Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Diazaborines Oxidize Slowly with H_2O_2 But Rapidly with Peroxynitrite in Aqueous Buffer

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Supplementary Materials

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1. Equipment and Materials

Unless otherwise noted, all chemicals and solvents were used as received from commercial sources. Water (dd-H_2O) used in ultraviolet-visible (UV-Vis) spectroscopy procedures was deionized using Barnstead E-pure Series 1090 water purification system (Thermo Fisher Scientific, USA). UV-Vis spectroscopy experiments were carried out with Evolution 260 Bio UV-visible spectrophotometer, equipped with an 8-cell holder and a Peltier Control and Cooling Unit (PCCU1) (Thermo Fisher Scientific, USA). Standard 10mm rectangular quartz UV-Vis cuvettes were purchased from Thomas Scientific, USA (catalog number: 8490-D42). Nuclear magnetic resonance (NMR) spectroscopy experiments were carried out with JEOL ECA-500 NMR spectrometer (JEOL, USA). High-field nuclear magnetic resonance (NMR) spectroscopy experiments were carried out with a Varian 900 MHz Direct Drive spectrometer at the University of Colorado Anschutz Medical Campus (Varian, USA). Chemical shifts are expressed as parts per million (ppm). Coupling constants are reported in hertz (Hz). HRMS was carried out with Waters Synapt G2 HDMS at the University of Colorado Boulder. Gas chromatography mass spectrometry (GC-MS) analysis was carried out with Agilent Technologies 7890B GC system paired with a 7693 Autosampler and 5977B MSD.

Monobasic sodium phosphate (>98%), hydrochloric acid (36.5 – 38.0%), isoamyl nitrite (96%), ammonium-d_4 detuteroxide (25 wt. % in D_2O, 99 atom %D), and dimethyl sulfone (*Trace*CERT®) were purchased from Millipore Sigma (USA). Tribasic sodium phosphate (>98%), dimethyl sulfoxide (99.9%), and hydrogen peroxide (30%) were purchased from Fisher Scientific (USA). Sodium hydroxide (pellets), 2-carboxybenzene boronic acid (96%), HEPES (99%), and 2-formylphenylboronic acid (>98%) were purchased from Oakwood Chemicals (USA). Acethydrazide (>98%), ammonium acetate (>97%), and *O*-methylhydroxylamine hydrochloride (>97%) were purchased from TCI America (USA). Salicylaldehyde (99%), sodium hypochlorite (5% active chlorine), manganese (IV) oxide (99%), pivalic acid hydrazide (>98%), deuterium chloride (20% w/w), and sodium deuteroxide (40% w/w) were purchased from Acros Organics (USA). Dimethyl sulfoxide-d_6 and deuterium oxide were purchased from Cambridge Isotope Laboratories (USA). 2-(methoxymethyl)phenol (99%) was purchased from Ambeed (USA). *p*-toluenesulfonyl hydrazide (98%) and *tert*-butyl hydroperoxide (70 wt. in water) were purchased from Beantown Chemical (USA). Benzeneboronic acid (>98%) was purchased from Alfa Aesar (USA). 2-((methoxymethyl)phenyl)boronic acid (97%) was purchased from Synthonix (USA). *N,N*-((dimethylamino)methyl)phenylboronic acid (97%) was purchased from Matrix Scientific (USA). Methylhydrazine (>98%) was purchased from Fluka Analytical (DE). Isopropanol (99%) was purchased from Pharmco (USA). (tris(2-carboxyethyl)phosphine) hydrochloride was purchased from Thermo Scientific (USA).

2. General Procedure for UV-Vis Spectrometer Experiments

Stock solutions of boronic acid (50 mM) were prepared in DMSO and diluted to the working concentration in phosphate buffer (100 mM) at pH 7.4. An aliquot (3 mL) of the solution was transferred to a UV-vis cuvette. The temperature control unit was set to 25°C, and the UV-Vis spectrometer was blanked with the phosphate buffer solution. A stock solution of H_2O_2 was prepared in dd-H_2O (50 mM). An aliquot of H_2O_2 stock solution (3 µL) was added and mixed, and the cuvette was capped and wrapped in Parafilm. The absorbance was measured as a function of time, converted to concentration, and the rate constant calculated.

3. General Procedure for Monitoring ROS Reactivity by 1H NMR

D_2O was buffered with tribasic sodium phosphate (200 mM), and the pD was adjusted with DCl and NaOD. Buffered D_2O (250 µL) was combined with boronic acid (50 µL), and hydrazide (50 µL). 1 molar equivalent of H_2O_2, NaOCl, and tBuOOH were added from 500 mM stock solutions. Samples were monitored as a function of time.

4. General Procedure for Monitoring ONOO- Reactivity by 1H NMR

D_2O was buffered with tribasic sodium phosphate (200 mM), and the pD was adjusted with DCl and NaOD. Buffered D_2O (250 µL) was combined with boronic acid (50 µL) and hydrazide (50 µL). $ONOO^-$ was added directly in 1 equivalent aliquots. Samples were monitored after each addition of $ONOO^-$.

5. Synthesis of Peroxynitrite

Isopropyl alcohol (52 mL), deionized water (22 mL), and sodium hydroxide (2.1 g) were combined and stirred until the sodium hydroxide dissolved. Hydrogen peroxide (9.8M, 4.18 mL) was added dropwise, and the mixture was stirred at room temperature for 5 minutes. Isoamyl nitrite (5 mL) was added dropwise. The reaction turned a dark golden color. The mixture was stirred for 15 minutes, then washed with dichloromethane (4 × 50 mL). MnO_2 (5.54 g) was added, giving a dark green mixture that gently fizzed and immediately turned black. The mixture was stirred for 5 minutes. MnO_2 was removed by filtration, affording an orange, viscous liquid. Sample concentration was monitored prior to use by UV-Vis (ϵ = 1670 $M^{-1}cm^{-1}$ at 302 nm).

6. Calculation of Extinction Coefficients for Compounds

Extinction coefficients (ϵ) of the products of oxidation were calculated according to Beer's Law. *A* = absorbance; *b* = pathlength; *c* = concentration.

$$A = \epsilon bc$$

in which

$$\epsilon = \frac{A}{bc}$$

Product concentrations in the kinetic traces were calculated with the experimentally determined extinction coefficients using Beer's law.

Phenol Derivative	**Wavelength (nm)**	**Extinction Coefficient ($M^{-1}cm^{-1}$)**
1-OH	281	408
2-OH	284	855
3-OH	310	3527
4-OH	285	593
5-OH	330	5759

7. Screening ROS Reactivity by 1H NMR

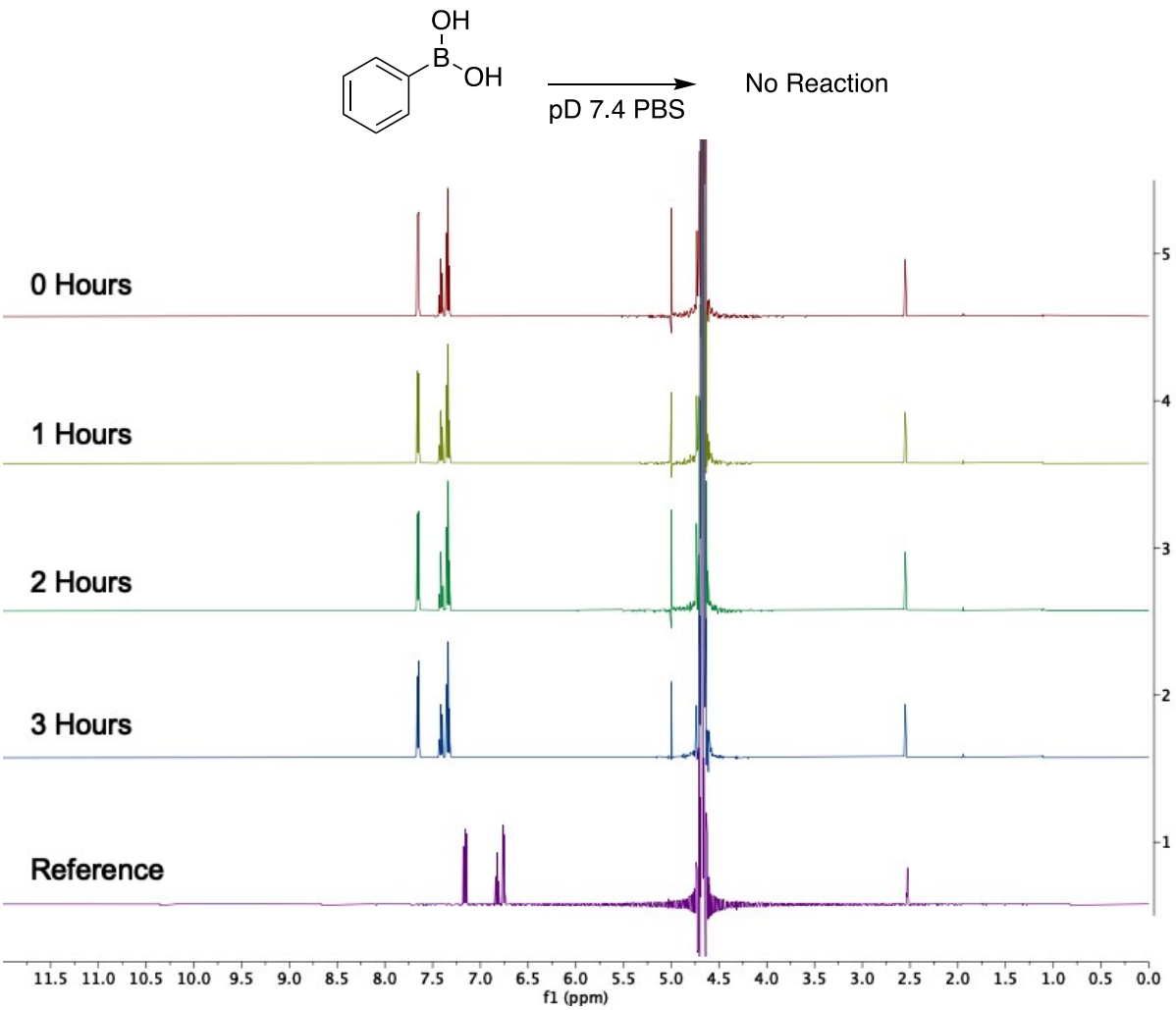


Figure S1. Phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included. No reaction is seen.

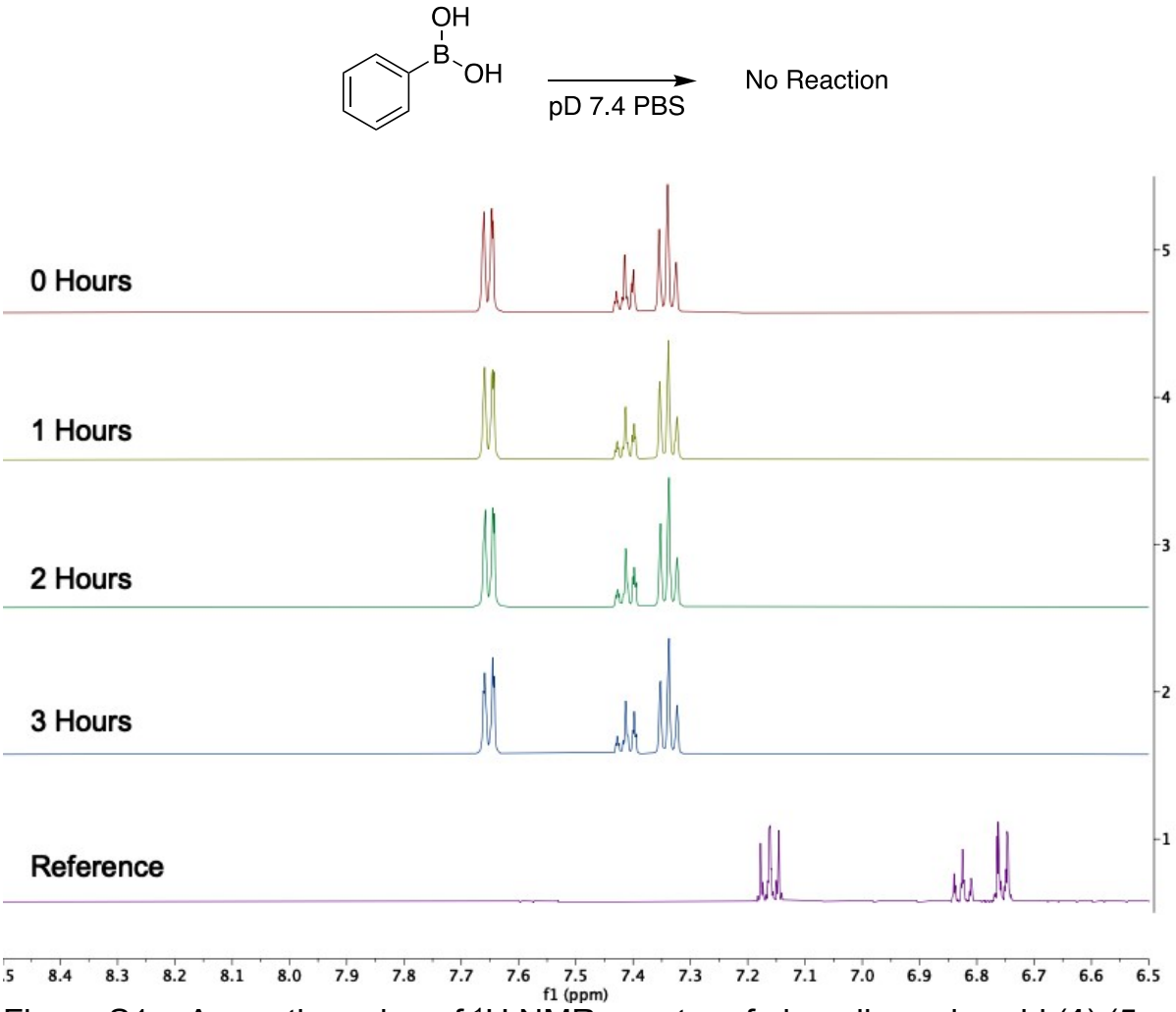


Figure S1a. Aromatic region of ^{1}H NMR spectra of phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included. No reaction is seen.

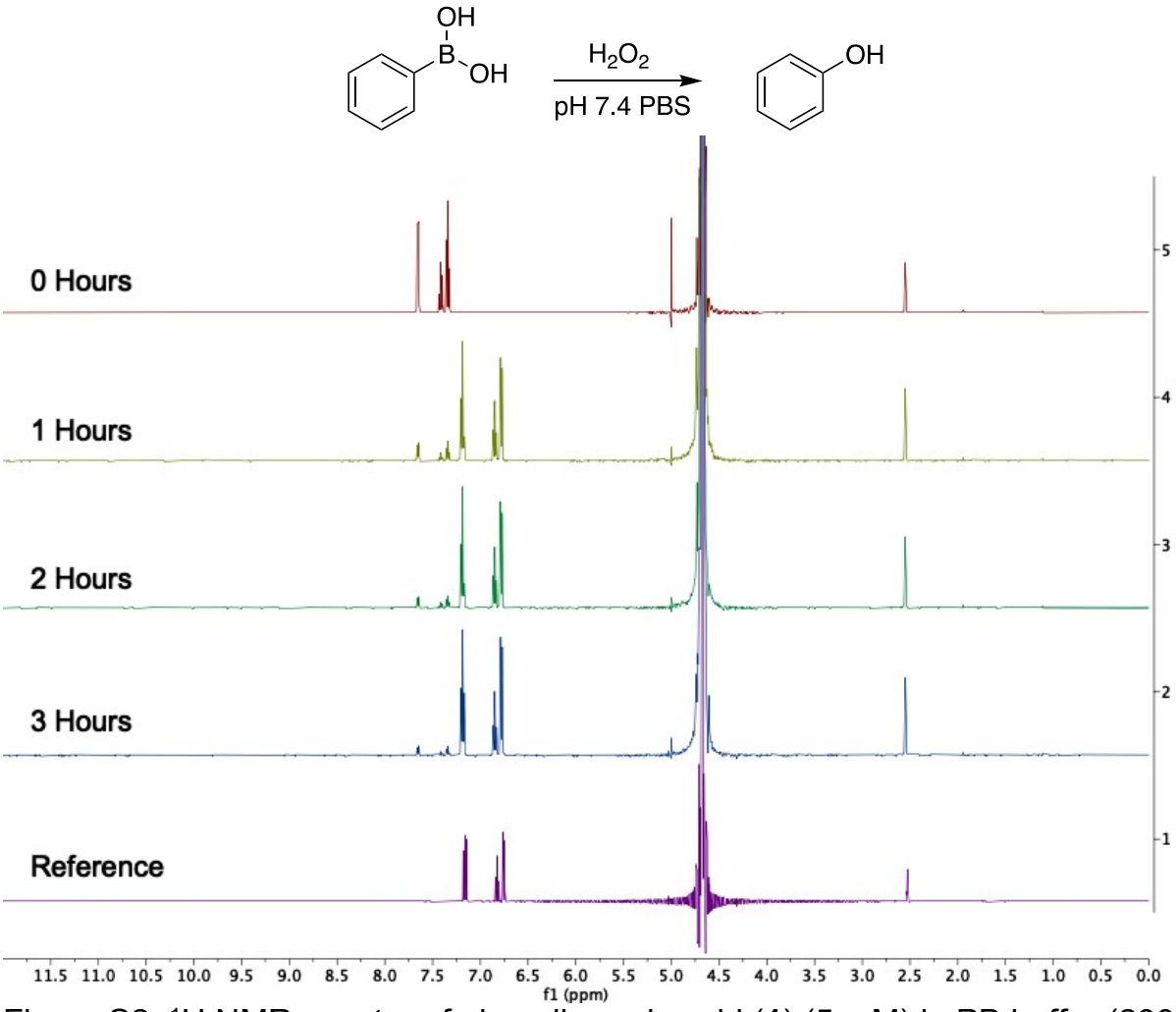


Figure S2. ^{1}H NMR spectra of phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included.

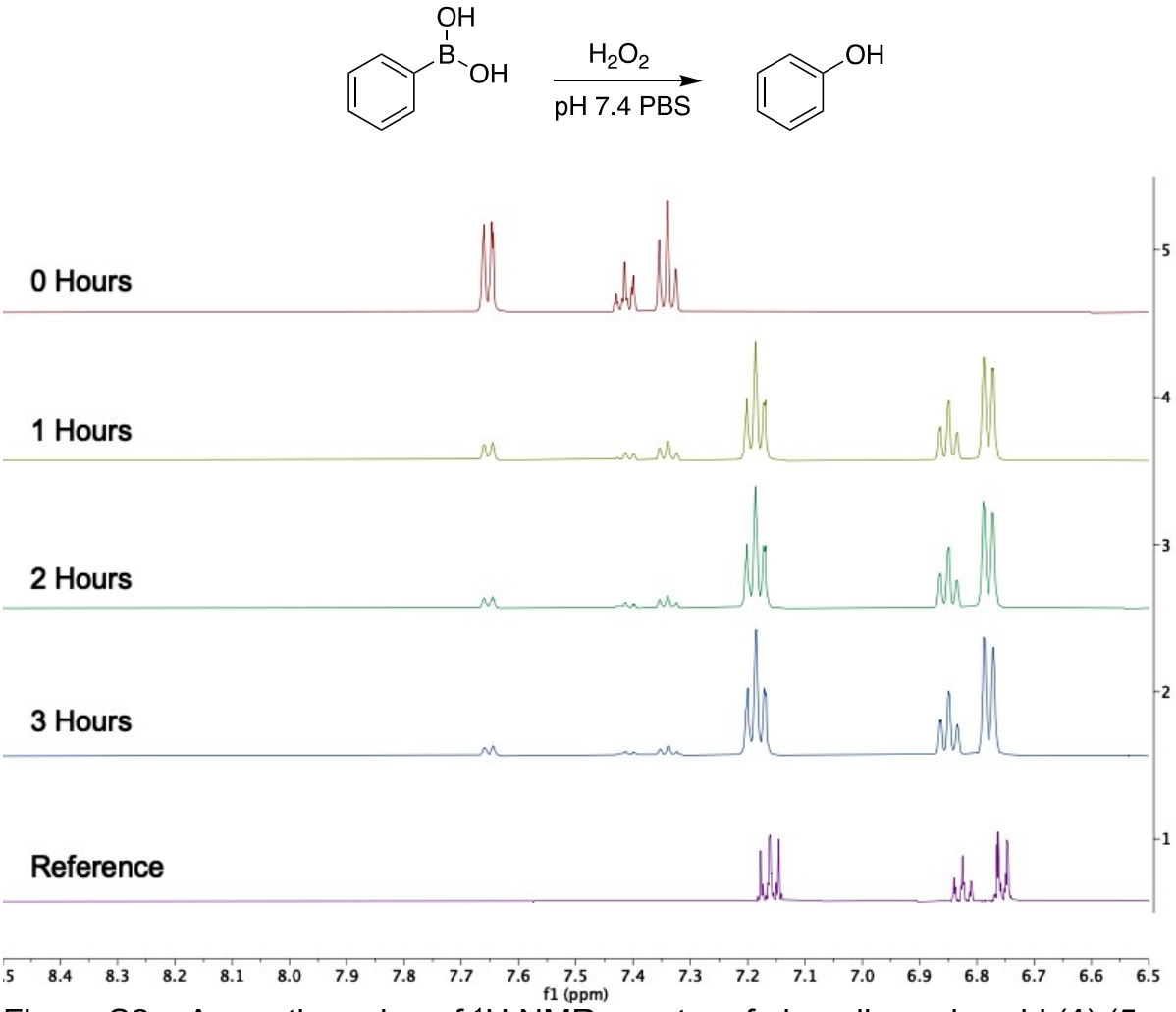


Figure S2a. Aromatic region of ^{1}H NMR spectra of phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included.

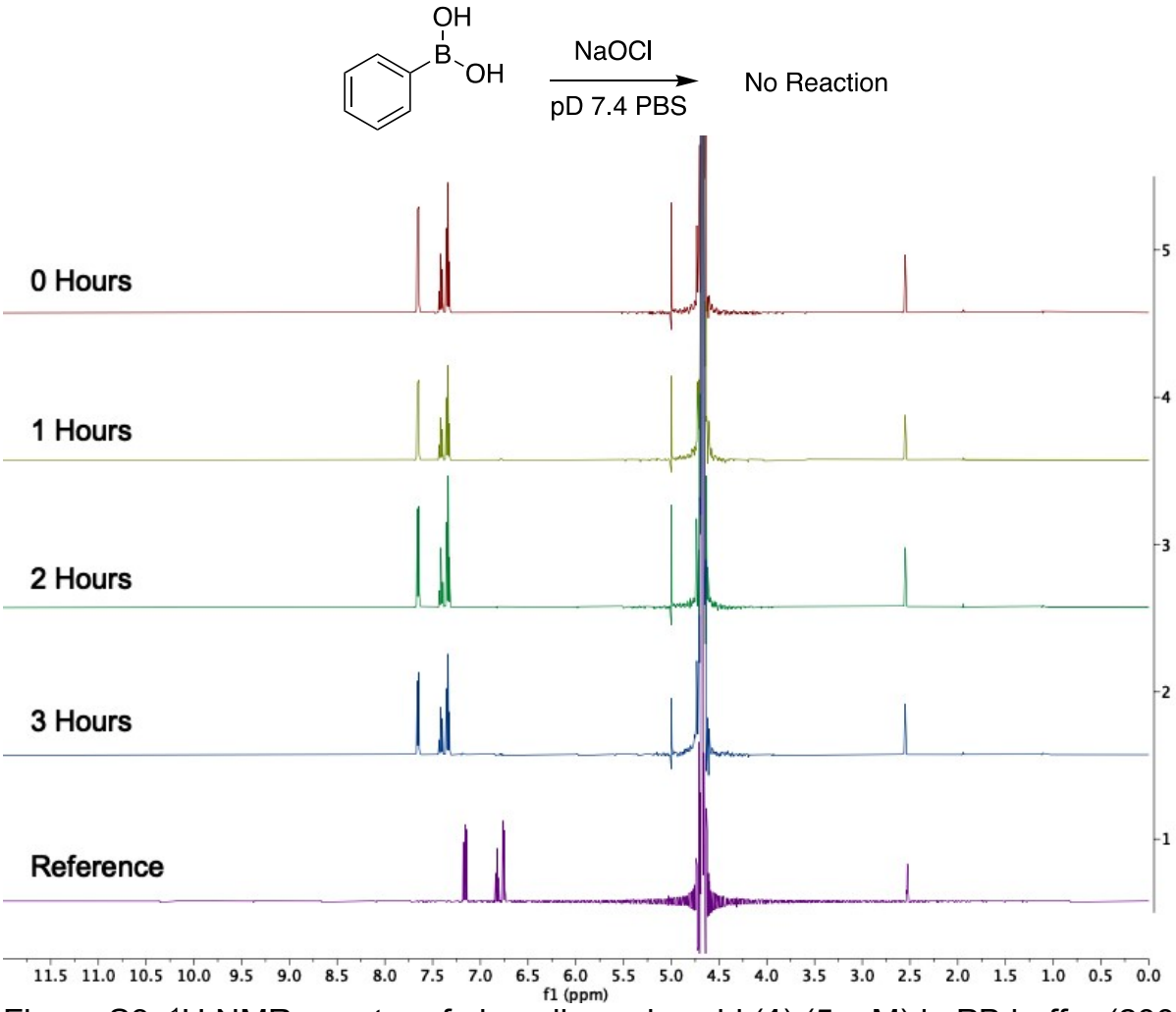


Figure S3. ^{1}H NMR spectra of phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for phenol also included.

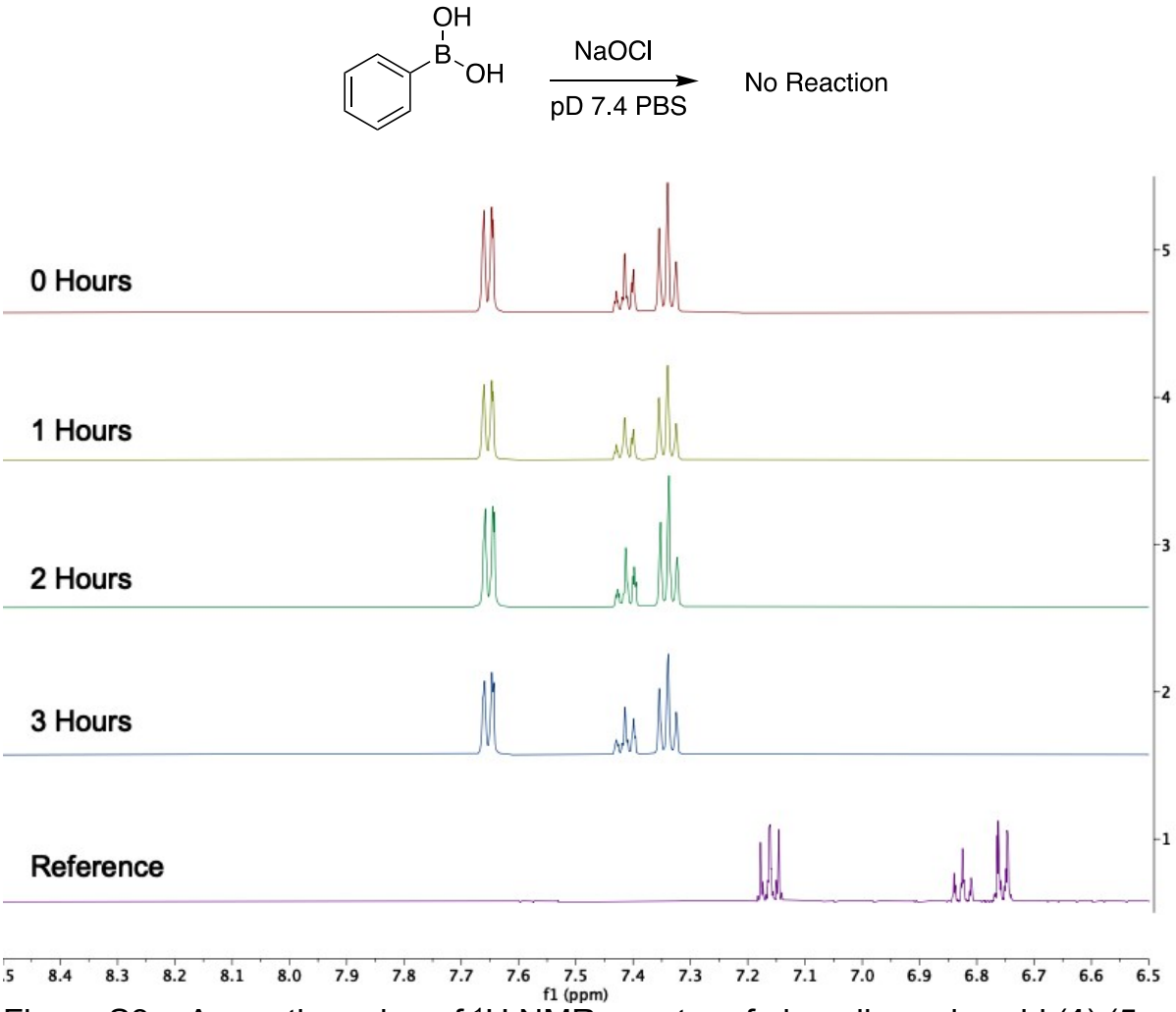


Figure S3a. Aromatic region of ^{1}H NMR spectra of phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included.

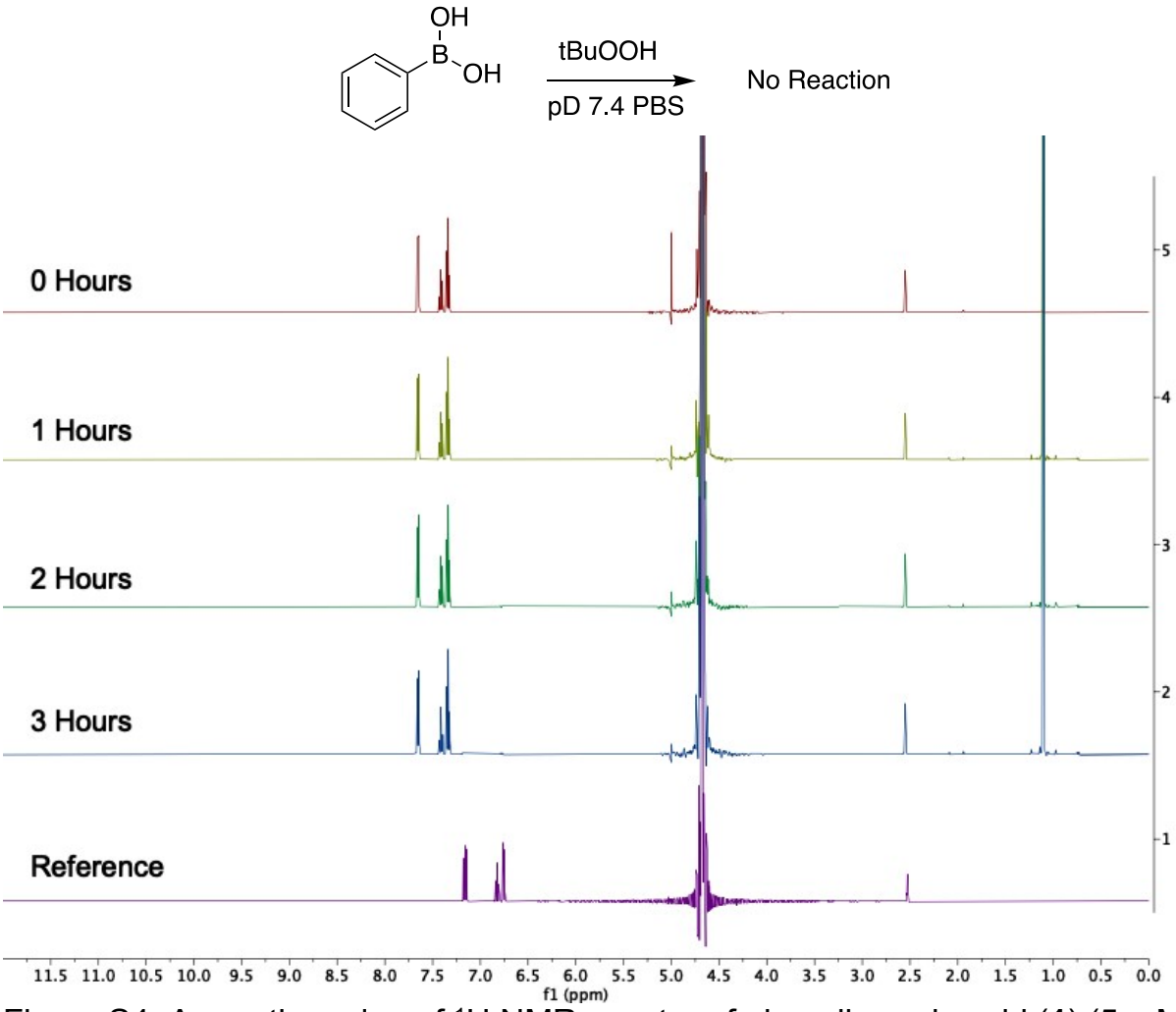


Figure S4. Aromatic region of ^{1}H NMR spectra of phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included.

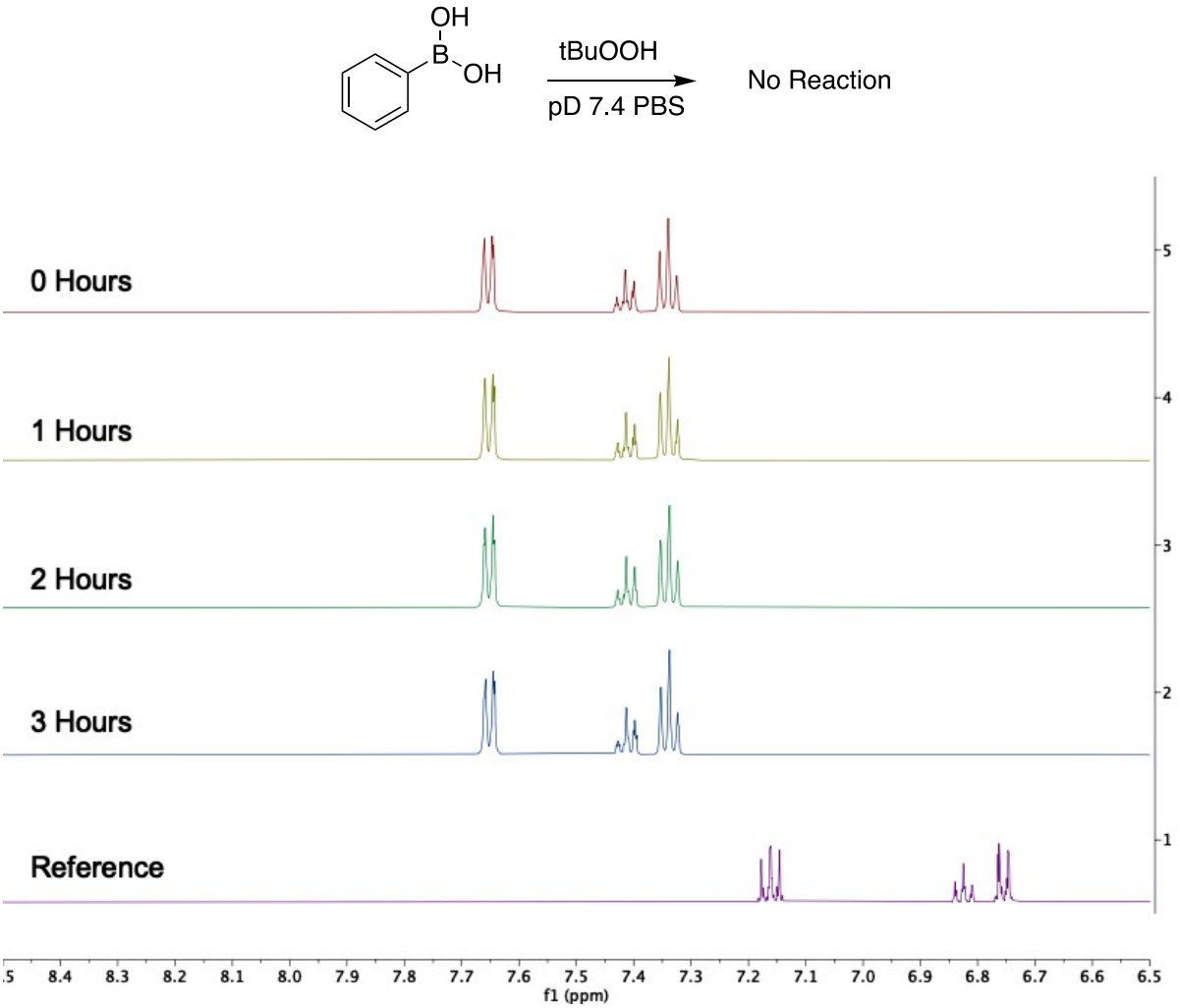


Figure S4a. ^{1}H NMR spectra of phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included.

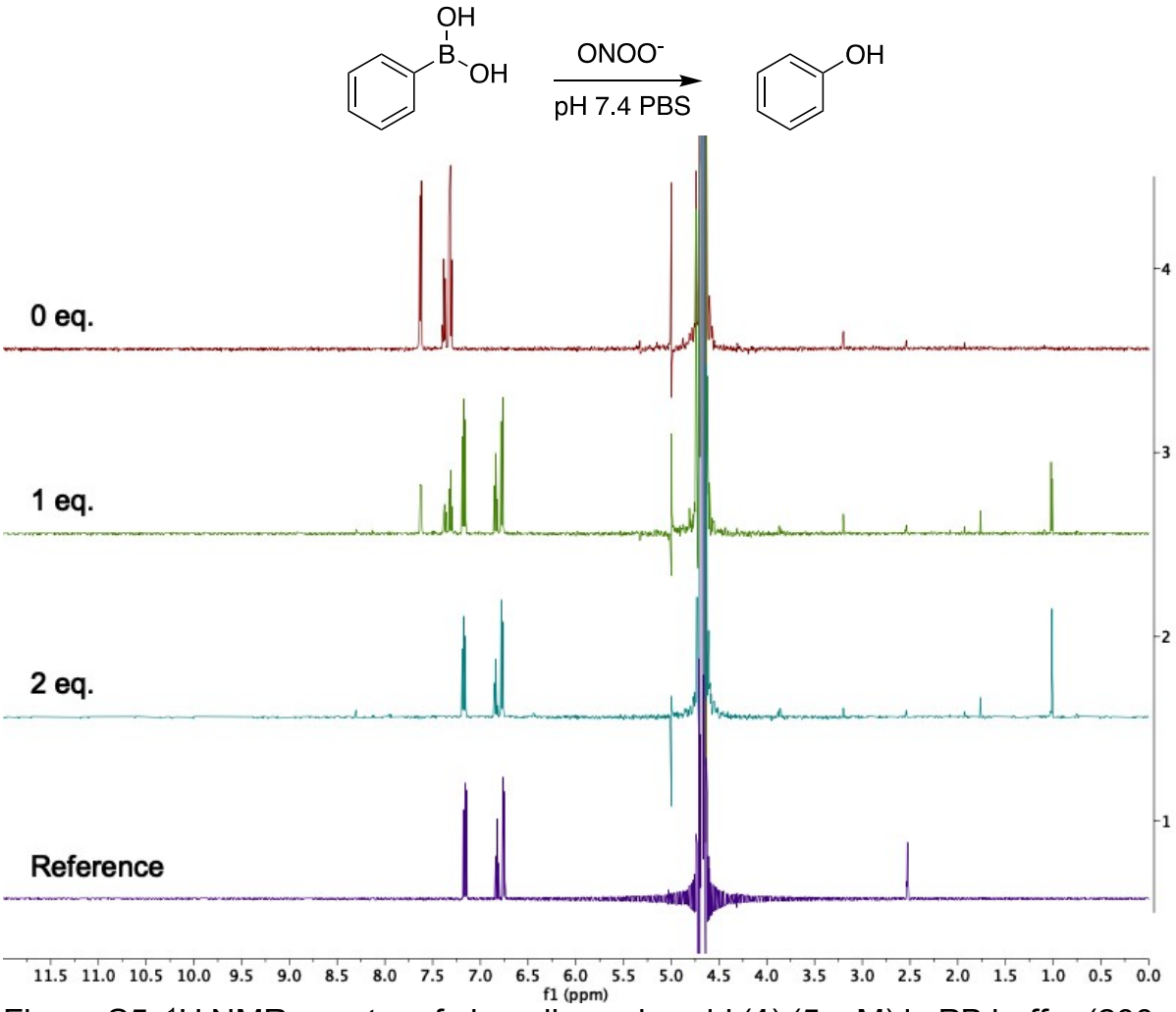


Figure S5. ^{1}H NMR spectra of phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. $ONOO^-$ was added in 1 equivalent aliquots with spectra collected immediately after addition. A reference spectrum for phenol is also included.

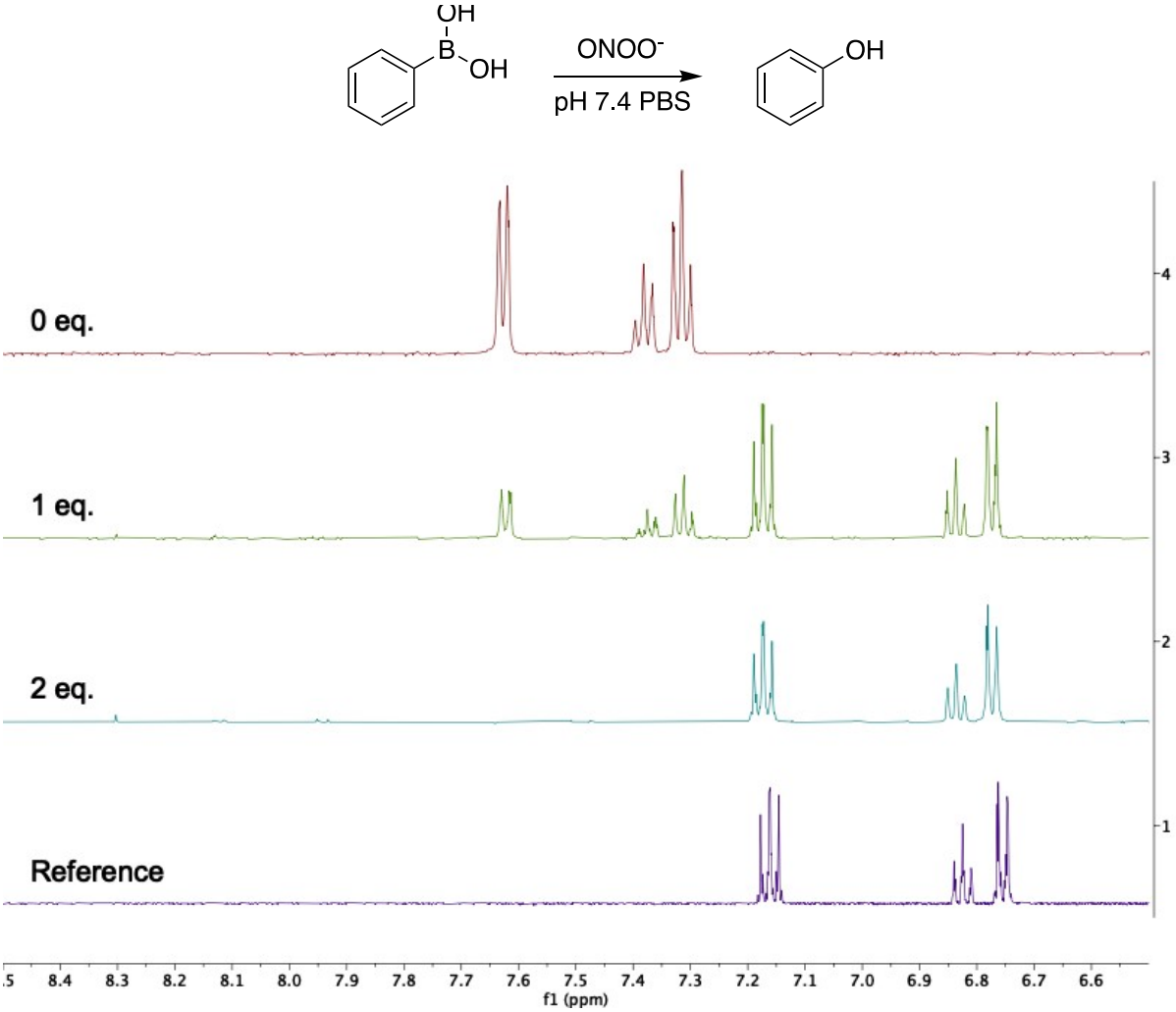


Figure S5a. Aromatic region of ^{1}H NMR spectra of phenylboronic acid (**1**) (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. $ONOO^-$ was added in 1 equivalent aliquots with spectra collected immediately after addition. A reference spectrum for phenol is also included.

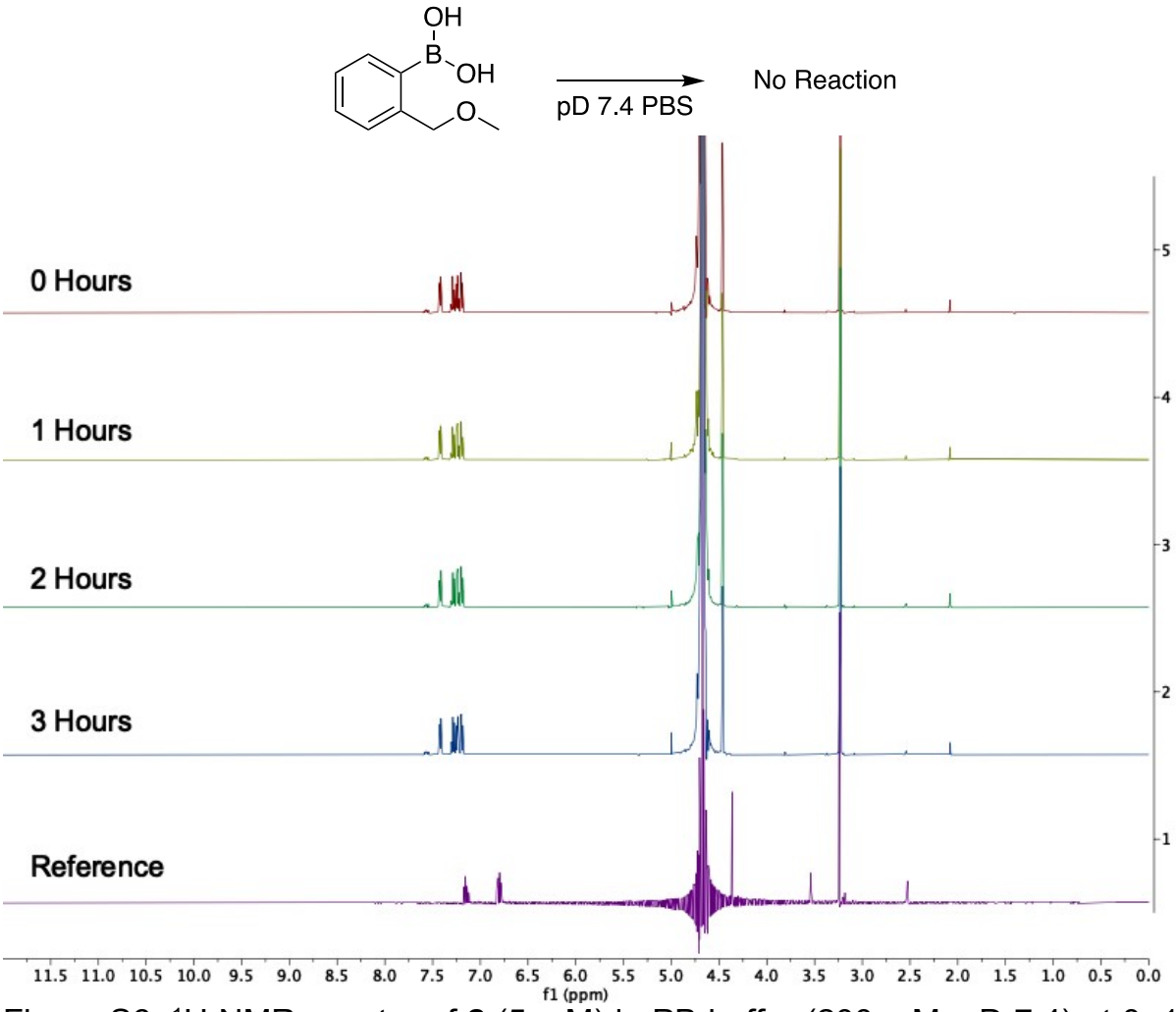
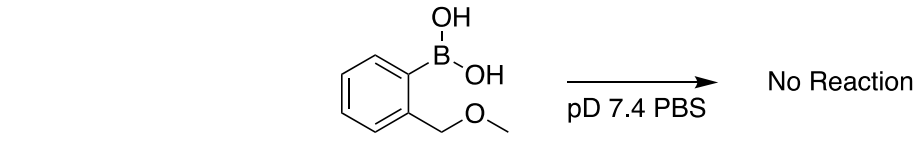


Figure S6. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.



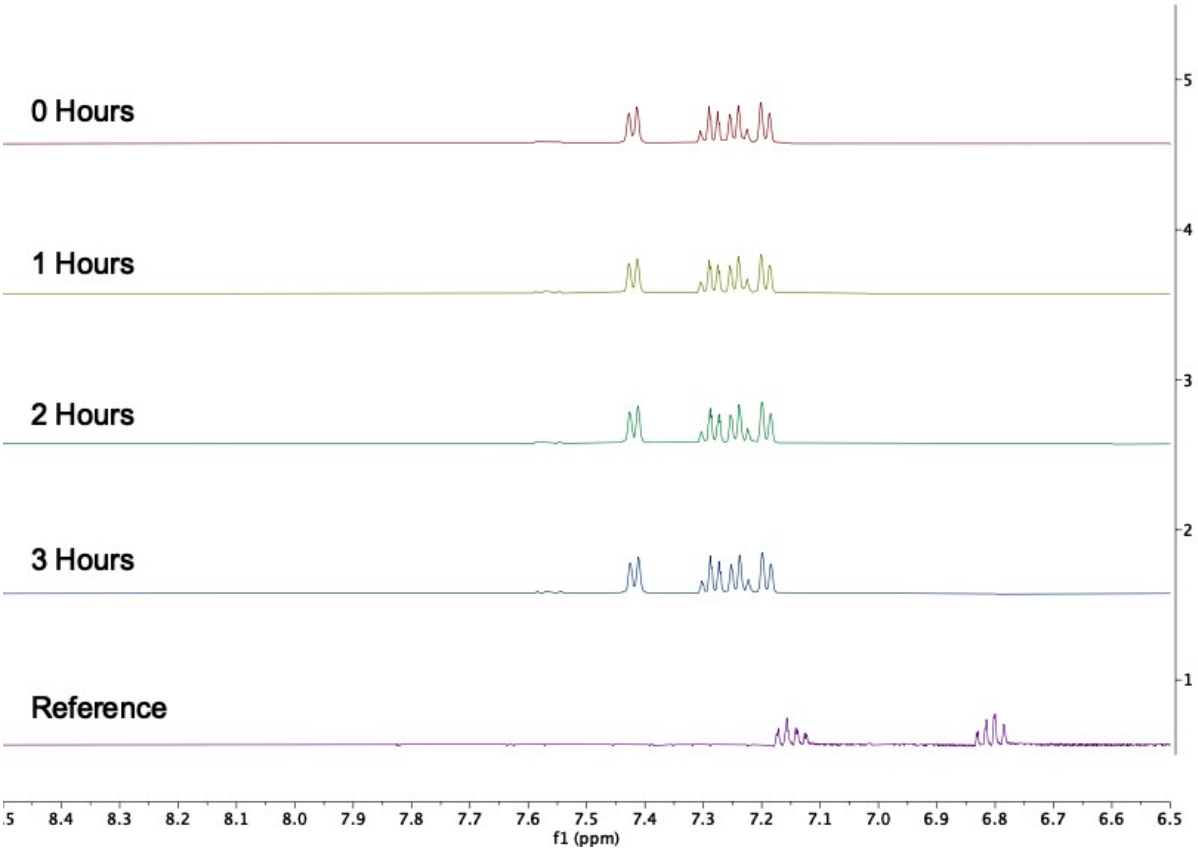


Figure S6a. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

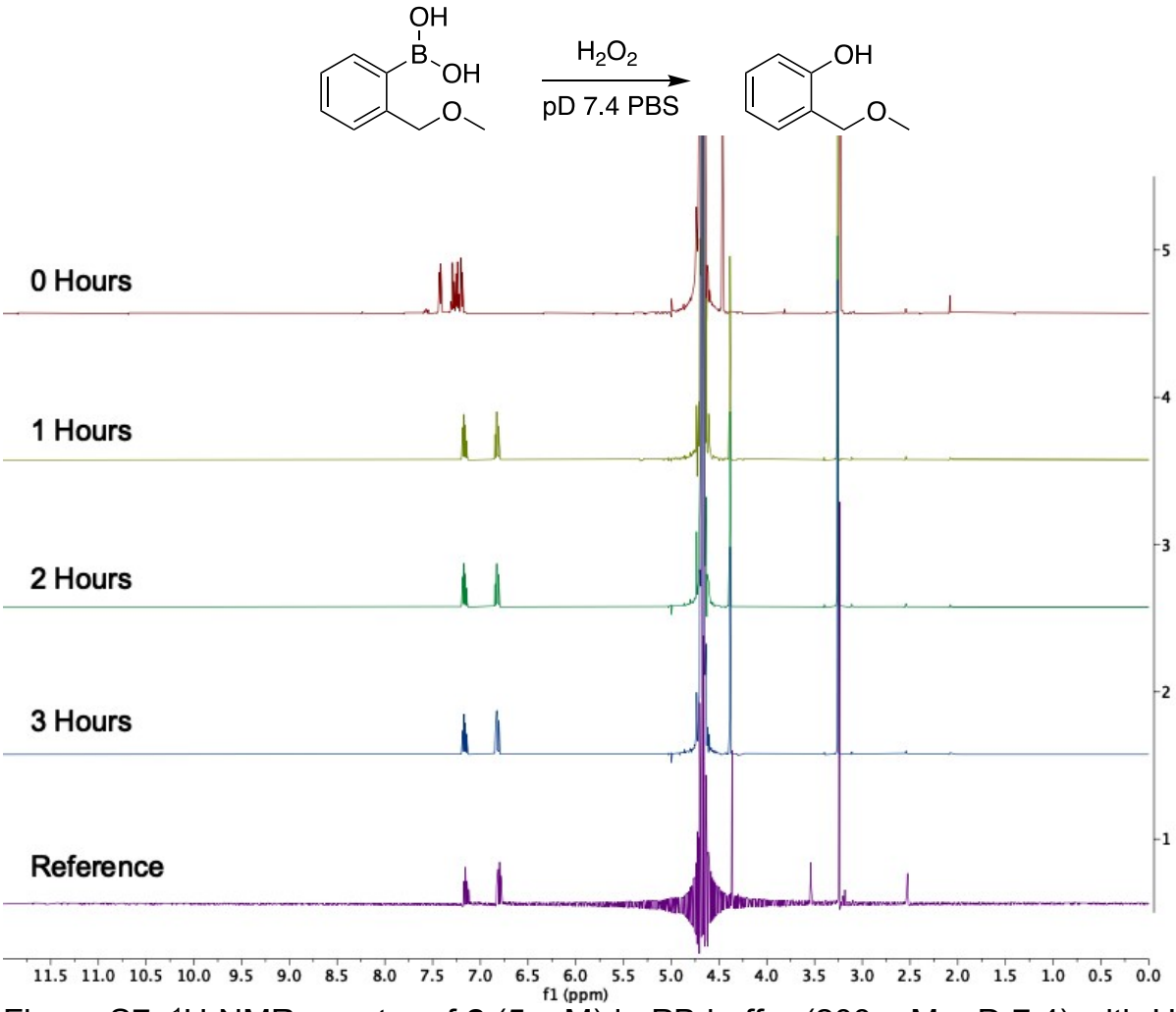


Figure S7. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

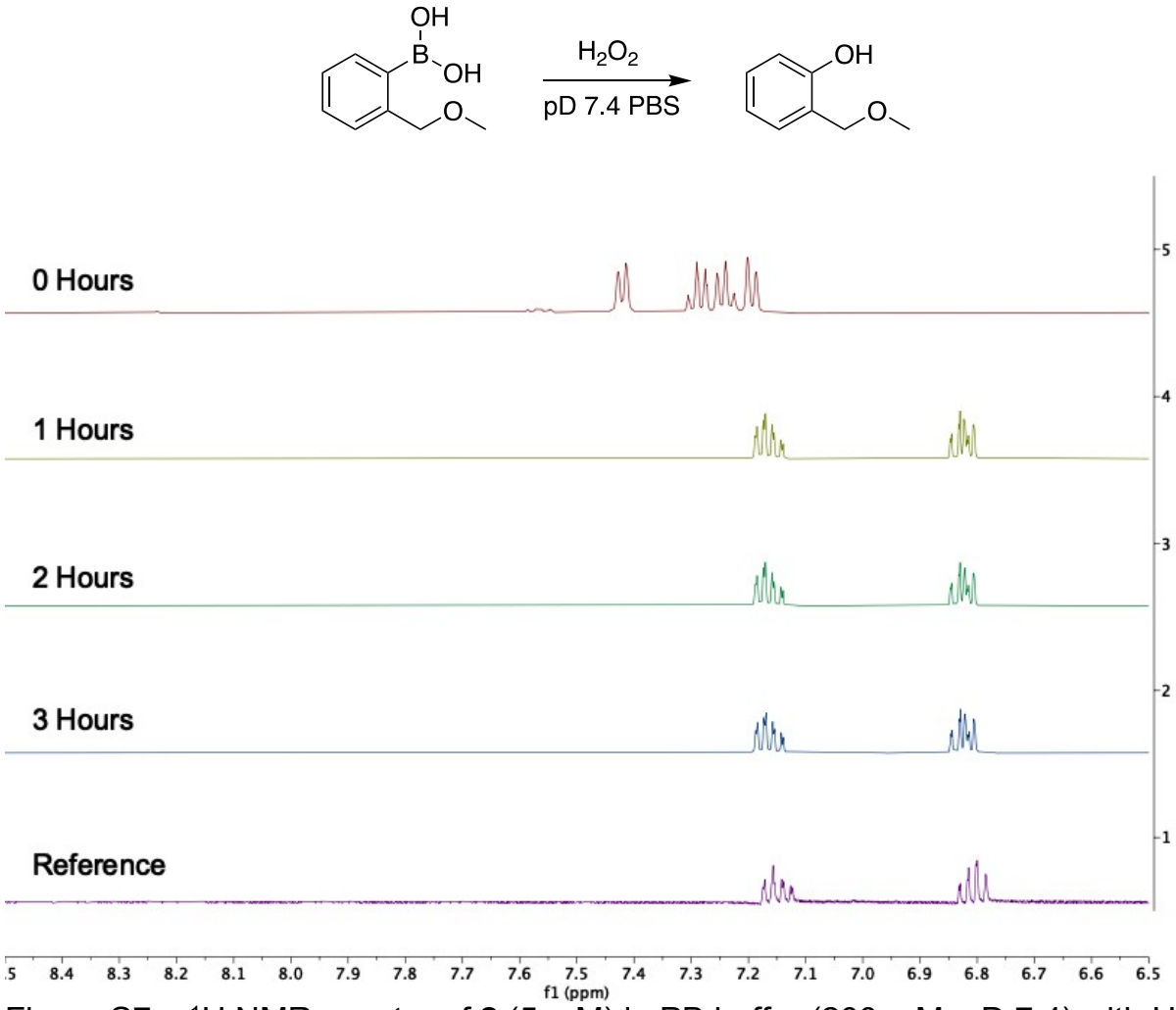


Figure S7a. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

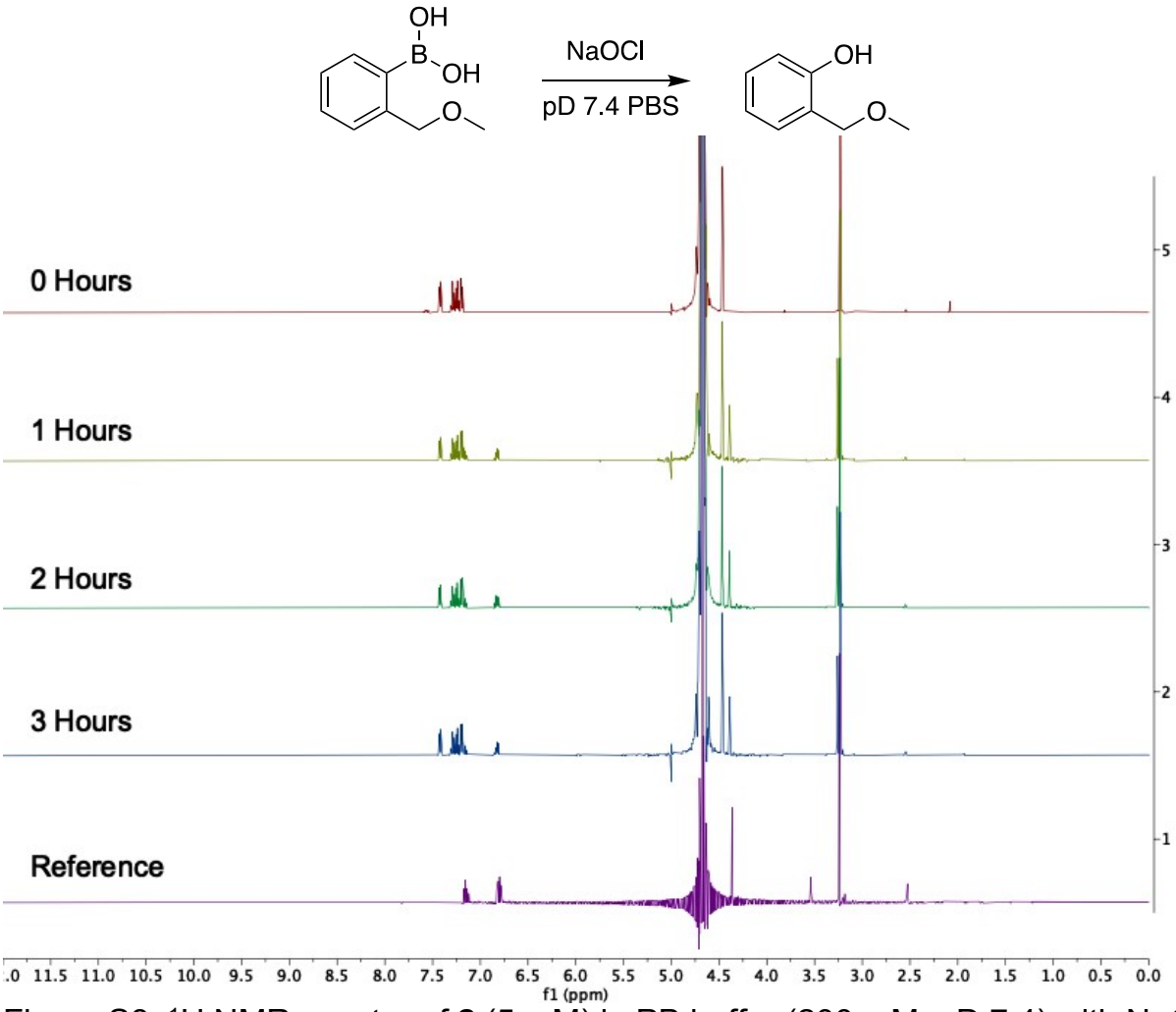


Figure S8. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

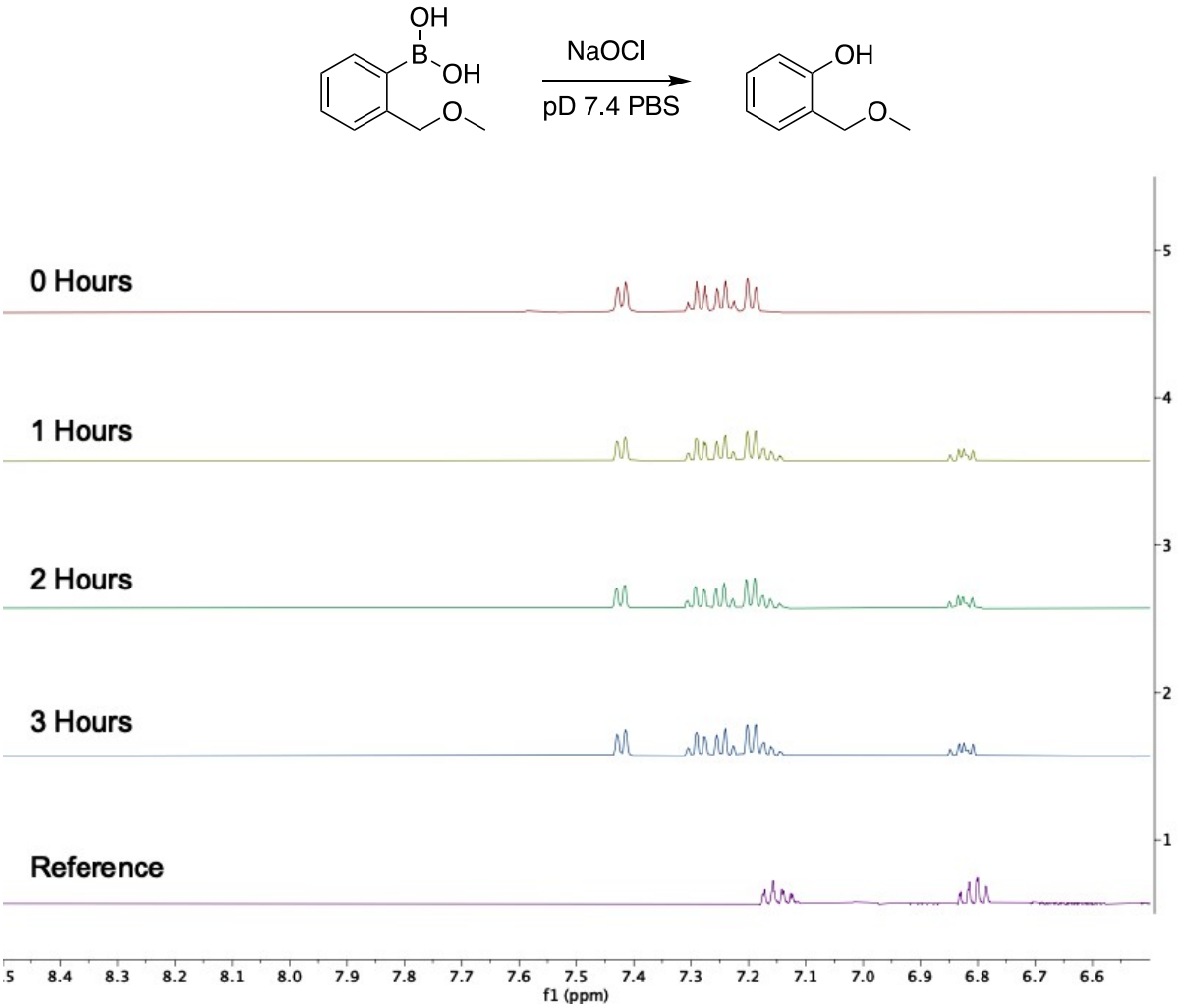


Figure S8a. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

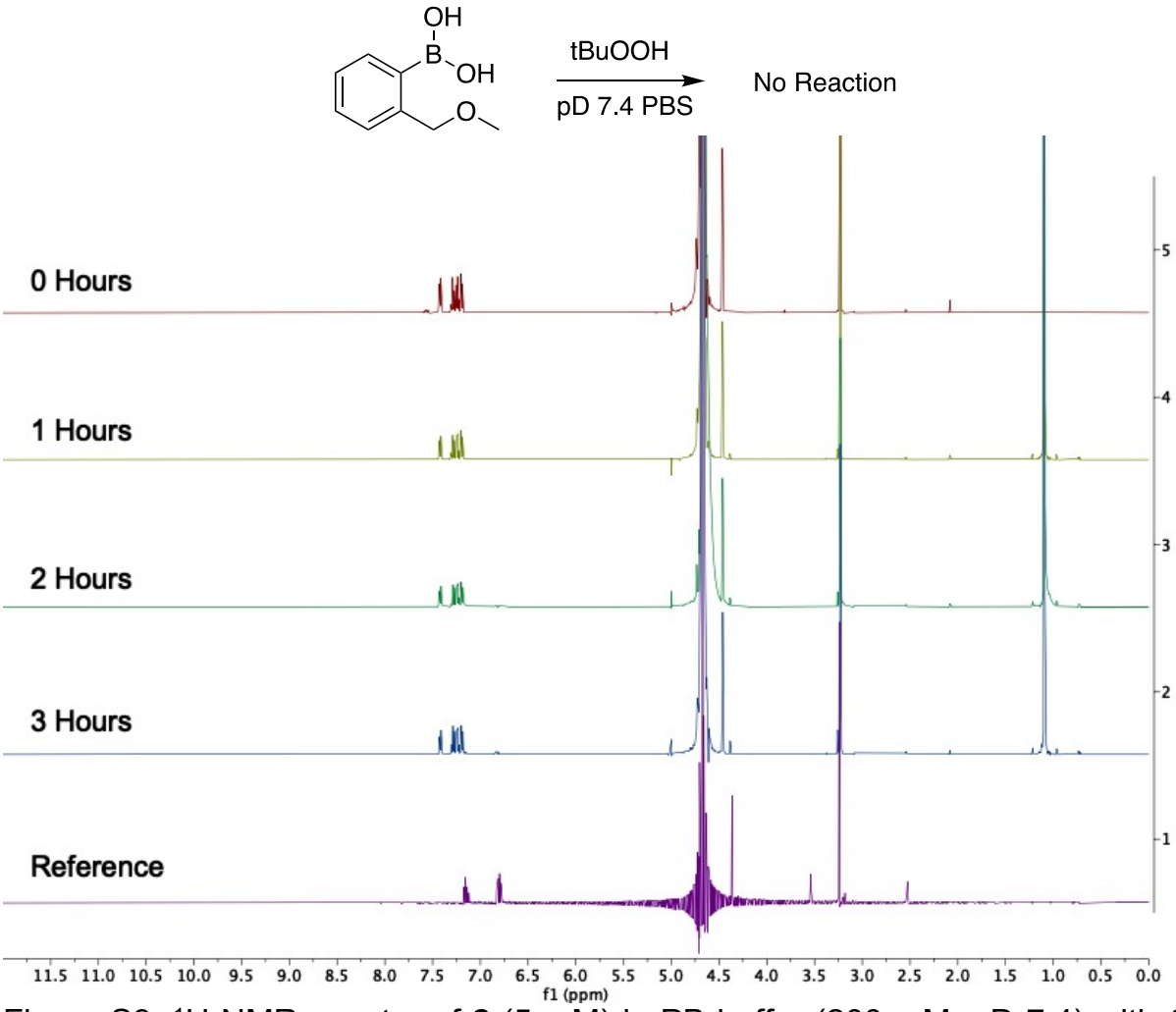
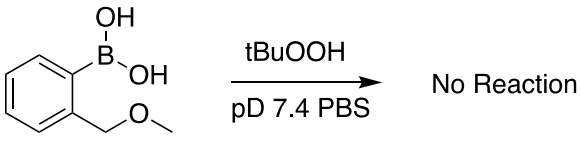


Figure S9. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.



