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Copper(I)-Catalyzed Chemoselective Reduction of Benzofuran-2-yl Ketones to Alcohols with B_2pin_2 via a Domino-Borylation-Protodeboronation Strategy

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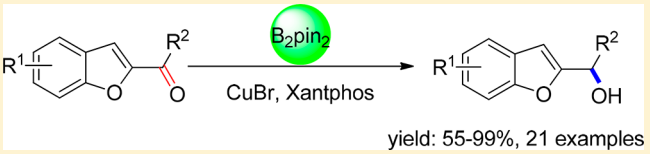
Supporting Information

ABSTRACT: A novel copper(I)-catalyzed chemoselective reduction of the carbonyls of benzofuran-2-yl ketones over furan rings with B_2pin_2 has been developed. This reaction proceeded under mild conditions. High valuable secondary alcohol derivatives of benzofurans were obtained in good to excellent yields with a broad substrate scope. The mechanistic studies suggested that a domino-borylation-protodeboronation pathway was involved in this reaction.



As one of the most fundamental reactions in organic chemistry, reductions are widely employed in the research laboratory as well as in industry.[1] Among them, the reduction of ketones has received special attention due to the versatility of secondary alcohols in organic synthesis.[2] Numerous methods have been developed for reduction of ketones to secondary alcohols. Hydrogen gas,[3] charged hydrides,[4] hydrogen donors (2-propanol, triethylamine/formic acid, sodium formate),[5] silanes,[6] and boranes[7] have been explored as reductants. Despite significant progress having been made in those fields, challenges still remain and certain shortcomings need to be solved. H_2 is an ideal reducing agent in terms of cost and atom efficiency, however, lack of selectivity, the flammability of the gas and the specialized equipment required in transformation led to the search for alternatives. Aluminum and boron hydrides are highly sensitive toward air and moisture, hence careful operation is usually required to avoid any risk. Reductions employing alcohols (mainly 2-propanol) as the hydrogen donor lead to an equilibrium, and high dilution is usually preferred to reach high conversions. Triethylamine/formic acid releases unrecyclable triethylamine and CO_2, and silanes and boranes always need a precious metal catalyst to assist the transformation.[8] Therefore, the development of new reductive systems that are efficient, selective, and operationally simple with low environmental impact and toxicity is highly desirable.

In the past few years, copper-catalyzed borylation reactions have been profoundly studied.[9] Those transformations have also aroused our interest, as we discovered recently that the C−B bond of alkylboronic esters could be easily transformed into a C−H bond in the presence of base. We envisioned that it will be a novel, simple, and efficient way to reduce carbon π bonds by combining copper-catalyzed borylation reactions of carbon π bonds with protodeboronation pathway (Scheme 1a). Based on this domino-borylation-protodeboronation (DBP) reductive strategy, we reported lately the first copper-catalyzed selective reduction of the C−C unsaturated bonds of α,β-unsaturated ketones over unconjugated C−C unsaturated bonds with B_2pin_2 as water activator and H_2O as a hydrogen source under simple and mild conditions (Scheme 1b).[10] Very recently, we applied the same strategy to arylacetylenes and vinyl arenes under transition-metal free conditions, rendering alkylboronates with good to excellent yields (Scheme 1c).[11] In this article, we applied this strategy to chemoselectively reduce the carbonyls of benzofuran-2-yl ketones over furan rings, highly valuable racemic benzofuran-2-yl alcohol derivatives were afforded under mild conditions (Scheme 1d).

Scheme 1. Domino-Borylation-Protodeboronation Reductive Strategy and Its Applications

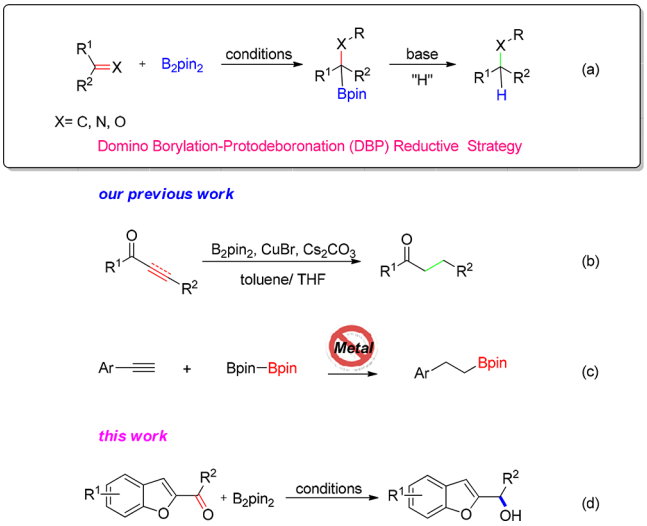


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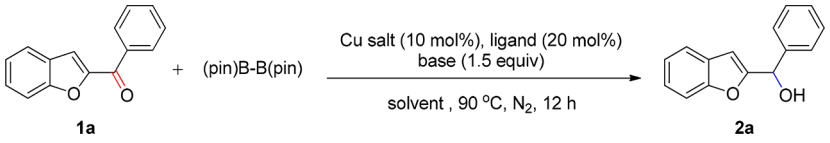
Table 1. Results for the Optimization of the Reaction Conditions[a]

