Supplementary Information

Aryl C-H amination initiated by laccase-mediated oxidation of 4-phenylurazole

Yu-Jue Chen, Guo-Yan Zhang, Yan-Hong He*, Zhi Guan*

Key Laboratory of Applied Chemistry of Chongqing Municipality, School of Chemistry and Chemical Engineering,
Southwest University, Chongqing 400715, China

E-mails: heyh@swu.edu.cn (for Y.-H. He); guanzhi@swu.edu.cn (for Z. Guan)

Contents

1. Materials .......................................................................................................................................2
2. General methods ...........................................................................................................................2
3. Cyclic voltammetry ......................................................................................................................2
4. Characterization data of the products ...........................................................................................4
5. References ..................................................................................................................................10
6. $^1$H NMR and $^{13}$C NMR spectra of the products. .................................................................11
7. HRMS spectra...............................................................................................................................27
1. Materials

Laccase (Novozym 51003): purified from *Myceliophthora* which is produced by genetically modified *Aspergillus oryzae* was purchased from Sigma-Aldrich, Shanghai, China. [SAE0050-250 ML, Lot#SLBQ7425V, 1123.5 U/mL liquid. One unit: LAMU (Laccase Unit). 1 LAMU is defined as the amount of enzyme which oxidizes 1 mmol of syringaldazine per minute, at pH 7.5 and 30 °C. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification.

2. General methods

Reactions were monitored by thin-layer chromatography (TLC) with Haiyang GF254 silica gel plates (Qingdao Haiyang chemical industry Co Ltd. Qingdao, China) using UV light and vanillic aldehyde as visualizing agents. Flash column chromatography was performed using 200-300 mesh silica gel at increased pressure. ¹H NMR and ¹³C NMR spectra were recorded on Bruker-AM 600 (600 MHz) (Bruker BioSpin AG Ltd., Beijing, China). Chemical shifts were reported in ppm from TMS with the solvent resonance as the internal standard. Data were reported as follows: chemical shifts (δ) in ppm, coupling constants (J) in Hz, and solvent (DMSO-đ or CDCl₃). High-resolution mass spectra were obtained by using ESI ionization sources (Varian QFT-ESI).

3. Cyclic voltammetry

The cyclic voltammetry experiments were performed, and the oxidation potentials of 1a and 2 were determined as: 1a (Eox = +0.839 V in EtOH/H₂O=1:9) (Figure S1), 2 (Eox = +0.707 V in EtOH/H₂O=1:9) (Figure S2) and 3a (Eox = +0.643 V in EtOH/H₂O=1:9). The electrochemical measurements were carried out by a computer-controlled electrochemical analyzer. Cyclic voltammetry was performed in a three-electrode cell (volume 10 mL; LiClO₄ 0.1 M as the supporting electrolyte, 5 mM concentration of the tested compound) with glassy carbon (diameter 3 mm) as the working electrode, Pt wire as the auxiliary electrode, and Ag/AgCl (saturate KCl) as the reference electrode.
Figure S1. Cyclic voltammetry (CV) of 1a.

Figure S2. Cyclic voltammetry (CV) of 2.
4. Characterization data of the products

**1-(4-(dimethylamino)phenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3a):** White solid; m.p. 216.0-218.0 °C; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 11.36 (s, 1H), 7.51 (d, $J = 4.3$ Hz, 4H), 7.45-7.37 (m, 3H), 6.80 (d, $J = 9.0$ Hz, 2H), 2.91 (s, 6H); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 152.4, 150.1, 149.3, 132.3, 129.3, 128.4, 126.9, 126.0, 122.7, 112.9, 40.7.