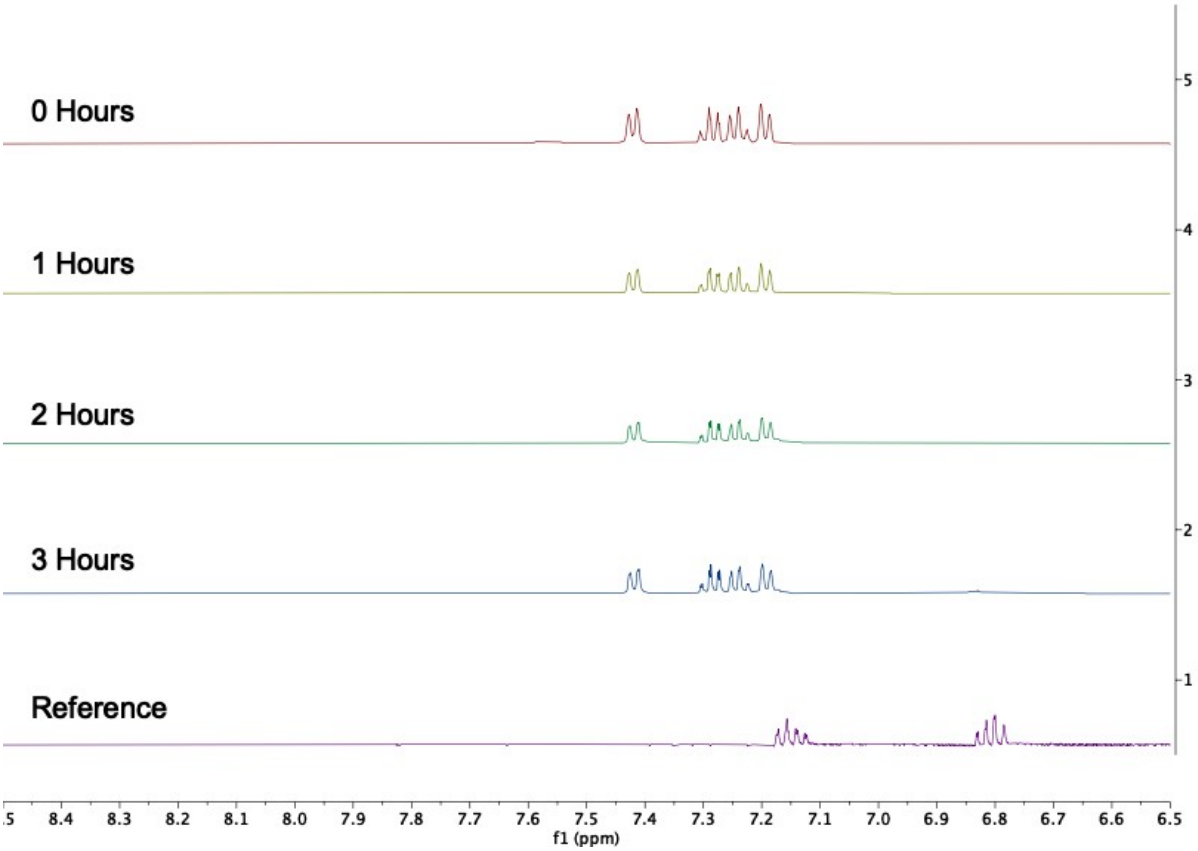


Figure S9a. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

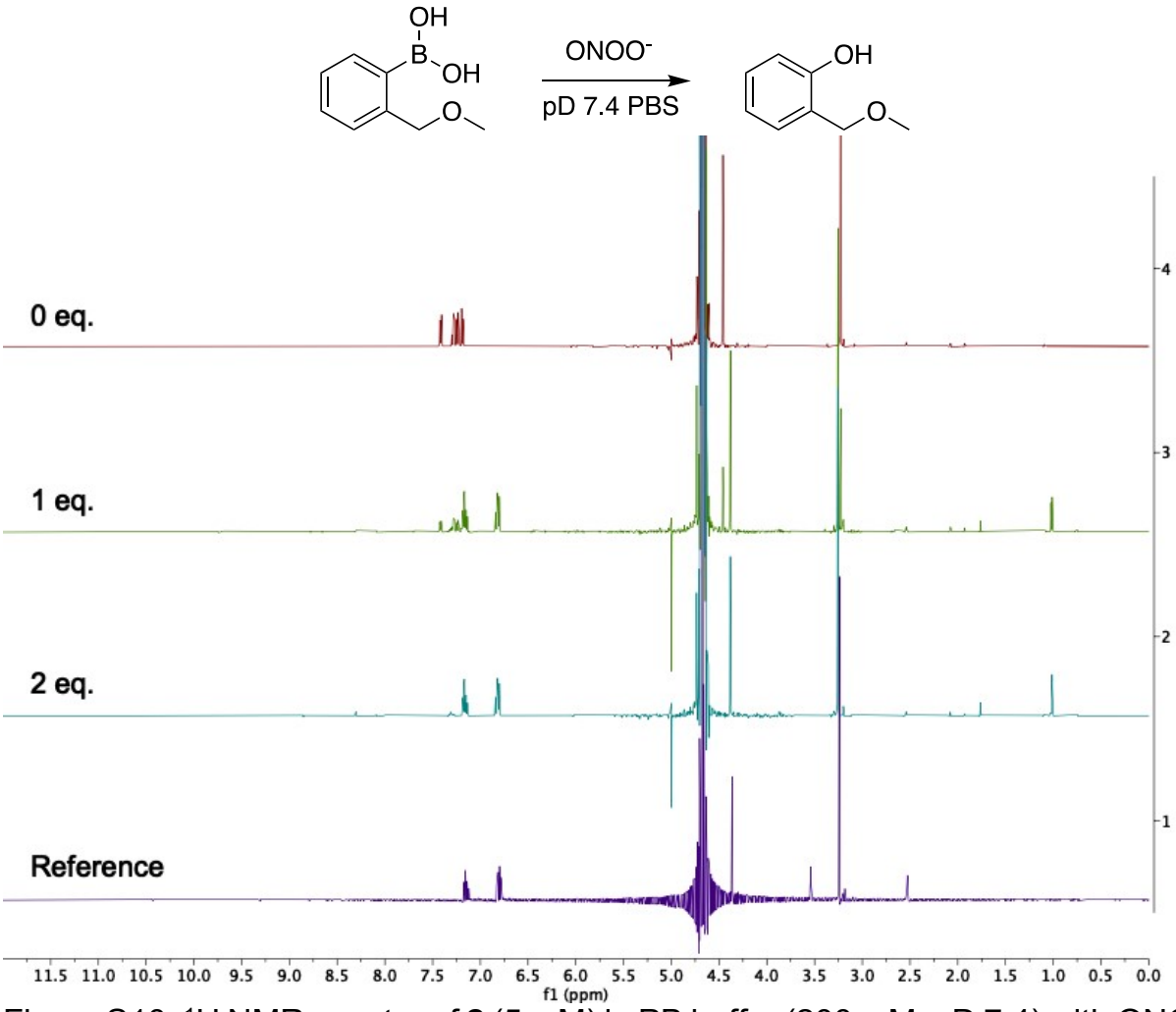
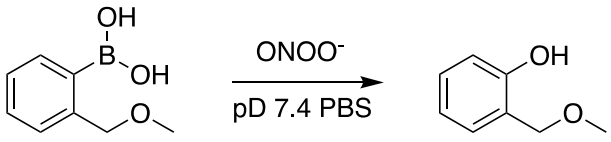


Figure S10. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. $ONOO^-$ was added in 1 equivalent aliquots with spectra collected immediately after addition. A reference spectrum for the corresponding phenol is also included.



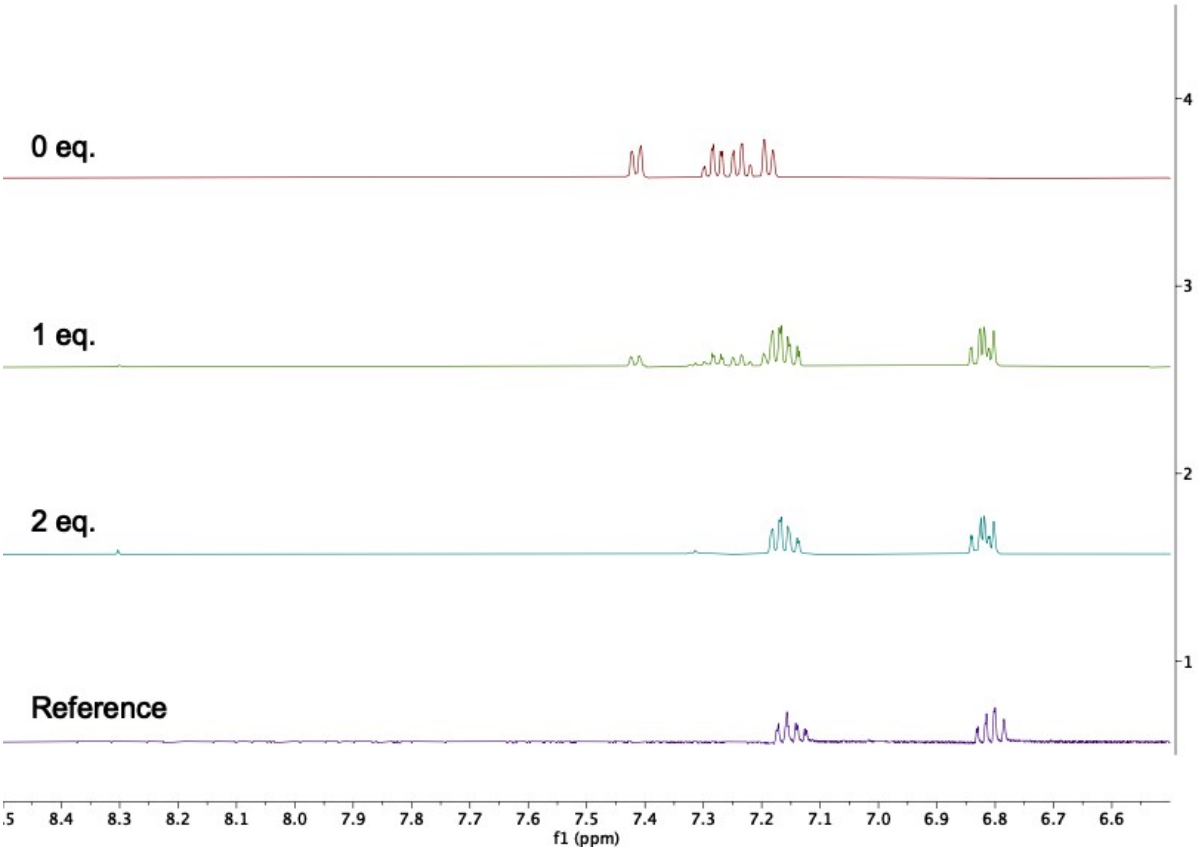


Figure S10a. Aromatic region of ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. $ONOO^-$ was added in 1 equivalent aliquots with spectra collected immediately after addition. A reference spectrum for the corresponding phenol is also included.

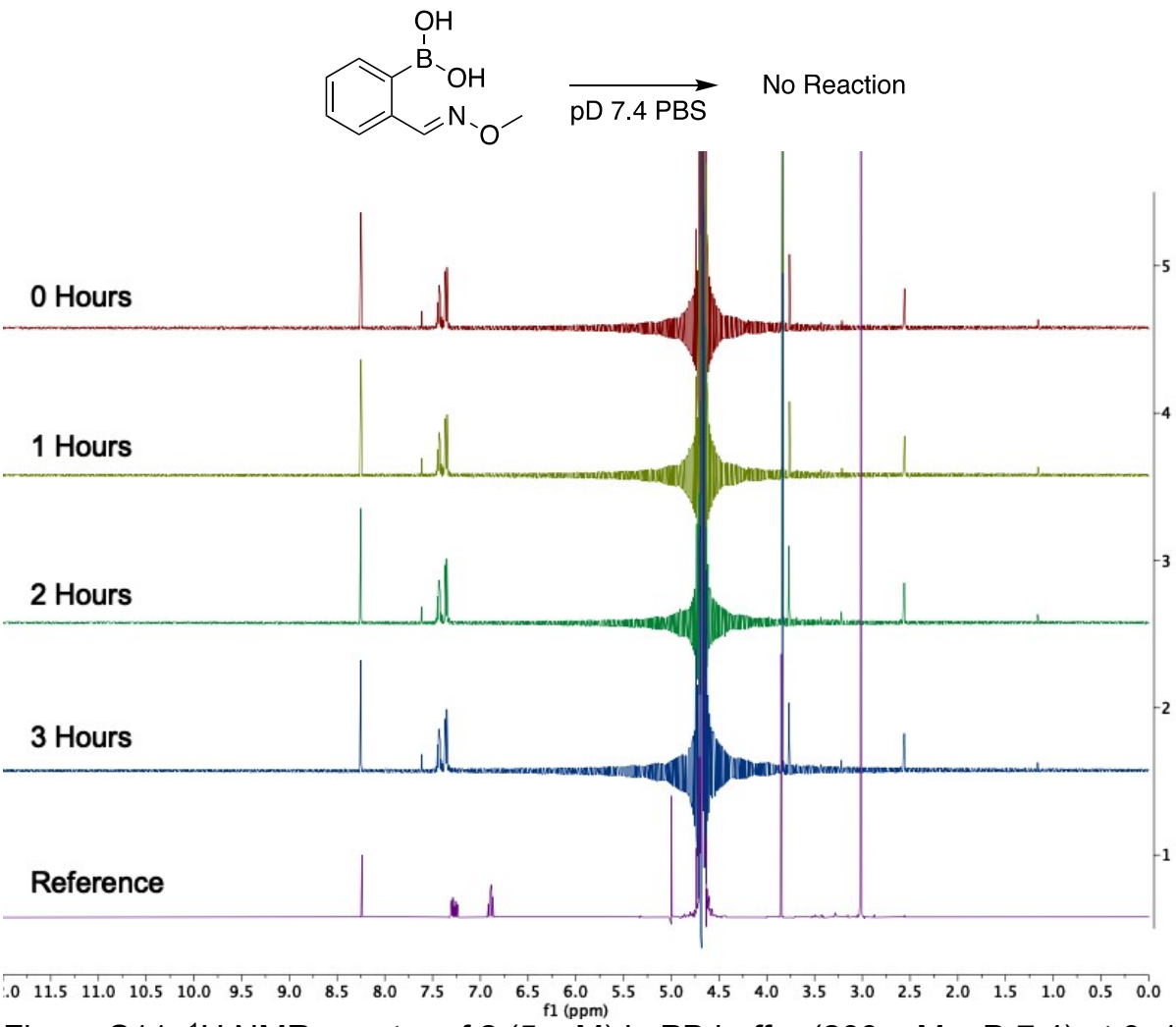


Figure S11. ^{1}H NMR spectra of **2** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

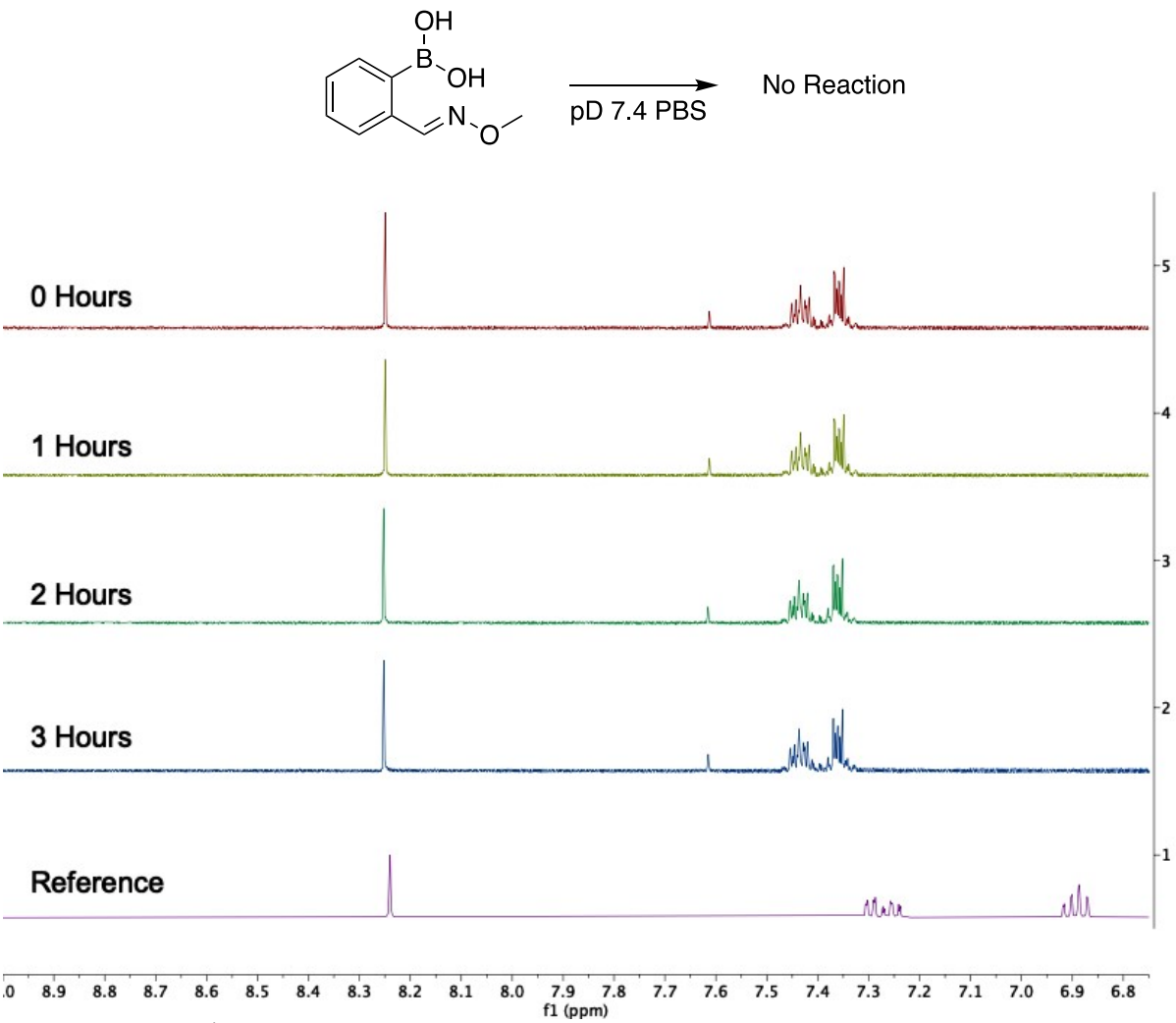


Figure S11a. ^{1}H NMR spectra of **3** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

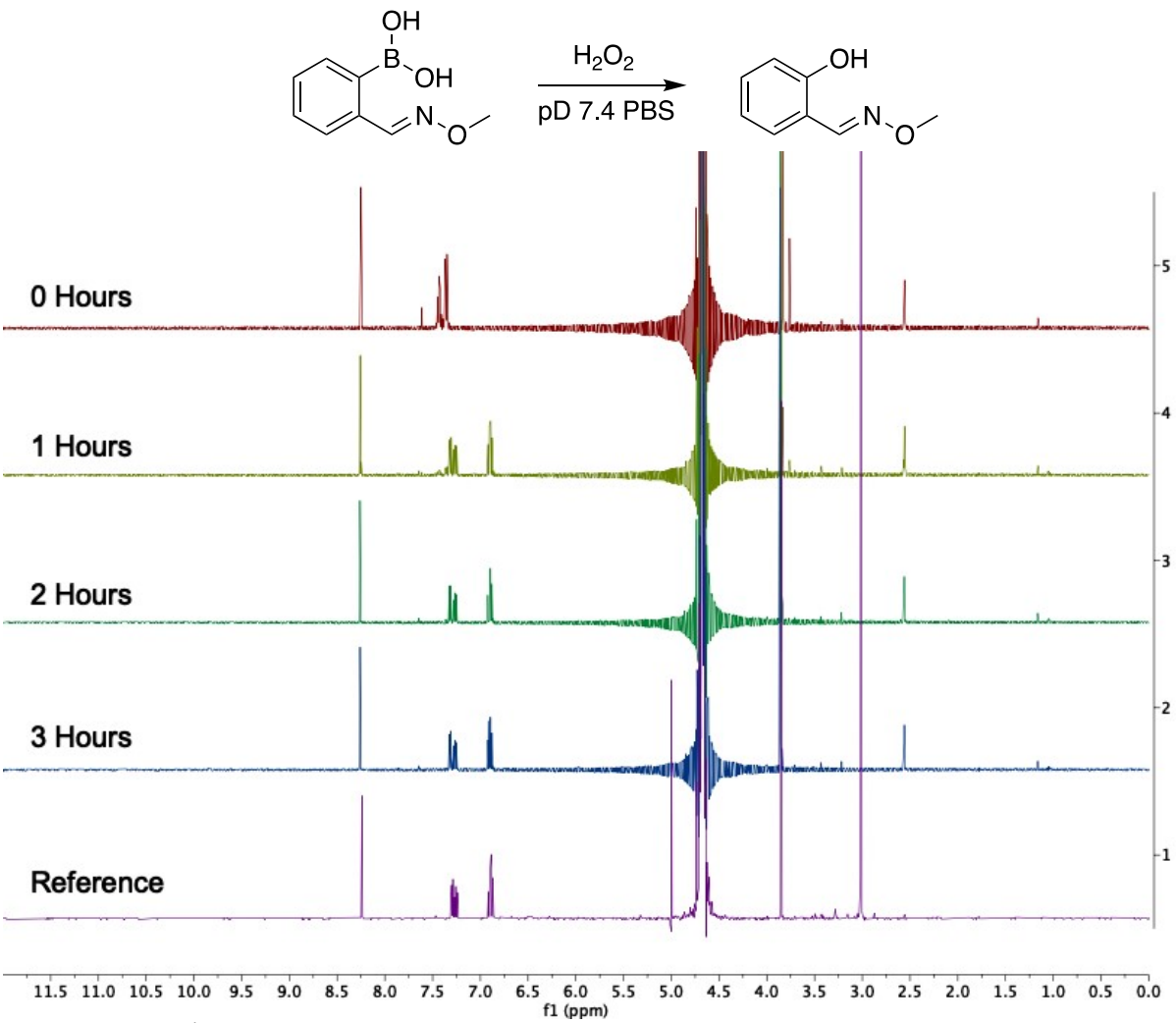


Figure S12. ^{1}H NMR spectra of **3** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

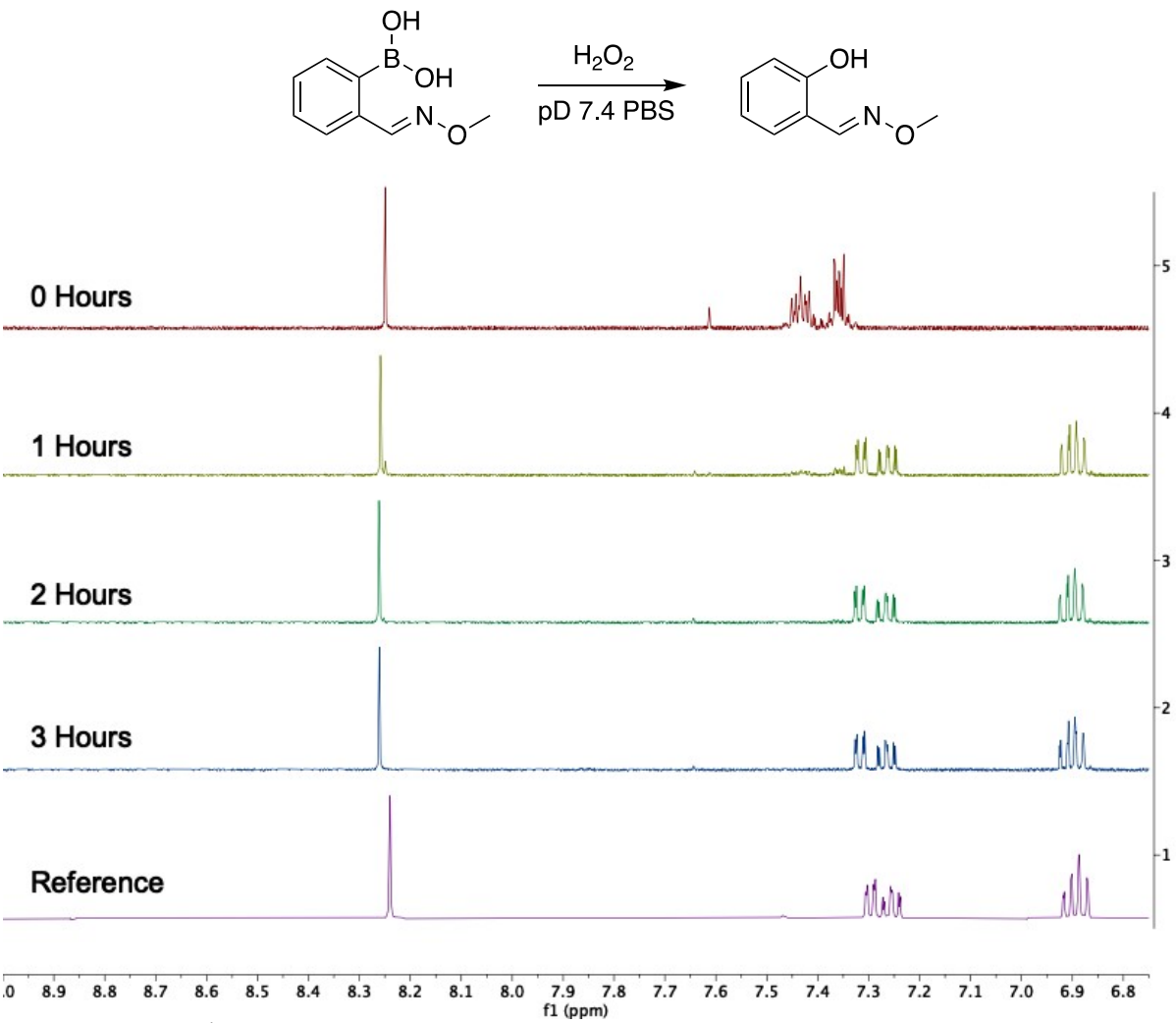


Figure S12a. ^{1}H NMR spectra of **3** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

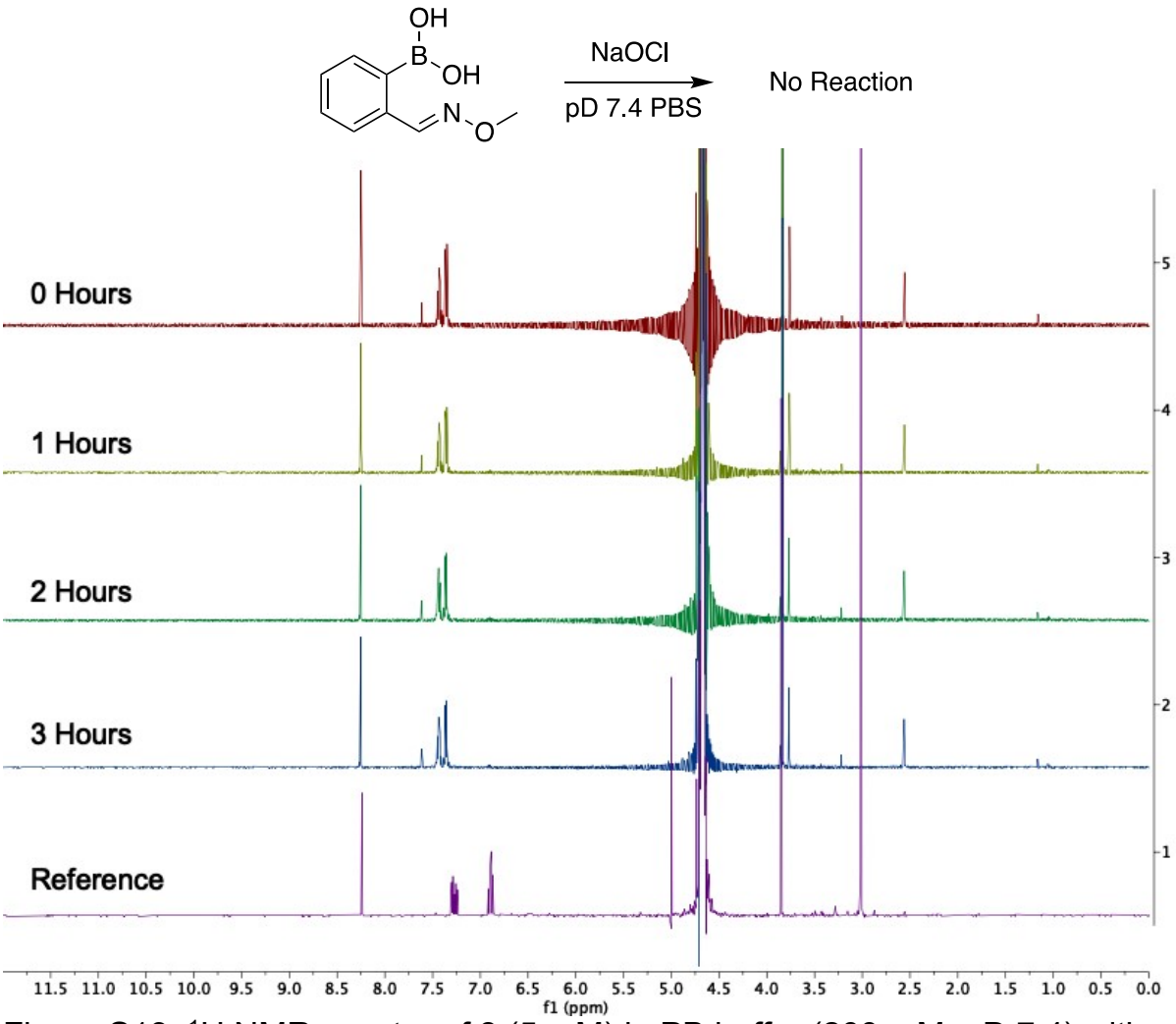


Figure S13. ^{1}H NMR spectra of **3** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

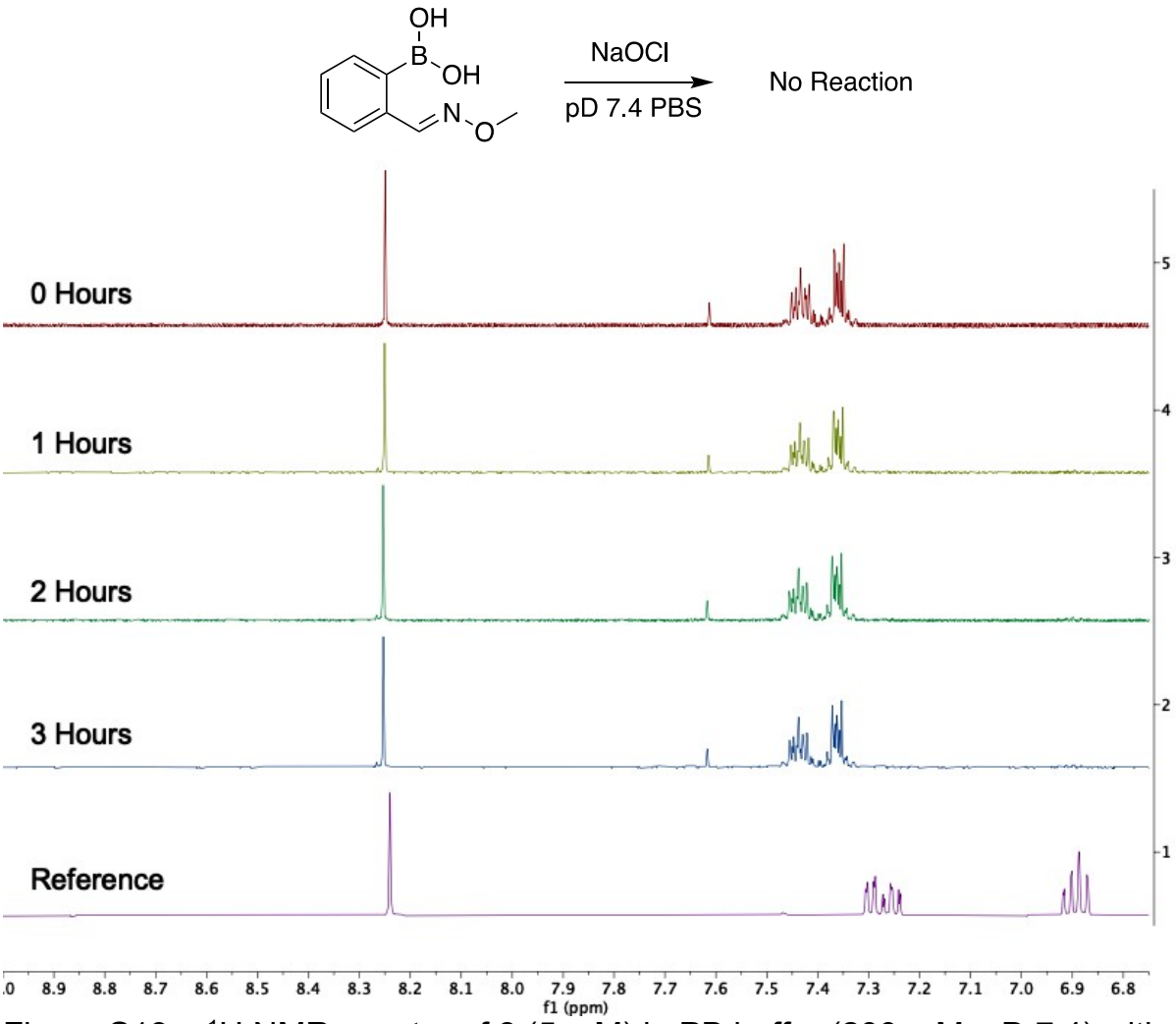


Figure S13a. ^{1}H NMR spectra of **3** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

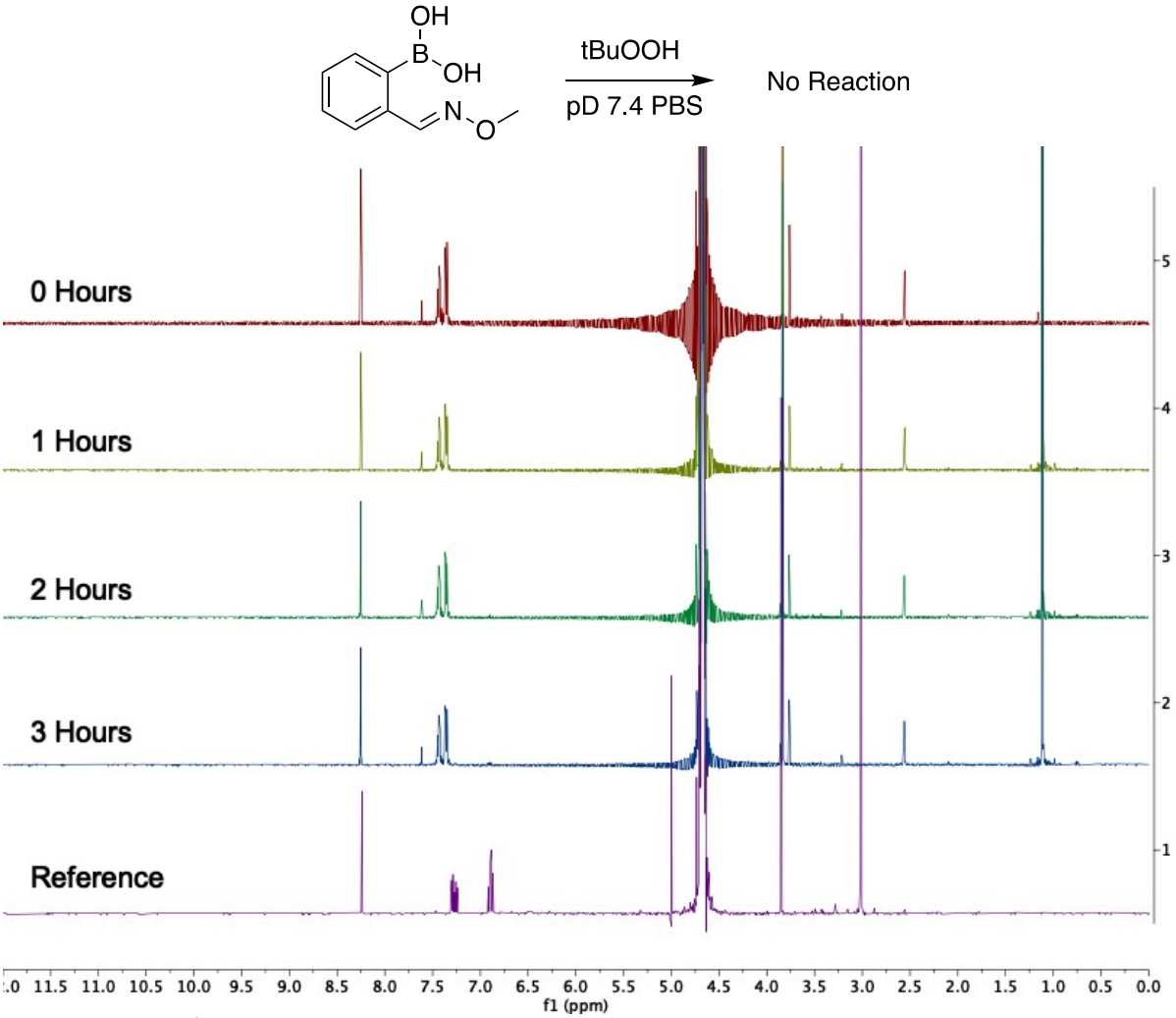


Figure S14. ^{1}H NMR spectra of **3** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

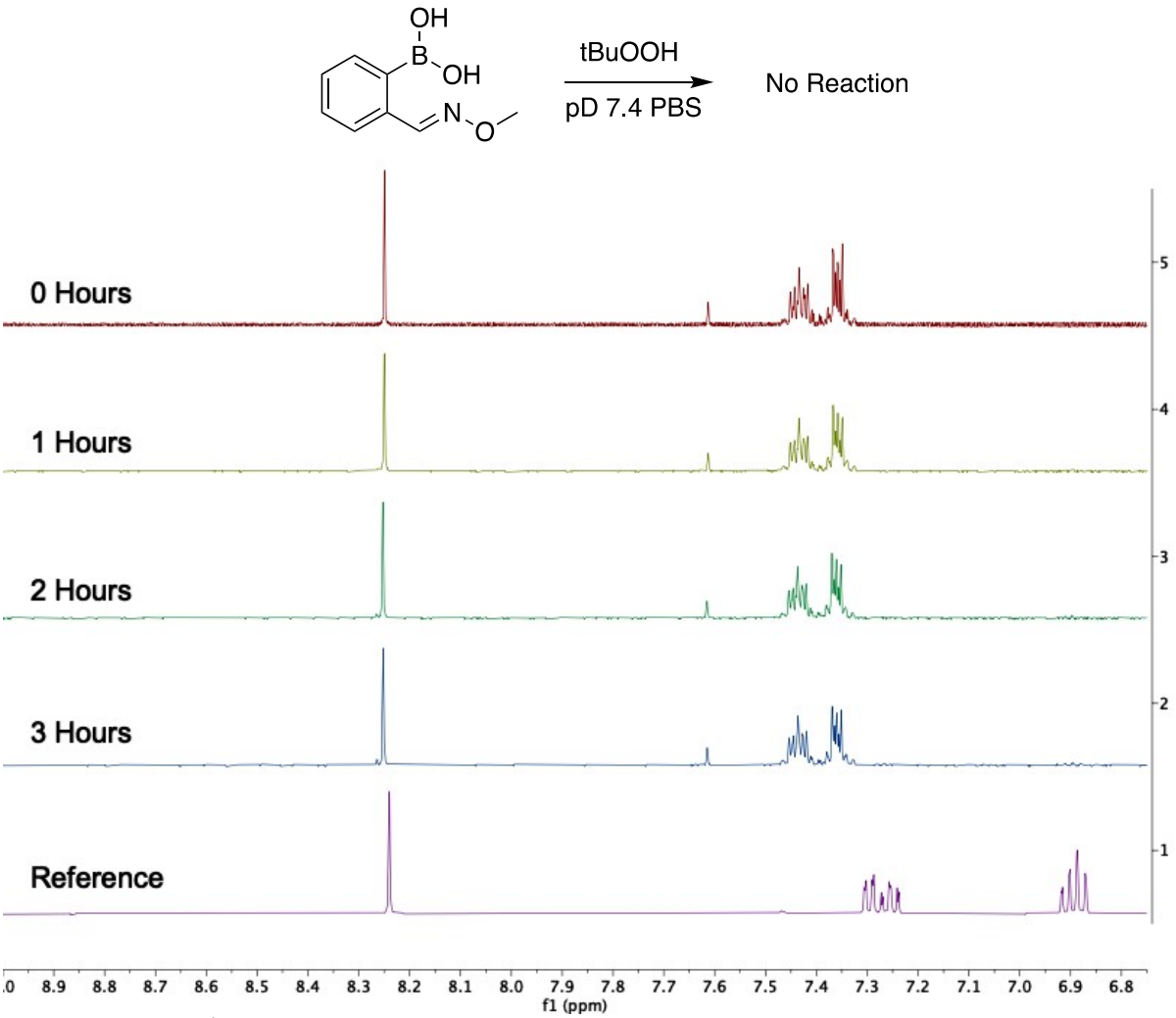


Figure S14a. ^{1}H NMR spectra of **3** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

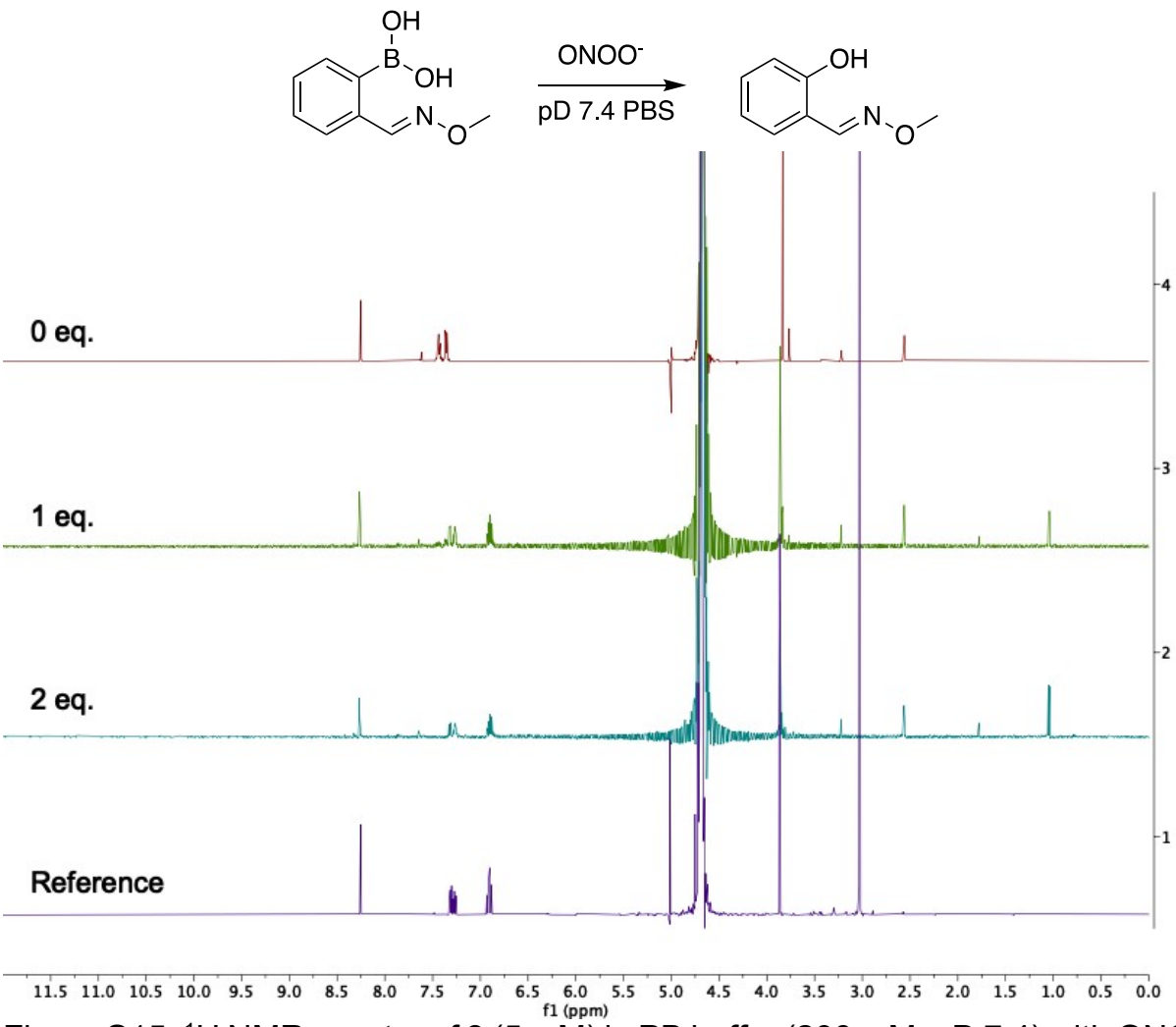


Figure S15. ^{1}H NMR spectra of **3** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. Aliquots of $ONOO^-$ (1 equivalent each) were added with spectra collected immediately after addition. A reference spectrum for the corresponding phenol is also included.

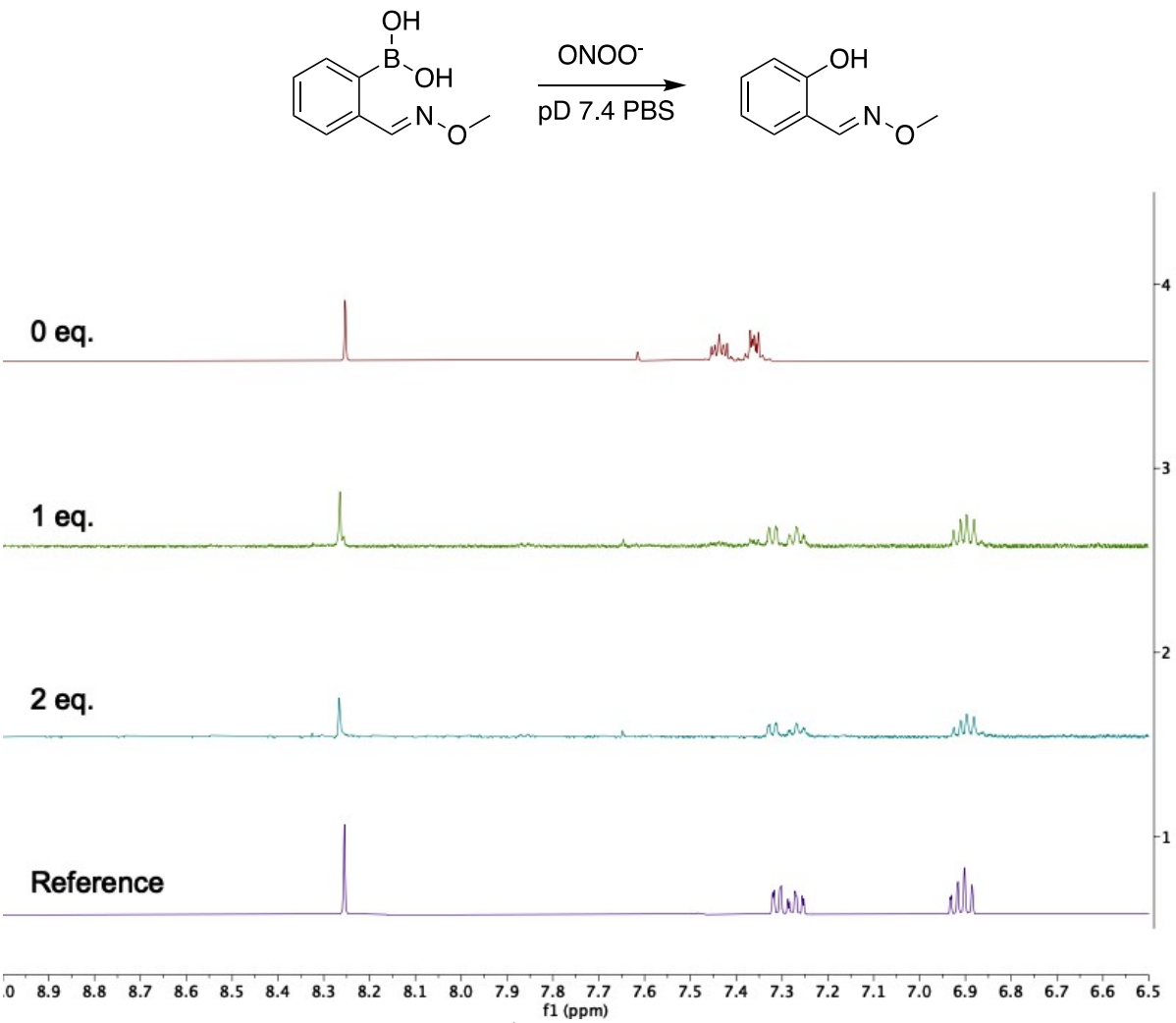


Figure S15a. Aromatic region of ^{1}H NMR spectra of **3** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. Aliquots of $ONOO^-$ (1 equivalent each) were added with spectra collected immediately after addition. A reference spectrum for the corresponding phenol is also included.