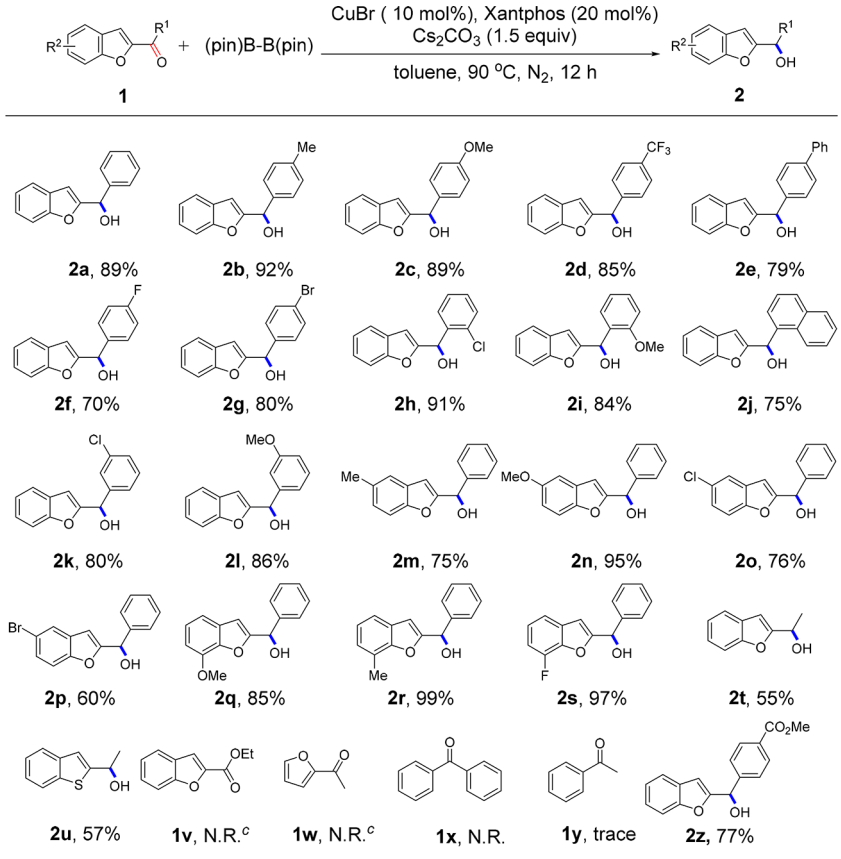


1a 2a

entry	Cu salt	ligand	base	solvent	yield[b] (%)
1	CuBr	xantphos	Cs_2CO_3	toluene	90[b](89[c])
2	CuBr	PPh_3	Cs_2CO_3	toluene	40
3	CuBr	PCy_3	Cs_2CO_3	toluene	46
4	CuBr	dppf	Cs_2CO_3	toluene	53
5	CuBr	dppe	Cs_2CO_3	toluene	55
6	CuBr	xantphos	KO^{t}Bu	toluene	70
7	CuBr	xantphos	NaOMe	toluene	43
8	CuBr	xantphos	KF	toluene	78
9	CuBr	xantphos	Cs_2CO_3	DMF	20
10	CuBr	xantphos	Cs_2CO_3	THF	28
11	CuBr	xantphos	Cs_2CO_3	CH_3CN	22
12	CuBr	xantphos	Cs_2CO_3	toluene	75[d]
13	CuBr	xantphos	Cs_2CO_3	toluene	69[e]

[a]Reaction conditions: **1a** (0.25 mmol), B_2pin_2 (2 equiv), Cu salt (10 mol%), ligand (20 mol%), base (1.5 equiv), solvent (3 mL), 12 h, temp. [b]GC yield. [c]Isolated yield. [d]B_2pin_2 (1.2 equiv). [e]Air atmosphere.

Scheme 2. Substrate Scope of the Chemoselective Reduction[a]



1 2

[a]Reaction conditions: **1a** (0.25 mmol), B_2pin_2 (2 equiv), CuBr (10 mol%), Xantphos (20 mol%), Cs_2CO_3 (1.5 equiv), toluene (3 mL), 12 h, 90 °C. [b]Isolated yield. [c]N.R.= no reaction.

Benzofurans are highly valuable molecular motifs which are often found in various natural products.[12] These privileged pharmacophore containing molecules exhibit therapeutical properties over wide ranges of targets.[13] Owing to their prevalence in natural products as well as pharmaceuticals, many efforts have been devoted to the synthesis and functionalization of benzofurans. Under this context, we chose benzofuran-2-yl(phenyl)methanone (**1a**) as the model substrate to evaluate the possibility of our DBP reductive strategy in reduction of ketones. Initial screening of copper salts found that benzofuran-

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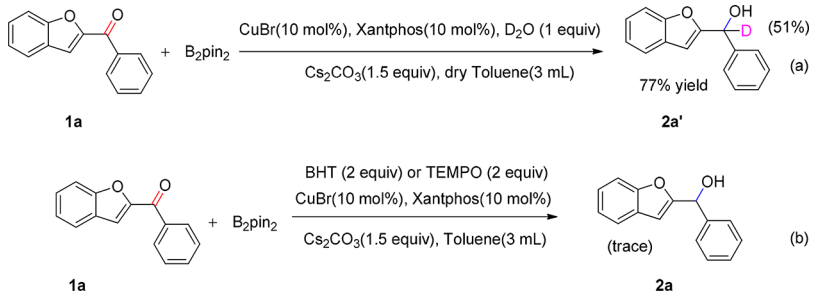
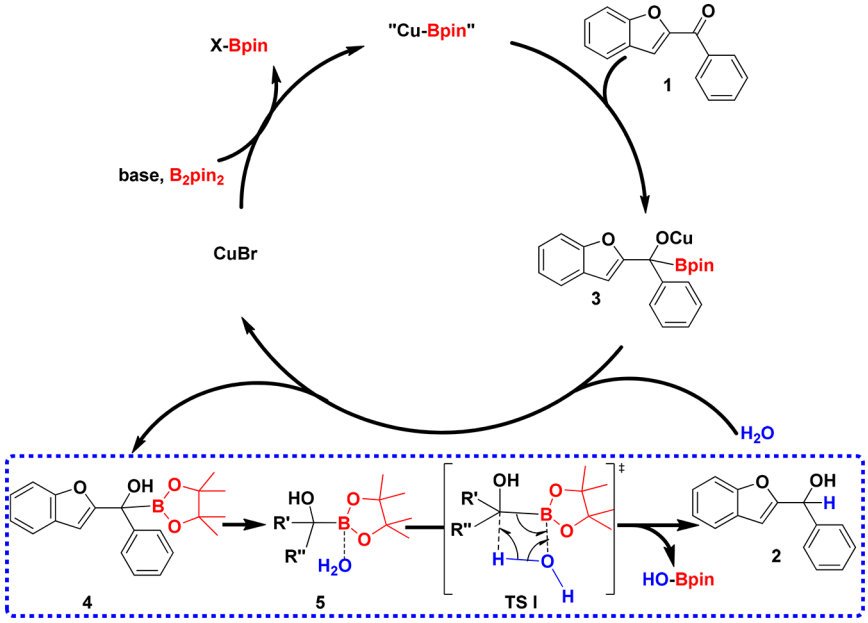
Scheme 3. Hydrogen Isotope Labeling and Radical Trapping Experiments



