Electronic Supplementary Information

Iron-Catalyzed Cascade Cyanoalkylation/Radical
Dearomatization of N-phenylcinnamamides:
Access to Cyanoalkylated 1-Azaspiro[4.5]decanes
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1. General Information

All regents were commercial available and used without further purification. All reactions were conducted under argon atmosphere. The reaction was detected using Thin Layer Chromatography (TLC). The products were separated using TLC. $^1$H, $^{19}$F and $^{13}$C NMR spectra were conducted by 400 MHz spectrometer at room temperature, using CDCl$_3$ as solvent with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are determined in ppm downfield from tetramethylsilane. Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; m, multiplet. HRMS data were recorded by a TOF LC/MS. Substrates were prepared according to reported literatures. 1, 2

2. Experiment procedure

$N$-(4-hydroxyphenyl)-$N$-alkyl-cinnamamides (1, 0.2 mmol), Fe(acac)$_2$ (0.04 mmol, 20 mol%), DTBP (0.4 mmol, 2.0 equiv.), nitriles (2 mL) and a stir bar were added into a sealed tube. The sealed tube was degassed by freeze-thaw-pump for three times. Then the sealed tube was heated at 120 °C for 12 h as the TLC showed that the reaction was finished. The mixture was cooled to room temperature and concentrated in vacuum. The residue was purified using TLC on silica gel (GF254) to give the corresponding products (3).

3. Research on the Mechanism

3.1 Free Radical Capture Experiments

$N$-(4-hydroxyphenyl)-$N$-benzyl-cinnamamide (1d, 0.2 mmol), Fe(acac)$_2$ (0.020 mmol, 20 mol%), DTBP (0.4 mmol, 2.0 equiv), MeCN (2 mL), 2,2,6,6-tetramethylpiperidine oxide (TEMPO) (0.4 mmol, 2.0 equiv.) and a stir bar were added into a sealed tube. The sealed tube was degassed by freeze-thaw-pump for three times. Then the sealed tube was heated at 120 °C for 12 h as the TLC showed that the reaction was finished. The mixture was cooled to room temperature and concentrated in vacuum. The residue was separated using preparative TLC on silica gel (GF254).

![Reaction Scheme](image)

3.2 The KIE Studies

The KIE studies on solvent (competition reaction)

$N$-(4-hydroxyphenyl)-$N$-benzyl-cinnamamide (1d, 0.2 mmol), Fe(acac)$_2$ (0.025 mmol, 20 mol%), DTBP (0.4 mmol, 2.0 equiv), CH$_3$CN (1 mL), CD$_3$CN (1 mL) and a stir bar were added into a sealed tube. The sealed tube was degassed by freeze-thaw-pump for three times. Then the sealed tube was heated at 120 °C for 12 h. And the mixture was concentrated in vacuum and the residue was purified using preparative TLC on silica gel (GF254) to give the corresponding product 3d and [D$_2$]-3d. On the $^1$H NMR spectra, the signal of H at δ 3.10-3.01 belongs to the α-C-H of cyan group. The integral of C-H at δ 3.10-3.01 is 1.0 for 3d and it is 0.86 for the mixture of 3d and [D$_2$]-3d. The KIE value can be calculated as $k_H/k_D = 0.86/(1-0.86) ≈ 6.1$ (Figure S1).
Figure S1. The $^1$H NMR spectrum of the KIE results.

The Kinetic Isotopic Effect Studies on Solvent (parallel reaction)

In ten parallel sealed tubes, N-(4-hydroxyphenyl)-N-benzyl-cinnamamide (1d, 0.2 mmol) was treated by standard condition in CH$_3$CN or D$_3$-CH$_3$CN (five experiments for each). Then the reactions were quenched by cooling to room temperature in specified time. The mixture was analyzed by $^1$H NMR with CH$_2$Br$_2$ as inert standard to record the yield of products 3d or [D$_2$]-3d. A significant intermolecular kinetic isotope effect ($k_H/k_D$ = 3.8) was observed. The results were listed below:
$^1$H NMR of [D$_2$]-3d (400 MHz, CDCl$_3$): $\delta$ 7.28–7.23 (m, 6H), 7.21 – 7.19 (m, 1H), 7.03 (dd, $J = 6.5, 3.0$ Hz, 2H), 6.59 (dd, $J = 10.1, 3.1$ Hz, 1H), 6.44 (dd, $J = 10.2, 3.1$ Hz, 1H), 6.25 (dd, $J = 10.1, 2.0$ Hz, 1H), 5.79 (dd, $J = 10.2, 2.0$ Hz, 1H), 4.51 (d, $J = 14.9$ Hz, 1H), 4.27 (d, $J = 14.9$ Hz, 1H), 3.23 – 3.14 (m, 2H).

