Supporting Information

Direct Aerobic α,β-Dehydrogenation of Aldehydes and Ketones with a $Pd(TFA)_2$/4,5-Diazafluorenone Catalyst

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1. General considerations.

All commercially available compounds were used as received. Substrates that were not commercially available were prepared according to literature procedures: 4-(4-methoxyphenyl)-2-butanone (Table 2, entry 2) and 4-[4-(trifluoromethyl)phenyl]-2-butanone (Table 2, entry 4),[1] 1,3-diphenyl-propan-1-one (Table 2, entry 5),[2] and 4-methyl 3-benzoylpropionate (Table 2, entry 6).[3] The bicyclo[3.1.0]hexane-2-one-6-carboxylic acid ethyl ester **1** was donated by Eli Lilly.

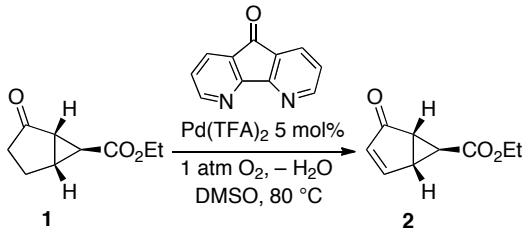
^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 MHz or a Varian Mercury-300 MHz spectrometer. The chemical shifts (δ) are given in parts per million and referenced to residual solvent peaks or a TMS internal standard. Gas chromatography was performed on a Shimadzu GC-17A using a Stabilwax®-DB column (15 m) and referenced to an internal standard (nitrobenzene). Flash column chromatography was performed on an Isco Combiflash system using silica gel 60 (Silicycle) and eluted with ethyl acetate/hexane.

CAUTION: The combination of organic solvents and O_2 creates the risk of an explosion. To minimize risks, all reactions carried out at pressures above 1 atm utilized a dilute oxygen gas mixture (9% O_2 in N_2) to ensure that the O_2 content remains below the lower explosive limit of O_2/organic mixtures.[4] All reactions should be performed with care and

carried out behind a blast shield.

2. General procedure for catalyst optimization.

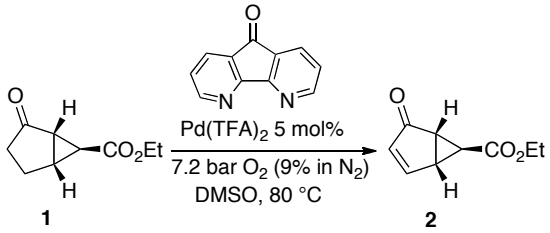
Catalytic aerobic oxidation reactions were performed using a custom reaction apparatus that enabled several reactions to be performed simultaneously under a constant pressure of O_2 (approximately 1 atm) with controlled temperature and orbital agitation.



1 **2**

To a disposable 13 mm thick-walled culture tube was added **1** (0.1 mmol, 16.8 mg). The reaction tubes were placed in a 48-well parallel reactor mounted on a Glas-Col large capacity mixer. The headspace was purged with O_2 for 10 min, after which a stock solution of $Pd(TFA)_2$, (1.65 mg, 0.005 mmol, 0.05 equiv) and diazafluorenone (0.9 mg, 0.01 mmol, 0.1 equiv) in DMSO (0.5 mL) was injected via syringe. The solution was agitated vigorously at 80 °C for 24 h. After 24 h, the reaction vessel was cooled to room temperature and vented. The solution was then diluted with CH_2Cl_2 and analyzed by GC.

3. Procedure for dehydrogenation of 1 in a Parr pressure vessel and product isolation.

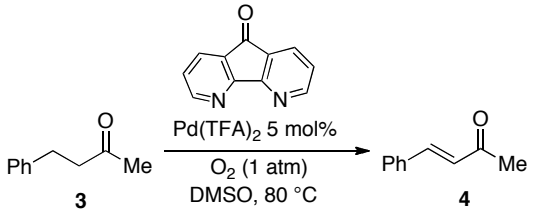


1 **2**

The oxidation of **1** under 1 atm O_2 afforded 40% conversion due to catalyst decomposition. We speculated that the catalyst would be more stable with elevated pressures of O_2, and the reaction was carried out in a Hastelloy Parr pressure vessel. A supply of dilute O_2 (9% in N_2) was used to avoid explosion hazard, and a typical protocol for this reaction format is as follows:

To a 2 ml GC vial with a stir bar was added **1** (33.6 mg, 0.2 mmol), followed by a solution of $Pd(TFA)_2$ (3.3 mg, 0.01 mmol, 0.05 equiv) and 4,5-diazafluorenone (1.8 mg, 0.01 mmol, 0.05 equiv) in DMSO (0.5 mL). The vial was immediately placed in a 45 mL Hastelloy Parr pressure vessel, and sealed. 80 atm of 9% O_2 in N_2 (7.2 atm partial pressure of O_2) was introduced and the vessel was heated to 80 °C with vigorous stirring for 48 h. After 48 h, the vessel was vented. The solution was diluted with H_2O and extracted three times with CH_2Cl_2. The CH_2Cl_2 solution was concentrated and loaded on silica gel and placed on Isco Combiflash column. The product was isolated with an eluent gradient of 10%-40% ethyl acetate in hexane, affording **2** in 79% as a white solid.

