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Two-Chamber Hydrogen Generation and Application: Access to Pressurized Deuterium Gas

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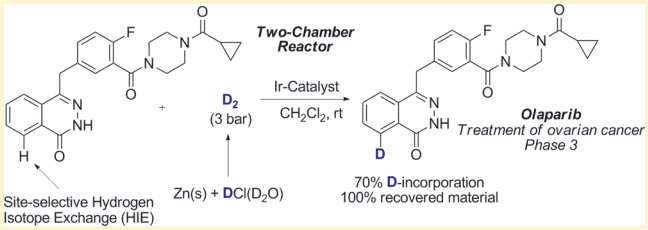
Supporting Information

ABSTRACT: Hydrogen and deuterium gas were produced and directly applied in a two-chamber system. These gaseous reagents were generated by the simple reaction of metallic zinc with HCl in water for H_2 and DCl in deuterated water for D_2. The setup proved efficient in classical Pd-catalyzed reductions of ketones, alkynes, alkenes, etc. in near-quantitative yields. The method was extended to the synthesis and isotope labeling of quinoline and 1,2,3,4-tetrahydroquinoline derivatives. Finally, CX-546 and Olaparib underwent efficient Ir-catalyzed hydrogen isotope exchange reactions.



Stable isotope labeling is an important tool in numerous disciplines, including mechanistic investigations, structural elucidation, construction of materials, and in the determination of biomolecule metabolism. Hydrogen is omnipresent in biologically relevant compounds, and their isotopes represent a means to obtain information on these compounds without changing their inherent structure. Isotopes of hydrogen offer important tools in all phases of drug development, where the radioactive isotope ^3H is extensively used in the determination of pharmacokinetic and pharmacodynamic properties.[1] The stable isotope deuterium (D) is applied in the construction of analytical standards for GC- and LC-MS analysis.[2] Recently, D has received considerable attention for its ability to improve on the metabolic stability of pharmaceuticals, via selective substitution of protons on metabolically labile positions, known as metabolic shunting.[3]

Hydrogenation and hydrogen isotope exchange (HIE) reactions are important tools for the incorporation of deuterium and tritium into molecules as they offer late stage incorporation due to the mild conditions applied in such transformations.[4] Recent advances in this area have focused on transfer hydrogenation with deuterated low molecular weight alcohols or deuterium oxide (D_2O), using transition metal catalysts based on rhodium,[5] palladium,[5] platinum,[6] and iridium.[7,8] D_2O has been studied extensively as a precursor for D_2-gas, as it is the least expensive and most readily available source of D. In particular, a pre-equilibration of a H_2 atmosphere over Pd/C in D_2O has proven useful for obtaining small quantities of D_2-gas.[9]

Here, we wish to report a simple tool for H_2 and D_2 generation and direct application in a two-chamber reactor. The straightforward setup applies metallic zinc and HCl or DCl as the precursor system providing simple access to pressurized H_2 and D_2 in standard fumehood settings. To demonstrate the method, measured quantities of the gaseous reagents were applied in classical reductions and HIE reactions of biological relevant structures with pressurized D_2-gas.

All reactions were performed in a two-chamber system (COware), in which H_2 or D_2 was generated in chamber A by reacting aqueous HCl or DCl with granular metallic zinc (Figure 1).[10] The produced gaseous reagents were utilized directly in transition metal catalyzed reductions or HIE reactions in Chamber B. The choice of conditions for H_2 and D_2 gas generation was based on the broad commercial availability of zinc, aqueous HCl or DCl, and the ease of setup. Special PTFE caps (H-Caps) fitted with O-rings were used to seal the COware system thereby efficiently preventing loss of H_2 or D_2 due to diffusion (Figure 1).[11] Alternative

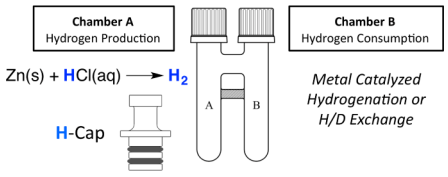


Figure 1. Production and application of H_2 or D_2 in the two-chamber reactor.

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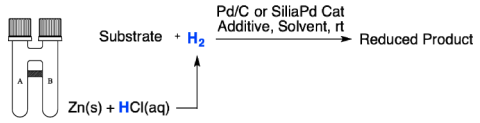
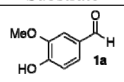
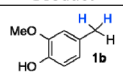
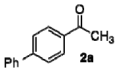
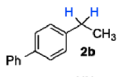
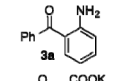
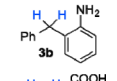
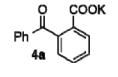
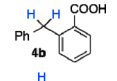
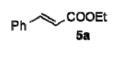
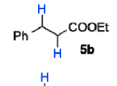
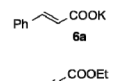
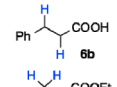
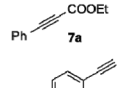
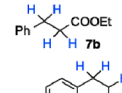
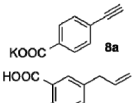
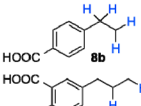
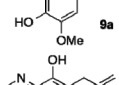
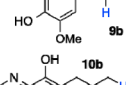
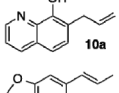
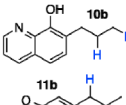
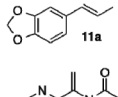
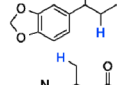
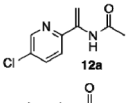
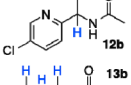
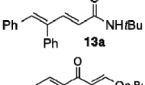
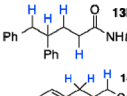
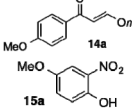
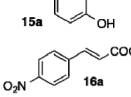
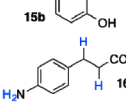
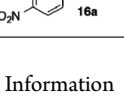
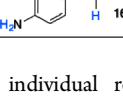
means toward the production of H_2 or D_2 would undoubtedly also prove useful in the same COware setup. Regardless of whether HCl or zinc was applied as the limiting reagent, the gaseous reagent was provided in a reliable manner. We found that HCl (4−6 M) and granular zinc (30 mesh) provided a release rate which was sufficiently slow to allow the system to be sealed with insignificant loss of hydrogen and fast enough to effectively imitate balloon or low autoclave pressure (2−4 bar of hydrogen).[12]