4. Reference

5. Characterization for the Products
5.1 2D NOE spectra of 3a and 3d
Figure S2. 2D NOE spectra of 3a and 3d
5.2 Characterization Data for the Products

2-(1-methyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3a)

67%, 19.4 mg, white solid, m.p.: 52.0–54.2 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.34-7.29 (m, 3H), 7.16-7.11 (m, 2H), 6.86 (dd, \(J = 10.1, 3.1\) Hz, 1H), 6.61 (dd, \(J = 10.2, 3.1\) Hz, 1H), 6.45 (dd, \(J = 10.1, 1.9\) Hz, 1H), 6.07 (dd, \(J = 10.2, 1.9\) Hz, 1H), 3.57 (d, \(J = 12.5\) Hz, 1H), 3.46-3.39 (m, 1H), 2.99 (dd, \(J = 17.1, 4.8\) Hz, 1H), 2.79 (s, 3H), 2.66 (dd, \(J = 17.1, 5.1\) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 184.0, 171.7, 148.0, 145.1, 133.0, 132.2, 131.7, 129.0, 129.0, 128.0, 116.7, 65.0, 53.7, 40.5, 27.4, 17.6. HRMS (ESI) calcd. for C\(_{18}\)H\(_{17}\)N\(_2\)O\(_2\)+ (M+H\(^+\)) : 293.1285, found: 293.1283.

1,3-dimethyl-4-phenyl-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (3a')

30%, 8.2 mg, white solid, m.p.: 136.2-138.7 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.31 – 7.25 (m, 3H), 7.11 – 7.08 (m, 2H), 6.78 (dd, \(J = 10.1, 3.1\) Hz, 1H), 6.57 (dd, \(J = 10.2, 3.1\) Hz, 1H), 6.42 (dd, \(J = 10.1, 2.0\) Hz, 1H), 6.04 (dd, \(J = 10.2, 2.0\) Hz, 1H), 3.22 (d, \(J = 12.2\) Hz, 1H), 3.12 (dd, \(J = 12.4, 6.5\) Hz, 1H), 2.76 (d, \(J = 0.5\) Hz, 3H), 1.29 (d, \(J = 6.7\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 184.3, 176.0, 149.1, 146.0, 132.6, 131.8, 128.7, 128.3, 127.9, 57.1, 38.8, 28.8, 27.1, 14.6. HRMS (ESI) calcd. for C\(_{17}\)H\(_{17}\)NNaO\(_2\)+ (M+Na\(^+\)) : 290.1151, found: 290.1149.

2-(4-(4-chlorophenyl)-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3b)
58%, 18.7 mg, white solid, m.p.: 136.2-138.7 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.30 (d, \(J = 8.4\) Hz, 2H), 7.06 (d, \(J = 8.4\) Hz, 2H), 6.81 (dd, \(J = 10.1, 3.1\) Hz, 1H), 6.53 (dd, \(J = 10.2, 3.1\) Hz, 1H), 6.47 (dd, \(J = 10.1, 1.9\) Hz, 1H), 6.13 (dd, \(J = 10.2, 1.9\) Hz, 1H), 3.54 (d, \(J = 12.5\) Hz, 1H), 3.34 – 3.25 (m, 1H), 3.00 (dd, \(J = 10.2, 1.9\) Hz, 1H), 2.81 (s, 3H), 2.69 (dd, \(J = 17.1, 4.8\) Hz, 1H). \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 183.6, 171.1, 147.5, 144.4, 135.2, 133.3, 132.6, 130.2, 129.3, 129.3, 116.3, 64.8, 53.3, 40.6, 27.4, 17.7. HRMS (ESI) calcd. for C\(_{18}\)H\(_{15}\)ClN\(_2\)O\(_2\)+ (M+Na\(^+\)): 349.0714, found: 349.0711.

