JOC The Journal of Organic Chemistry
Note
Cite This: J. Org. Chem. 2018, 83, 9464−9470
pubs.acs.org/joc

Rhodium(III)-Catalyzed Redox-Neutral C−H Activation/Annulation of *N*-Aryloxyacetamides with Alkynyloxiranes: Synthesis of Highly Functionalized 2,3-Dihydrobenzofurans

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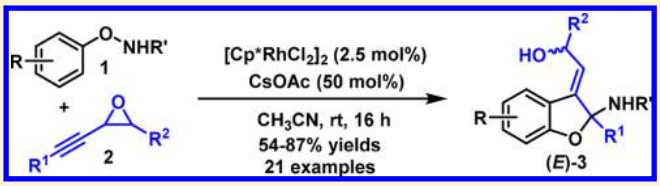
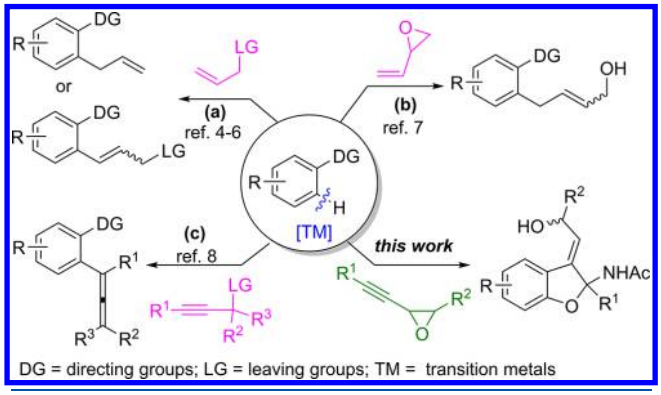
Supporting Information

ABSTRACT: Alkynyloxiranes have been employed for the first time as effective coupling partners in Cp*Rh^{III}-catalyzed C−H functionalization reactions. Their annulation with *N*-aryloxyamides then offers a redox-neutral and efficient synthesis of functionalized 2,3-dihydrobenzofurans bearing an exocyclic *E*-allylic alcohol and a tetrasubstituted carbon center in good yields with a broad substrate scope. The products can be easily converted to molecules with more complexity, which provides an opportunity for rapid assembly of structurally diverse heterocycles.



Transition-metal-catalyzed C−H activation has been established as a creative and straightforward strategy in organic synthesis.[1] In this regard, redox-neutral C−H activations utilizing oxidizing directing groups are even more intriguing, which could not only enrich the reaction patterns of C−H functionalization but also abstain from the use of a stoichiometric amount of external oxidants.[2,3] Among various unsaturated coupling partners applied in C−H activations,[1−3] allylic compounds with different leaving groups have been extensively explored toward C−H allylations[4] under various transition metal catalysis[5] (Scheme 1a). Under control conditions, the allylation can be switched to alkenylation via β-H elimination instead of the departure of leaving groups.[5d,6] Cyclic vinyl compounds, e.g., vinyloxiranes, have also been applied in transition-metal-catalyzed C−H allylations to afford corresponding allylic alcohols via ring-opening reactions (Scheme 1b).[7] Similar to allylic derivatives, propargylic compounds with appropriate leaving groups also exhibit versatile reactivity toward transition-metal-catalyzed C−H activation, leading to either allene products[8] or various cyclic structures[9,3c] (Scheme 1c). In view of the rich reactivity of propargylic compounds as well as the ring opening potential of oxiranes, it occurs to us that alkynyloxiranes as coupling partners in transition-metal-catalyzed C−H activation would bring up new reaction patterns, which, to the best of our knowledge, remains to be unexplored. Herein, we report an efficient Cp*Rh^{III}-catalyzed redox-neutral C−H activation/annulation of *N*-aryloxyacetamides with alkynyloxiranes, which affords 2,3-dihydrobenzofurans bearing a useful exocyclic (*E*)-allylic alcohol,[10] and a tetrasubstituted carbon center in good yields with a broad substrate scope (Scheme 1).

Scheme 1. Transition-Metal-Catalyzed C−H Functionalization with Allylic or Propargylic Coupling Partners



In connection with our recent work on the C−H activation/anulation of *N*-aryloxyacetamides with 1,1-disubstituted alkenes,[11] we commenced our studies on the coupling of *N*-phenoxyacetamide (**1a**) with 2-(phenylethynyl)oxirane (**2a**) with 2.5 mol % $[Cp^*RhCl_2]_2$ and 50 mol % CsOAc in MeOH at room temperature for 16 h (Table 1, entry 1). To our delight, the reaction gave an annulative product dihydrobenzofuran **3aa** bearing an exocyclic allylic alcohol with a tetrasubstituted carbon center in 86% yield with exclusive *E*-selectivity. The *E*-configuration of the double bond was confirmed by NOE analysis (see Supporting Information). Compared to CsOAc,[12] other additives such as KOAc, NaOAc, AgOAc, and $Cu(OAc)_2$ all led to lower yields (entries 1−5). Further screening of solvents revealed that THF, DCE, PhMe, and dioxane delivered the product **3aa** in less than 51% yields, while CH_3CN gave a slightly higher yield of 87% (entries 6−10). A longer reaction time of 24 h exerted little effect on the reaction, whereas a shorter time of 10 h resulted in a decreased 66% yield (entries 11 and 12). Reducing the amount of **2a** to 1.2 equiv also gave a

Received: May 7, 2018
Published: June 22, 2018

DOI: 10.1021/acs.joc.8b01166
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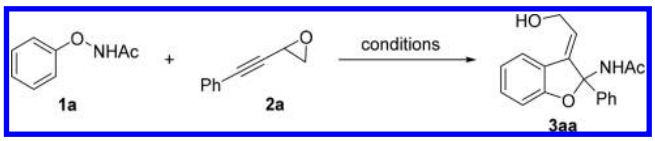
Table 1. Optimization of Reaction Conditions[a]