4. Procedure for dehydrogenation of benzylacetone 3



3 **4**

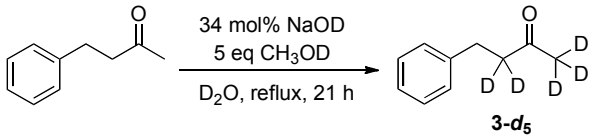
Good gas-liquid mixing is critical for these aerobic oxidation reactions. Analysis of different reaction formats showed that the best results are obtained with orbital agitation. Nevertheless, similar results can be obtained on bench using a standard cultured tube equipped with a balloon of O_2 and magnetic stir bar.

*Dehydrogenation of **3** with orbital agitation.* To a disposable 13 mm thick-walled culture tube were added $Pd(TFA)_2$ (6.6 mg, 0.02 mmol, 0.05 equiv), 4,5-diazafluorenone (3.6 mg, 0.02 mmol, 0.05 equiv), and DMSO (0.5 ml). The reaction tubes were placed in a 48-well parallel reactor mounted on a Glas-Col large capacity mixer. The headspace was purged with O_2 for 10 min, after which benzylacetone (60 μl, 0.4 mmol, 1 equiv) was added via syringe. The solution was agitated vigorously at 80 °C for 48 h. After 48 h, the reaction was cooled down, and O_2 was vented from the reactor. The reaction mixture was purified as described above. The 4-phenylbutenone product **4** was obtained in 87% yield as a colorless liquid. The by-product, benzaldehyde, was obtained as a colorless liquid in 8% yield.

*Dehydrogenation of **3** in a cultured tube with magnetic stirring.* To a cultured tube (VWR 89000-488) equipped with a stir bar was added $Pd(TFA)_2$ (6.6 mg, 0.02 mmol, 0.05 equiv), 4,5-diazafluorenone (3.6 mg, 0.02 mmol, 0.05 equiv), and DMSO (0.5 ml). The tube was sealed with a septum. A balloon was then attached via a long needle. The tube and balloon were purged and refilled with O_2 three times, submerging the needle in catalyst solution during purging to allow O_2 saturation via bubbling. After filling the balloon with O_2 a final time, the solution was stirred and benzylacetone **3** (60 μl, 0.4 mmol, 1 equiv) was injected via syringe. After reacting at 80 °C for 48 h, the mixture was cooled to room temperature, and an external standard (nitrobenzene, 10 μl, 0.097 mmol) was added. The mixture was diluted with CH_2Cl_2, and analyzed by GC to afford 79% GC yield.

5. Synthesis of the deuterated substrates 3-d_5 and 3-d_2.

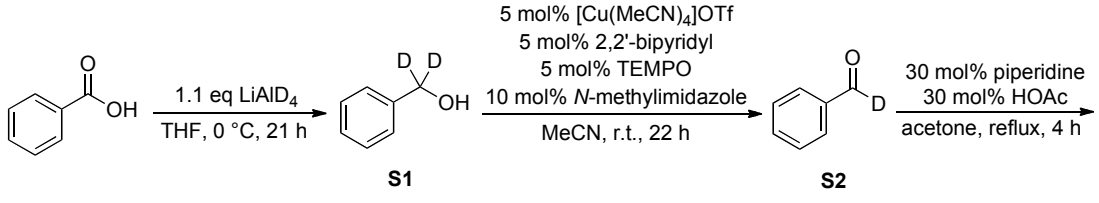
*Synthesis of [1,1,1,3,3-d$_5$]-4-Phenyl-2-butanone (**3-d$_5$**)*[5]



3-d_5

An oven-dried 100 mL round bottom flask was equipped with a stir bar and condenser. After purging with N_2, the flask was charged with 8.5 mL D_2O, benzylacetone (1.48 g, 10.0 mmol), CH_3OD (1.72 g, 52.0 mmol, 5.2 equiv.), and a solution of 40% NaOD in D_2O (300 μL, 3.40 mmol, 0.34 equiv.) with stirring. The reaction mixture was stirred at reflux for 21 h and allowed to cool to room temperature before 8 mL diethyl ether was added via syringe. Following 1 h of stirring, the layers were separated and the aqueous layer was washed with ether (1 x 20 mL). The combined organic layers were washed with water (2 x 20 mL) and brine (1 x 20 mL), dried over Na_2SO_4, and concentrated by evaporation. The crude product was shown to be ca. 95 % deuterated material, and was distilled *in vacuo* to yield **3-d_5 (**1.06 g, 70%) as a colorless oil. ^{1}H NMR data match previously reported data.[5] ^{1}H NMR ($CDCl_3$): δ 7.31-7.17 (m, 5H), 2.88 (s, 2H).

