Isoquinoline N-oxide synthesis under Pd-catalysed C-H activation/annulation processes

Bingyao Li, Pingxuan Jiao, Hongban Zhong, Jianhui Huang*

Tianjin Key Laboratory for Modern Drug Delivery & High-Efficiency, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China.

Tel.: +86-22-2740-5316; fax: +86-22-2740-4031; e-mail: jhuang@tju.edu.cn

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General Information

Flash chromatography was performed on silica gel 100-200 m. The solvent system used was a gradient of petroleum ether/ethyl acetate, increasing in polarity to ethyl acetate. Thin layer chromatography (TLC) was performed on glass backed plates pre-coated with silica (GF254), which were developed using standard visualizing agents. $^1$H and $^{13}$C NMR spectra were recorded on a 600 MHz BRUKER AVANCE spectrometer at 25°C (except for noted). $^1$H: Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CHCl$_3$: $\delta$ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants (J) in Hz. $^{13}$C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl$_3$: $\delta$ 77.0 ppm). High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on a Q-TOF micro (Waters) spectrometer. Melting points were performed on recrystallized solids and recorded on a national standard melting point apparatus and are uncorrected.
General Procedures:

All the known oximes 1a-1i were prepared following literature procedure\(^1\) and the analytical data are agreed with those data which have been reported previously.

**General Procedure A: Synthesis of isoquinoline oxides**

A solution of oxime (0.3 mmol), alkyne (0.45 mmol), Pd(OAc)\(_2\) (10 mol%), ZnBr\(_2\) (0.3 mmol), TFA (0.06 mmol) in PhCl : dioxane = 2 : 1 (1.5 mL) was heated at 120 °C under air. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was cooled down to room temperature. The mixture was washed with sat. aq NaHCO\(_3\) (15 mL) to neutralize acid. The aqueous layers were extracted with ethyl acetate (15 mL x 3). The combined organic layer was dried over anhydrous Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure to provide the crude product. The crude product was purified by flash column chromatography on silica gel.

**Analytical data of compounds 3a-l**

**1-Methyl-3,4-diphenylisoquinoline 2-oxide (3a)**

Following general procedure A, oxime 1a (0.3 mmol, 40.5 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)\(_2\) (6.7 mg, 10 mol%), ZnBr\(_2\) (62.5 mg, 0.3 mmol), TFA (6.84 mg, 0.06 mmol) in PhCl : dioxane = 2 : 1 (1.5 mL) was heated at 120 °C for 6 h to give the desired isoquinoline oxide 3a (83.1 mg, 89%) as a pale yellow solid: Mp:
237-239 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 8.05 (d, \(J = 8.5\) Hz, 1H), 7.65-7.62 (m, 1H), 7.47 (d, \(J = 7.5\) Hz, 2H), 7.27-7.20 (m, 7H), 7.19-7.17 (m, 1H), 7.13 (d, \(J = 7.5\) Hz, 2H), 2.99 (s, 3H). The analytical data are consistently agreed with those have been previously reported in the literature.\(^2\)

### 1,6-Dimethyl-3,4-diphenylisoquinoline 2-oxide (3b)

Following general procedure A, oxime 1b (0.3 mmol, 45 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)\(_2\) (6.7 mg, 10 mol%), ZnBr\(_2\) (63 mg, 0.3 mmol), TFA (6.8 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 5 h to give the desired isoquinoline oxide 3b (75 mg, 77%) as a pale yellow solid: Mp: 245-247 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.94 (d, \(J = 8.5\) Hz, 1H), 7.46 (d, \(J = 8.5\) Hz, 1H), 7.28-7.17 (m, 9H), 7.12 (d, \(J = 6.7\) Hz, 2H), 2.98 (s, 3H), 2.39 (s, 3H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 145.7, 145.4, 138.8, 135.4, 133.9, 133.3, 130.8, 130.7, 130.6, 129.5, 128.1, 127.9, 127.7, 127.6, 126.4, 125.8, 124.1, 21.9, 13.6; HRMS (ESI) m/z calcd for C\(_{29}\)H\(_{19}\)NO (M+H) 326.1545, found 325.1546.