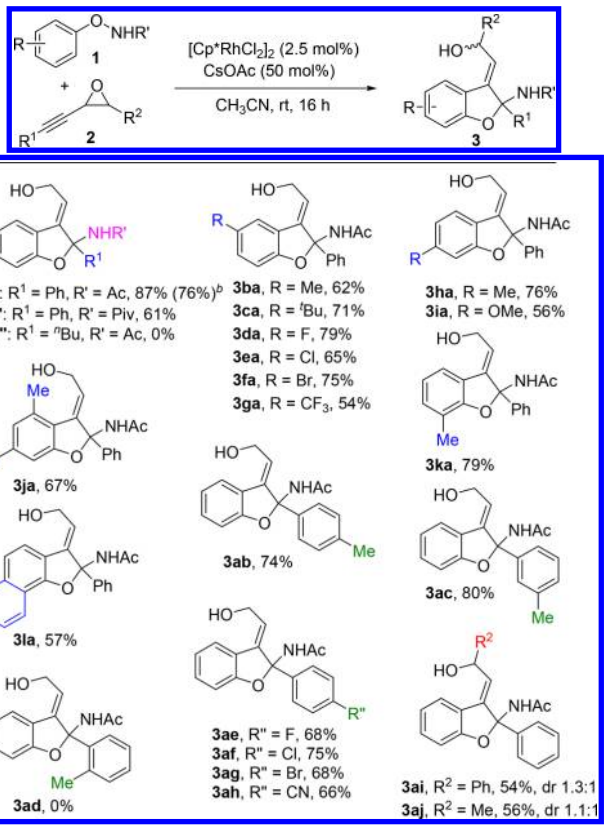
entry	catalyst	solvent	additive	yield[b] (%)
1	$[RhCp^*Cl_2]_2$	MeOH	CsOAc	86
2	$[RhCp^*Cl_2]_2$	MeOH	KOAc	69
3	$[RhCp^*Cl_2]_2$	MeOH	NaOAc	75
4	$[RhCp^*Cl_2]_2$	MeOH	AgOAc	69
5[c]	$[RhCp^*Cl_2]_2$	MeOH	$Cu(OAc)_2$	67
6	$[RhCp^*Cl_2]_2$	THF	CsOAc	38
7	$[RhCp^*Cl_2]_2$	DCE	CsOAc	51
8	$[RhCp^*Cl_2]_2$	PhMe	CsOAc	33
9	$[RhCp^*Cl_2]_2$	dioxane	CsOAc	29
10	$[RhCp^*Cl_2]_2$	CH_3CN	CsOAc	87
11[d]	$[RhCp^*Cl_2]_2$	CH_3CN	CsOAc	87
12[e]	$[RhCp^*Cl_2]_2$	CH_3CN	CsOAc	66
13[f]	$[RhCp^*Cl_2]_2$	CH_3CN	CsOAc	84
14	$[IrCp^*Cl_2]_2$	CH_3CN	CsOAc	trace
15	$[RuCl_2(p\text{-cymene})]_2$	CH_3CN	CsOAc	trace
16	$Pd(OAc)_2$	CH_3CN	CsOAc	trace

[a]Unless specified, the reactions were carried out under N_2 using 2.5 mol % catalyst, 50 mol % additive, 1.0 equiv of **1a** (0.2 mmol) and 1.5 equiv of **2a** (0.3 mmol) in 2 mL solvent at rt for 16 h. [b]Isolated yields. [c]25 mol % $Cu(OAc)_2$ was used. [d]The reaction was carried out for 24 h. [e]The reaction was performed for 10 h. [f]1.2 equiv of **2a** was used.

comparable yield of 84% (entry 13). Noteworthy is that other transition metal catalysts such as ruthenium, iridium, and palladium are ineffective for the annulation. Thus, the optimized condition was established by performing the reaction in CH_3CN or MeOH in the presence of 50 mol % CsOAc with 2.5 mol % $[Cp^*RhCl_2]_2$ at room temperature for 16 h.

Under the optimized conditions, the reaction scope was then investigated (Table 2). With 2-(phenylethynyl)oxirane (**2a**) as a partner, a range of *N*-aryloxyamides **1** were examined. It was found that switch of the acetamide to a bulky pivalamide also gave the desired product **3aa′** in 61% yield. Substition with electron-donating or electron-withdrawing groups on the *para* position of the benzene ring could be well tolerated, providing dihydrobenzofuran products **3ba−ga** in good yields (57−79%). *meta*-Substituted aryloxyacetamides afforded the corresponding products **3ha−ja** in 56−76% yields as single regioisomers, with the C−H activation taken place at less hindered C−H bonds. Notably, *ortho*-methylphenoxyacetamide also occurred smoothly, affording product **3ka** in 79% yield. Furthermore, *N*-(naphthalen-1-yloxy)acetamide was compatible giving product **3la** in a good yield of 57%. Subsequently, a range of alkynyloxiranes **2** were tested in the annulation with *N*-phenoxyacetamide **1a**. Under standard reaction conditions, 2-(arylethynyl)oxiranes with a *para*- or *meta*-methyl on the benzene ring worked well giving products **3ab** and **3ac** in 74% and 80% yields, respectively; however, *ortho*-substitution with a methyl group completely blocked the reaction probably due to the bulkiness that impeded the binding to the Rh center. The electronic property of the aryl ring of substrates **2** exerts little impact on the reaction as shown in products **3ae−ah**, which were obtained in 66−75% yields. Finally, it was found that 1,2-disubstituted alkynyloxirane **2i−j**, with R^2 as an aryl or alkyl group, were also compatible, generating the corresponding products **3ai** and **3aj** in 54% and 56% yield, respectively, albeit with poor diastereoselectivity.

Table 2. Scope Investigations[a]



[a]Isolated yields are given; reaction conditions: under N_2, **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), CsOAc (0.1 mmol, 0.5 equiv) and CH_3CN (2 mL) were sealed in a 25 mL Schlenk tube at rt for 16 h. [b]Yield of 2 mmol scale.

However, alkyl substituted alkynyloxiranes (e.g., R^1 = ^{n}Bu, **3aa″**) were ineffective in the annulation leading to complex mixtures under the standard conditions.

As 2,3-dihydrobenzofurans are privileged scaffolds in a variety of natural products, bioactive compounds, and pharmaceuticals,[13] their synthesis has attracted a long-standing interests from synthetic community.[14] As shown in Table 2, the Cp^*Rh^{III}-catalyzed annulation of *N*-aryloxyacetamides with alkynyloxiranes thus offers a mild redox-neutral protocol for the synthesis of highly functionalized 2,3-dihydrobenzofurans. To demonstrate the practicality, running the reaction in 2 mmol scale could also afford a 76% yield of the product **3aa** (Table 2). Taking advantage of the allylic alcohol moiety,[10] cyclization of **3aa** was achieved with triethyl orthoformate and propionic acid to produce a tricyclic heterocycle **4** with two adjacent quaternary stereogenic centers in 62% yield (Scheme 2a). In addition, a two-step sequence of oxidization and NHC-catalyzed rearrangement of **3aa** was exemplified to furnish a coumarin product **5** in 61% overall yield (Scheme 2b).