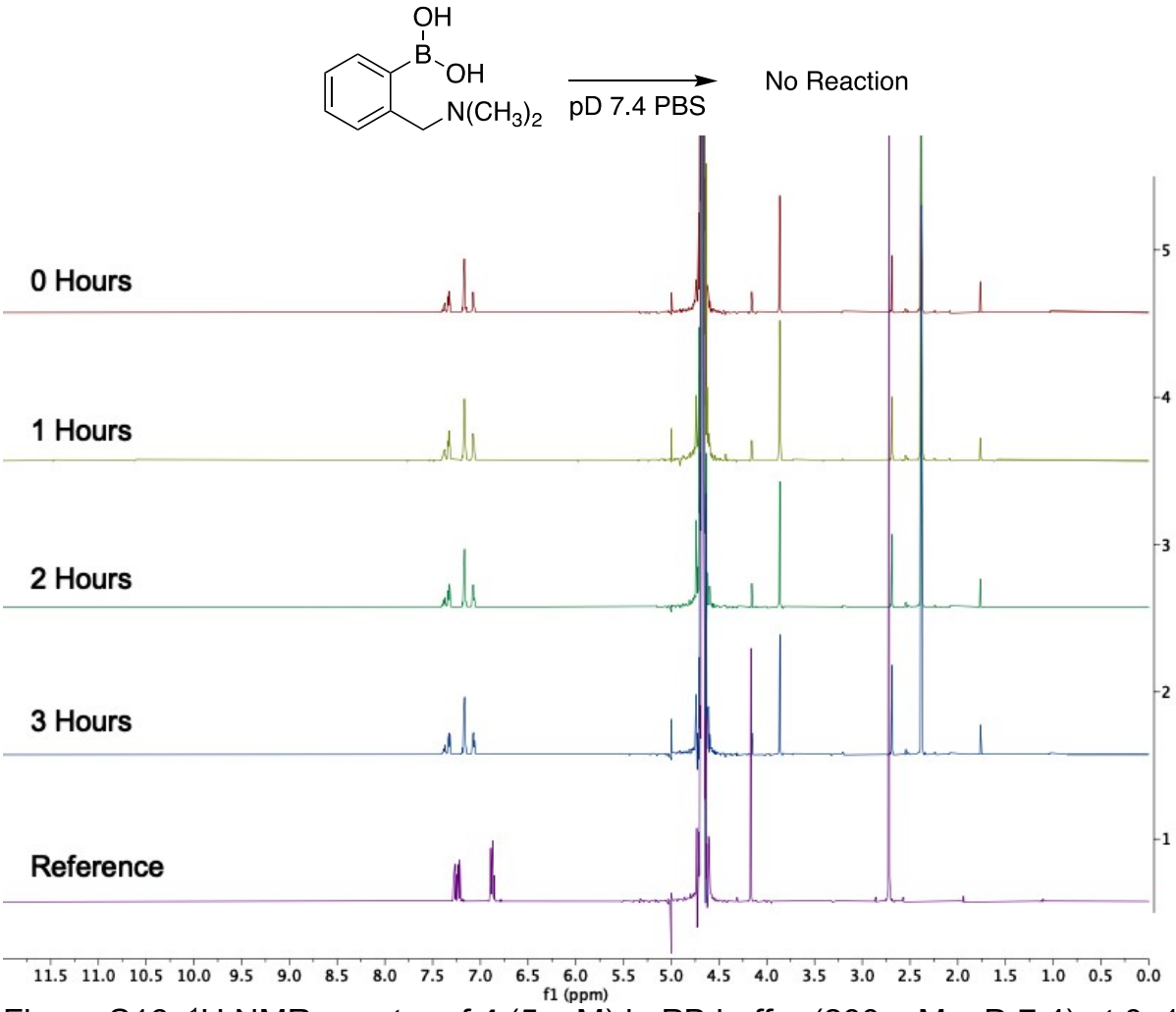


Figure S16. ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

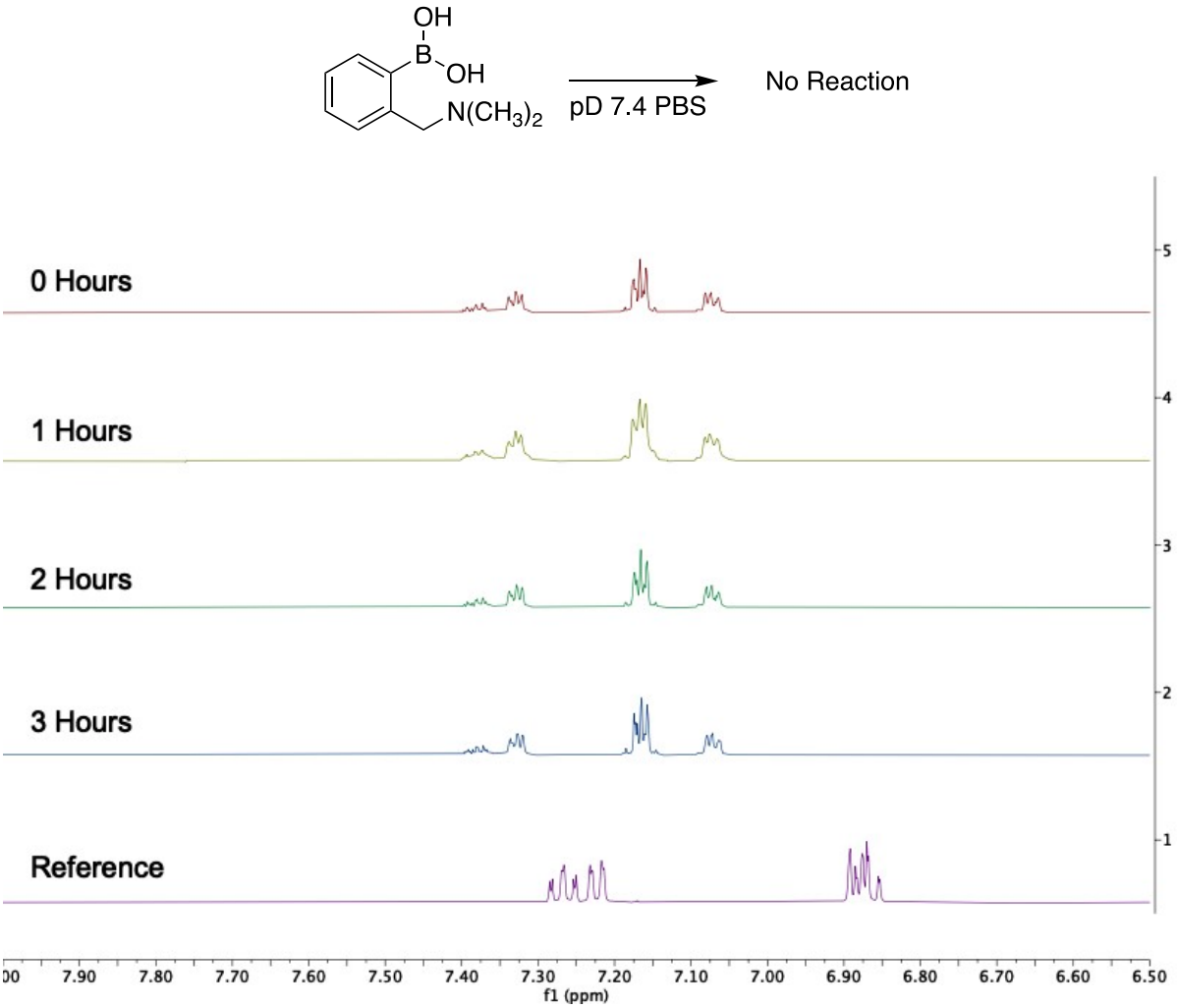


Figure S16a. ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

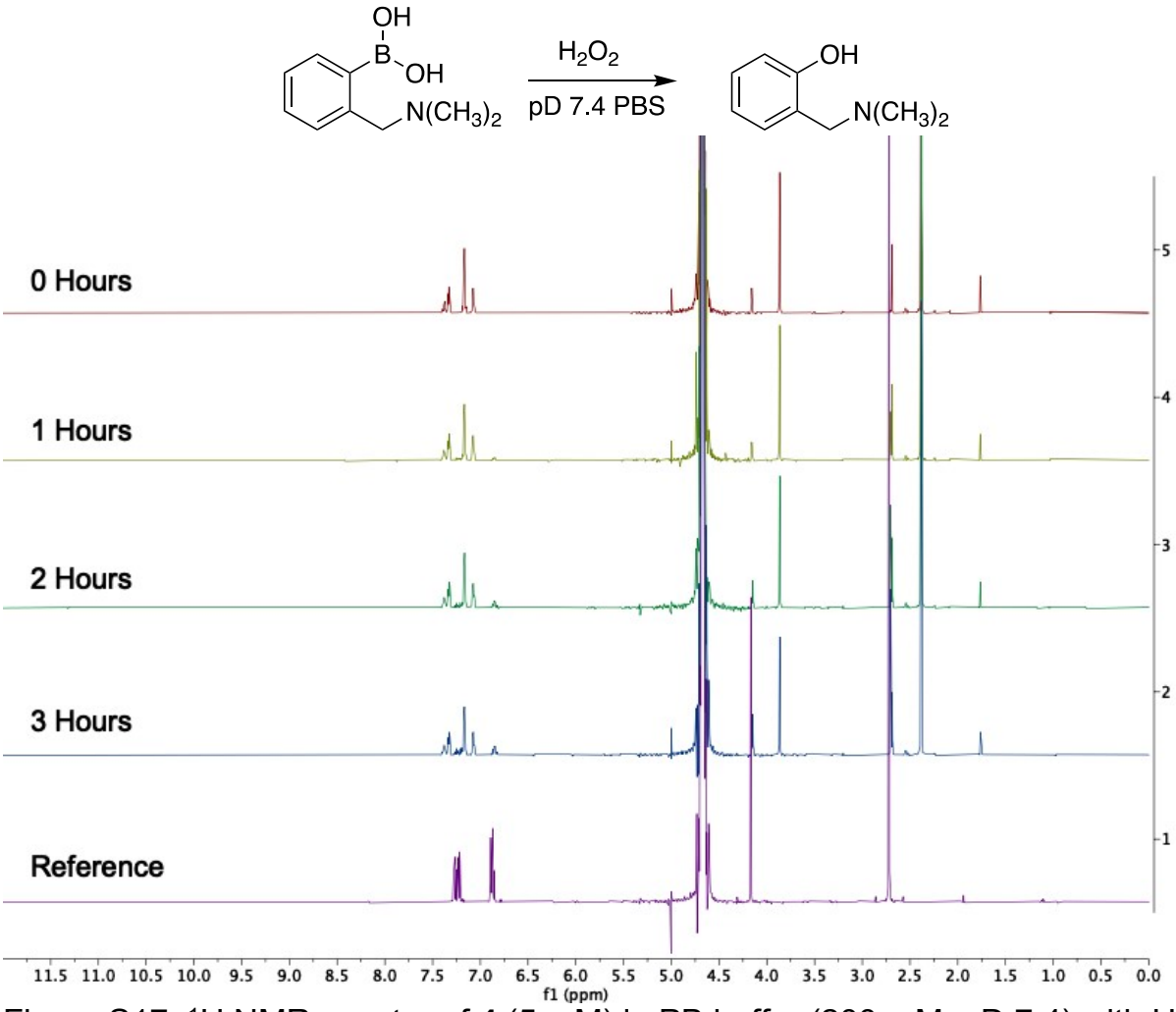


Figure S17. ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

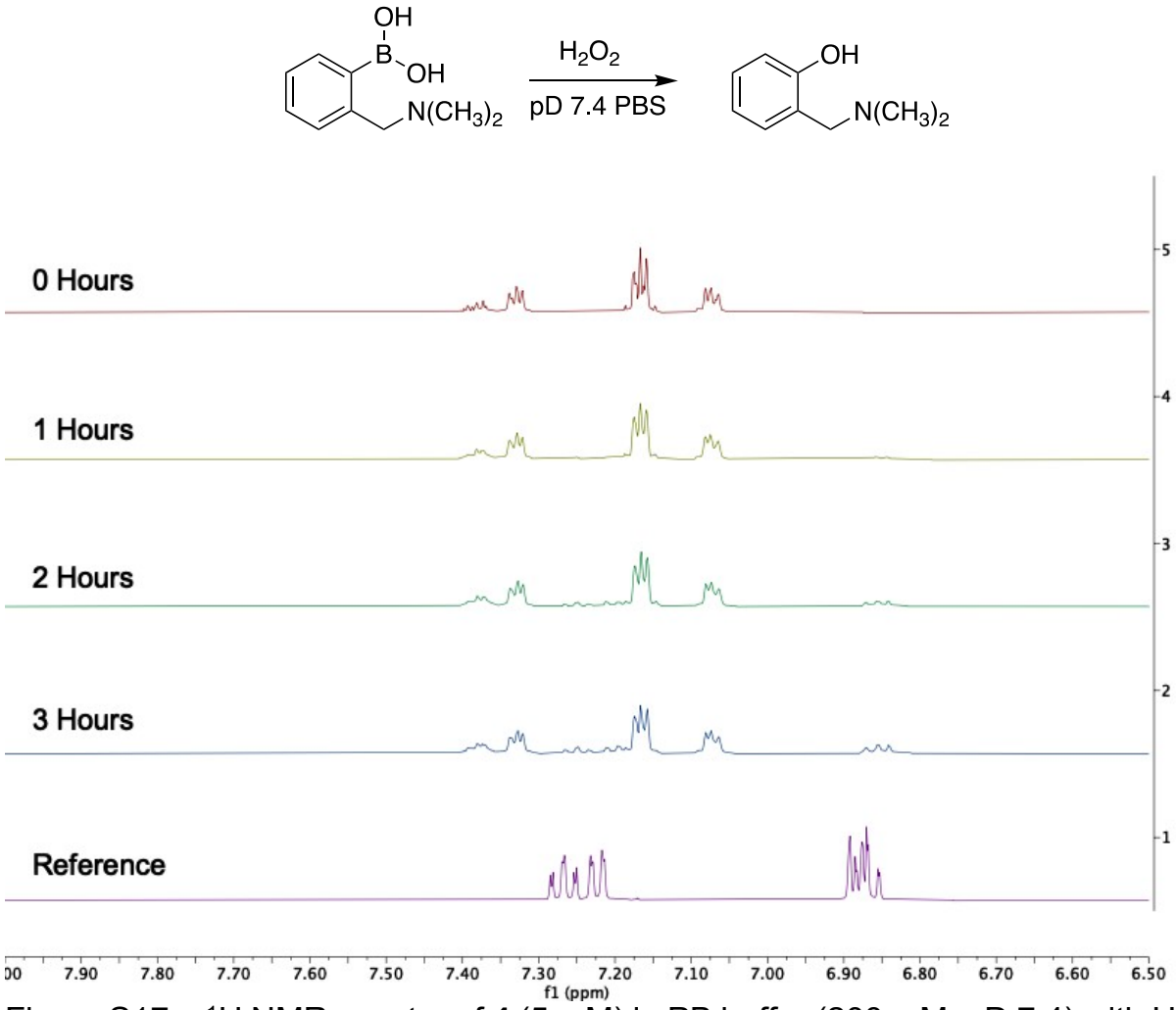


Figure S17a. ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

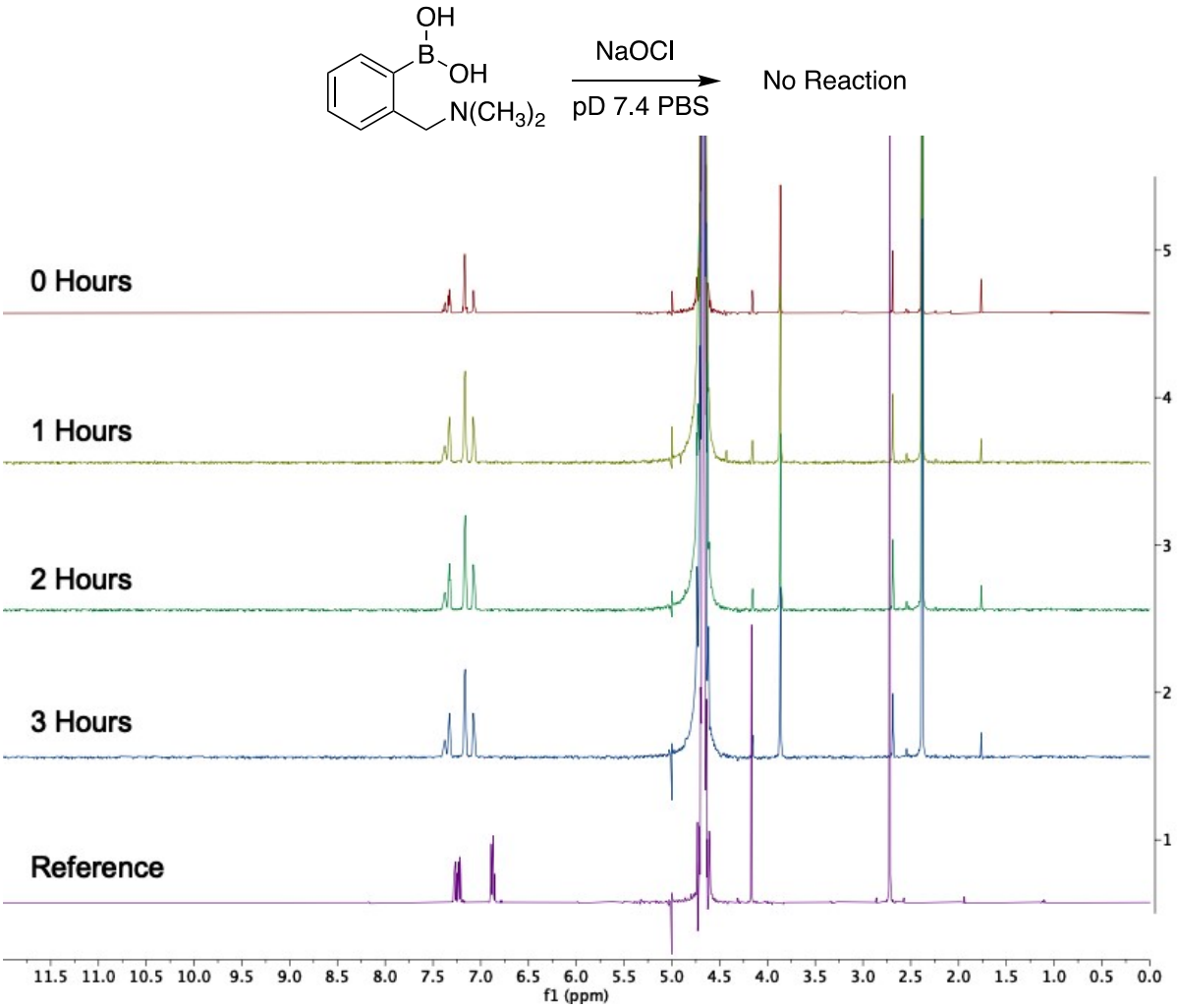


Figure S18. ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

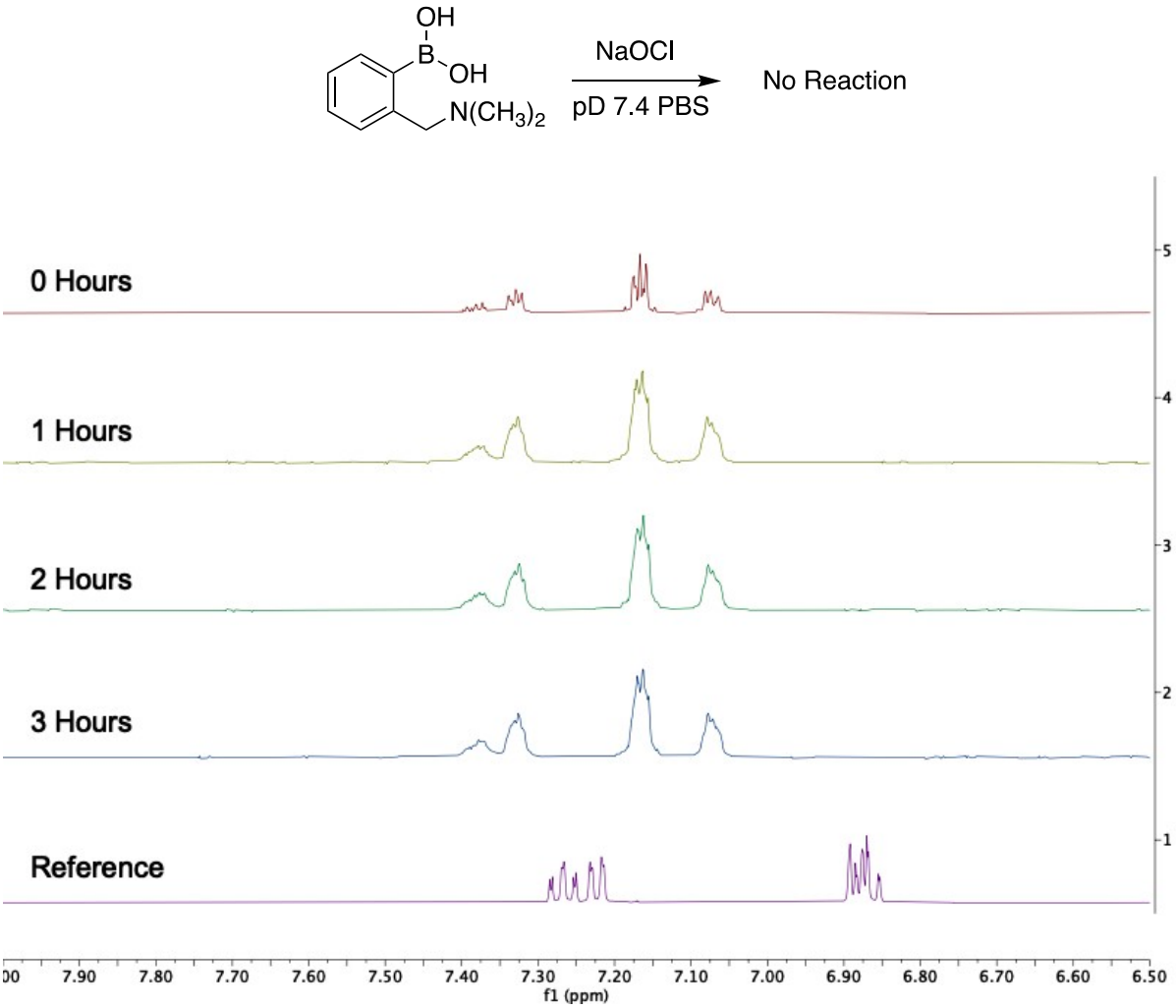


Figure S18a. ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

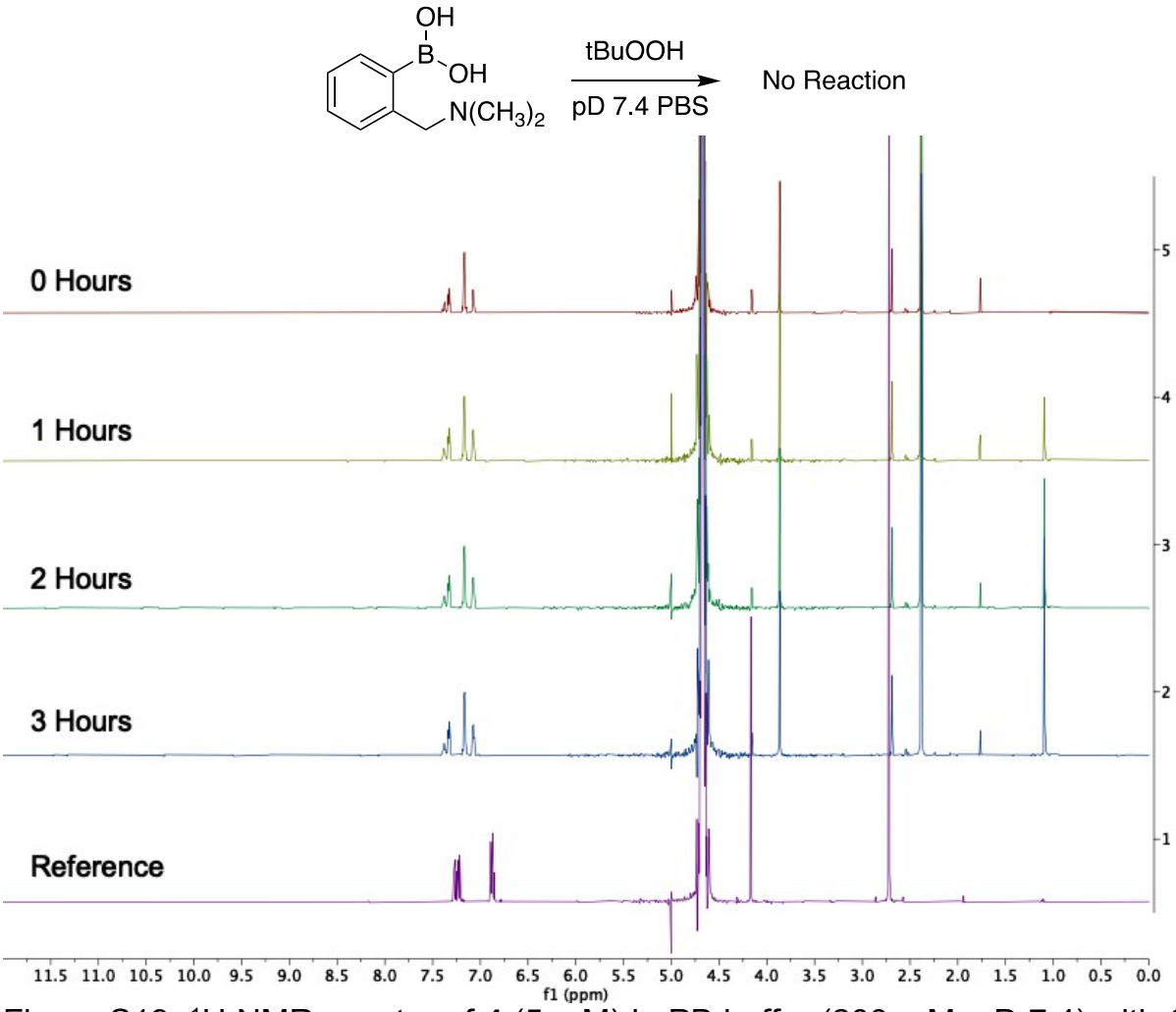


Figure S19. ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

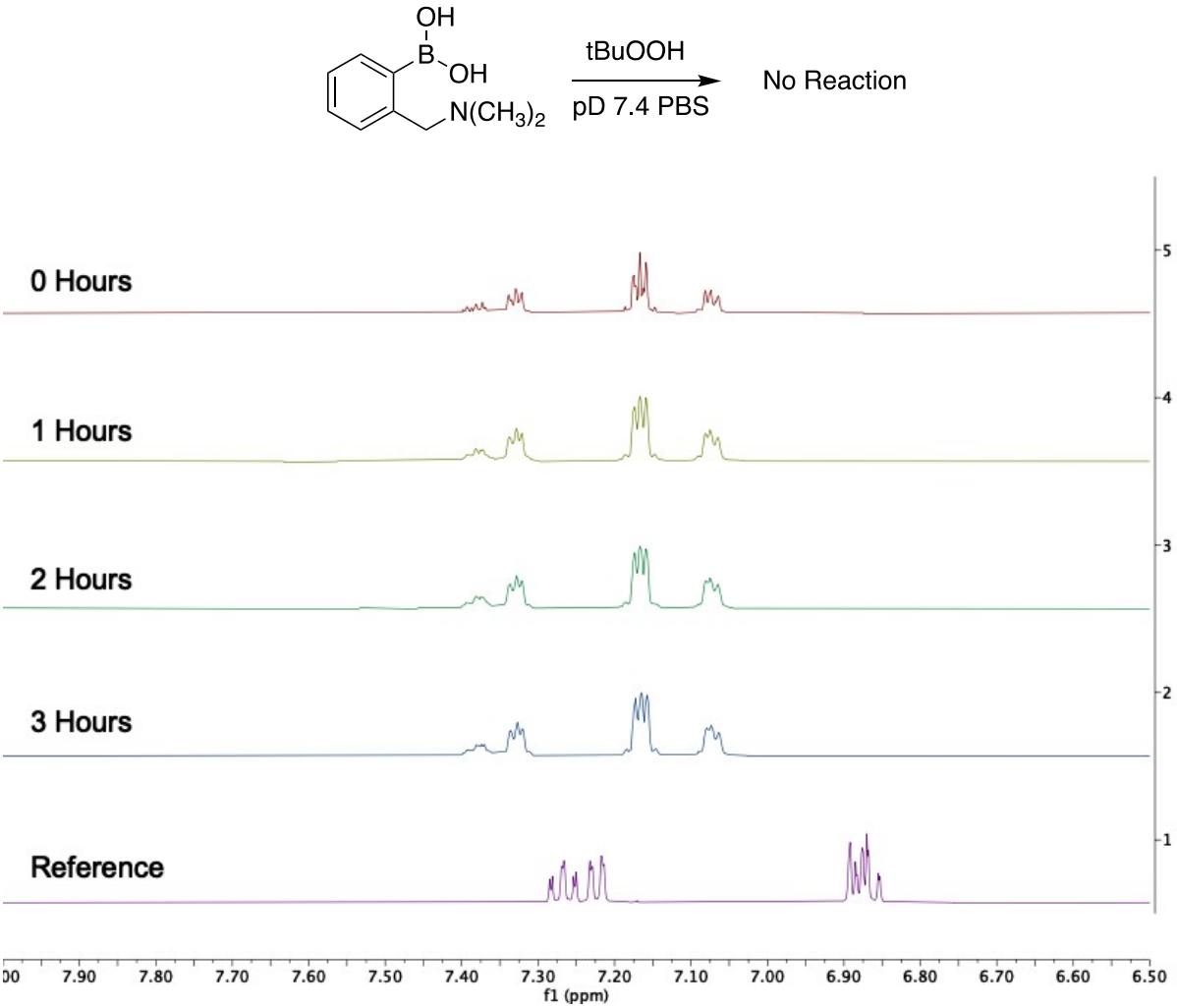


Figure S19a. ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

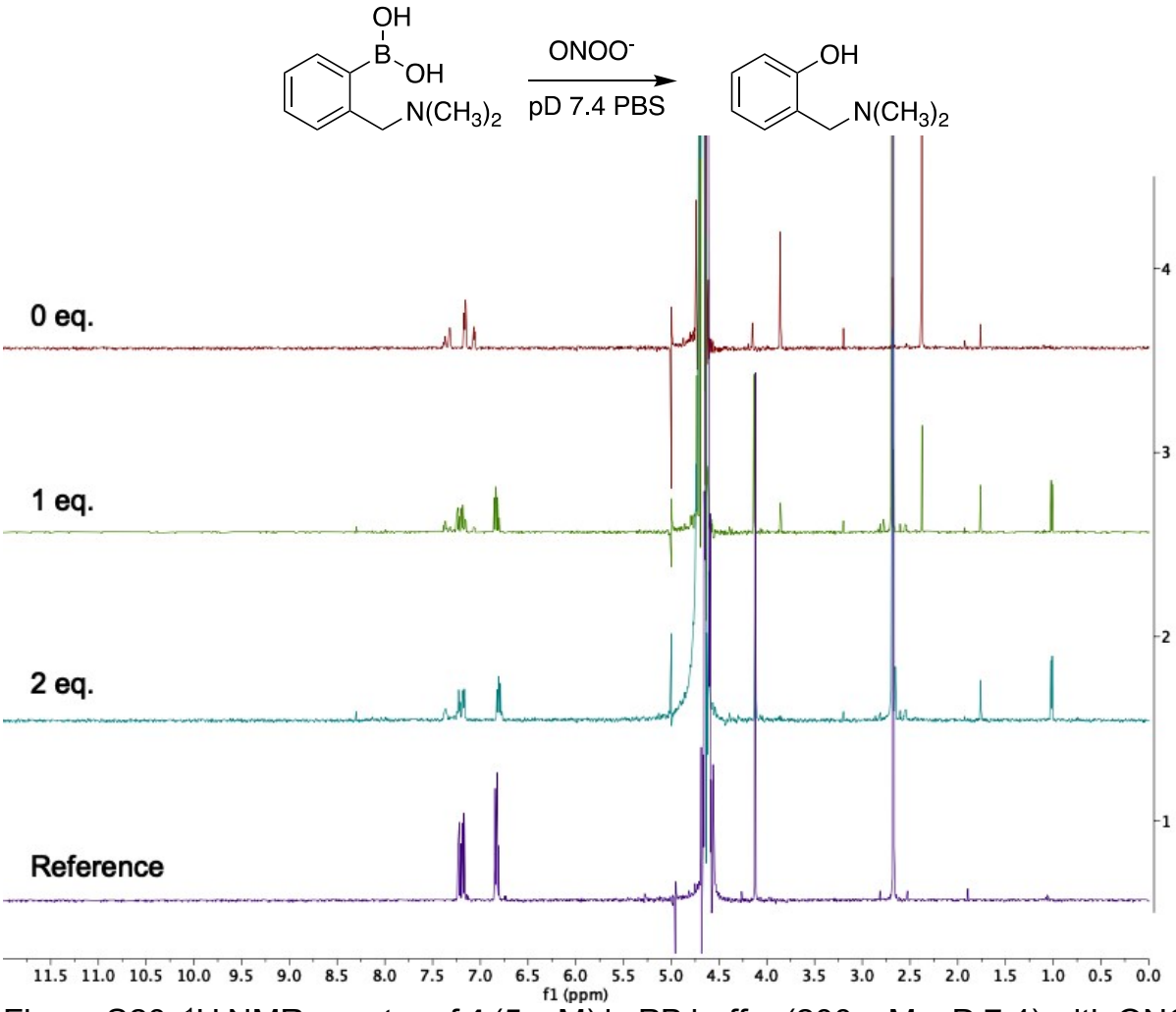


Figure S20. ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. Aliquots of $ONOO^-$ (1 equivalent each) were added with spectra collected immediately after addition. A reference spectrum for the corresponding phenol is also included.

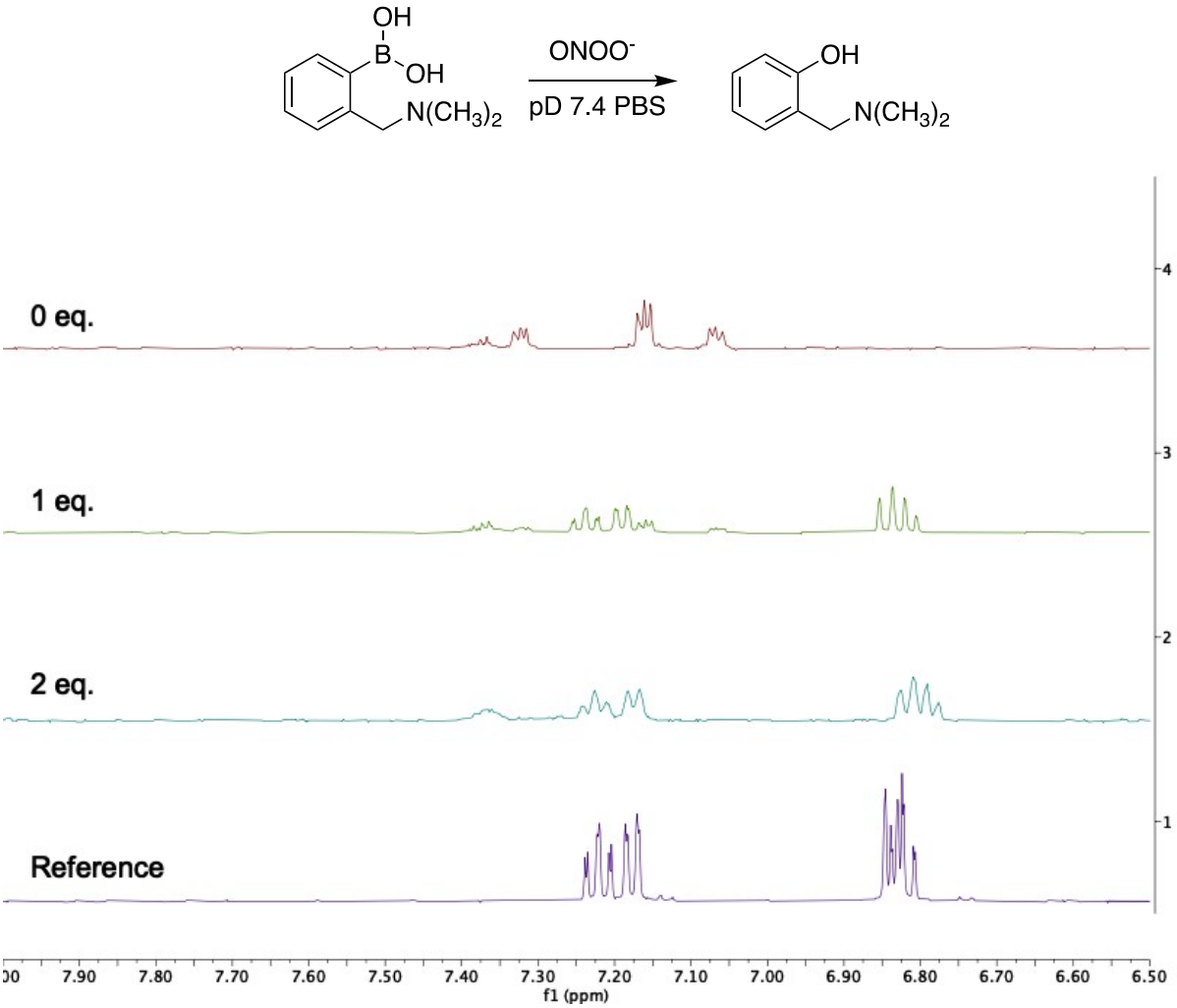


Figure S20a. Aromatic region of ^{1}H NMR spectra of **4** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. Aliquots of $ONOO^-$ (1 equivalent each) were added with spectra collected immediately after addition. A reference spectrum for the corresponding phenol is also included.

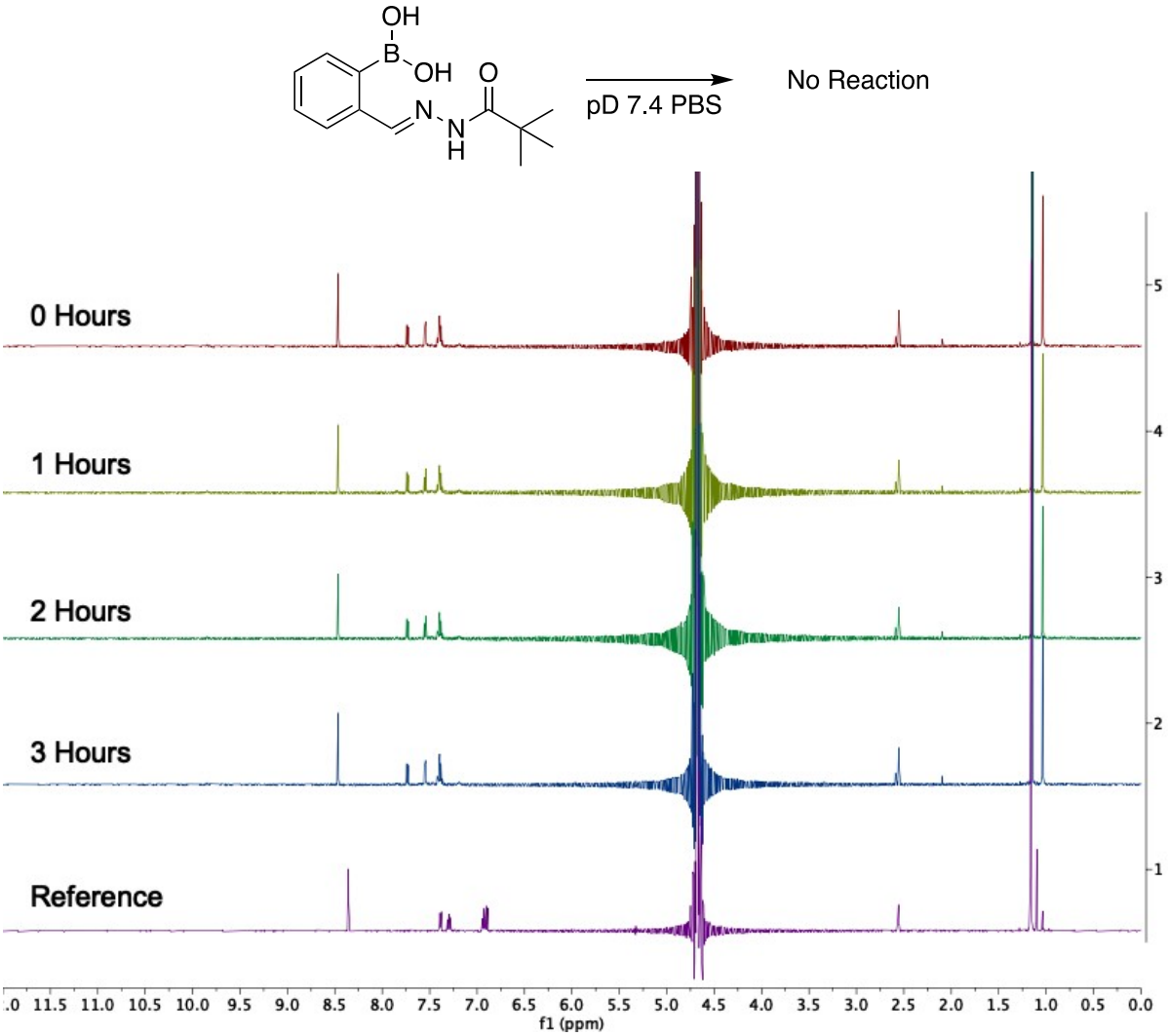


Figure S21. ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

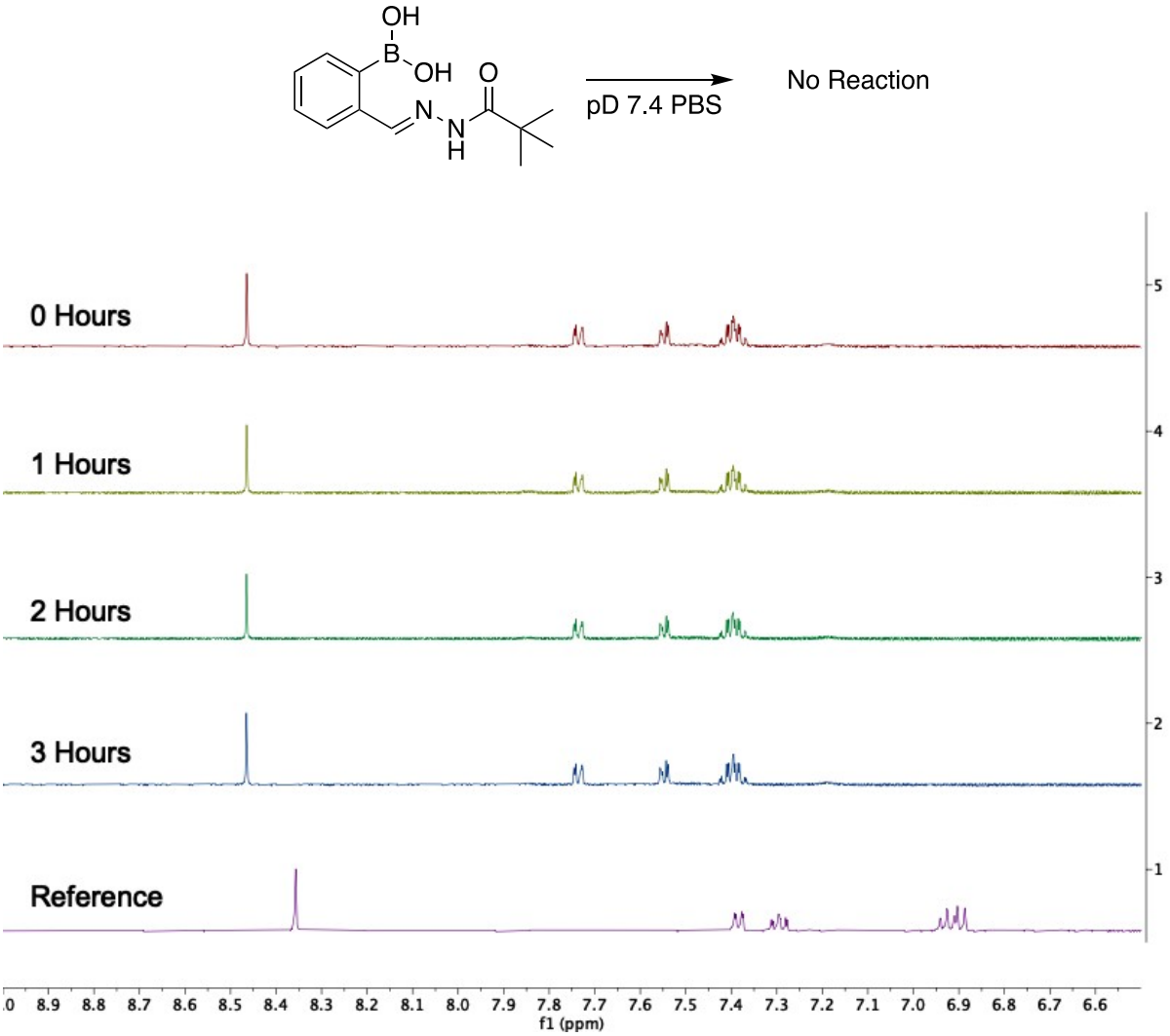


Figure S21A. ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for phenol also included. A reference spectrum for the corresponding phenol is also included.

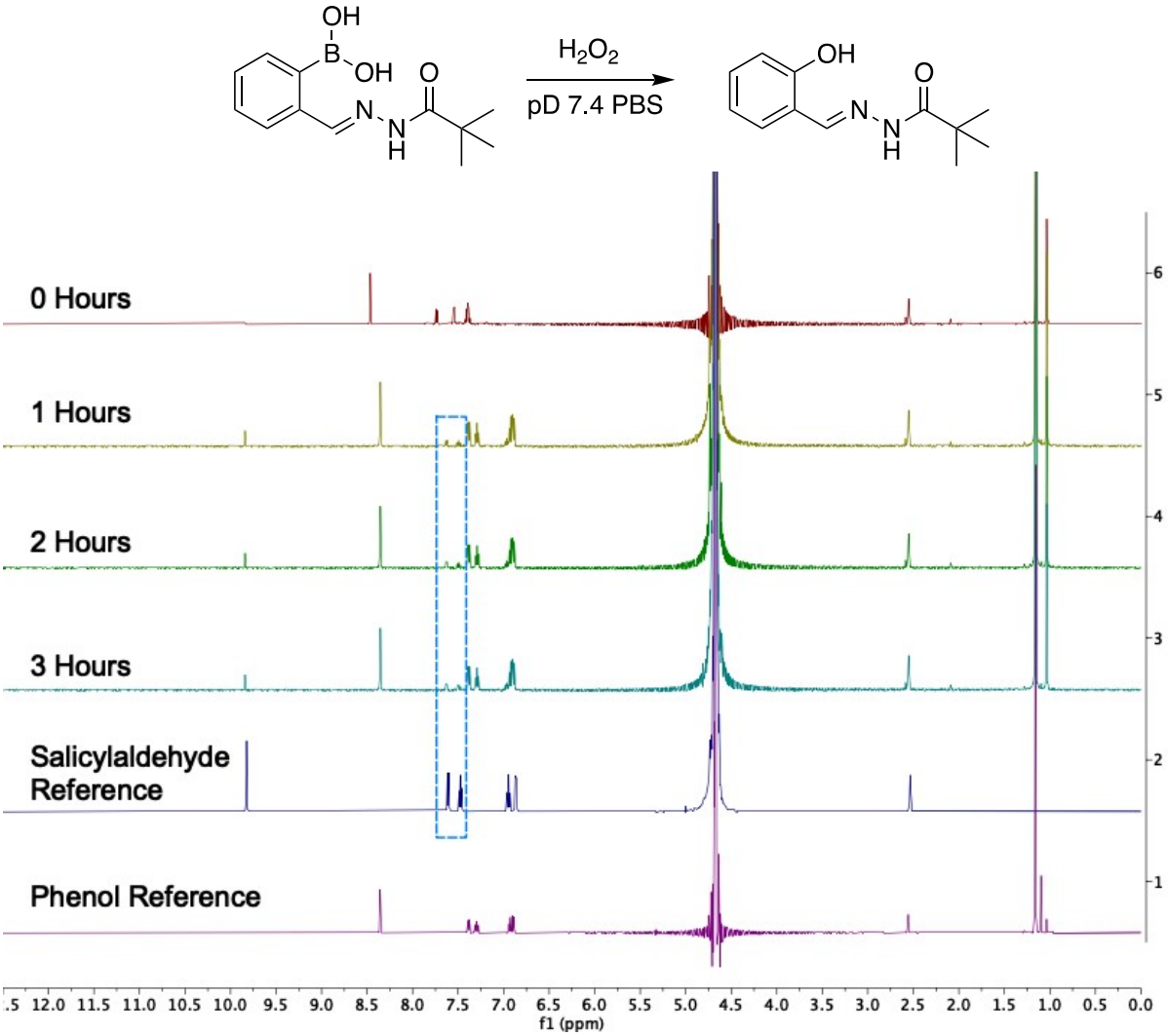


Figure S22. ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included. Trace hydrolysis to salicylaldehyde is also observed.

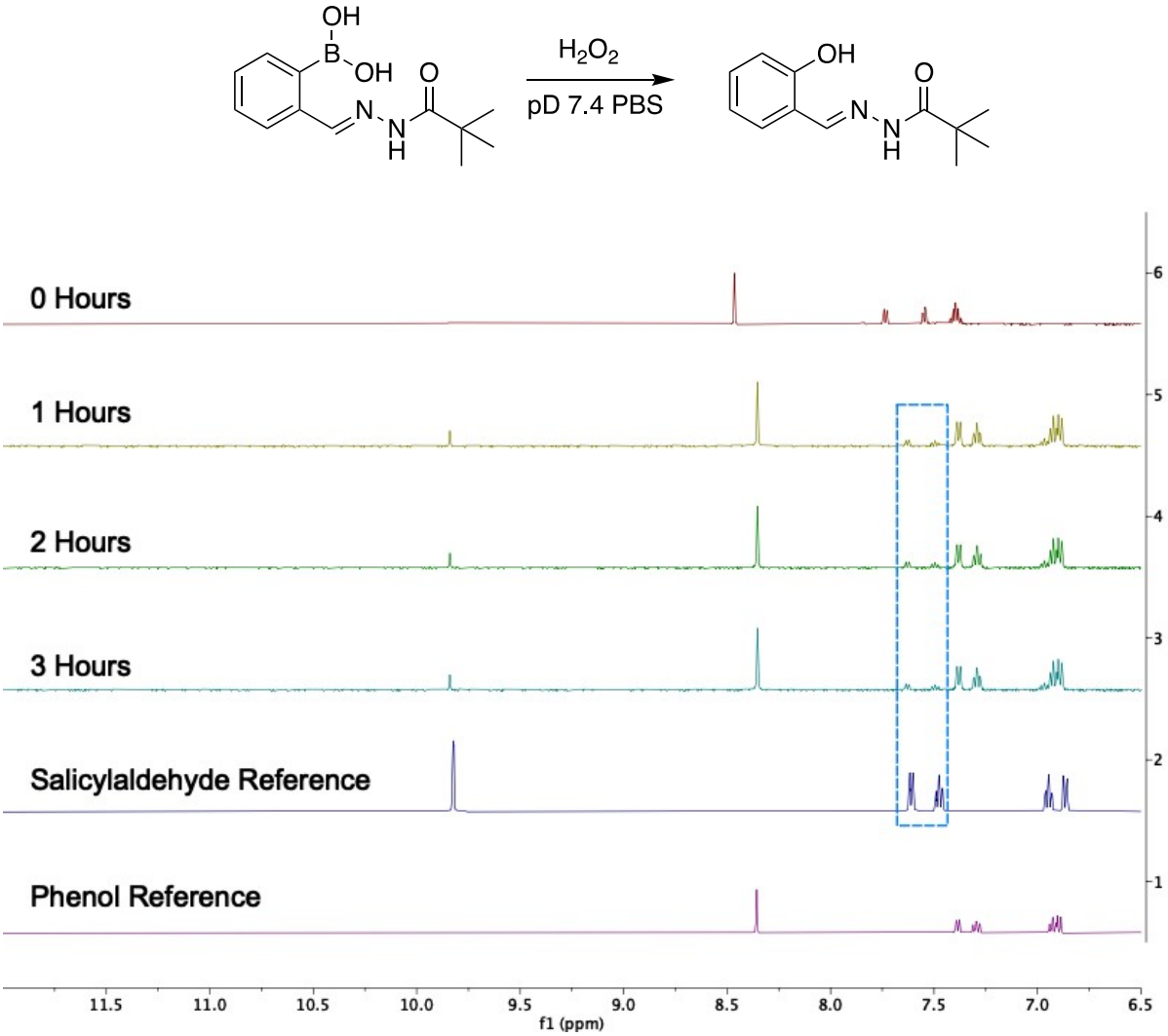


Figure S22a. ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included. Signals in the dashed blue box arise from salicylaldehyde, the product of oxidation and hydrazone hydrolysis.

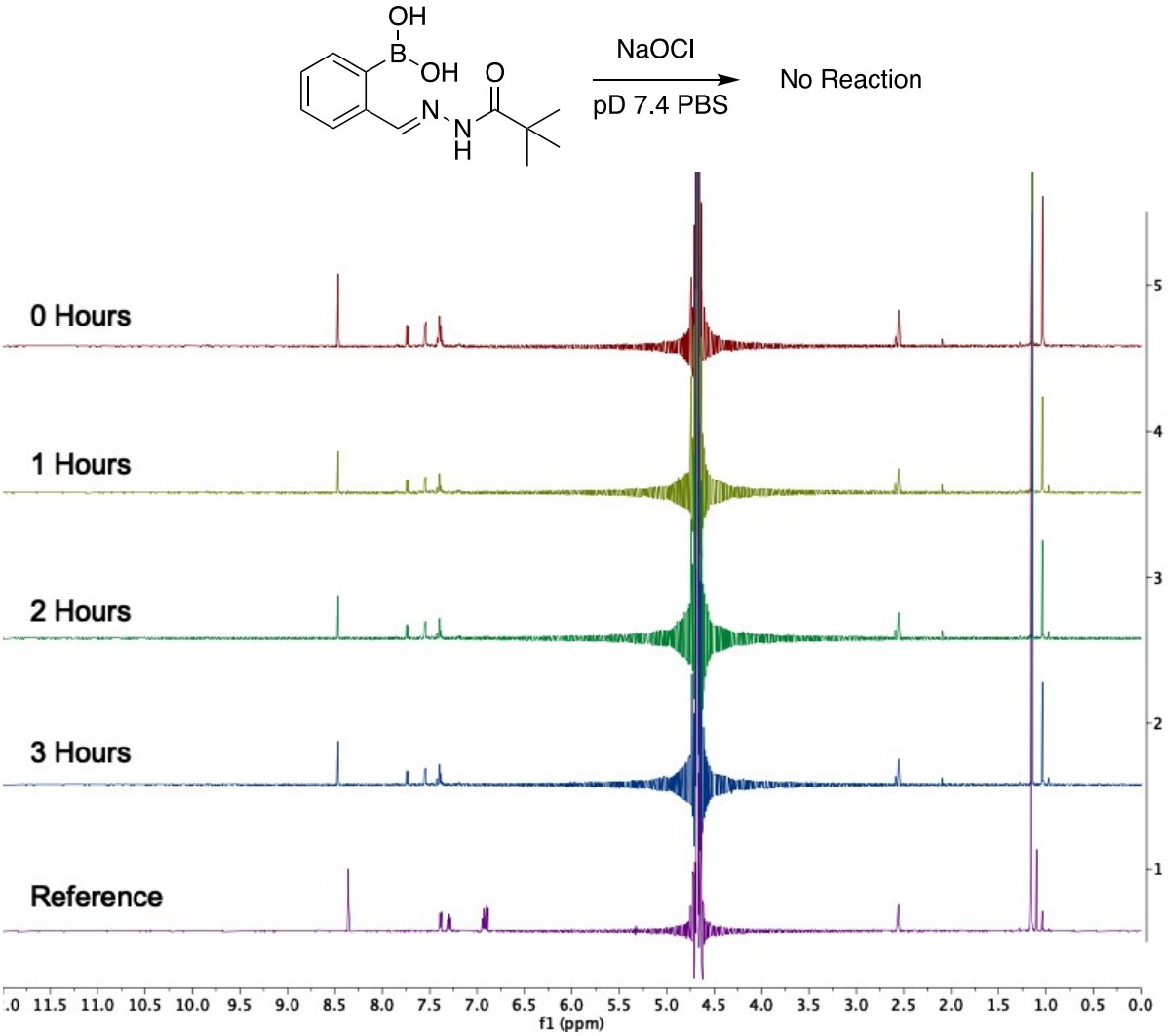


Figure S23. ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

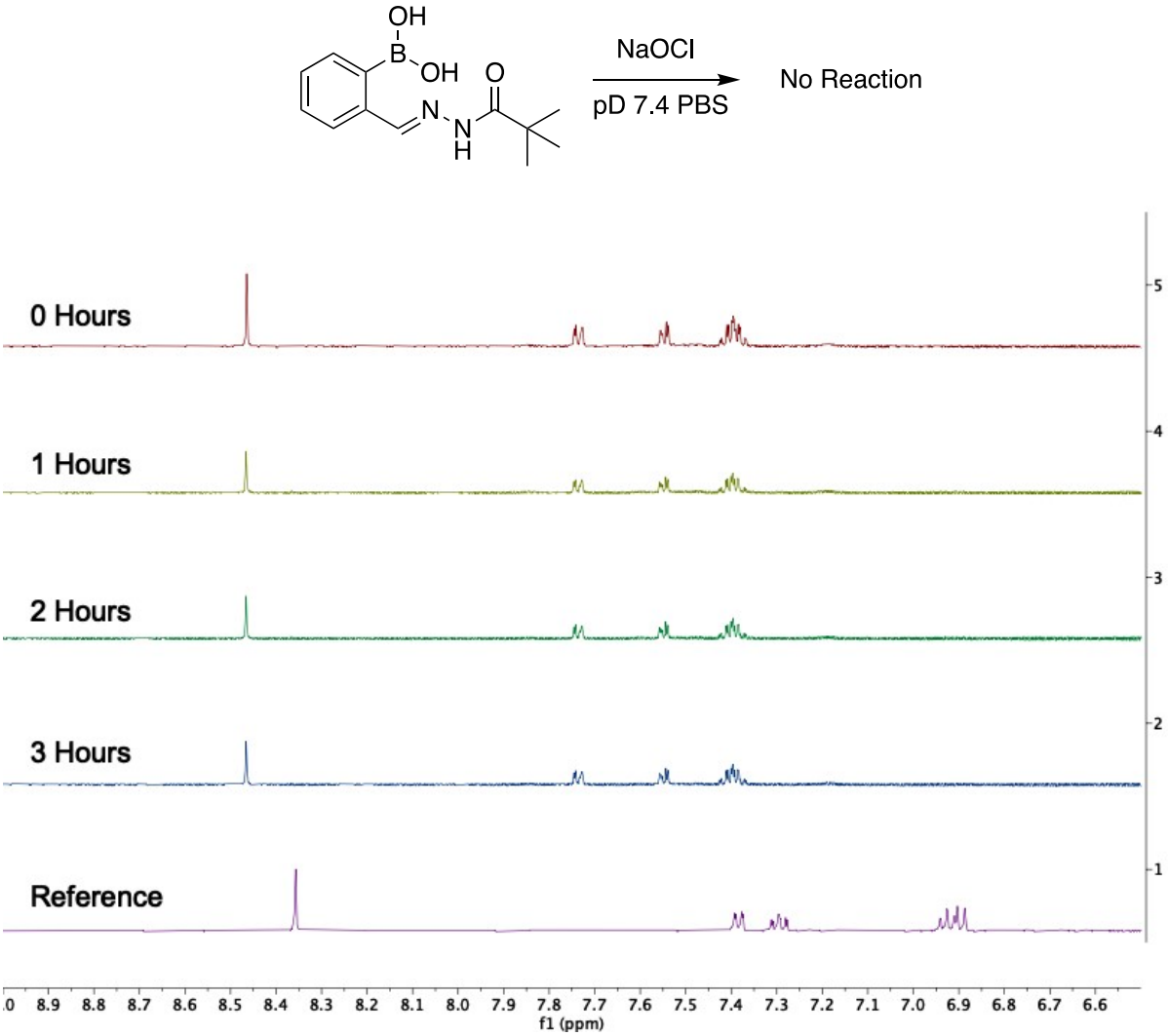


Figure S23a. ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

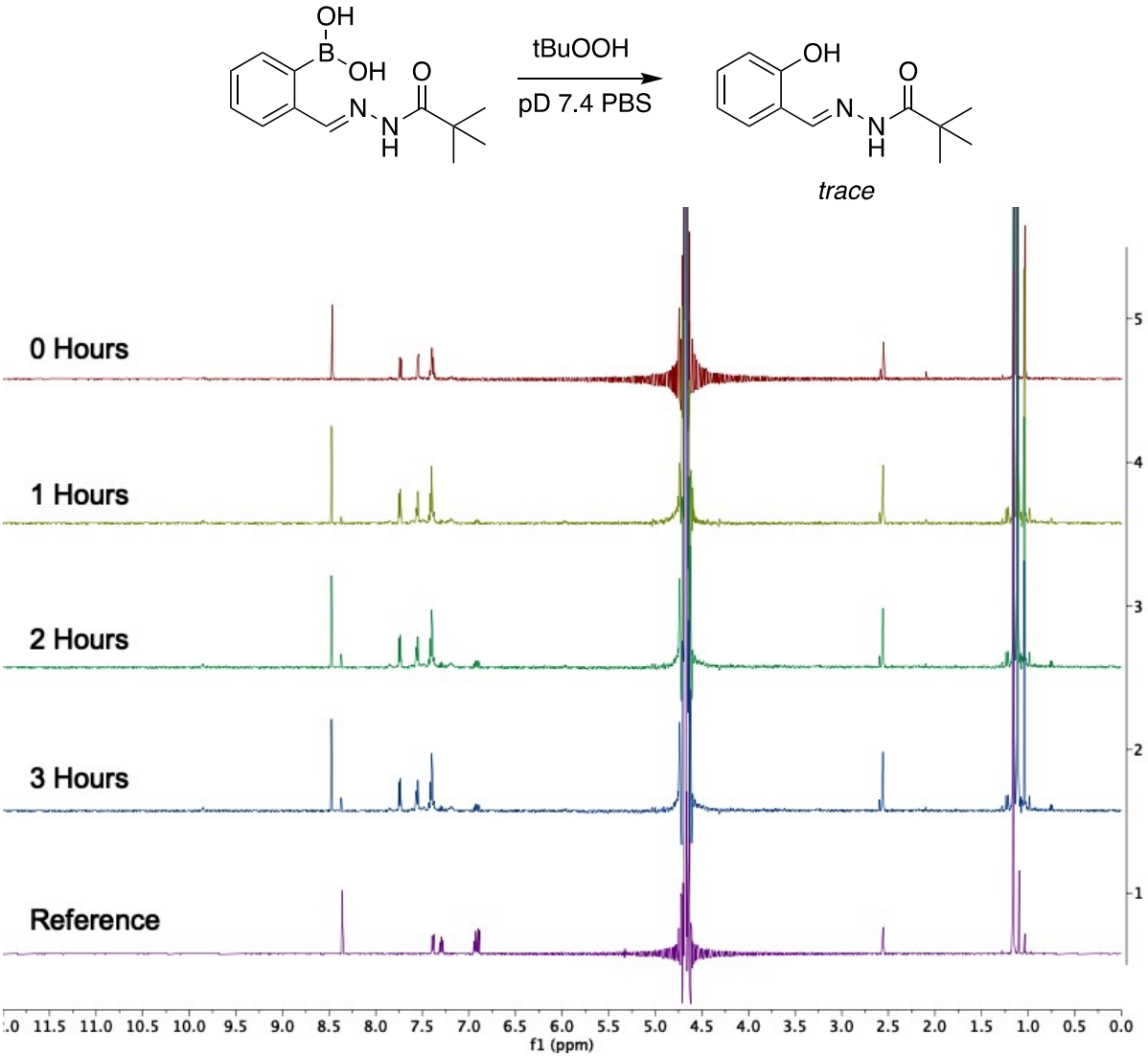


Figure S24. ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol also included.

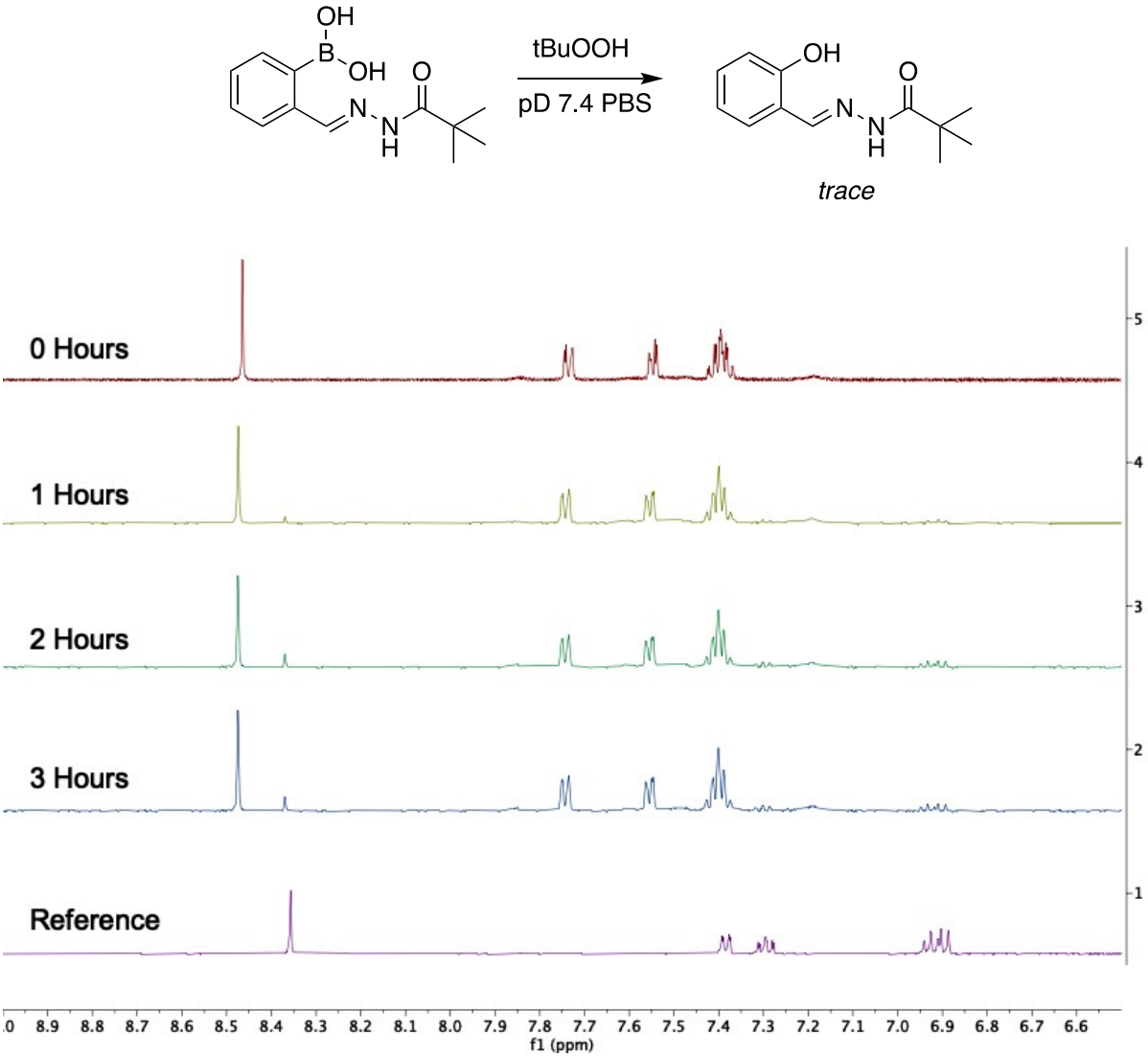


Figure S24a. ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included.

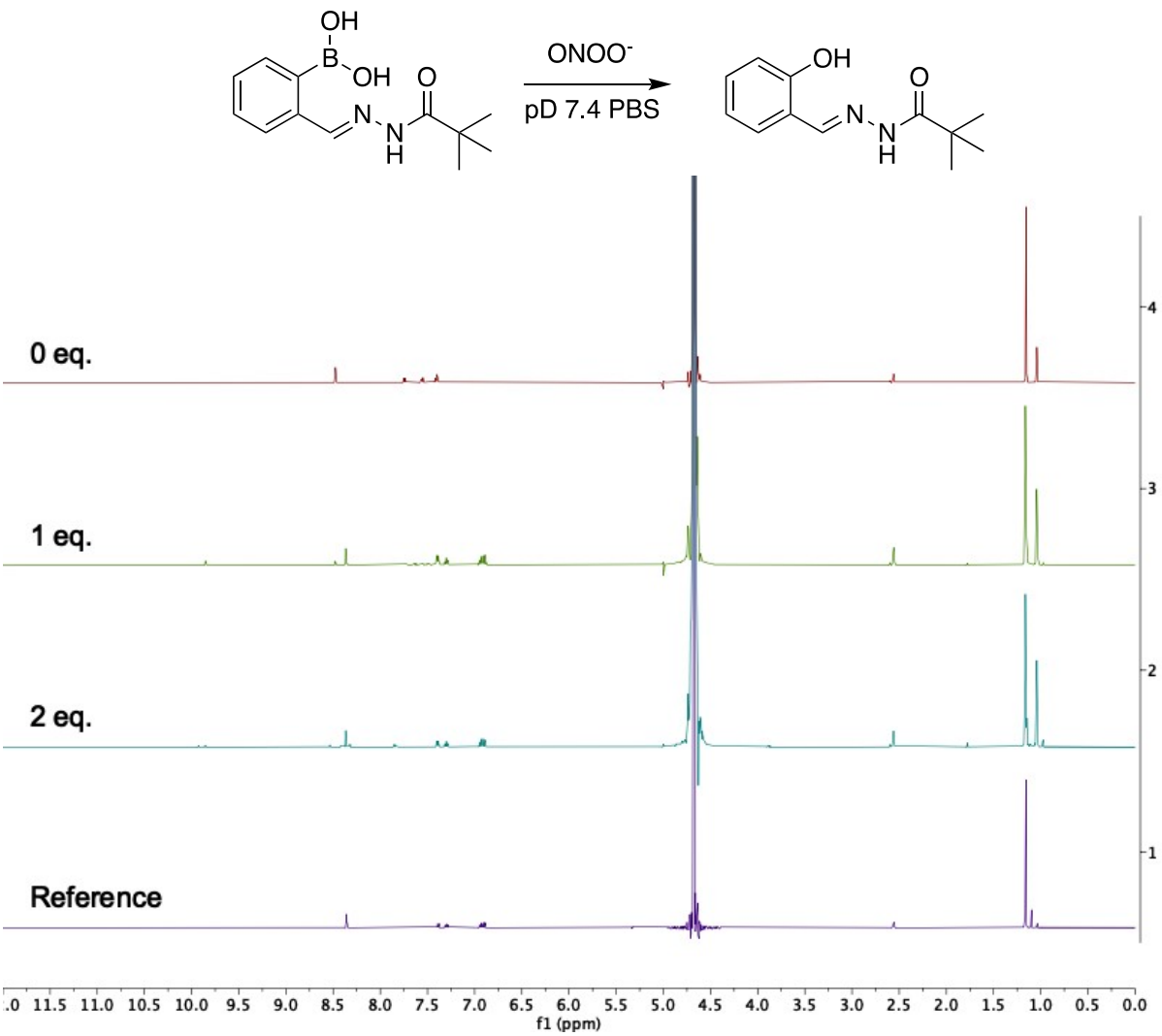


Figure S25. ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. Aliquots of $ONOO^-$ (1 equivalent each addition) were added with spectra collected immediately after addition. A reference spectrum for phenol is also included.

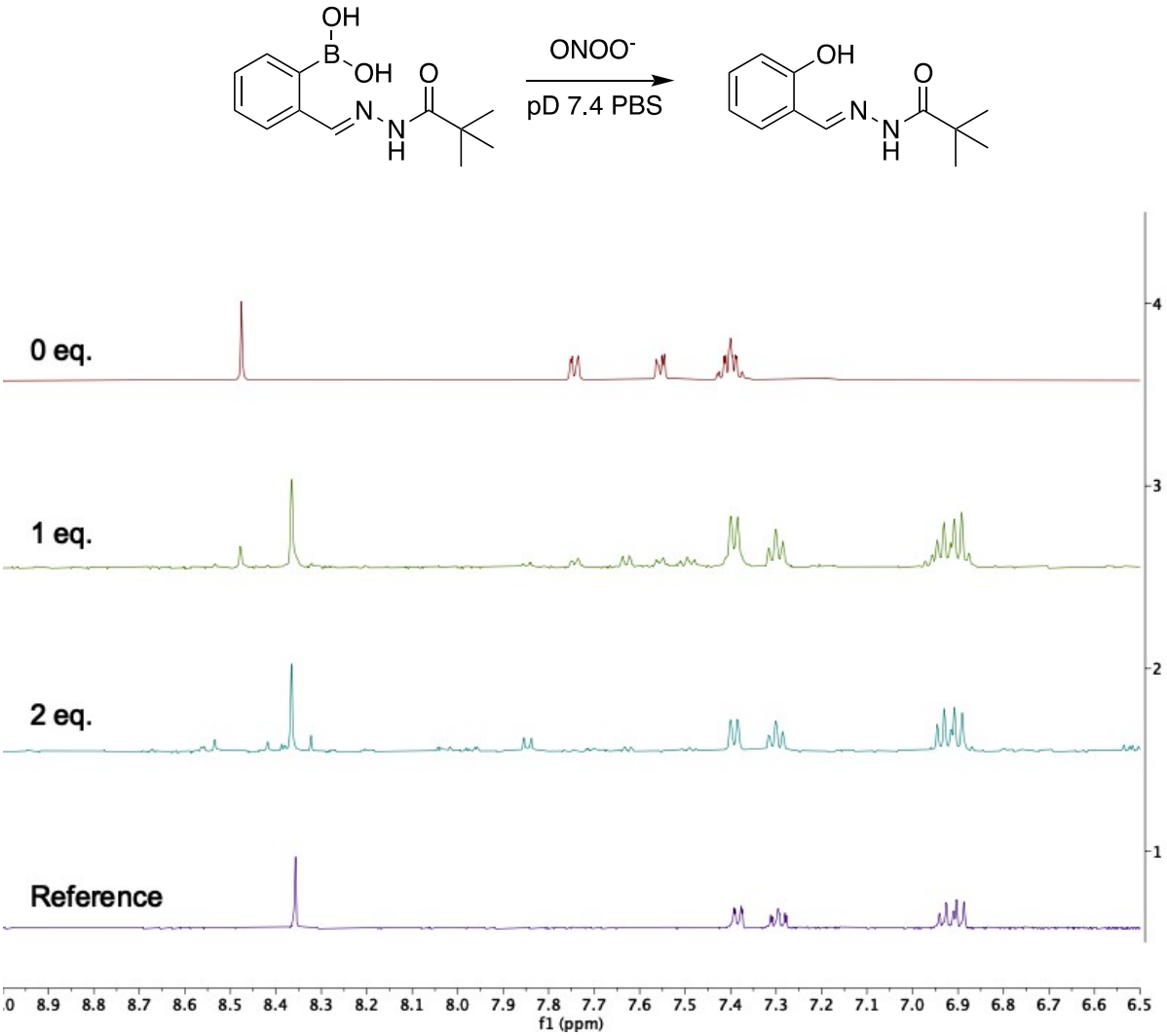


Figure S25a. Aromatic region of ^{1}H NMR spectra of **5** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. Aliquots of $ONOO^-$ were added (1 equivalent each addition) with spectra collected immediately after addition. A reference spectrum for phenol is also included.

8. DAB reactivity screen with ROS.

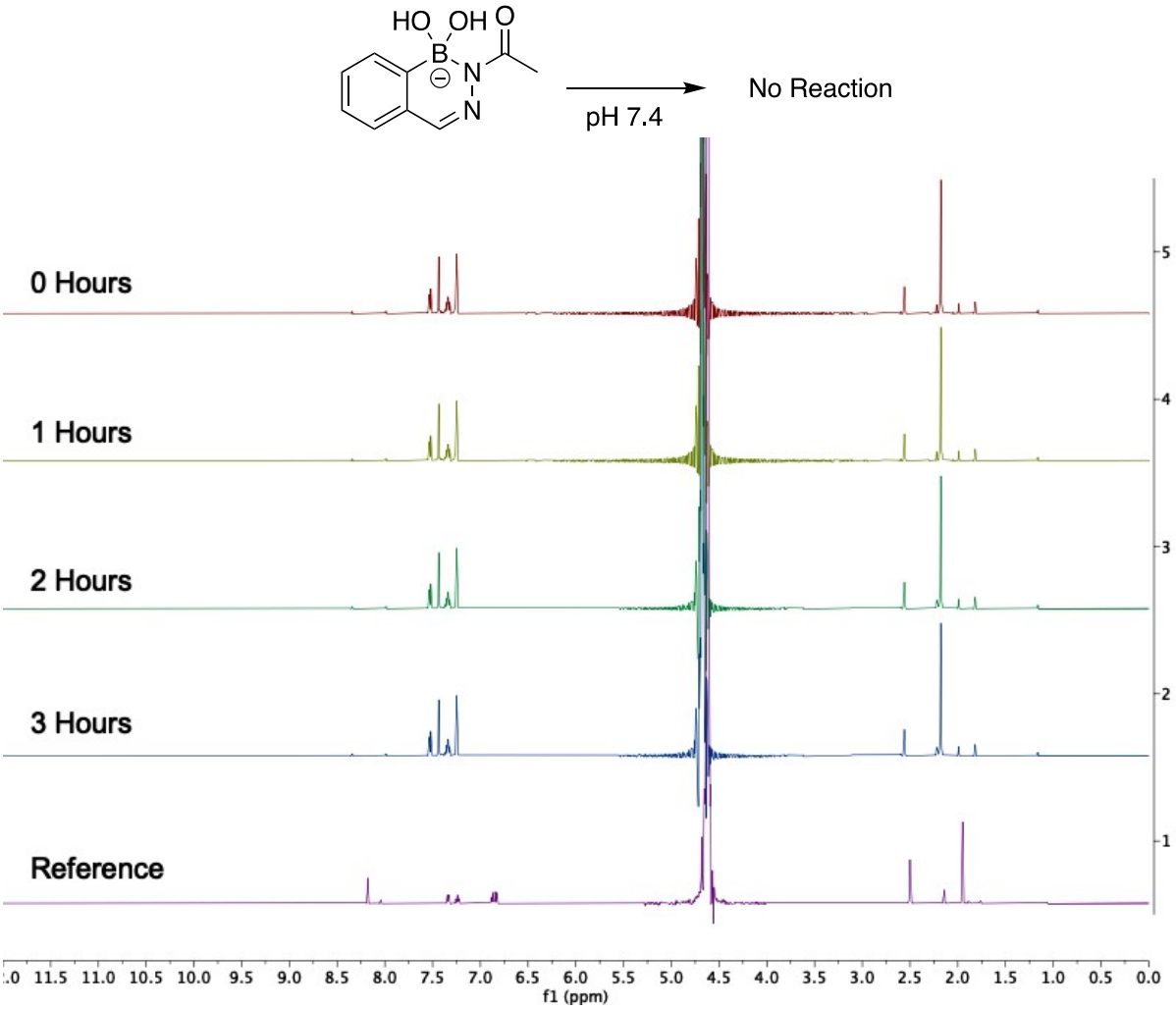


Figure S26. ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

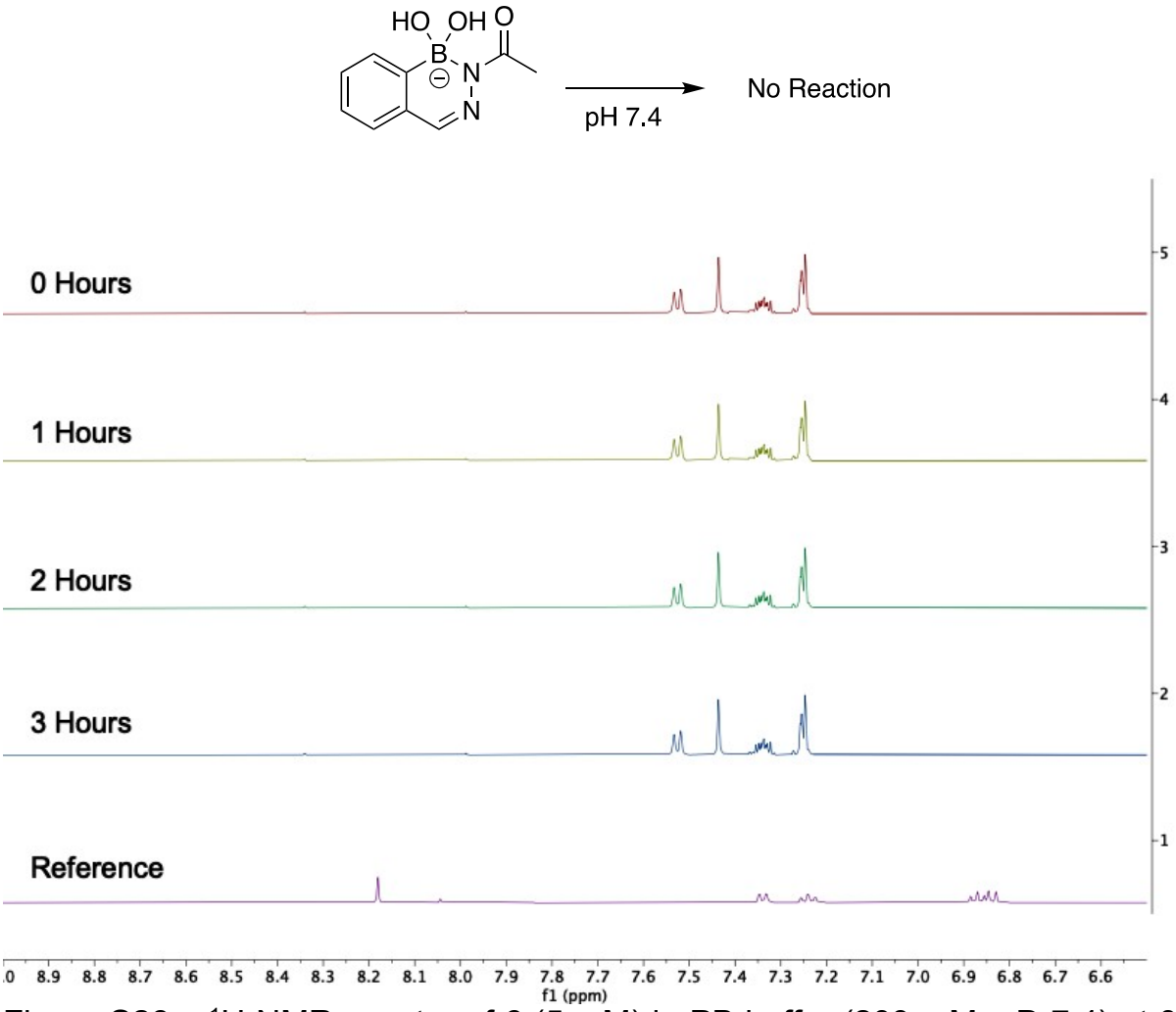


Figure S26a. ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

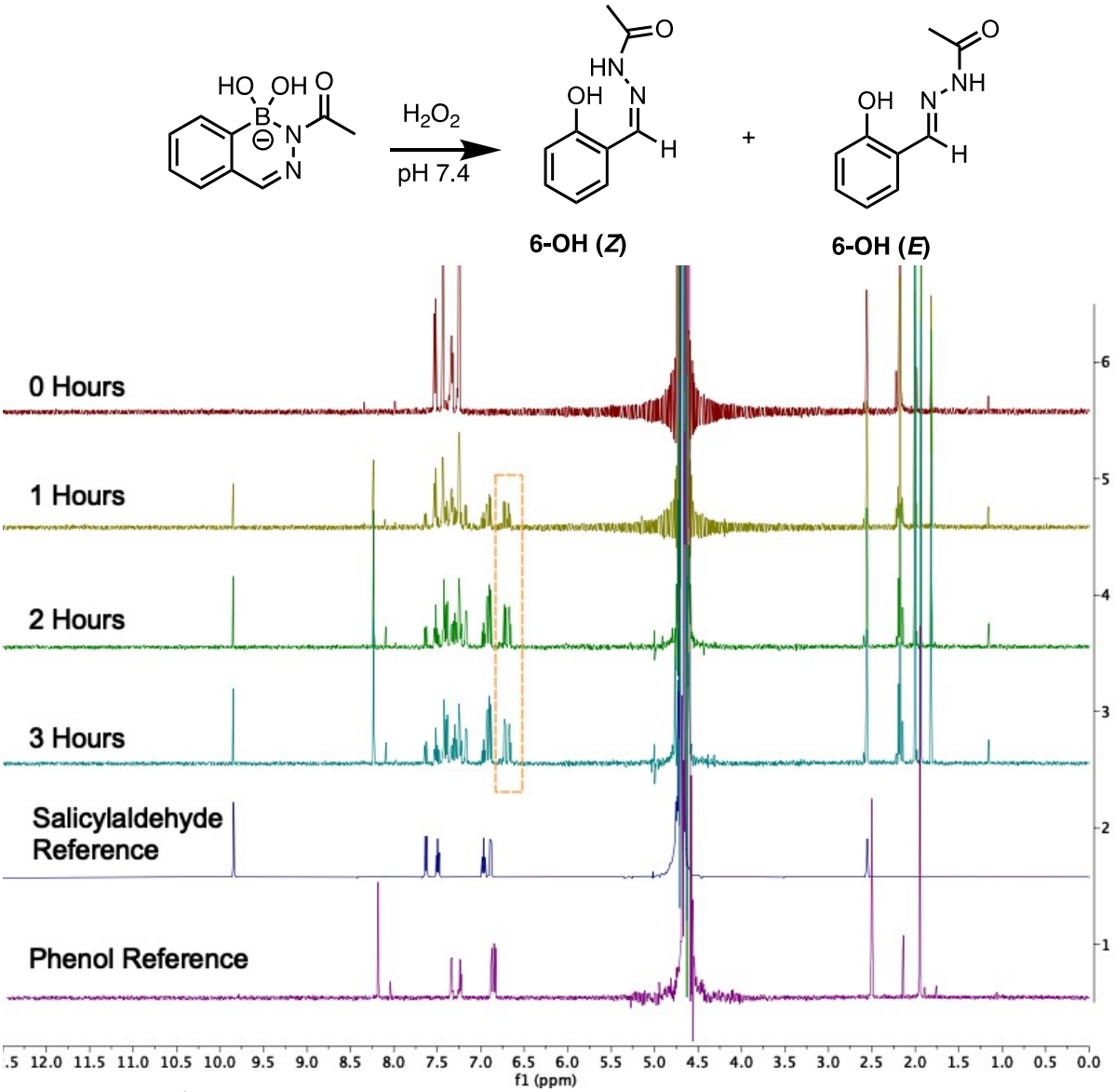


Figure S27. ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. After 3 hours, the reaction contains a mixture of starting material, *Z*-isomer and *E*-isomer of the phenol hydrazone (**6-OH**). Reference spectra for salicylaldehyde and the phenol hydrazone are included.