**1-(2-bromo-4-(dimethylamino)phenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3b):** White solid; m.p. 178.5-180.1 °C; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.26 (s, 1H), 7.56 (d, $J = 7.5$ Hz, 2H), 7.47 (t, $J = 7.7$ Hz, 2H), 7.38 (t, $J = 7.4$ Hz, 1H), 7.30 (d, $J = 8.8$ Hz, 1H), 6.91 (d, $J = 2.4$ Hz, 1H), 6.63-6.61 (m, 1H), 2.98 (s, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 153.4, 151.9, 151.6, 131.4, 130.5, 129.1, 128.3, 125.8, 123.8, 122.4, 116.0, 111.5, 40.3; HRMS (ESI) calcd for C$_{16}$H$_{13}$BrN$_4$O$_2$ (M+Na$^+$): 397.0271, found 397.0270.
1-(4-(dimethylamino)-2-methylphenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3c): White solid; m.p. 167.7-168.8 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.40 (s, 1H), 7.55 (d, \(J = 7.8\) Hz, 2H), 7.47 (t, \(J = 7.8\) Hz, 2H), 7.37 (t, \(J = 7.4\) Hz, 1H), 7.20 (d, \(J = 9.4\) Hz, 1H), 6.57 (s, 2H), 2.96 (s, 6H), 2.30 (s, 3H); \(^1\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 153.2, 151.0, 137.4, 131.5, 129.1, 128.2, 128.1, 125.7, 114.3, 110.6, 40.5, 18.3; HRMS (ESI) calcd for C\(_{17}\)H\(_{18}\)N\(_4\)O\(_2\) (M+Na\(^+\)): 333.1322, found 333.1320.

1-(4-(dimethylamino)-2-methoxyphenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3d): White solid; m.p. 183.4-184.8 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.66 (s, 1H), 7.56 (d, \(J = 7.6\) Hz, 2H), 7.46 (t, \(J = 7.8\) Hz, 2H), 7.37-7.33 (m, 2H), 6.28-6.26 (m, 1H), 6.23 (s, 1H), 3.83 (s, 3H), 2.97 (s, 6H); \(^1\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 155.5, 153.4, 152.2, 151.3, 131.7, 129.0, 128.2, 128.0, 125.8, 104.4, 96.1, 55.6, 40.5; HRMS (ESI) calcd for C\(_{17}\)H\(_{18}\)N\(_4\)O\(_3\) (M+Na\(^+\)): 349.1271, found 349.1272.

1-(4-(diethylamino)phenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3e): White solid; m.p.
175.0-176.8 °C; $^1$H NMR (600 MHz, DMSO-$d_6$): δ 11.31 (s, 1H), 7.52 (d, $J$ = 4.2 Hz, 4H), 7.44-7.42 (m, 1H), 7.36 (d, $J$ = 8.9 Hz, 2H), 6.74 (d, $J$ = 8.9 Hz, 2H), 3.34 (q, $J$ = 6.8 Hz, 4H), 1.10 (t, $J$ = 7.0, 6H); $^{13}$C NMR (150 MHz, DMSO-$d_6$): δ 152.4, 150.2, 146.5, 132.3, 129.3, 128.4, 126.8, 124.9, 123.5, 112.1, 44.3, 12.8. HRMS (ESI) calcd for C$_{18}$H$_{20}$N$_4$O$_2$ (M+H$^+$): 325.1659, found 325.1663.

1-(4-(benzyl(methyl)amino)phenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3f): White solid; m.p. 130.0-132.0 °C; $^1$H NMR (600 MHz, DMSO-$d_6$): δ 11.31 (s, 1H), 7.51 (d, $J$ = 4.3 Hz, 4H), 7.43 (dd, $J$ = 8.8, 4.4 Hz, 1H), 7.37 (d, $J$ = 9.0 Hz, 2H), 7.32 (t, $J$ = 7.5 Hz, 2H), 7.24 (d, $J$ = 7.2 Hz, 1H), 7.21 (d, $J$ = 7.6 Hz, 2H), 6.80 (d, $J$ = 9.0 Hz, 2H), 4.61 (s, 2H), 3.05 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$): δ 152.4, 150.2, 148.0, 139.2, 132.3, 129.3, 128.9, 128.4, 127.2, 127.2, 126.9, 125.8, 122.9, 112.6, 55.8, 39.2. HRMS (ESI) calcd for C$_{22}$H$_{20}$N$_4$O$_2$ (M+Na$^+$): 395.1478, found 395.1483.