With this setup in hand, we set forth to test the H_2-generator applicability in the Pd-catalyzed reduction of alkynes, olefins, ketones, and aldehydes (Table 1). Reactions were performed applying an excess of 1 equiv of H_2 compared to that required by theory, to complete the reduction in the secondary chamber.[13,14] Vanillin (**1a**) was successfully transformed to its corresponding tolyl-derivative **1b** in 92% isolated yield (entry 1). Simple and substituted ketones were tested, and all products could be isolated in yields ranging from 76% to 99% yield (entries 2−4). Different alkenes, a diene, and alkynes (terminal and internal) were reduced using Pd/C or SiliaCat as the catalyst furnishing the reduced products in yields attaining quantitative (entries 5−11 and 13). The reduction of cinnamic acid (**6a**) on a 40 mmol scale afforded an excellent 99% isolated yield of 3-phenylpropanoic acid (**6b**) (entry 6, yield in brackets). Applying an excess of only 1 equiv of H_2 gas left the chloride unreduced in the reduction of *N*-(1-(5-chloro-2-pyridinyl)vinyl)acetamide (**12a**) (entry 12).[15] Reduction of both the ketone and the vinyl ether moiety in **14a** took place, and a 78% yield of **14b** could be secured upon column chromatography (entry 14). Finally, nitro-compounds **15a** and **16a** underwent reduction and their corresponding anilines were obtained in 97% and 99% isolated yields (entries 15 and 16, respectively).

Satisfied with the results obtained utilizing H_2-gas, we turned our attention toward the application of D_2-gas. The simple substitution of the aqueous HCl (4 M) for DCl (4 M) in D_2O would produce D_2-gas, reflecting the combined isotopic purity of the DCl and D_2O applied. For comparison, entries from Table 1 were selected for D-labeling, the results of which are depicted in Table 2. To avoid isotopic contamination, all carboxylic acid derivatives were converted into potassium carboxylates prior to reduction (entries 2, 4, 6, and 8). The reduction of ketones resulted in excellent isolated yields and

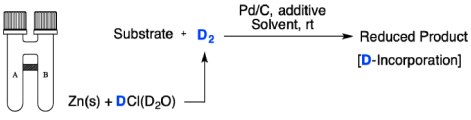
Table 1. Hydrogenations Using HCl and Zn as a Hydrogen Source in COware[a]

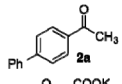
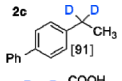
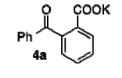
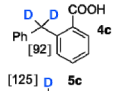
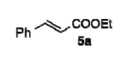
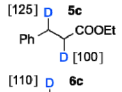


Entry	Substrate	Product	Yield[b]
1			92
2			99
3			76
4			99
5			99
6			94 (99)[c]
7			99
8			91
9			99[d]
10			99[d]
11			99
12			74
13			84
14			78
15			97
16			99

[a]See Supporting Information for individual reaction conditions. [b]Isolated yields after column chromatography. [c]Reaction performed on 40 mmol scale with a theroretical 1.25 equiv of H_2 generated in chamber A. [d]SiliaCat was used as the catalyst.

Table 2. Hydrogenations Using D_2 Generated from DCl and Zn in COware[a]



Entry	Substrate	Product	Yield[b]
1			99
2			99
3			98
4			94
5			99
6			97
7			92
8			96[c]

[a]See Supporting Information for individual reaction conditions. [b]Isolated yields after column chromatography. [c]Reaction performed on 13 mmol scale.

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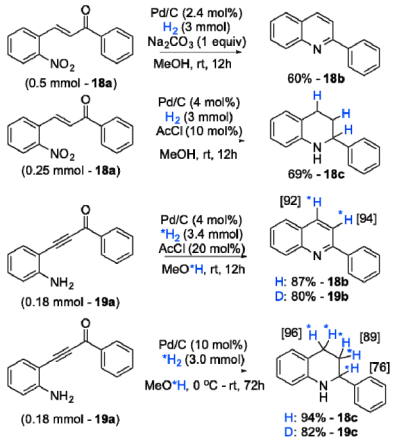
good 91% and 92% isotopic incorporation at the benzylic position (entries 1 and 2, respectively).

Next, the ethyl ester and potassium salt derivatives of cinnamic acid (**5a** and **6a**) were reacted with D_2-gas generating the reduced products in 98% and 94% isolated yields (compounds **5c** and **6c**). The D-incorporation at the benzylic position in both **5c** and **6c** exceeds 100%, as secondary HIE occurs with excess D_2-gas remaining in the reactor headspace. The reduction of ethyl-3-phenyl propiolate (**7a**) and potassium 4-ethynylbenzoate (**8a**) occurred in near-quantitative yields (entries 5 and 6). D-incorporation in **8c** was only 84% at the benzylic position, which could be a result of H/D scrambling at the terminal alkyne position prior to the reduction events, leading to a lower isotopic purity of the D_2-gas. This same argument would also explain the >100% D-incorporation at the 2-position in **8c** (entry 6). An example of a very efficient benzylic HIE reaction, occurring after the reduction, is presented for isosafrole (**11a**). Here, the reduction afforded **11c** in 92% isolated yields, with a near-quantitative D-incorporation at the benzylic position. Finally, reduction of potassium 4-bromobenzoate (**17a**) on a 13 mmol scale was performed, affording 4-D-benzoic acid (**17c**) in 96% isolated yield with >98% D-incorporation (entry 8).

Given our interest in labeling of the Tau-binding quinoline-core ligands, we decided to apply the generator system for the formation and labeling of 2-phenylquinoline and its reduced counterpart (Scheme 1). The idea was to apply the nitro-

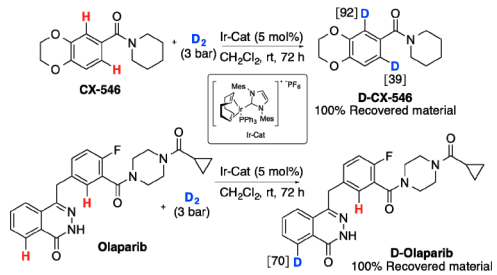
Scheme 1. Synthesis and D_2-Labeling of 2-Phenyl-quinoline and 2-Phenyl-1,2,3,4-tetrahydroquinoline in COware



chalcone **18a**, where the reduced nitro-group would condense with the ketone to form the quinoline core. Furthermore, reduction of the α,β-unsaturation prior to ring condensation would provide the fully reduced quinoline system **18c**. Although both of these reactions did occur, only 60% and 69% of the desired products **18b** and **18c**, respectively, could be isolated. Instead, **19a** was tested, as this would also provide access to the fully labeled analogues. After optimization, it was found that, by reacting **19a** with Pd/C in methanol under 5 bar of H_2 in the presence of acetyl chloride (20 mol %), **18b** was obtained in 87% isolated yield. By omitting acetyl chloride and increasing the Pd/C-loading, higher selectivity for the fully reduced **18c** was induced. Initiating the reaction at 0 °C for 2 h, before slowly warming up to ambient temperature, afforded full selectivity for the 1,2,3,4-tetrahydroquinoline adduct. By this approach, **18c** could be secured in an excellent 94% isolated yield. Next, both **19b** and **19c** could be synthesized using identical conditions applying a pressurized atmosphere of D_2-gas, being isolated in 80% and 82% yield, respectively, with excellent D-incorporation.