*Synthesis of [4,4-d$_2$]-4-Phenyl-2-butanone (**3-d$_2$**)*



[1,1-d_2]-Benzyl alcohol (S1). An oven-dried 250 mL round bottom flask was equipped with a stir bar. After purging with N_2, the flask was charged with $LiAlD_4$ (513 mg, 13.5 mmol, 1.1 equiv.) and 50 mL THF and stirred at 0 °C. A oven-dried 100 mL round bottom flask equipped with stir bar and septum was purged with N_2. A solution of benzoic acid (1.50 g, 12.3 mmol, 1 equiv) in 50 mL THF were added to the 100 mL flask and stirred at 0 °C. Above benzoic acid solution were added dropwise to the $LiAlD_4$ suspension at 0 °C using a cannula. The reaction mixture was slowly warmed to room temperature and allowed stirring for overnight. The mixture was diluted to 2 x its original volume with ethyl acetate and quenched by dropwise addition of water at 0 °C. The mixture was extracted with diethyl ether (3 x 50 mL), and the combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, and concentrated by evaporation. Distillation *in vacuo* yielded **S1 (**450 mg, 33%) as a colorless oil. ^{1}H NMR data match previously reported data.[6] ^{1}H NMR ($CDCl_3$): δ 7.37-7.25 (m, 5H), 1.73 (s, 1H).

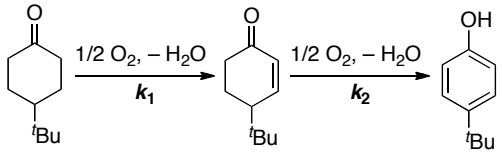
[1-*d*]-Benzaldehyde (S2).[7] A 100 mL round bottom flask equipped with a stir bar was charged with 20 mL acetonitrile and **S1** (380 mg, 3.44 mmol). A solution of $[Cu(CH_3CN)_4]OTf$ (64 mg, 0.17 mmol, 0.05 equiv.) and 2,2'-bipyridine (27 mg, 0.17 mmol, 0.05 equiv.) in 4 mL acetonitrile, a solution of TEMPO (27 mg, 0.17 mmol, 0.05 equiv.) in 4 mL acetonitrile, and *N*-methylimidazole (27 μL, 0.34 mmol, 0.10 equiv.) were added with stirring. The solution was stirred at room temperature and consumption of starting material was monitored by TLC. Upon reaction completion, the reaction mixture was diluted to 2 x its original volume with a 1:1 ether:pentane solution, filtered through a plug of silica. Removal of solvent afforded **S2** (330 mg, 90%) as a colorless oil. ^{1}H NMR data match previously reported data.[8] ^{1}H NMR ($CDCl_3$): δ 7.91-7.88 (m, 2H), 7.68-7.62 (m, 1H), 7.57-7.52 (m, 2H).

[4-*d*]-4-Phenyl-3-buten-2-one (S3).[9] A 25 mL three-neck flask equipped with condenser and stir bar was purged with N_2. An acetone (3 mL) solution of **S2** (330 mg, 3.08 mmol) was added, followed by dropwise addition of piperidine (90 μL, 0.91 mmol, 0.30 equiv) and acetic acid (52 μL, 0.91 mmol, 0.30 equiv). The mixture was stirred under reflux for 4 h. The resulting mixture was diluted with EtOAc, quenched with saturated $NaHCO_3$ (1 x 10 mL), and washed with water (2 x 10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (1 x 10 mL), dried over Na_2SO_4 and concentrated by evaporation. Purification by flash column chromatography (Hex:EtOAc, 0-15% EtOAc) yielded **S3** (174 mg, 39%) as a colorless oil. ^{1}H NMR data match previously reported data.[10] ^{1}H NMR ($CDCl_3$) δ 7.56-7.53 (m, 2H), 7.41-7.38 (m, 3H), 6.71 (t, 1H, J = 2.1 Hz), 2.38 (s, 3H).