2-(4-(2-chlorophenyl)-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3c) 52%, 16.8 mg, white solid, m.p.: 158.2-160.2 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.43-7.37 (m, 1H), 7.31 – 7.19 (m, 3H), 6.94 (dd, \(J = 10.1, 3.1\) Hz, 1H), 6.69 (dd, \(J = 10.2, 2.8\) Hz, 1H), 6.39 (dd, \(J = 10.1, 1.9\) Hz, 1H), 6.19 (dd, \(J = 10.2, 1.9\) Hz, 1H), 4.33 (d, \(J = 12.3\) Hz, 1H), 3.32 (s, 1H), 2.88 (dd, \(J = 16.9, 5.6\) Hz, 1H), 2.80 (s, 3H), 2.70 (dd, \(J = 17.1, 4.9\) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 183.9, 171.2, 148.2, 144.4, 135.8, 132.57, 131.0, 130.2, 129.9, 128.7, 127.1, 116.2, 64.8, 50.0, 42.2, 27.2, 17.9. HRMS (ESI) calcd. for C\(_{18}\)H\(_{15}\)ClN\(_2\)O\(_2\)+ (M+Na\(^+\)): 349.0714, found: 349.0710.

2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3d) 71%, 26.0 mg, white solid, m.p.: 84.7-86.3 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.32 – 7.24 (m, 1H), 7.23-7.15 (m, 1H), 7.10-7.03 (m, 1H), 6.63 (dd, \(J = 10.1, 3.1\) Hz, 1H), 6.44 (dd, \(J = 10.2, 3.1\) Hz, 1H), 6.26 (dd, \(J = 10.1, 2.0\) Hz, 1H), 5.83 (dd, \(J = 10.2, 2.0\) Hz, 1H), 4.57 (d, \(J = 15.0\) Hz, 1H), 4.30 (d, \(J = 15.0\) Hz, 1H), 3.56 (d, \(J = 12.6\) Hz, 1H), 3.45 (dt, \(J = 12.6, 4.8\) Hz, 1H), 3.07 (dd, \(J = 17.0, 4.7\) Hz, 1H), 2.68 (dd, \(J = 17.0, 4.9\) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 184.1, 171.8, 147.7, 145.3, 136.9, 132.2, 131.3, 131.2, 129.1, 128.9, 128.7, 128.6, 128.1, 128.1, 116.5, 65.2, 54.2, 45.7, 40.5, 28.8, 17.7. HRMS (ESI) calcd. for C\(_{24}\)H\(_{21}\)N\(_2\)O\(_2\)+ (M+H\(^+\)): 369.1598, found: 369.1585.

2-(1-benzyl-2,8-dioxo-4-(4-(trifluoromethyl)phenyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3e) 66%, 28.6 mg, white solid, m.p.: 183.6-185.3 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.56 (d, \(J = 8.3\) Hz, 2H), 7.32 – 7.24 (m, 4H), 7.20 (dd, \(J = 11.2, 4.7\) Hz, 4H), 6.64 (dd, \(J = 10.1, 3.1\) Hz, 1H), 6.42 (dd, \(J = 10.2, 3.1\) Hz, 1H), 6.30 (dd, \(J = 10.1, 1.9\) Hz, 1H), 5.87 (dd, \(J = 10.2, 1.9\) Hz, 1H), 4.57 (d, \(J = 15.0\) Hz, 1H), 4.32 (d, \(J = 15.0\) Hz, 1H).
Hz, 1H), 3.62 (d, J = 12.6 Hz, 1H), 3.45 (dt, J = 12.5, 4.8 Hz, 1H), 3.08 (dd, J = 17.1, 4.9 Hz, 1H), 2.70 (dd, J = 17.1, 4.8 Hz, 1H). $^1$H NMR (100 MHz, CDCl$_3$): $\delta$ 183.6, 171.2, 147.2, 144.5, 136.7, 135.6, 132.5, 131.5, 128.8, 128.6, 128.5, 128.2, 126.0, 126.0, 123.5 (d, J = 270.8 Hz), 116.2, 64.9, 53.9, 45.8, 40.6, 17.7. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.6. HRMS (ESI) calcd. for C$_{25}$H$_{20}$F$_3$N$_2$O$_2$·(M+H$^+$): 437.1471, found: 437.1468.

2-(1-benzyl-4-(4-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3f)

53%, 21.2 mg, white solid, m.p.: 181.7-183.0°C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.32 – 7.23 (m, 4H), 7.20 – 7.16 (m, 2H), 7.06 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.66 – 6.58 (m, 1H), 6.48 – 6.40 (m, 1H), 6.32 – 6.21 (m, 1H), 5.91 – 5.79 (m, 1H), 4.61-4.51 (m, 1H), 4.35 – 4.25 (m, 1H), 3.53 (dd, J = 12.6, 2.5 Hz, 1H), 3.46 – 3.35 (m, 1H), 3.09-2.98 (m, 1H), 2.73-2.61 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 184.3, 171.9, 147.5, 145.5, 138.9, 136.9, 135.0, 132.1, 131.4, 130.0, 129.6, 129.2, 128.8, 128.6, 128.0, 116.6, 65.3, 53.9, 45.7, 40.6, 21.1, 17.7. HRMS (ESI) calcd. for C$_{24}$H$_{20}$ClN$_2$O$_2$·(M+H$^+$): 403.1208, found: 403.1204.