Finally, HIE reactions were attempted with CX-546, an ampakine drug developed for the treatment of schizophrenia, and Olaparib, a compound for the treatment of ovarian cancer currently undergoing phase three studies (Scheme 2). Under an

Scheme 2. Hydrogen Isotope Exchange Reactions on CX-546 and Olaparib in COware



excess of D_2-gas (3 bar) and with a 5 mol % loading of the iridium catalyst depicted in Scheme 2, HIE was effectively observed on both substrates.[7] For CX-546, exchange occurred at both *ortho*-positions to the carbonyl functionality. Electronic factors play an important role with the more electron-rich position undergoing an excellent 92% isotope exchange compared to the 39% exchange for the less electron-rich position (D-CX-546).

In the case of Olaparib, two potential positions could undergo HIE, both being positioned *ortho* to a carbonyl directing group. Examination of the ^{1}H NMR spectrum obtained after product purification revealed that HIE had occurred selectively on the phthalazinone moiety. Whether this selectivity is due to electronic or sterical effects is unknown; however, an excellent 70% D-incorporation was obtained in D-Olaparib. Although, it is not known by the authors whether the H/D exchanged positions in both CX-546 and Olaparib are involved in metabolic pathways, these examples clearly demonstrate simple labeling of highly functionalized targets, something which could be directly transferred to tritium-labeling under identical conditions.

In conclusion, a highly efficient, yet simple method for the production and application of H_2 and D_2 gas has been developed. The gaseous reactants were produced from readily available metallic zinc and aqueous HCl or DCl. The method proved useful in reductions of carbonyl groups, alkynes, and olefins in excellent yields. The method was further applied for the synthesis and isotope labeling of 2-phenylquinolines and penta-isotoptically labeled 2-phenyl-1,2,3,4-tetrahydro-quinoline. Finally, Ir-catalyzed HIE reactions were performed directly on the active pharmaceutical ingredients CX-546 and Olaparib with high D-incorporations. We believe that this method will find use in numerous chemical transformations in the general synthetic laboratory due to its ease of setup and access to pressurized H_2 and D_2 gas using simple "off the shelf" chemicals.

EXPERIMENTAL SECTION

General Methods. Dry solvents were prepared according to standard literature procedures.[16] All other chemicals were used as received from the suppliers unless mentioned otherwise. Starting

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materials were made according to literature procedures. Flash column chromatography was performed on silica gel 60 (230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. All D-incorporations were determined by ^{1}H NMR recorded with the relaxation time set to 60 s; see Supporting Information for general formula and calculation method. Chemical shifts are reported in ppm downfield to TMS (∂ = 0) and referenced to the solvent residual peak,[17] using the following peak pattern abbreviations: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; pent, pentet; sext, sextet; sept, septet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets, and td, triplet of doublets. HRMS was recorded on an LC TOF (ES).

General Method for Reductive Hydrogenation. The substrate (X mmol), Pd-catalyst, and solvent were added to chamber B. Chamber B was sealed with a screw cap fitted with an H-Cap. To chamber A of the COware were added zinc granular and 4 M HCl or DCl with a syringe. Then chamber A was sealed directly after the addition of HCl or DCl, using a screw cap fitted with an H-Cap. The reaction was left at the temperatures and reaction times stated for each example below. The crude reaction product was applied to flash column chromatography to yield the desired compounds.

4-Ethyl-2-methoxyphenol (1b).[18] General method with 1-(4-hydroxy-3-methoxyphenyl)ethan-1-one (152.0 mg, 1.0 mmol), Pd/C (15.2 mg, 10 wt %), AcCl (7.1 μL, 10 mol %), and methanol (2 mL) in chamber B. To chamber A were added zinc granular (294.0 mg, 4.5 mmol) and 2.4 M HCl (2.5 mL, 6.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was filtrated through Celite and concentrated to give the title compound as a yellow oil (126.9 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.81 (d, J = 7.8 Hz, 1H), 6.68−6.65 (m, 2H), 5.43 (s, 1H), 3.87 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 146.3, 143.3, 129.6, 121.5, 114.2, 111.7, 55.8, 21.0.

4-Ethyl-1,1′-biphenyl (2b). General method with 1-([1,1′-biphenyl]-4-yl)ethan-1-one (196.2 mg, 1.0 mmol), Pd/C (19.6 mg, 10 wt %), and cyclopentyl methyl ether (CPME) (2 mL) in chamber B. To chamber A were added zinc granular (196.2 mg, 3.0 mmol) and 4 M HCl (2.25 mL, 9 mmol). The reaction was left at 50 °C overnight. The crude reaction product was filtrated through Celite and silica and concentrated to give the title compound as a colorless oil (180.4 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72−7.70 (m, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.53 (t, J = 7.4, 2H), 7.45−7.41 (m, 1H), 7.38 (d, J = 8.3 Hz, 2H), 2.81 (q, J = 7.6 Hz, 2H), 1.41 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 143.5, 141.3, 138.7, 128.8 (2C), 128.4 (2C), 127.2 (2C), 127.1 (2C), 127.1, 28.6, 15.7. HRMS (ESI-TOF) m/z: $[M + K]^+$ calculated for $C_{14}H_{14}K$: 221.0727; found: 221.0729.

2-Benzylaniline (3b).[19] General method with (2-aminophenyl)-(phenyl)methanone (197.0 mg, 1.0 mmol), Pd/C (19.7 mg, 10 wt %), AcCl (3.6 μL, 5 mol %), and methanol (1 mL) in chamber B. To chamber A were added zinc granular (294 mg, 4.5 mmol) and 4 M HCl (2.5 mL, 6.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was applied to flash column chromatography (20% ether in pentane) to give the title compound as a beige solid (139.5 mg, 76%); mp 49−54 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (dt, J = 1.6 Hz, J = 5.2 Hz, 2H), 7.28−7.23 (m, 3H), 7.17−7.10 (m, 2H), 6.83 (dt, J = 1.3 Hz, J = 7.5 Hz, 1H), 6.71 (dd, J = 0.9 Hz, J = 7.8 Hz, 1H), 3.95 (s, 2H), 3.52 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.8, 139.4, 130.9, 128.7 (2C), 128.6 (2C), 127.7, 126.4, 125.1, 118.8, 116.0, 38.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{14}H_{13}N$: 184.1121, found: 184.1120.