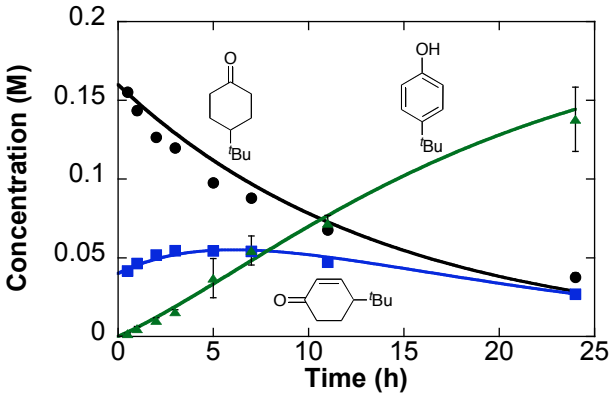
[3,4,4-d_3]-4-Phenyl-2-butanone (S4).[11] A 50 mL round bottom flask equipped with stir bar and septum was charged with methanol (4 mL), **S3** (174 mg, 1.19 mmol), diphenyl sulfide (2.2 mg, 0.012 mmol, 0.01 equiv.), and 5% Pd/C (20 wt % of the substrate). A balloon was purged three times with D_2, and introduced to the reaction via a needle. The reaction was allowed to stir at room temperature under D_2 (ca. 1 atm) for 19 h. Filtration through a plug of celite and concentration by evaporation afforded **S4**(171 mg, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.31-7.26 (m, 2H), 7.22-7.16 (m, 3H), 2.75 (s, 1H), 2.14 (s, 3H).

[4,4-d_2]-4-Phenyl-2-butanone (3-d_2).[5] A 50 mL round bottom flask equipped with a stir bar and condenser was charged **S4** (171 mg, 1.13 mmol), 1 mL H_2O, CH_3OH (223 μL, 5.66 mmol, 5.0 equiv.), and a solution of NaOH (15.0 mg, 0.38 mmol, 0.34 equiv.) in 1 mL H_2O with stirring. The reaction mixture was stirred at reflux for 20 h and allowed to cool to room temperature. 2 mL diethyl ether was added via syringe. After stirring for 30 min, the solution was quenched with 0.1 M HCl. The aqueous layer was washed with ether (2 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), and dried over $MgSO_4$. Purification by flash column chromatography (Hex:EtOAc, 0-15% EtOAc) yielded **3-d_2 (**53 mg, 31%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.32-7.13 (m, 5H), 2.74 (s, 2H), 2.13 (s, 3H). ^{2}H NMR ($CHCl_3$): δ 2.88 (s, 2D). ^{13}C NMR ($CDCl_3$): δ 208.15, 141.12, 128.70, 128.48, 126.32, 45.24, 30.28. HRMS (ESI) $[M + Na^+]/z$ calcd. 150.1009, found 150.1010.

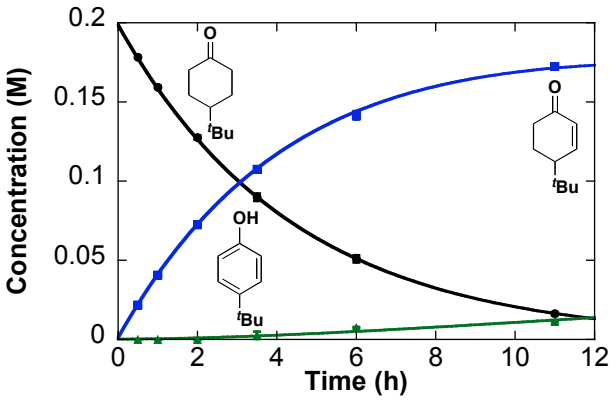
6. Reaction profiles and kinetic fittings of oxidizing 4-*tert*-butylcyclohexanone with different catalysts.[a]