Scheme 4. Proposed Reaction Pathway



2-yl(phenyl)methanol (**2a**) could be afforded in 89% isolated yield using 10 mol% of CuBr and 20 mol% of xantphos with B_2pin_2 (2 equiv) and Cs_2CO_3 (1.5 equiv) at 90 °C in toluene (3 mL) under N_2 in a sealed tube (Table 1, entry 1). Based on these reaction conditions, more details about the reaction conditions were further studied. Ligands had a strong effect on the reactions, and changing xantphos to other phosphine ligands led to a significant decrease in yields (entry 1−5). KO^{t}Bu and KF could also promote the reaction with slightly decreased yields, however, NaOMe gave inferior results (entry 6−8). Further screening of solvents revealed that toluene was still the best choice (entry 9−11). When 1.5 equiv B_2pin_2 was used in the reaction, the yield of the desired product **2a** dropped to 75% (entry 12). In addition, the reaction was partially inhibited under air (entry 13).

To investigate the scope and limitations of this reaction, a panel of substituted benzofuran-2-yl ketone derivatives (**1a**−**1s**) were synthesized via Rap−Stoermer reaction.[14] To our delight, all of them were competent candidates in this transformation, delivering the corresponding desired products in good to excellent yields (Scheme 2). It worked well with both electron-donating substituents, such as a methyl group (**2b**), methoxy group (**2c**), and electron-withdrawing substituents, such as fluoro, bromo, chloro, and trifluoromethyl groups (**2d**, **2f**−**2h**). Phenyl and 1-naphthyl could also give satisfied results (**2e**, **2j**). It should be noted that the position of substituents had little influence on our reaction (**2b** and **2m**; **2c**, **2i**, and **2l**; **2h** and **2k**). Subsequently, we also investigated the effect of R^2 group. Generally, the reaction with electron-donating substituents on 5-position (**2m**, **2n**) could afford better results than halogen substituents on 5-position (**2o**, **2p**). The electronic nature of substituents on 7-position has no significant effect on the reaction, both of them afford the corresponding alcohols in good to excellent yields (**2q**−**2s**). Moreover, 1-(benzofuran-2-yl)ethanone (**1t**) and 1-(benzo[b]-thiophen-2-yl)ethanone (**1s**) were also amenable to the reaction, giving **2t** and **2u** in moderate yields. To further study the scope of this new reductive system, ethyl benzofuran-2-carboxylate (**1v**) and other types of ketones (**1w**-**1y**) were tested in our reactions. Dismayingly, both of them gave sluggish results.

Isotope labeling experiment and radical trapping experiment were conducted to gain insight into the mechanism of this new reductive system. Benzofuran-2-yl(phenyl)methanone (**1a**) in anhydrous toluene was subjected to D_2O (1 equiv) under the standard conditions (Scheme 3a). **2a′** gave 77% isolated yield with 51% deuterium incorporated on the carbon atom of α-position of OH (determined by ^{1}H NMR, see details in the ESI). It should be noted here that too much water has a deteriorated effect on the reduction, and the transformation was strongly inhibited when 2 equiv of water was added. When radical scavenger (BHT or TEMPO) was added into the

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reaction, the reaction was not carried out, which revealed that a radical pathway might be involved in reaction (Scheme 3b).

Based on the above isotope labeling experiment, radical traps experiments, and the mechanistic studies in our previous work about copper-catalyzed conjugated reduction of α, β-unsaturated ketones, we proposed a plausible pathway (Scheme 4). Cu−B intermediate was generated through transmetalation process from B_2pin_2 and CuBr in the presence of base. Then substrate **1** was attacked by Cu−B intermediates affording the borylated alkoxy copper intermediate **3**, which could be hydrolyzed promptly to give alcohol **4**. Then the formed alcohol **4** was coordinated with one molecule of H_2O giving complex **5**, due to the Lewis acid property of the boron atom. It is deemed that the DBP process went through via itramolecular radical pathway. In complex **5** the C−B and O−H bonds became weaker due to the coordination, thus under high temperature the homolytic cleavage of the two bonds were expected to occur through cyclic four member transition state (**TS I**). Next the generated radicals swiftly reacted via **TS I** to give alcohol **2** and byproduct HO-Bpin.