2-(1-benzyl-4-(4-bromophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3g)

51%, 22.6 mg, white solid, m.p.: 221.5-223.6°C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 (d, J = 8.5 Hz, 2H), 7.29 – 7.25 (m, 3H), 7.23 – 7.15 (m, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.60 (dd, J = 10.1, 3.1 Hz, 1H), 6.39 (dd, J = 10.2, 3.1 Hz, 1H), 6.28 (dd, J = 10.1, 2.0 Hz, 1H), 5.88 (dd, J = 10.2, 2.0 Hz, 1H), 4.56 (d, J = 15.0 Hz, 1H), 4.32 (d, J = 15.0 Hz, 1H), 3.51 (d, J = 12.4Hz, 1H), 3.41-3.08 (dt, J = 12.6, 4.9 Hz, 1H), 3.06 (dd, J = 17.1, 4.9 Hz, 1H), 2.69 (dd, J = 17.1, 4.8 Hz, 1H). $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 183.8, 171.3, 147.4, 144.8, 136.7, 132.4, 132.2, 131.5, 130.4, 129.7, 128.8, 128.6, 128.2, 123.3, 116.3, 77.4, 77.3, 77.0, 76.7, 65.0, 53.7, 45.8, 40.6, 17.7. HRMS (ESI) calcd. for C$_{24}$H$_{19}$BrN$_2$O$_2$·(M+Na$^+$): 469.0522, found: 469.0517.

2-(1-benzyl-4-(4-nitrophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3h)

46%, 18.8 mg, white solid, m.p.: 249.3-251.7°C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.16 (d, J = 8.7 Hz, 2H), 7.28 (dd, J = 6.3, 2.1 Hz, 4H), 7.19 (dd, J = 6.5, 2.8 Hz, 2H), 6.64 (dd, J = 10.1, 3.1 Hz, 1H), 6.41 (dd, J = 10.2, 3.1 Hz, 1H), 6.32 (dd, J = 10.1, 1.9 Hz, 1H), 5.87 (dd, J = 10.2, 1.9 Hz, 1H), 3.66 (d, J = 12.5 Hz, 1H), 3.46 (dt, J = 12.4, 5.0 Hz, 1H), 3.06 (dd, J = 17.2, 5.5 Hz, 1H), 2.77 (dd, J = 17.2, 4.7 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 183.4, 170.8, 146.9, 144.3, 138.8, 136.5, 132.7, 131.7, 129.2, 128.9, 128.6, 128.3,
2-(1-benzyl-2,8-dioxo-4-(m-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3i)

68%, 25.8 mg, white solid, m.p.: 132.4-135.7 °C. 1H NMR (400 MHz, CDCl₃): δ 7.33 – 7.27 (m, 3H), 7.24-7.19 (m, 2H), 7.16 – 7.09 (m, 3H), 7.08 – 7.03 (m, 1H), 6.67-6.59 m, 2H), 6.18 (dd, J = 9.9, 1.7 Hz, 1H), 5.95 (dd, J = 10.1, 1.8 Hz, 1H), 4.58 (d, J = 15.0 Hz, 1H), 4.29 (d, J = 15.0 Hz, 1H), 3.99 (d, J = 12.4 Hz, 1H), 3.36 (dt, J = 12.3, 4.7 Hz, 1H), 3.07 (dd, J = 17.0, 4.3 Hz, 1H), 2.55 (dd, J = 17.0, 5.1 Hz, 1H), 2.31 (s, 3H). 13C NMR (100 MHz, CDCl₃): δ 184.2, 171.8, 147.8, 145.4, 138.6, 136.9, 132.1, 131.3, 131.1, 129.8, 128.9, 128.8, 128.7, 128.6, 128.0, 125.0, 116.5, 65.2, 54.1, 45.7, 40.6, 21.4, 17.6. HRMS (ESI) calcd. for C₂₅H₂₂N₂O₂Na⁺(M+Na⁺): 405.1573, found: 405.1570.