To gain insight into the mechanism, several mechanistic experiments were conducted. First, kinetic isotope effect was determined using **1a**/**1a**-d_5 as substrates for parallel reactions (Scheme 3a). A value of $k_{H/D}$ = 1.6 was identified, which indicates that the C−H bond cleavage might not be involved in the rate-limiting step.[15] In addition, the reaction of **1a** and **2a** was performed in CD_3OD solvent under otherwise identical conditions (Scheme 3b). The product **3aa** was isolated in 31% yield with no deuterium incorporation observed, suggesting that the C−H activation step might be irreversible under the reaction conditions.

DOI: 10.1021/acs.joc.8b01166
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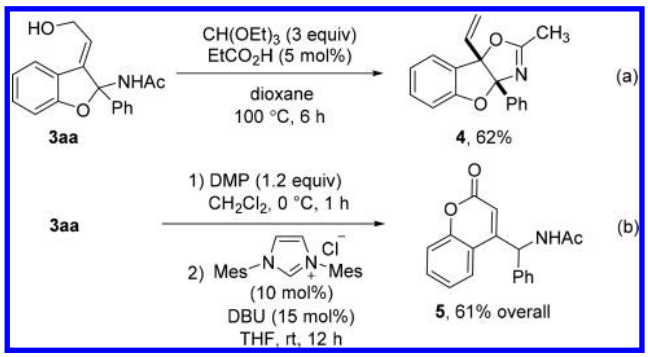
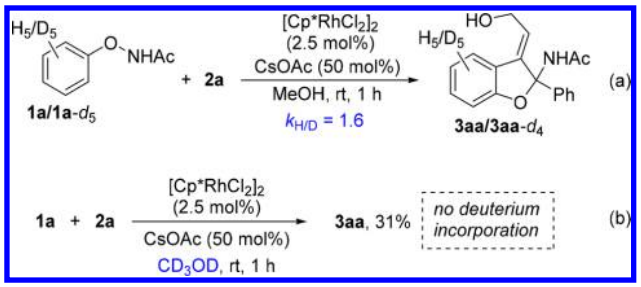
Scheme 2. Derivatization of Product 3aa

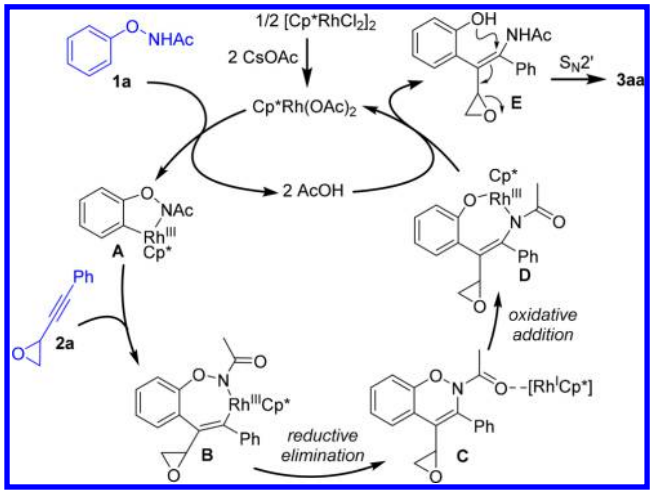


Scheme 3. Mechanistic Studies



On the basis of the results and literature precedents,[3c,5,11] a plausible mechanism is proposed in Scheme 4. In the presence

Scheme 4. Proposed Mechanism



of CsOAc, an active catalytic species Cp*Rh(OAc)$_2$ is formed through anion exchange, which promotes a facile and irreversible *ortho*-C−H activation of **1a** to afford a 5-membered rhodacycle intermediate **A**. Regioselective alkyne insertion with **2a** forms a 7-membered rhodacycle **B** with the epoxide group away from rhodium center, probably due to avoiding steric clash in the coupling.[8,16] Subsequent reductive elimination of **B** occurs to furnish intermediate **C** bearing rhodium(I) species, which undergoes oxidative addition to the N−O bond to generate a rhodium(III) species **D**. Proto-demetalation then occurs to regenerate the active catalyst Cp*Rh(OAc)$_2$ and affords an enamide compound **E**, which delivers the final product **3aa** via an intramolecular S_N2' ring opening of oxirane.[3c]

In conclusion, we have developed a Cp*Rh^{III}-catalyzed regio- and stereoselective C−H activation/annulation of *N*-aryloxyamides with alkynyloxiranes, which provides 2,3-dihydrobenzofurans with an exocyclic *E*-allylic alcohol and a tetrasubstituted carbon center in good yields with a broad substrate scope under mild redox-neutral conditions. This transformation marks the first use of alkynyloxiranes as coupling partners in transition-metal-catalyzed C−H functionalization. The products can be easily converted to molecules with more complexity, which provides an opportunity for rapid assembly of structurally diverse heterocycles. Further studies to explore synthetic applications of the methodology and developing new transition-metal-catalyzed C−H functionalization reactions are undergoing in this lab.

■ EXPERIMENTAL SECTION

General Methods. All reactions and manipulations involving air-sensitive compounds were performed using standard Schlenk techniques. Anhydrous THF and dioxane were distilled from sodium. Anhydrous CH_2Cl_2, $ClCH_2CH_2Cl$ were distilled from CaH_2 under an atmosphere of N_2. Anhydrous MeOH was distilled from magnesium under N_2 atmosphere. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 400 MHz Bruker AV400 spectrometer. Chemical shifts (δ values) were reported in ppm with internal TMS (^{1}H NMR), $CDCl_3$ (^{13}C NMR), or external CF_3CO_2H (^{19}F NMR) references, respectively. HRMS (ESI) were determined on Agilent Technologies 6224 TOF LC−MS or Q-TOF or LTQ Orbitrap XL micro spectrometer. The IR spectra were measured on a NICOLET iS10 spectrometer. Column chromatography was performed on silica gel (200−300 mesh) using a mixture of petroleum ether (60−90 °C)/ethyl acetate as the eluent.