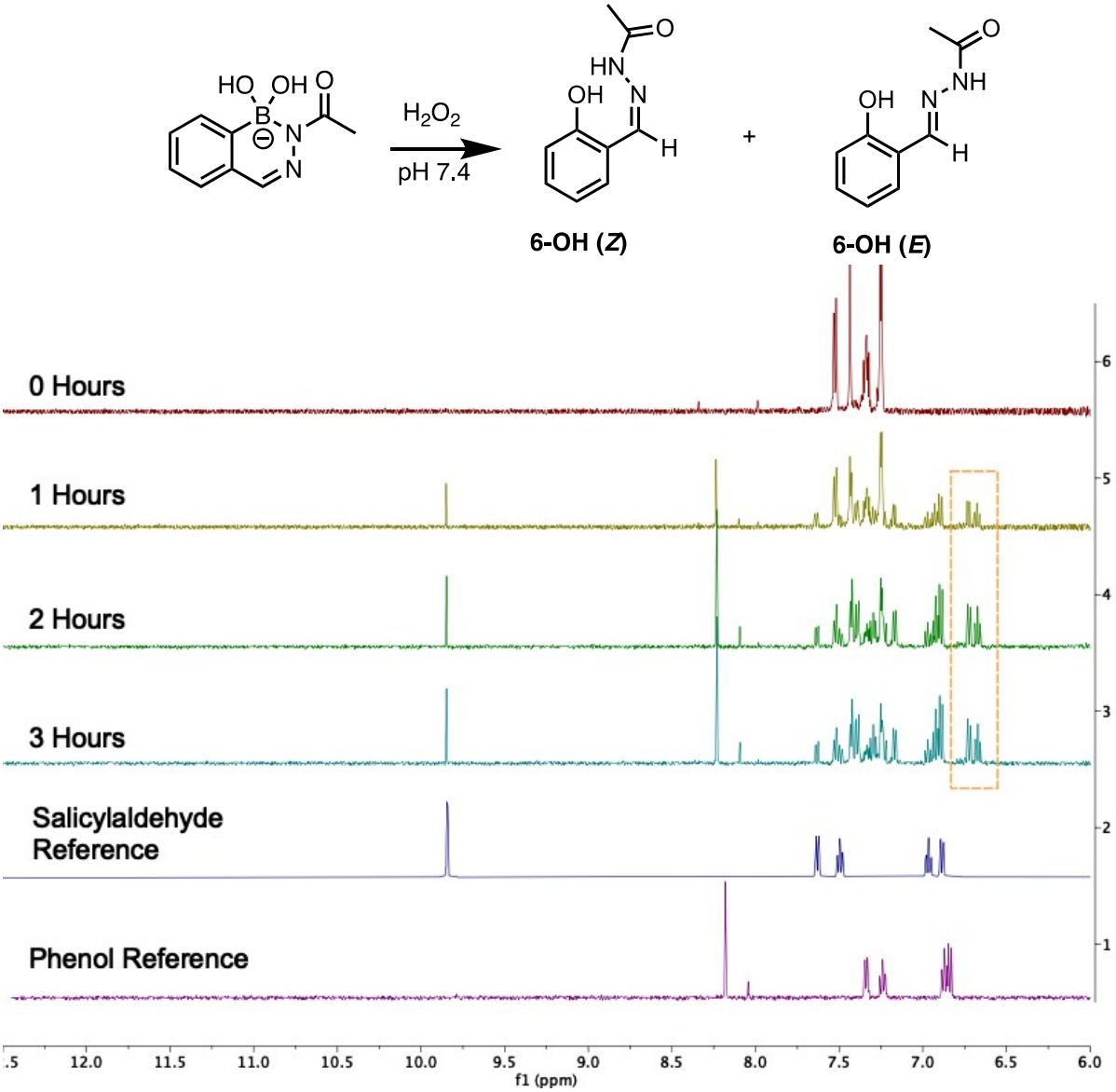


Figure S27a. ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. After 3 hours, the reaction contains a mixture of starting material and a mixture of *E/Z* isomers of the phenol (**6-OH**), and salicylaldehyde (as result of hydrazone hydrolysis). A reference spectrum for the phenol hydrazone is included. The orange dashed line indicates characteristic signals from the *Z*-isomer.

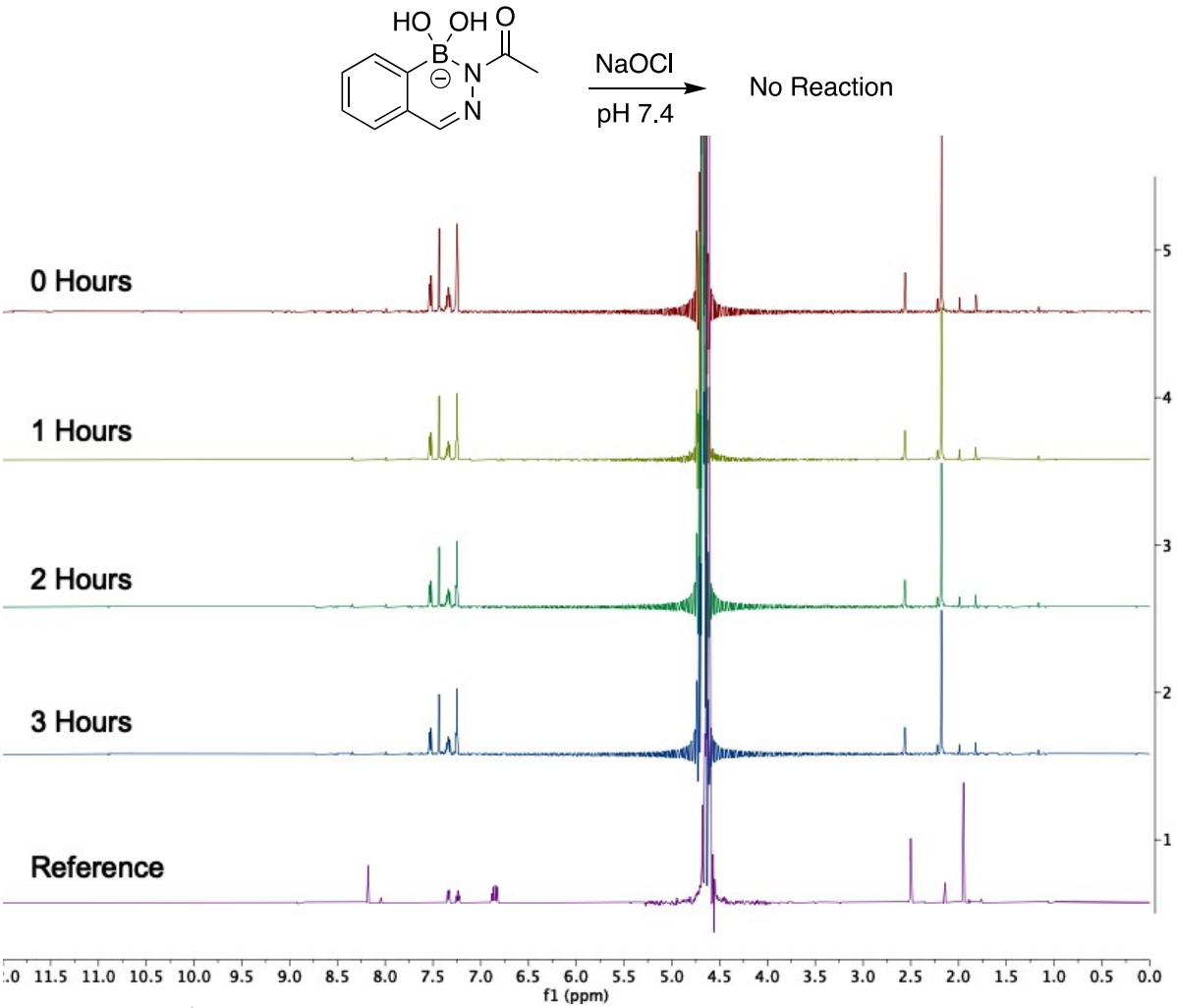


Figure S28. ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

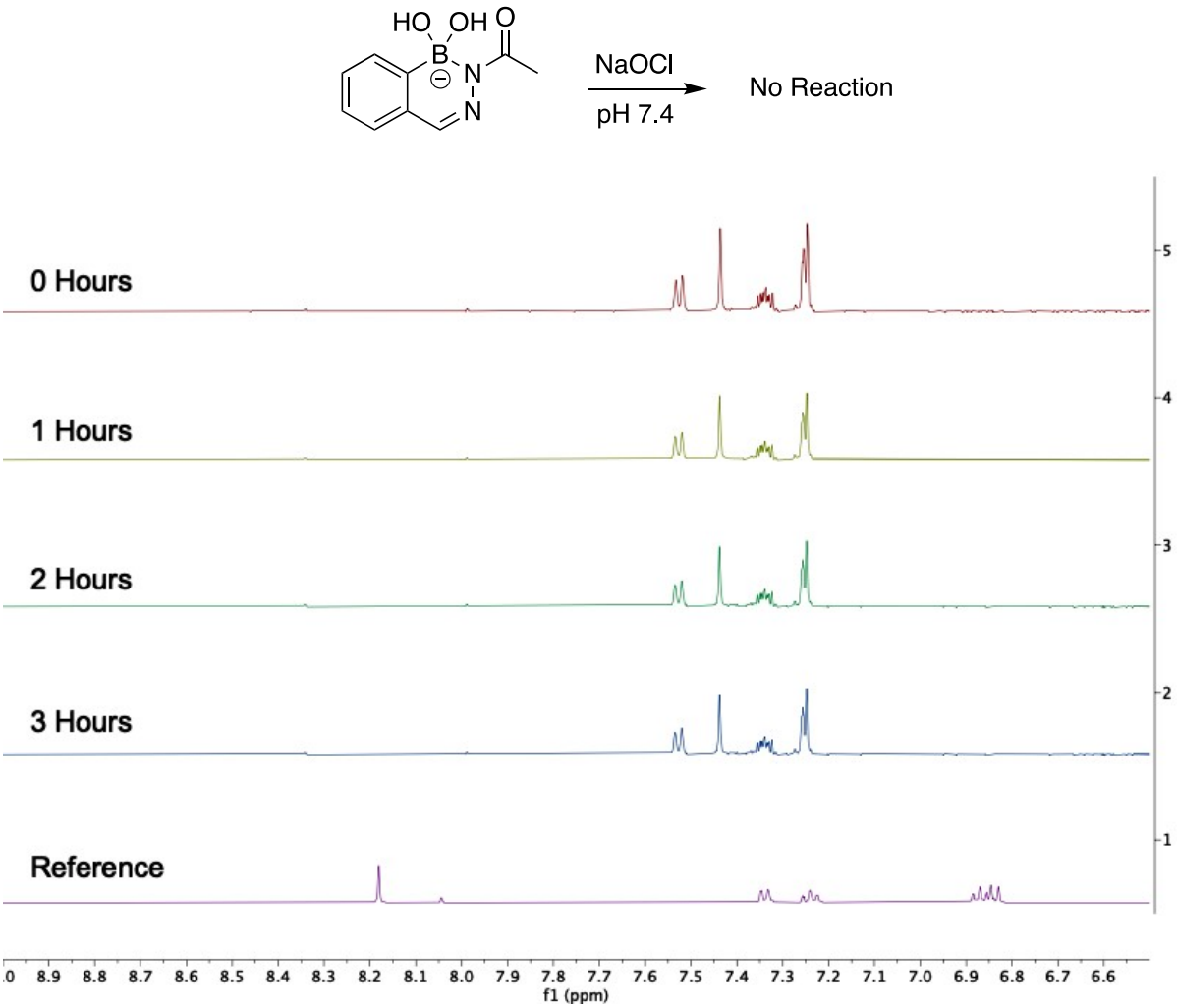


Figure S28a. ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

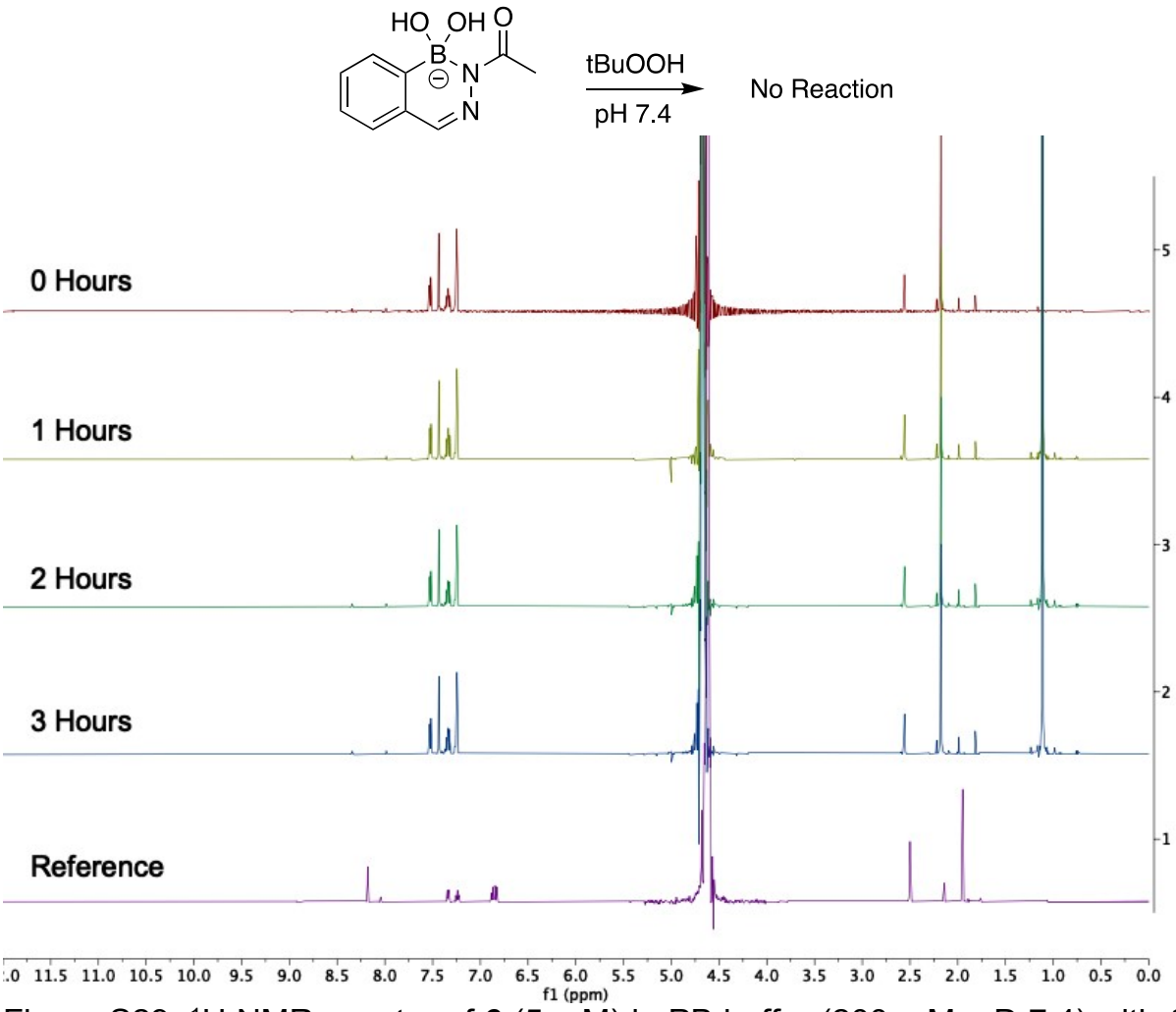


Figure S29. ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

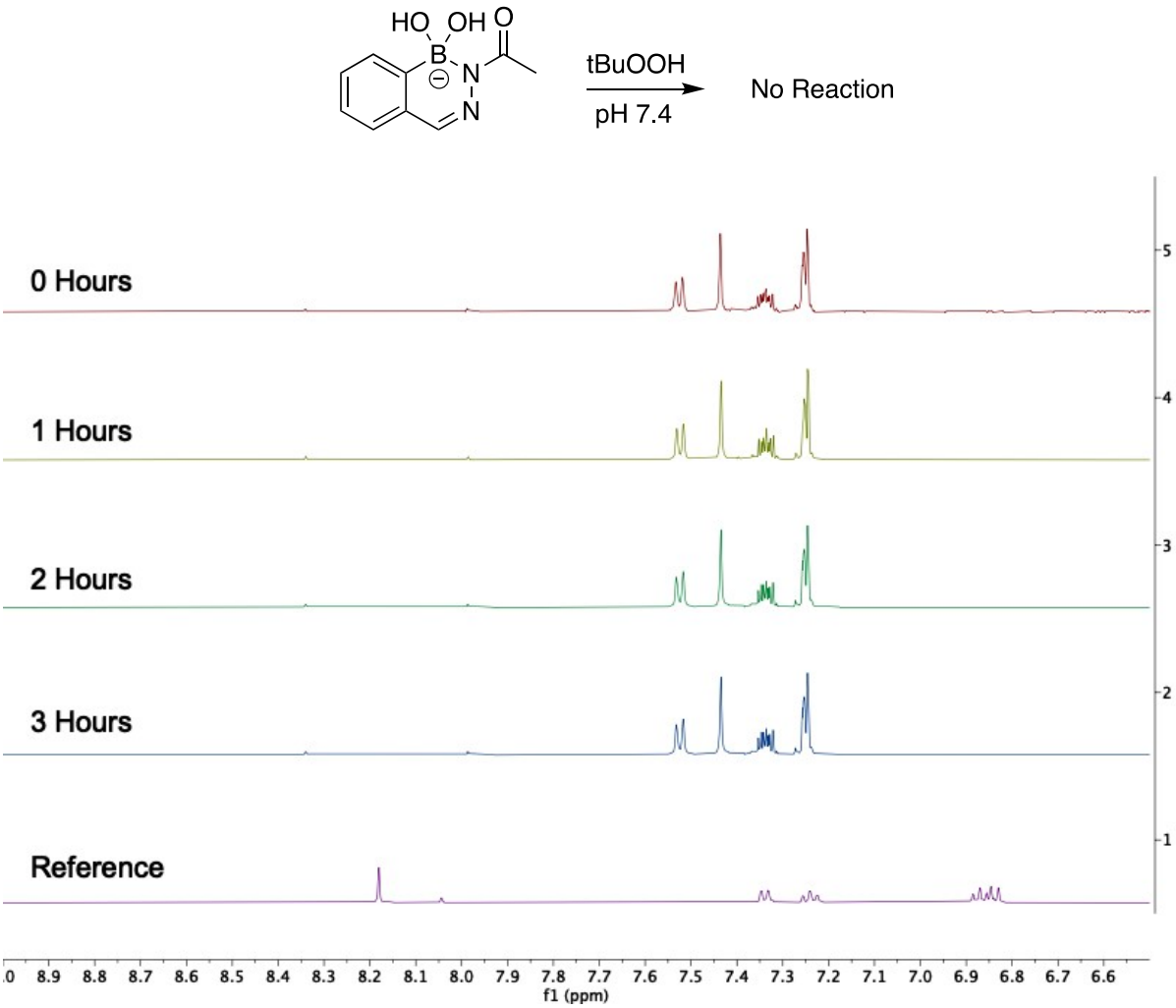


Figure S29a. ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1.0 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

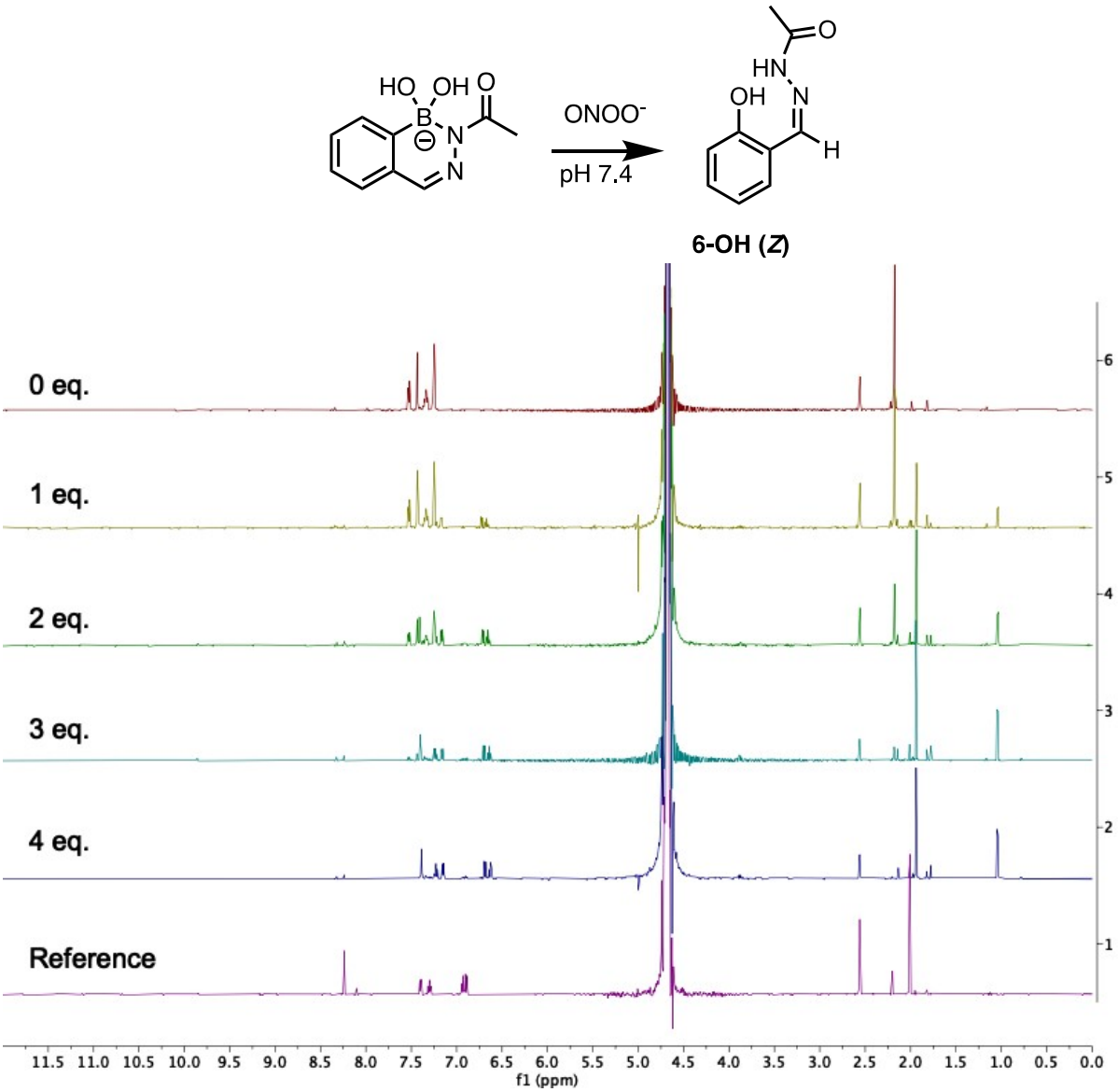


Figure S30. ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. Aliquots of $ONOO^-$ (1 equivalent aliquot each) were added with spectra collected immediately after addition. A reference spectrum for the corresponding *E*-isomer phenol is also included. $ONOO^-$ yields a near-quantitative conversion to the *Z*-isomer.

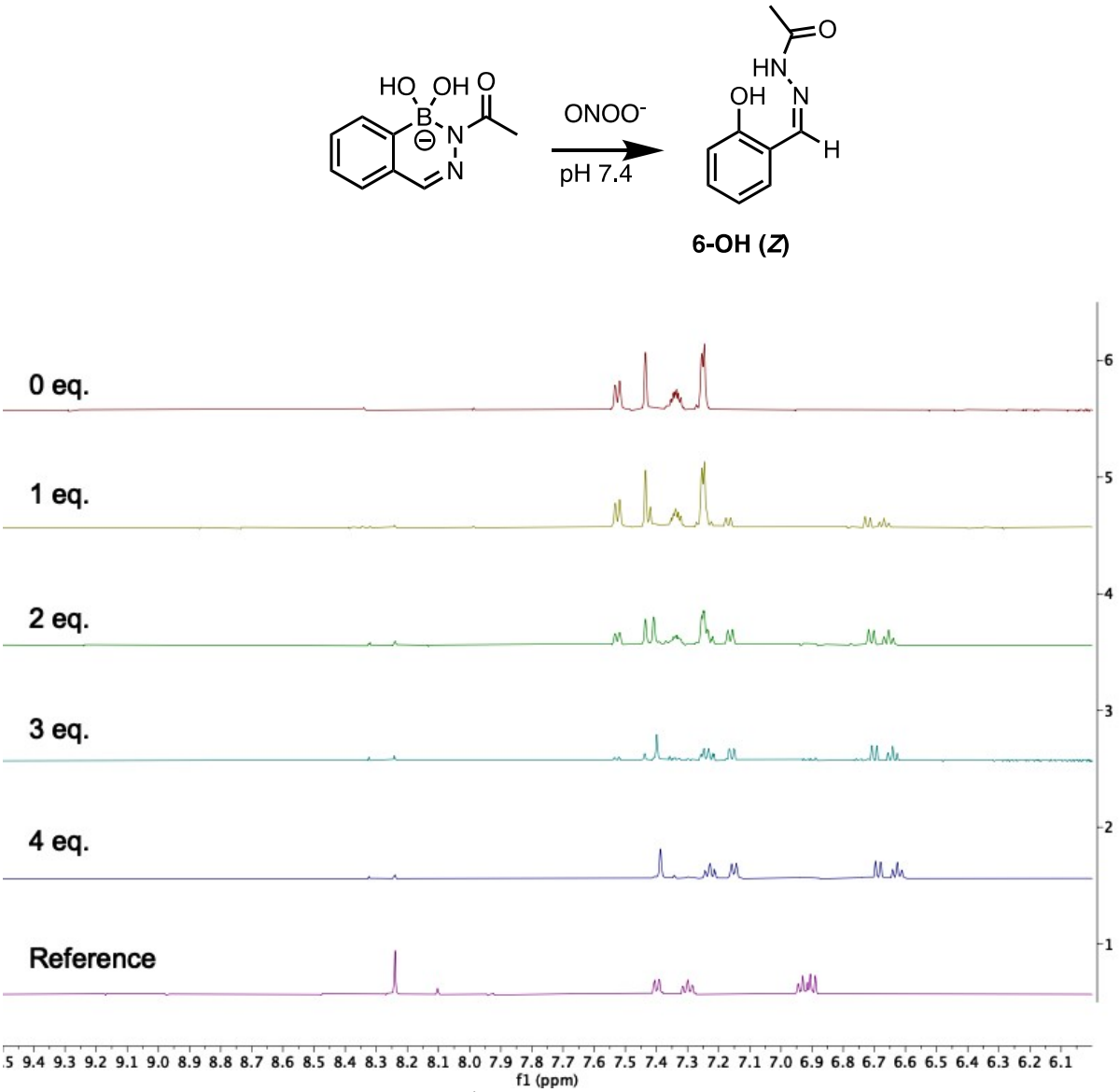
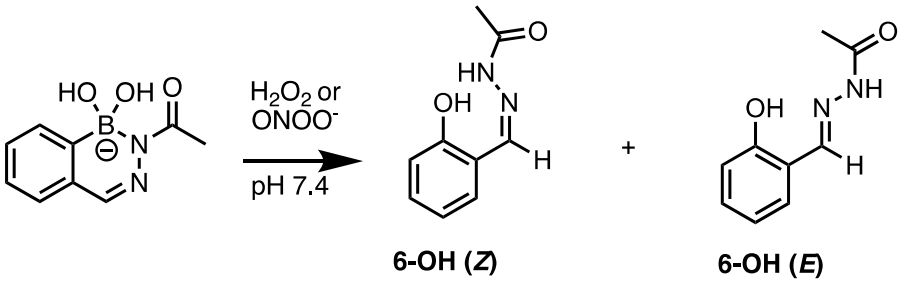


Figure S30a. Aromatic region of ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. $ONOO^-$ was added in 1 equivalent aliquots with spectra collected immediately after addition. A reference spectrum for the corresponding *E*-isomer phenol is also included. $ONOO^-$ yields a near-quantitative conversion to the *Z*-isomer.



6-OH (*Z*) **6-OH (*E*)**

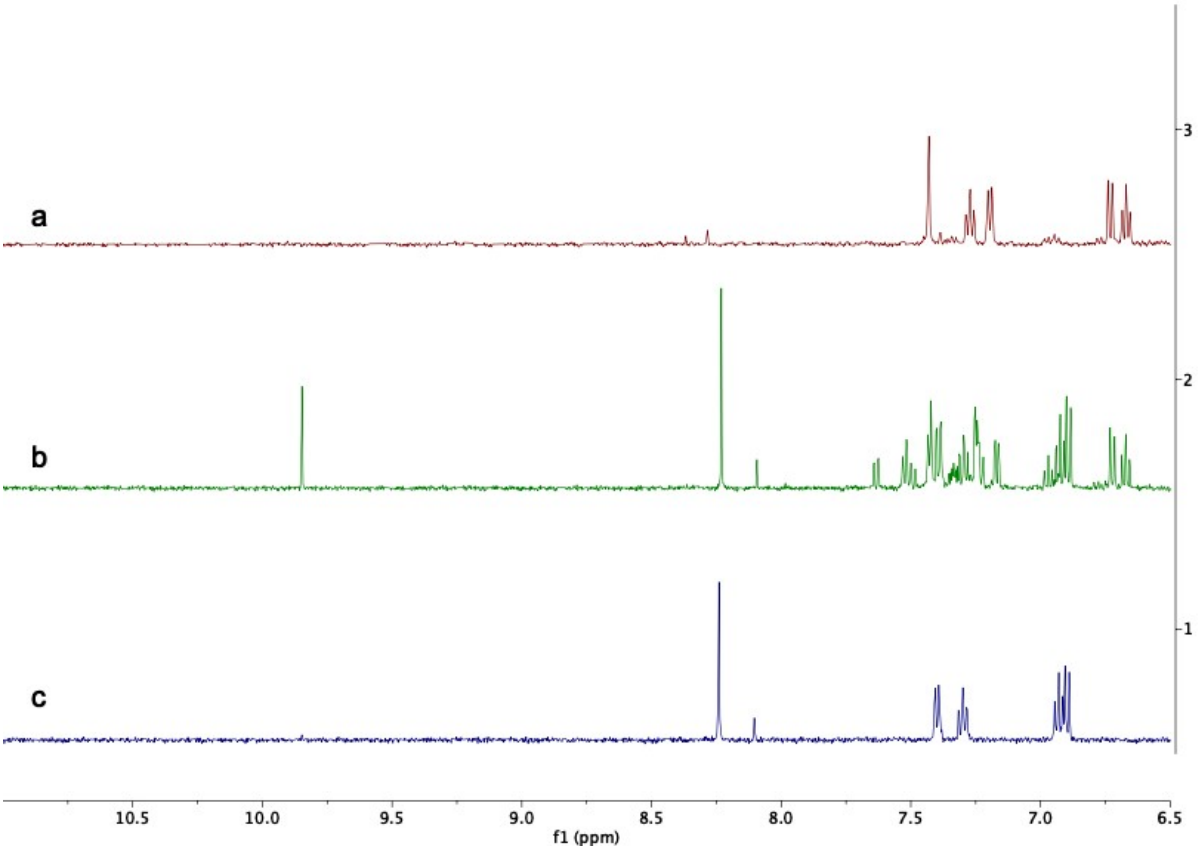


Figure S30b. Aromatic region of ^{1}H NMR spectra of **6** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$ (4 eq.) (**a**) overlapped with ^{1}H NMR spectrum of **6** with H_2O_2 (1 equivalent, 3 hours) (**b**). A reference spectrum for the as-synthesized phenol hydrazone (*E*) is also included (**c**).

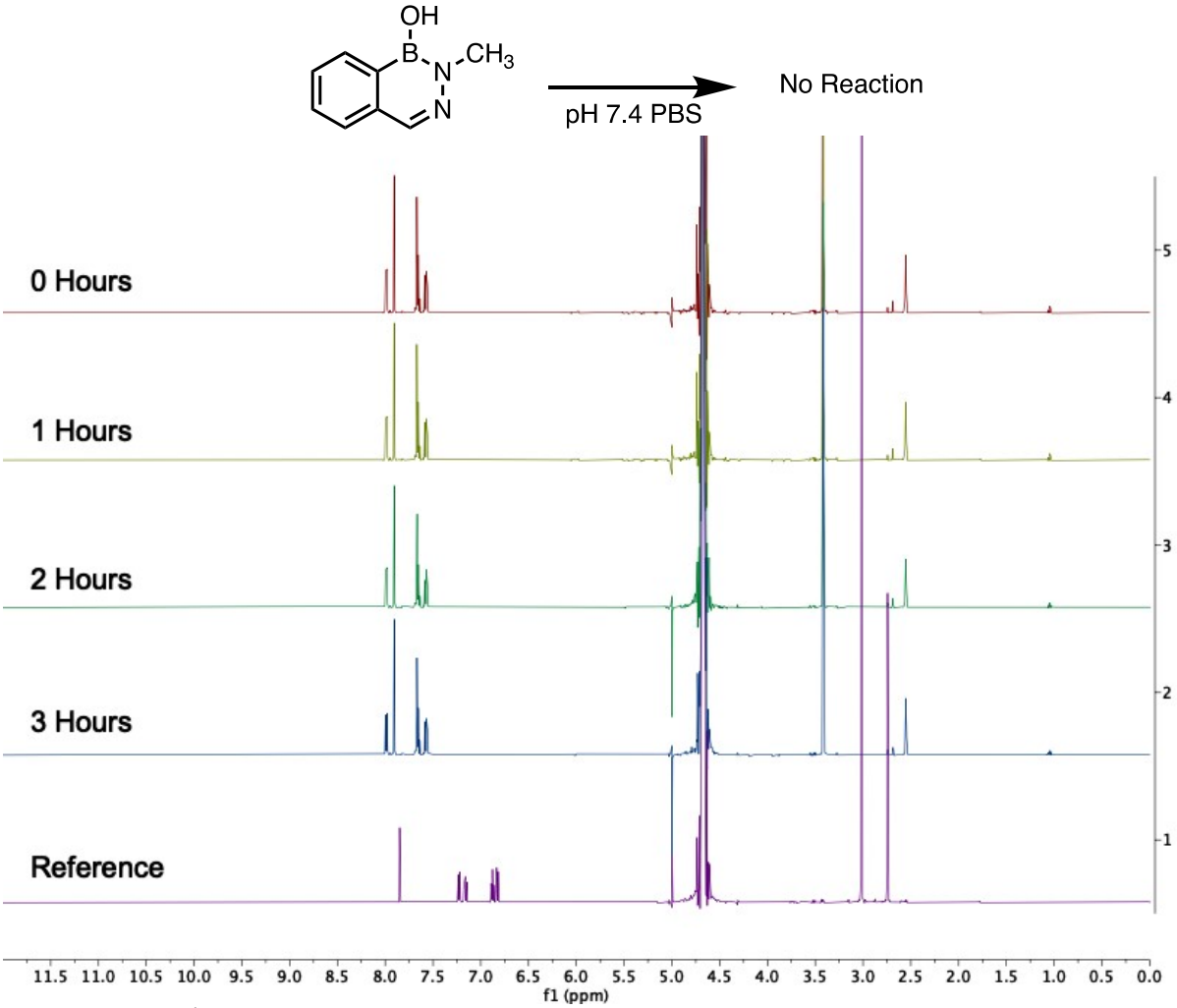


Figure S31. ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

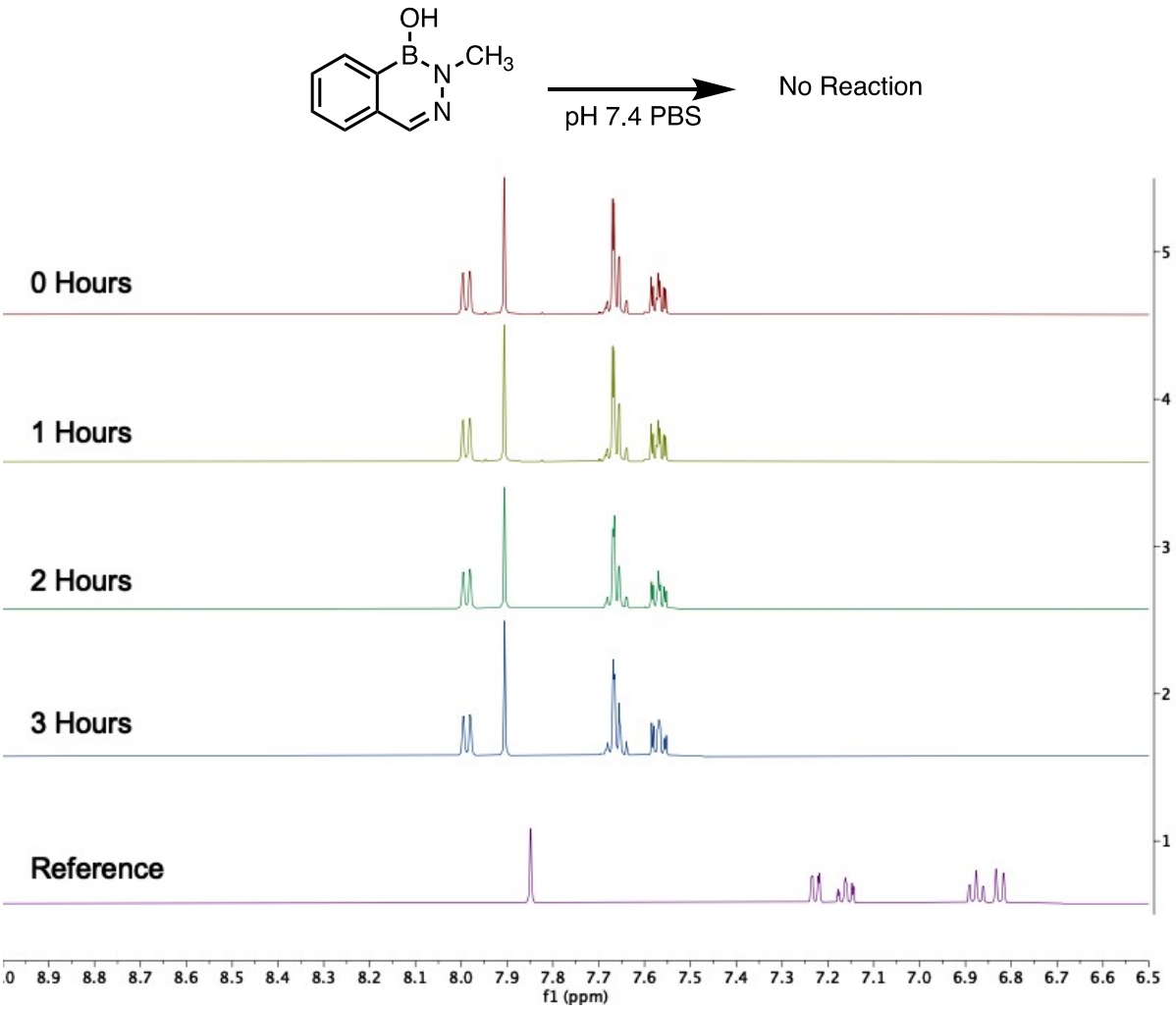


Figure S31a. ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

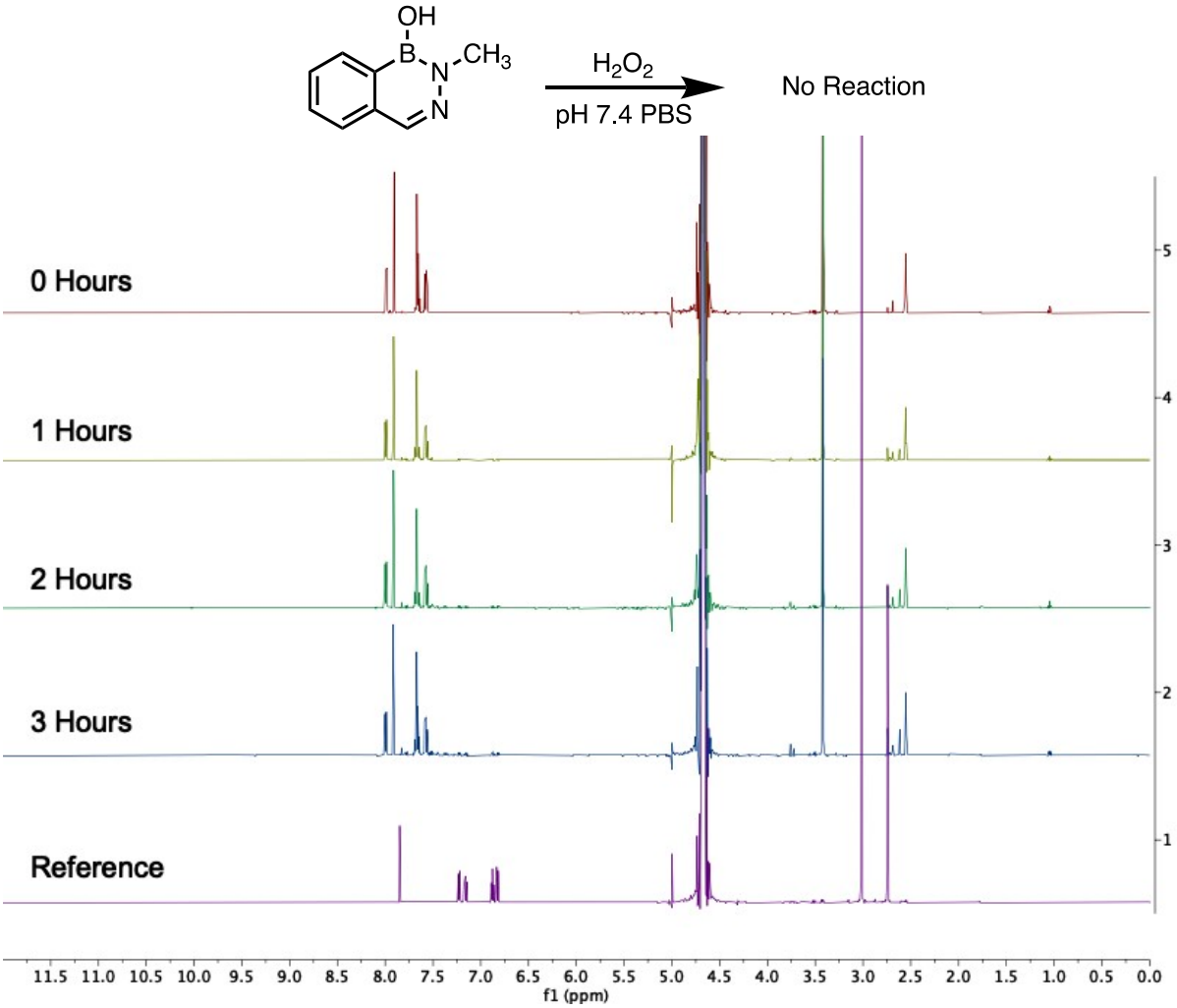


Figure S32. ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

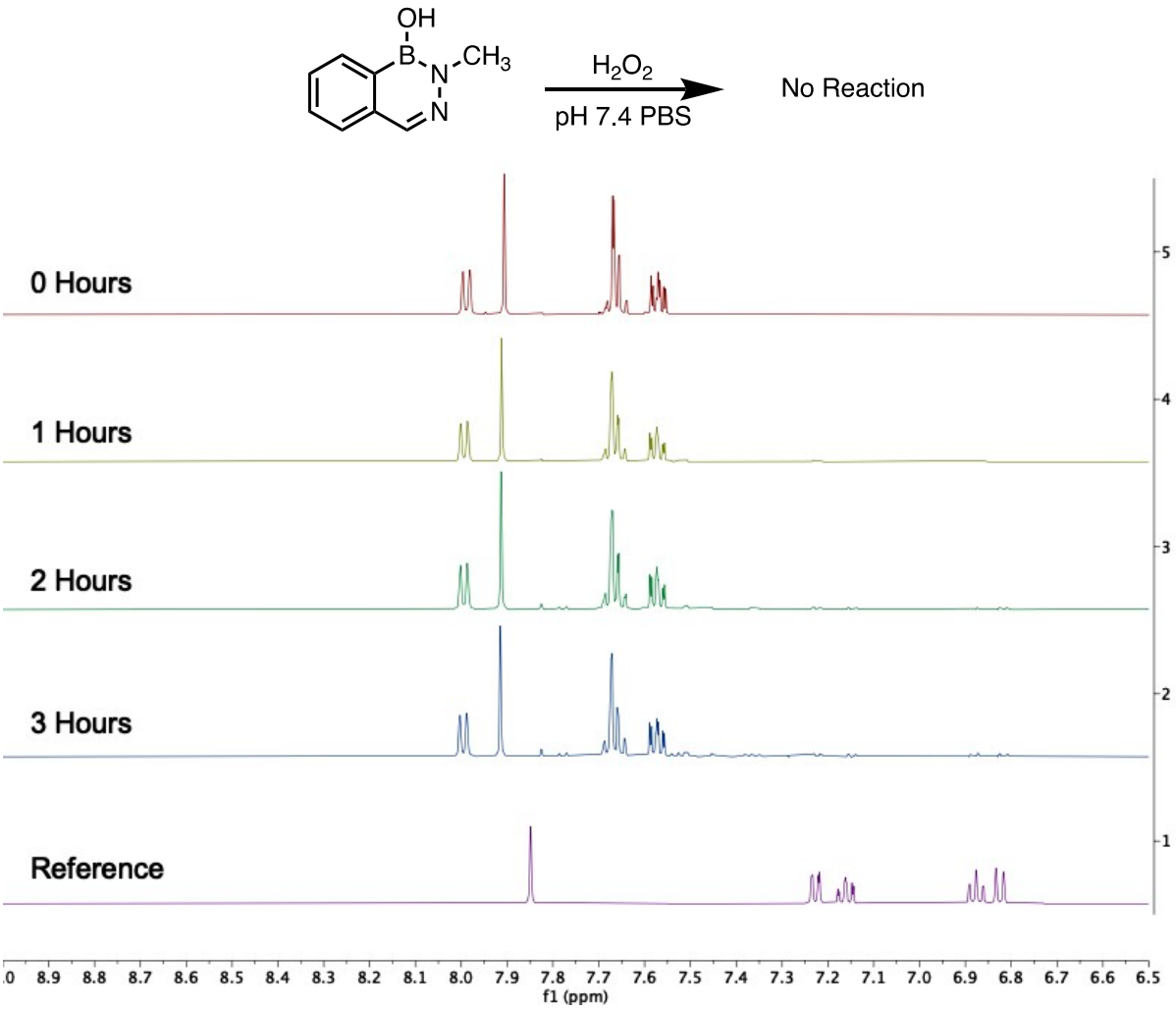


Figure S32a. ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

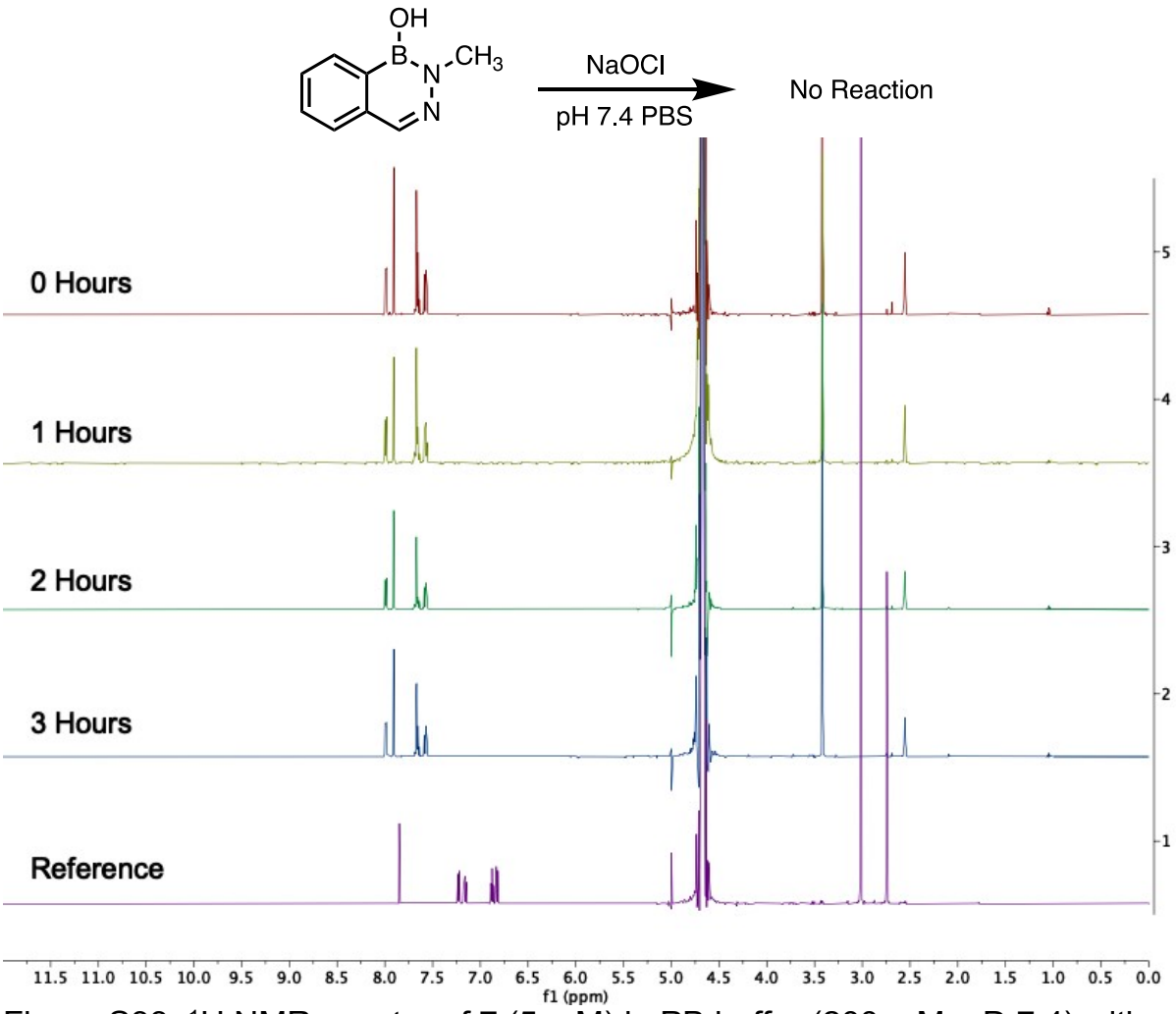


Figure S33. ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

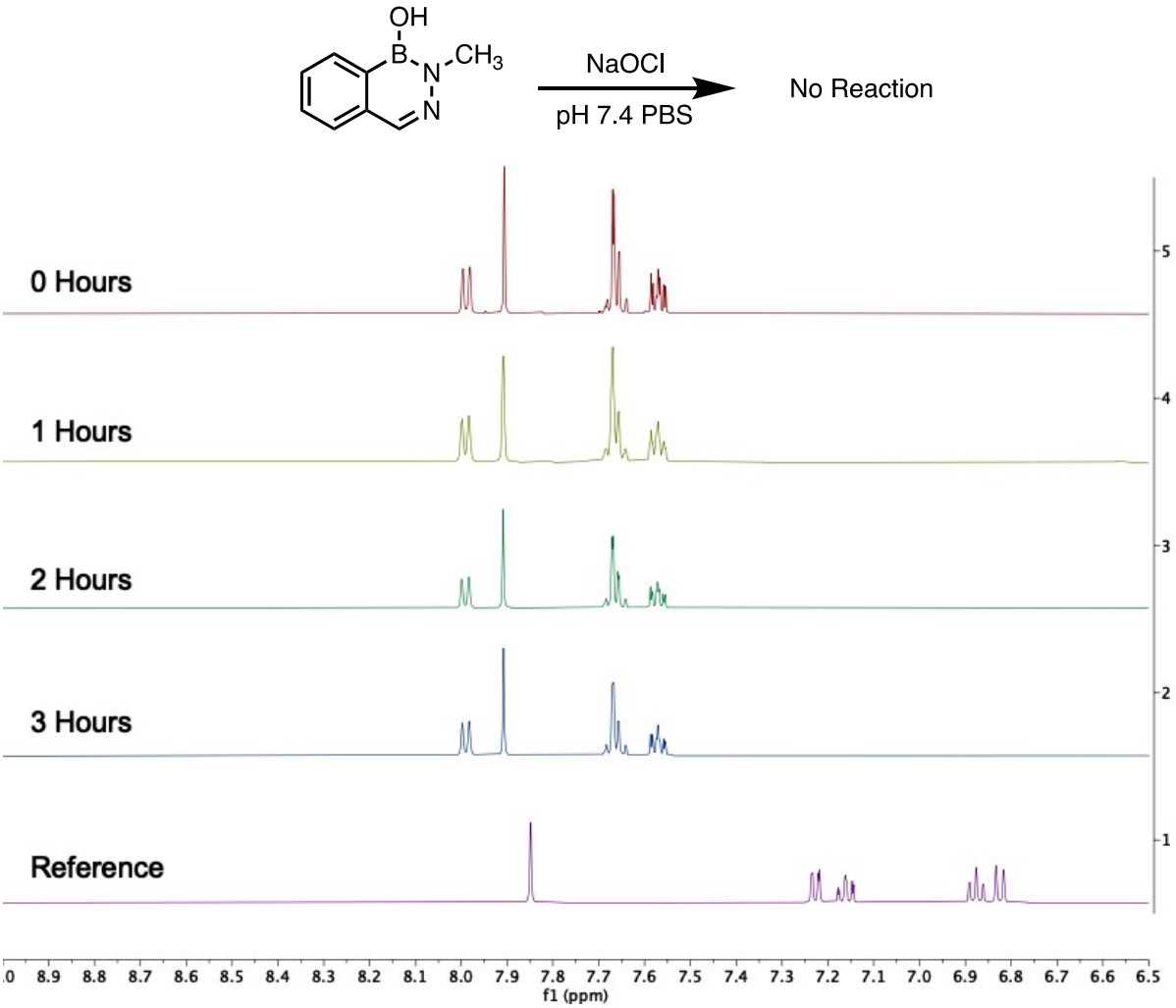


Figure S33a. ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

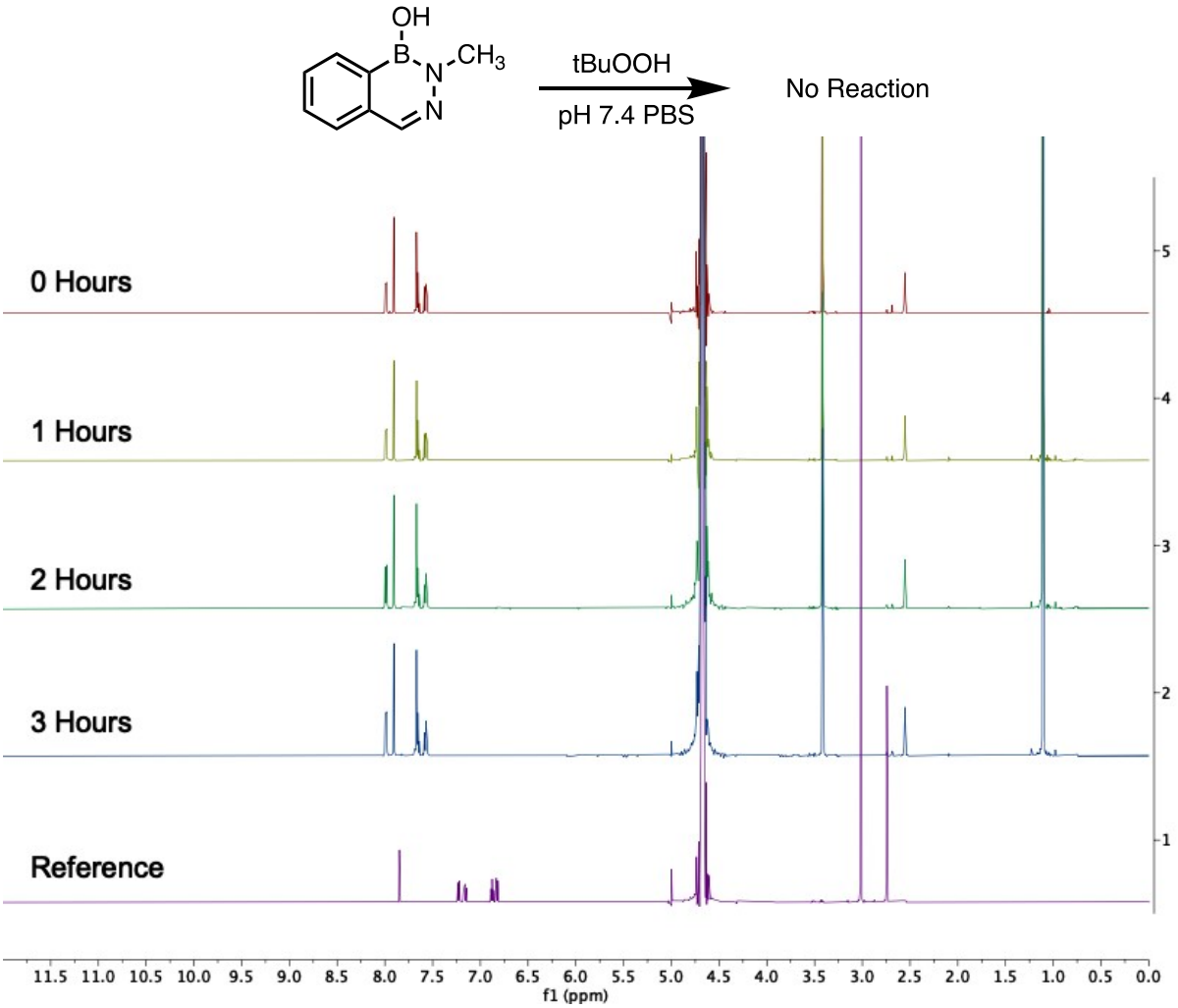


Figure S34. ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

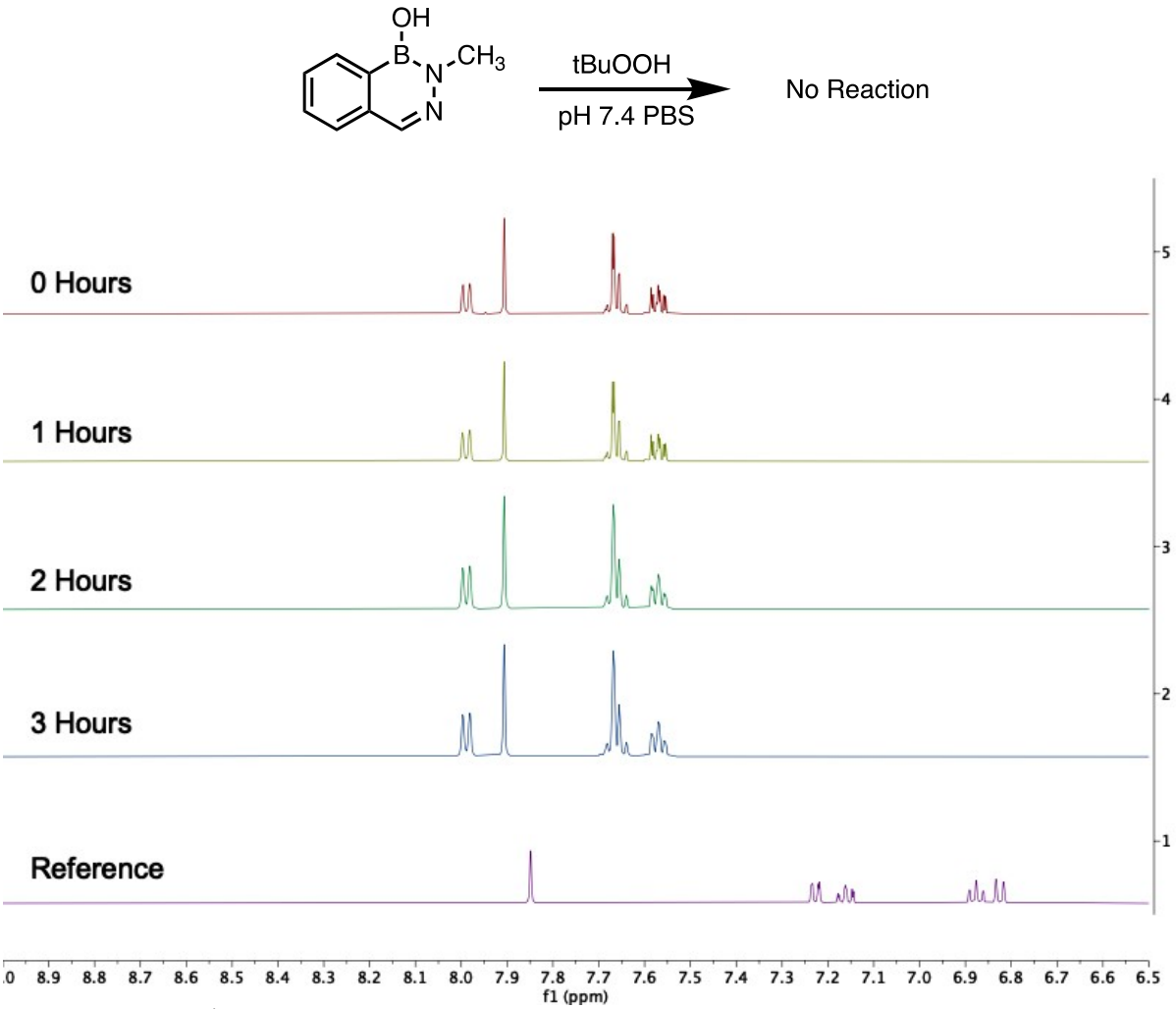


Figure S34a. ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

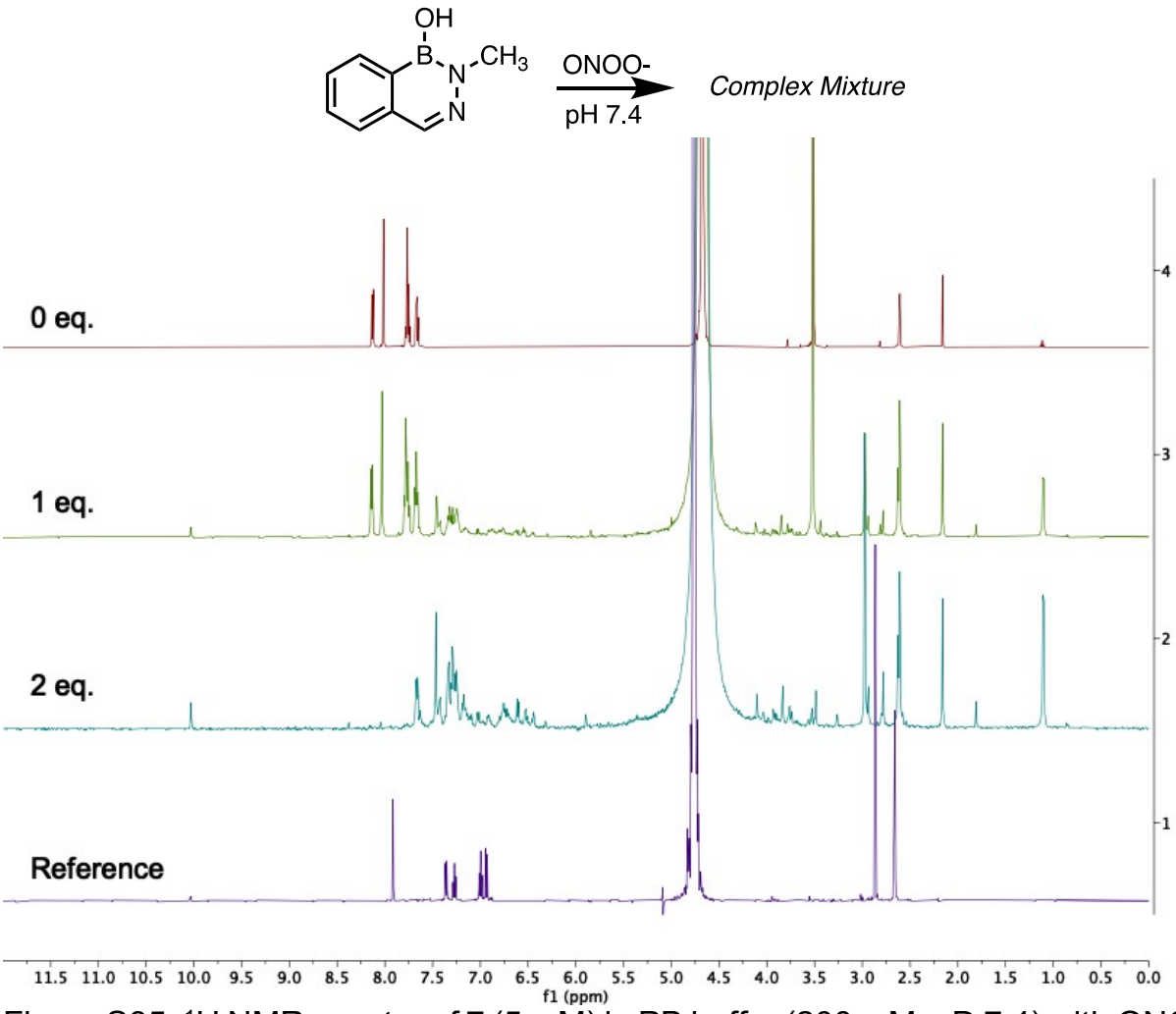


Figure S35. ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. 1 equivalent (5 mM) aliquots were added with spectra collected immediately after addition. A reference spectrum for phenol is also included.

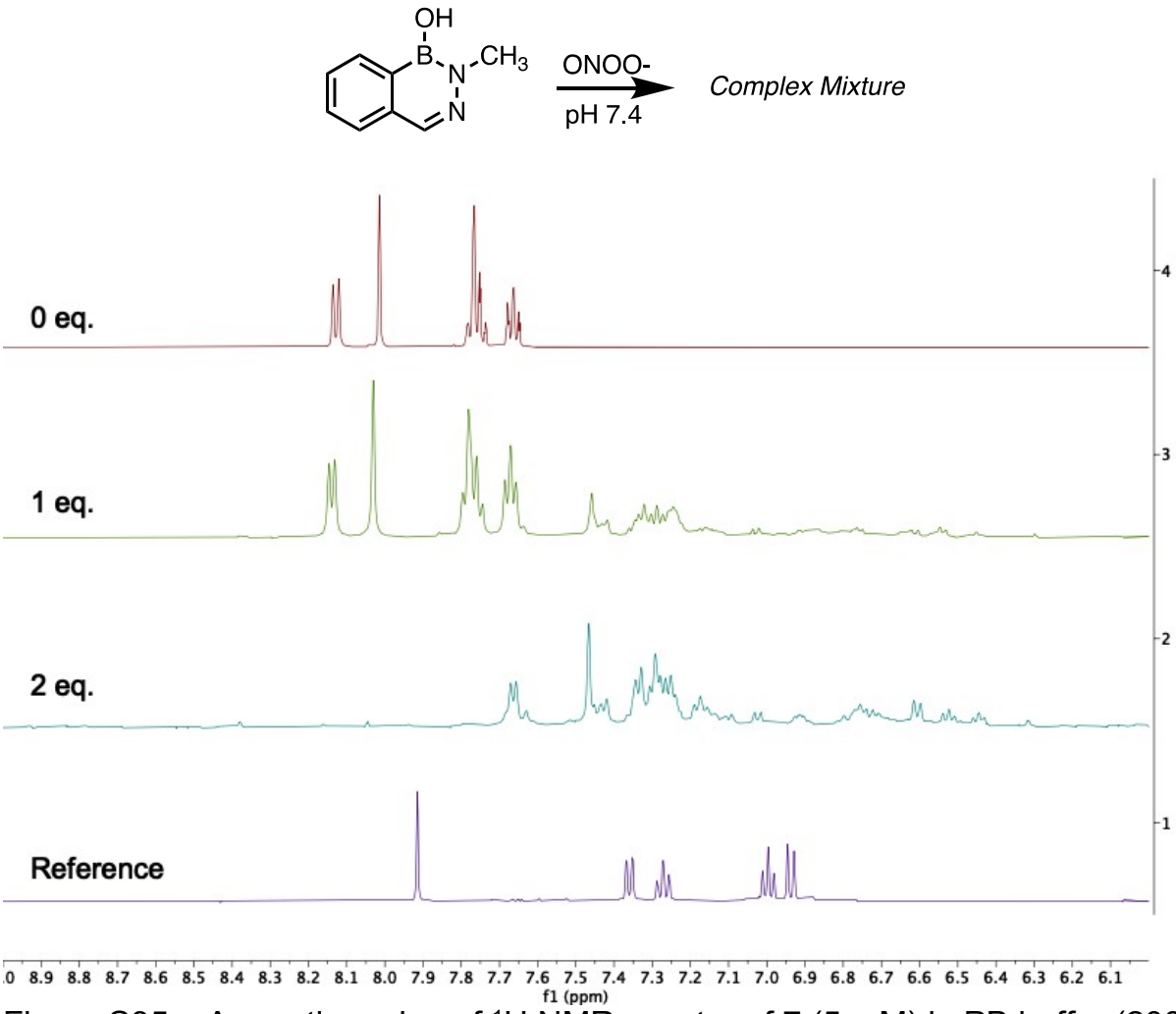


Figure S35a. Aromatic region of ^{1}H NMR spectra of **7** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^{-}$. 1 equivalent (5 mM) aliquots were added with spectra collected immediately after addition. A reference spectrum for phenol is also included.