2-(1-benzyl-4-(3-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3j)

54%, 21.6 mg, white solid, m.p.: 153.2-155.6 °C. 1H NMR (400 MHz, CDCl₃): δ 7.31 – 7.26 (m, 1H), 7.24 – 7.18 (m, 3H), 7.18 – 7.07 (m, 5H), 6.65 (dd, J = 10.1, 3.1 Hz, 1H), 6.48 (dd, J = 10.2, 2.7 Hz, 1H), 6.13 (dd, J = 10.1, 2.0 Hz, 1H), 5.87 (dd, J = 10.2, 2.0 Hz, 1H), 4.48 (d, J = 14.9 Hz, 1H), 4.34 – 4.17 (m, 2H), 3.43-3.20 (br, 1H), 2.85 (dd, J = 17.1, 5.6 Hz, 1H), 2.63 (dd, J = 17.1, 4.9 Hz, 1H). 13C NMR (100 MHz, CDCl₃): δ 183.0, 170.4, 147.1, 143.9, 135.8, 130.7, 130.4, 129.9, 129.1, 128.6, 127.7, 127.6, 127.1, 125.9, 115.3, 59.4, 44.6, 41.1, 16.8. HRMS (ESI) calcd. for C₂₄H₂₀ClN₂O₂(M+H⁺): 403.1208, found: 403.1204.

2-(1-benzyl-4-(3-bromophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3k)

64%, 28.4 mg, white solid, m.p.: 175.4-177.0 °C. 1H NMR (400 MHz, CDCl₃): δ 7.42 (dd, J = 8.0, 0.8 Hz, 1H), 7.31 – 7.25 (m, 4H), 7.24 – 7.12 (m, 4H), 7.00 (d, J = 7.8 Hz, 1H), 6.61 (dd, J = 10.1, 3.1 Hz, 1H), 6.41 (dd, J = 10.2, 3.1 Hz, 1H), 6.30 (dd, J = 10.1, 2.0 Hz, 1H), 5.88 (dd, J = 10.2, 2.0 Hz, 1H), 4.54 (d, J = 15.0 Hz, 1H), 4.34 (d, J = 15.0 Hz, 1H), 3.52 (d, J = 12.6 Hz, 1H), 3.37 (dt, J = 12.6, 4.8 Hz, 1H), 3.09 (dd, J = 17.1, 4.7 Hz, 1H), 2.69 (dd, J = 17.1, 4.9 Hz, 1H). 13C NMR (100 MHz, CDCl₃): δ 183.8, 171.2, 147.3, 144.7, 136.7, 133.8, 132.5, 132.3, 131.4, 130.9, 130.5, 128.8, 128.6, 128.2, 127.1, 123.0, 116.2, 65.0, 53.7, 45.7, 40.5, 17.7. HRMS (ESI) calcd. for C₂₄H₂₀BrN₂O₂(M+H⁺): 447.0703, found: 447.0706.
2-(1-benzyl-4-(2-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3m)

45%, 18.1 mg, white solid, m.p.: 165.3-167.0 °C. 'H NMR (400 MHz, CDCl₃):  δ 7.37 – 7.33 (m, 1H), 7.30 – 7.26 (m, 3H), 7.25 – 7.14 (m, 5H), 6.73 (dd, J = 10.1, 3.1 Hz, 1H), 6.56 (dd, J = 10.1, 2.6 Hz, 1H), 6.21 (dd, J = 10.1, 2.0 Hz, 1H), 5.94 (dd, J = 10.2, 2.0 Hz, 1H), 4.60 – 4.52 (m, 1H), 4.39 – 4.26 (m, 2H), 3.39 (s, 1H), 2.99 (dd, J = 17.1, 4.7 Hz, 1H), 2.70 (dd, J = 17.1, 4.9 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 184.1, 171.5, 148.2, 144.9, 136.8, 131.74, 131.5, 130.9, 130.2, 129.6, 128.8, 128.6, 128.1, 127.0, 116.3, 65.1, 50.4, 45.6, 42.2, 17.9. HRMS (ESI) calcd. for C₂₅H₁₉ClN₂O₂⁺(M+Na⁺): 425.1027, found: 425.1024.

