAc 9:1), it was isolated as a white solid. Rf 0.25 (9:1 hexane/EtOAc); 1H-NMR (300 MHz, CDCl 3) δ 8.28 [s, 1H], 8.63–8.54 (m, 1H), 8.20 (dd, j = 8.1, 1.3 Hz, 1H), 8.03 (br d, j = 7.9 Hz, 1H), 7.84 (ddd, j = 8.4, 7.1, 1.4 Hz, 1H), 7.78–7.63 (m, 2H) ppm; 13C-NMR (75 MHz, CDCl 3) δ 153.7 (CH), 144.6 (C), 132.7 (C), 131.1 (CH), 130.3 (CH), 128.9 (CH), 127.6 (CH), 127.2 (CH), 126.5 (C), 124.2 (C), 122.3 (CH), 122.0 (CH) ppm; IR ν 2924, 2851, 1457, 1245, 890, 745 cm−1; LRMS (EI) m/z (%) = 179 (M+, 100), 151 (13), 76 (100), 179 (8).

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Notes and references


A similar result was observed by the group of Ji (ref. 13a) with 1,4-dioxane and TBPB as the oxidant.

This regiochemistry was observed by the group of Chen, using 1,4-dioxane and BPO as the oxidant. A plausible explanation is given in ref. 13b.


It is worth noting that compound 4a is significantly formed with TBPB in the absence of base (ref. 13a and checked by us in Table 1, entry 7); or with BPO in neutral media (ref. 13b and checked by us in Table 1, entry 1).


The following rate constants are reported for α-hydrogen abstraction of THF: 

\[
\begin{align*}
& k (t-{\text{BuO}}^+) \sim 8.3 \times 10^6 \text{ vs. } k (\text{PhCOO}^-) \sim 2.5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}.
\end{align*}
\]


An intramolecular electrophilic aromatic substitution might also be considered as a plausible pathway for the formation of byproduct 4a. Due to the extremely high acidity of cyclohexadienyl radical I, a proton transfer to the isonitrile moiety of 1a would form a cationic intermediate that could undergo Friedel–Crafts-type cyclization to give 4a.