General Procedure for Synthesis of *N*-Aryloxyacetamides 1a−l and 1a′. The *N*-aryloxyacetamides **1a−l** and **1a′** were synthesized following a procedure reported by Kelly[17] and Lu.[3c] Compounds **1a−l** and **1a′** are known compounds and all data were in agreement with those reported.[3i,11]

General Procedure for Synthesis of Substrates 2a−i. Propargyl epoxides **2a**, **2c−d**, **2f**, **2h**, and **2i−j** were synthesized according to the literature, and all data were in agreement with those reported[18a−c] and **2j** was obtained as trans/cis isomers (trans/cis = 5/1).[18d] The propargyl epoxides **2b**, **2e**, **2g** were synthesized as a following procedure analogous to that reported by Chang.[18] In an oven-dried flask, to a solution of ethynylbenzenes (10 mmol, 1 equiv) in Et_3N (5 mL) were added CuI (0.5 mmol, 95.2 mg), $Pd(PPh_3)_4$ (0.3 mmol, 210 mg), and vinyl bromide (15 mmol, 1 M, 15.0 mL) at 0 °C. After being stirred for 16 h at 25 °C, the mixture was allowed to cool to rt and then filtered through a pad of Celite with Et_2O (100 mL). The ether solution was washed with water (3 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was then taken up in CH_2Cl_2 (50 mL) and cooled to 0 °C, and *m*-CPBA (15 mmol, 1.5 equiv) was added. After 30 min, the reaction mixture was warmed to rt, and stirred for additional 12 h. The reaction mixture was then washed with sat. $NaHCO_3$ (100 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by alkaline Al_2O_3 column chromatography (petroleum ether/ethyl acetate = 30/1 to 20/1) to afford the phenylethynyloxiranes **2**.

*2-p-Tolylethynyloxirane (**2b**).* Colorless liquid, yield 880 mg (56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 3.57 (t, J = 3.3 Hz, 1H), 3.00 (d, J = 3.2 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.1, 131.9, 129.2, 119.0, 85.2, 83.7, 49.2, 40.4, 21.6; FTIR (neat) υ 2920, 2235, 1727, 1509, 1376, 1032, 927, 840, 814, 772, 751, 533 cm^{-1}; HRMS calculated for $C_{11}H_{11}O$ $(M + H)^+$: 159.0804, found 159.0804.

*2-(4-Fluorophenylethynyl)oxirane (**2e**).* Colorless liquid, yield 730 mg (45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42−7.37 (m, 2H), 7.01−6.95 (m, 2H), 3.55−3.53 (m, 1H), 2.99−2.95 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.8 (d, J = 250.2 Hz), 133.9 (d, J = 8.5 Hz), 118.0 (d, J = 3.5 Hz), 115.7 (d, J = 22.1 Hz), 85.6 (d, J = 1.3 Hz), 82.3, 49.0, 40.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −109.9;

DOI: 10.1021/acs.joc.8b01166
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FTIR (neat) υ 2991, 2239, 1653, 1601, 1505, 1377, 1230, 927, 834, 807, 777, 646, 533, 513, 490 cm^{-1}; HRMS calculated for $C_{10}H_8FO$ $(M + H)^+$: 163.0554, found 163.0548.

*2-((4-Bromophenyl)ethynyl)oxirane (**2g**).* Colorless liquid, yield 1110 mg (50%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.47−7.44 (m, 2H), 7.32−7.29 (m, 2H), 3.58−3.56 (m, 1H), 3.04−2.99 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 133.5, 131.8, 123.3, 121.0, 87.0, 82.5, 49.2, 40.3; FTIR (neat) υ 2961, 2246, 1583, 1485, 1370, 1285, 1068, 1011, 922, 865, 792, 776, 701, 569, 520, 477 cm^{-1}; HRMS calculated for $C_{10}H_8BrO$ $(M + H)^+$: 222.9753, found 222.9752.

General Procedure for Synthesis of (*E*)-3. A Schlenk tube (25 mL) with a stir bar was added aryloxyacetamides **1** (0.20 mmol, 1 equiv), propargyl epoxides **2** (0.30 mmol, 1.5 equiv), $[RhCp^*Cl_2]_2$ (0.005 mmol, 2.5 mol %) and CsOAc (0.10 mmol, 0.5 equiv). The tube was purged three times by vacuum and N_2, then the solvent (2 mL, 0.1 M) was added. The mixture was stirred at room temperature for 16 h, which was then concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1 to 1/1) to give products (*E*)-**3**.

*(E)-N-(3-(2-Hydroxyethylidene)-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3aa**).* White solid, yield 51 mg (86%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.92 (s, 1H), 7.42−7.25 (m, 7H), 6.98−6.94 (m, 2H), 5.65 (t, J = 5.6 Hz, 1H), 5.03 (t, J = 5.2 Hz, 1H), 4.41-4.28 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.5, 160.2, 141.6, 137.7, 129.9, 128.3, 127.8, 126.4, 124.9, 124.6, 123.7,121.0, 109.4, 96.3, 58.2, 23.3; FTIR (neat) υ 3049, 2923, 2151, 1593, 1485, 1439, 1025, 915, 848, 752, 684 cm^{-1}; HRMS calculated for $C_{18}H_{17}NNaO_3$ $(M + Na)^+$: 318.1101, found 318.1098.

*(E)-N-(3-(2-Hydroxyethylidene)-2-phenyl-2,3-dihydrobenzofuran-2-yl)pivalamide (**3aa′**).* White solid, yield 41 mg (61%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.17 (s, 1H), 7.39−7.26 (m, 7H), 6.99−6.93 (m, 2H), 5.63 (t, J = 5.6 Hz, 1H), 5.00 (t, J = 5.3 Hz, 1H), 4.40−4.28 (m, 2H), 1.13 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 177.3, 160.3, 142.0, 137.9, 129.9, 128.4, 127.7, 125.9, 124.95, 124.5, 123.96, 120.9, 109.5, 96.5, 58.2, 39.1, 26.9; IR (neat) ν 3336, 2921, 2852, 1680, 1606, 1460, 1366, 1244, 1173, 1018, 855, 799, 746, 700, 566, 428 cm^{-1}; HRMS calculated for $C_{21}H_{24}NO_3$ $(M + H)^+$: 338.1751, found 338.1748.

*(E)-N-(3-(2-Hydroxyethylidene)-5-methyl-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3ba**).* White solid, yield 38 mg (62%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.88 (s, 1H), 7.40−7.27 (m, 5H), 7.14 (s, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 5.61 (t, J = 5.6 Hz, 1H), 5.02 (t, J = 5.1 Hz, 1H), 4.41−4.29 (m, 2H), 2.27 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.5, 158.4, 141.8, 137.98, 130.4, 129.8, 128.3, 127.7, 126.1, 125.2, 124.7, 123.7, 109.0, 96.4, 58.2, 23.3, 20.5; IR (neat) ν 3268, 2924, 2093, 1748, 1731, 1715, 1681, 1541, 1480, 1374, 1244, 1035, 920, 809, 704, 674, 590, 533 cm^{-1}; HRMS calculated for $C_{19}H_{23}N_2O_3$ $(M + NH_4)^+$: 327.1703, found 327.1699.