In summary, we have developed a novel and efficient method for chemoselective reduction of benzofuran-2-yl ketones to their alcohol derivatives via copper(I)-catalyzed borylation/protodeboronation reductive strategy. The reaction features high efficiency and broad substrate scope. The success of the reaction confirms the potential of DBP reductive strategy as a new reductive system.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Anhydrous toluene was dried over Na with benzophenone-ketyl intermediate as indicator. For chromatography, 200−300 mesh silica gel (Qingdao, China) was employed. ^{1}H NMR spectra were recorded on a Bruker AVIII-500 MHz spectrometers. Chemical shifts (in ppm) were referenced to $CDCl_3$ (δ = 7.26 ppm) as an internal standard. ^{13}C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ (δ = 77.00 ppm). The following abbreviations are used to illuminate the diversities: δ, chemical shift; J, coupling constant; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were recorded using a Thermo Fisher Scientific LTQ FT Ultra.

General Procedure for Synthesize Benzofuran-2-yl Ketones through the Rap−Soermer Condensation. To a solution of 2-bromo-1-phenylethanone (1.2 equiv) in acetone were added potassium carbonate (4.0 equiv) and the appropriate 2-hydroxybenzaldehyde (1.0 equiv) under N_2. The resulting mixture was stirred at reflux overnight. After removal of the solvent, water and EtOAc were added. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford the desired product.[14]

General Procedure for Copper(I)-Catalyzed Chemoselective Reduction of Benzofuran-2-yl Ketones to Alcohols with B_2pin_2. To a 25 mL flame-dried Schlenk tube equipped with a magnetic stir bar were added benzofuran-2-yl ketones (0.25 mmol), B_2pin_2 (2 equiv), CuBr (10 mol%), xantphos (20 mol%), Cs_2CO_3 (1.5 equiv). The tube was evacuated and backfilled with N_2 three times, 3 mL toluene was then added. The reaction was vigorously stirred at 90 °C (oil bath temperature) for 12 h. The solution was cooled, diluted with EtOAc, and washed with water. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford the desired product.

Isotope Labeling and Radical Trapping Experiments. *Isotope Labeling Experiments.* To a 25 mL flame-dried Schlenk tube equipped with a magnetic stir bar were added benzofuran-2-yl(phenyl)methanone (**1a**, 0.25 mmol), B_2pin_2 (2 equiv), CuBr (10 mol%), xantphos (20 mol%), Cs_2CO_3 (1.5 equiv). The tube was evacuated and backfilled with N_2 three times, D_2O (1 equiv) and 3 mL dry toluene were then added. The reaction was vigorously stirred at 90 °C (oil bath temperature) for 12 h. The solution was cooled, diluted with EtOAc, and washed with water. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford the desired product.

Radical Trapping Experiments. To a 25 mL flame-dried Schlenk tube equipped with a magnetic stir bar were added benzofuran-2-yl(phenyl)methanone (**1a**, 0.25 mmol), TEMPO or BHT (2 equiv), B_2pin_2 (2 equiv), CuBr (10 mol%), xantphos (20 mol%), Cs_2CO_3 (1.5 equiv). The tube was evacuated and backfilled with N_2 three times, 3 mL toluene were then added. The reaction was vigorously stirred at 90 °C (oil bath temperature) for 12 h. The solution was cooled, diluted with EtOAc. The amount of desired product was detected by TLC and GC.

Characterization Data for Products. *Benzofuran-2-yl(phenyl)-methanol (**2a**).* Product was isolated via column chromatography (PE/EA 4:1) as white solid (49.8 mg, 89%), mp 64.3−66.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, J = 9.3, 7.8 Hz, 3H), 7.45 (d, J = 8.1 Hz, 1H), 7.43−7.38 (m, 2H), 7.36 (ddd, J = 7.3, 3.5, 1.2 Hz, 1H), 7.27 (ddd, J = 8.3, 6.6, 1.3 Hz, 1H), 7.24−7.19 (m, 1H), 6.53 (s, 1H), 5.95 (s, 1H), 2.63 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 155.1, 140.2, 128.6, 128.4, 128.0, 126.8, 124.3, 122.9, 121.2, 111.4, 104.1, 70.7; HRMS (DART Positive) calcd for: $C_{15}H_{11}O_2$ $[M-H]^-$ 223.0754; found: 223.0753.

*Benzofuran-2-yl(p-tolyl)methanol (**2b**).* Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (54.7 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 7.6, 0.7 Hz, 1H), 7.50−7.45 (m, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.29 (ddd, J = 8.3, 7.1, 1.4 Hz, 1H), 7.26−7.21 (m, 3H), 6.56 (s, 1H), 5.94 (d, J = 3.8 Hz, 1H), 2.70 (d, J = 4.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 155.1, 138.2, 137.4, 129.3, 128.1, 126.8, 124.2, 122.8, 121.1, 111.4, 103.9, 70.6, 21.2; HRMS (DART Positive) calcd for: $C_{16}H_{13}O_2$ $[M-H]^-$ 237.0910; found: 237.0909.

*Benzofuran-2-yl(4-methoxyphenyl)methanol (**2c**).* Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (56.5 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58−7.52 (m, 1H), 7.50−7.45 (m, 1H), 7.45−7.39 (m, 2H), 7.33−7.26 (m, 1H), 7.24 (dd, J = 11.0, 3.9 Hz, 1H), 6.99−6.90 (m, 2H), 6.55 (d, J = 0.8 Hz, 1H), 5.91 (s, 1H), 3.84 (s, 3H), 2.79 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 158.8, 155.1, 132.6, 128.2, 128.1, 124.2, 122.8, 121.1, 114.0, 111.3, 103.8, 70.3, 55.4; HRMS (DART Positive) calcd for: $C_{16}H_{13}O_3$ $[M-H]^-$ 253.0859; found: 253.0859.