### 6-Fluoro-1-methyl-3,4-diphenylisoquinoline 2-oxide (3c)

Following general procedure A, oxime 1c (0.3 mmol, 46 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)\(_2\) (6.7 mg, 10 mol%), ZnBr\(_2\) (63 mg, 0.3 mmol), TFA (6.8 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 8 h to give the desired isoquinoline oxide 3c (54 mg, 50%) as a pale yellow solid: Mp: 177-178°C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 8.05 (dd, \(J = 9.0\), 3.5 Hz, 1H), 7.44-7.36 (m, 1H), 7.29-7.27 (m, 3H), 7.25-7.19 (m, 5H) 7.13-7.08 (m, 3H), 2.99 (s, 3H), \(^{13}\)C NMR (151
MHz, CDCl₃): δ 161.3 (d, J = 250.5 Hz), 146.72, 144.95, 134.90, 133.82 (d, J = 5.3 Hz), 132.93, 130.47, 130.36 (d, J = 9.0 Hz), 128.29, 128.10, 127.93, 127.77, 126.84 (d, J = 8.7 Hz), 125.43, 118.76 (d, J = 25.3 Hz), 110.90 (d, J = 22.9 Hz), 13.81; HRMS (ESI) m/z calcd for C₂₂H₁₆FNO (M+H) 330.1294, found 330.1290.

6-Chloro-1-methyl-3,4-diphenylisoquinoline 2-oxide (3d)

Following general procedure A, oxime 1d (0.3 mmol, 51 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)₂ (6.7 mg, 10 mol%), ZnBr₂ (62.5 mg, 0.3 mmol), TFA (6.84 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 8 h to give the desired isoquinoline oxide 3d (47 mg, 45%) as a pale yellow solid: Mp: 206-208 °C; ¹H NMR (600 MHz, CDCl₃): δ 7.96 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.42 (s, 1H), 7.29-7.26 (m, 3H), 7.24-7.18 (m, 5H), 7.11 (d, J = 6.0 Hz, 2H), 2.96 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 146.9, 144.9, 134.7, 134.3, 133.6, 132.8, 130.5, 130.4, 129.7, 129.5, 128.3, 128.1, 128.0, 127.8, 126.7, 125.7, 125.6, 13.7; HRMS (ESI) m/z calcd for C₂₂H₁₆³⁵ClNO (M+H) 346.0999, found 346.1001.

6-Methoxy-1-methyl-3,4-diphenylisoquinoline 2-oxide (3e)

Following general procedure A, oxime 1e (0.3 mmol, 50 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)₂ (6.7 mg, 10 mol%), ZnBr₂ (63 mg, 0.3 mmol), TFA (6.8 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 6 h to give the desired isoquinoline oxide 3e (42 mg, 41%) as a pale yellow solid: Mp: 236-237 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.96 (d, J = 8.5 Hz, 1H), 7.29-7.15 (m, 9H), 7.13 (d, J = 5.5 Hz, 2H), 6.75 (s, 1H), 3.68 (s, 3H), 2.96 (s, 3H); ¹³C NMR (151 MHz, CDCl₃):
δ159.5, 145.9, 145.3, 135.5, 133.4, 133.3, 131.1, 130.6, 130.5, 128.2, 127.9, 127.68, 127.65, 126.1, 123.5, 120.7, 105.7, 55.3, 13.8; HRMS (ESI) m/z calcd for C_{23}H_{19}NO_{2} (M+H) 342.1494, found 342.1496.