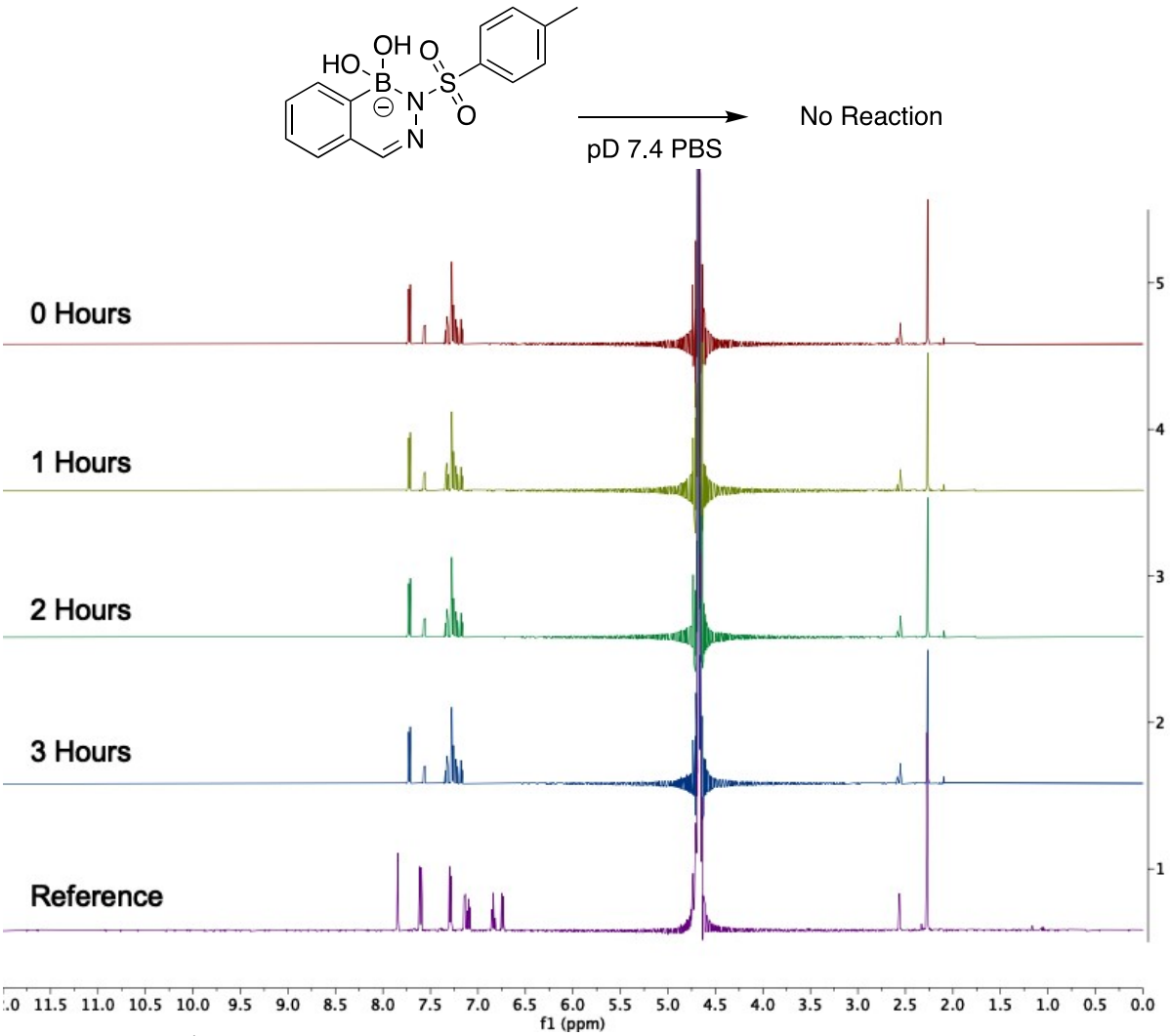


Figure S36. ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included.

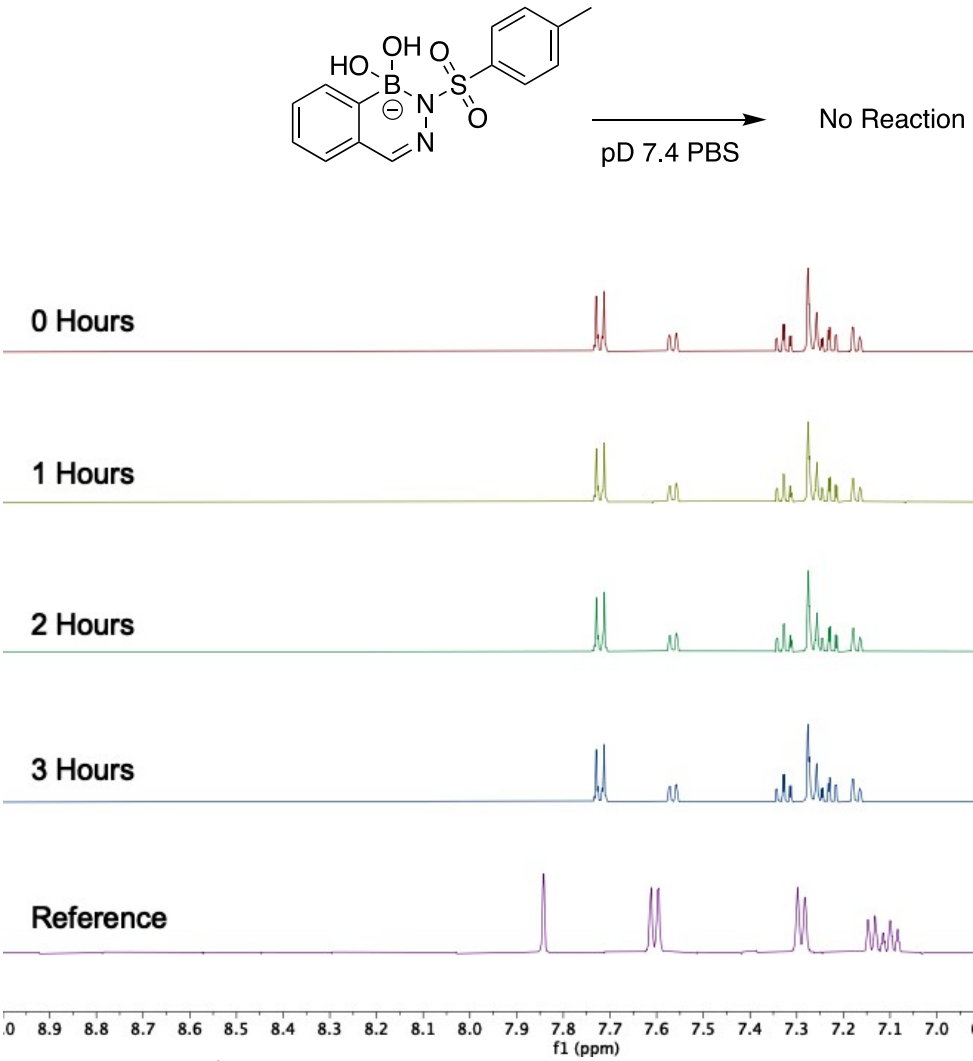


Figure S36a. ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) at 0, 1, 2, and 3 h. A reference spectrum for phenol is also included.

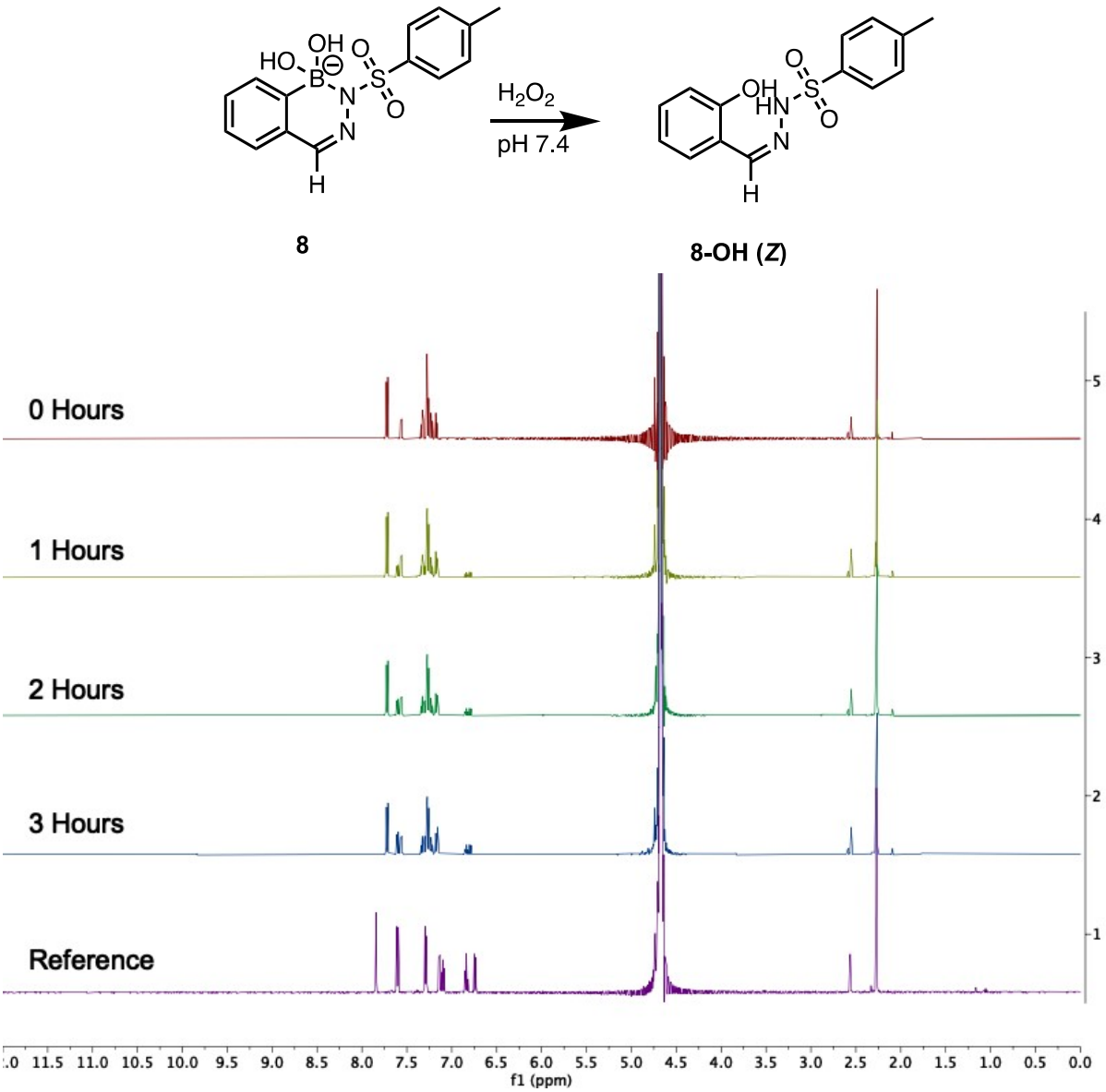


Figure S37. ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding *E*-isomer phenol is also included. Only *Z*-isomer and starting material is observed after 3 h.

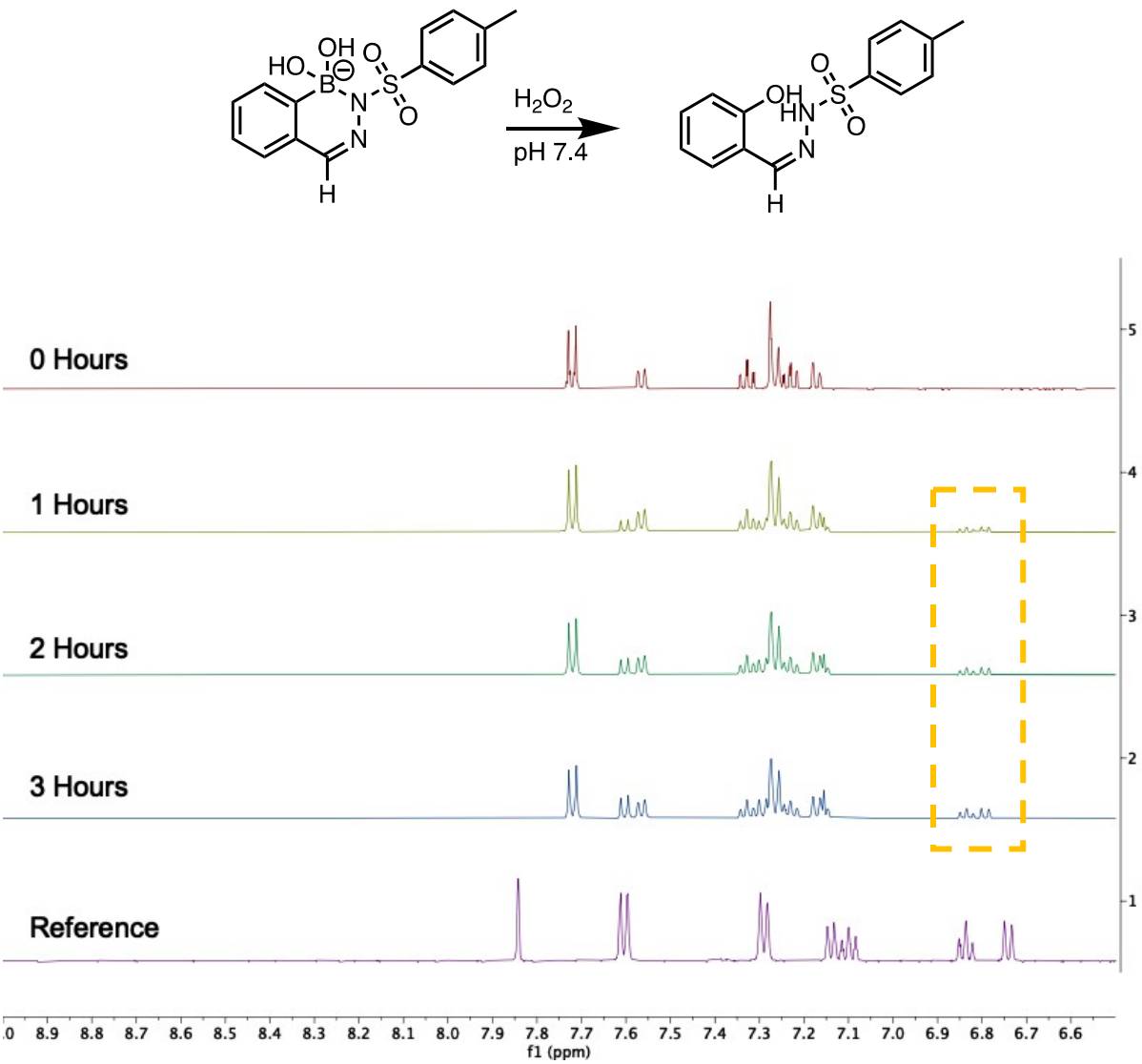


Figure S37a. ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) with H_2O_2 (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding *E*-isomer phenol is also included. Only *Z*-isomer and starting material is observed after 3 h. The dashed orange box are characteristic signals of the *Z*-isomer.

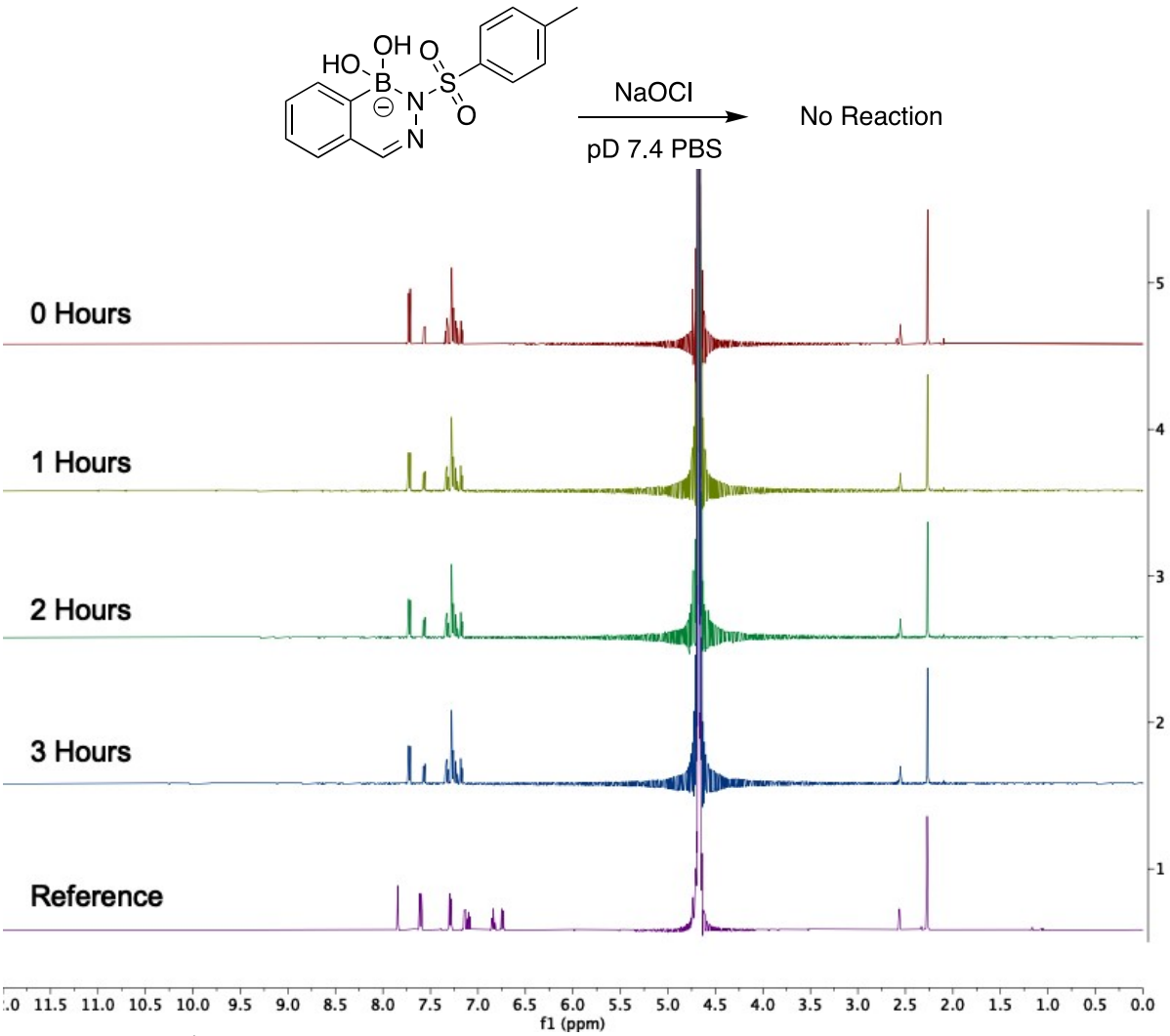


Figure S38. ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

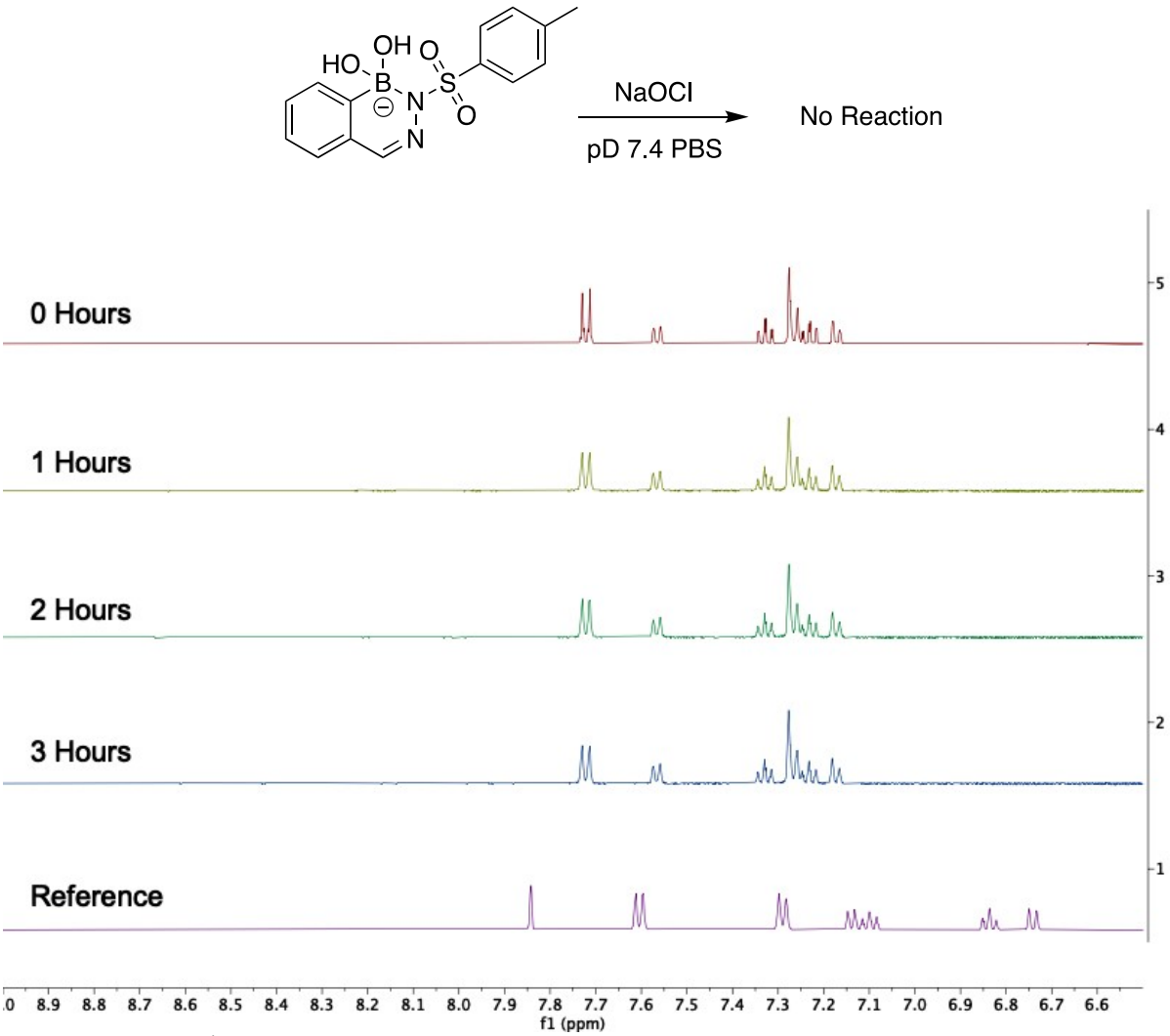


Figure S39a. ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) with NaOCl (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol also included.

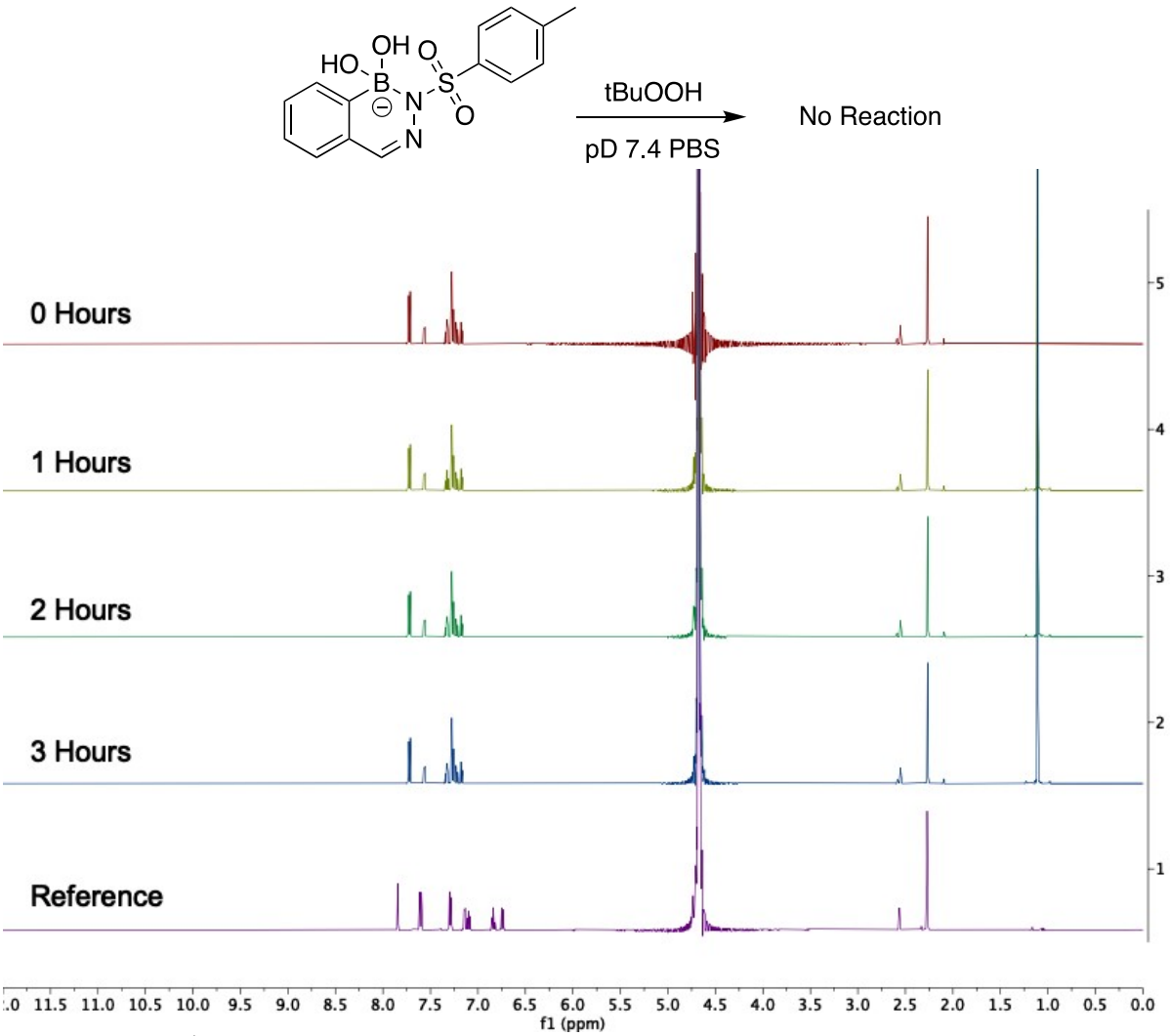


Figure S39. ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

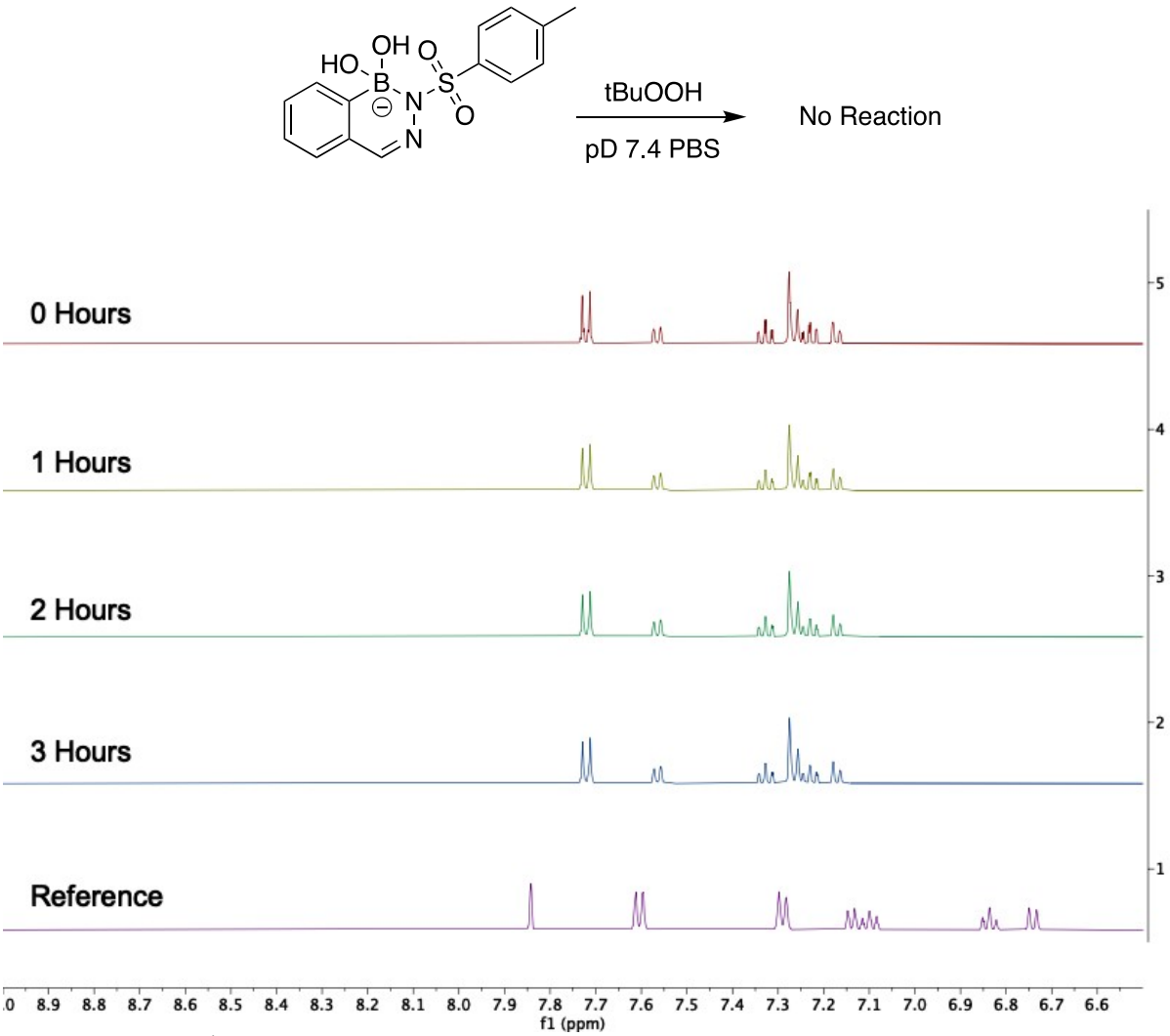


Figure S39a. ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) with *tert*-butyl hydroperoxide (t-BuOOH) (5 mM, 1 equivalent) at 0, 1, 2, and 3 h. A reference spectrum for the corresponding phenol is also included.

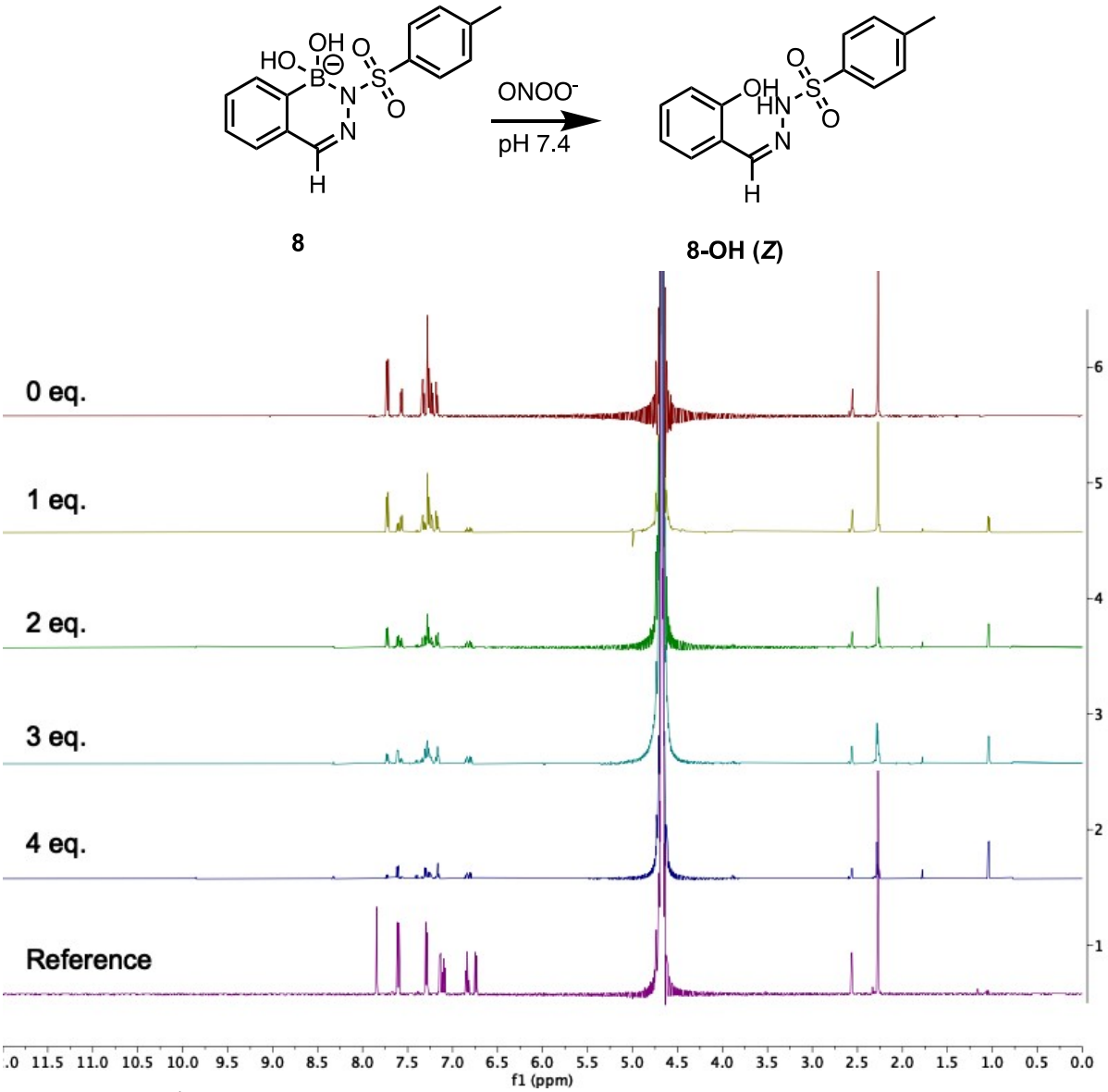


Figure S40. ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. Aliquots of $ONOO^-$ were added in 1 equivalent aliquots with spectra collected immediately after addition. A reference spectrum for the **8-OH** *E*-isomer is also included. The major product is the **8-OH** *Z*-isomer.

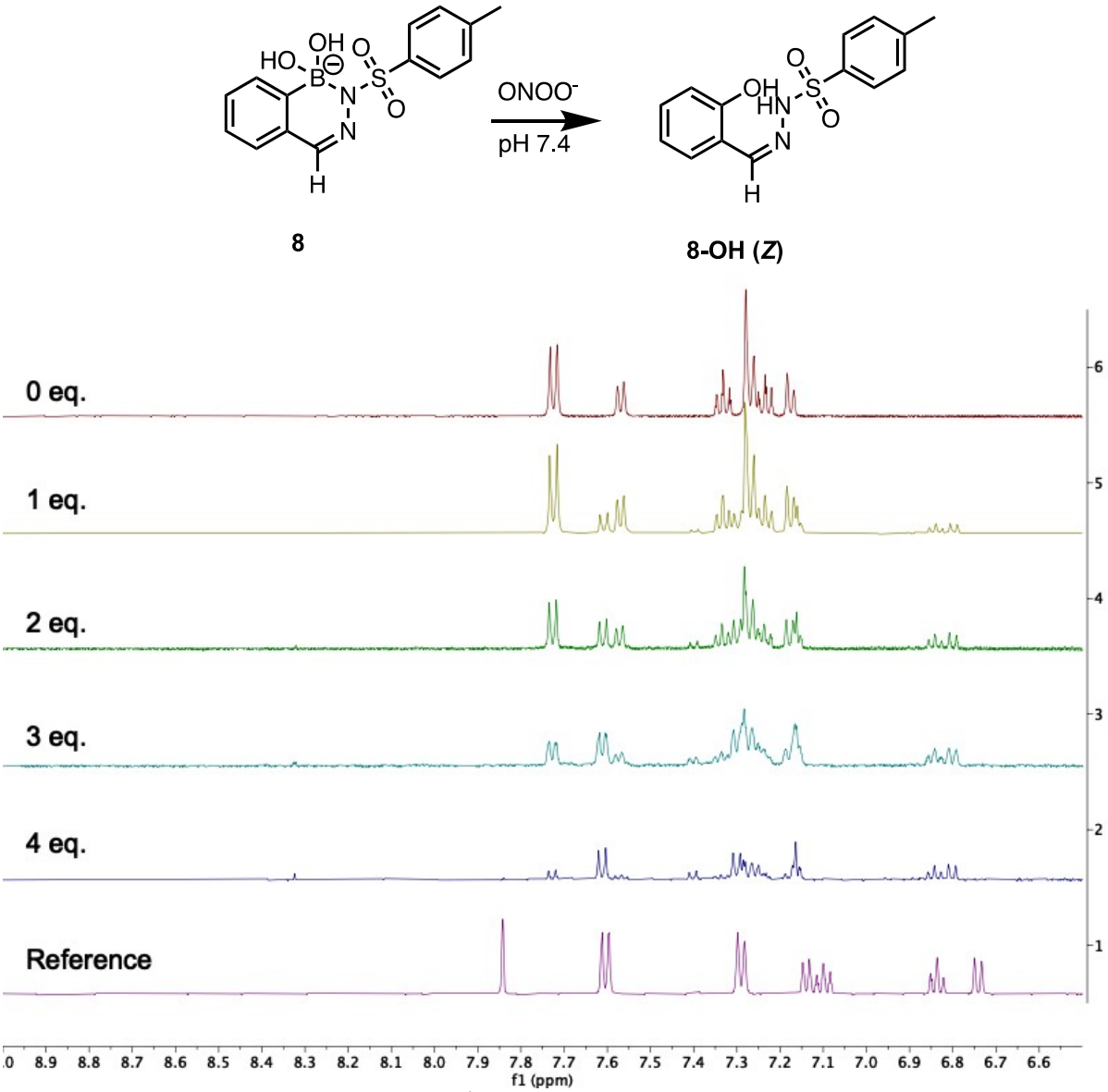


Figure S40a. Aromatic region of ^{1}H NMR spectra of **8** (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. $ONOO^-$ was added in 1 equivalent aliquots with spectra collected immediately after addition. A reference spectrum for the **8-OH** *E*-isomer is also included. The major product is the **8-OH** *Z*-isomer.

9. H_2O_2-mediated Oxidation of **8** with varying equivalents of H_2O_2

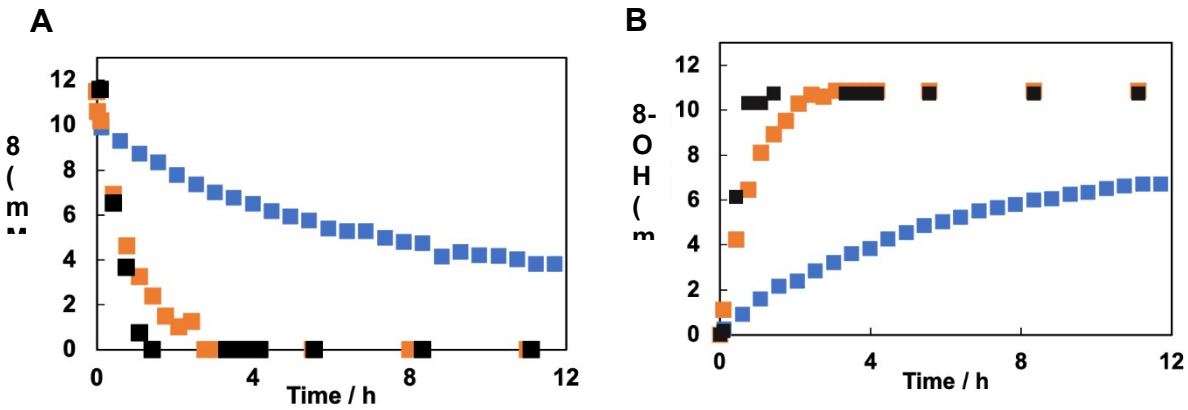
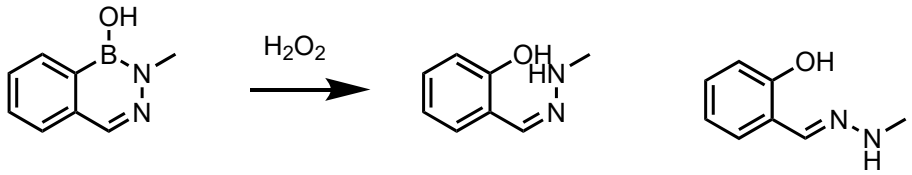


Figure S41. Rate of oxidation of **8** with 1 eq. (blue squares), 10 eq. (orange squares), and 100 eq. (black squares) of H_2O_2 as determined by disappearance of starting material. (A) Starting material disappearance as a function of time was determined by ^{1}H NMR by integrating the resonance at 7.75 ppm against a dimethylsulfone internal standard (10 mM). (B) Phenol production was determined by ^{1}H NMR by integrating the resonances at 6.78 and 6.83 ppm against a dimethylsulfone internal standard (10 mM).

10. Time-course oxidation of DABs with H_2O_2



7 **7-OH (*Z*)** Z-isomer **7-OH (*E*)** E-isomer

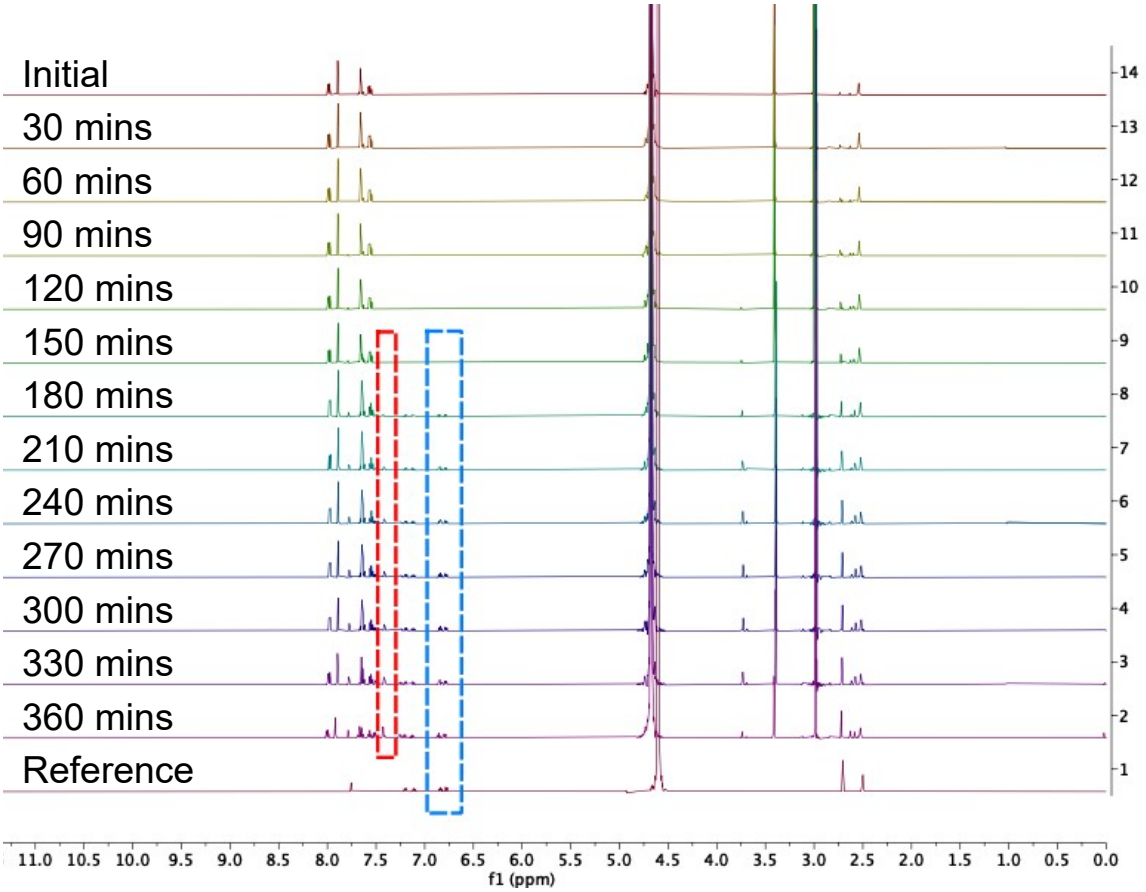


Figure S42. H_2O_2-mediated oxidation of **7** (10 mM) in PBS (200 mM, pD 7.4). *E*-isomer phenol (**7-OH**) peaks are highlighted with a dotted blue line. *Z*-isomer peaks are highlighted with a dotted red line. Starting material concentration was determined by integrating the peak at a resonance of 7.98. *Z*-isomer concentration was determined by integrating resonance at 7.42 ppm. Phenol concentration was determined by integrating resonances at 6.75 and 6.85 ppm.

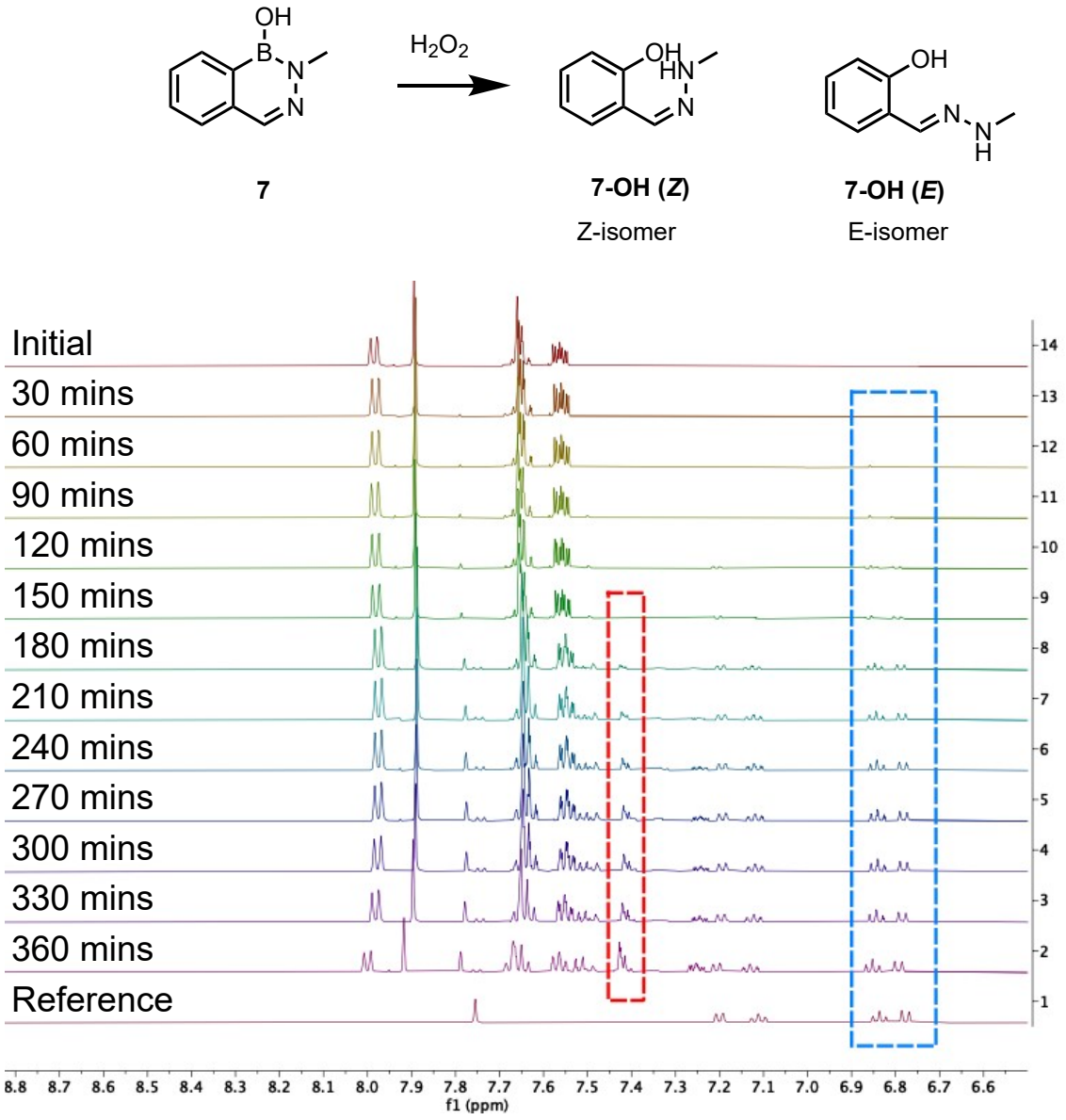


Figure S42a. H_2O_2-mediated oxidation of **7** (10 mM) in PBS (200 mM, pH 7.4). *E*-isomer phenol peaks are highlighted with a dotted blue line. *Z*-isomer peaks are highlighted with a dotted red line. Starting material concentration was determined by integrating the peak at a resonance of 7.98. *Z*-isomer concentration was determined by integrating resonance at 7.42 ppm. Phenol concentration was determined by integrating resonances at 6.75 and 6.85 ppm.

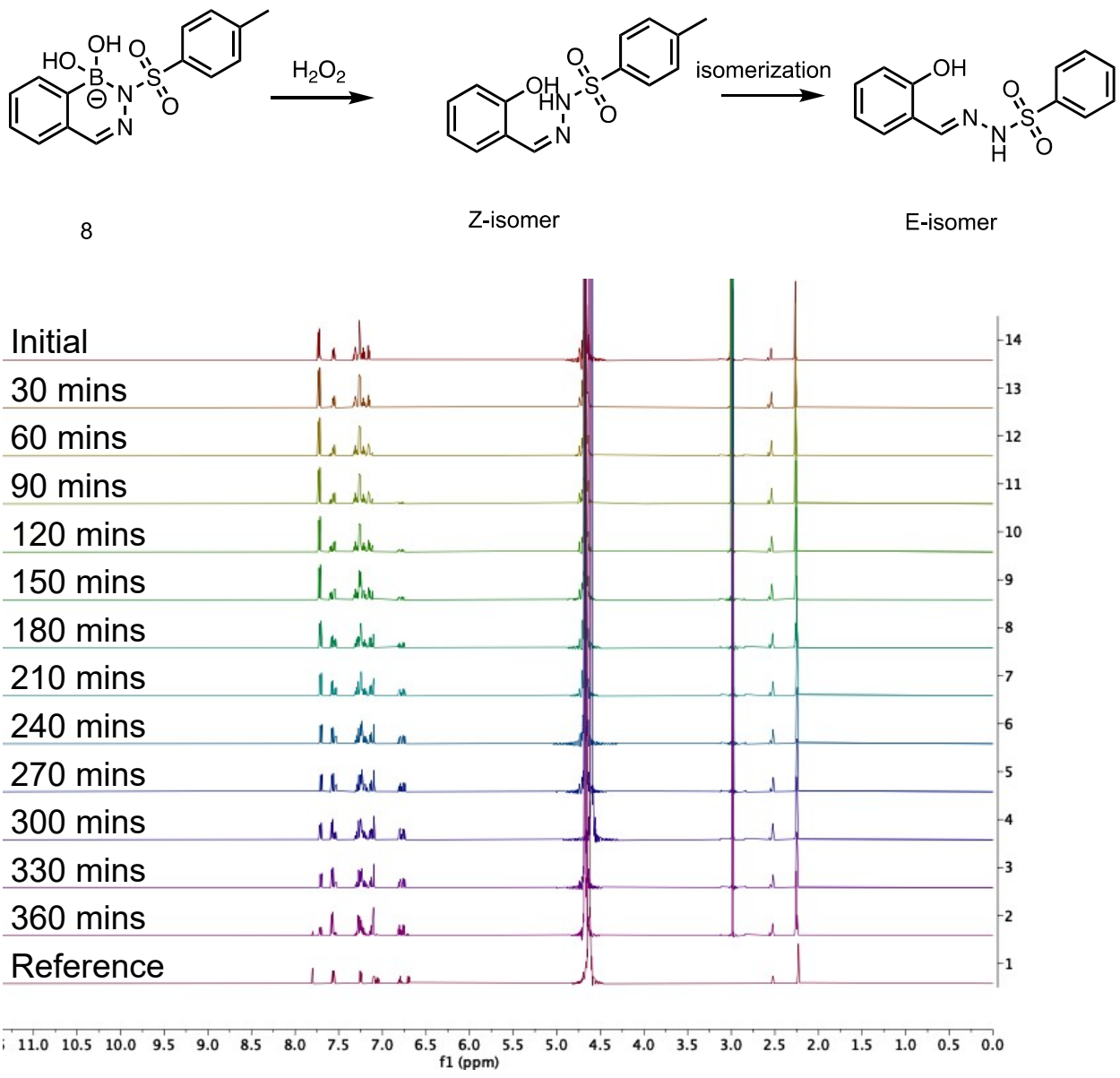


Figure S43. Time-course ^{1}H NMR spectra of the reaction between **8** (10 mM) with H_2O_2 (10 mM, 1 equivalent) in PBS (200 mM, pH 7.4). **8** does not convert directly to the *E*-isomer phenol, but instead, cleanly forms the *Z*-isomer with only trace *E*-isomer observed after 6 hours. Starting material concentration was determined by integrating resonance at 7.71 ppm. *Z*-isomer concentration was determined by integrating the peak at a resonance of 6.75.

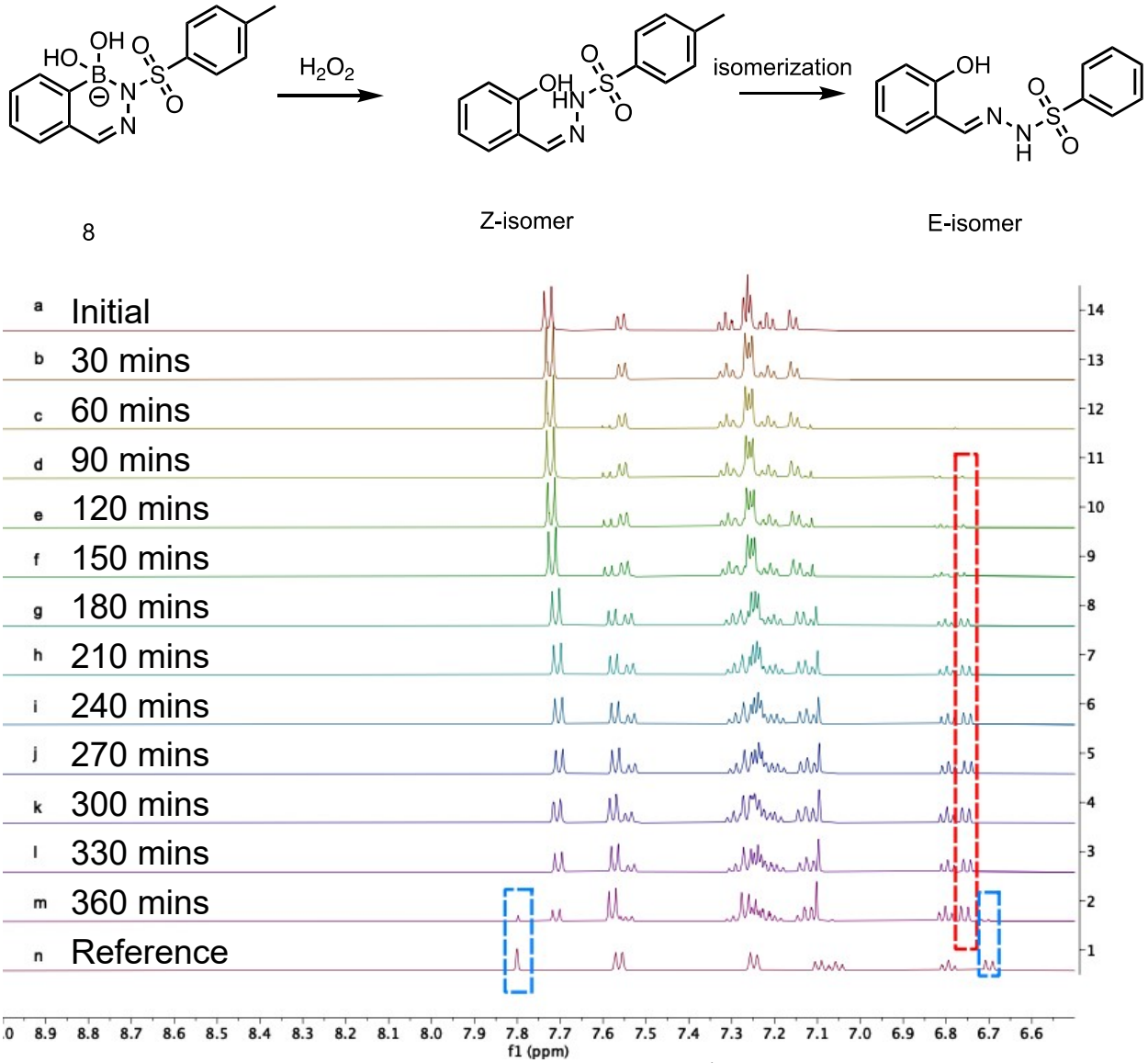
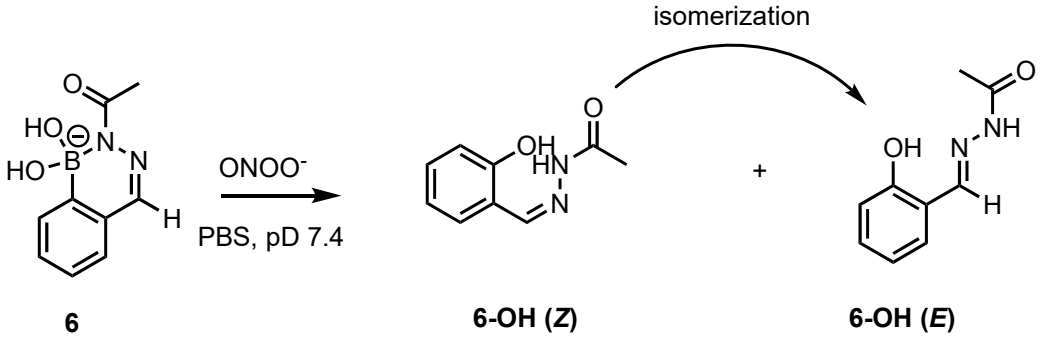


Figure S43a. Aromatic region of the time-course ^{1}H NMR spectra of the reaction between **8** (10 mM) with H_2O_2 (10 mM, 1 equivalent) in PBS (200 mM, pH 7.4). **8** does not convert directly to the *E*-isomer phenol, but instead, cleanly forms the *Z*-isomer. Starting material concentration was determined by integrating resonance at 7.71 ppm. *Z*-isomer concentration was determined by integrating the peak at a resonance of 6.75 ppm.

11. Time-course conversion of DAB oxidation *Z*-isomers to *E*-isomers



6 **6-OH (*Z*)** **6-OH (*E*)**

mixture of E/Z amide isomers mixture of E/Z amide isomers

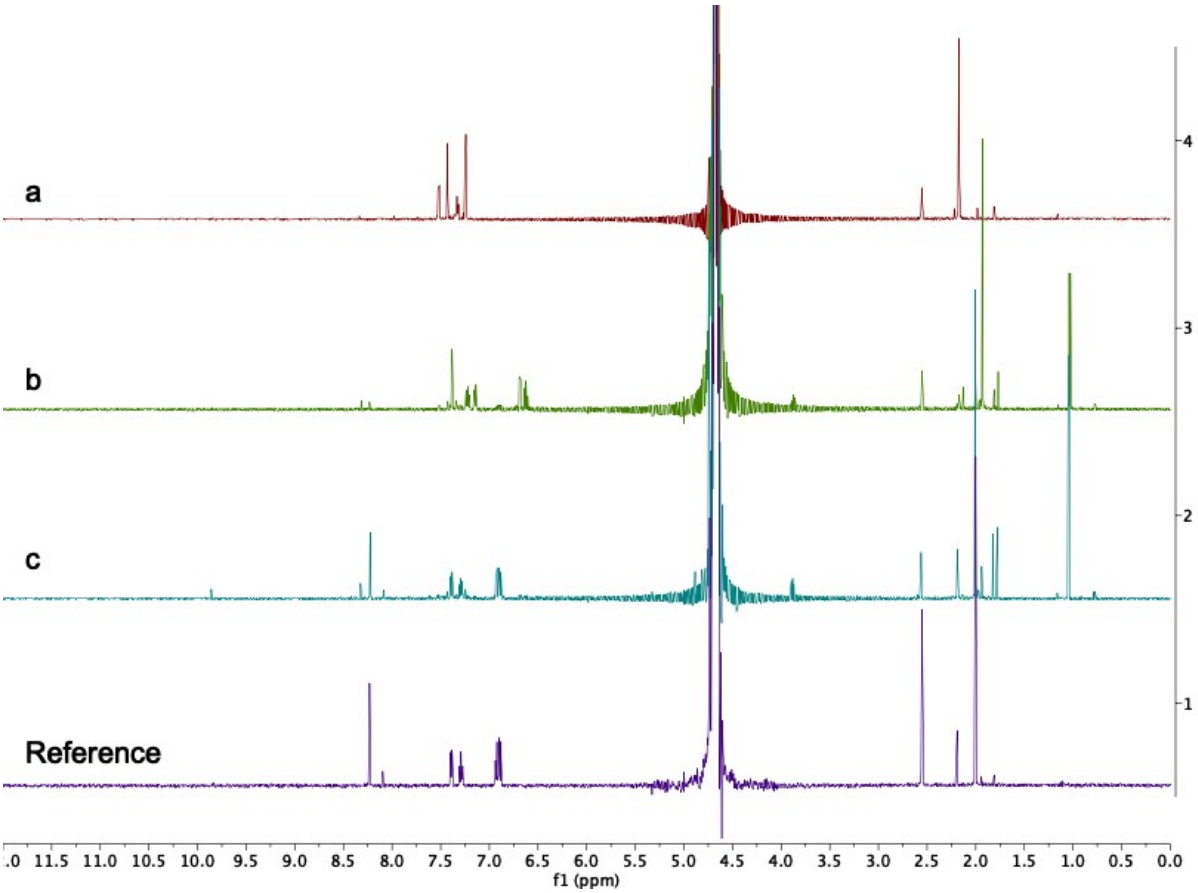


Figure S44. ^{1}H NMR spectrum of **6** (**a**) before and (**b**) after addition of 4 equivalents of peroxynitrite. The *Z*-isomer forms predominantly with trace *E*-isomer phenol. (**c**) After 14 hours at room temperature, the *Z*-isomer has resolved to give *E*-isomer phenol **(6-OH)**.

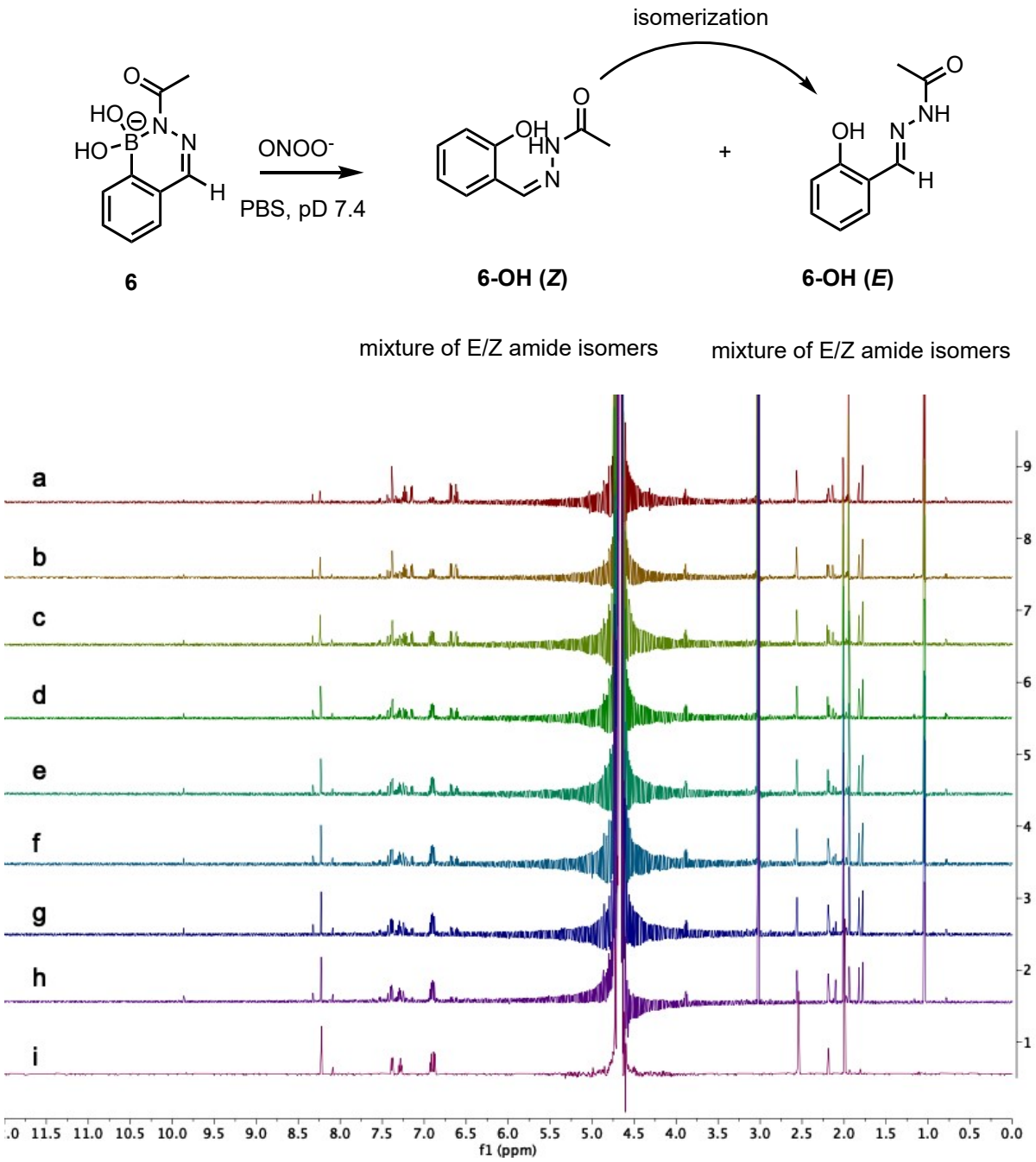


Figure S44a. Stacked ^{1}H NMR spectra of the time-course isomerization of **6-OH** *Z*-isomer into *E*-isomer **6-OH**. The *Z*-isomer was prepared by adding 4 molar equivalents of $ONOO^-$ (a). Spectra were collected in 2-hour increments (b-h). A reference spectrum of the *E*-isomer phenol is included (i). Phenol concentration was determined by integrating the peak at a resonance of 6.89.