2-Benzylbenzoic Acid (4b). General method with potassium 2-benzoylbenzoate (226.2 mg, 1.0 mmol), Pd/C (22.6 mg, 10 wt %), concentrated HCl (0.1 mL), and methanol/CPME (1:1) (2 mL) in chamber B. To chamber A were added zinc granular (196.2 mg, 3.0 mmol) and 4 M HCl (2.5 mL, 9.0 mmol). The reaction was left at room temperature overnight. The product was obtained by acidic extraction with 1 M HCl, followed by filtration through Celite and silica, to give the title compound as a colorless solid (210.1 mg, 99%); mp 113−115 °C. ^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 7.90 (d, J = 7.7 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.34−7.24 (m, 4H), 7.16 (m, 3H), 4.38 (s, 2H). ^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 169.4, 143.4, 142.3, 133.2, 132.6, 131.7, 130.6, 129.7 (2C), 129.2 (2C), 127.3, 126.8, 39.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{14}H_{13}O_2$: 213.0910, found: 213.0907.

Ethyl-3-phenylpropanoate (5b). General method with ethyl cinnamate (176.2 mg, 1.0 mmol), Pd/C (17.6 mg, 10 wt %), and CPME (2 mL) in chamber B. To chamber A were added zinc granular (130.8 mg, 2.0 mmol) and 4 M HCl (1.5 mL, 6.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was filtrated through Celite and silica to give the title compound as a colorless oil (176.4 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36−7.24 (m, 5H), 4.17 (q, J = 7.2 Hz, 2H), 3.00 (t, J = 7.7 Hz, 2H), 2.67 (t, J = 8.0 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.9, 140.6, 128.5 (2C), 128.3 (2C), 126.2, 60.4, 36.0, 31.0, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{11}H_{15}O_2$: 179.1067; found: 179.1065.

3-Phenylpropanoic Acid (6b). General method with potassium cinnamate (186.2 mg, 1.0 mmol), Pd/C (18.6 mg, 10 wt %), and methanol (2 mL) in chamber B. To chamber A were added zinc granular (130.8 mg, 2.0 mmol) and 4 M HCl (1.5 mL, 6.0 mmol). The reaction was left at room temperature overnight. The product was obtained by acidic extraction with 1 M HCl, followed by filtration through Celite and silica, to give the title compound as a colorless solid (141.2 mg, 94%); mp 46−48 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.12 (br s, 1H), 7.36−7.33 (m, 2H), 7.29−7.25 (m, 3H), 3.01 (t, J = 7.6 Hz, 2H), 2.73 (t, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 179.4, 140.2, 128.6 (2C), 128.3 (2C), 126.4, 35.7, 30.6. HRMS (ESI-TOF) m/z: [M + H]+ calculated for $C_9H_{11}O_2$: 151.0754; found: 151.0761.

Ethyl 3-Phenylpropanoate (7b). General method with ethyl 3-phenylpropriolate (174.2 mg, 1.0 mmol), Pd/C (17.4 mg, 10 wt %), and CPME (2 mL) in chamber B. To chamber A were added zinc granular (196.2 mg, 3.0 mmol) and 4 M HCl (2.25 mL, 9.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was filtrated through Celite and silica to give the title compound as a colorless oil (176.4 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35−7.22 (m, 5H), 4.17 (q, J = 7.1 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 2.67 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 140.6, 128.4 (2C), 128.3 (2C), 126.2, 60.3, 35.9, 31.0, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{11}H_{15}O_2$: 179.1067; found: 179.1066.

4-Ethylbenzoic Acid (8b). General method with potassium 4-ethynylbenzoate (92.1 mg, 0.5 mmol, Pd/C (9.2 mg, 10 wt %) and methanol (3 mL) in chamber B. In chamber A were added zinc granular (98.1 mg, 1.5 mmol) and 4 M HCl (1.13 mL, 4.5 mmol). The reaction was left at room temperature overnight. The reaction product was obtained by acidic extraction with 1 M HCl, followed by filtration through Celite and silica to give the title compound as a light yellow solid (68.3 mg, 91%); mp 111−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 12.42 (br s, 1H), 8.05 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 2.73 (q, J = 7.4 Hz, 2H), 1.28 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.5, 150.8, 130.4 (2C), 128.0 (2C), 126.8, 29.1, 15.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_9H_{11}O_2$: 151.0754; found: 151.0755.

2-Hydroxy-3-methoxy-5-propylbenzoic Acid (9b). General method with 5-allyl-2-hydroxy-3-methoxybenzoic acid (208.2 mg, 1.0 mmol), SiliaCat (20.0 mg, 0.1 mol %), and CPME (2 mL) in chamber B. To chamber A were added zinc granular (196.2 mg, 3.0 mmol) and 1.7 M HCl (2.33 mL, 4.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was filtrated through Celite to give the title compound as a colorless solid (210.0 mg, 99%); mp 121−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.39 (br s, 1H), 7.33 (d, J = 1.9 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 3.91 (s, 3H), 2.54 (t, J = 7.4 Hz, 2H), 1.60 (sext, J = 7.5 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.2, 150.6, 148.2, 133.4, 120.9, 118.4, 111.1, 56.2, 37.4, 24.4, 13.6. HRMS (ESI-TOF) m/z: [M - H] calculated for $C_{11}H_{13}O_4$: 209.0819; found: 209.0821.

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7-Propylquinolin-8-ol (10b). General method with 7-allylquinolin-8-ol (185.2 mg, 1.0 mmol), SiliaCat (20.0 mg, 0.1 mol %), and CPME (2 mL) in chamber B. To chamber A were added zinc granular (196.2 mg, 3.0 mmol) and 1.7 M HCl (2.33 mL, 4.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was filtrated through Celite to give the title compound as a brown oil (186.2 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.76 (dd, J = 1.5 Hz, J = 4.2 Hz, 1H), 8.48 (br s, 1H), 8.10 (dd, J = 1.6 Hz, J = 8.2 Hz, 1H), 7.45−7.41 (m, 2H), 7.28 (d, J = 8.4 Hz, 1H), 2.94 (t, J = 7.5 Hz, 2H), 1.77 (sext, J = 7.4 Hz, 2H), 1.11 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.2, 147.7, 138.1, 135.9, 129.9, 126.8, 124.4, 120.8, 117.0, 32.0, 23.2, 14.1. HRMS (ESI-TOF) m/z: [M + H]+ calculated for $C_{12}H_{14}NO$: 188.1070; found: 188.1071.