2-(1-benzyl-2,8-dioxo-4-(o-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3n)

47%, 17.8 mg, white solid, m.p.: 114.3-116.5 °C. 'H NMR (400 MHz, CDCl₃):  δ 7.23 – 7.18 (m, 3H), 7.16 – 7.12 (m, 2H), 7.09 – 7.03 (m, 3H), 7.02 – 6.95 (m, 1H), 6.63-6.51 (m, 2H), 6.10 (dd, J = 9.9, 2.0 Hz, 1H), 5.87 (dt, J = 7.0, 3.6 Hz, 1H), 4.51 (d, J = 15.0 Hz, 1H), 4.22 (d, J = 15.0 Hz, 1H), 3.92 (d, J = 12.4 Hz, 1H), 3.29 (dt, J = 12.4, 4.7 Hz, 1H), 2.99 (dd, J = 17.0, 4.4 Hz, 1H), 2.47 (dd, J = 17.0, 5.1 Hz, 1H), 2.24 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 183.1, 170.8, 147.3, 144.8, 137.1, 135.9, 130.7, 130.6, 130.1, 129.0, 127.7, 127.6, 127.5, 127.0, 126.4, 125.1, 115.5, 64.4, 59.4, 44.6, 41.9, 19.3, 16.5. HRMS (ESI) calcd. for C₂₅H₂₂N₂O₂⁺(M+Na⁺): 405.1573, found: 405.1576.

2-(1-benzyl-2,8-dioxo-4-(p-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3o)

51%, 19.4 mg, white solid, m.p.: 151.3-153.7 °C. 'H NMR (400 MHz, CDCl₃):  δ 7.31 – 7.24 (m, 3H), 7.24 – 7.16 (m, 2H), 7.06 (d, J = 7.9 Hz, 2H), 6.93 (d, J = 8.1 Hz, 2H), 6.60 (dd, J = 10.1, 3.1 Hz, 1H), 6.42 (dd, J = 10.2, 3.1 Hz, 1H), 6.25 (dd, J = 10.1, 2.0 Hz, 1H), 5.84 (dd, J = 10.2, 2.0 Hz, 1H), 4.56 (d, J = 15.0 Hz,
1H), 4.30 (d, J = 15.0 Hz, 1H), 3.52 (d, J = 12.6 Hz, 1H), 3.39 (dt, J = 12.6, 4.8 Hz, 1H), 3.06 (dd, J = 17.0, 4.7 Hz, 1H), 2.67 (dd, J = 17.0, 4.9 Hz, 1H), 2.28 (s, 3H). HRMS (ESI) calcd. for C_{25}H_{23}N_{2}O_{2}+(M+H\rangle): 383.1754, found: 383.1753.

2-(1-(4-methylbenzyl)-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3p)

68%, 25.8 mg, white solid, m.p.: 73.6-76.8 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.30 – 7.25 (m, 3H), 7.11 – 7.02 (m, 6H), 6.63 (dd, J = 10.1, 3.1 Hz, 1H), 6.44 (dd, J = 10.2, 3.1 Hz, 1H), 6.26 (dd, J = 10.1, 2.0 Hz, 1H), 5.83 (dd, J = 10.2, 2.0 Hz, 1H), 4.51 (d, J = 14.9 Hz, 1H), 4.26 (d, J = 14.9 Hz, 1H), 3.55 (d, J = 12.6 Hz, 1H), 3.44 (dt, J = 12.6, 4.8 Hz, 1H), 3.05 (dd, J = 17.0, 4.7 Hz, 1H), 2.67 (dd, J = 17.0, 4.9 Hz, 1H), 2.31 (s, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 184.2, 171.7, 147.9, 145.4, 137.8, 133.8, 132.1, 131.3, 131.1, 129.3, 128.9, 128.5, 128.1, 116.5, 65.2, 54.1, 45.4, 40.5, 21.1, 17.6. HRMS (ESI) calcd. for C_{25}H_{22}N_{2}O_{2}Na+(M+Na\rangle): 405.1573, found: 405.1576.

2-(1-benzyl-7-fluoro-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3q)

55%, 21.1 mg, white solid, m.p.: 105.0-107.3 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.33 – 7.30 (m, 3H), 7.28 – 7.25 (m, 3H), 7.25 – 7.21 (m, 2H), 7.10 – 7.05 (m, 3H), 6.46 (dd, J = 10.1, 2.8 Hz, 1H), 6.21 (dd, J = 11.7, 2.8 Hz, 1H), 5.86 (dd, J = 10.1, 7.1 Hz, 1H), 4.51 (d, J = 15.1 Hz, 1H), 4.33 (d, J = 15.1 Hz, 1H), 3.61 (d, J = 12.6 Hz, 1H), 3.49-3.43 (m, 1H), 3.07 (dd, J = 17.1, 4.7 Hz, 1H), 2.70 (dd, J = 17.1, 4.9 Hz, 1H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 176.9, 176.7, 171.5, 154.9 (d, J = 272.4 Hz), 146.1, 138.6, 134.9, 130.7, 130.2, 130.0, 129.4, 129.2, 128.5, 128.5, 127.9, 126.6, 123.4, 123.2, 116.3, 66.8, 66.7, 54.7, 45.1, 40.4, 17.6. HRMS (ESI) calcd. for C_{24}H_{20}FN_{2}O_{2}+(M+H\rangle): 387.1503, found: 387.1507.