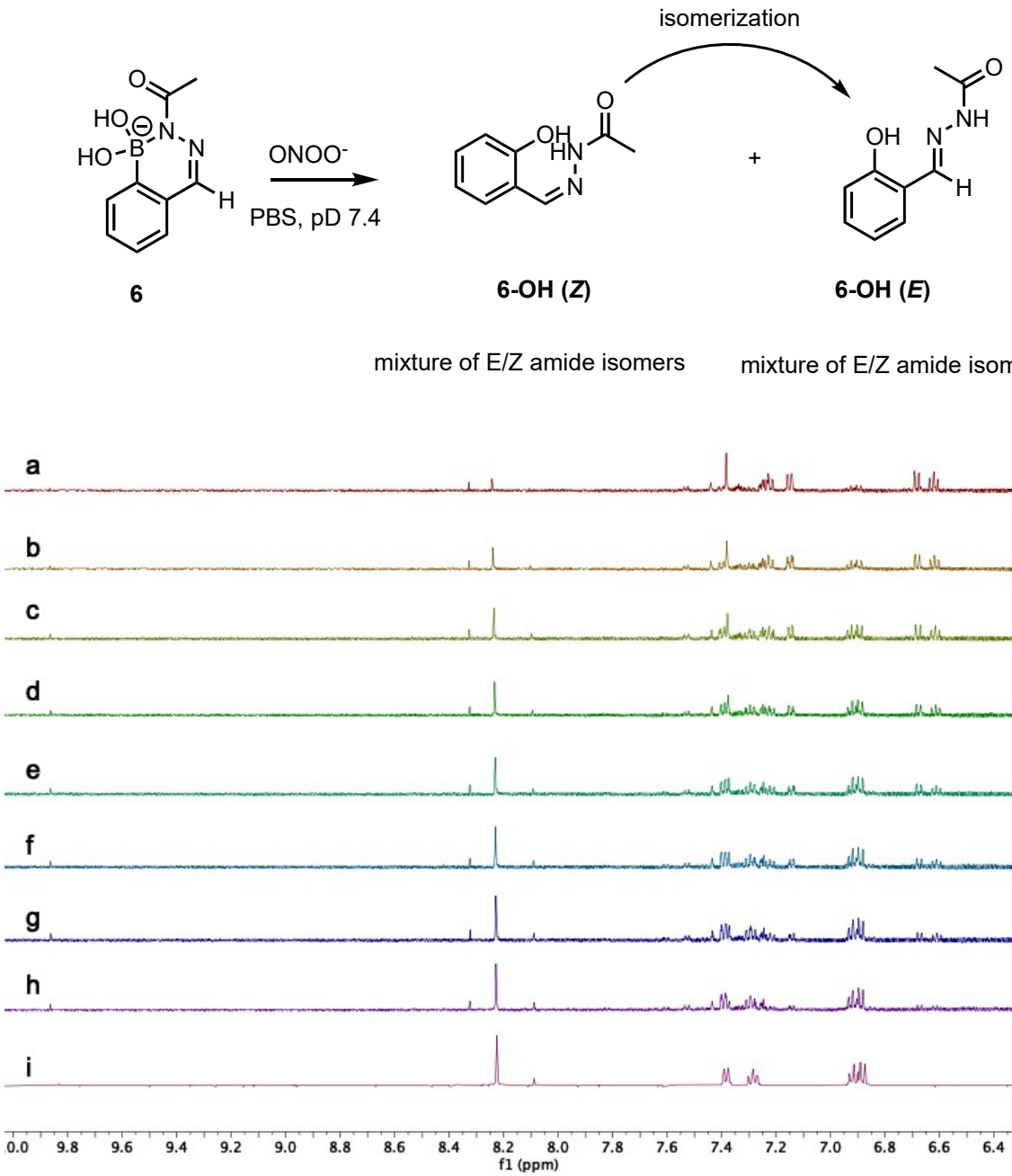
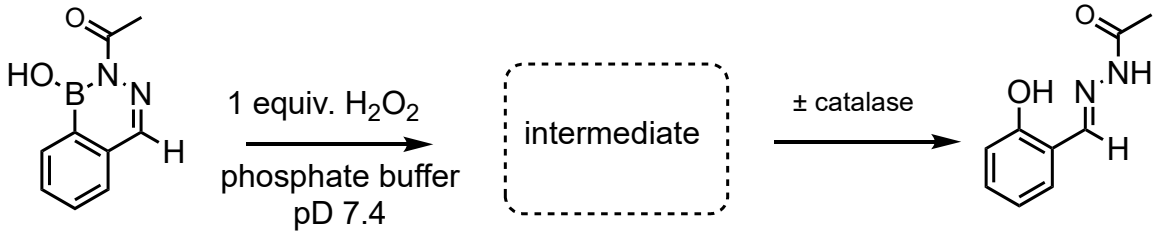


Figure S44b. Aromatic region of the ^{1}H NMR spectra of time-course conversion of the time-course isomerization of **6-OH** *Z*-isomer into *E*-isomer **6-OH**. The *Z*-isomer was prepared by adding 4 molar equivalents of $ONOO^-$ (a). Spectra were collected in 2-hour increments (b-h). A reference spectrum of the *E*-isomer phenol is included (i). Phenol concentration was determined by integrating the peak at a resonance of 6.89.

12. Effect of catalase on the intermediate and conversion to phenol



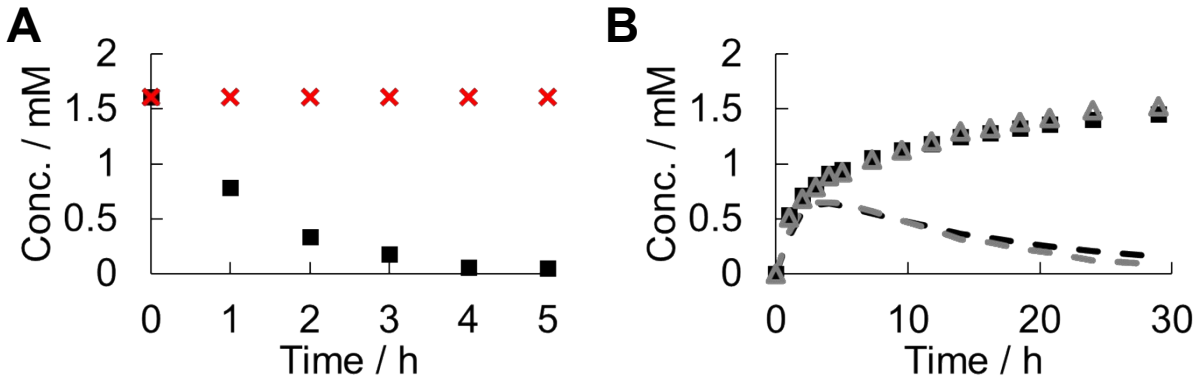
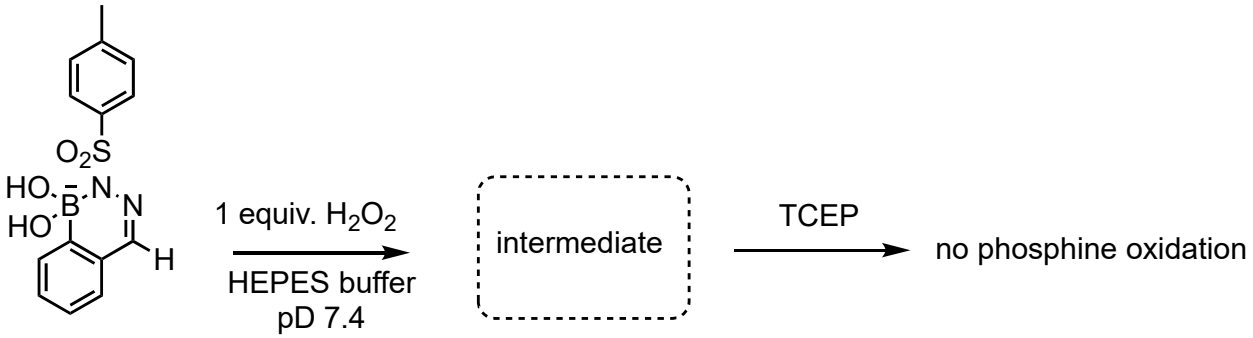


Figure S45. To determine if the intermediate (later determined to be the *Z*-isomer) is a reversible complex formed between H_2O_2 and the DAB, we determined if catalase could convert the intermediate back to the starting DAB. (A) DAB **6** (1.5 mM) in phosphate buffer (200 mM, pD 7.4) was pre-treated with catalase (0.5 mg) and then H_2O_2 (4.5 mM). No reaction is seen (×). In the absence of catalase, treatment of **6** with H_2O_2 (4.5 mM) consumes the starting material in 5 h (black squares). (B) Phenol and *Z*-isomer concentrations as a function of time in the presence and absence of catalase (0.5 mg, added at 4 h). Phenol formation from **6** with H_2O_2 in the absence of catalase (black squares) and the presence of catalase (0.5 mg, added at 4 h) (open triangle) is identical. *Z*-isomer concentration as a function of time in the absence of catalase (black dash) and presence of catalase (0.5 mg, added at 4 h) (gray dash) is also unaffected by catalase. We thus conclude that the intermediate is not a reversible complex between H_2O_2 and the DAB.

13. DAB **8** *Z*-isomer cannot oxidize a phosphine



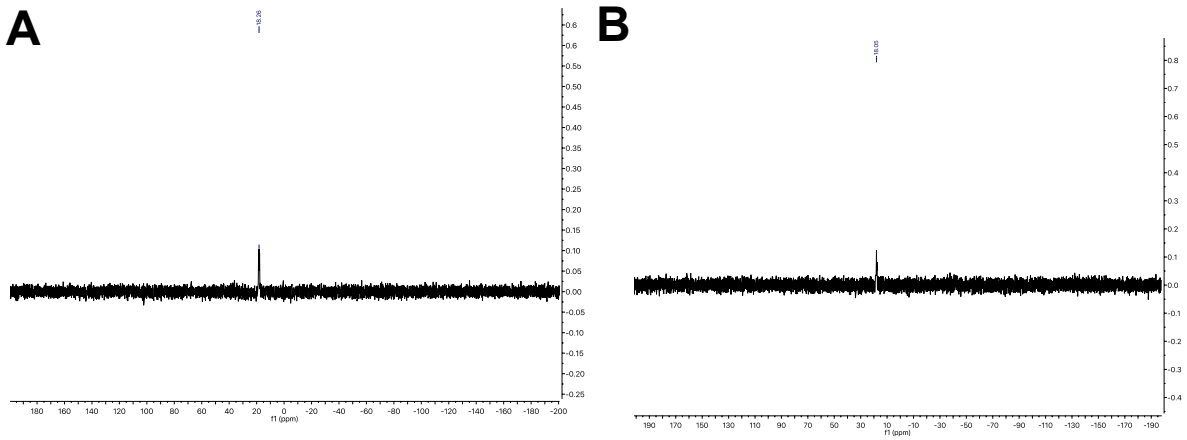


Figure S46. To determine if the intermediate (later determined to be the *Z*-isomer) may be a stable boron-peroxide intermediate, we sought to determine if it could oxidize a phosphine. DAB **8** (10 mM) was dissolved in phosphate buffer (HEPES, 50 mM, pD 7.4) and treated with H_2O_2 (10 mM) and allowed to react overnight to form the intermediate. Catalase (0.5 mg) was added to decompose excess H_2O_2. TCEP (1.5 equiv. pre-dissolved in buffer and adjusted to pD 7.4) was added, and a ^{31}P NMR was acquired 30 minutes later. (B) Reference spectrum of TCEP in HEPES buffer. No oxidation is seen. We thus conclude that the intermediate is not a stable boron-peroxide intermediate.

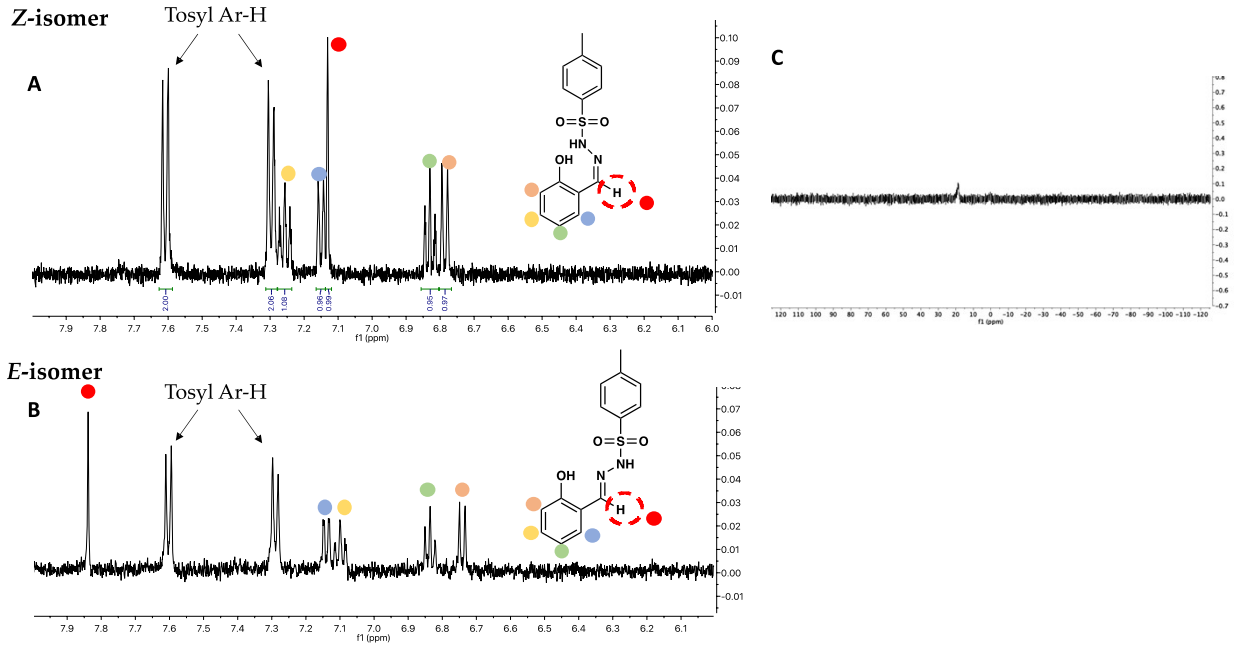


Figure S47. (A) ^{1}H NMR analysis of the immediate product with reaction between DAB **8** and H_2O_2 (10 equiv.) after 3 h reveals clean production of the intermediate. This is assigned as the *Z*-isomer of the phenol hydrazone. (B) A reference spectrum of the as-synthesized hydrazone from salicylaldehyde and *p*-toluenesulfonyl hydrazide. (C) The ^{11}B NMR of (A) shows a single ^{11}B resonance at 18.35 ppm. Spiking the reaction mixture with borate confirmed the ^{11}B signal arises from borate.

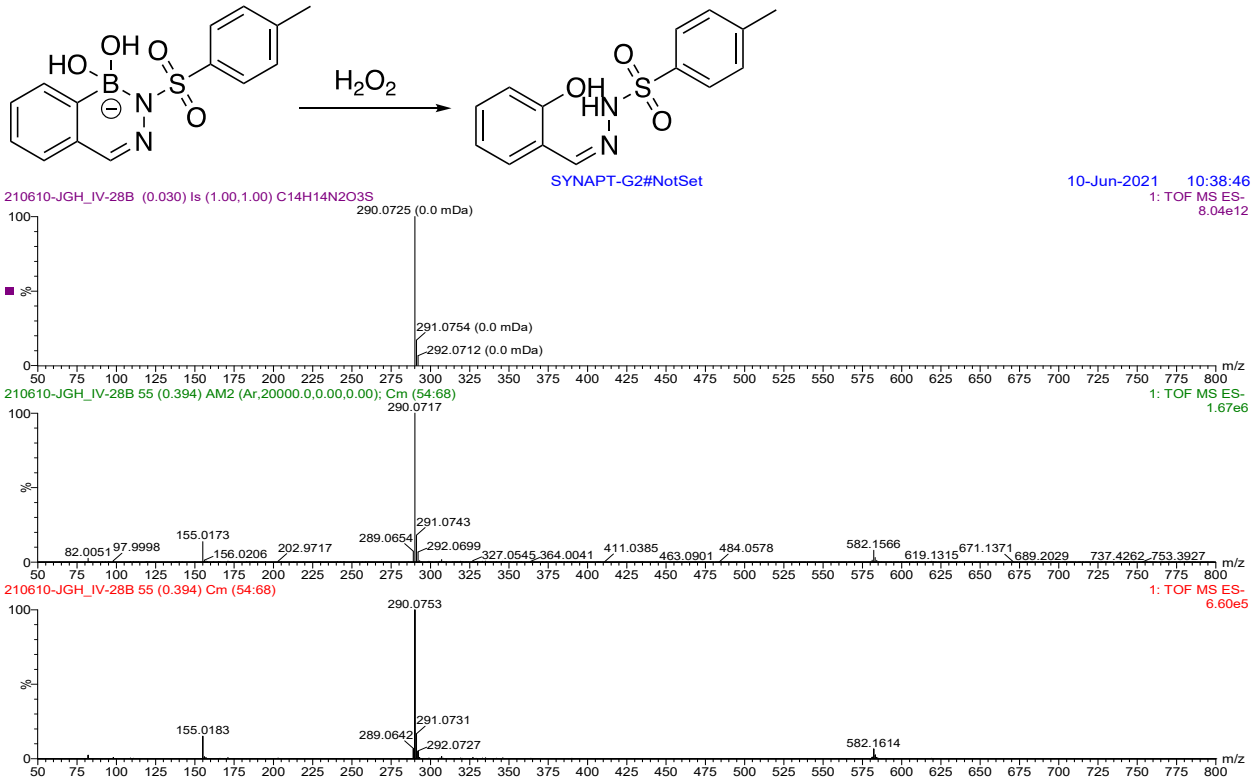


Figure S48. Mass spectrum of **8** after oxidation with 1 eq. of H_2O_2 in pH 7.4 ammonium acetate buffer. Consumption of starting material and formation of the intermediate was confirmed by ^{1}H NMR.

14. DFT Calculations

Definition of conformers and isomers examined

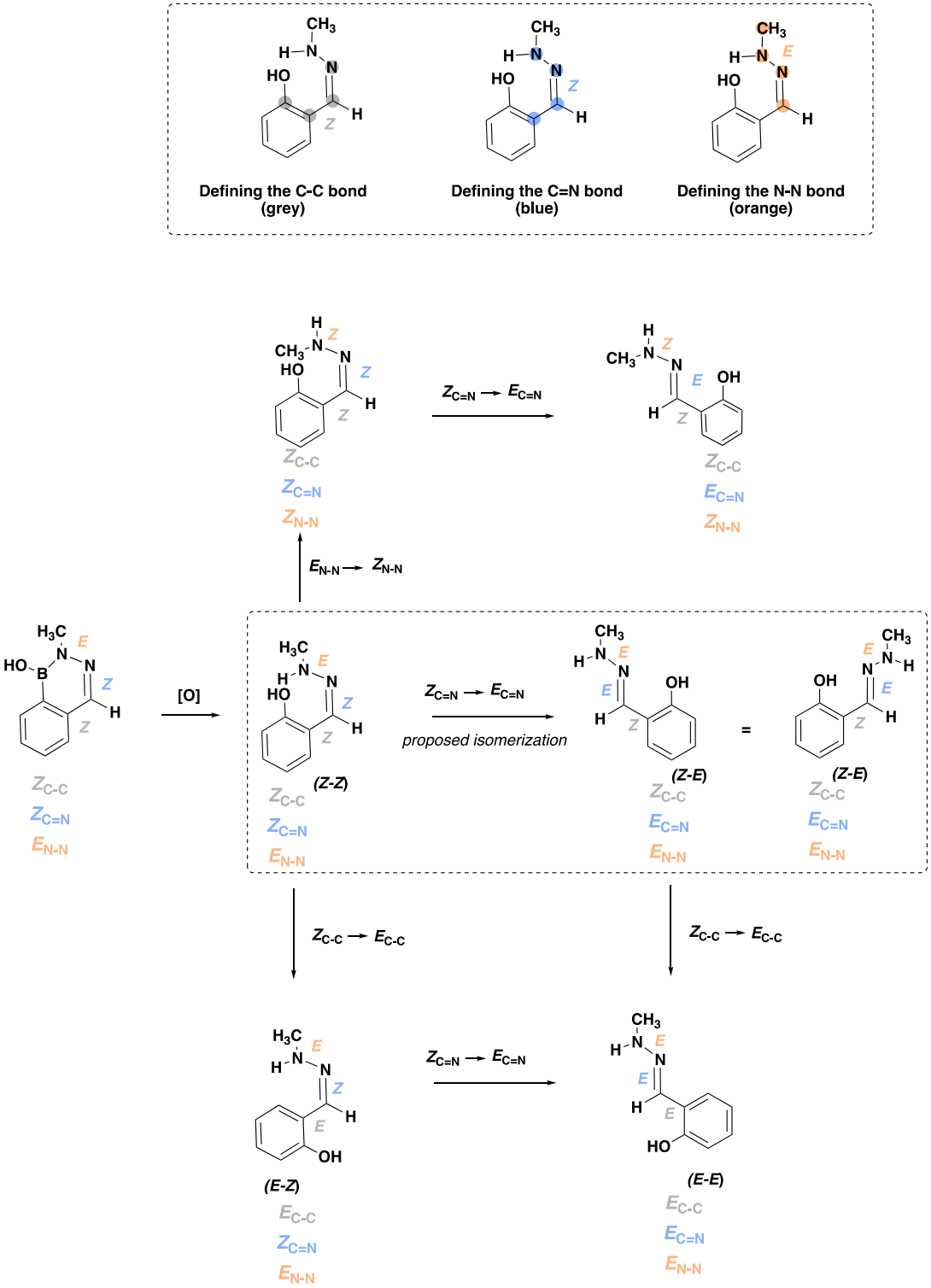


Figure S49A. Description of the isomers and conformers examined by DFT.

Computational Methods

All computations were conducted with Gaussian16 (Rev. C01)[1] software suite using Density Functional Theory (DFT). For the optimization of the ground and transition state structures, the hybrid exchange-correlation functional from Becke, Lee, Yang and Parr[2] (commonly referred to as B3LYP), together with a double-zeta 6-31++G(2d,2p) all-electron atomic basis sets, including diffuse and two sets of polarization functions, on all atoms. Analytical frequencies were obtained to characterize stationary points as a minimum energy or a transition state structure by identifying zero or one imaginary vibrational mode, respectively. IEFPCM implicit solvation calculations were conducted with the SMD solvation model.[3]

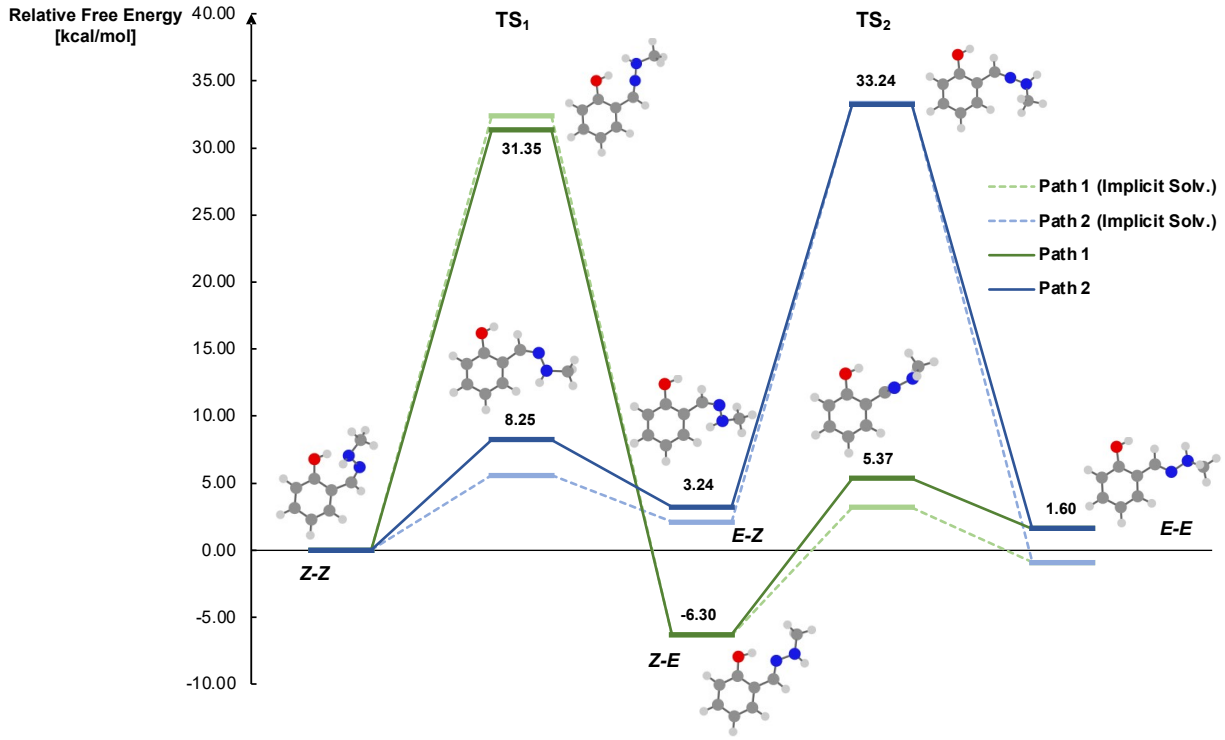


Figure S49B. Computed Free Energy surface of the C=N *Z*-*E*-isomerization through rotation. Atoms are represented by grey (carbon), white (hydrogen), red (oxygen) and blue (nitrogen) spheres. Isomerization of $Z_{C=N}$ → $E_{C=N}$ (i.e., *Z*-*Z* → *Z*-*E*) proceeds through an >30 kcal/mol energy barrier kcal/mol barrier. Z-E is the most thermodynamically stable isomer and conformation. Repeating the calculations with implicit solvent lowers the energy barrier to rotation by *ca.* 3 kcal/mol.

Discussion. We find it helpful to clarify the conformations and isomers that this class of compounds can adopt.

We do not consider $Z_{N\text{-}N}$ conformers because of the steric clash that develops in this conformation.[4] However, C-C conformers are possible in addition to *E*/*Z* geometric isomers that result in the exchange of the relative positions of the substituents around the C=N bond. We have thus mapped the reaction coordinate for all four species (all with $E_{N\text{-}N}$ conformations): ($Z_{C\text{-}C}$, $Z_{C=N}$) ; ($Z_{C\text{-}C}$, $E_{C=N}$) ; ($E_{C\text{-}C}$, $Z_{C=N}$) ; ($E_{C\text{-}C}$, $E_{C=N}$).

We anticipate that the $Z_{C\text{-}C}$, $Z_{C=N}$ ("Z-Z") species is immediately formed upon oxidation because this is the requisite geometry and conformation to form the DAB. Isomerization about the C=N bond gives ($Z_{C\text{-}C}$, $E_{C=N}$) ("Z-E"). Proceeding through a linear transition state has an associated energy barrier of 31.35 kcal/mol. We do not expect this is the route of isomerization in our system. Because acid rapidly triggers C=N isomerization, we hypothesize that in aqueous buffer isomerization proceeds through a hemi-aminal intermediate (i.e., carbinol) as noted by Otto *et. al* to temporarily form a C-N single bond and permit rotation, followed by reformation of the hydrazone.[5] Z-E is calculated to be the most thermodynamically stable species of the four (-6.30 kcal/mol relative to Z-Z). These are the two C=N isomers referred to in the main text of the initial resubmission.

For completeness, we also considered the effect of C-C rotation. Starting from Z-Z, rotation about the C-C bond requires overcoming an 8.25 kcal/mol energy barrier to yield $E_{C\text{-}C}$, $Z_{C=N}$ ("E-Z"), which is destabilized relative to Z-Z by 3.25 kcal/mol. E-Z can also undergo C=N isomerization through a similarly large energy barrier (*ca*. >30 kcal/mol) to yield $E_{C\text{-}C}$, $E_{C=N}$ ("E-E"). Z-E can undergo C-C rotation, proceeding through an energy barrier of 11.67 kcal/mol to yield E-E. E-E is destabilized relative to Z-E by 7.9 kcal/mol.

We thus conclude the Z-Z is formed immediately after oxidation, and it isomerizes its more thermodynamically stable Z-E isomer.

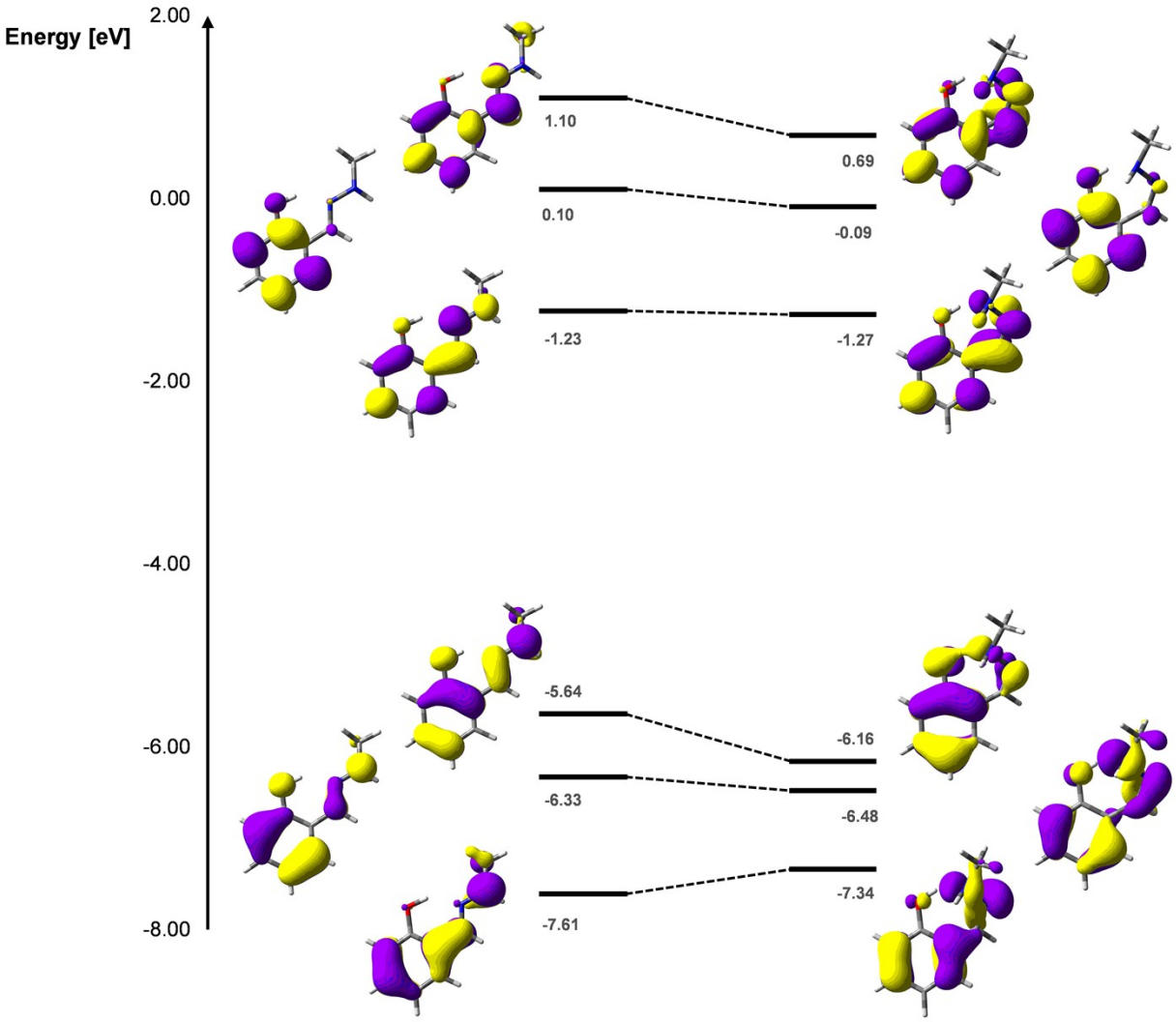


Figure S49C**.** Frontier Molecular Orbitals of the *E*-Isomer (left) and the *Z*-Isomer (right), with Isovalue=0.04. Calculated at the B3-LYP/6-311G(2df,2pd) level of theory. The occupied MOs change the most upon isomerization, while the virtual orbitals change only slightly. The most significant change is that the HOMO in the *Z*-isomer decreases by 0.5 eV compared to the HOMO in the *E*-isomer. The double bond character of the carbon-nitrogen bond is lower in the *Z*-isomer than in the *E*-isomer, which is in agreement with the relative free energies and the nonplanarity of the *Z*-isomer which results in a worse p-orbital overlap between nitrogen and carbon.

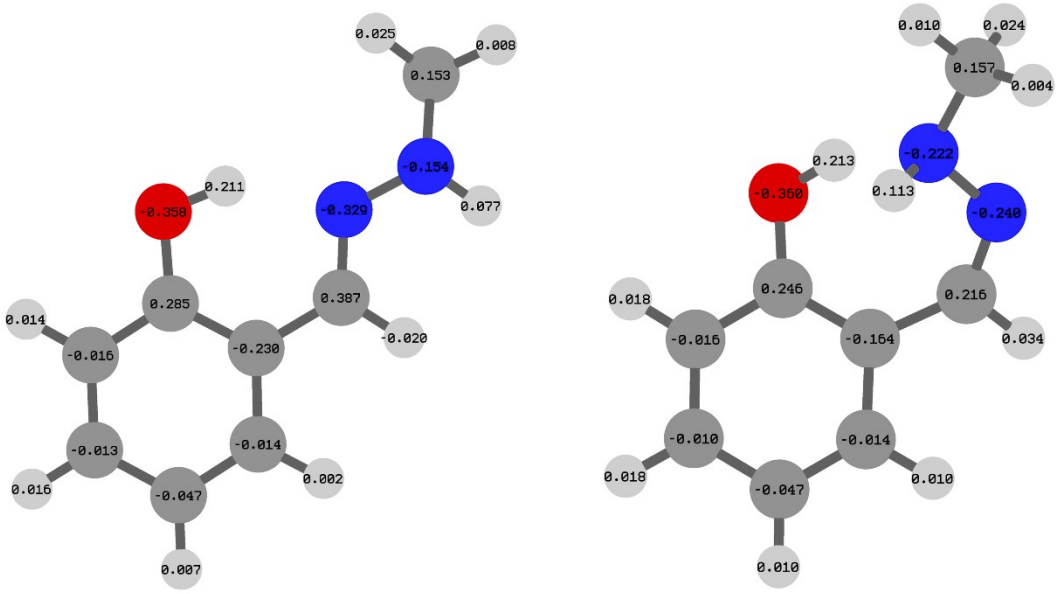


Figure S49D**.** Computed Mulliken charges of the *E*-Isomer (left) and the *Z*-Isomer (right). Calculated at the B3-LYP/6-311G(2df,2pd) level of theory. In agreement with the frontier orbital analysis, the carbon-nitrogen bond loses electron density, while the charge on the other nitrogen becomes more negative.

References

[1] Frisch, M. J. et al. Gaussian 16 Revision C.01. Gaussian Inc. Wallingford CT 2019.

[2] Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *The Journal of Chemical Physics* **1993**, *98*, 5648-5652.

[3] A. V. Marenich, C. J. Cramer, and D. G. Truhlar, “Universal solvation model based on solute electron density and a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions,” J. Phys. Chem. B 2009, 113, 6378-6396.

[4] V. V. Syakaev, S. N. Podyachev, B. I. Buzykin, S. K. Latypov, W. D. Habicher and A. I. Konovalov, Journal of Molecular Structure, 2006, 788, 55–62.

[5] I. Cvrtila, H. Fanlo-Virgós, G. Schaeffer, G. Monreal Santiago and S. Otto, *J. Am. Chem. Soc.*, 2017, **139**, 12459–12465.

15. UV-Vis spectra of transition from **8-OH** (*Z*) to (*E*)

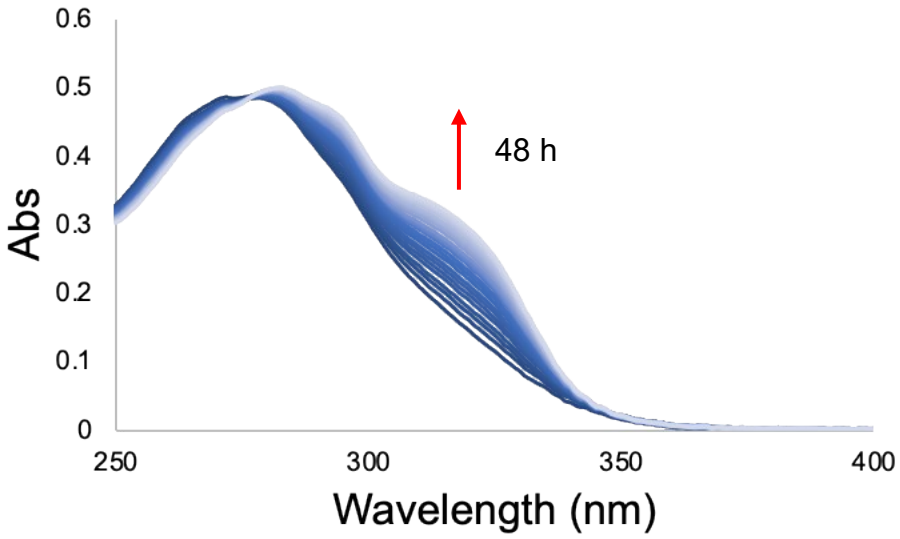
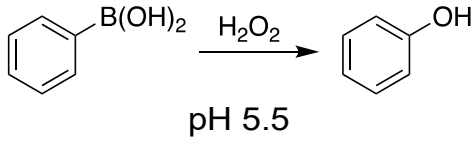


Figure S50. UV-Vis spectra of **8-OH** (*Z*) isomerization to **8-OH** (*E*) at room temperature in pH 7.4 PBS. **8-OH** (*Z*) was synthesized by treating DAB **8** with H_2O_2 (10 equiv.) for 3 h, its presence confirmed by ^{1}H NMR, and an aliquot was diluted in PBS, pH 7.4 buffer for UV-vis analysis. Spectra were collected every 3 hours over the course of 48 h. The initial spectrum is indicated by the darkest blue trace.

16. Phenylboronic acid oxidation at different pH conditions



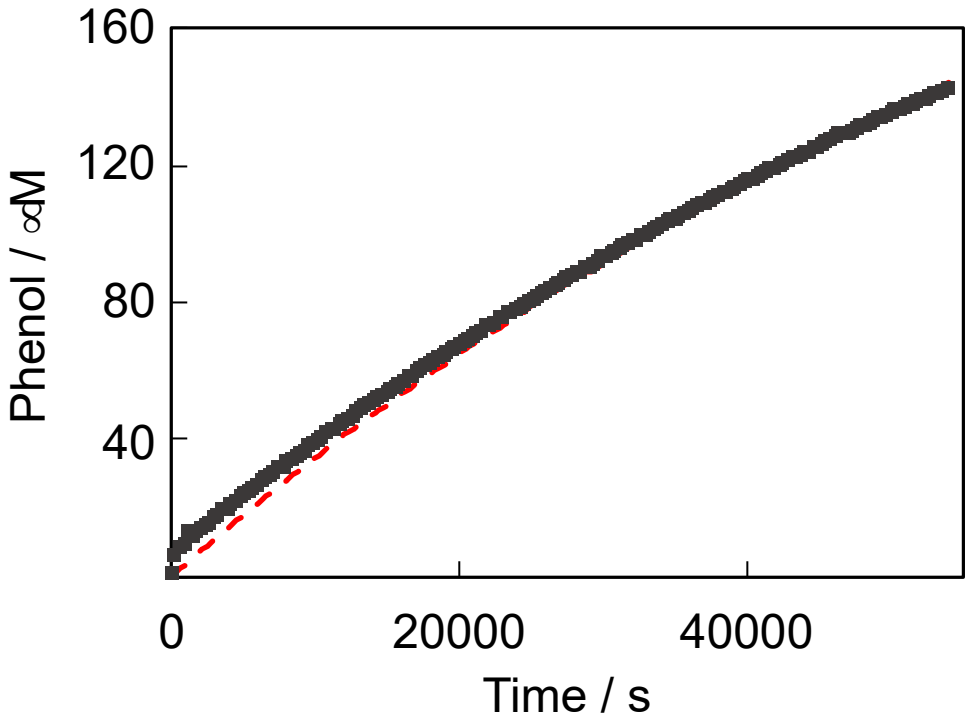


Figure S51. H_2O_2-mediated oxidation of **1** (500 μM) in PBS (100 mM, pH 5.5). The measured rate is 0.013 ± 0.002 $M^{-1}s^{-1}$

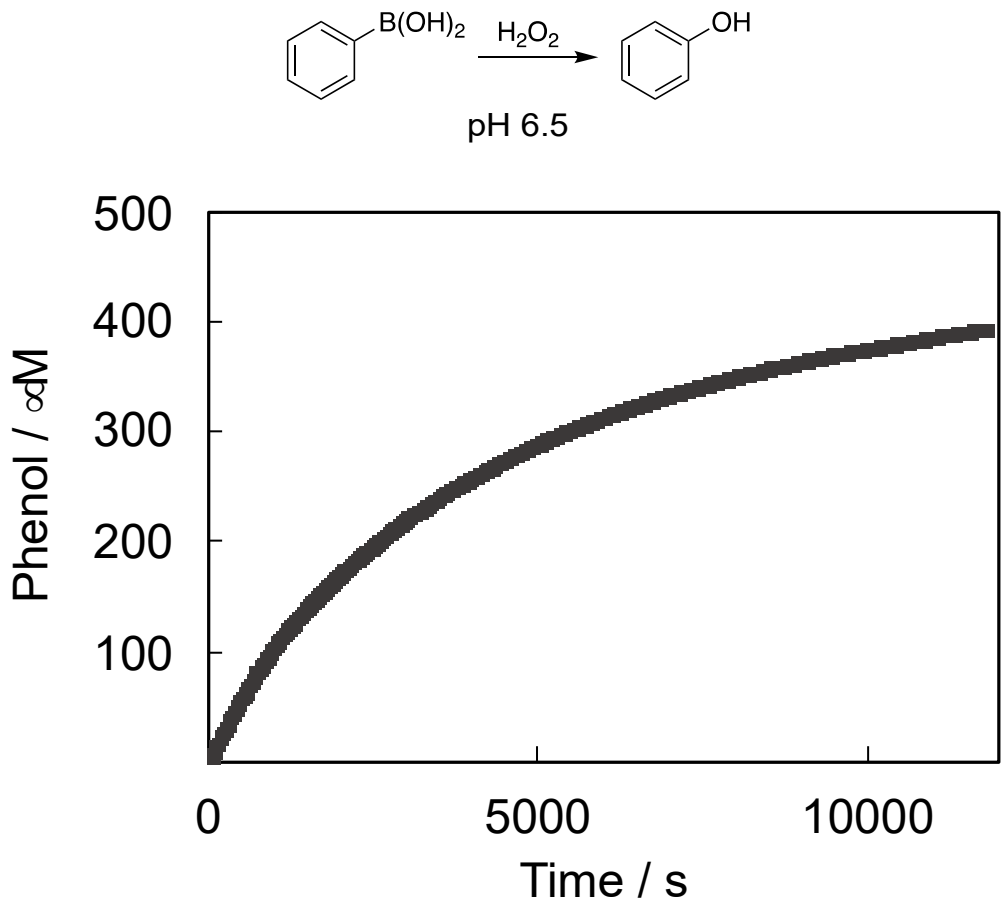


Figure S52. H_2O_2-mediated oxidation of **1** (500 μM) in PBS (100 mM, pH 6.5) with H_2O_2 (500 μM, 1 equivalent). Data points represent the concentration of phenol at the corresponding time points. Red dashed line is a fit to a second-order kinetic model. The measured rate is $k = 0.49 \pm 0.08\ M^{-1}\ s^{-1}$.

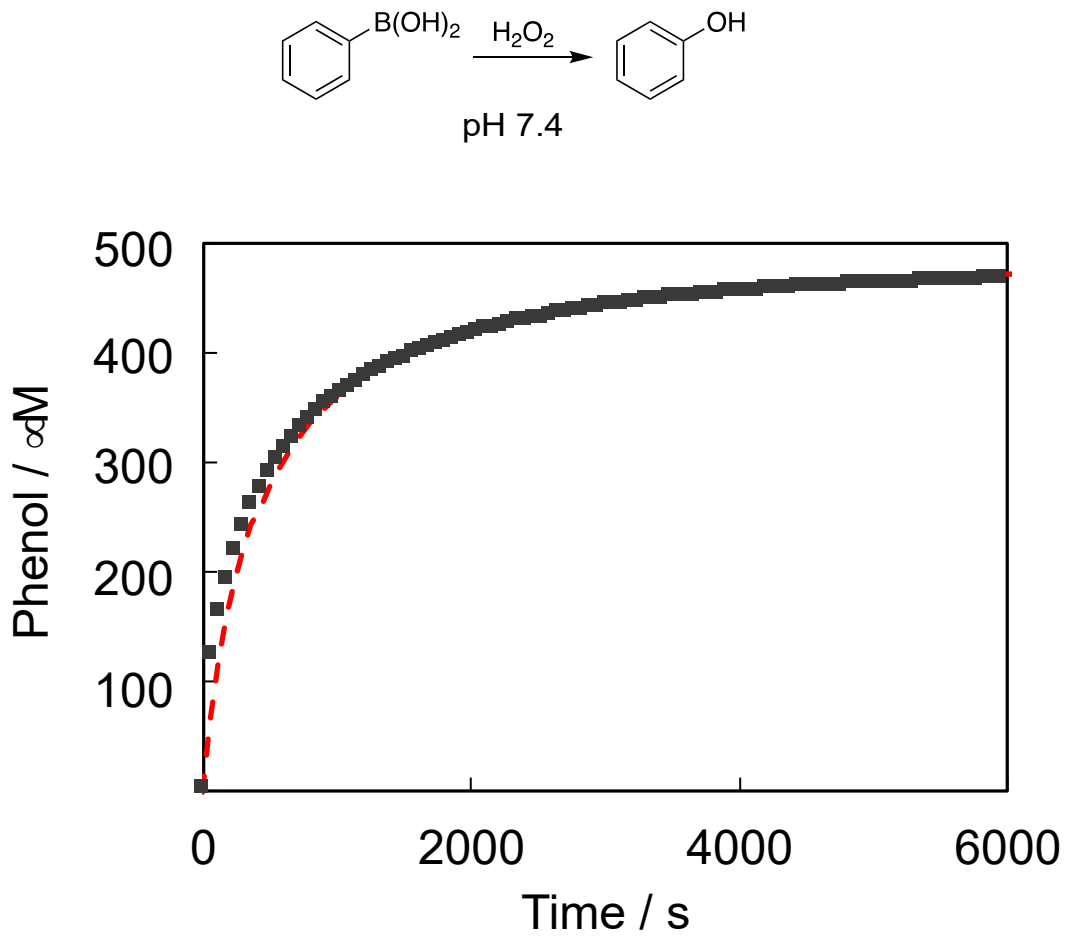


Figure S53. H_2O_2-mediated oxidation of **1** (500 μM) in PBS (100 mM, pH 7.4). Data points represent the concentration of phenol at the corresponding time points. Red dashed line is a fit to a second-order kinetic model. The measured rate constant is k = 4.94 ± 0.82 $M^{-1}s^{-1}$.

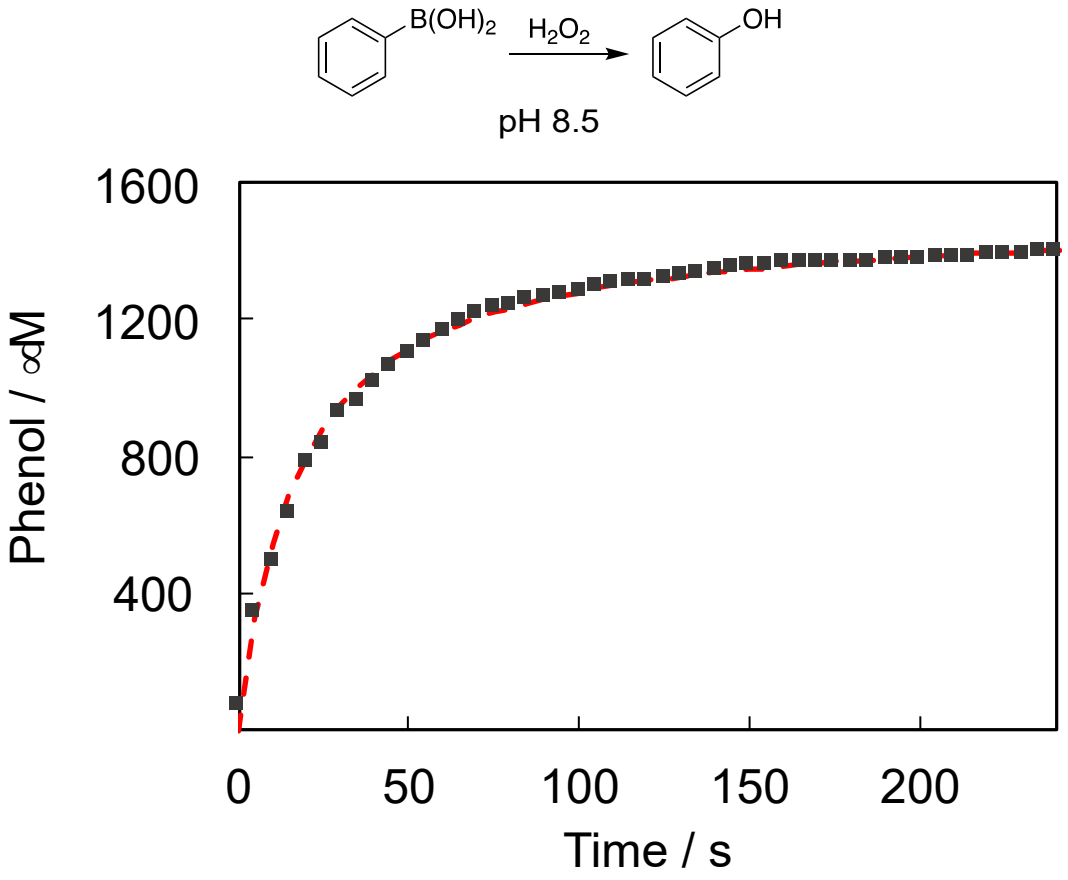


Figure S54. Oxidation of **1** (1.5 mM) in PBS (100 mM, pH 8.5) with H_2O_2 (1.5 mM, 1 equivalent). Data points represent the concentration of phenol at the corresponding time points. Red dashed line is a fit to a second-order kinetic model. The measured rate constant is 39.0±1.0 $M^{-1}s^{-1}$.

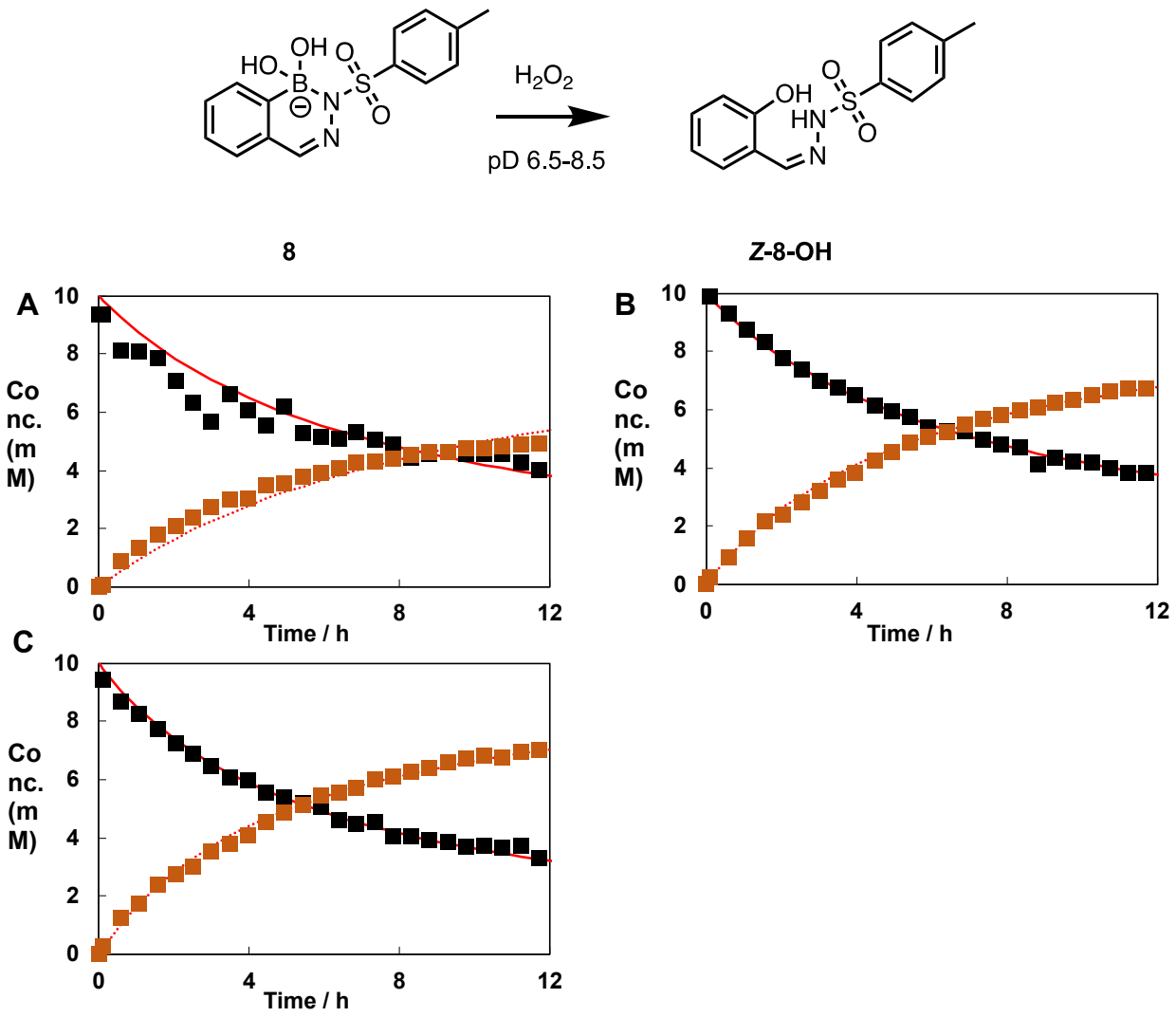
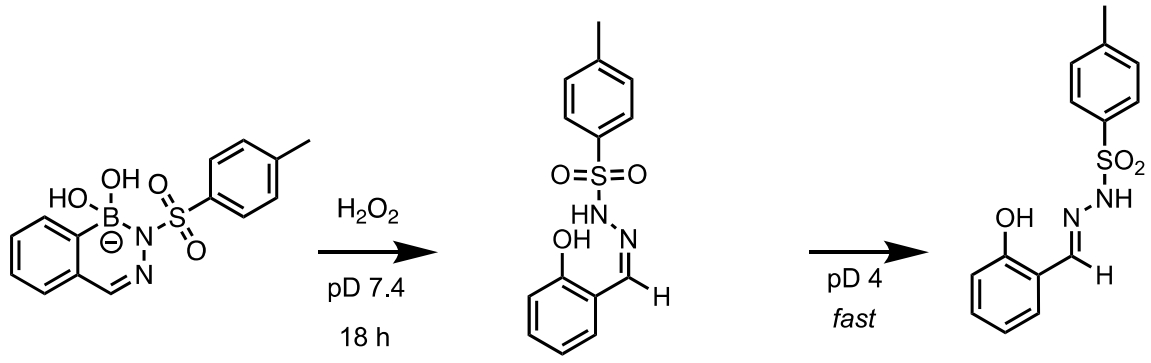


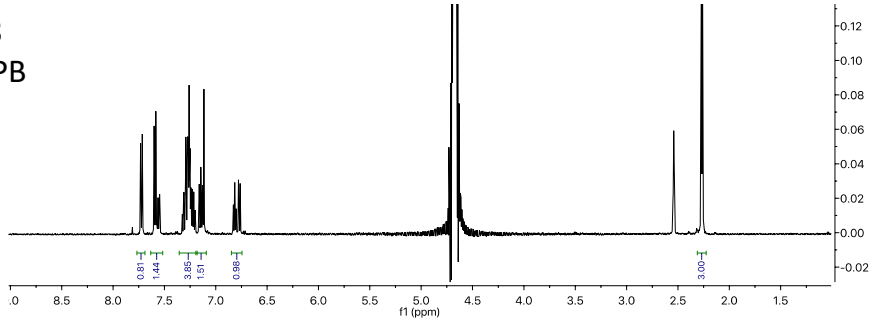
Figure S55. Oxidation of **8** with H_2O_2 at (A) pD 6.5; (B) pD 7.4; and (C) pD 8.5. DAB **8** (10 mM) was prepared in 200 mM PB in D_2O at the indicated pD and treated with H_2O_2 (1 equivalent). The samples were monitored by ^1H NMR. Datapoints represent the indicated species as a function of time. Black squares indicate the concentration of DAB **8**; orange squares indicate the concentration of the phenol *Z*-isomer. Red lines represent a fit to a second-order kinetic model. DAB **8** concentration was determined by integrating the peak at a resonance of 7.71. *Z*-isomer phenol concentration was determined by integrating the peaks at a resonance of 6.75 and 6.79.

17. Effect of pH on *Z*-isomer formed from DAB **8**.

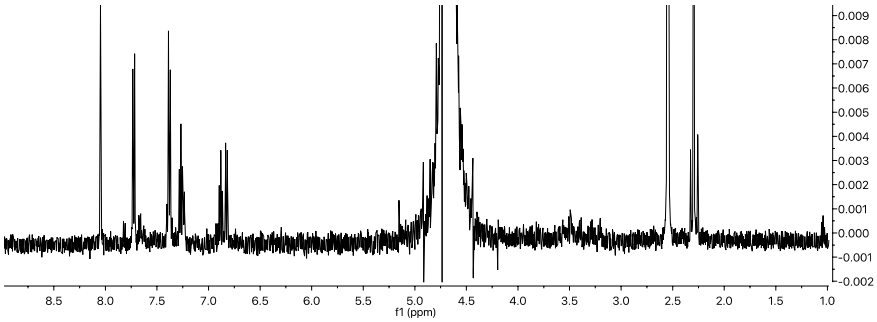


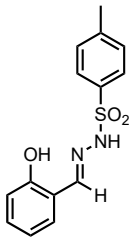
8 **8-OH (*Z*)** **8-OH (*E*)**

Intermediate of **8**
pD 7.4, 200 mM PB



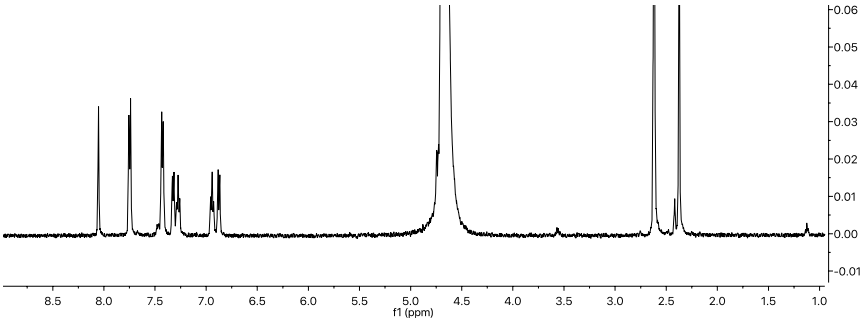
Adjust pD to ~4





8-OH

in pD 4 D_2O



F 8-OH (Z)
mM) in 200 mM PB buffer, pD 7.4 was treated with H_2O_2
(10 allowed to react for 18 h to form the *Z*-isomer (top). Adjusting the pD

to 4 prompts rapid conversion to **8-OH** (middle; taken ~5 minutes after pD adjustment). A reference spectrum of **8-OH**, independently synthesized from salicylaldehyde and tosylhydrazide in pD 4 D_2O is also shown (bottom).

18. 2-carboxyphenylboronic acid does not oxidize with $ONOO^-$

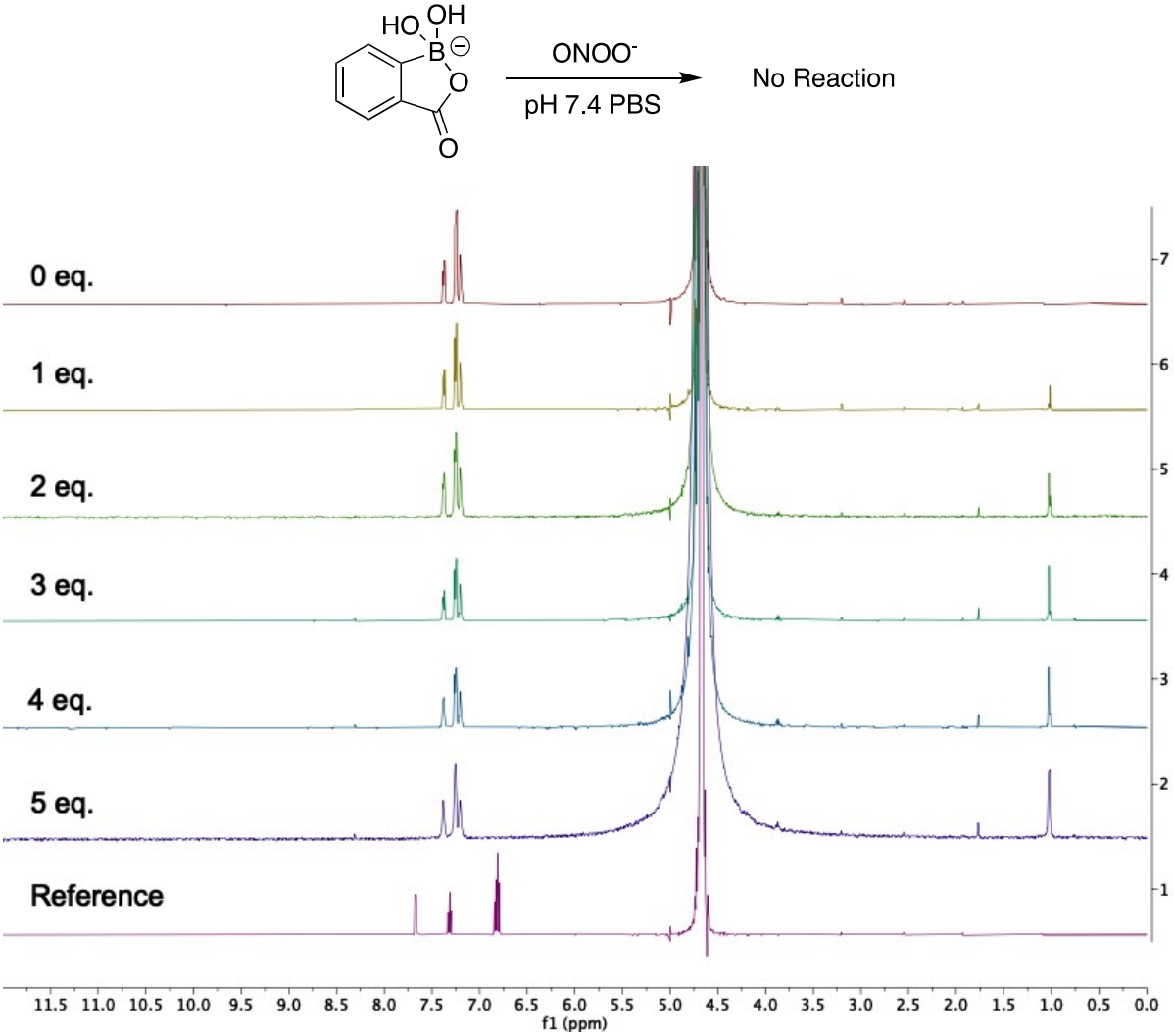
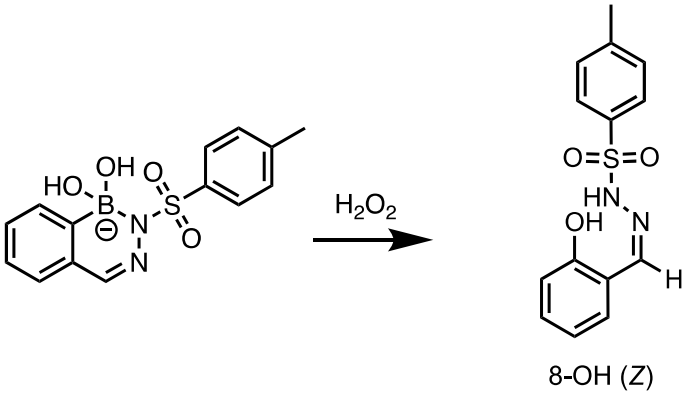


Figure S57. ^1H NMR spectra of 2-carboxyphenylboronic acid (5 mM) in PB buffer (200 mM, pD 7.4) with $ONOO^-$. 1 equivalent (5 mM) aliquots were added with spectra collected immediately after addition. A reference spectrum for phenol also included.

19. ^{11}B NMR of *Z*-isomer formation and conversion to phenol



8-OH (*Z*)

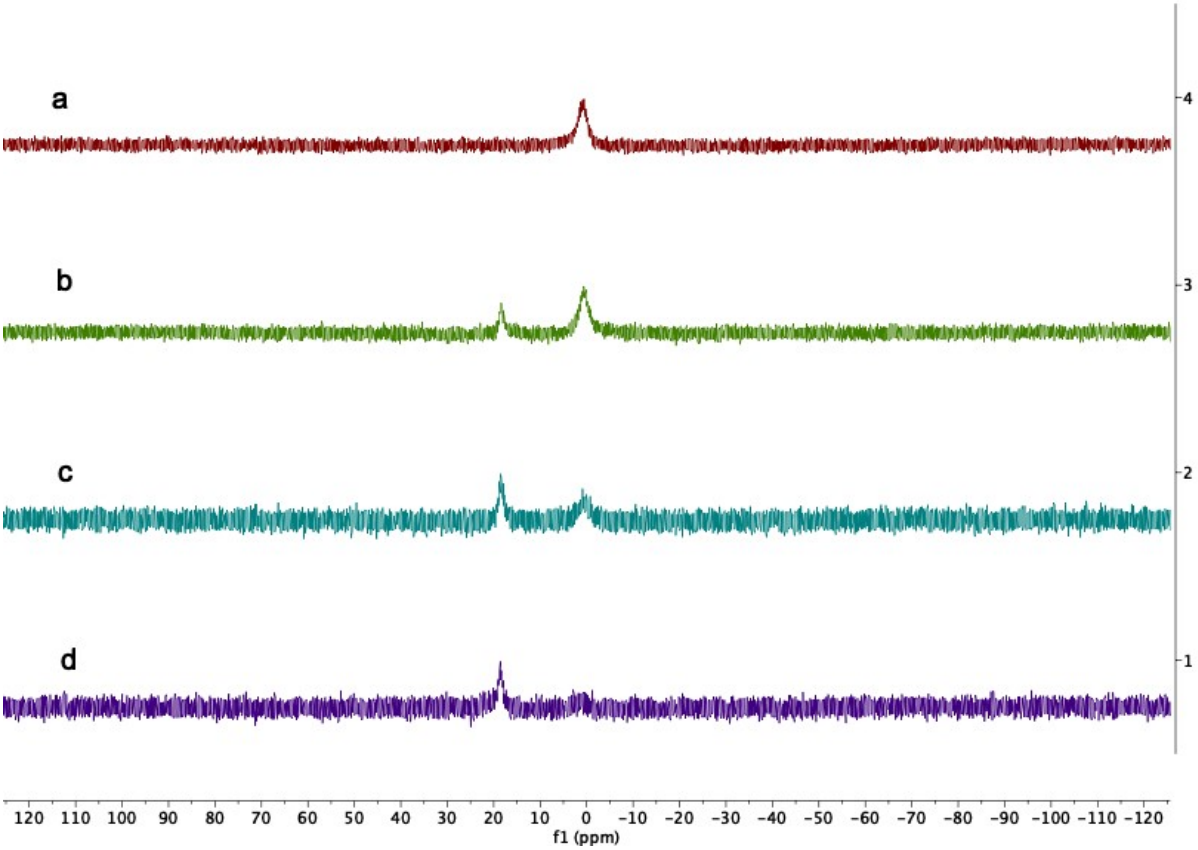
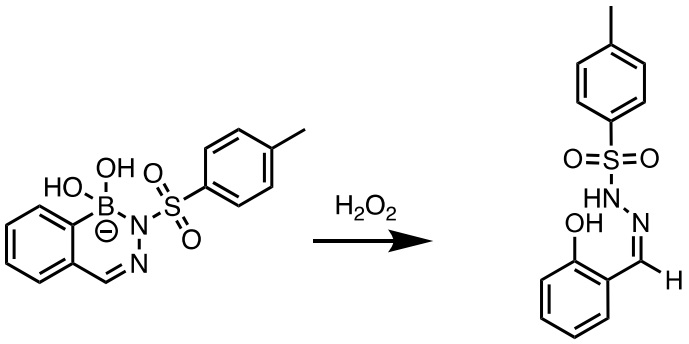


Figure S58. ^{11}B NMR spectra of the H_2O_2-mediated oxidation of **8** at t = 0 (a), 3 hours (b), 6 hours (c), and 28 hours (d). With complete consumption of starting material but no *E*-isomer present by ^{1}H NMR, only a signal for borate is seen.