5-Propylbenzo[*d*][1,3]dioxole (11b).[20] General method with isosafrole ((*E*)-5-(prop-1-en-1-yl)benzo[*d*][1,3]dioxole) (810.9 mg, 5.0 mmol), Pd/C (81.1 mg, 10 wt %), and methanol (10 mL) in chamber B. To chamber A was added zinc granular (654.0 mg, 10.0 mmol) and 4 M HCl (7.5 mL, 30.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was filtrated through Celite and silica to give the title compound as a colorless oil (812.8 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.73 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 1.5 Hz, 1H), 6.63 (dd, J = 1.6, J = 7.9 Hz, 1H), 5.92 (s, 2H), 2.52 (t, J = 7.4 Hz, 2H), 1.61 (sext, J = 7.4 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 147.5, 145.4, 136.6, 121.1, 108.9, 108.0, 100.7, 37.8, 24.8, 13.7. HRMS could not be obtained for this compound. Instead GCMS was performed. GCMS $C_{10}H_{12}O_2$ [M + e$^-$]; calculated: 164; found: 164 (60%), 135 (100%), 77 (30%).

***N*-(1-(5-Chloropyridin-2-yl)ethyl)acetamide (12b).** General method with *N*-(1-(5-chloropyridin-2-yl)vinyl)acetamide (196.6 mg, 1.0 mmol), Pd/C (10 mg, 5 wt %), and CPME (2 mL) in chamber B. To chamber A were added zinc granular (196.2 mg, 3.0 mmol) and 1.7 M HCl (2.33 mL, 4.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was purified by flash column chromatography (ethyl acetate) to give the title compound as a pale brown oil (147.8 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.41 (d, J = 2.4 Hz, 1H), 7.55 (dd, J = 2.4 Hz, J = 8.3 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 5.3 Hz, 1H), 5.06 (pent, J = 7.0 Hz, 1H), 1.95 (s, 3H), 1.37 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.5, 159.4, 147.8, 136.5, 130.5, 122.3, 49.3, 23.3, 22.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for $C_9H_{12}ClN_2O$: 199.0633; found: 199.0636.

***N*-(*tert*-Butyl)-4,5-diphenylpentanamide (13b).** General method with (2E,4Z)-*N*-(*tert*-butyl)-4,5-diphenylpenta-2,4-dienamide (76.6 mg, 0.25 mmol), Pd/C (7.6 mg, 10 wt %), and CPME (1 mL) in chamber B. To chamber A were added zinc granular (49.1 mg, 0.75 mmol) and 4 M HCl (0.56 mL, 2.25 mmol). The reaction was left at room temperature overnight. The crude reaction product was purified by flash column chromatography (30% ether in pentane) to give the title compound as a colorless solid (65.3 mg, 84%); mp 68−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29−7.25 (m, 2H), 7.21−7.16 (m, 3H), 7.15−7.10 (m, 3H), 7.03−7.01 (m, 2H), 5.04 (br s, 1H), 2.95−2.89 (m, 2H), 2.86−2.79 (m, 1H), 2.16−2.05 (m, 1H), 1.96−1.79 (m, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.9, 144.1, 140.3, 129.1 (2C), 128.4 (2C), 128.1 (2C), 127.8 (2C), 126.3, 125.8, 51.0, 47.5, 44.0, 35.5, 31.1, 28.8 (3C). HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for $C_{21}H_{28}NO$: 310.2165; found: 310.2169.

1-(3-Butoxypropyl)-4-methoxybenzene (14b). General method with (*E*)-3-butoxy-1-(4-methoxyphenyl)prop-2-en-1-one (117 mg, 0.5 mmol), Pd/C (11.7 mg, 10 wt %), and *n*-BuOH (2 mL) in chamber B. To chamber A were added zinc granular (130.8 mg, 2.0 mmol) and 4 M HCl (1.5 mL, 6.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was purified by flash column chromatography (2.5% ether in pentane) to give the title compound as a colorless oil (86.7 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26−7.10 (m, 2H), 6.86−6.82 (m, 2H), 3.79 (s, 3H), 3.44−3.41 (m, 4H), 2.65 (t, J = 7.4 Hz, 2H), 1.88 (pent, J = 6.5 Hz, 2H), 1.59 (pent, J = 6.6 Hz, 2H), 1.41 (sext, J = 7.1 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.7, 134.1, 129.3 (2C), 113.7 (2C), 70.7, 69.9, 55.2, 31.9, 31.6, 31.4, 19.4, 13.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for $C_{14}H_{23}O_2$: 223.1693; found: 223.1692.

2-Amino-4-methoxyphenol (15b). General method with 4-methoxy-2-nitrophenol (85.3 mg, 0.5 mmol), Pd/C (8.5 mg, 10 wt %), and methanol (2 mL) in chamber B. To chamber A were added zinc granular (163.5 mg, 2.5 mmol) and 4 M HCl (1.88 mL, 7.5 mmol). The reaction was left at room temperature overnight. The crude reaction product was purified by flash column chromatography (2.5% ether in pentane) to give the title compound as an off-white solid (67.8 mg, 97%); mp 135−140 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3): δ (ppm) 8.45 (br s, 1H), 6.54 (d, J = 8.5 Hz, 1H), 6.22 (d, J = 3.0 Hz, 1H), 5.97 (dd, J = 3.0 Hz, J = 8.5 Hz, 1H), 4.53 (br s, 2H). 3.59 (s, 3H). ^{13}C NMR (100 MHz, CD_3SOCD_3): δ (ppm) 153.5, 138.5, 137.9, 115.0, 101.4, 100.8, 55.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for $C_7H_{10}NO_2$: 140.0706; found: 140.0706.

3-(4-Aminophenyl)propanoic Acid (16b).[21] General method with (*E*)-3-(4-nitrophenyl)acrylic acid (97.0 mg, 0.5 mmol), Pd/C (9.7 mg, 10 wt %), and acetic acid (2 mL) in chamber B. To chamber A were added zinc granular (163.5 mg, 2.5 mmol) and 4 M HCl (1.88 mL, 7.5 mmol). The reaction was left at room temperature overnight. The crude reaction product was purified by flash column chromatography (2.5% ether in pentane) to give the title compound as a colorless solid (84.1 mg, 99%); mp 142−144 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3): δ (ppm) 6.85 (d, J = 8.2 Hz, 2H), 6.47 (d, J = 8.2 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 2.41 (t, J = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, CD_3SOCD_3): δ (ppm) 174.5, 147.0, 129.0 (2C), 128.4 (2C), 114.4, 36.4, 30.2. HRMS (ESI-TOF) m/z: [M + H]+ calculated for $C_9H_{12}NO_2$: 166.0863; found: 166.0858.