*Benzofuran-2-yl(4-(trifluoromethyl)phenyl)methanol (**2d**).* Product was isolated via column chromatography (PE/EA 4:1) as white solid (62.1 mg, 85%), mp 55.2−57.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (q, J = 8.5 Hz, 4H), 7.53 (d, J = 7.6 Hz, 1H), 7.48−7.42 (m, 1H), 7.31−7.27 (m, 1H), 7.22 (t, J = 7.5 Hz, 1H), 6.54 (s, 1H), 6.02 (d, J = 3.9 Hz, 1H), 2.88−2.48 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5, 155.1, 143.9, 130.6, 130.3, 127.8, 127.1, 125.5 (q, J = 3.7 Hz), 124.7, 123.1, 121.3, 111.4, 104.5, 69.9; HRMS (DART Positive) calcd for: $C_{16}H_{10}O_2F_3$ $[M-H]^-$ 291.0627; found: 291.0625.

*[1,1′-Biphenyl]-4-yl(benzofuran-2-yl)methanol (**2e**).* Product was isolated via column chromatography (PE/EA 4:1) as white solid (59.3 mg, 79%), mp 112.8−114.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66−7.59 (m, 4H), 7.59−7.55 (m, 2H), 7.54 (dd, J = 7.7, 0.7 Hz, 1H), 7.49−7.42 (m, 3H), 7.40−7.34 (m, 1H), 7.31−7.26 (m, 1H), 7.22 (td, J = 7.5, 0.9 Hz, 1H), 6.60 (t, J = 0.8 Hz, 1H), 6.01 (s, 1H), 2.68 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 155.1, 141.3, 140.7, 139.3, 128.8, 128.0, 127.5, 127.4, 127.3, 127.2, 124.4, 122.9, 121.2, 111.4, 104.1, 70.5; HRMS (DART Positive) calcd for: $C_{21}H_{15}O_2$ $[M-H]^-$ 299.1067; found: 299.1065.

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Benzofuran-2-yl(4-fluorophenyl)methanol (**2f**). Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (42.4 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.7, 0.7 Hz, 1H), 7.49−7.43 (m, 3H), 7.30−7.26 (m, 1H), 7.22 (td, J = 7.5, 0.9 Hz, 1H), 7.11−7.05 (m, 2H), 6.51 (t, J = 0.8 Hz, 1H), 5.92 (d, J = 3.3 Hz, 1H), 2.84 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.66 (d, J = 246.7 Hz) 158.3, 155.1, 136.1 (d, J = 3.2 Hz), 128.6 (d, J = 8.3 Hz), 127.9, 124.5, 122.9, 121.2, 115.5 (d, J = 21.6 Hz), 111.4, 104.1, 69.9; HRMS (DART Positive) calcd for: $C_{15}H_{10}O_2F$ $[M-H]^-$ 241.0659; found: 241.0658.

Benzofuran-2-yl(4-bromophenyl)methanol (**2g**). Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (60.6 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (ddd, J = 8.4, 3.8, 2.8 Hz, 3H), 7.44 (dd, J = 8.2, 0.7 Hz, 1H), 7.37−7.33 (m, 2H), 7.30−7.25 (m, 1H), 7.24−7.20 (m, 1H), 6.51 (d, J = 4.7 Hz, 1H), 5.95−5.81 (m, 1H), 2.95−2.63 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 155.1, 139.2, 131.7, 128.5, 127.9, 124.6, 123.0, 122.3, 121.2, 111.4, 104.3, 69.9; HRMS (DART Positive) calcd for: $C_{15}H_{10}O_2Br$ $[M-H]^-$ 300.9859; found: 300.9858.

Benzofuran-2-yl(2-chlorophenyl)methanol (**2h**). Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (58.9 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, J = 7.6, 1.8 Hz, 1H), 7.56−7.52 (m, 1H), 7.51−7.47 (m, 1H), 7.44−7.40 (m, 1H), 7.37 (ddd, J = 9.0, 5.5, 1.4 Hz, 1H), 7.34−7.28 (m, 2H), 7.24 (ddd, J = 10.9, 4.4, 2.2 Hz, 1H), 6.50 (t, J = 0.8 Hz, 1H), 6.36 (t, J = 17.8 Hz, 1H), 3.03 (t, J = 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 155.1, 137.7, 132.7, 129.6, 129.5, 128.4, 127.9, 127.2, 124.5, 122.9, 121.3, 111.4, 104.7, 67.3; HRMS (DART Positive) calcd for: $C_{15}H_{10}O_2Cl$ $[M-H]^-$ 257.0364; found: 257.0362.

Benzofuran-2-yl(2-methoxyphenyl)methanol (**2i**). Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (53.3 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.52 (m, 1H), 7.50−7.47 (m, 1H), 7.42 (dd, J = 7.5, 1.6 Hz, 1H), 7.39−7.34 (m, 1H), 7.30−7.26 (m, 1H), 7.23 (td, J = 7.5, 1.0 Hz, 1H), 7.03 (td, J = 7.5, 0.9 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.52 (s, 1H), 6.21 (d, J = 6.1 Hz, 1H), 3.87 (s, 3H), 3.39 (t, J = 13.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 156.9, 155.0, 129.5, 128.5, 128.3, 128.2, 124.0, 122.7, 121.0, 120.9, 111.4, 110.9, 103.6, 67.2, 55.6; HRMS (DART Positive) calcd for: $C_{16}H_{13}O_3$ $[M-H]^-$ 253.0859; found: 253.0858.