1-(4-(benzyl(ethyl)amino)phenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3g): White solid; m.p. 170.0-172.0 °C; $^1$H NMR (600 MHz, DMSO-$d_6$): δ 11.32 (s, 1H), 7.50 (d, $J$ = 4.7 Hz, 4H), 7.43-7.39 (m, 1H), 7.32-7.30 (m, 4H), 7.26-7.20 (m, 3H), 6.73 (d, $J$ = 8.6 Hz, 2H), 4.56 (s, 2H), 3.50 (q, $J$ = 6.7 Hz, 2H), 1.14 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$): δ 160, 152.4, 150.2, 147.0, 139.6, 132.3, 129.3, 128.9, 128.4, 127.1, 127.0, 126.9, 125.4, 124.1, 123.3, 119.6, 112.5, 53.6, 45.6, 12.5. HRMS (ESI) calcd for C$_{23}$H$_{22}$N$_4$O$_2$ (M+Na$^+$): 409.1635, found 409.1642.
1-(4-(methyl(phenyl)amino)phenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione \((3h)\): White solid; m.p. 148.0-149.0 °C; \(^1\)H NMR (600 MHz, DMSO-\(d_6\)): \(\delta\) 11.41 (s, 1H), 7.52 (t, \(J = 6.5\) Hz, 6H), 7.48-7.41 (m, 1H), 7.31 (t, \(J = 7.8\) Hz, 2H), 7.08 (d, \(J = 8.8\) Hz, 2H), 7.03 (d, \(J = 7.9\) Hz, 2H), 6.98 (t, \(J = 7.3\) Hz, 1H), 3.28 (s, 3H); \(^1\)C NMR (150 MHz, DMSO-\(d_6\)): \(\delta\) 152.6, 150.1, 149.0, 146.7, 129.8, 129.4, 128.5, 127.0, 122.0, 121.7, 121.4, 120.9, 120.7, 40.6. HRMS (ESI) calcd for \(\text{C}_{21}\text{H}_{18}\text{N}_{4}\text{O}_{2}\) (M+Na\(^+\)): 381.1322, found 381.1326.

1-(2-hydroxynaphthalen-1-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione \((3i)\): White solid; m.p. 194.8-195.7 °C; \(^1\)H NMR (600 MHz, DMSO-\(d_6\)): \(\delta\) 10.95 (s, 2H), 7.98 (d, \(J = 9.0\) Hz, 1H), 7.92 (d, \(J = 8.1\) Hz, 1H), 7.83 (d, \(J = 8.4\) Hz, 1H), 7.60-7.55 (m, 5H), 7.45 (t, \(J = 7.2\) Hz, 1H), 7.41 (t, \(J = 7.32\) Hz, 1H), 7.30 (d, \(J = 8.9\) Hz, 1H); \(^1\)C NMR (150 MHz, DMSO-\(d_6\)): \(\delta\) 154.2, 152.7, 152.0, 133.1, 132.7, 132.0, 129.4, 128.6, 128.4, 128.2, 128.1, 126.7, 124.0, 121.7, 119.2, 114.6. HRMS (ESI) calcd for \(\text{C}_{18}\text{H}_{13}\text{N}_{3}\text{O}_{3}\) (M+Na\(^+\)): 342.0849, found 342.0850.

1-(6-bromo-2-hydroxynaphthalen-1-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione \((3j)\): Yellowish liquid; \(^1\)H NMR (600 MHz, DMSO-\(d_6\)): \(\delta\) 11.07 (s, 2H), 8.21 (d, \(J = 1.7\) Hz, 1H), 7.97 (d, \(J = 9.0\) Hz, 1H), 7.83 (d, \(J = 9.0\) Hz, 1H), 7.69 (dd, \(J = 9.0, 1.9\) Hz, 1H), 7.60-7.53 (m, 4H), 7.49-7.42 (m,
1H), 7.34 (d, J = 9.0 Hz, 1H); 13C NMR (150 MHz, DMSO-d$_6$): δ 154.6, 152.8, 152.1, 132.6, 131.9, 131.2, 130.9, 130.3, 129.6, 129.4, 128.3, 126.6, 124.3, 120.5, 116.8, 115.0. HRMS (ESI) calcd for C$_{18}$H$_{12}$BrN$_3$O$_3$ (M+Na$^+$): 419.9954, found 419.9956.