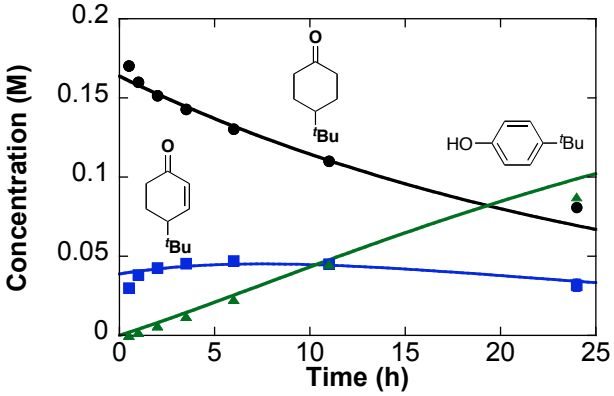
(A) $Pd(TFA)_2$/2-Me_2Npy/TsOH



(B) $Pd(DMSO)_2(TFA)_2$



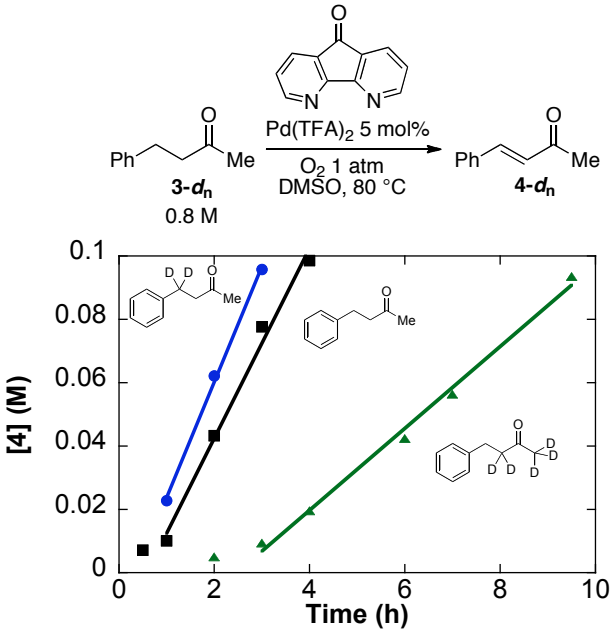
(C) $Pd(TFA)_2$/4,5-diazafluorenone



[a] Conditions: [substrate] = 0.2 M (15.4 mg, 0.1 mmol), [catalyst] = 0.05 M (0.005 mmol), solvent (0.5 mL), 1 atm O_2, 80 °C.

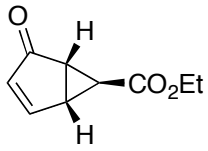
7. Investigation of Kinetic Isotope Effects.

Reactions were performed using orbital shakers under standard conditions, as described above. The catalyst was heated to 80 °C and the temperature was allowed to equilibrate for 5 min. Nitrobenzene (10 μL) was injected via syringe as internal standard. Injection of substrates dissolved in solvent established the t = 0 point. At various time intervals, aliquots were withdrawn from the reaction mixture via pipet, diluted with CH_2Cl_2 and analyzed by GC. Accordingly, initial rates were determined as the slope of [product] vs. time at 10% conversion.

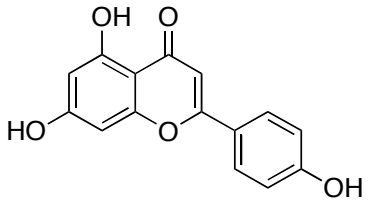


8. ^{1}H NMR Spectroscopic Data.

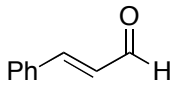
All compounds in Table 1, Scheme 4 and eq 2 have been reported previously. In all cases, the product identities were established by comparison of the ^{1}H NMR spectra with previously reported data. In one case (scheme 5, **3-*d*$_2$**), full characterization was not previously reported; these data are included below.



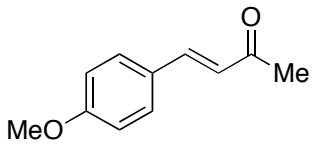
(**2**, Table 1, entry 22): Prepared as described above. Purified by silica gel column chromatography using a gradient of 10%-40% EtOAc in hexane elution to give 79% yield of the product as a white solid. ^{1}H NMR matches previously reported data.[12] ^{1}H NMR ($CDCl_3$): δ 7.61 (ddd, 1H, J =5.6, 2.6, 0.7 Hz), 5.74 (d, 1H, J = 5.6 Hz), 4.15 (q, 2H, J = 7.2 Hz), 2.85 (dt, 1H, J = 4.7, 2.6 Hz), 2.47 (ddd, 1H, J = 4.7, 2.6, 0.7 Hz), 2.26 (t, 1H, J = 2.6 Hz), 1.27 (t, 3H, J = 7.2 Hz).



(apigenin, Scheme 4): Prepared as described above. The reaction mixture was washed with water and extracted with ethyl acetate. The mixture was purified by silica gel column chromatography using a gradient 30-70% EtOAc in hexane elution to give 81% yield of the product as a yellow solid. ^{1}H NMR matches previously reported data.[13] ^{1}H NMR (DMSO-d_6): δ 12.96 (s, 1H), 10.81 (br, 1H), 10.36 (br, 1H), 7.93 (d, 2H, J = 8.9 Hz), 6.92 (d, 2H, J =8.9 Hz), 6.78 (s, 1H), 6.48 (d, 1H, J = 2.2), 6.19 (d, 1H, J = 2.2).