Benzofuran-2-yl(naphthalen-1-yl)methanol (**2j**). Product was isolated via column chromatography (PE/EA 4:1) as white solid (51.4 mg, 75%), mp 82.4−85.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.24−8.17 (m, 3H), 7.91 (dd, J = 8.6, 1.7 Hz, 1H), 7.89−7.83 (m, 3H), 7.80 (dd, J = 8.2, 0.7 Hz, 1H), 7.65−7.59 (m, 1H), 7.59−7.54 (m, 1H), 6.89 (t, J = 0.8 Hz, 1H), 6.44 (d, J = 3.6 Hz, 1H), 3.28 (d, J = 4.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 155.1, 137.6, 133.3, 133.2, 128.5, 128.2, 128.1, 127.8, 126.4, 126.4, 125.8, 124.6, 124.4, 122.9, 121.2, 111.4, 104.3, 70.8; HRMS (DART Positive) calcd for: $C_{19}H_{13}O_2$ $[M-H]^-$ 273.0910; found: 273.0909.

Benzofuran-2-yl(3-chlorophenyl)methanol (**2k**). Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (51.7 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56−7.50 (m, 2H), 7.45 (dd, J = 8.2, 0.6 Hz, 1H), 7.38−7.34 (m, 1H), 7.34−7.30 (m, 2H), 7.28 (dt, J = 7.4, 1.7 Hz, 1H), 7.23 (ddd, J = 10.7, 4.3, 2.2 Hz, 1H), 6.54 (d, J = 0.5 Hz, 1H), 5.90 (s, 1H), 3.00−2.67 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 155.1, 142.2, 134.53, 129.9, 128.5, 127.9, 126.9, 124.9, 124.6, 123.0, 121.3, 111.4, 104.3, 69.9; HRMS (DART Positive) calcd for: $C_{15}H_{10}O_2Cl$ $[M-H]^-$ 257.0364; found: 257.0363.

Benzofuran-2-yl(3-methoxyphenyl)methanol (**2l**). Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (54.6 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.52 (m, 1H), 7.46 (dt, J = 15.4, 7.6 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.29 (ddd, J = 8.2, 6.6, 1.4 Hz, 1H), 7.24 (td, J = 7.6, 1.0 Hz, 1H), 7.09 (dd, J = 9.4, 1.5 Hz, 2H), 7.00−6.85 (m, 1H), 6.56 (s, 1H), 5.93 (d, J = 3.7 Hz, 1H), 3.83 (s, 3H), 2.96 (dd, J = 78.4, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 158.4, 155.1, 141.9, 129.7, 128.0, 124.3, 122.9, 121.18, 119.1, 113.9, 112.3, 111.4, 104.1, 70.6, 55.3; HRMS (DART Positive) calcd for: $C_{16}H_{13}O_3$ $[M-H]^-$ 253.0859; found: 253.0858.

(5-Methylbenzofuran-2-yl)(phenyl)methanol (**2m**). Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (44.6 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.47 (m, 2H), 7.43−7.38 (m, 2H), 7.36 (dt, J = 5.6, 2.3 Hz, 1H), 7.34 (d, J = 2.9 Hz, 1H), 7.31 (d, J = 9.5 Hz, 1H), 7.08 (dd, J = 8.4, 1.6 Hz, 1H), 6.46 (s, 1H), 5.92 (d, J = 4.2 Hz, 1H), 2.77 (d, J = 4.3 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 153.5, 140.4, 132.3, 128.6, 128.4, 128.1, 126.8, 125.6, 121.0, 110.9, 103.9, 70.7, 21.4; HRMS (DART Positive) calcd for: $C_{16}H_{13}O_2$ $[M-H]^-$ 237.0910; found: 237.0910.

(5-Methoxybenzofuran-2-yl)(phenyl)methanol (**2n**). Pale yellow oil.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.45 (m, 2H), 7.42−7.37 (m, 2H), 7.35 (ddd, J = 7.4, 3.6, 1.4 Hz, 1H), 7.33−7.30 (m, 1H), 6.97 (d, J = 2.6 Hz, 1H), 6.86 (dt, J = 8.0, 4.0 Hz, 1H), 6.46 (s, 1H), 5.90 (s, 1H), 3.81 (s, 3H), 2.92 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 155.9, 150.1, 140.4, 128.6, 128.4, 126.8, 112.9, 111.8, 104.2, 103.7, 70.7, 55.9; HRMS (DART Positive) calcd for: $C_{16}H_{13}O_3$ $[M-H]^-$ 253.0859; found: 253.0857.

(5-Chlorobenzofuran-2-yl)(phenyl)methanol (**2o**). Product was isolated via column chromatography (PE/EA 4:1) as pale yellow oil (49.2 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.45 (m, 3H), 7.40 (tt, J = 8.1, 2.0 Hz, 2H), 7.38−7.35 (m, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.20 (dt, J = 10.8, 3.7 Hz, 1H), 6.48 (s, 1H), 5.91 (d, J = 1.8 Hz, 1H), 2.91−2.58 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 153.5, 139.9, 129.4, 128.7, 128.6, 128.4, 126.8, 124.5, 120.7, 112.3, 103.6, 70.6; HRMS (DART Positive) calcd for: $C_{15}H_{10}O_2Cl$ $[M-H]^-$ 257.0364; found: 257.0363.

(5-Bromobenzofuran-2-yl)(phenyl)methanol (**2p**). Product was isolated via column chromatography (PE/EA 4:1) as white oil (45.5 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 1.9 Hz, 1H), 7.47 (dt, J = 3.1, 2.0 Hz, 2H), 7.43−7.38 (m, 2H), 7.38−7.33 (m, 2H), 7.30 (d, J = 8.7 Hz, 1H), 6.49 (d, J = 0.8 Hz, 1H), 5.92 (d, J = 3.4 Hz, 1H), 2.66 (d, J = 4.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 153.8, 139.9, 130.0, 128.7, 128.6, 127.2, 126.8, 123.8, 115.9, 112.8, 103.5, 70.6; HRMS (DART Positive) calcd for: $C_{15}H_{10}O_2Br$ $[M-H]^-$ 300.9859; found: 300.9858.