4-(Ethyl-1,1-d_2)-1,1′-biphenyl (2c). General method with 1-([1,1′-biphenyl]-4-yl)ethan-1-one (196.2 mg, 1.0 mmol), Pd/C (19.6 mg, 10 wt %), and cyclopentyl methyl ether (CPME) (2 mL) in chamber B. To chamber A were added zinc granular (196.2 mg, 3.0 mmol) and 4 M DCl (2.25 mL, 9 mmol). The reaction was left at 50 °C overnight. The crude product was filtrated through Celite and silica and concentrated to give the title compound as a colorless oil (182.4 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72−7.70 (m, 2H), 7.64 (dt, J = 2.0 Hz, J = 8.3 Hz, 2H), 7.54 (t, J = 7.4 Hz, 2H), 7.44 (dt, J = 1.1 Hz, J = 6.6 Hz, 1H), 7.39 (dd, J = 1.8 Hz, J = 6.5 Hz, 2H), 2.79 (m, 0.18H), 1.38 (d, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 143.4, 141.3, 138.7, 128.8 (2C), 128.4 (2C), 127.2 (2C), 127.1 (2C), 127.1, 28.0 (m, C−D), 15.5. HRMS could not be obtained for this compound. Instead GCMS was performed. GCMS $C_{14}H_{12}D_2$ [M + e$^-$]; calculated: 184; found: 184 (70%), 169 (100%), 153 (15%).

2-(Phenylmethyl-d_2)benzoic Acid (4c). General method with potassium 2-benzoylbenzoate (226.2 mg, 1.0 mmol), Pd/C (22.6 mg, 10 wt %), concentrated DCl (0.1 mL), and methanol/CPME (1:1) (2 mL) in chamber B. To chamber A were added zinc granular (196.2 mg, 3.0 mmol) and 4 M DCl (2.5 mL, 9.0 mmol). The reaction was left at room temperature overnight. The product was obtained by acidic extraction with 1 M HCl, followed by filtration through Celite and silica, to give the title compound as a colorless solid (212.1 mg, 99%); mp 113−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15 (d, J = 7.8 Hz, 1H), 7.55 (td, J = 1.0 Hz, J = 7.6 Hz, 1H), 7.42−7.24 (m, 7H), 4.51 (s, 0.17H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.2, 143.6, 140.8, 133.2, 131.9, 131.9, 129.2 (2C), 128.6, 128.5 (2C), 126.5, 126.2, 39.6−39.1 (m, C−D). HRMS (ESI-TOF) m/z: [M + H]+ calculated for $C_{14}H_{11}D_2O_2$: 215.1036; found: 215.1034.

Ethyl 3-Phenylpropanoate-2,3-d_2 (5c). General method ethyl cinnamate (176.2 mg, 1.0 mmol), Pd/C (17.6 mg, 10 wt %), and CPME (2 mL) in chamber B. To chamber A were added zinc granular (130.8 mg, 2.00 mmol) and 4 M DCl (1.5 mL, 6.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was filtrated through Celite and silica to give the title compound as a colorless oil (176.6 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33−7.22 (m, 5H), 4.14 (q, J = 7.1 Hz, 2H), 2.95 (m, 0.75H), 2.61 (m, 1.0H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.9, 140.6, 128.5 (2C), 128.3 (2C), 126.2, 60.4, 35.9−35.3 (m, C−D), 30.9−30.3 (m, C−D), 14.2. HRMS (ESI-

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TOF) m/z: $[M + H]^+$ calculated for $C_{11}H_{13}D_2O_2$: 181.1192; found: 181.1191.

3-Phenylpropanoic-2,3-d_2 Acid (6c). General method with potassium cinnamate (186.2 mg, 1.0 mmol), Pd/C (18.6 mg, 10 wt %), and methanol (2 mL) in chamber B. To chamber A were added zinc granular (130.8 mg, 2.0 mmol) and 4 M DCl (1.5 mL, 6.0 mmol). The reaction was left at room temperature overnight. The product was obtained by acidic extraction with 1 M HCl, followed by filtration through Celite and silica, to give the title compound as a colorless solid (143.1 mg, 94%); mp 46−48 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.58 (br s, 1H), 7.43−7.31 (m, 5H), 3.05 (d, J = 5.1 Hz, 0.90H), 2.77 (d, J = 5.1 Hz, 1.01H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 179.8, 140.2, 128.7 (2C), 128.4 (2C), 126.5, 35.5 (dd, J = 20 Hz, J = 39 Hz, C−D), 32.0 (dd, J = 20 Hz, J = 39 Hz, C−D). HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_9H_9D_2O_2$: 153.0879; found: 153.0883.

Ethyl 3-Phenylpropanoate-2,2,3,3-d_4 (7c). General method with ethyl 3-phenylpropriolate (174.2 mg, 1.0 mmol), Pd/C (17.4 mg, 10 wt %), and CPME (2 mL) in chamber B. To chamber A were added zinc granular (196.2 mg, 3.0 mmol) and 4 M DCl (2.25 mL, 9.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was filtrated through Celite and silica to give the title compound as a colorless oil (180.4 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33−7.21 (m, 5H), 4.15 (q, J = 7.2 Hz, 2H), 2.98−2.94 (m, 0.07H), 2.64−2.60 (m, 0.10H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.9, 140.5, 128.5 (2C), 128.3 (2C), 126.3, 60.4, 35.7−35.0 (m, C−D), 30.6−30.0 (m, C−D), 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{11}H_{11}D_4O_2$: 183.1318; found: 183.1319.

4-(Ethyl-1,1,2,2-d_4)benzoic Acid (8c). General method with potassium 4-ethynylbenzoate (92.1 mg, 0.50 mmol), Pd/C (9.2 mg, 10 wt %), and methanol (3 mL) in chamber B. To chamber A were added zinc granular (98.1 mg, 1.5 mmol) and 4 M DCl (1.13 mL, 4.5 mmol). The reaction was left at room temperature overnight. The reaction product was obtained by acidic extraction with 1 M HCl, followed by filtration through Celite and silica, to give the title compound as a light yellow solid (74.5 mg, 97%); mp 111−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.86 (br s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 2.70 (m, 0.32H), 1.24 (m, 0.75H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.8, 150.7, 130.4 (2C), 128.0 (2C), 126.7. HRMS (ESI-TOF) m/z: [M + H]+ calculated for $C_9H_7D_4O_2$: 155.1005; found: 155.1005.