1-(7-bromo-2-hydroxynaphthalen-1-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3k): Yellowish liquid; 1H NMR (600 MHz, DMSO-d$_6$): δ 11.04 (s, 2H), 8.15 (d, J = 1.7 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.62-7.58 (m, 2H), 7.58-7.52 (m, 3H), 7.46-7.44 (m, 1H), 7.35 (d, J = 9.0 Hz, 1H); 13C NMR (150 MHz, DMSO-d$_6$): δ 154.9, 153.0, 152.6, 134.8, 132.7, 132.0, 130.8, 129.4, 129.3, 127.0, 126.8, 126.7, 123.8, 122.0, 119.8, 114.5. HRMS (ESI) calcd for C$_{18}$H$_{12}$BrN$_3$O$_3$ (M+Na$^+$): 419.9954, found 419.9956.

1-(2-hydroxy-7-methoxynaphthalen-1-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3l): White solid; m.p. 192.8-193.9 ºC; 1H NMR (600 MHz, DMSO-d$_6$) δ 10.82 (s, 2H), 7.83 (dd, J = 24.2, 8.9 Hz, 2H), 7.58-7.53 (m, 4H), 7.43 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 7.04 (dd, J = 8.9, 2.4 Hz, 1H), 3.88 (s, 3H); 13C NMR (150 MHz, DMSO-d$_6$) δ 159.3, 154.6, 153.0, 152.5, 134.9, 132.8, 131.5, 130.3, 129.4, 128.2, 126.6, 123.8, 116.3, 115.9, 114.7, 100.9, 55.8. HRMS (ESI) calcd for C$_{19}$H$_{15}$N$_3$O$_4$ (M+Na$^+$): 372.0955, found 372.0958.
methyl 5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-6-hydroxy-2-naphthoate (3m): White solid; m.p. 204.8-206.4 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) δ 11.17 (s, 2H), 8.63 (s, 1H), 8.19 (d, $J = 9.0$ Hz, 1H), 8.05 (dd, $J = 8.8$, 1.3 Hz, 1H), 7.97 (d, $J = 8.8$ Hz, 1H), 7.59-7.54 (m, 4H), 7.44 (t, $J = 7.2$ Hz, 1H), 7.38 (d, $J = 9.0$ Hz, 1H), 3.91 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 166.8, 156.5, 152.8, 152.2, 135.8, 133.7, 132.7, 131.4, 129.4, 128.3, 127.4, 127.0, 126.7, 125.1, 122.4, 120.3, 115.0, 52.6; HRMS (ESI) calcd for C$_{20}$H$_{15}$N$_3$O$_5$ (M+Na$^+$): 400.0904, found 400.0905.

5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-6-hydroxy-2-naphthonitrile (3n): White solid; m.p. 240.1-241.3 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) δ 11.26 (s, 2H), 8.56 (s, 1H), 8.11 (d, $J = 9.0$ Hz, 1H), 8.03 (d, $J = 8.8$ Hz, 1H), 7.83 (dd, $J = 8.7$, 1.5 Hz, 1H), 7.59-7.52 (m, 4H), 7.45-7.42 (m, 2H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 157.0, 152.9, 152.2, 135.2, 134.9, 132.9, 132.6, 129.4, 128.6, 128.3, 127.2, 126.6, 123.4, 121.1, 119.7, 115.2, 106.2; HRMS (ESI) calcd for C$_{19}$H$_{12}$N$_4$O$_3$ (M+Na$^+$): 367.0802, found 367.0807.
1-(7-hydroxyquinolin-8-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3o): Yellow oil; $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 11.03 (s, 2H), 8.84 (d, $J = 4.1$ Hz, 1H), 8.33 (d, $J = 8.1$ Hz, 1H), 8.00 (d, $J = 9.0$ Hz, 1H), 7.57-7.53 (m, 4H), 7.44-7.40 (m, 2H), 7.36 (d, $J = 9.0$ Hz, 1H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 158.0, 153.2, 152.7, 151.6, 146.5, 136.8, 132.9, 131.6, 129.4, 128.2, 126.5, 123.3, 120.0, 120.0, 116.1; HRMS (ESI) calcd for C$_{17}$H$_{12}$N$_4$O$_3$ (M+Na$^+$): 343.0802, found 343.0803.