(7-Methoxybenzofuran-2-yl)(phenyl)methanol (**2q**). Product was isolated via column chromatography (PE/EA 4:1) as white oil (54.0 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.45 (m, 2H), 7.42−7.31 (m, 3H), 7.12 (tdd, J = 7.8, 5.8, 2.3 Hz, 2H), 6.91−6.68 (m, 1H), 6.47 (d, J = 0.8 Hz, 1H), 5.96 (d, J = 3.2 Hz, 1H), 3.97 (s, 3H), 2.95 (d, J = 3.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 145.3, 144.3, 140.2, 129.7, 128.6, 128.3, 126.9, 123.6, 113.5, 106.4, 104.4, 70.5, 55.9; HRMS (DART Positive) calcd for: $C_{16}H_{13}O_3$ $[M-H]^-$ 253.0859; found: 253.0857.

(7-Methylbenzofuran-2-yl)(phenyl)methanol (**2r**). Product was isolated via column chromatography (PE/EA 4:1) as pale yellow oil (58.9 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.48 (m, 2H), 7.44−7.39 (m, 2H), 7.39−7.33 (m, 2H), 7.15−7.10 (m, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.49 (d, J = 0.8 Hz, 1H), 5.96 (d, J = 2.6 Hz, 1H), 2.80 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 154.2, 140.4, 128.6, 128.3, 127.5, 126.9, 125.3, 122.9, 121.6, 118.6, 104.4, 70.7, 15.2; HRMS (DART Positive) calcd for: $C_{16}H_{13}O_2$ $[M-H]^-$ 237.0910; found: 237.0908.

(7-Fluorobenzofuran-2-yl)(phenyl)methanol (**2s**). Product was isolated via column chromatography (PE/EA 4:1) as pale brown oil (58.7 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53−7.47 (m, 2H), 7.43−7.34 (m, 3H), 7.29−7.24 (m, 1H), 7.12 (td, J = 7.9, 4.4 Hz, 1H), 7.03−6.96 (m, 1H), 6.55 (dd, J = 2.9, 0.8 Hz, 1H), 5.96 (s, 1H), 2.75 (d, J = 2.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 147.9 (d, J = 249.4 Hz), 142.1 (d, J = 11.1 Hz), 139.9, 131.6 (d, J = 3.2 Hz), 129.6, 128.6, 127.8 (d, J = 237.4 Hz), 123.5 (d, J = 5.9 Hz), 116.8 (d, J = 3.9 Hz), 110.7 (d, J = 16.1 Hz), 104.4 (d, J = 2.2 Hz), 70.5; HRMS (DART Positive) calcd for: $C_{15}H_{10}O_2F$ $[M-H]^-$ 241.0659; found: 241.0658.

1-(Benzofuran-2-yl)ethanol (**2t**). Product was isolated via column chromatography (PE/EA 4:1) as white solid (22.3 mg, 55%), mp 61.7−62.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 7.6, 0.6 Hz, 1H), 7.46 (dd, J = 8.1, 0.6 Hz, 1H), 7.30−7.25 (m, 1H), 7.22 (td, J = 7.5, 1.0 Hz, 1H), 6.61 (s, 1H), 5.02 (dd, J = 6.0, 4.1 Hz, 1H), 2.21 (dd, J = 36.7, 11.6 Hz, 1H), 1.64 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126

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MHz, $CDCl_3$) δ 160.2, 154.8, 128.2, 124.2, 122.8, 121.1, 111.2, 101.8, 64.2, 21.4; HRMS (DART Positive) calcd for: $C_{10}H_9O_2$ $[M-H]^-$ 161.0597; found: 161.0596.

*1-(Benzo[b]thiophen-2-yl)ethanol (**2u**).* Product was isolated via column chromatography (PE/EA 4:1) as pale yellow solid (25.4 mg, 57%), mp 59.6–60.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 15.6, 7.9 Hz, 1H), 7.75–7.68 (m, 1H), 7.38–7.27 (m, 2H), 7.18 (s, 1H), 5.20 (d, J = 5.5 Hz, 1H), 2.39–2.14 (m, 1H), 1.66 (d, J = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 139.6, 139.3, 124.3, 124.2, 123.5, 122.5, 119.5, 66.9, 25.1; HRMS (DART Positive) calcd for: $C_{10}H_9OS$ $[M-H]^-$ 177.0369; found: 177.0368.

*Methyl-4-(benzofuran-2-yl(hydroxy)methyl)benzoate (**2z**).* Product was isolated via column chromatography (PE/EA 4:1) as yellow oil (54.3 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.29 (dd, J = 5.3, 4.2 Hz, 1H), 7.25–7.23 (m, 1H), 6.55 (s, 1H), 6.03 (s, 1H), 3.94 (s, 3H), 2.95 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.87 (s), 157.72 (s), 155.09 (s), 145.11 (s), 133.80 (s), 129.88 (s), 127.84 (s), 126.70 (s), 124.58 (s), 122.98 (s), 121.26 (s), 111.38 (s), 104.38 (s), 70.12 (s), 52.25 (s); HRMS (DART Positive) calcd for: $C_{10}H_9OS$ $[M-H]^-$ 281.0809; found: 281.0810.

2a′. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dt, J = 8.2, 6.2 Hz, 2H), 7.47–7.43 (m, 1H), 7.43–7.38 (m, 2H), 7.38–7.33 (m, 1H), 7.29–7.24 (m, 1H), 7.21 (td, J = 7.5, 1.0 Hz, 1H), 6.60–6.48 (m, 1H), 5.95 (d, J = 3.1 Hz, o.49 H), 2.65 (dd, J = 17.0, 12.5 Hz, 1H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00596.