5-(Propyl-1,2-d_2)benzo[d][1,3]dioxole (11c). General method with isosafrole ((*E*)-5-(prop-1-en-1-yl)benzo[d][1,3]dioxole) (81.1 mg, 0.5 mmol), Pd/C (8.1 mg, 10 wt %), and CD_3OD (3 mL) in chamber B. To chamber A were added zinc granular (65.4 mg, 1 mmol) and 4 M DCl (0.75 mL, 3.0 mmol). The reaction was left at room temperature overnight. The crude reaction product was filtrated through Celite and silica to give the title compound as a colorless oil (76.5 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.73 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 1.6 Hz, 1H), 6.62 (dd, J = 1.7 Hz, J = 7.8 Hz, 1H), 5.92 (s, 2H), 2.48 (m, 0.08H), 1.59 (m, 1.06H), 0.93 (t, J = 7.2 Hz, 2.80H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 147.6, 145.6, 136.7, 121.2, 109.0, 108.1, 100.8, 37.4−36.9 (m, C−D), 24.8−24.2 (m, C−D), 13.8−13.4 (m, C−D). HRMS could not be obtained for this compound. Instead GCMS was performed. GCMS $C_{10}H_{10}D_2O_2$ [M + e^-]; calculated: 166; found: 166 (30%), 136 (100%), 78 (10%).

Benzoic-4-*d* Acid (17c).[22] General method with potassium 4-bromobenzoate (3.11 g, 13.0 mmol), Pd/C (137.0 mg, 10 mol %), K_2CO_3 (1.8 g, 13 mmol), and D_2O (26 mL) in chamber B. To chamber A was added zinc granular (1.70 g, 26.0 mmol) and 6 M DCl (17.3 mL, 104 mmol). The reaction was left at room temperature overnight. The reaction product was obtained by acidic extraction with 4 M HCl and ether, followed by filtration through Celite, to give the title compound as a colorless solid (1.53 g, 96%). Mp 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.14 (dd, J = 1.8 Hz, J = 6.6 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 133.9−133.3 (m, C−D), 130.2, 129.3, 128.4. HRMS (ESI-TOF) m/z: $[M - H]^+$ calculated for $C_7H_4DO_2$: 122.0358; found: 122.0358.

2-Phenylquinoline (18b). General method with (*E*)-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one (126.6 mg, 0.50 mmol), Pd/C (12.6 mg, 10 wt %), Na_2CO_3 (53.0 mg, 0.5 mmol), and MeOH (3 mL) in chamber B. To chamber A were added zinc granular (196.1 mg, 3.0 mmol) and 4 M HCl (2.25 mL, 9 mmol). The reaction was left at room temperature for 12 h. The crude reaction product was filtrated through Celite and purified by flash column chromatography (2.5% EtOAc in pentane) to give the title compound as a colorless solid (62 mg, 60%); mp 82−84 °C.

Alternatively, the title compound was prepared by the general method with 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one (40.0 mg, 0.18 mmol), Pd/C (8 mg, 10 wt %), acetyl chloride (2.5 μL, 0.04 mmol), and MeOH (2 mL) in chamber B. To chamber A were added zinc granular (141 mg, 2.16 mmol) and 4 M HCl (1.6 mL, 6.48 mmol). The reaction was left at room temperature for 12 h. The crude reaction product was filtrated through Celite and purified by flash column chromatography (increasing polarity 0−1.5% EtOAc in pentane) to give the title compound as a colorless solid (32.3 mg, 87%); mp 82−84 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.21 (d, J = 4.8 Hz, 1H), 8.21−8.17 (m, 3H), 7.87 (d, J = 8.4 Hz, 1H), 7.82 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 7.74 (ddd, J = 1.6 Hz, J = 6.8 Hz, J = 9.2 Hz, 1H), 7.57−7.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.5, 148.4, 139.8, 136.9, 129.9, 129.8, 129.4, 128.9 (2C), 127.7 (2C), 127.6, 127.3, 126.4, 119.1. HRMS (ESI-TOF) m/z: [M + H]+ calculated for $C_{15}H_{12}N$: 206.0964; found: 206.0974.

2-Phenyl-1,2,3,4-tetrahydroquinoline (18c). General method with (*E*)-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one (63.6 mg, 0.25 mmol), Pd/C (6.3 mg, 10 wt %), acetyl chloride (1.8 μL, 0.03 mmol), and MeOH (3 mL) in chamber B. To chamber A were added zinc granular (196.1 mg, 3.0 mmol) and 4 M HCl (2.25 mL, 9 mmol). The reaction was left at room temperature for 12 h. The crude reaction product was filtrated through Celite and purified by flash column chromatography (increasing polarity 0.5−1% EtOAc in pentane) to give the title compound as a colorless oil (36.3 mg, 69%).

Alternatively, the title compound was prepared by the general method with 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one (39.3 mg, 0.18 mmol), Pd/C (20 mg, 10 wt %), and MeOH (2 mL) in chamber B. To chamber A were added zinc granular (200 mg, 3.1 mmol) and 4 M HCl (2.6 mL, 12.9 mmol). The reaction was left at 0 °C, slowly heating to room temperature, for 72 h. The crude reaction product was filtrated through Celite and purified by flash column chromatography (increasing polarity 0−1.5% EtOAc in pentane) to give the title compound as a colorless oil (35 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45−7.38 (m, 4H), 7.35−7.31 (m, 1H), 7.06 (m, 2H), 6.70 (t, J = 7.6 Hz, 1H), 6.58 (d, J = 8 Hz, 1H), 4.48 (dd, J = 3.2 Hz, J = 9.2 Hz, 1H), 4.06 (br s, 1H), 2.97 (ddd, J = 5.2 Hz, J = 10.4 Hz, J = 16.0 Hz, 1H), 2.78 (dt, J = 4.8 Hz, J = 16.4 Hz, 1H), 2.20−2.13 (m, 1H), 2.09−1.99 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.9, 144.8, 129.4, 128.7 (2C), 127.5, 127.0, 126.7 (2C), 121.0, 117.3, 114.1, 56.4, 31.1, 26.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{15}H_{16}N$: 210.1277; found: 210.1278.

2-Phenylquinoline-3,4-d_2 (19b). General method with 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one (40.0 mg, 0.18 mmol), Pd/C (8 mg, 10 wt %), acetyl chloride (2.5 μL, 0.04 mmol), and CD_3OD (2 mL) in chamber B. To chamber A were added zinc granular (141 mg, 2.16 mmol) and 4 M DCl (1.6 mL, 6.48 mmol). The reaction was left at room temperature for 12 h. The crude reaction product was filtrated through Celite and purified by flash column chromatography (increasing polarity 0.4−2% EtOAc in pentane) to give the title compound as a colorless solid (30 mg, 80%); mp 82−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.22−8.16 (m, 3H), 7.88 (m, 0.06H), 7.83 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 7.74 (ddd, J = 1.6 Hz, J = 6.8 Hz, J = 9.2 Hz, 1H), 7.57−7.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.4, 148.4, 139.7, 136.5 (t, J = 24 Hz, C−D), 129.8, 129.8, 129.5, 128.9 (2C), 127.7 (2C), 127.5, 127.2, 126.4. 118.7 (t, J = 24 Hz, C−D). HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{15}H_{10}D_2N$: 208.1090; found: 208.1098.