*(E)-N-(5-(tert-Butyl)-3-(2-hydroxyethylidene)-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3ca**).* White solid, yield 46 mg (66%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.88 (s, 1H), 7.43−7.18 (m, 7H), 6.90 (d, J = 8.4 Hz, 1H), 5.64 (t, J = 5.7 Hz, 1H), 5.04 (t, J = 5.1 Hz, 1H), 4.44−4.31 (m, 2H), 1.90 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.5, 158.2, 143.3, 141.7, 138.3, 128.3, 127.8, 127.1, 125.7, 124.8, 123.3, 121.4, 108.8, 96.5, 58.2, 34.1, 31.4, 23.4; IR (neat) ν 3457, 3306, 2959, 1656, 1482, 1363, 1260, 1243, 1155, 1047, 959, 817, 732, 696, 665, 567, 509, 491 cm^{-1}; HRMS calculated for $C_{22}H_{29}N_2O_3$ $(M + NH_4)^+$: 369.2173, found 369.2168.

*(E)-N-(5-Fluoro-3-(2-hydroxyethylidene)-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3da**).* White solid, yield 49 mg (79%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.98 (s, 1H), 7.45−7.31 (m, 5H), 7.19 (dd, J = 8.9, 2.6 Hz, 1H), 7.12 (td, J = 9.0, 2.7 Hz, 1H), 6.98 (dd, J = 8.8, 4.3 Hz, 1H), 5.73 (t, J = 5.7 Hz, 1H), 5.08 (t, J = 5.2 Hz, 1H), 4.39−4.28 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.6, 156.9 (d, J = 234.6 Hz), 156.4, 141.4, 137.6, 128.4, 128.0, 127.6, 124.8, 124.7, 116.1 (d, J = 24.5 Hz), 111.5 (d, J = 25.6 Hz), 109.9 (d, J = 8.6 Hz), 97.1, 58.0, 23.3; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −123.00; IR (neat,cm^{-1}) ν 3280, 2924, 2853, 1679, 1471, 1370, 1251, 1196, 1034, 940, 860, 811, 734, 698, 659, 556, 491; HRMS calculated for $C_{18}H_{20}FN_2O_3$ $(M + NH_4)^+$: 331.1452, found 331.1449.

*(E)-N-(5-Chloro-3-(2-hydroxyethylidene)-2-phenyl-2,3-dihydrobenzofuran-2-yl)pivalamide (**3ea**).* White solid, yield 43 mg (65%); ^1H NMR (400 MHz, DMSO-d_6) δ = 9.01 (s, 1H), 7.46−7.18 (m, 7H), 6.99 (t, J = 8.5 Hz, 1H), 5.74 (t, J = 5.7 Hz, 1H), 5.08 (t, J = 5.2 Hz, 1H), 4.38−4.25 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.7, 158.9, 141.1, 137.1, 129.5, 128.5, 128.1, 127.7, 125.7, 124.7, 124.6, 124.4, 110.8, 97.3, 58.0, 23.3; IR (neat) ν 3412; 3273, 2923, 2851, 1682, 1461, 1368, 1245, 1159, 1059, 891, 870, 811, 771, 699 cm^{-1}; HRMS calculated for $C_{18}H_{20}ClN_2O_3$ $(M + NH_4)^+$: 347.1157, found 347.1155.

*(E)-N-(5-Bromo-3-(2-hydroxyethylidene)-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3fa**).* White solid, yield 56 mg (75%); ^1H NMR (400 MHz, DMSO-d_6) δ = 9.02 (s, 1H), 7.47−7.31 (m, 7H), 6.95 (d, J = 8.5 Hz, 1H), 5.74 (t, J = 5.8 Hz, 1H), 5.08 (t, J = 5.2 Hz, 1H), 4.36−4.26 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.7, 159.3, 141.1, 136.97, 132.3, 128.6, 128.2, 127.6, 127.2, 126.3, 124.7, 112.2, 111.4, 97.2, 57.9, 23.3; IR (neat) ν 3360, 2918, 1679, 1525, 1459, 1245, 1024, 990, 824, 699, 552, cm^{-1}; HRMS calculated for $C_{18}H_{20}BrN_2O_3$ $(M + NH_4)^+$: 391.0652, found 391.0651.

*(E)-N-(3-(2-Hydroxyethylidene)-2-phenyl-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)acetamide (**3ga**).* White solid, yield 39 mg (54%); ^1H NMR (400 MHz, DMSO-d_6) δ = 9.12 (s, 1H), 7.65−7.63 (m, 2H), 7.46−7.33 (m, 5H), 7.15 (d, J = 8.2 Hz, 1H), 5.81 (t, J = 5.8 Hz, 1H), 5.13 (t, J = 5.2 Hz, 1H), 4.42−4.29 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.8, 162.6, 140.7, 136.6, 128.6, 128.4, 128.0, 127.5 (q, J = 4.2 Hz), 124.85, 124.81, 124.6 (q, J = 270.2 Hz), 121.9 (q, J = 3.0 Hz), 121.7 (q, J = 31.0 Hz), 110.0, 97.8, 57.9, 23.3; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −59.54; IR (neat) ν 3417, 3267, 2918, 1683, 1614, 1529, 1489, 1314, 1154, 1116, 1056, 890, 823, 764, 697, 545, 437 cm^{-1}; HRMS calculated for $C_{19}H_{20}F_3N_2O_3$ $(M + NH_4)^+$: 381.1421, found 381.1417.

*(E)-N-(3-(2-Hydroxyethylidene)-6-methyl-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3ha**).* White solid, yield 47 mg (76%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.88 (s, 1H), 7.40−7.20 (m, 6H), 6.80−6.77 (m, 2H), 5.57 (t, J = 5.6 Hz, 1H), 4.99 (t, J = 5.2 Hz, 1H), 4.38−4.26 (m, 2H), 2.31 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.5, 160.5, 141.7, 140.2, 137.9 128.3, 127.7, 125.0, 124.66, 124.61, 121.9, 121.2, 110.0, 96.5, 58.2, 23.3, 21.3; IR (neat) ν 3275, 3034, 2922, 1673, 1618, 1521, 1492, 1447, 1369, 1336, 1259, 1146, 1033, 948, 809, 734, 699, 569 cm^{-1}; HRMS calculated for $C_{19}H_{23}N_2O_3$ $(M + NH_4)^+$: 327.1703, found 327.1696.