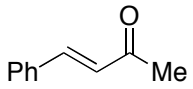


(Table 2, entry 1): Prepared as described in section **3** with orbital agitation. Purified by silica gel column chromatography using a 10% EtOAc in hexane elution to give 91% yield of the product as a colorless solid. ^{1}H NMR matches previously reported data.[14] ^{1}H NMR ($CDCl_3$): δ 9.71 (d, 1H, J = 7.6 Hz), 7.62-7.49 (m, 2H), 7.48 (d, 1H, J = 15.8 Hz), 7.46-7.41 (m, 3H), 6.72 (dd, 1H, J = 15.8, 7.6 Hz).

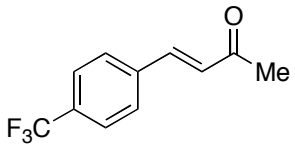


(Table 2, entry 2): Prepared as described above. Purified by silica gel column chromatography using a gradient 10%-20% EtOAc in hexane elution to give 83% yield of the product as a white solid. ^{1}H NMR matches previously reported data.[16] ^{1}H NMR

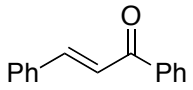
($CDCl_3$): δ 7.50 (d, 2H, J = 8.9 Hz), 7.48 (d, 1H, J = 16.5 Hz), 6.92 (d, 2H, J = 8.9 Hz), 6.61 (d, 1H, J = 16.5 Hz), 3.85 (s, 3H), 2.36 (s, 3H).



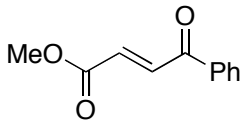
(Table 2, entry 3): Prepared as described above. Purified by silica gel column chromatography using a gradient 0%-15% EtOAc in hexane elution to give 87% yield of the product as a colorless liquid. ^{1}H NMR matches previously reported data.[15] ^{1}H NMR ($CDCl_3$): δ 7.60-7.49 (m, 3H), 7.46-7.37 (m, 3H), 6.72 (1H, d, J = 16.2 Hz), 2.39 (s, 3H).



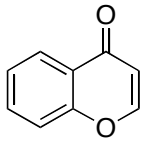
(Table 2, entry 4): Prepared as described above. Purified by silica gel column chromatography using a gradient 0%-20% EtOAc in hexane elution to give 86% yield of the product as a colorless oil. ^{1}H NMR matches previously reported data.[16] ^{1}H NMR ($CDCl_3$): δ 7.66 (s, 4H), 7.53 (d, 1H, J= 16.1 Hz), 6.78 (d, 1 H, J = 16.1 Hz), 2.42 (s, 3H).



(Table 2, entry 5): Prepared as described above. Purified by silica gel column chromatography using a 20% EtOAc in hexane elution to give 87% yield of the product as a white solid. ^{1}H NMR matches previously reported data.[17] ^{1}H NMR ($CDCl_3$): δ 8.07-7.99 (m, 2H), 7.70-7.62 (m, 2H), 7.61-7.48 (m, 3H), 7.82 (d, 1H, J = 15.8 Hz), 7.54 (d, 1 H, J = 15.8 Hz), 7.46-7.39, (m, 3 H).

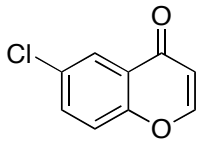


(Table 2, entry 6): Prepared as described above. Purified by silica gel column chromatography using a gradient 0%-15% EtOAc in hexane elution to give 74% yield of the product as a colorless liquid. ^{1}H NMR matches previously reported data.[18] ^{1}H NMR ($CDCl_3$): δ 8.03-7.80 (m, 2H), 7.94 (d, 1H, J = 15.5 Hz), 7.67-7.60 (m, 1H), 7.56-7.48 (2H, m), 6.90 (d, 1H, J = 15.5 Hz), 3.86 (s, 3H).

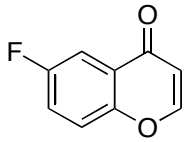


(Table 2, entry 7): Prepared as described above. Purified by silica gel column chromatography using a 20-40% EtOAc in hexane gradient elution to give 96% yield of the product as a white solid. ^{1}H NMR data match previously reported data.[19] ^{1}H NMR ($CDCl_3$): δ 8.22 (dd, 1H, J = 8.0, 1.4 Hz), 7.87 (d, 1H, J = 6.1 Hz), 7.68 (ddd, 1H, J = 8.6,

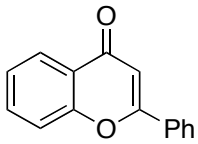
8.0, 1.4 Hz), 7.47 (d, 1H, J = 8.6 Hz), 7.42 (t, 1H, J = 8.0 Hz), 6.36 (d, 1H, J = 6.1 Hz).