1-Ethyl-6-methyl-3,4-diphenylisoquinoline 2-oxide (3f)

Following general procedure A, oxime 1f (0.3 mmol, 49 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)$_2$ (6.7 mg, 10 mol%), ZnBr$_2$ (63 mg, 0.3 mmol), TFA (6.84 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 5 h to give the desired isoquinoline oxide 3f (73 mg, 72%) as a pale yellow solid: Mp: 260-262 °C; $^1$H NMR (600 MHz, CDCl$_3$): δ 8.01 (d, $J = 8.0$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.30-7.20 (m, 6H), 7.20-7.08 (m, 5H), 3.58 (d, $J = 6.3$ Hz, 2H), 2.39 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 145.6, 140.4, 135.2, 134.5, 132.6, 131.1, 130.7, 129.4, 129.3, 128.1, 127.9, 127.6, 127.5, 125.9, 125.3, 124.8, 123.5, 22.0, 21.1, 11.8; HRMS (ESI) m/z calcd for C$_{24}$H$_{21}$NO (M+H) 340.1701, found 340.1703.

7-chloro-1-methyl-3,4-diphenylisoquinoline 2-oxide (3g)

Following general procedure A, oxime 1g (0.3 mmol, 51 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)$_2$ (6.7 mg, 10 mol%), ZnBr$_2$ (63 mg, 0.3 mmol), TFA (6.8 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 6 h to give the desired isoquinoline oxide 3g (50.7 mg, 49%) as a pale yellow solid: Mp: 247-249 °C; $^1$H NMR (600 MHz, CDCl$_3$): δ 8.01 (s, 1H), 7.43-7.37 (m, 2H), 7.30-7.26 (m, 5H), 7.25-7.19 (m, 5H), 7.13-7.09 (m, 2H), 2.96 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 146.16, 144.17, 134.90, 134.82, 134.29, 132.76, 130.52, 130.51, 129.14, 128.57,
128.6, 128.2, 128.1, 127.9, 127.8, 127.1, 122.8, 13.6; HRMS (ESI) m/z calcd for C_{22}H_{16}^{35}ClNO (M+H) 346.0999, found 346.1005.

7-Methoxy-1-methyl-3,4-diphenylisoquinoline 2-oxide (3h)

Following general procedure A, oxime 1h (0.3 mmol, 50 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)$_2$ (6.7 mg, 10 mol%), ZnBr$_2$ (63 mg, 0.3 mmol), TFA (6.8 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 8 h to give the desired isoquinoline oxide 3h (54 mg, 53%) as a pale yellow solid: Mp: > 300 °C; $^1$H NMR (600 MHz, CDCl$_3$): δ 7.37 (d, $J = 9.0$ Hz, 1H), 7.28-7.20 (m, 8H), 7.20-7.16 (m, 1H), 7.14-7.08 (m, 3H), 3.98 (s, 3H), 2.96 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 159.6, 143.8, 143.6, 135.6, 134.2, 133.4, 130.8, 130.6, 129.7, 128.5, 128.0, 127.8, 127.7, 127.6, 124.0, 119.9, 102.7, 55.6, 13.6; HRMS (ESI) m/z calcd for C$_{23}$H$_{19}$NO$_2$ (M+H) 342.1494, found 342.1494.

1,3,4-Triphenylisoquinoline 2-oxide (3i)

Following general procedure A, oxime 1i (0.3 mmol, 59 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)$_2$ (6.7 mg, 10 mol%), ZnBr$_2$ (63 mg, 0.3 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 4 h to give the desired isoquinoline oxide 3i (86 mg, 77%) as a pale yellow solid: Mp: 264-266 °C; $^1$H NMR (600 MHz, CDCl$_3$): δ 7.64 (d, $J = 7.5$ Hz, 2H), 7.61-7.56 (m, 3H), 7.55-7.50 (m, 2H), 7.50-7.42 (m, 2H), 7.35-7.27 (m, 5H), 7.25-7.16 (m, 5H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 146.4, 135.9, 135.4, 132.7, 131.6, 130.9, 130.6, 130.6, 129.3, 129.1, 129.0, 128.6, 128.5, 128.2,
128.0, 127.9, 127.8, 127.6, 126.4, 125.7, 100.0; HRMS (ESI) \textit{m/z} calcd for C_{27}H_{19}NO (M+H) 374.1545, found 374.1545.