Copies of ^{1}H and ^{13}C NMR spectra data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Reductions in Organic Synthesis. Recent Advances and Practical Applications; ACS Symposium Series*; Abdel-Magid, A. F., Ed.; American Chemical Society: Washington, DC, 1998. (b) *Reductions in Organic Chemistry*; Hudlicky, M., Ed.; John Wiley & Sons, Ltd.: Chichester, U.K., 1984.

(2) Magano, J.; Dunetz, J. R. *Org. Process Res. Dev.* **2012**, *16*, 1156.

(3) (a) *Heterogeneous Catalytic Hydrogenations for Organic Synthesis*; Nishimura, S., Ed.; John Wiley & Sons, Inc.: New York, 2001. (b) *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH Verlag GmbH: Weinheim, 2008. (c) Ager, D. J.; de Vries, A. H. M.; de Vries, J. G. *Chem. Soc. Rev.* **2012**, *41*, 3340. (d) Klingler, F. D. *Acc. Chem. Res.* **2007**, *40*, 1367. (e) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(4) (a) Brown, H. C.; Ramachandran, P. V. Sixty Years of Hydride Reductions. In *Reductions in Organic Synthesis*; Abdel-Magid, A. F., Ed.; American Chemical Society: Washington, DC, 1996; Chapter 1, pp 1–30. (b) *Reduction by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed.; Seyden-Penne, J., Ed.; Wiley-VCH: New York, 1997.

(5) (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Bäckvall, J.-E. *J. Organomet. Chem.* **2002**, *652*, 105. (c) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (d) Václavík, J.; Kačer, P.; Kuzma, M.; Červený, L. *Molecules* **2011**, *16*, 5460. (e) Wu, X.; Xiao, J. *Chem. Commun.* **2007**, *24*, 2449. (f) Wang, C.; Wu, X.; Xiao, J. *Chem. - Asian J.* **2008**, *3*, 1750. (g) Robertson, A.; Matsumoto, T.; Ogo, S. *Dalton Trans.* **2011**, *40*, 10304.

(6) (a) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788. (b) *Pharmaceutical Substances*; Kleemann, U., Engel, U., Kutscher, B., Reichert, D., Eds.; Georg Thieme Verlag: Stuttgart, 2001. (c) *Classics in Total Synthesis*; Nicolaou, K. C., Jorensen, S E., Ed.; Verlag Chemie: Weinheim, 1996. (d) Sauer, D. C.; Wadepohl, H.; Gade, L. H. *Inorg. Chem.* **2012**, *51*, 12948. (e) Ren, X.; Du, H. *J. Am. Chem. Soc.* **2016**, *138*, 810.

(7) (a) Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553. (b) Burkhardt, E. R.; Matos, K. *Chem. Rev.* **2006**, *106*, 2617. (c) Staubitz, A.; Robertson, A. P. M.; Sloan, M. E.; Manners, I. *Chem. Rev.* **2010**, *110*, 4023.

(8) (a) Fail, P. A.; Chapin, R. E.; Price, C. J.; Heindel, J. J. *Reprod. Toxicol.* **1998**, *12*, 1. (b) Liu, B. H.; Li, Z. P. *J. Power Sources* **2009**, *187*, 527.

(9) (a) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179. (b) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392. (c) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091. (d) Cuenca, A. B.; Shishido, R.; Ito, H.; Fernández, E. *Chem. Soc. Rev.* **2017**, *46*, 415. (e) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036. (f) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2015**, *137*, 420. (g) Yang, K.; Song, Q. *J. Org. Chem.* **2016**, *81*, 1000. (h) Zhao, Y.-W.; Feng, Q.; Song, Q.-L. *Chin. Chem. Lett.* **2016**, *27*, 571. (i) Xuan, Q.; Song, Q. *Org. Lett.* **2016**, *18*, 4250.

(10) Ding, W.; Song, Q. *Org. Chem. Front.* **2016**, *3*, 14.

(11) Yang, K.; Song, Q. *Green Chem.* **2016**, *18*, 932.

(12) (a) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796. (b) Kirilmis, C.; Ahmedzade, M.; Servi, S.; Koca, M.; Kizirgil, A.; Kazaz, C. *Eur. J. Med. Chem.* **2008**, *43*, 300. (c) Abdel-Wahab, B. F.; Abdel-Aziz, H. A.; Ahmed, E. M. *Eur. J. Med. Chem.* **2009**, *44*, 2632. (d) Carrër, A.; Florent, J.-C.; Auvrouin, E.; Rousselle, P.; Bertounesque, E. *J. Org. Chem.* **2011**, *76*, 2502.

(13) (a) Saku, O.; Saki, M.; Kurokawa, M.; Ikeda, K.; Takizawa, T.; Uesaka, N. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1090. (b) Kucklaender, U.; Bollig, R.; Frank, W.; Gratz, A.; Jose, J. *Bioorg. Med. Chem.* **2011**, *19*, 2666. (c) Wempe, M. F.; Jutabha, P.; Quade, B.; Iwen, T. J.; Frick, M. M.; Ross, I. R.; Rice, P. J.; Anzai, N.; Endou, H. *J. Med. Chem.* **2011**, *54*, 2701. (d) Santín, E. P.; Khanwalkar, H.; Voegel, J.; Collette, P.; Mauvais, P.; Gronemeyer, H.; de Lera, Á. R. *ChemMedChem* **2009**, *4*, 780.

(14) Carrer, A.; Brinet, D.; Florent, J.-C.; Rousselle, P.; Bertounesque, E. *J. Org. Chem.* **2012**, *77*, 1316.

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