*(E)-N-(3-(2-Hydroxyethylidene)-6-methoxy-2-phenyl-2,3-dihydrobenzofuran-2-yl)pivalamide (**3ia**).* White solid, yield 36 mg (56%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.88 (s, 1H), 7.41−7.23 (m, 6H), 6.62 (d, J = 2.2 Hz, 1H), 6.53 (dd, J = 8.5, 2.3 Hz, 1H), 5.48 (t, J = 5.7 Hz, 1H), 4.96 (t, J = 5.2 Hz, 1H), 4.34−4.24 (m, 2H), 3.77 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.5, 161.9, 161.5, 141.7, 137.7, 128.3, 127.7, 125.5, 124.7, 123.1, 116.5, 107.5, 97.2, 95.5, 58.2, 55.4, 24.3; IR (neat) ν 3275, 2924, 1679, 1614, 1588, 1521, 1493, 1443, 1369, 1282, 1196,1156, 956, 826, 804, 732, 698, 635, 591 cm^{-1}; HRMS calculated for $C_{19}H_{23}N_2O_4$ $(M + NH_4)^+$: 343.1652, found 343.1649.

*(E)-N-(3-(2-Hydroxyethylidene)-4,6-dimethyl-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3ja**).* White solid, yield 43 mg (67%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.78 (s, 1H), 7.40−7.27 (m, 5H), 6.57 (d, J = 15.1 Hz, 2H), 5.48 (t, J = 6.2 Hz, 1H), 4.89 (t, J = 5.1 Hz, 1H), 4.36−4.19 (m, 2H), 2.32 (s, 3H), 2.24 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.2, 160.9, 141.2, 140.3, 137.8, 133.6, 128.1, 127.8, 125.3, 124.8, 124.5, 119.9, 107.9, 97.5, 59.4, 23.5, 21.8, 21.1; IR (neat) ν 3268, 2923, 1670, 1620, 1525, 1447, 1373, 1264, 1174, 1031, 836, 804, 737, 699, 574 cm^{-1}; HRMS calculated for $C_{20}H_{25}N_2O_3$ $(M + NH_4)^+$: 341.1860, found 341.1855.

*(E)-N-(3-(2-Hydroxyethylidene)-7-methyl-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3ka**).* White solid, yield 49 mg (79%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.88 (s, 1H), 7.43−7.28 (m, 5H), 7.15−7.10 (m, 2H), 6.86 (t, J = 7.5 Hz, 1H), 5.65 (t, J = 5.6 Hz, 1H), 5.01 (t, J = 5.2 Hz, 1H), 4.39−4.27 (m, 2H), 2.23 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.5, 158.6, 141.7,

DOI: 10.1021/acs.joc.8b01166
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138.2, 130.9 128.4, 127.8, 125.8, 124.6, 123.1, 122.4, 120.9, 118.8, 96.0, 58.2, 23.4, 14.9; IR (neat) ν 3282, 2925, 1679, 1490, 1371, 1363, 1032, 967, 856, 731, 699, 550, 527 cm^{-1}; HRMS calculated for $C_{19}H_{23}N_2O_3$ $(M + NH_4)^+$: 327.1703, found 327.1696.

*(E)-N-(3-(2-Hydroxyethylidene)-2-phenyl-2,3-dihydronaphtho-[1,2-b]furan-2-yl)acetamide (**3la**).* White solid, yield 39 mg (57%); ^1H NMR (400 MHz, DMSO-d_6) δ = 9.05 (s, 1H), 8.04−8.02 (m, 1H), 7.95−7.93 (m, 1H), 7.59−7.47 (m, 6H), 7.39−7.29 (m, 3H), 5.67 (t, J = 5.9 Hz, 1H), 5.04 (t, J = 5.3 Hz, 1H), 4.51−4.37 (m, 2H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.6, 156.3, 141.5, 138.9 134.1, 128.4, 127.9, 127.1, 125.9, 124.7, 124.1, 122.2, 121.5, 120.8, 119.4, 117.8, 97.5, 57.9, 23.4; IR (neat) ν 3272, 2922, 2852, 1659, 1517, 1441, 1391, 1265, 1066, 968, 947, 876, 807, 733, 700, 566, 544 cm^{-1}; HRMS calculated for $C_{22}H_{23}N_2O_3$ $(M + NH_4)^+$: 363.1703, found 363.1700.

*(E)-N-(3-(2-Hydroxyethylidene)-2-(p-tolyl)-2,3-dihydrobenzofuran-2-yl)acetamide (**3ab**).* White solid, yield 46 mg (74%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.88 (s, 1H), 7.35−7.25 (m, 4H), 7.17 (d, J = 8.1 Hz, 2H), 6.95 (t, J = 8.4 Hz, 2H), 5.64 (t, J = 5.6 Hz, 1H), 5.04 (t, J = 5.2 Hz, 1H), 4.41−4.31 (m, 2H), 2.28 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.5, 160.3, 138.8, 137.9, 137.2, 129.9, 128.9, 126.2, 125.0, 124.7, 123.9, 121.0, 109.5, 96.4, 58.3, 23.4, 20.6; IR (neat) ν 3283, 2925, 1679, 1525, 1592, 1524, 1489, 1371, 1263, 1032, 967, 856, 786, 731, 693, 657 cm^{-1}; HRMS calculated for $C_{19}H_{23}N_2O_3$ $(M + NH_4)^+$: 327.1703, found 327.1697.

*(E)-N-(3-(2-Hydroxyethylidene)-2-(m-tolyl)-2,3-dihydrobenzofuran-2-yl)acetamide (**3ac**).* White solid, yield 49 mg (80%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.90 (s, 1H), 7.35−7.11 (m, 6H), 6.99−6.94 (m, 2H), 5.65 (t, J = 5.6 Hz, 1H), 5.05 (t, J = 5.2 Hz, 1H), 4.42−4.30 (m, 2H), 2.30 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.5, 160.3, 141.6, 137.8, 137.5, 130.0, 128.5, 128.3, 126.3, 125.2, 125.0, 123.9, 121.9, 121.0, 109.5, 96.3, 58.3, 23.4, 21.2; IR (neat) ν 3272, 3039, 2923, 1674, 1607, 1520, 1459, 1371, 1238, 1017, 968, 866, 785, 734, 699, 581, 490 cm^{-1}; HRMS calculated for $C_{19}H_{23}N_2O_3$ $(M + NH_4)^+$: 327.1703, found 327.1697.

*(E)-N-(2-(4-Fluorophenyl)-3-(2-hydroxyethylidene)-2,3-dihydrobenzofuran-2-yl)acetamide (**3ae**).* White solid, yield 42 mg (68%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.93 (s, 1H), 7.45−7.41 (m, 2H), 7.35 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.21−7.16 (m, 2H), 6.99−6.95 (m, 2H), 5.65 (t, J = 5.6 Hz, 1H), 5.05 (t, J = 5.2 Hz, 1H), 4.42−4.31 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.6, 161.8 (d, J = 244.1 Hz), 160.0, 137.9 (d, J = 2.8 Hz), 137.7, 130.1, 126.9 (d, J = 8.4 Hz), 126.7, 125.1, 123.6, 121.2, 115.1 (d, J = 21.6 Hz), 109.6, 96.0, 58.2, 23.3; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −115.09; IR (neat) ν 3259, 3046, 2925, 1672, 1602, 1506, 1460, 1274, 1227, 1159, 1018, 967, 839, 748, 545, 487 cm^{-1}; HRMS calculated for $C_{18}H_{20}FN_2O_3$ $(M + NH_4)^+$: 331.1452, found 331.1450.