1-Phenyl-3,4-dipropylisoquinoline 2-oxide (3j)

Following general procedure A, oxime 1i (0.3 mmol, 59 mg), dipropylacetylene (50 mg, 0.45 mmol), Pd(OAc)$_2$ (6.7 mg, 10 mol%), ZnBr$_2$ (63 mg, 0.3 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 5 h to give the desired isoquinoline oxide 3j (54 mg, 59%) as a pale yellow solid: Mp: 172-174 °C; $^1$H NMR (600 MHz, CDCl$_3$): δ 8.15 (d, $J = 8.0$ Hz, 1H), 7.97 (t, $J = 8.0$ Hz, 1H), 7.79-7.72 (m, 3H), 7.66 (t, $J = 7.5$ Hz, 1H), 7.64-7.60 (m, 3H), 3.47-3.36 (m, 2H), 3.22-3.12 (m, 2H), 1.89-1.88 (m, 2H), 1.80-1.79 (m, 2H), 1.22-1.17 (m, 3H), 1.15-1.10 (m, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$): δ 147.0, 136.2, 135.7, 134.5, 130.8, 130.5, 130.3, 129.6, 128.6, 128.2, 127.1, 124.0, 100.0, 31.0, 30.9, 24.0, 22.1, 14.7, 14.4; HRMS (ESI) \textit{m/z} calcd for C$_{21}$H$_{23}$NO (M+H) 306.1858, found 306.1861.

4-Ethyl-1,3-diphenylisoquinoline 2-oxide (3k)

Following general procedure A, oxime 1i (59 mg, 0.3 mmol), 1-phenyl-1-butyne (59 mg, 0.45 mmol), Pd(OAc)$_2$ (6.7 mg, 10 mol%), ZnBr$_2$ (63 mg, 0.3 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 5 h to give the desired isoquinoline oxide 3k (69 mg, 71%) as pale yellow solid: Mp: 202-203 °C; $^1$H NMR (600 MHz, CDCl$_3$): δ 8.02 (d, $J = 8.0$ Hz, 1H), 7.59 (t, $J = 8.0$ Hz, 1H), 7.57-7.45 (m, 9H), 7.45-7.40 (m, 3H), 2.89 (q, $J = 7.5$ Hz, 2H), 1.25 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR
(151 MHz, CDCl₃): δ 146.4, 144.6, 135.4, 133.5, 131.6, 130.6, 129.7, 129.2, 128.9, 128.5, 128.4, 128.3, 128.2, 128.0, 126.4, 123.9, 100.0, 22.8, 14.9; HRMS (ESI) m/z calcd for C₂₃H₁₉NO (M+H) 326.1545, found 326.1543.

3-(4-Methoxyphenyl)-1-methyl-4-phenylisoquinoline 2-oxide (3l)
4-(4-Methoxyphenyl)-1-methyl-3-phenylisoquinoline 2-oxide (3l')

Following general procedure A, oxime 1a (0.3 mmol, 41 mg), 1-methoxy-4-phenylethynyl)benzene (94 mg, 0.45 mmol), Pd(OAc)₂ (6.7 mg, 10 mol%), ZnBr₂ (63 mg, 0.3 mmol), TFA (6.8 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 7 h to give the desired isoquinoline oxide 3l and 3l' as a 2:1 mixture (57 mg, 56%) as a pale yellow solid; ¹H NMR (600 MHz, CDCl₃): δ 8.11 (d, J = 8.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.58-7.47 (m, 2H), 7.31-7.16 (m, 6H), 7.13 (d, J = 8.5 Hz, 1.34H), 7.03 (d, J = 8.5 Hz, 0.65H), 6.79 (d, J = 8.5 Hz, 0.69H), 6.73 (d, J = 8.5 Hz, 1.32H), 3.77 (s, 1H), 3.72 (s, 2H), 3.03 (s, 3H); ¹³C NMR (151 MHz, CDCl₃): δ 159.1, 158.9, 145.5, 135.4, 134.7, 133.1, 132.1, 131.8, 130.6, 129.7, 128.6, 128.1, 127.9, 127.7, 127.6, 126.9, 126.8, 125.1, 124.4, 113.6, 113.2, 55.2, 55.1, 13.8; HRMS (EI+): calcd for C₂₃H₁₉NO₂ 341.1416, found 341.1413.
General Procedure B: Synthesis of isoquinolines