2-(1-benzyl-7-chloro-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3r)

54%, 21.6 mg, white solid, m.p.: 125.6-128.3 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.35 – 7.28 (m, 6H), 7.22 – 7.16 (m, 2H), 7.08-7.01 (m, 2H), 6.72 (d, J = 2.9 Hz, 1H), 6.45 (dd, J = 10.1, 2.9 Hz, 1H), 5.91 (d, J = 10.1 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 4.24 (d, J = 14.8 Hz, 1H), 3.58 (d, J = 12.6 Hz, 1H), 3.47-3.40 (m, 1H), 3.07 (dd, J = 17.0, 4.7 Hz, 1H), 2.69 (dd, J = 17.0, 4.9 Hz, 1H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 177.2, 171.3, 145.6, 143.8, 136.7, 135.4, 130.9, 130.0, 129.3, 129.2, 128.9, 128.7, 128.3, 127.9, 116.3, 66.9, 54.3, 45.9, 40.4, 17.7. HRMS (ESI) calcd. for C_{24}H_{19}ClN_{2}O_{2}+(M+Na\rangle): 425.1027, found: 425.1029.
1-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)cyclopropane-1-carbonitrile (3s)

53%, 20.7 mg, white solid, m.p.: 104.3-106.8 °C. 

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.26 – 7.22 (m, 6H), 7.22 – 7.18 (m, 2H), 7.03 (dd, $J = 6.5$, 3.1 Hz, 2H), 6.59 (dd, $J = 10.1$, 3.1 Hz, 1H), 6.44 (dd, $J = 10.2$, 3.1 Hz, 1H), 6.25 (dd, $J = 5.5$Hz, 1H), 5.79 (dd, $J = 5.5$Hz, 1H), 4.52 (d, $J = 14.9$ Hz, 1H), 4.27 (d, $J = 14.9$ Hz, 1H), 3.25 – 3.13 (m, 2H), 1.39 – 1.26 (m, 4H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 184.5, 176.1, 149.0, 146.3, 137.7, 133.1, 131.8, 130.7, 128.7, 128.6, 128.4, 128.0, 127.8, 65.4, 57.5, 54.5, 38.7, 14.6. HRMS (ESI) calcd. for C$_{26}$H$_{23}$N$_2$O$_2$+(M+H$^+$): 395.1754, found: 395.1752.

2-(-1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)-2-methylpropanenitrile (3t)

(d.r.= 1.0: 0.4)

34%, 13.2 mg, white solid, m.p.: 85.7-87.1 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.39 – 7.10 (m, 9H), 7.08 – 6.99 (m, 1H), 6.62 – 6.53 (m, 1H), 6.46-6.33 (m, 3.0 Hz, 1H), 6.28 – 6.16 (m, 1H), 5.80 (dd, $J = 10.2$, 1.8 Hz, 1H), 4.61 (dd, $J = 78.1$, 1.8 Hz, 1H), 1.67 (d, $J = 7.3$ Hz, 1H), 1.23 (d, $J = 18.0$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 184.2, 171.8, 149.0, 148.2, 146.6, 137.1, 134.2, 131.8, 131.5, 130.8, 128.7, 128.6, 128.5, 128.0, 127.9, 123.0, 64.5, 57.5, 52.6, 50.5, 45.5, 35.9, 25.6, 14.6. HRMS (ESI) calcd. for C$_{26}$H$_{25}$N$_2$O$_2$+(M+H$^+$): 397.1911, found: 397.1914.

2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)pentanenitrile (3u)

37%, 14.5 mg, white solid, m.p.: 94.3-95.6 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.33 – 7.16 (m, 8H), 7.12 – 7.01 (m, 2H), 6.65 – 6.52 (m, 1H), 6.51 – 6.38 (m, 1H), 6.27-6.17 (m, 2.0 Hz, 1H), 5.85 – 5.76 (m, 1H), 4.68 – 4.48 (m, 1H), 4.30-4.11 (m, 1H), 3.69 – 3.53 (m, 1H), 3.39 – 3.16 (m, 1H), 1.55-1.41 (m, 1H), 1.36 – 1.17 (m, 5H), 1.01 – 0.86 (m, 1H), 0.79 (t, $J = 7.1$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 184.5, 184.2, 176.1, 172.1, 149.0, 148.1, 146.3, 146.2, 137.72, 136.9, 133.1, 131.8, 131.7, 130.9, 130.7, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 119.4, 65.4, 65.2, 57.5, 52.8, 45.7, 45.4, 38.7, 33.9, 32.6, 29.7, 20.8, 14.6, 13.1. HRMS (ESI) calcd. for C$_{27}$H$_{27}$N$_2$O$_2$+(M+H$^+$): 411.2067, found: 411.2070.