2-Phenyl-1,2,3,4-tetrahydroquinoline-2,3,3,4,4-d_5 (19c). General method with 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one

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(20.0 mg, 0.09 mmol), Pd/C (10 mg, 10 wt %), and CD_3OD (2 mL) in chamber B. To chamber A were added zinc granular (200 mg, 3.1 mmol) and 4 M DCl (2.6 mL, 12.9 mmol). The reaction was left at 0 °C, slowly heating to room temperature, for 72 h. The crude reaction product was filtrated through Celite to give the title compound as a pale oil (15.4 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45−7.34 (m, 4H), 7.32−7.27 (m, 1H), 7.06 (m, 2H), 6.67 (dt, J = 1.2 Hz, J = 7.2 Hz, 1H), 6.58 (d, J = 7.6 Hz, 1H), 4.44 (s, 0.24H), 4.03 (br s, 1H), 2.92−2.88 (m, 0.11H), 2.74−2.70 (m, 0.12H), 2.12−2.08 (m, 0.04H), 1.99−1.95 (m, 0.04H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.9, 144.9, 129.4, 128.7 (2C), 127.5, 127.0, 126.7 (2C), 121.0, 117.3, 114.1, 56.2, 30.6, 25.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{15}H_{11}D_5N$: 215.1591; found: 215.1600.

(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl-5,7-d_2)(piperidin-1-yl)-methanone (D-CX-546). *This experiment was conducted in a glovebox under an argon atmosphere.* To chamber B of a two-chamber system were added triphenylphosphine(1,5-cyclooctadiene)[1,3-bis(2,4,6-trimethylphenyl)imidazole-2-yl-idene]iridium(I) hexafluorophosphate (3.5 mg, 5 mol %), CX-546 (24.7 mg, 0.07 mmol), and dry CH_2Cl_2 (1 mL). Chamber B was sealed with a screw cap fitted with an H-Cap. To chamber A were added zinc granular (137.3 mg, 2.1 mmol) and 4 M ^{2}HCl (1.6 mL, 6.3 mmol) generating a pressure of 3 bar of D_2-gas. Then chamber A was sealed directly after the addition of ^{2}HCl using a screw cap fitted with an H-Cap. The reaction was left at room temperature over the weekend (72 h). The crude product was purified by flash column chromatography (increasing polarity from 5% to 30% Et_2O in CH_2Cl_2) to give a brown oil (24.7 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.93 (s, 0.08H), 6.89−6.84 (m, 1.61 H), 4.26 (s, 4H), 3.53−3.49 (m, 4H), 1.68−1.64 (m, 2H), 1.59−1.55 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.8, 144.6, 143.2, 129.5 (d, J = 10 Hz, ^{13}C−D), 120.5, 117.1 (d, J = 11 Hz, ^{13}C−D), 116.5−116.0 (m, ^{13}C−D), 64.5, 64.3, 49.0 (br), 43.2 (br), 25.9 (br, 2C), 24.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{14}H_{16}D_2NO_3$: 250.1401; found: 250.1400.

4-(3-(4-(Cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2*H*)-one-8-d (D-Olaparib). *This experiment was conducted in a glovebox under an argon atmosphere.* To chamber B of a two-chamber system were added triphenylphosphine-(1,5-cyclooctadiene)[1,3-bis(2,4,6-trimethylphenyl)imidazole-2-yl-idene]iridium(I) hexafluorophosphate (3.5 mg, 5 mol %), Olaparib (30 mg, 0.07 mmol), and dry CH_2Cl_2 (1 mL). Chamber B was sealed with a screw cap fitted with an H-Cap. To chamber A were added zinc granular (137.3 mg, 2.1 mmol) and 4 M ^{2}HCl (1.6 mL, 6.3 mmol) generating a pressure of 3 bar of D_2-gas. Then chamber A was sealed directly after the addition of ^{2}HCl using a screw cap fitted with an H-Cap. The reaction was left at room temperature over a weekend (72 h). The crude product was purified by flash column chromatography (4% MeOH, 48% EtOAc and 48% CH_2Cl_2) to give a light gray amorphous solid (30 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.36 (br s, 1H), 8.46 (dd, J = 1.9 Hz, J = 8.3 Hz, 0.30H), 7.78−7.72 (m, 3H), 7.34−7.31 (m, 2H), 7.03 (t, J = 8.8 Hz, 1H), 4.29 (s, 2H), 3.76 (br s, 4H), 3.59 (br s, 2H), 3.29 (br s, 2H), 1.70 (m, 1H), 0.99 (s, 2H), 0.78 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.5, 165.3 (m), 160.3, 157.2 (d, J = 248 Hz, C−F), 145.6, 134.5 (d, J = 3 Hz, C−F), 133.9, 131.8 (d, J = 8 Hz, C−F), 131.7, 129.7, 129.4 (m), 128.5, 127.4, 125.2, 123.9 (d, J = 21 Hz, C−F), 116.4 (d, J = 23 Hz, C−F), 58.6 (ethanol), 47.0, 45.3 (2C), 42.4 (2C), 37.8, 29.8 (grease), 18.6 (ethanol), 11.2, 7.9, 1.2 (silicon grease). HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{24}H_{23}DFN_4O_3$: 436.1884; found: 436.1887.

■ ASSOCIATED CONTENT

Supporting Information

General methods, description of COware and the H-Cap system, determination of D-incorporation, pressure curves for H_2-release, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) For release curves of H_2 under these conditions, see Supporting Information.

(13) The loading of H_2 in the system is based on the loading of Zn or HCl corresponding to the equation shown in Figure 1. A maximum of 1 equiv of H_2 gas can be produced from 1 equiv of Zn and 2 equiv of HCl. Unless exchanged, the reactor headspace will contain oxygen which could be catalytically consumed with H_2 or D_2 producing water. With an excess of at least 0.17 mmol or more of H_2 or D_2, this loss of gaseous reagent does not effect the desired transformation.

(14) In several of the following reactions cyclopentyl methyl ether (CPME) is used as the solvent. CPME is aprotic ensuring that H-contamination from the solvent is avoided in the D_2 work allowing this solvent to be used for both H_2 and D_2. CPME is not reduced (inert solvent) under the applied conditions. Furthermore, CPME holds a boiling point of 106 °C at atmospheric pressure allowing heating of the reaction without pressure addition from a boiling solvent. Other ether-based solvents (i.e., Et_2O), or any other aprotic, nonreducable, and nonhydrogenolyzable solvent, could in principle also have been used.
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