8-OH (*Z*)

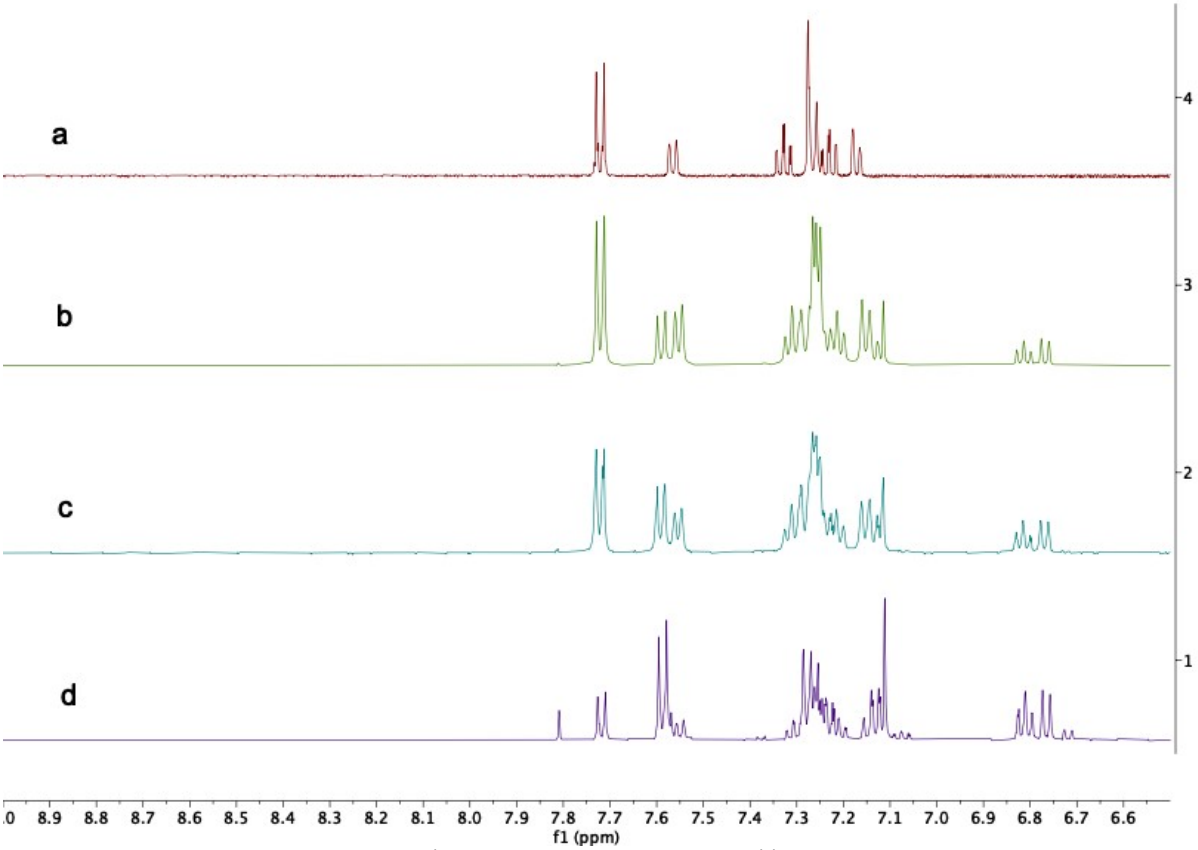


Figure S59. Corresponding ^{1}H NMR spectra of **8** ^{11}B NMR experiment (Fig S58).

20. Absorbance Spectra of **8**, **8-OH** (*Z*), and **8-OH** (*E*)

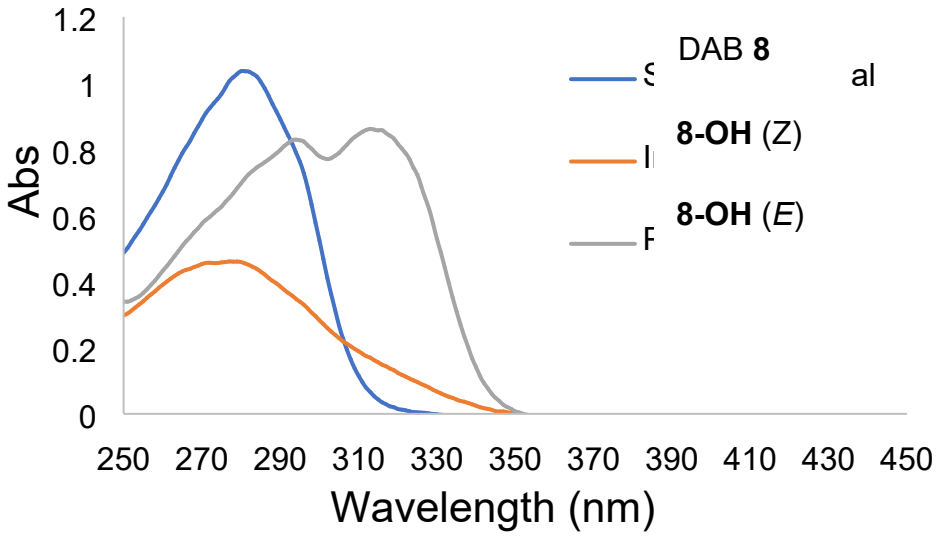
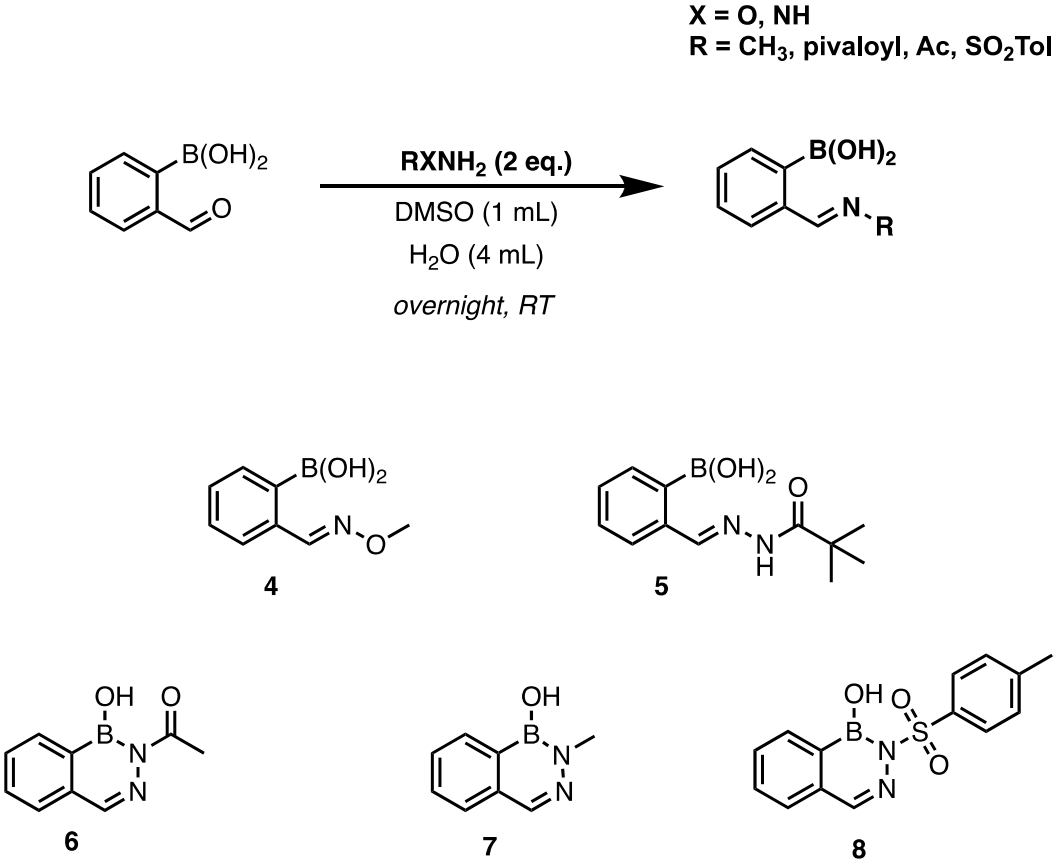


Figure S60. Absorbance spectra of **8**, oxidation *Z*-isomer, and **8-OH**. The *Z*-isomer was formed by treating **8** with 1 eq. of H_2O_2 and incubating at room temperature for 15 hours. *Z*-isomer formation was confirmed by ^{1}H NMR.

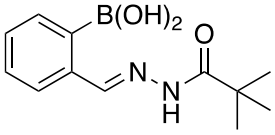
20. Synthesis of o-phenylboronic acids



Scheme S1. General procedure to synthesize hydrazone, oxime, and diazaborines from 2-formylphenylboronic acid (2-fPBA).

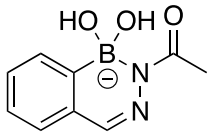
Synthesis of **3**. *O*-methylhydroxylamine hydrochloride (470 mg, 5.3 mmol) was dissolved in phosphate buffer (4 mL, 1.0 M, pH 7.4). The pH was monitored with pH paper and adjusted to pH 7.4 as necessary with NaOH in water (2.0 M). Separately, 2-formylphenylboronic acid (427 mg, 2.7 mmol) was dissolved in DMSO (1 mL) and added to the *O*-methylhydroxylamine hydrochloride phosphate solution. After stirring the reaction mixture overnight, a white precipitate formed. The precipitate was filtered, rinsed with dd-H_2O, dried *in vacuo*, and obtained as white powder (206 mg, 43%). E/Z isomers are observed. ^{1}H NMR (500 MHz, Deuterium Oxide) δ 8.25 (s, 1H), 7.43 (d, *J* = 17.0 Hz, 2H), 7.36 (d, *J* = 9.3 Hz, 2H), 3.83 and 3.76 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.92, 150.42, 136.87, 135.51, 135.10, 134.43, 129.62, 129.21, 125.77, 61.95. HRMS (ESI-TOF) m/z [M-H] Calculated: 339.1330; Found: 339.1329

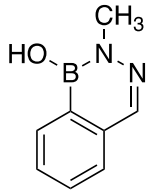
Synthesis of **5**. **5** was prepared according to a previously published procedure.[1]



^{1}H NMR (500 MHz, Deuterium Oxide) δ 8.50 (s, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.42 (d, *J* = 30.8 Hz, 2H), 1.17 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.33, 148.78, 138.09, 134.61, 130.40, 128.63, 126.47, 38.29, 27.68. HRMS (ESI-TOF) m/z [M-H] Calculated: 247.1254; Found: 247.1256

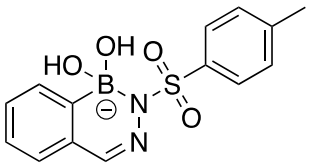
Synthesis of **6**. Acetohydrazide (397.9 mg, 5.3 mmol) was dissolved in dd-H_2O (4 mL). Separately, 2-formylphenylboronic acid (403.4 mg, 2.7 mmol) was dissolved in 1 mL of DMSO and added to the acetohydrazide solution. After stirring the reaction mixture overnight at room temperature, white precipitate formed. The precipitate was filtered, rinsed with dd-H_2O, dried *in-vacuo*, and obtained as white powder (447 mg, 81%). ^{1}H NMR (500 MHz, Deuterium Oxide) δ 7.53 (d, *J* = 7.3 Hz, 1H), 7.44 (s, 1H), 7.34 (d, *J* = 15.9 Hz, 1H), 7.24 (s, 2H), 2.18 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 177.64, 149.56, 131.17, 130.21, 130.18, 128.41, 128.31, 18.62. HRMS (ESI-TOF) m/z [M-H] Calculated: 205.0790; Found: 205.0786

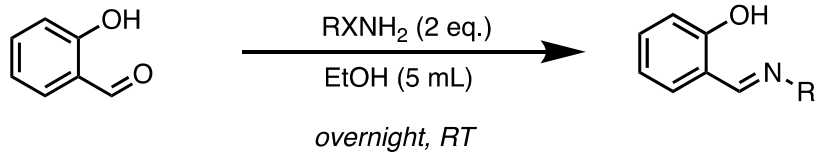


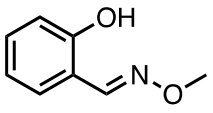


Synthesis of **7.** 2-formylphenylboronic acid (384 mg, 2.7 mmol) was dissolved in ethanol (5 mL) and stirred at room temperature. Methylhydrazine (419 µL, 8.0 mmol) was added dropwise. After stirring the reaction overnight, the solvent was removed, and the remaining solid was dried *in* vacuo and obtained as a waxy, white solid (279 mg, 61%) ^{1}H NMR (500 MHz, Deuterium Oxide) δ 7.98 (d, *J* = 6.8 Hz, 1H), 7.89 (s, 1H), 7.65 (d, *J* = 7.1 Hz, 2H), 7.56 (d, *J* = 16.0 Hz, 1H), 3.41 (s, 3H). ^{13}C NMR (126 MHz, acetone-d_6 + 1 drop D_2O) δ 137.79, 135.99, 130.82, 128.54, 126.89, 38.40. HRMS (ESI-TOF) m/z [M-H] Calculated: 159.0735; Found: 159.0739.

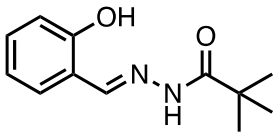
Synthesis of **8**. *para*-toluenesulfonyl hydrazide (1.0 g, 5.3 mmol) was dissolved in dd-H_2O (4 mL) and methanol (10 mL). 2-formylphenylboronic acid (390 mg, 2.6 mmol) was separately dissolved in DMSO (1 mL) and then added dropwise. After 5 minutes, a bright white precipitate began to form. The mixture stirred for 3 hours, after which the precipitate was collected by filtration. The precipitate was crystallized in hot ethanol and water, dried *in-vacuo*, and obtained as colorless needles (447 mg, 54.6%). ^{1}H NMR (500 MHz, Deuterium Oxide) δ 7.73 (s, 1H), 7.71 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 16.0 Hz, 1H), 7.28 (s, 2H), 7.26 (s, 1H), 7.23 (d, *J* = 16.3 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 144.99, 142.93, 137.06, 134.13, 133.21, 132.35, 131.15, 130.29, 128.43, 128.31, 23.25. HRMS (ESI-TOF) m/z [M-H] Calculated: 317.0773; Found: 317.0770.



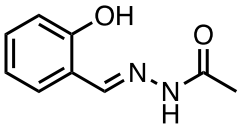




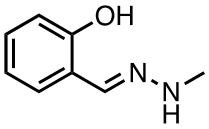
3-OH



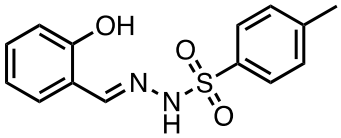
5-OH



6-OH



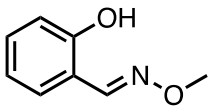
7-OH



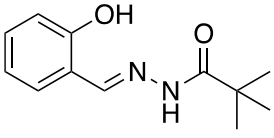
8-OH

Scheme S2. General procedure for the synthesis of *o*-phenols from salicylaldehyde.

Synthesis of **3-OH**. *O*-methylhydroxylamine hydrochloride (274.1 mg, 3.2 mmol) was dissolved in ethanol (5 mL). The pH was monitored with pH paper and adjusted to pH 7.4 with pyridine (1 mL). Salicylaldhyde (253.2 µL, 1.6 mmol) was added to the solution. After stirring the reaction mixture overnight, the mixture was taken up in EtOAc (5 mL), washed with dd-H_2O (5 mL, 2X), washed with saturated sodium chloride solution (5 mL, 1X), dried with anhydrous sodium sulfate, filtered, and condensed. The material was dried *in vacuo* to give a white solid (207.5 mg, 83.8%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.86 (s, 1H), 8.16 (s, 1H), 7.30 (s, 1H), 7.15 (d, *J* = 9.1 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 15.7 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.44, 150.75, 131.70, 130.03, 119.70, 117.33, 115.33, 62.60. HRMS (ESI-TOF) m/z [M-H] Calculated: 150.05605; Found: 150.0565.

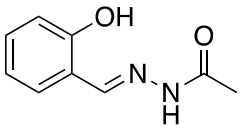


Synthesis of **5-OH**. Pivalohydrazide (380.6 mg, 3.3 mmol) was dissolved in ethanol (5 mL) in a 15 mL round-bottom flask.

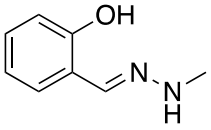


Salicylaldehyde (200 mg, 1.6 mmol) was added directly. After stirring the reaction mixture at room temperature overnight, dd-H_2O (10 mL) was added, and the mixture became cloudy. The reaction was extracted into dichloromethane (1 × 10 mL), washed with dd-H_2O (2 × 10 mL), washed with brine (1 × 10 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, dried under vacuum, and obtained as waxy, white solid (305 mg, 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.38 (s, 1H), 11.18 (s, 1H), 8.54 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 14.4 Hz, 1H), 6.90 (d, J = 14.7 Hz, 2H), 1.20 (s, 10H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.44, 160.20, 150.35, 134.32, 132.41, 121.98, 120.90, 118.74, 40.44, 29.79. HRMS (ESI-TOF) m/z [M-H] Calculated: 219.1134; Found: 219.1134.

Synthesis of **6-OH**.Acetohydrazide (148 mg, 2.0 mmol) was dissolved in dd-H_2O (4 mL) in a 15 mL round-bottom flask. Separately, salicylaldehyde (122 mg, 1.0 mmol) was added to DMSO (1 mL) and then added to the acetohydrazide solution. After stirring the reaction mixture at room temperature overnight, a white precipitate formed. The precipitate was filtered, washed with dd-H_2O, dried *in vacuo*, and obtained as white powder (163 mg, 91%). Both E/Z isomers are observed by ^{1}H NMR and ^{13}C NMR in DMSO-d_6. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.58 (s, 0H), 11.18 (d, J = 21.1 Hz, 1H), 8.29 (s, 1H), 7.46 (d, J = 9.4 Hz, 1H), 7.21 (d, J = 39.8 Hz, 1H), 6.84 (d, J = 36.1 Hz, 2H), 2.14 (s, 1H), 1.94 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.05, 165.94, 157.83, 156.88, 146.77, 141.32, 131.69, 131.42, 129.47, 127.25, 120.53, 119.94, 119.80, 119.12, 116.85, 116.64, 22.50, 20.88. HRMS (ESI-TOF) m/z [M-H] Calculated: 177.0742; Found: 177.0664.

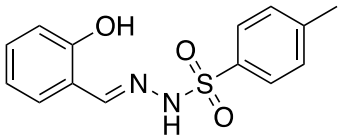


Synthesis of **7-OH**.



Salicylaldehyde (253.2 uL, 1.6 mmol) was dissolved in ethanol (5 mL). Methylhydrazine (171.5 uL, 3.3 mmol) was added dropwise. The reaction stirred at room temperature overnight. The solvent was removed by rotary evaporation, dried *in-vacuo*, and obtained as a waxy white solid (122 mg, 49.6 %). ^{1}H NMR (500 MHz, Deuterium Oxide) δ 7.76 (s, 1H), 7.20 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 15.0 Hz, 1H), 6.84 (d, J = 14.8 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 2.70 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 156.90, 140.53, 129.24, 119.40, 119.19, 116.51, 36.09.

Synthesis (**8-OH**)



p-Toluenesulfonyl hydrazide (632 mg, 3.3 mmol) was dissolved in methanol (5 mL) in a 15 mL round-bottom flask. Salicylaldehyde (200 mg, 1.6 mmol) was added. After stirring the reaction mixture at room temperature overnight, dd-H_2O (10 mL) was added, and a white precipitate immediately formed. The precipitate was filtered, washed with dd-H_2O, air-dried, and obtained as a white solid (354 mg, 74%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 (s, 1H), 10.20 (s, 1H), 8.17 (s, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 9.2 Hz,

1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 12.7 Hz, 1H), 6.83 (d, *J* = 25.0 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, DMOS-d_6) δ 159.26, 148.85, 146.32, 138.60, 134.21, 132.53, 130.20, 129.94, 122.18, 121.81, 118.95, 24.24. HRMS (ESI-TOF) m/z [M-H] Calculated: 290.07251; Found: 290.0717.

21. NMR spectra of synthesized materials

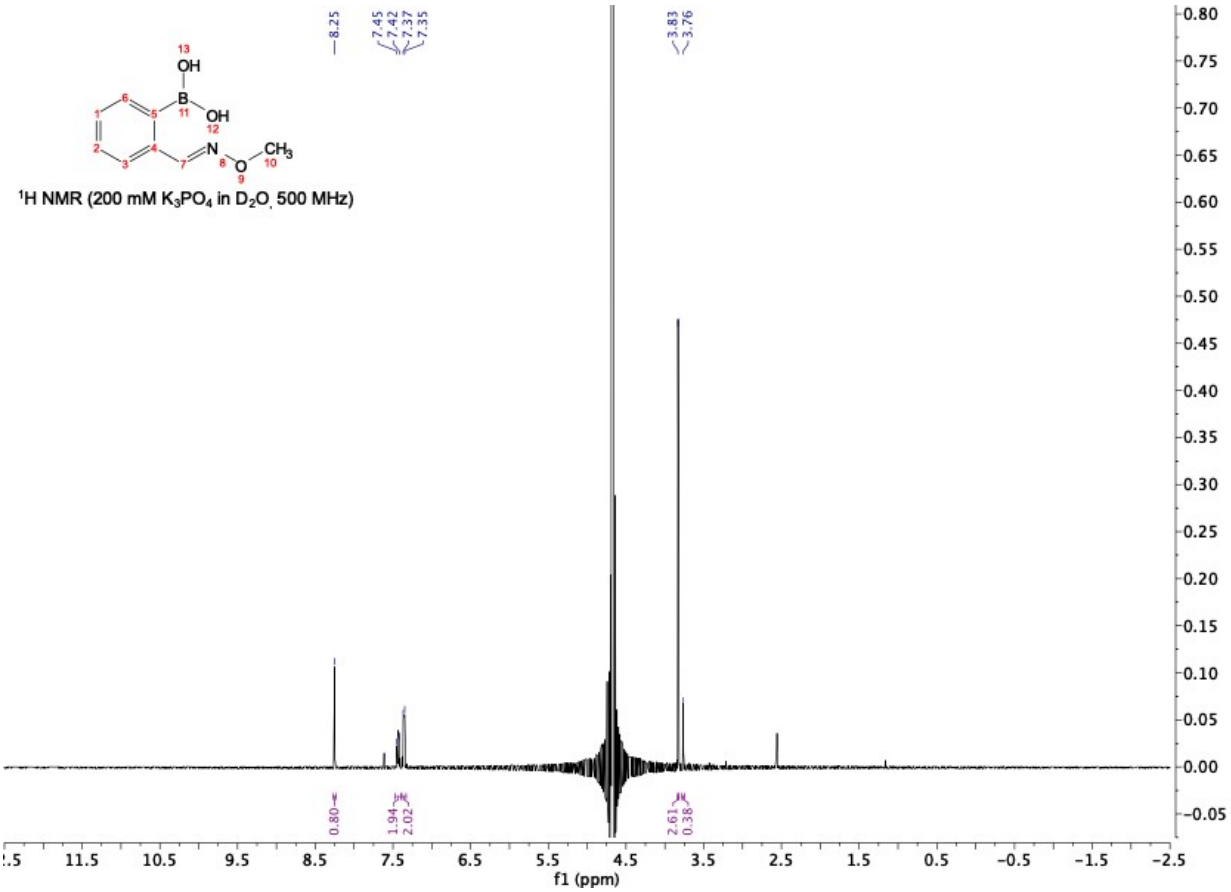


Figure S61. ^{1}H NMR spectrum of **3** in 200 mM K_3PO_4 in D_2O.

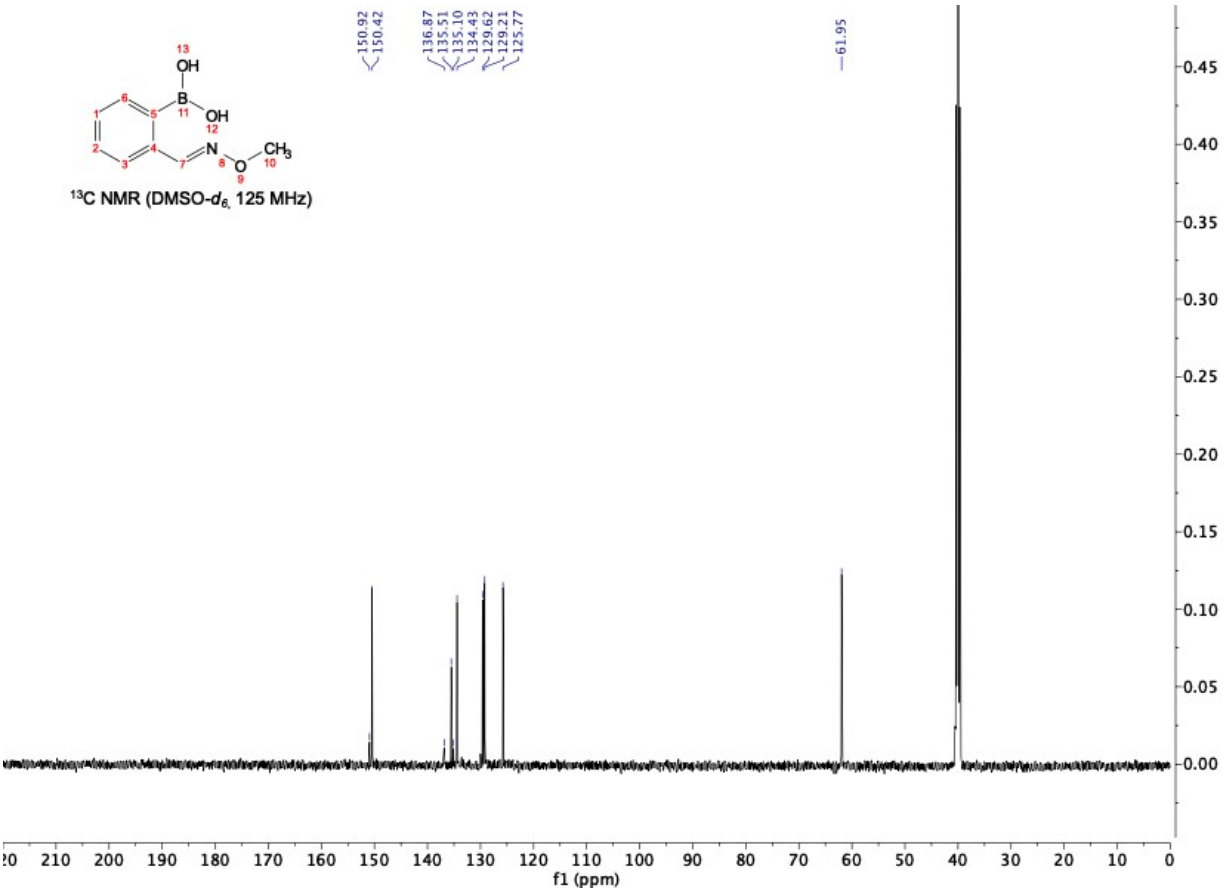


Figure S62. ^{13}C NMR spectrum of **3** in DMSO-d_6.

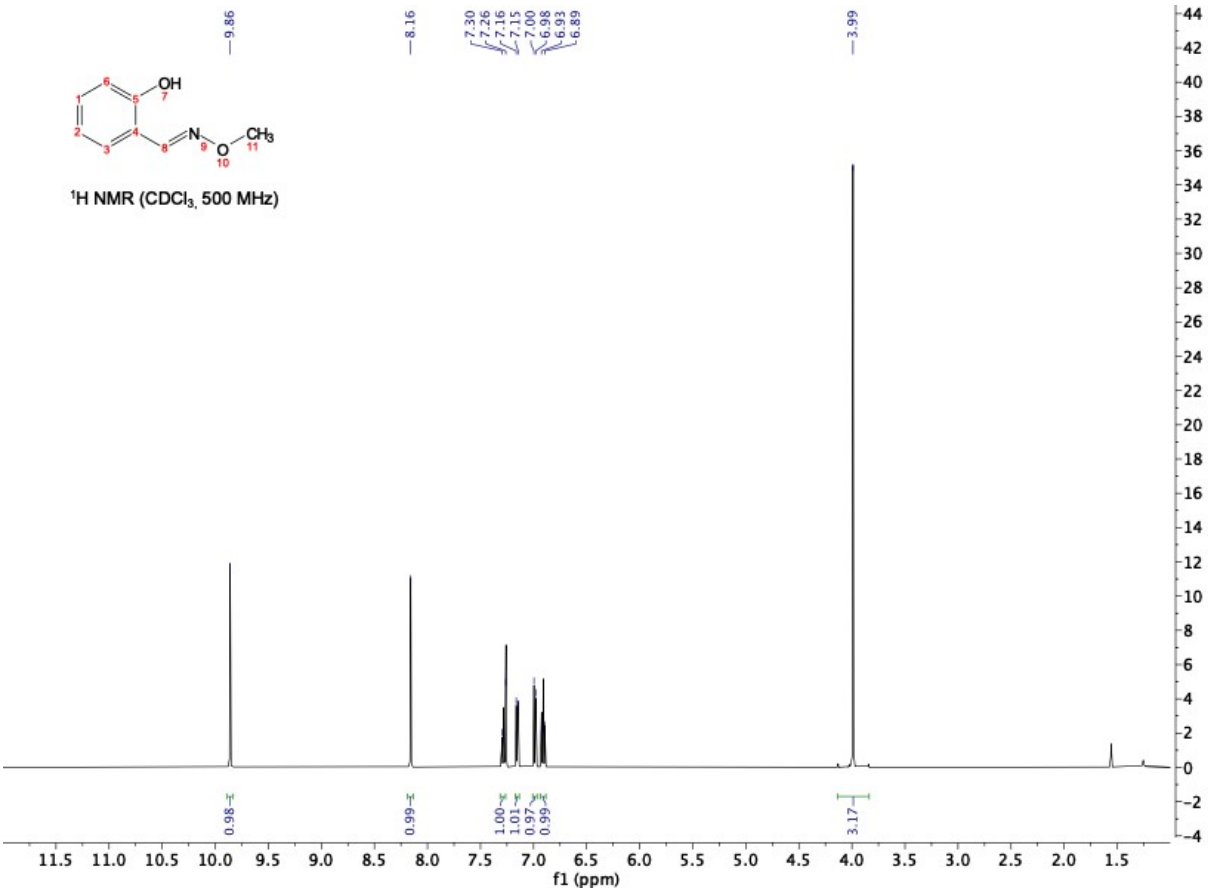


Figure S63. ^{1}H NMR spectrum of **3-OH** in $CDCl_3$.

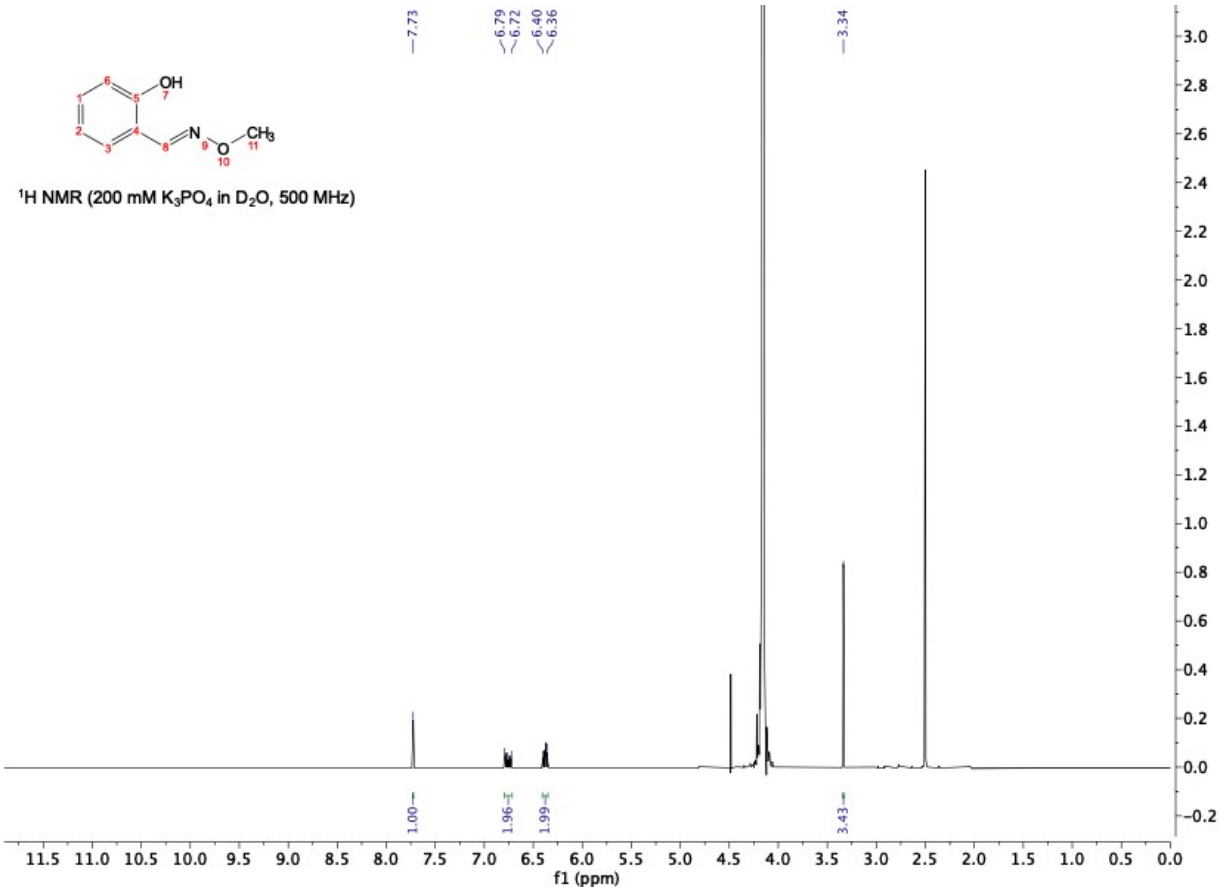


Figure S64. ^{1}H NMR spectrum of **3-OH** in pD 7.4 200 mM K_3PO_4 in D_2O.

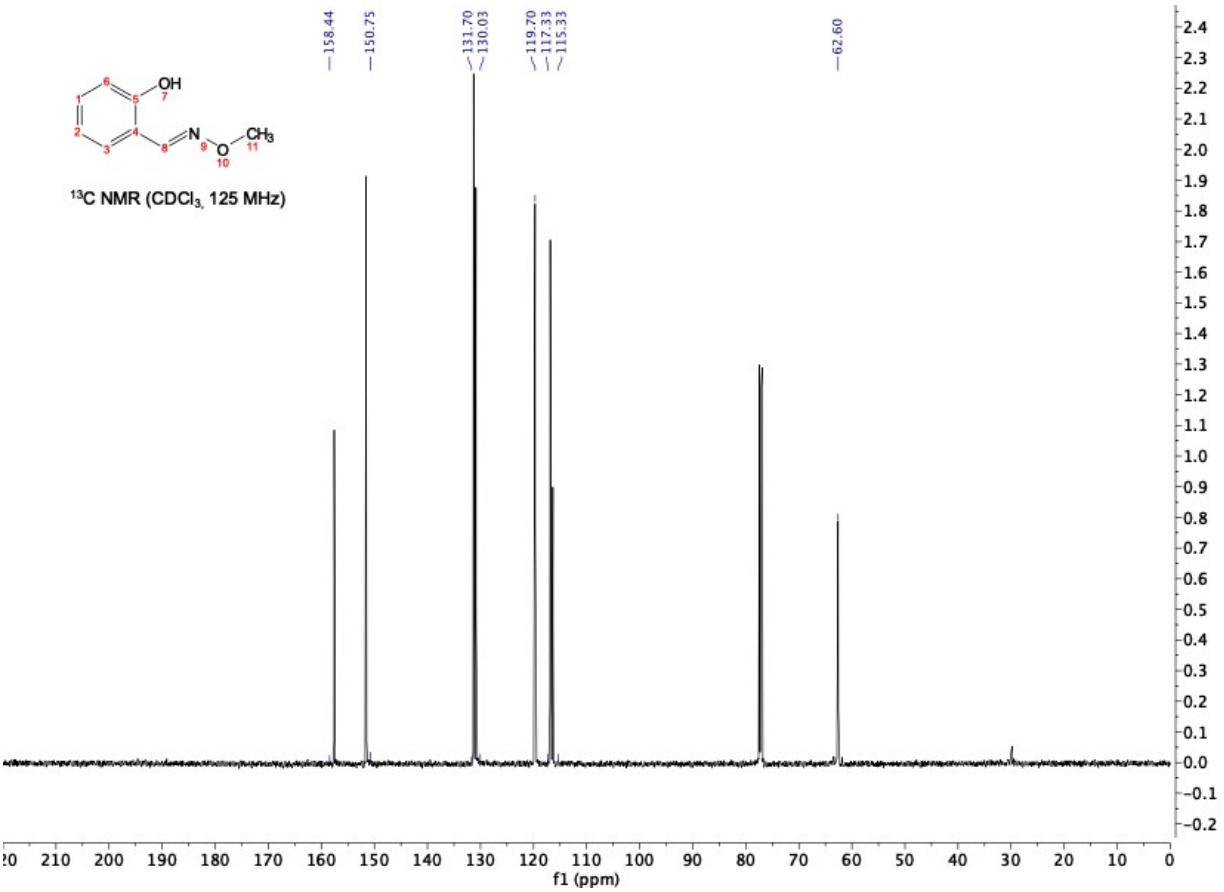


Figure S65. ^{13}C NMR spectrum of **3-OH** in $CDCl_3$.

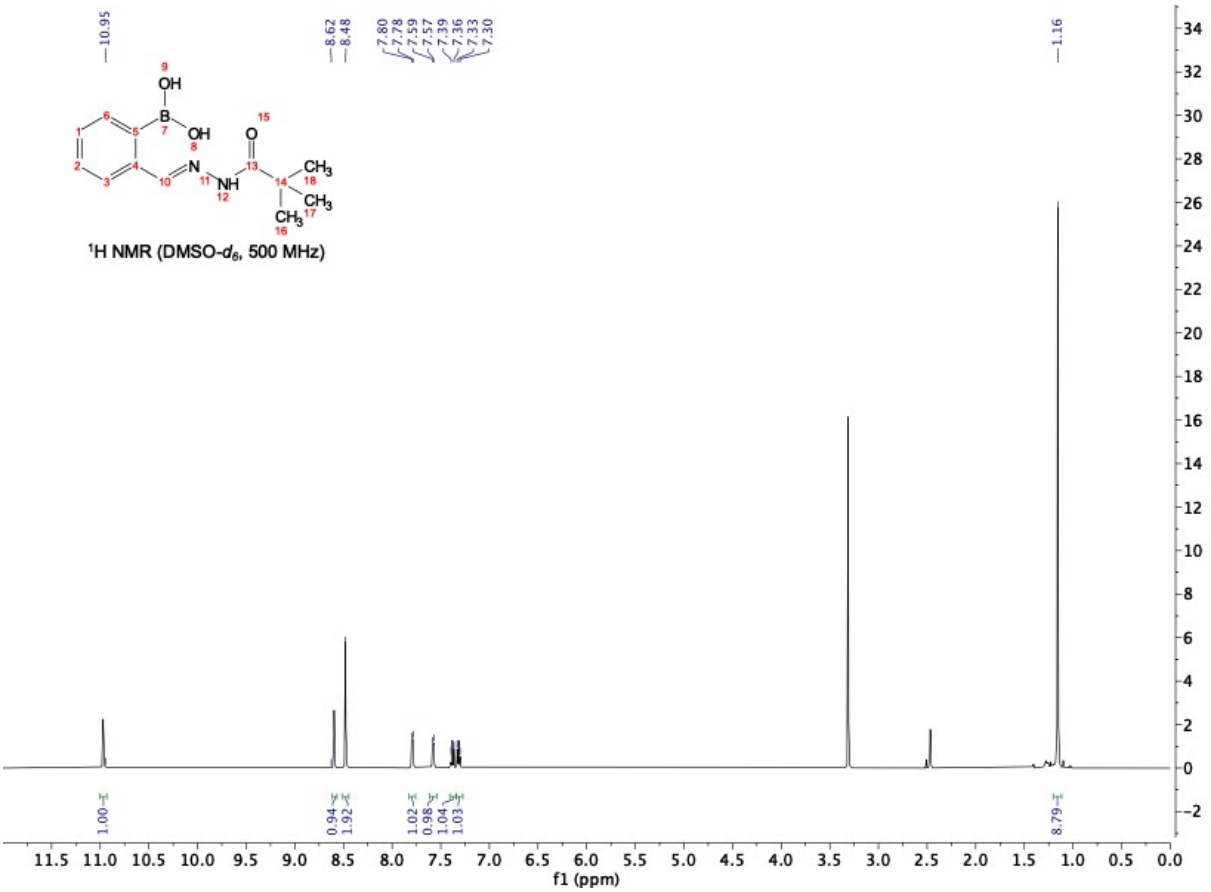


Figure S66. ^{1}H NMR spectrum of **5** in DMSO-d_6.

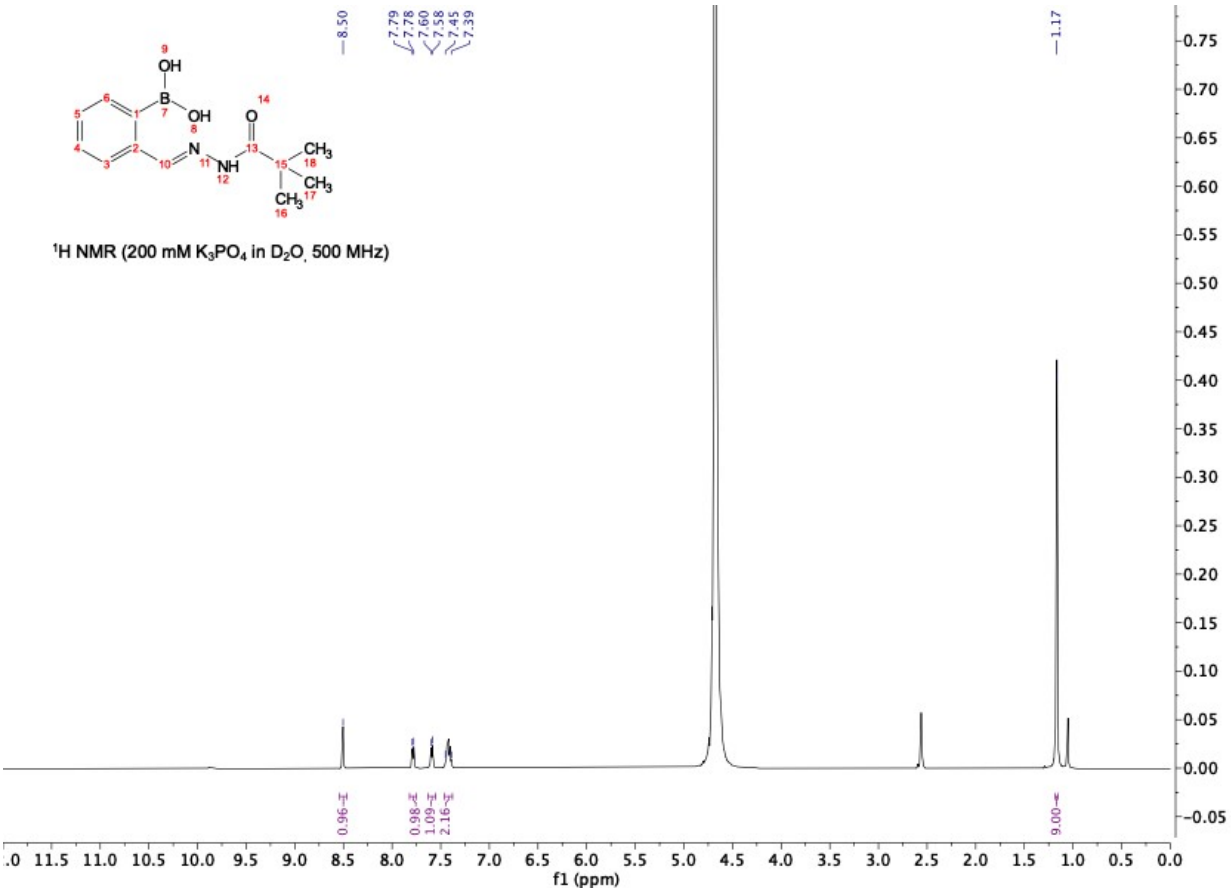


Figure S67. ^{1}H NMR spectrum of **5** in pD 7.4 200 mM K_3PO_4 in D_2O.

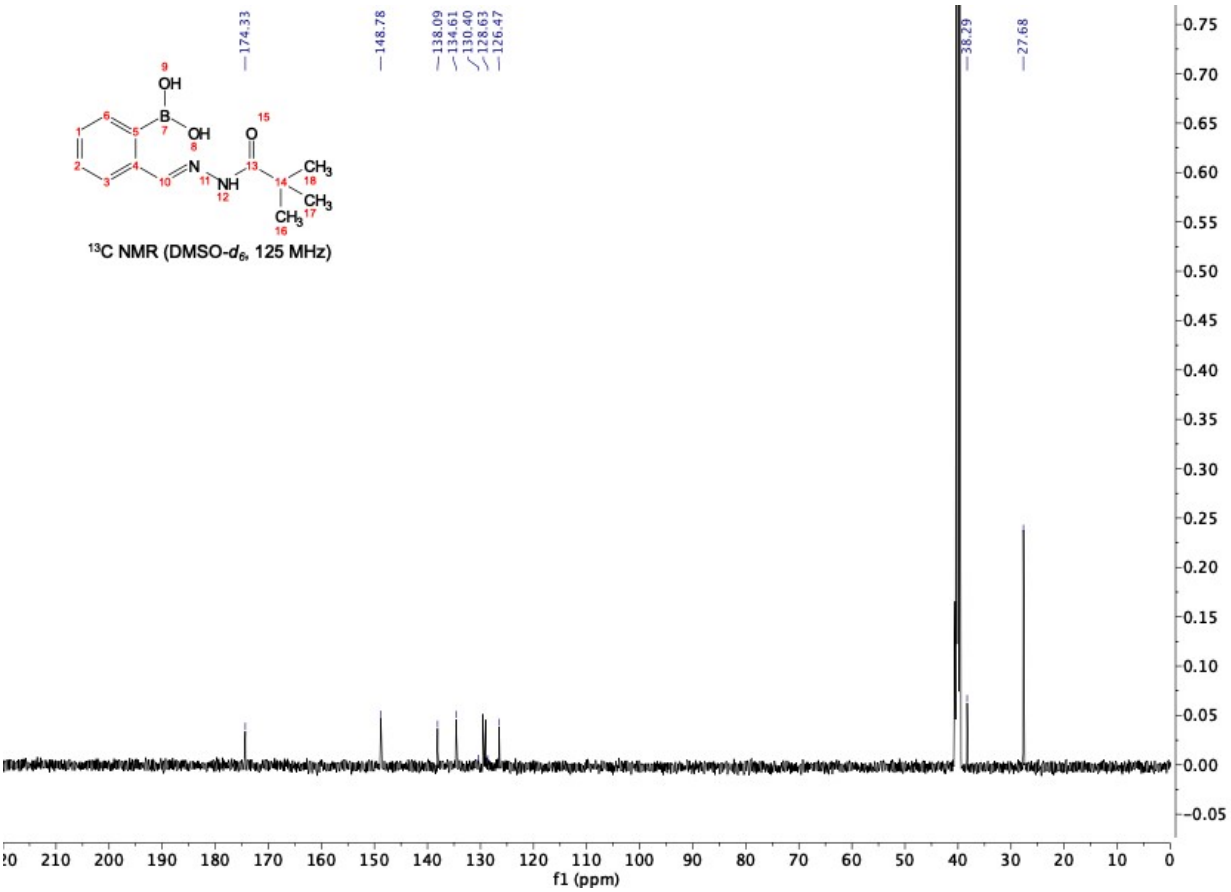


Figure S68. ^{13}C NMR spectrum of **5** in DMSO-d_6.

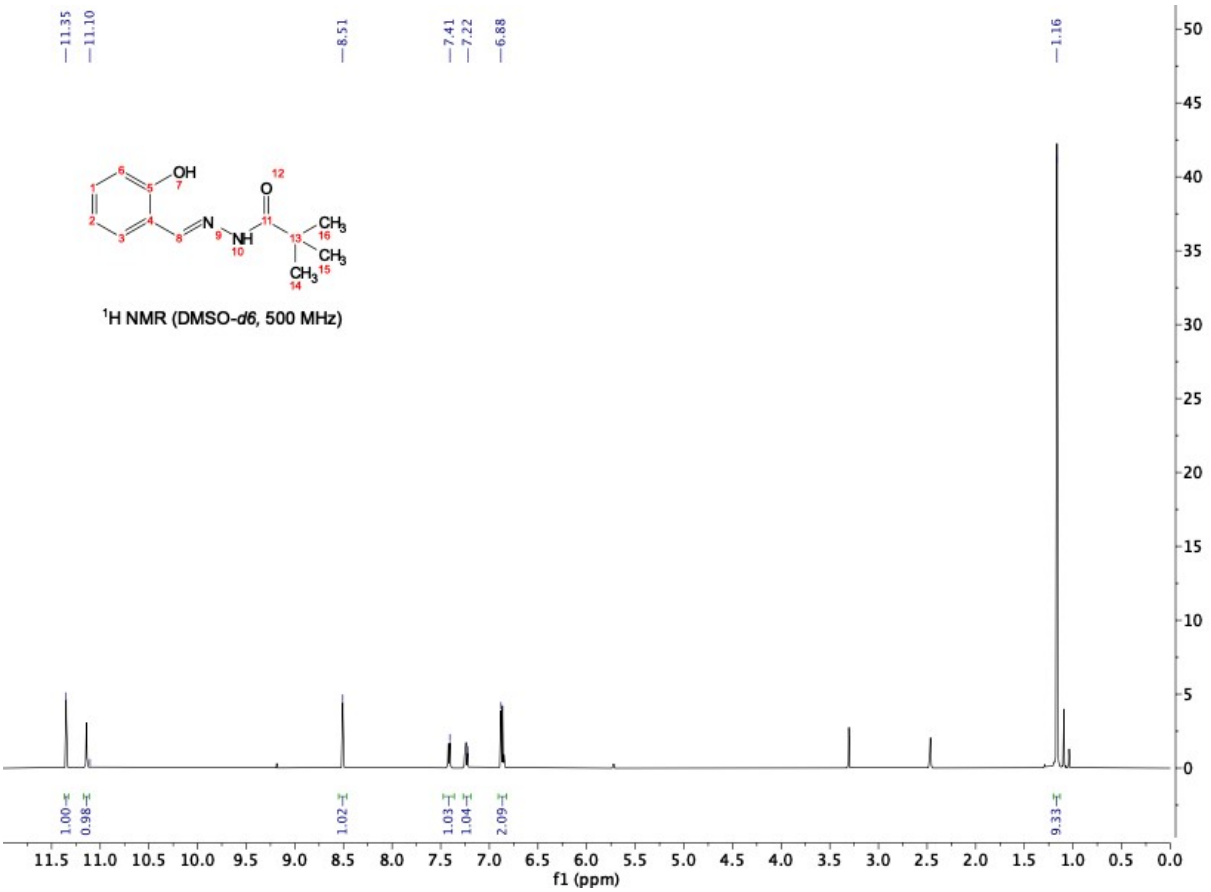


Figure S69. ^{1}H NMR spectrum of **5-OH** in DMSO-d_6.

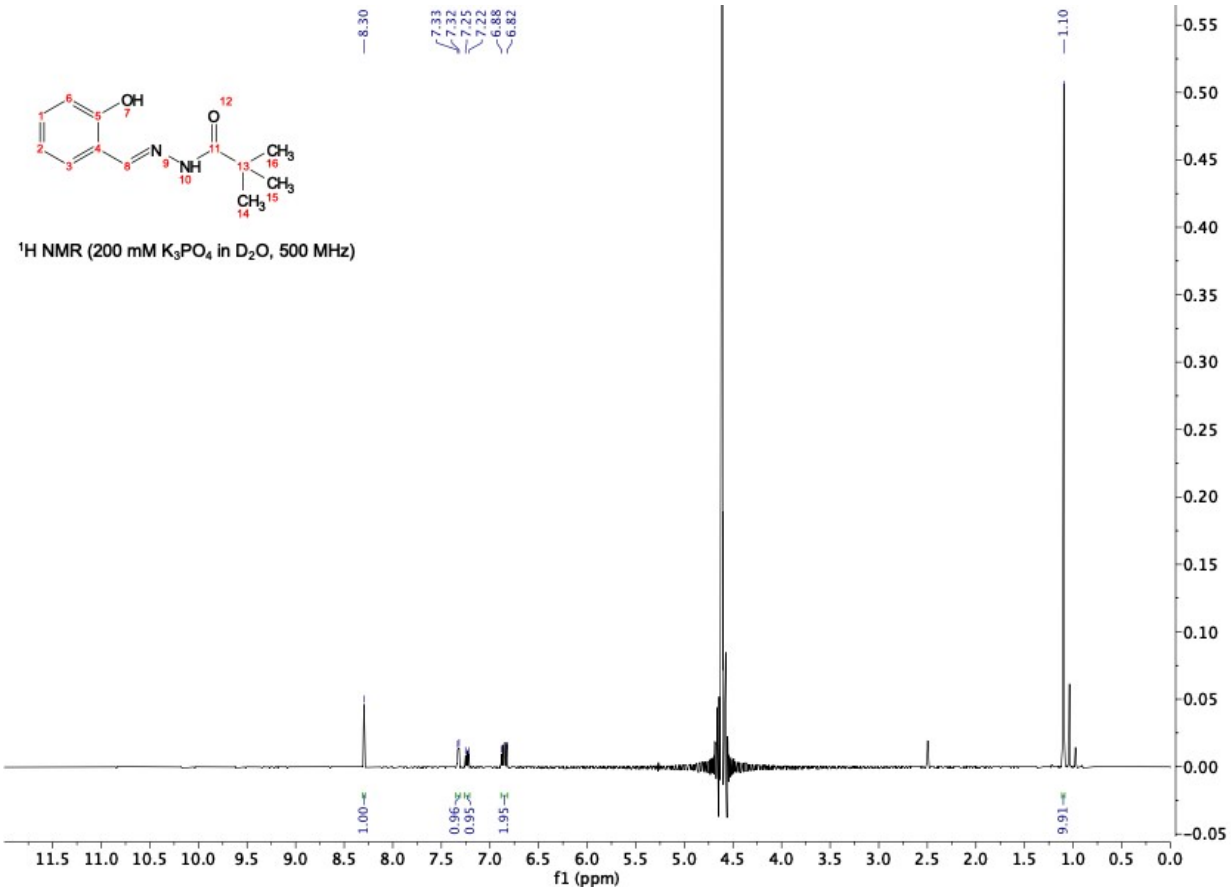


Figure S70. ^{1}H NMR spectrum of **5-OH** in 200 mM K_3PO_4 in D_2O.

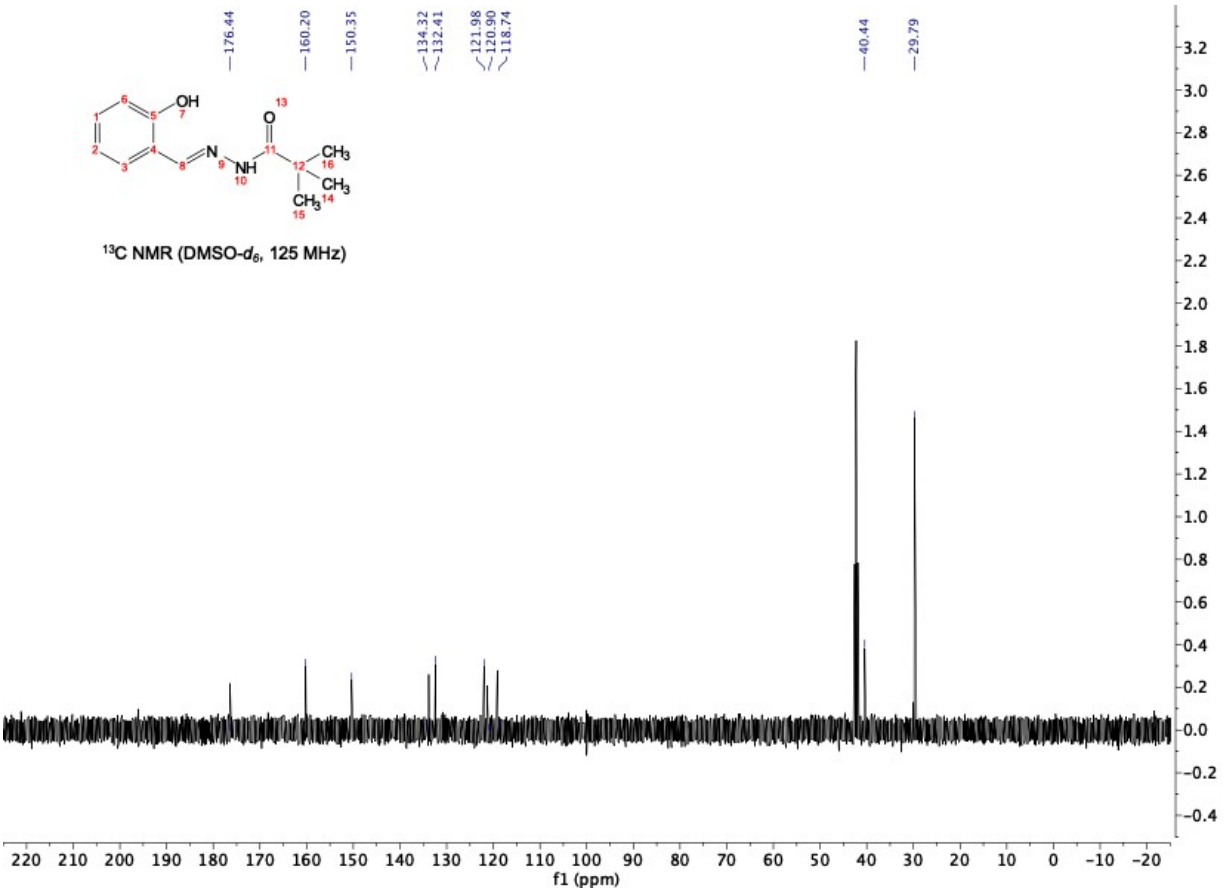


Figure S71.^{13}C NMR spectrum of **5-OH** in DMSO-d_6.

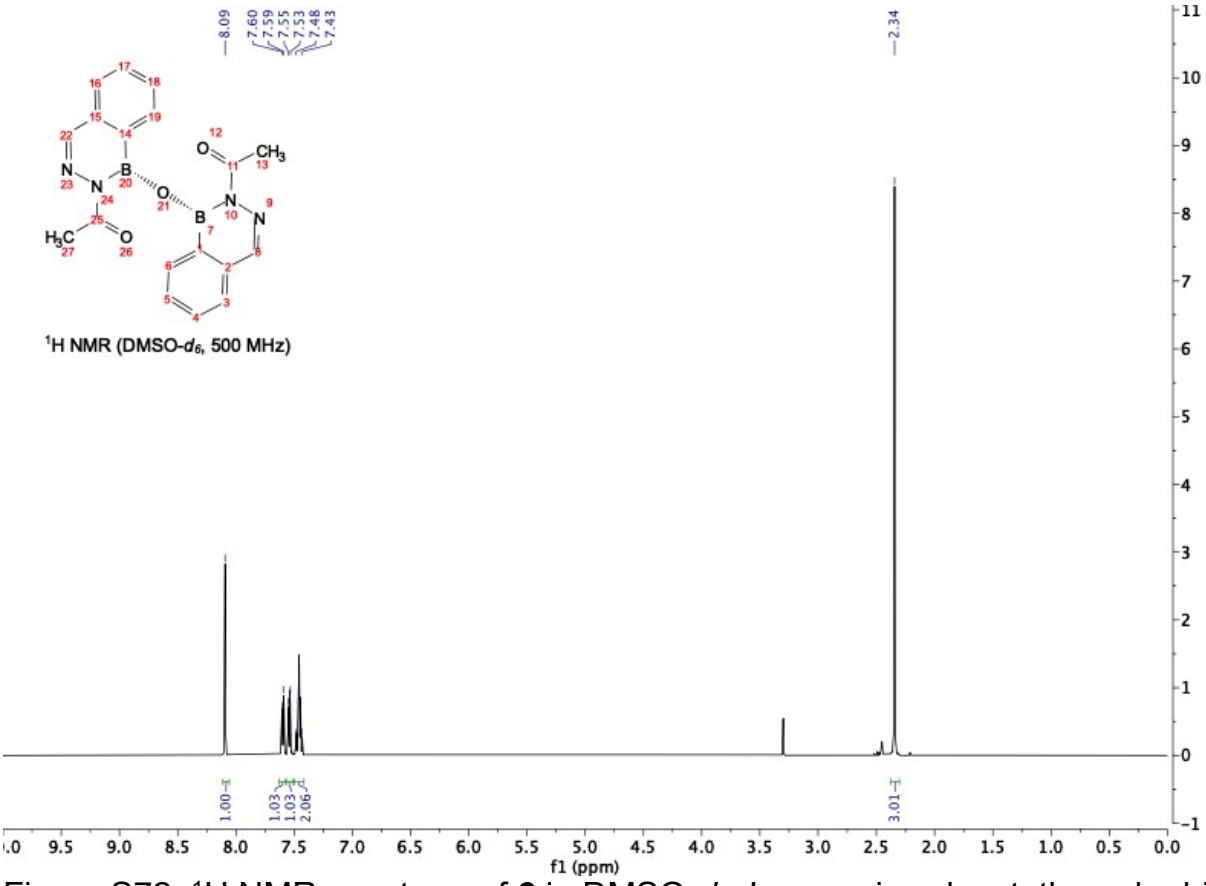


Figure S72. ^{1}H NMR spectrum of **6** in DMSO-d_6. In organic solvent, the anhydride dimer is observed.

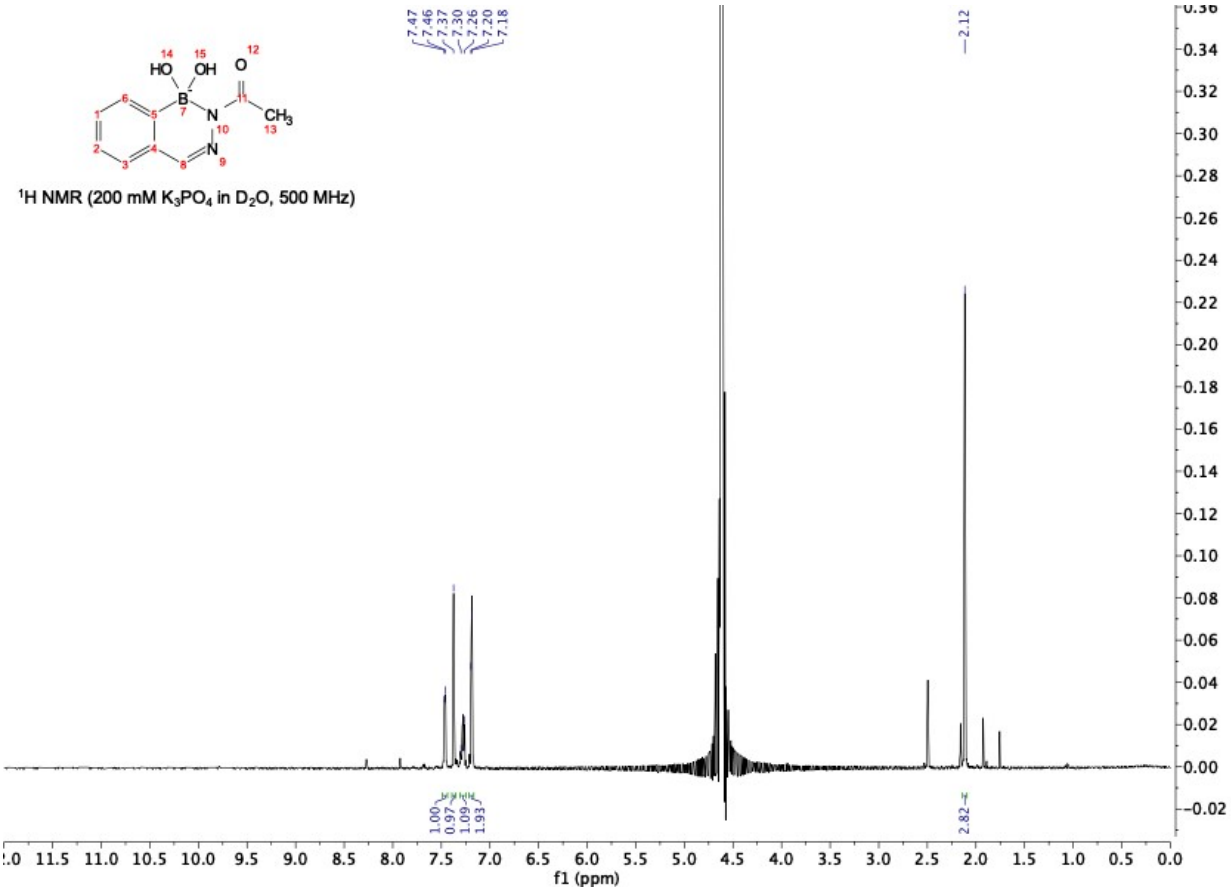


Figure S73. ^{1}H NMR spectrum of **6** in pD 7.4 200 mM K_3PO_4 in D_2O. Our data are in excellent agreement with Gu *et. al. Org. Biomol. Chem.*, *15*, **2017**, 7543-7548.

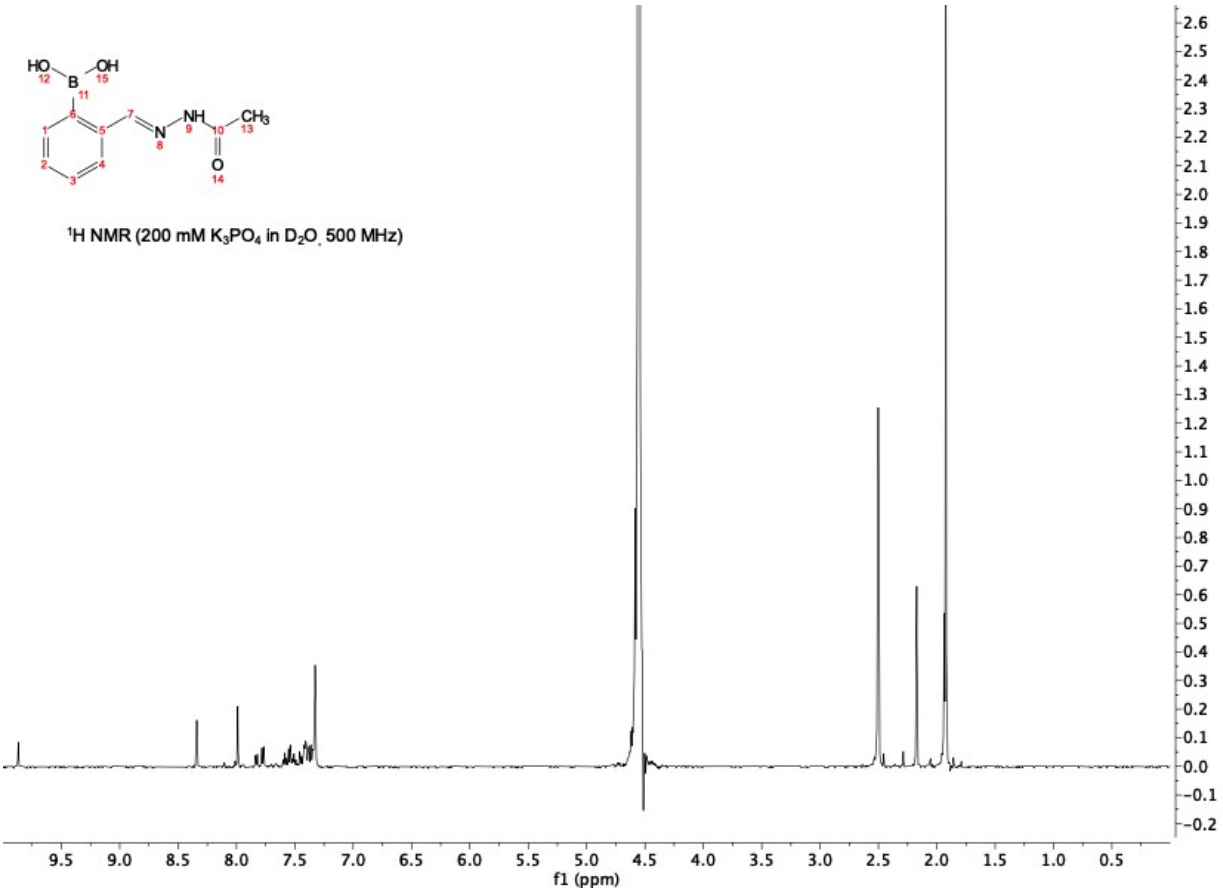


Figure S74. ^{1}H NMR spectrum of **6** in pD 4.0 200 mM K_3PO_4 in D_2O showing ring-opening of the DAB to the acyclic hydrazone in acidic conditions. Our data are in excellent agreement with Gu *et. al. Org. Biomol. Chem.*, *15*, **2017**, 7543-7548.