2-(-1-benzyl-2,8-dioxo-4-propyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3v)

32%, 11.2 mg, white solid, m.p.: 73.4-75.1 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.69 – 7.45 (m, 6H), 7.22 – 7.18 (m, 2H), 7.03 (dd, $J = 6.5$, 3.1 Hz, 2H), 6.59 (dd, $J = 10.1$, 3.1 Hz, 1H), 6.44 (dd, $J = 10.2$, 3.1 Hz, 1H), 6.25 (dd, $J = 5.5$Hz, 1H), 5.79 (dd, $J = 5.5$Hz, 1H), 4.52 (d, $J = 14.9$ Hz, 1H), 4.27 (d, $J = 14.9$ Hz, 1H), 3.25 – 3.13 (m, 2H), 1.39 – 1.26 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 184.5, 176.1, 149.0, 146.3, 137.7, 133.1, 131.8, 130.7, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 119.4, 65.4, 65.2, 57.5, 52.8, 45.7, 45.4, 38.7, 33.9, 32.6, 29.7, 20.8, 14.6, 13.1. HRMS (ESI) calcd. for C$_{27}$H$_{27}$N$_2$O$_2$+(M+H$^+$): 411.2067, found: 411.2070.
7.25 (d, \( J = 1.5 \) Hz, 4H), 7.15 (dd, \( J = 7.2, 2.3 \) Hz, 2H), 6.51-6.43 (m, 2H), 6.30-6.23 (m, 2H), 4.54 (d, \( J = 15.0 \) Hz, 1H), 4.16 (d, \( J = 15.0 \) Hz, 1H), 3.11 (dd, \( J = 17.1, 4.5 \) Hz, 1H), 2.84 – 2.76 (m, 1H), 2.62 (dt, \( J = 11.3, 4.7 \) Hz, 1H), 2.39 – 2.32 (m, 1H), 2.26 – 2.17 (m, 1H), 1.38 – 1.31 (m, 3H), 0.86 (t, \( J = 7.1 \) Hz, 3H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 184.5, 172.4, 149.1, 145.3, 137.0, 131.7, 131.6, 128.7, 128.4, 127.9, 116.8, 64.1, 47.2, 45.3, 43.3, 31.7, 21.2, 18.9, 14.1. HRMS (ESI) calcd. for C\(_{21}\)H\(_{22}\)N\(_2\)NaO\(_2^+\) (M+Na\(^+\)) : 357.1573, found: 357.1571.

5. Copies of \(^1H\), \(^{19}F\) and \(^{13}C\) NMR spectra

2-(1-methyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3a)
1,3-dimethyl-4-phenyl-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (3a’)

...
2-(4-(4-chlorophenyl)-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3b)
2-(4-(2-chlorophenyl)-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3c)
2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3d)
2-(1-benzyl-2,8-dioxo-4-(4-(trifluoromethyl)phenyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3e)
2-(1-benzyl-4-(4-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3f)
2-(1-benzyl-4-(4-bromophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3g)
2-(1-benzyl-4-(4-nitrophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3h)
2-(1-benzyl-2,8-dioxo-4-(m-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3i)
2-(1-benzyl-4-(3-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3j)
2-(1-benzyl-4-(3-bromophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3k)
2-(1-benzyl-4-(3,5-difluorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3l)
2-(1-benzyl-4-(2-chlorophenyl)-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3m)
2-(1-benzyl-2,8-dioxo-4-(o-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-y)acetonitrile (3n)
2-(1-benzyl-2,8-dioxo-4-(p-tolyl)-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3o)
2-(1-(4-methylbenzyl)-2,8-dioxo-4-phenyl-1-azaspiro[4,5]deca-6,9-dien-3-yl)acetonitrile (3p)
S30

2-(1-benzyl-7-fluoro-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3q)
2-(1-benzyl-7-chloro-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3r)
1-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)cyclopropane-1-carbonitrile (3s)
2-((1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)-2-methylpropanenitrile (3t)
2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)pentanenitrile (3u)
2-(1-benzyl-2,8-dioxo-4-propyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile (3v)
2-(1-benzyl-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-6,9-dien-3-yl)acetonitrile ([D$_2$]-3d)