*(E)-N-(2-(4-Chlorophenyl)-3-(2-hydroxyethylidene)-2,3-dihydrobenzofuran-2-yl)acetamide (**3af**).* White solid, yield 49 mg (75%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.96 (s, 1H), 7.44−7.28 (m, 6H), 7.02−6.97 (m, 2H), 5.66 (t, J = 5.6 Hz, 1H), 5.06 (t, J = 5.2 Hz, 1H), 4.42−4.31 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.6, 160.1, 140.7, 137.6, 132.4, 130.2, 128.4, 127.1, 126.6, 125.1, 123.4, 121.3, 109.7, 95.8, 58.2, 23.3; IR (neat) ν 3264, 2923, 1682, 1588, 1525, 1460, 1369, 1270, 1093, 1022, 1006, 822, 747, 732, 545, 501, 464 cm^{-1}; HRMS calculated for $C_{18}H_{20}ClN_2O_3$ $(M + NH_4)^+$: 347.1157, found 347.1154.

*(E)-N-(2-(4-Bromophenyl)-3-(2-hydroxyethylidene)-2,3-dihydrobenzofuran-2-yl)acetamide (**3ag**).* White solid, yield 51 mg (68%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.97 (s, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.36−7.27 (m, 4H), 7.01−6.96 (m, 2H), 5.65 (t, J = 5.6 Hz, 1H), 5.06 (t, J = 5.2 Hz, 1H), 4.41−4.29 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.7, 160.1, 141.2, 137.5, 131.3, 130.2, 127.2, 126.9, 125.1, 123.4, 121.4, 121.0, 109.7, 95.9, 58.2, 23.3; IR (neat) ν 3217, 2916, 2848, 1660, 1589, 1520, 1484, 1457, 1394, 1367, 1314, 1276, 1104, 909, 824, 750, 547 cm^{-1}; HRMS calculated for $C_{18}H_{16}BrKNO_3$ $(M + K)^+$: 411.9945, found 411.9941.

*(E)-N-(2-(4-Cyanophenyl)-3-(2-hydroxyethylidene)-2,3-dihydrobenzofuran-2-yl)acetamide (**3ah**).* White solid, yield 42 mg (66%); ^1H NMR (400 MHz, DMSO-d_6) δ = 9.06 (s, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.38−7.30 (m, 2H), 7.06−6.98 (m, 2H), 5.71 (t, J = 5.6 Hz, 1H), 5.08 (t, J = 5.2 Hz, 1H), 4.41−4.30 (m, 2H), 1.93 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.9, 160.1, 147.0, 137.2, 132.5, 130.4, 128.1, 125.5, 125.2, 123.0, 121.6, 118.7, 110.4, 109.8, 95.6, 58.2, 23.2; IR (neat) ν 3306, 3063, 2230, 1682, 1588, 1502, 1461, 1370, 1264, 1237, 1154, 1017, 696, 842, 731, 556, 483 cm^{-1}; HRMS calculated for $C_{19}H_{20}N_3O_3$ $(M + NH_4)^+$: 338.1499, found 338.1496.

*(E)-N-(3-(2-Hydroxy-2-phenylethylidene)-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3ai**).* White solid, yield 40 mg (54%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.95 (s, 1H), 7.58−7.16 (m, 12H), 6.97 (d, J = 8.0, 1H), 6.92 (t, J = 7.5, 1H), 5.79−5.67 (m, 3H), 1.88 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.6, 160.4, 143.9, 141.2, 139.3, 130.3, 128.4, 128.2, 128.1, 128.0, 126.9, 126.2, 125.2, 124.9, 123.7, 120.9, 109.6, 96.6, 67.9, 23.3; IR (neat) ν 3272, 3053, 2923, 2853, 1659, 1574, 1517, 1441, 1391, 1266, 1066, 1032, 968, 947, 808, 733, 700, 642, 566 cm^{-1}; HRMS calculated for $C_{24}H_{25}N_2O_3$ $(M + NH_4)^+$: 389.1860, found 389.1857. For the other isomer **3ai′**. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.95 (s, 1H), 7.51 (t, J = 6.3 Hz, 1H), 7.39−7.17 (m, 11H), 6.98 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 5.81−5.69 (m, 3H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.6, 160.5, 143.9, 141.5, 138.3, 130.4, 128.3, 128.2, 128.0, 127.7, 127.1, 126.2, 124.9, 124.8, 123.3, 121.0, 109.7, 96.6, 68.4, 23.4; IR (neat) ν 3268, 3030, 2922, 1668, 1603, 1520, 1460, 1368, 1316, 1241, 1015, 961, 860, 736, 697, 600, 491 cm^{-1}; HRMS calculated for $C_{24}H_{25}N_2O_3$ $(M + NH_4)^+$: 389.1860, found 389.1857.

*(E)-N-(3-(2-Hydroxypropylidene)-2-phenyl-2,3-dihydrobenzofuran-2-yl)acetamide (**3aj**).* White solid, yield 35 mg (56%); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.82 (s, 1H), 7.49−7.24 (m, 7H), 6.97−6.93 (m, 2H), 5.52 (d, J = 7.9 Hz, 1H), 4.93 (d, J = 4.7 Hz, 1H), 4.86−4.77 (m, 1H), 1.91 (s, 3H), 1.21 (d, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.4, 160.2, 141.5, 137.3, 130.5, 129.9, 128.3, 127.8, 125.0, 124.9, 123.5, 120.9, 109.6, 96.4, 62.7, 23.4, 23.1; IR (neat) ν 3282, 2959, 2924, 1676, 1588, 1525, 1460, 1240, 861, 773, 699, 583, 550, 470 cm^{-1}; HRMS calculated for $C_{19}H_{19}NNaO_3$ $(M + Na)^+$: 332.1257, found 332.1254. For the other isomer **3aj′**. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.83 (s, 1H), 7.45−7.24 (m, 7H), 6.96−6.93 (m, 2H), 5.59 (d, J = 7.7 Hz, 1H), 4.95 (d, J = 4.5 Hz, 1H), 4.88−4.79 (m, 1H), 1.91 (s, 3H), 1.14 (d, J = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.3, 160.1, 141.5, 136.7, 130.6, 129.9, 128.3, 127.9, 124.9, 124.8, 123.4, 120.9, 109.6, 96.4, 62.9, 23.4, 23.2; IR (neat) ν 3725, 3283, 2962, 1679, 1588, 1527, 1460, 1241, 1064, 976, 698, 667, 583, cm^{-1}; HRMS calculated for $C_{19}H_{19}NNaO_3$ $(M + Na)^+$: 332.1257, found 332.1256.