![Image of 1-(7-hydroxyquinolin-8-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3o)](image)

4-phenyl-1-(2,4,6-trimethoxyphenyl)-1,2,4-triazolidine-3,5-dione (3p): Colorless liquid; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.70 (s, 1H), 7.60-7.55 (m, 2H), 7.47 (dd, $J = 13.6$, 5.4 Hz, 2H), 7.37 (t, $J = 7.5$ Hz, 1H), 6.15 (s, 2H), 3.86-3.81 (m, 9H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 157.9, 153.7, 149.4, 147.2, 127.0, 124.3, 123.3, 121.0, 101.2, 86.4, 51.4, 50.9. HRMS (ESI) calcd for C$_{17}$H$_{17}$N$_3$O$_5$ (M+Na$^+$): 366.1060, found 366.1062.

![Image of 4-phenyl-1-(2,4,6-trimethoxyphenyl)-1,2,4-triazolidine-3,5-dione (3p)](image)

1,2-bis(4-(dimethylamino)phenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (4a): White solid; m.p. 224.0-226.0 °C; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 7.60 (d, $J = 7.9$ Hz, 2H), 7.55 (t, $J = 7.6$ Hz, 2H), 7.46 (t, $J = 7.2$ Hz, 1H), 7.25 (d, $J = 8.8$ Hz, 4H), 6.68 (d, $J = 8.8$ Hz, 4H), 2.88 (s, 12H); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 152.0, 150.3, 132.2, 129.4, 128.7, 127.6, 127.1, 124.5, 112.5, 40.4. HRMS (ESI) calcd for C$_{24}$H$_{25}$N$_5$O$_2$ (M+Na$^+$): 438.1900, found 438.1902.

5. References

6. \( ^1\)H NMR and \( ^{13}\)C NMR spectra of the products.

\(^1\)H NMR Spectrum (DMSO-\(d_6\)) of 3a

\(^{13}\)C NMR Spectrum (DMSO-\(d_6\)) of 3a
$^1$H NMR Spectrum (CDCl$_3$) of 3b

$^{13}$C NMR Spectrum (CDCl$_3$) of 3b
$^1$H NMR Spectrum (CDCl$_3$) of 3c

$^{13}$C NMR Spectrum (CDCl$_3$) of 3c
$^1$H NMR Spectrum (CDCl$_3$) of 3d

$^{13}$C NMR Spectrum (CDCl$_3$) of 3d
$^1$H NMR Spectrum (DMSO-$d_6$) of 3e

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3e
$^1$H NMR Spectrum (DMSO-$d_6$) of 3f

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3f
$^1$H NMR Spectrum (DMSO-$d_6$) of 3g

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3g
$^1$H NMR Spectrum (DMSO-$d_6$) of 3h

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3h
$^1$H NMR Spectrum (DMSO-$d_6$) of 3i

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3i
$^1$H NMR Spectrum (DMSO-$d_6$) of 3j

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3j
$^1$H NMR Spectrum (DMSO-$d_6$) of 3k

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3k
$^1$H NMR Spectrum (DMSO-$d_6$) of 3I

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3I
$^1$H NMR Spectrum (DMSO-$d_6$) of 3m

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3m
$^1$H NMR Spectrum (DMSO-$d_6$) of 3n

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 3n
$^1$H NMR Spectrum (CDCl$_3$) of 3p

$^{13}$C NMR Spectrum (CDCl$_3$) of 3p
$^1$H NMR Spectrum (DMSO-$d_6$) of 4a

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 4a
7. HRMS spectra

4a

3b
3m

3n