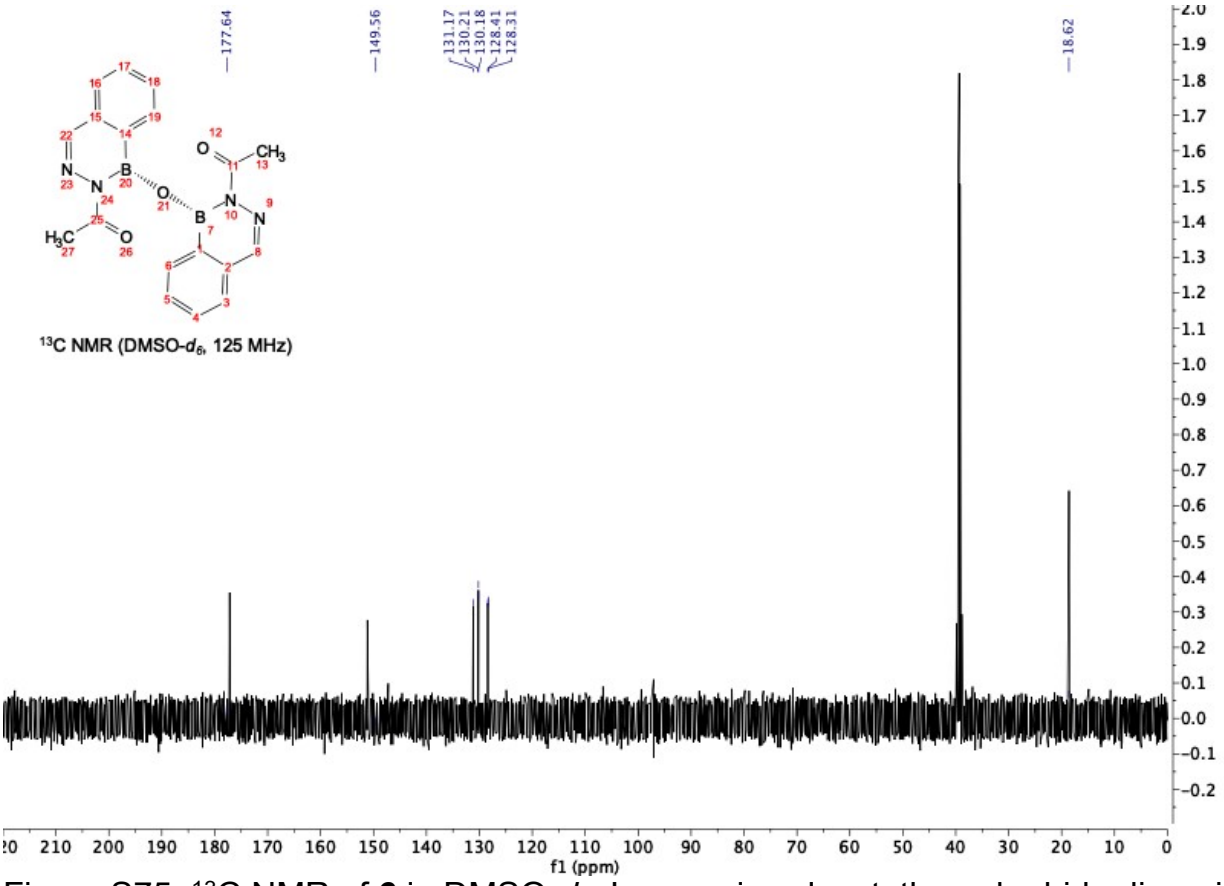


Figure S75. ^{13}C NMR of **6** in DMSO-d_6. In organic solvent, the anhydride dimer is observed.

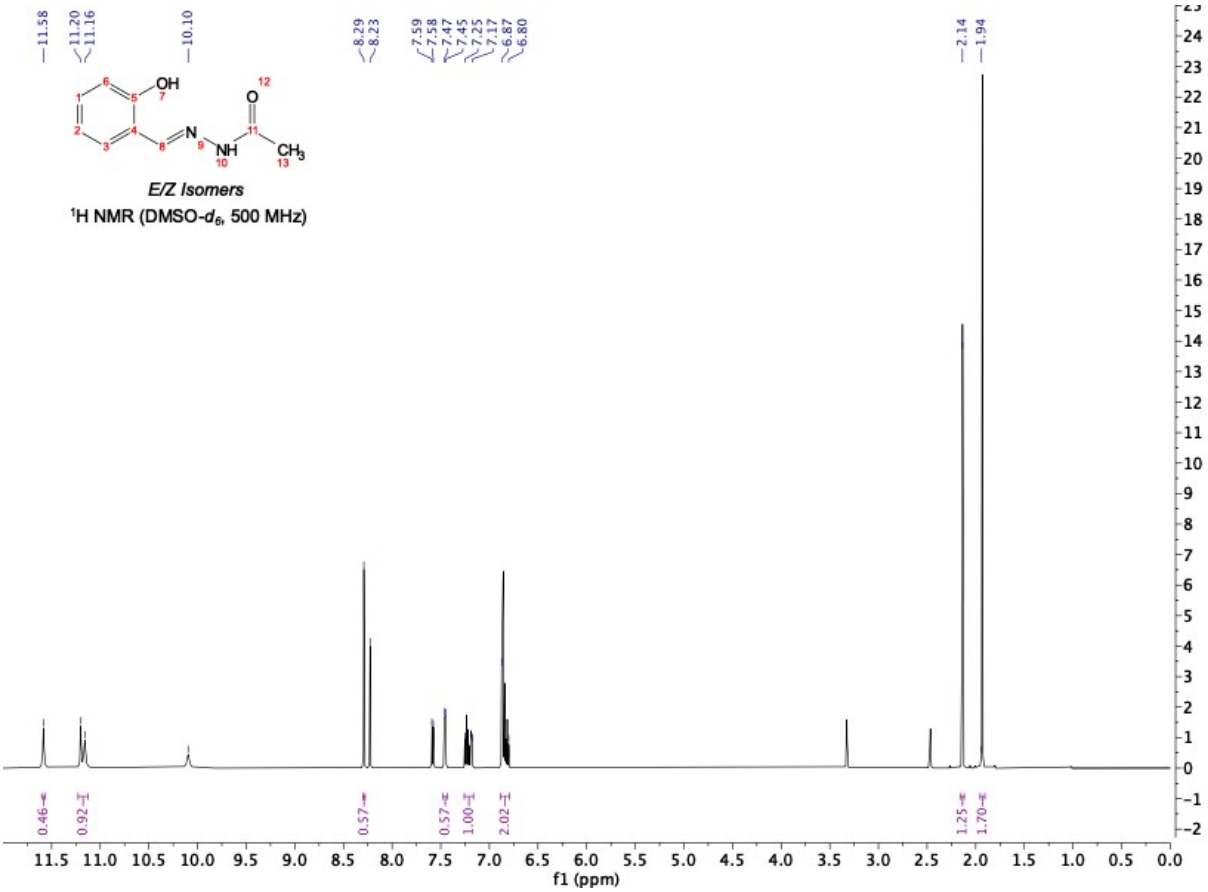


Figure S76. ^{1}H NMR of **6-OH** in DMSO-d_6. Amide E/Z isomers are observed.

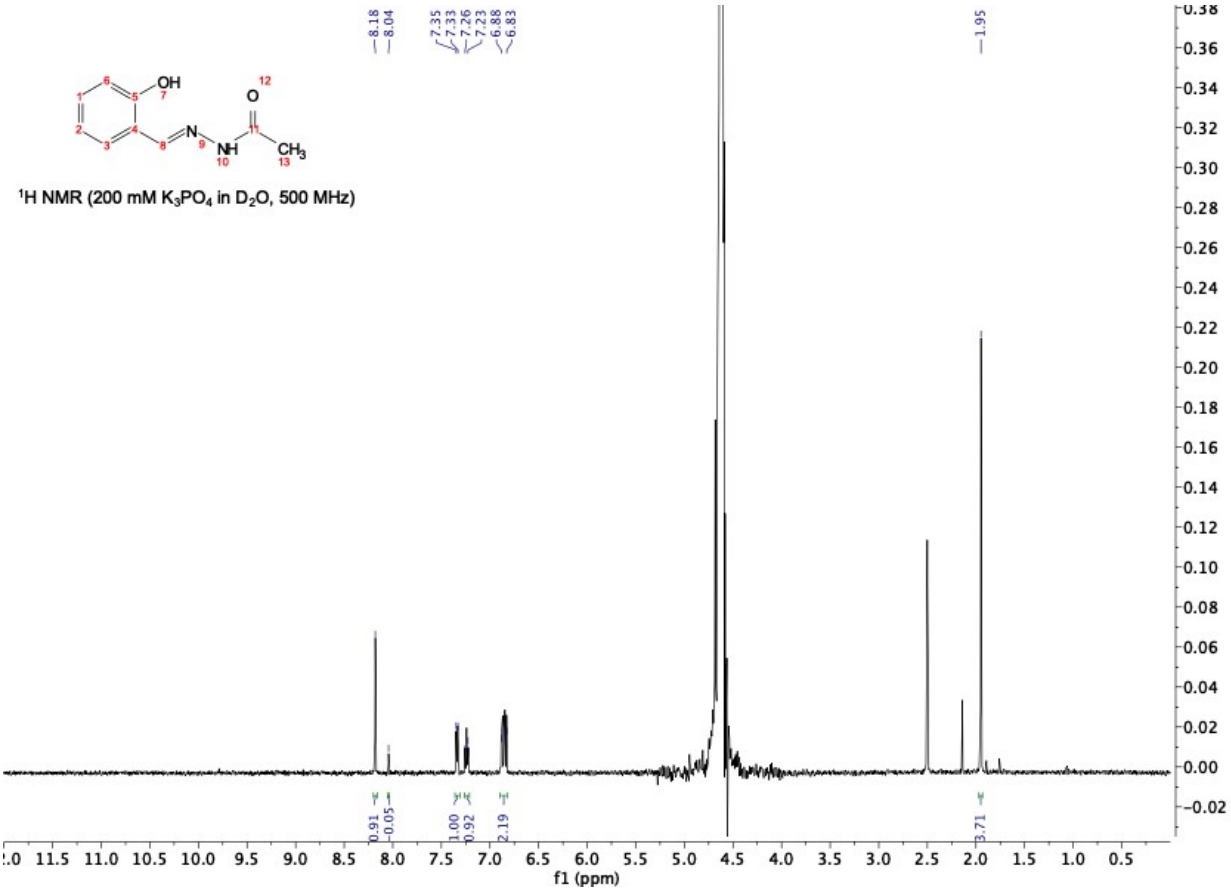


Figure S77. ^{1}H NMR of **6-OH** in pD 7.4 200 mM K_3PO_4 in D_2O.

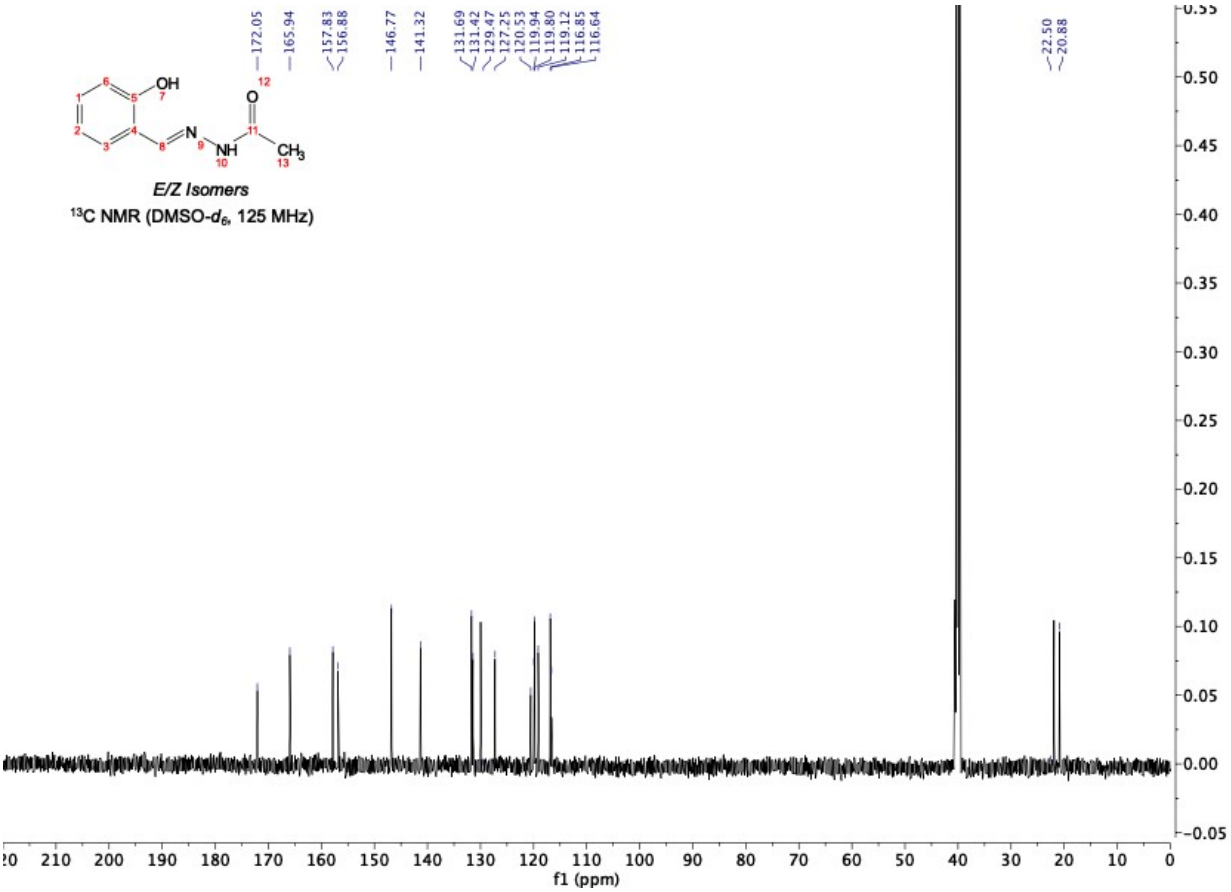


Figure S78. ^{13}C NMR of **6-OH** in DMSO-d_6. E/Z isomers are observed.

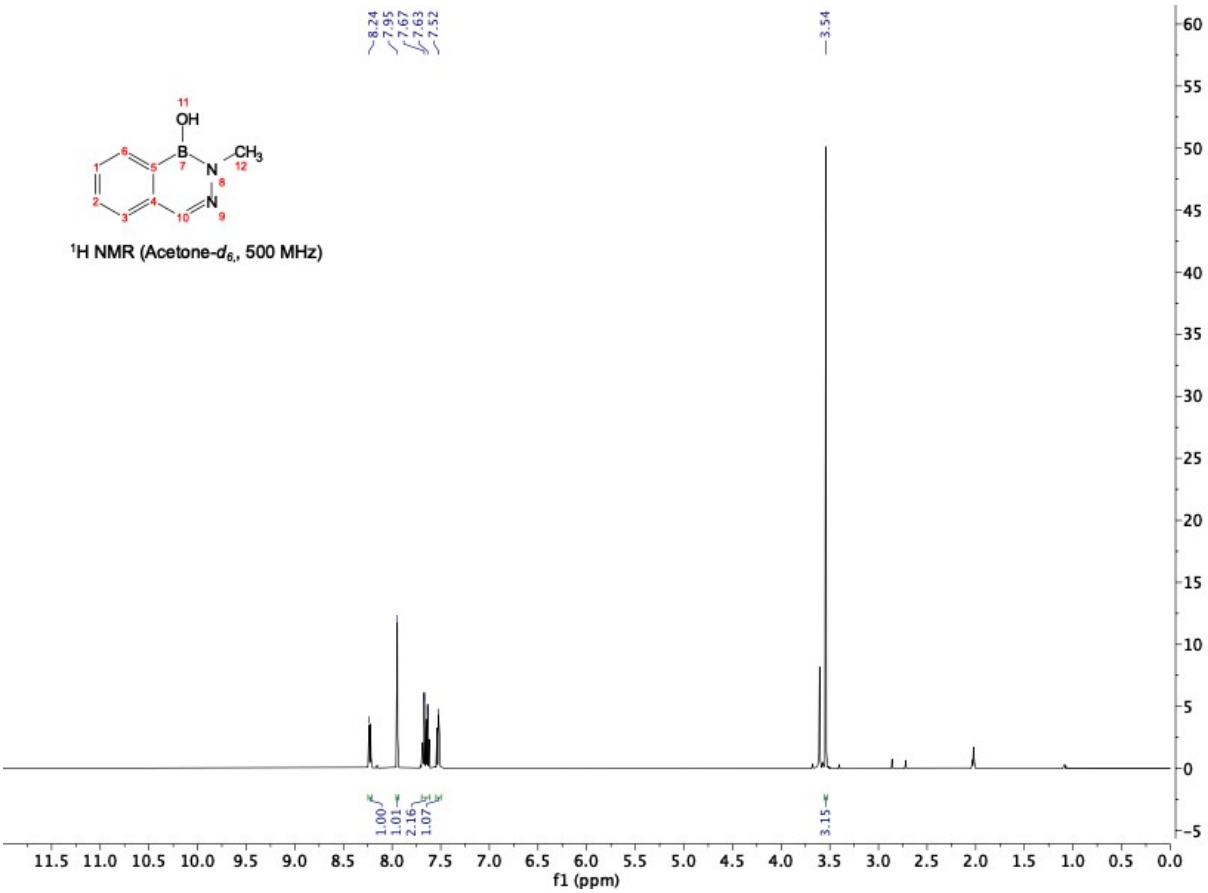


Figure S79. ^{1}H NMR spectrum of **7** in acetone-d_6. A drop of D_2O was added to prevent anhydride formation. Our data are in excellent agreement with Kazmi *et. al. J. Am. Chem. Soc,* 143 (27), **2021**, 10143-10156.

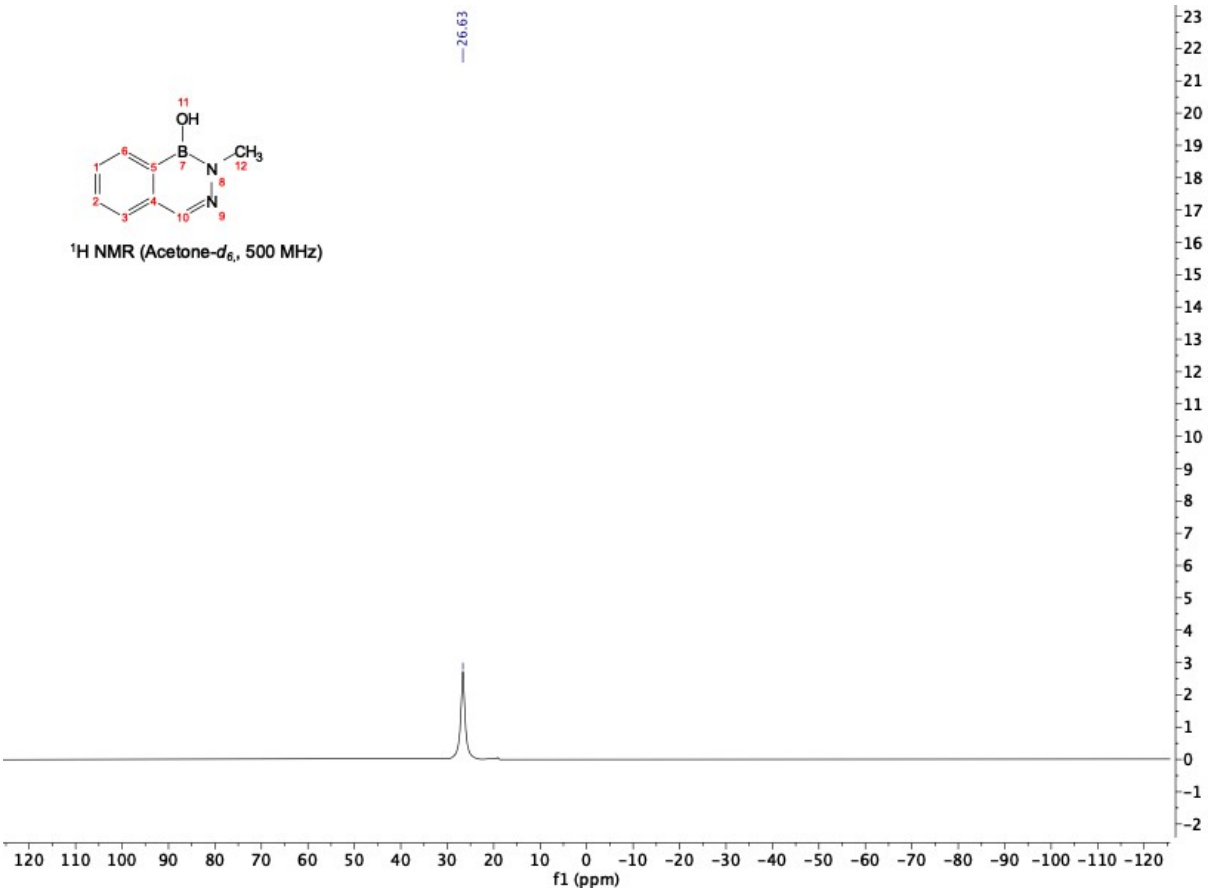


Figure S80. ^{11}B NMR spectrum of **7** in acetone-d_6. A drop of D_2O was added to prevent anhydride formation. Our data are in excellent agreement with Kazmi *et. al. J. Am. Chem. Soc,* 143 (27), **2021**, 10143-10156.

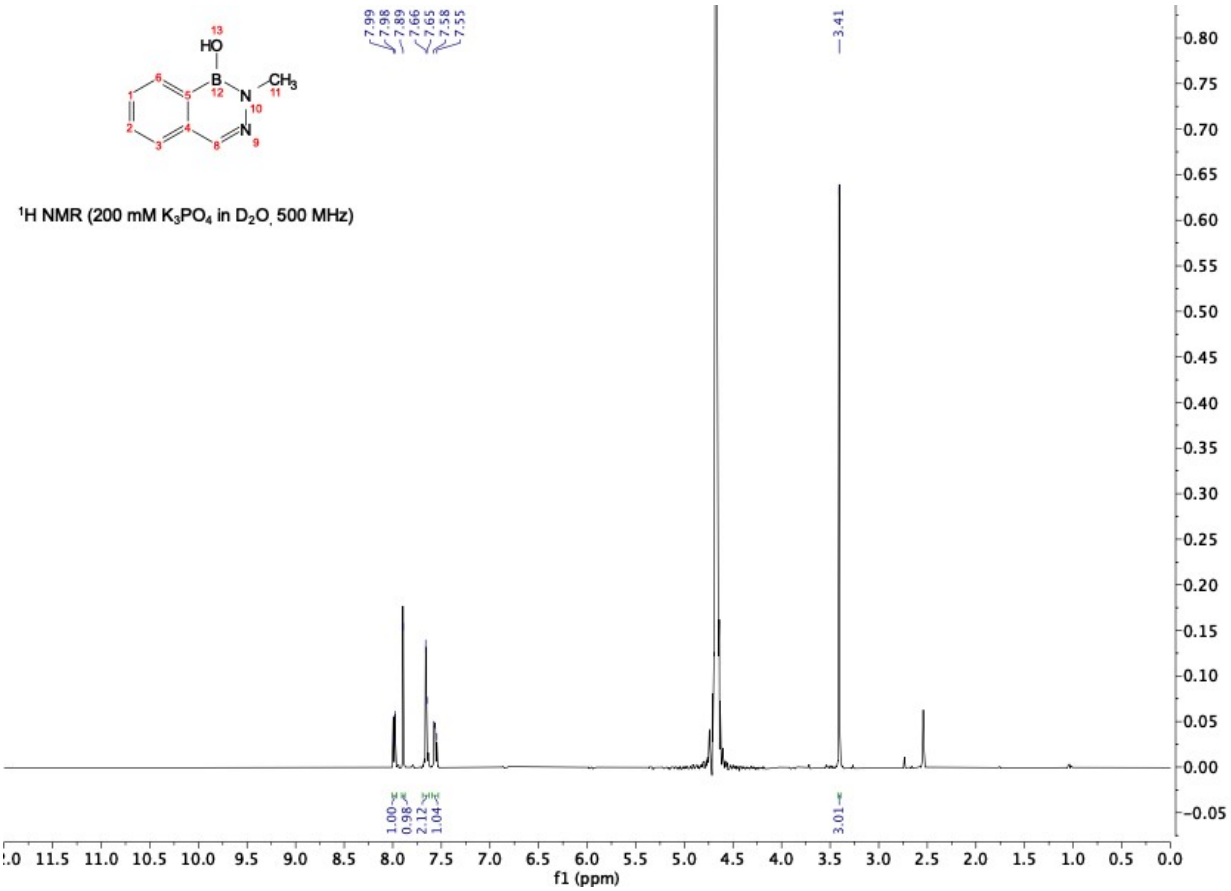


Figure S81. ^{1}H NMR spectrum of **7** in 200 mM K_3PO_4 in D_2O.

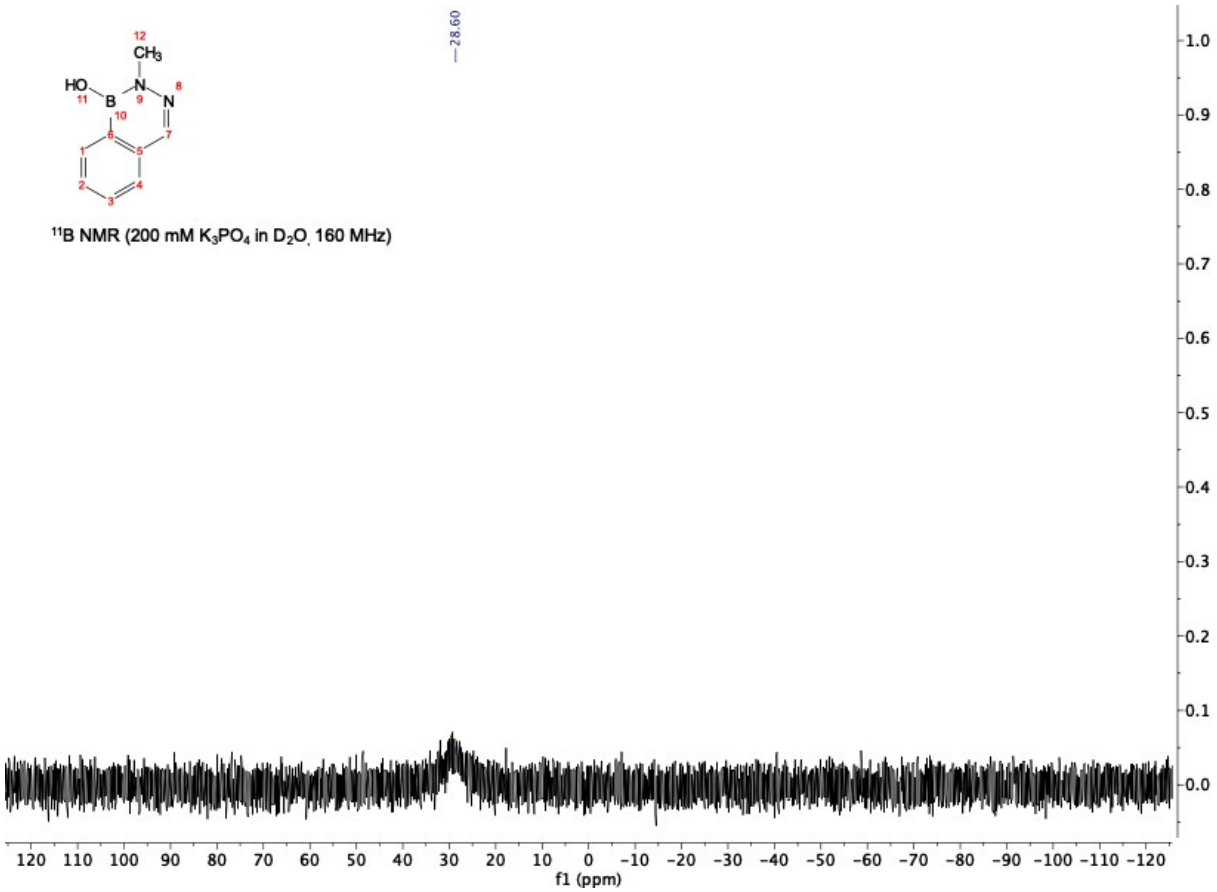


Figure S82. ^{11}B NMR spectrum of **7** in pD 7.4 200 mM K_3PO_4 in D_2O.

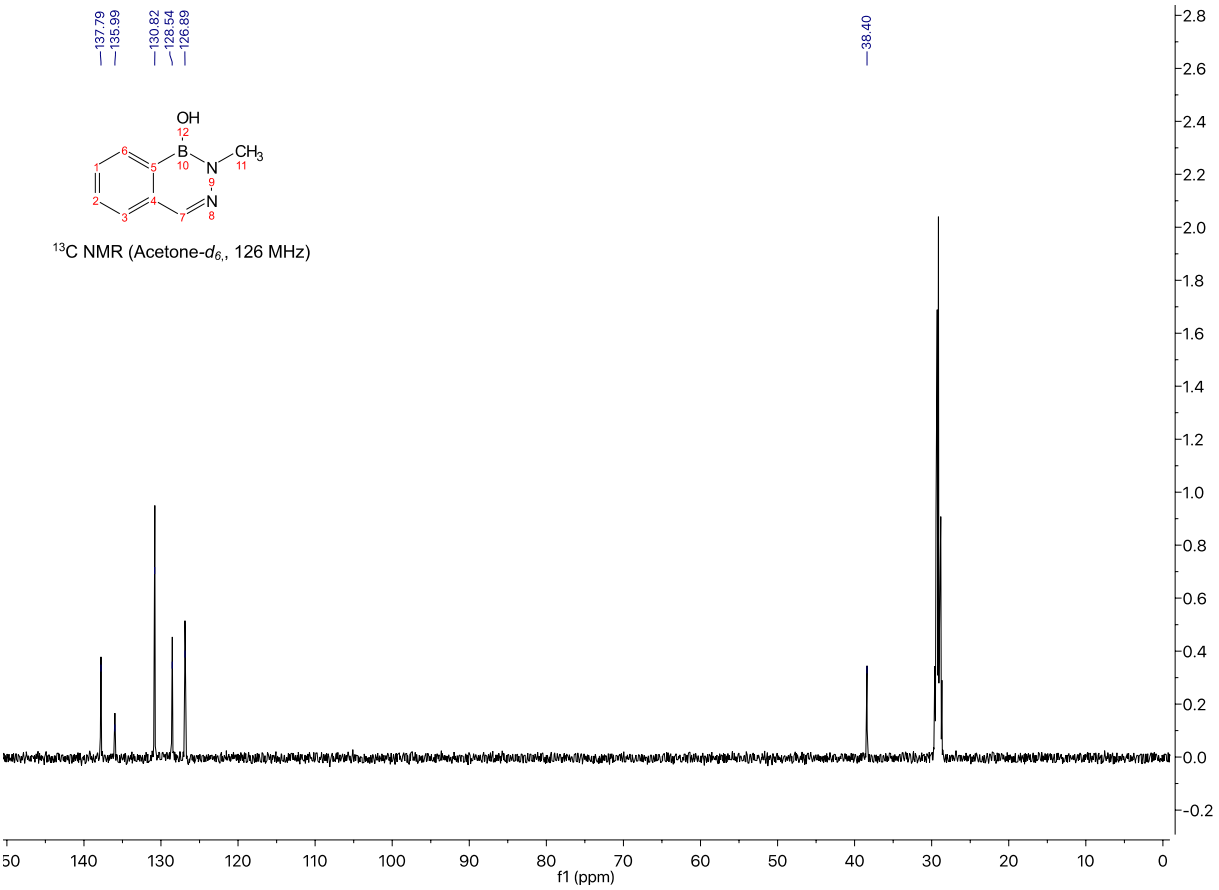


Figure S83. ^{13}C NMR spectrum of **7** in acetone + 1 drop D_2O.

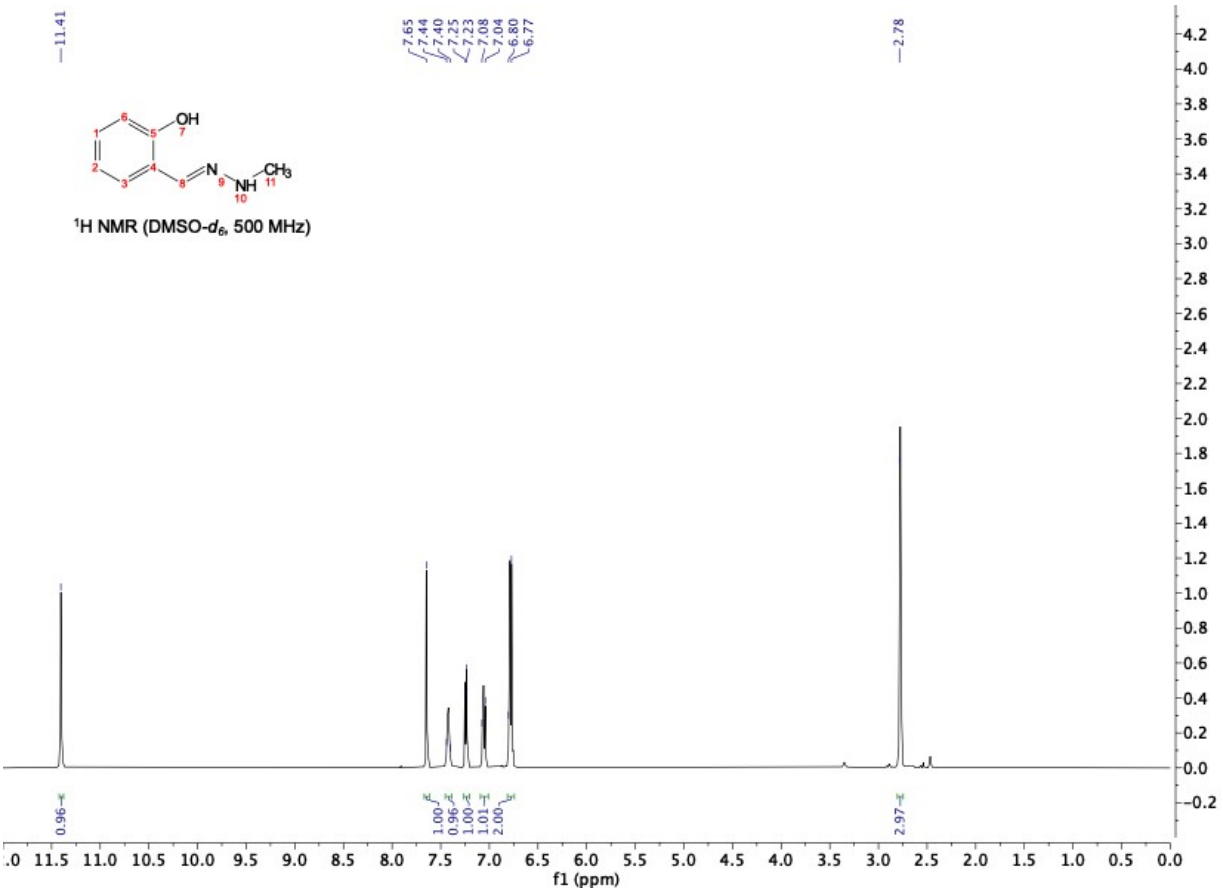


Figure S84. ^{1}H NMR spectrum of **7-OH** in DMSO-d_6.

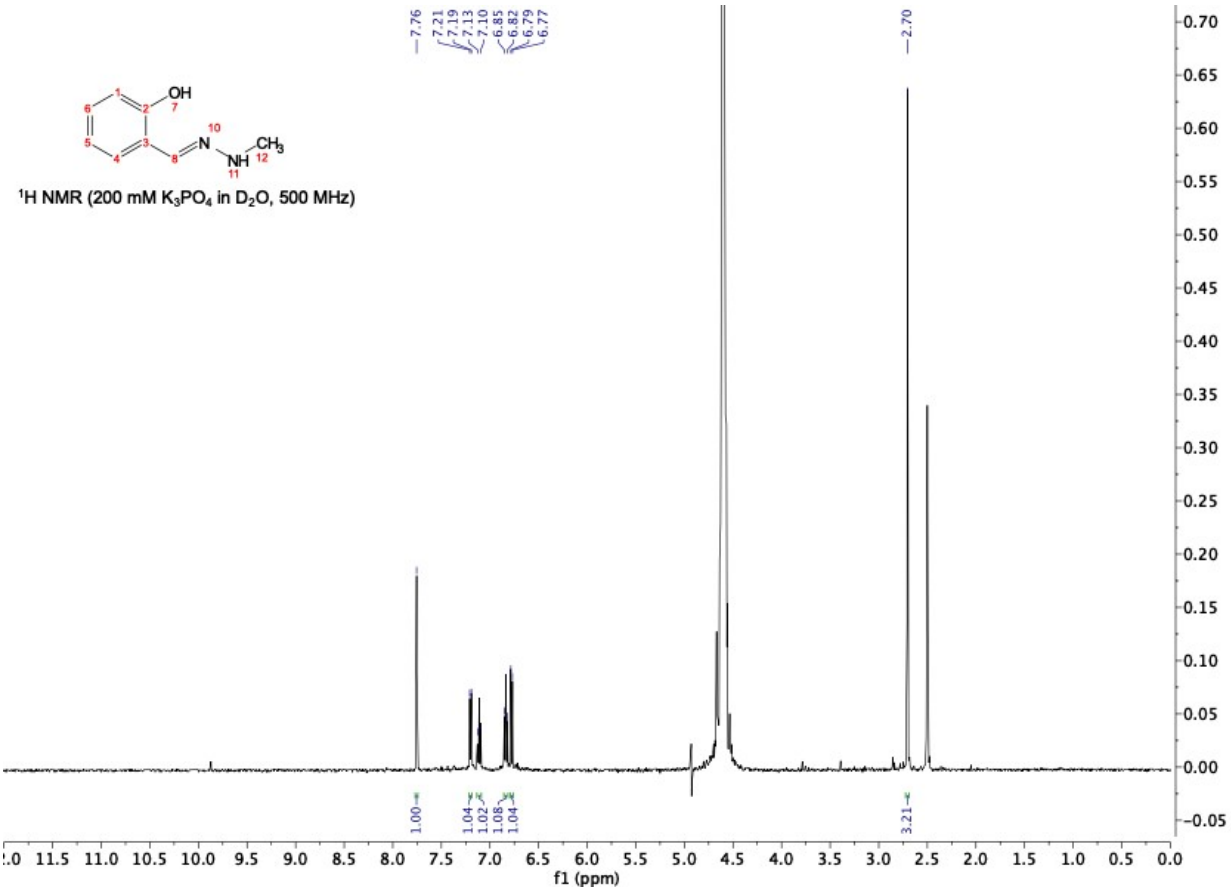


Figure S85. ^{1}H NMR spectrum of **7-OH** in 200 mM K_3PO_4 in D_2O.

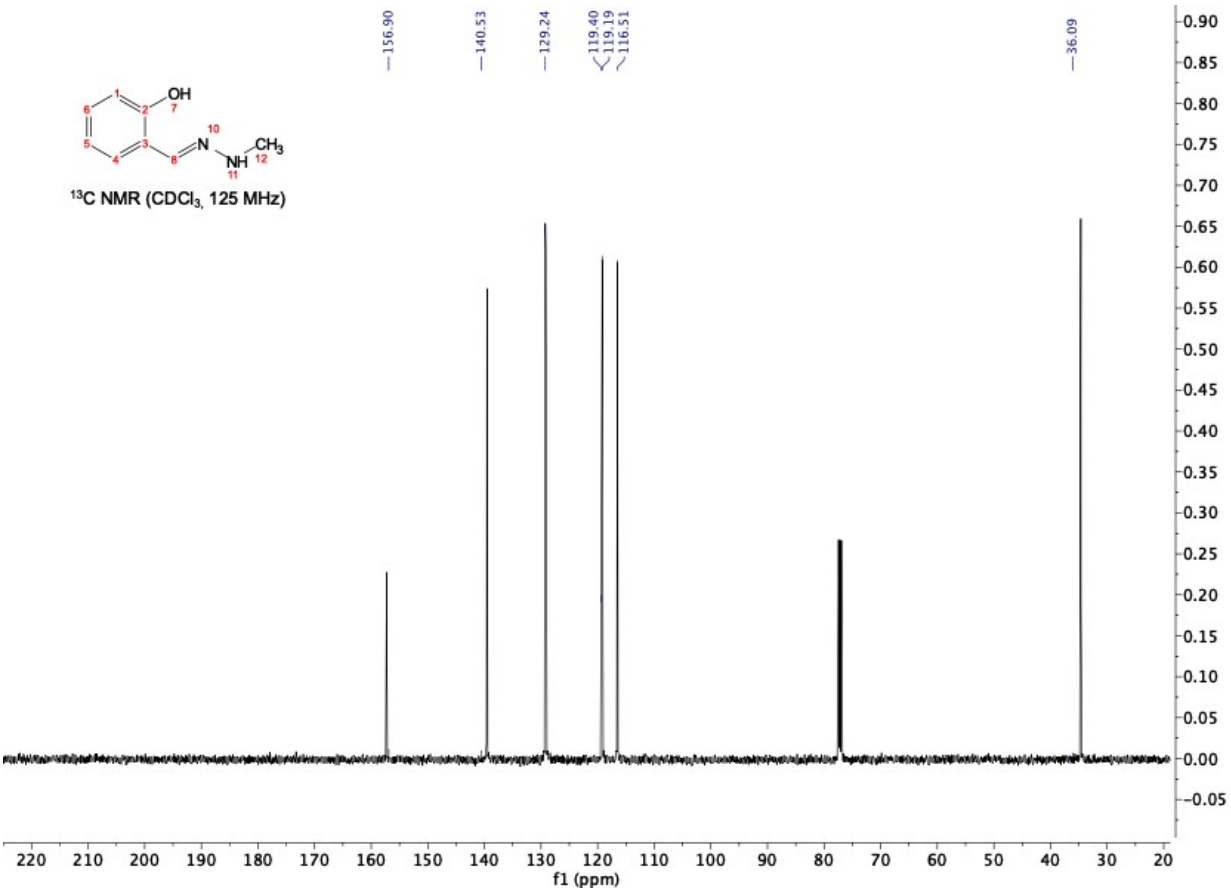


Figure S86. ^{13}C NMR spectrum of **7-OH** in $CDCl_3$.

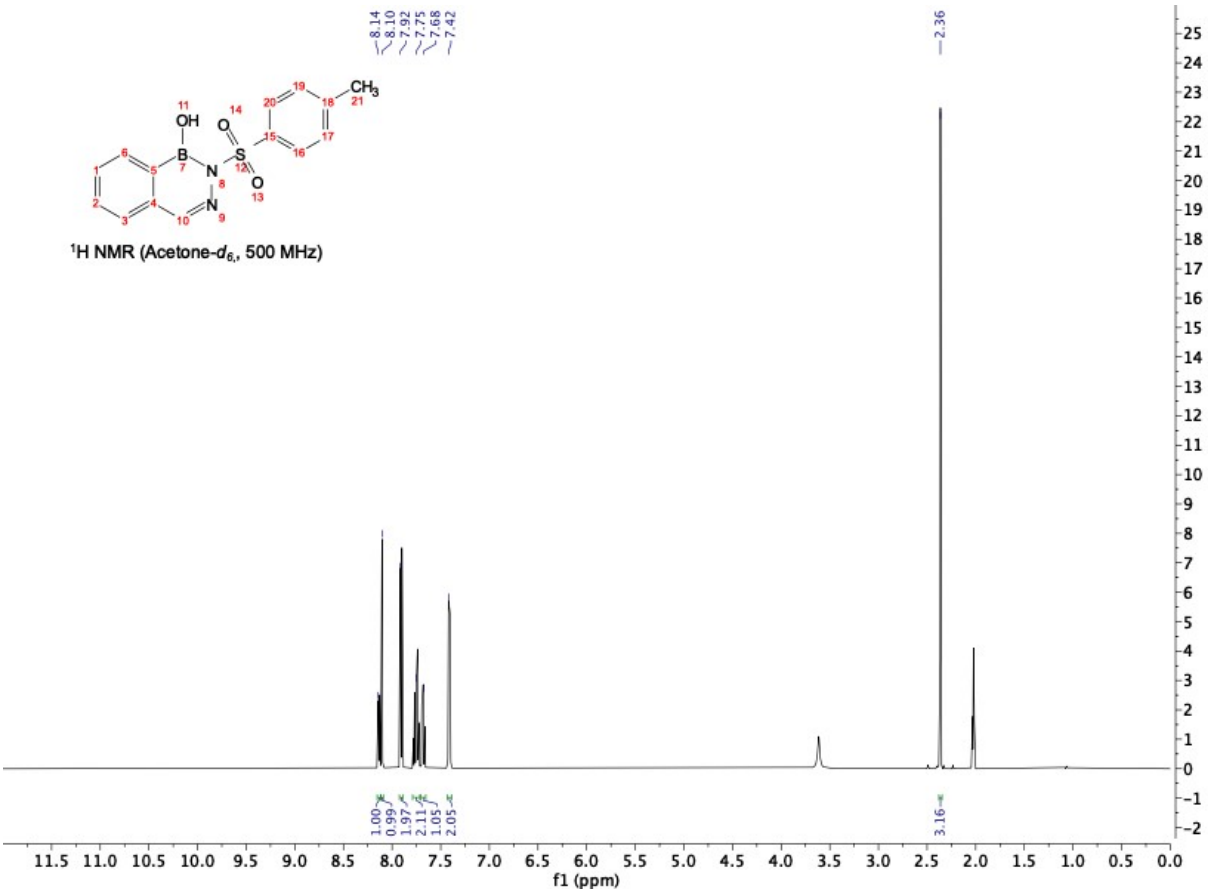


Figure S87. ^{1}H NMR spectrum of **8** in acetone-d_6. 1 drop of D_2O was added to prevent anhydride formation. Our data are in excellent agreement with Kazmi *et. al.J. Am. Chem. Soc,* 143 (27), **2021**, 10143-10156.

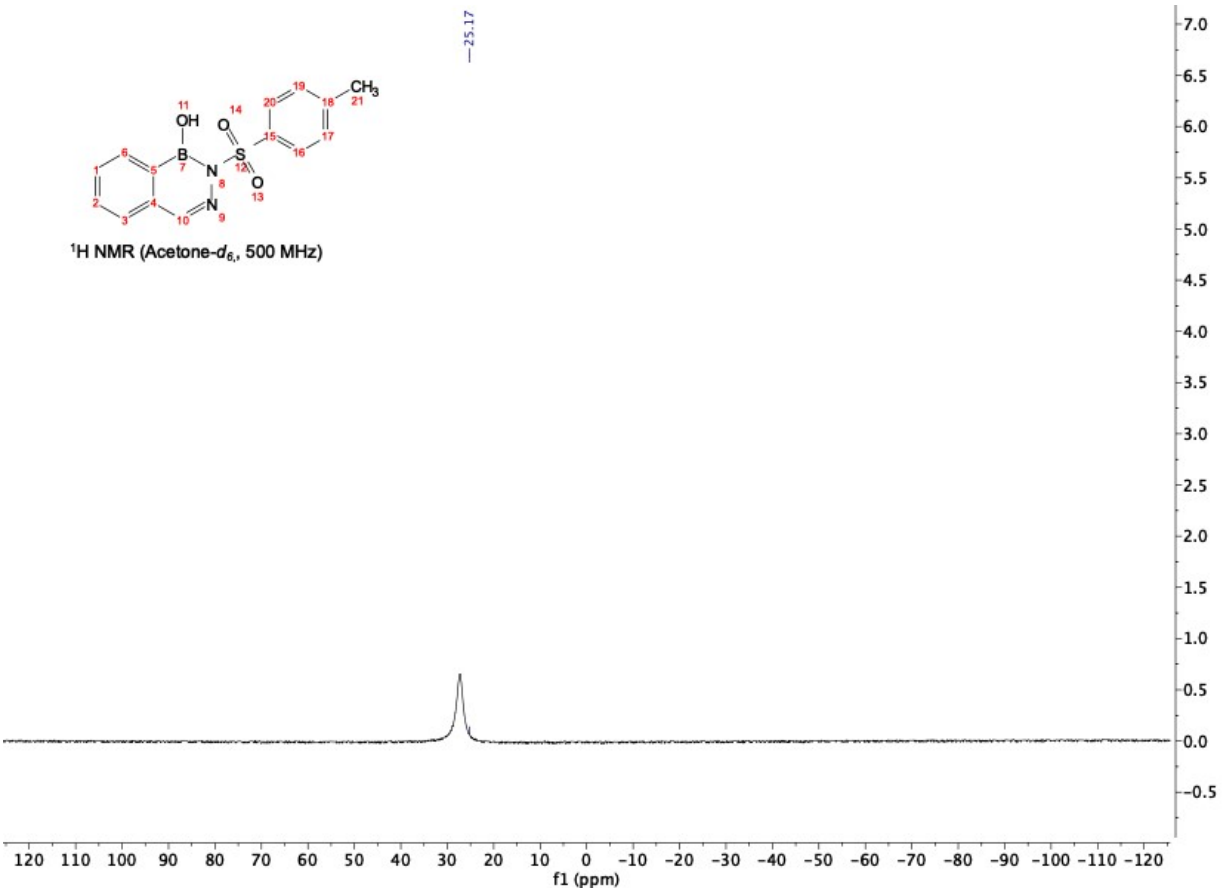


Figure S88. ^{11}B NMR spectrum of **8** in acetone-d_6. 1 drop of D_2O was added to prevent anhydride formation. Our data are in excellent agreement with Kazmi *et. al.J. Am. Chem. Soc,* 143 (27), **2021**, 10143-10156.

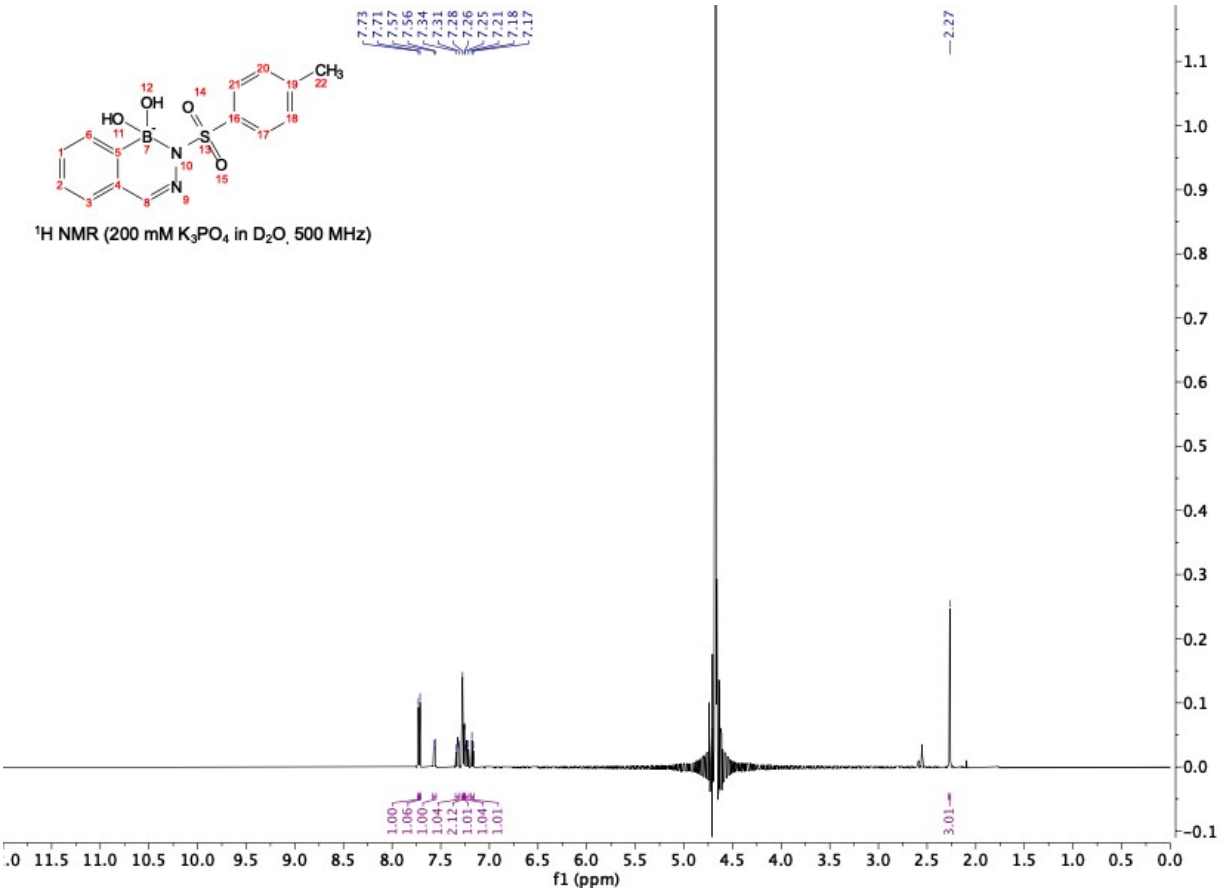
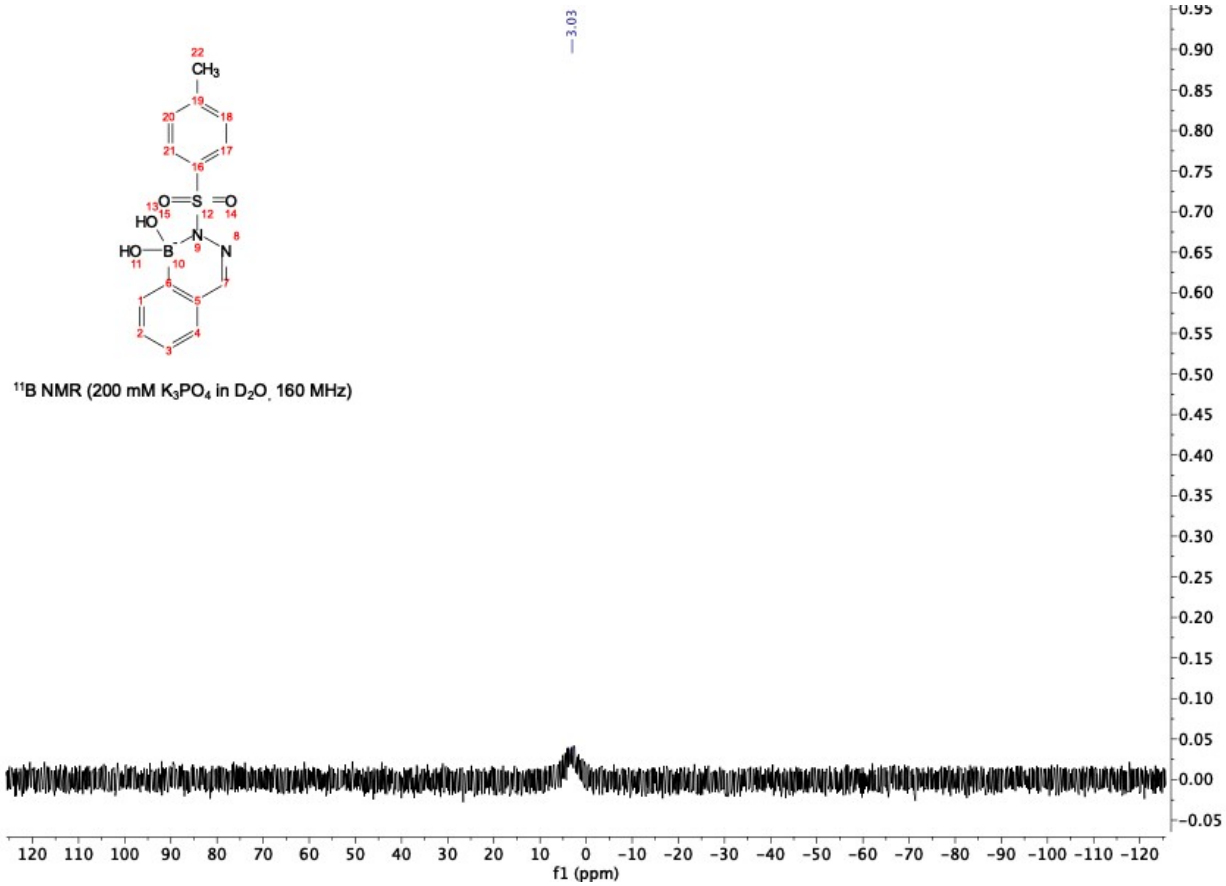


Figure S89. ^{1}H NMR spectrum of **8** in pD 7.4 200 mM K_3PO_4 in D_2O.



^{11}B NMR (200 mM K_3PO_4 in D_2O, 160 MHz)

Figure S90. ^{11}B NMR spectrum of **8** in pD 7.4 200 mM K_3PO_4 in D_2O.

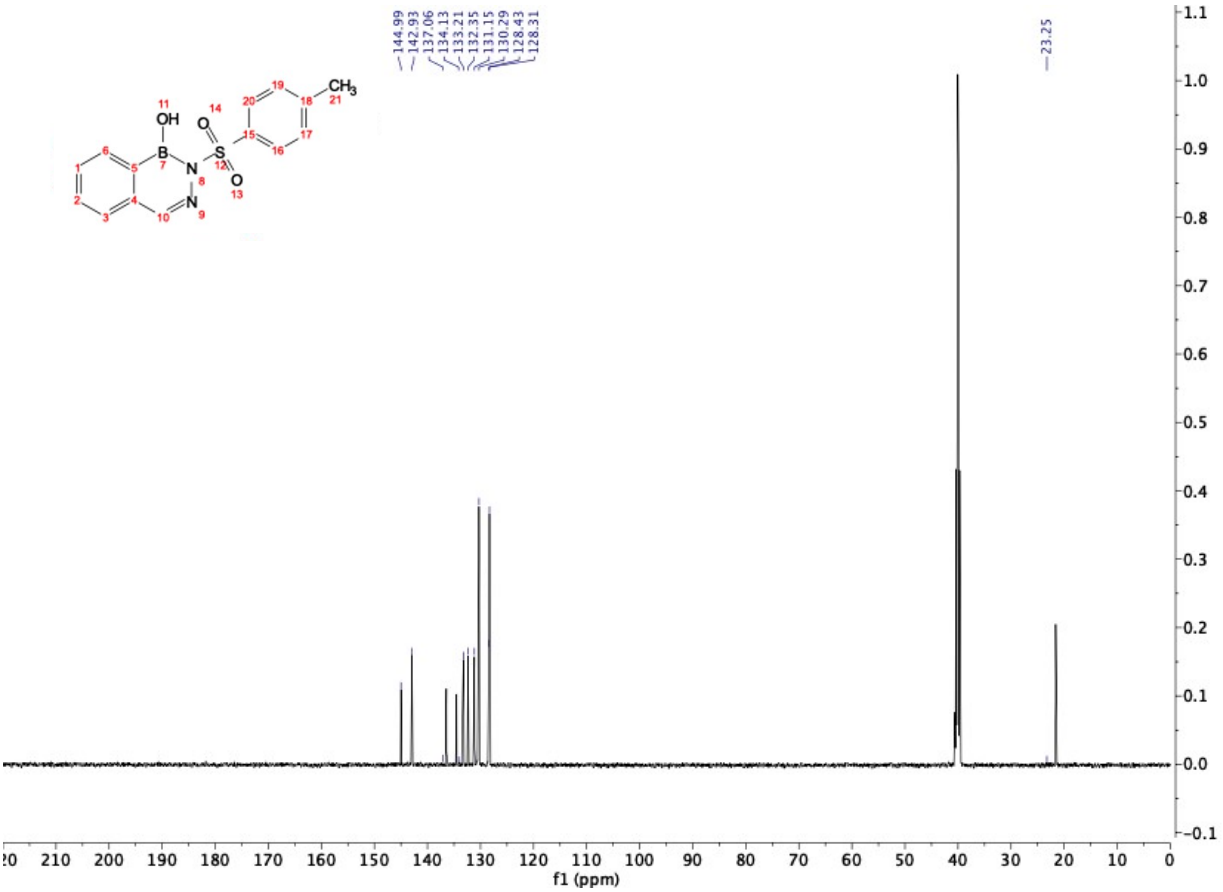


Figure S91. ^{13}C NMR spectrum of **8** in DMSO-d_6.

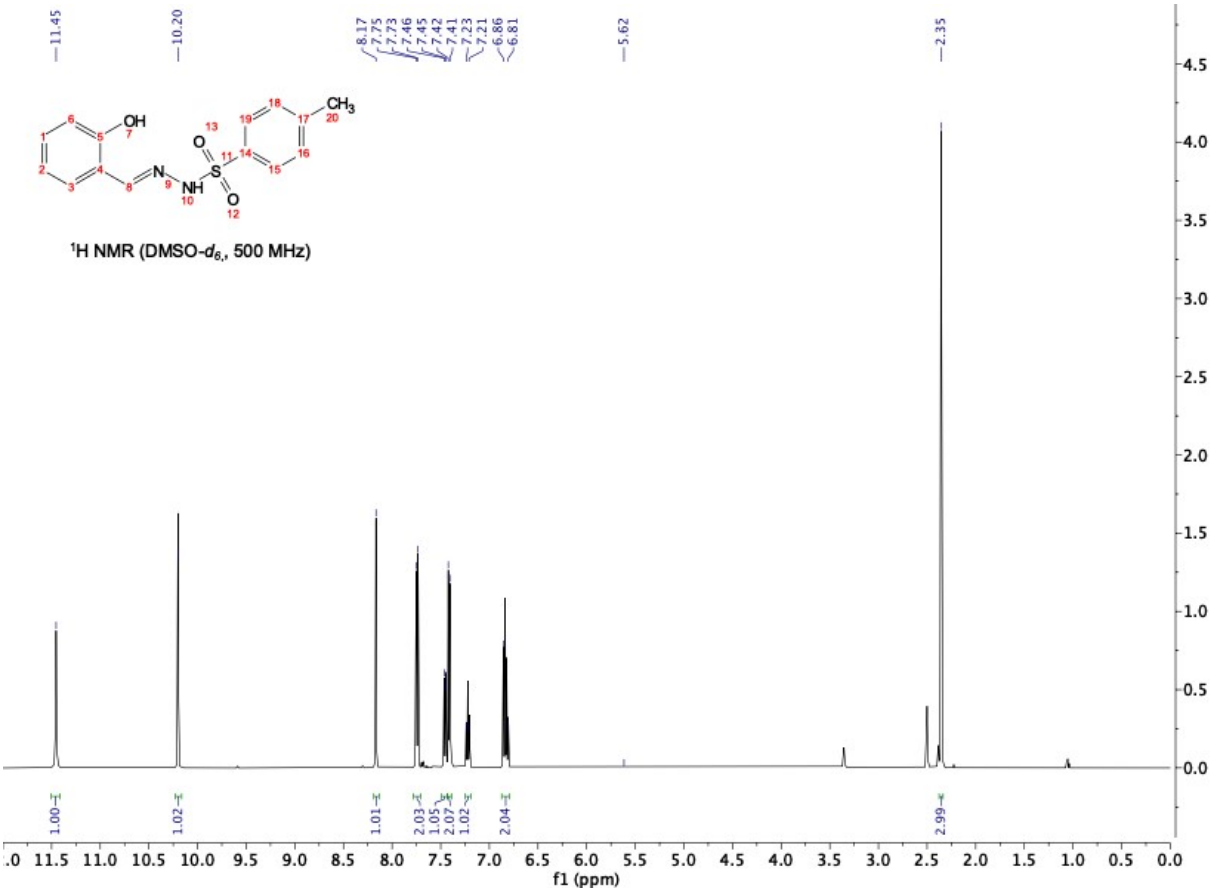


Figure S92. ^{1}H NMR spectrum of **8-OH** in DMSO-d_6.

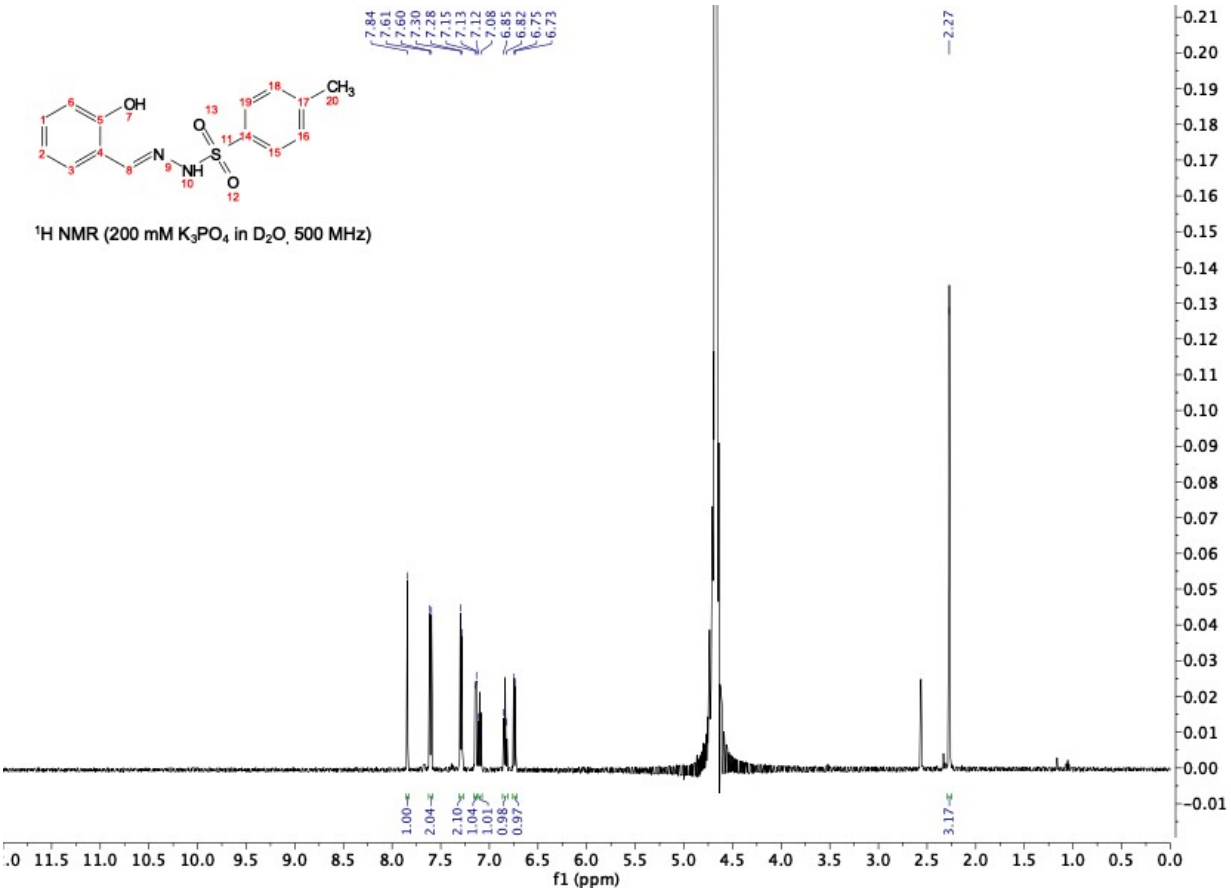


Figure S93. ^{1}H NMR spectrum of **8-OH (*E*)** in 200 mM K_3PO_4 in D_2O.

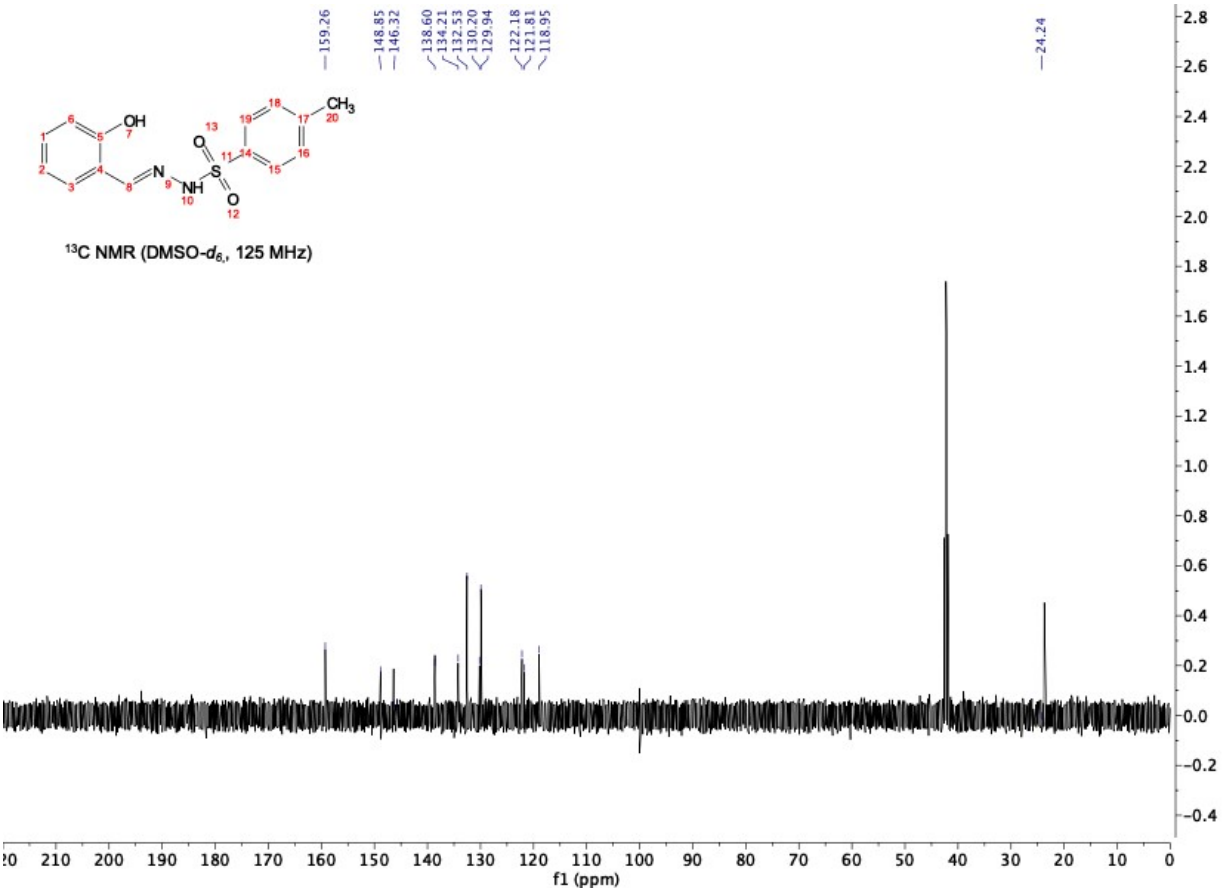


Figure S94. ^{13}C NMR spectrum of **8-OH** in DMSO-d_6.