(Table 2, entry 8): Prepared as described above. Purified by silica gel column chromatography using a 20-40% EtOAc in hexane gradient elution to give 94% yield of the product as a white solid. ^{1}H NMR data match previously reported data.[20] ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 1H, J = 2.6 Hz), 7.86 (d, 1H, J = 6.2 Hz), 7.62 (dd, 1H, J = 8.9, 2.6 Hz), 7.43 (d, 1H, J = 8.9 Hz), 6.36 (d, 1H, J = 6.2 Hz).

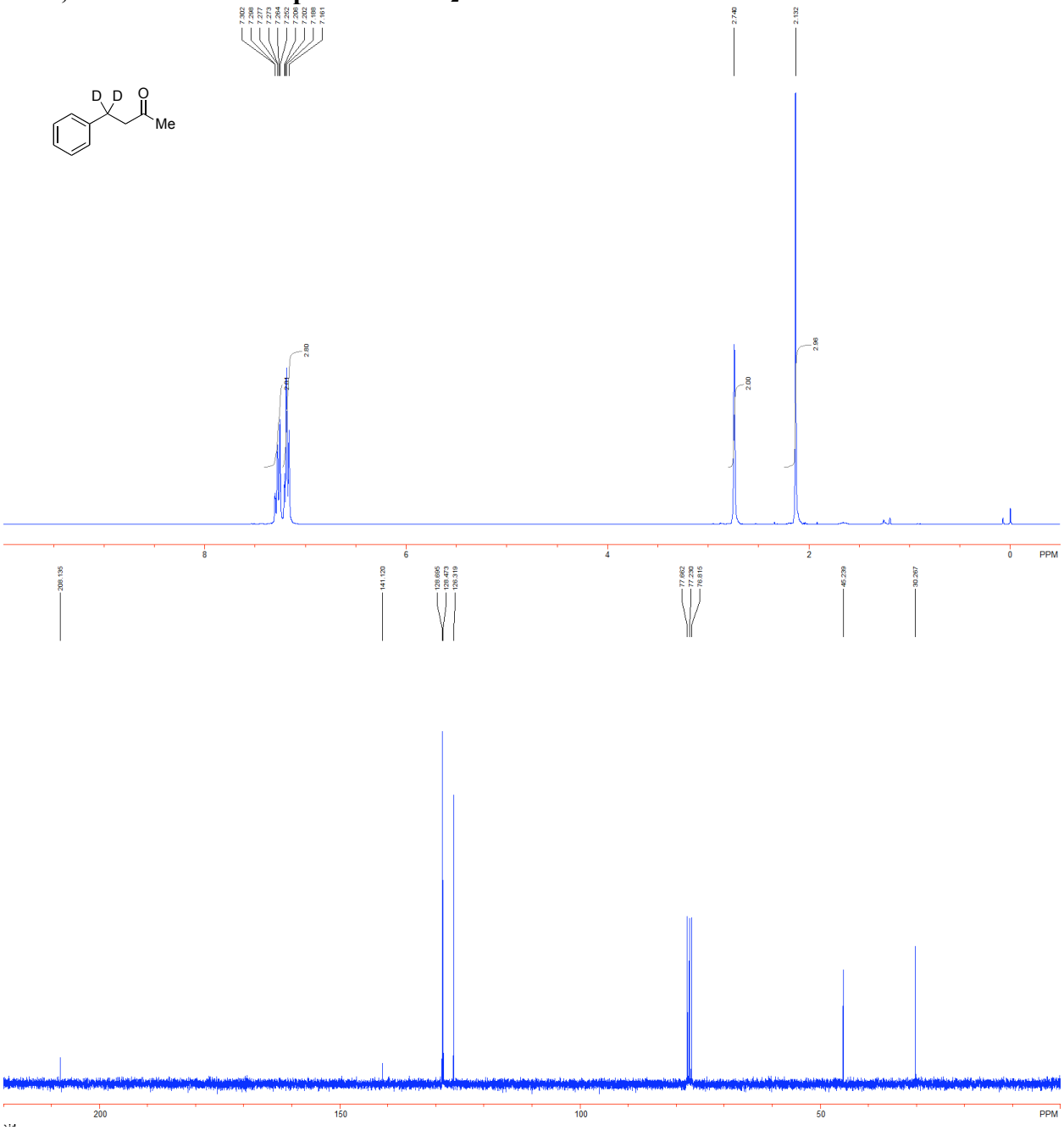


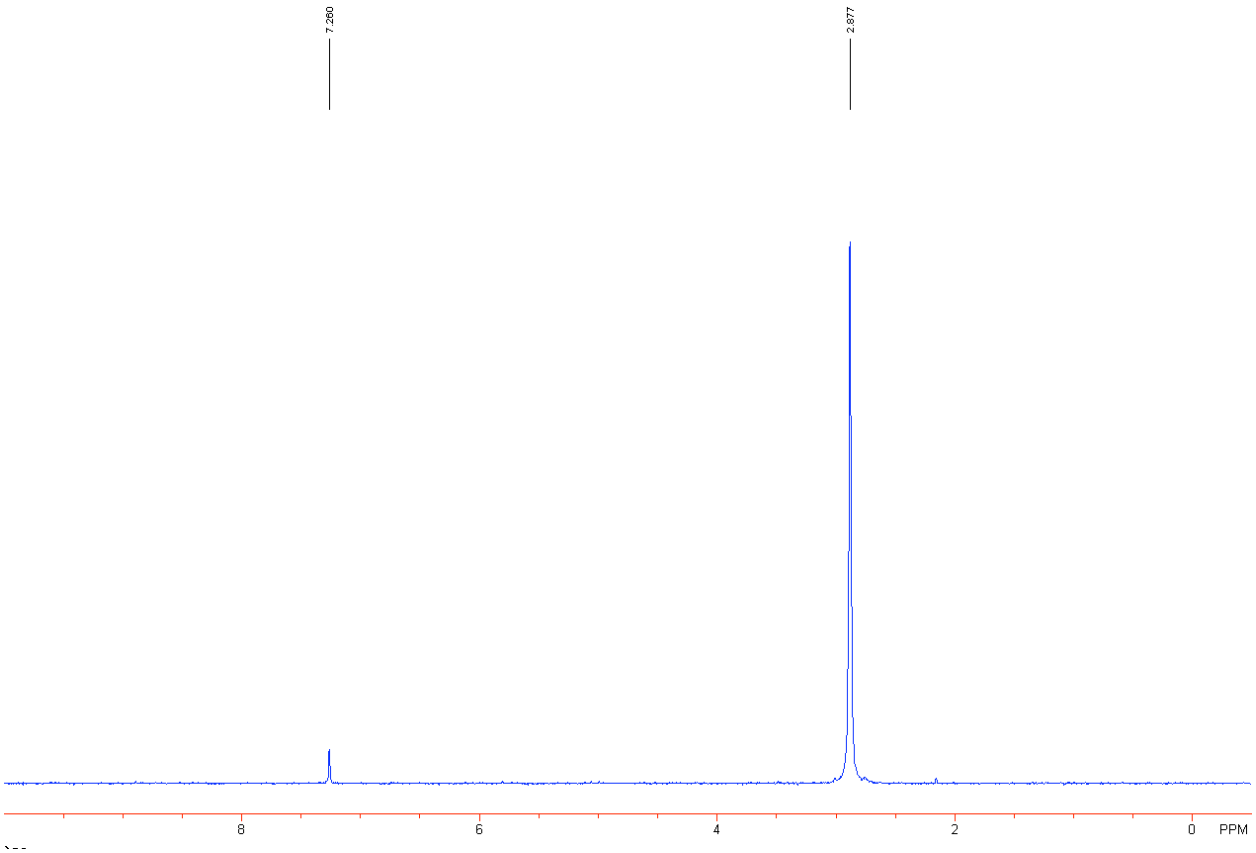
(Table 2, entry 9): Prepared as described above. Purified by silica gel column chromatography using a 30% EtOAc in hexane gradient elution to give 94% yield of the product as a white solid. ^{1}H NMR data match previously reported data.[21] ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J = 6.0 Hz), 7.85 (dd, 1H, J = 8.2, 3.2 Hz), 7.48 (dd, 1H, J = 9.0, 4.4 Hz), 7.40 (ddd, 1H, J = 9.0, 7.5, 3.2 Hz), 6.34 (d, 1H, J = 6.0 Hz).



(Table 2, entry 10): Prepared as described above. The reaction mixture was washed with water and extracted with ethyl acetate. The mixture was purified by silica gel column chromatography using a gradient 0%-30% EtOAc in hexane elution to give 88% yield of the product as a white solid. ^{1}H NMR matches previously reported data.[22] ^{1}H NMR ($CDCl_3$): δ 8.25 (dd, 1H, J = 8.0, 1.6 Hz), 7.99-7.89 (m, 2H), 7.72 (ddd, 1H, J = 8.6, 7.1, 1.6 Hz), 7.59 (dd, 1H, J = 8.6, 1.0 Hz), 7.57-7.49 (m, 3H), 7.44 (ddd, 1H, J = 8.0, 7.1, 1.0), 6.88 (s, 1H).

9. ^{1}H, ^{13}C and ^{2}H NMR Spectra for 3-d_2.




7.260
2.877
8
6
4
2
0
PPM

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