A solution of oxime (0.3 mmol), alkyne (0.45 mmol), Pd(OAc)$_2$ (10 mol%), ZnBr$_2$ (0.3 mmol), TFA (0.06 mmol) in PhCl : dioxane = 2 : 1 (1.5 mL) was heated at 120 °C under air. The reaction was monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure. Zn powder (1.5 mmol) and MeCN (1.5 mL) was added, and then the mixture was heated at 80 °C for 5-10 h. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature, and H$_2$O (15 mL) was added, extracted with ethyl acetate (15 mL x 3). The combined organic layer was dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure to provide the crude product. The crude product was purified by flash column chromatography on silica gel.

Analytical data of compounds 4a-d

1-Methyl-3,4-diphenylisoquinoline (4a)

Following general procedure B, oxime 1a (0.3 mmol, 41 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)$_2$ (6.7 mg, 10 mol%), ZnBr$_2$ (63 mg, 0.3 mmol), TFA (6.8 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 6 h, then the solvents were removed followed by the introduction of Zn powder (1.5 mmol) and MeCN (1.5 mL) was heated at 80 °C for 10 h to give the desired isoquinoline 4a (72.6 mg, 82%) as a white solid: Mp: 152-153 °C; $^1$H NMR (600 MHz, CDCl$_3$): δ 8.23-8.20 (m, 1H), 7.68-7.65 (m, 1H), 7.63-7.58 (m, 2H), 7.38-7.34 (m, 3H), 7.34-7.30 (m, 2H),
7.23 (d, \(J = 6.6\) Hz, 2H), 7.21-7.15 (m, 3H), 3.09 (s, 3H). The analytical data are consistently agreed with those have been previously reported in the literature.³

1,6-Dimethyl-3,4-diphenylisoquinoline (4b)

Following general procedure B, oxime 1b (0.3 mmol, 45 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)\(_2\) (6.7 mg, 10 mol%), ZnBr\(_2\) (63 mg, 0.3 mmol), TFA (6.8 mg, 0.06 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 5 h, then the solvents were removed followed by the introduction of Zn powder (1.5 mmol) and MeCN (1.5 mL) was heated at 80 °C for 10 h to give the desired isoquinoline 4b (62.1 mg, 67%) as a white solid: Mp: 168-169 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): δ 8.09 (d, \(J = 8.0\) Hz, 1H), 7.42-7.39 (m, 2H), 7.36-7.30 (m, 5H), 7.23-7.20 (m, 2H), 7.20-7.13 (m, 3H), 3.05 (s, 3H), 2.43 (s, 3H). The analytical data are consistently agreed with those have been previously reported in the literature.³

1,3,4-Triphenylisoquinoline (4c)

Following general procedure B, oxime 1i (0.3 mmol, 59 mg), diphenylethyne (80 mg, 0.45 mmol), Pd(OAc)\(_2\) (6.7 mg, 10 mol%), ZnBr\(_2\) (63 mg, 0.3 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 4 h, then the solvents were removed followed by the introduction of Zn powder (1.5 mmol) and MeCN (1.5 mL) was heated at 80 °C for 8 h to give the desired isoquinoline 4c (75 mg, 70%) as a white solid: Mp: 181-183 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): δ 8.18 (d, \(J = 8.5\) Hz, 1H), 7.82 (d, \(J = 7.0\) Hz, 2H), 7.72 (d, \(J = 8.5\) Hz, 1H), 7.59 (t, \(J = 7.1\) Hz, 1H), 7.57-7.53 (m, 2H),
7.52-7.47 (m, 2H), 7.44-7.41 (m, 2H), 7.40-7.34 (m, 3H), 7.31-7.28 (m, 2H), 7.22-7.13 (m, 3H). The analytical data are consistently agreed with those have been previously reported in the literature.³

1-Phenyl-3,4-dipropylisoquinoline (4d)

Following general procedure B, oxime 1i (0.3 mmol, 59 mg), dipropylacetylene (50 mg, 0.45 mmol), Pd(OAc)₂ (6.7 mg, 10 mol%), ZnBr₂ (63 mg, 0.3 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 5 h, then the solvents were removed followed by the introduction of Zn powder (1.5 mmol) and MeCN (1.5 mL) was heated at 80 °C for 8 h to give the desired isoquinoline 4d (45 mg, 52%) as a colorless oil; ¹H NMR (600 MHz, CDCl₃) δ 8.04 (dd, J = 8.5, 4.0 Hz, 2H), 7.70-7.65 (m, 3H), 7.52 (t, J = 7.5 Hz, 2H), 7.49-7.45 (m, 1H), 7.45-7.40 (m, 1H), 3.11-3.06 (m, 2H), 3.04 (td, J = 8.1, 2.4 Hz, 2H), 1.92-1.85 (m, 2H), 1.81-1.73 (m, 2H), 1.16 (t, J = 7.0 Hz, 3H), 1.08 (td, J = 7.0, 2.3 Hz, 3H). The analytical data are consistently agreed with those have been previously reported in the literature.³

Intramolecular KIE study experiments in [D5]1i

Oxime [D5]-1i (0.2 mmol, 39 mg), diphenylethyne (53 mg, 0.30 mmol), Pd(OAc)₂ (4.5 mg, 10 mol%), ZnBr₂ (45 mg, 0.2 mmol) in in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 1 h. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature, and H₂O (10 mL) was added, extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to provide the crude product. The crude product was purified by flash column chromatography on silica
gel to give a mixture of 3iD and 3iD' (18 mg, 24%) as a pale yellow solid. The ratio of 3iD:3iD' in the crude mixture of products was determined by $^1$H NMR spectroscopy. The kinetic isotopic effect value is $k_H/k_D$=2.

**Intermolecular KIE study experiments in 1a and [D5]1a**

A mixture of oxime 1a (0.1 mmol, 14 mg) and [D5]-1a (0.1 mmol, 14 mg), diphenylethyne (53 mg, 0.30 mmol), Pd(OAc)$_2$ (4.5 mg, 10 mol%), ZnBr$_2$ (45 mg, 0.2 mmol), TFA (4.6 mg, 0.04 mmol) in PhCl:dioxane (2:1) (1.5 mL) was heated at 120 °C for 1.5 h. After the reaction was completed, the reaction mixture was cooled down to room temperature. The mixture was washed with sat. aq NaHCO$_3$ (10 mL) to neutralize acid. The aqueous layers were extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure to provide the crude product. The crude product was purified by flash column chromatography on silica gel to give 3a and 3aD (28 mg, 44%) as a pale yellow solid. The ratio of 3a:3aD in the crude mixture of products was determined by $^1$H NMR spectroscopy. The kinetic isotopic effect value is $k_H/k_D$=3.

**References:**

$^{1}$H and $^{13}$C NMR Spectra:

1H spectrum of compound 3a
$^1$H and $^{13}$C NMR spectra of compounds 3l and 3l'
NOESY spectrum of compound 3l
$^1$H NMR spectrum of compound 4a

$^1$H NMR spectrum of compound 4b
$^1$H NMR spectrum of compound 4c

$^1$H NMR spectrum of compound 4d
$^1$H NMR spectrum of 3a and 3aD

$^1$H NMR spectrum of 3iD and 3iD'

Diagram showing the NMR spectra with detailed chemical shifts and structures.