Scaled-up Reaction. A Schlenk tube (25 mL) with a stir bar was added **1a** (2.0 mmol, 1 equiv), propargyl epoxides **2a** (3 mmol, 1.5 equiv), $[RhCp^*Cl_2]_2$ (0.05 mmol, 2.5 mol %) and CsOAc (1.0 mmol, 0.5 equiv). The tube was purged three times by vacuum and N_2, then the solvent (5 mL, 0.4 M) was added. The mixture was stirred at room temperature for 16 h, which was then concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1 to 1/1) to give product 450 mg **3aa** as white solid in 76% yield.

Synthesis of 4. A Schlenk tube (25 mL) with a stir bar was added **3aa** (0.2 mmol, 1 equiv) and the tube was purged three times by vacuum and N_2. Then triethyl orthoformate (0.6 mmol, 3.0 equiv), EtCOOH (0.01 mmol, 0.05 equiv) and dioxane (2 mL) was added. The mixture was stirred at 100 °C for 6 h, which then cooled to room temperature. After that the mixture was concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 5/1) to give product **4** as white solid in 62% yield.

*2-Methyl-3a-phenyl-8b-vinyl-3a,8b-dihydrobenzofuro[2,3-d]-oxazole (**4**).* White solid, yield 34 mg (62%); ^1H NMR (400 MHz, DMSO-d_6) δ = 7.46−7.34 (m, 4H), 7.29−7.22 (m, 3H), 7.13−7.05 (m, 2H), 5.34 (dd, J = 17.2, 10.5 Hz, 1H), 5.20−5.10 (m, 2H), 2.17 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.8, 158.6, 137.2, 133.8, 132.0, 128.6, 128.1, 126.6, 126.1, 125.1 121.8, 117.4, 115.8,

DOI: 10.1021/acs.joc.8b01166
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110.7, 95.9, 13.90; IR (neat) υ 3304, 2917, 2849, 1657, 1598, 1520, 1462, 1386, 1281, 1064, 983, 752, 698, 665, 491 cm^{-1}; HRMS calculated for $C_{18}H_{16}NO_2$ $(M + H)^+$: 278.1176, found 278.1173.

Synthesis of 5. To a solution of **3aa** (0.10 mmol, 1 equiv) in anhydrous dichloromethane (2 mL) at 0 °C was added Dess−Martin periodinane reagent (DMP) (0.12 mmol, 1.2 equiv) and the reaction mixture was stirred at that temperature for 1 h. The reaction was quenched by the addition of 2 mL saturated aqueous sodium thiosulfate and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed twice with saturated aqueous sodium bicarbonate and then dried over anhydrous sodium sulfate, filtered, concentrated and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 2/1) to give the desired unsaturated aldehyde as a *Z*/*E* mixture in a yield of 76%. A dry tube charged with a stir bar was added the unsaturated aldehyde (0.06 mmol, 1 equiv) and NHC (**6**, 0.006 mmol, 10 mol %). The tube was purged three times by vacuum and N_2, and then THF (2 mL) and DBU (0.009 mmol, 15 mol %) were added. The mixture was stirred at room temperature for 12 h, which then was quenched with sat. NH_4Cl. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, then dried over anhydrous sodium sulfate, filtered, concentrated and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 5/1) to give the desired product **5** in 80% isolated yield.

*N-((2-Oxo-2H-chromen-4-yl)(phenyl)methyl)acetamide (**5**).* White solid, 18 mg (61%) for two steps; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.85 (d, *J* = 7.9 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.63−7.56 (m, 1H), 7.44 (td, *J* = 5.5, 1.2 Hz, 3H), 7.41−7.25 (m, 4H), 6.48 (d, *J* = 7.9 Hz, 1H), 6.38 (s, 1H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.8, 159.9, 155.5, 153.2, 138.4, 132.1, 128.8, 128.2, 128.1, 125.2, 124.5, 117.5, 116.9, 112.9, 52.2, 22.4; FTIR (neat) υ 3797, 2922, 1719, 1644, 1604, 1526, 1445, 1371, 1291, 1257, 1179, 995, 752, 701, 616, 527 cm^{-1}; HRMS calculated for $C_{18}H_{16}NO_3$ $(M + H)^+$: 294.1125, found 294.1121.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01166.

Copies of ^{1}H and ^{13}C NMR spectra of new compounds and details of deuterium experiments; NOE spectra of the compound **3aa** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21602167, 21402149), the Natural Science Basic Research Plan in Shaanxi Province of China (Nos. 2016JQ2019, 2015JQ2050), the China Postdoctoral Science Foundation (Nos. 2015M580830, 2014M550484, 2015T81013), and the Fundamental Research Funds for the Central Universities.

■ REFERENCES

(1) For recent selected reviews: (a) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. Transition-Metal-Catalyzed C−H Alkylation Using Alkenes. *Chem. Rev.* **2017**, *117*, 9333−9403. (b) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. Transition-Metal-Catalyzed C−H Bond Addition to Carbonyls, Imines, and Related Polarized π Bonds. *Chem. Rev.* **2017**, *117*, 9163−9227. (c) Newton, C. G.; Wang, S. G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C−H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908−8976. (d) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild metal-catalyzed C−H activation: examples and concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900−2936. (e) Song, G.; Li, X. Substrate Activation Strategies in Rhodium(III)-Catalyzed Selective Functionalization of Arenes. *Acc. Chem. Res.* **2015**, *48*, 1007−1020. (f) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. Transition metal-catalyzed C−H bond functionalizations by the use of diverse directing groups. *Org. Chem. Front.* **2015**, *2*, 1107−1295.

(2) For reviews: (a) Mo, J.; Wang, L.; Liu, Y.; Cui, X. Transition-Metal-Catalyzed Direct C−H Functionalization under External-Oxidant-Free Conditions. *Synthesis* **2015**, *47*, 439−459. (b) Song, G.; Wang, F.; Li, X. C−C, C−O and C−N bond formation via rhodium(III)-catalyzed oxidative C−H activation. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678.

(3) For selected examples: (a) Wu, Y.; Chen, Z.; Yang, Y.; Zhu, W.; Zhou, B. Rh(III)-Catalyzed Redox-Neutral Unsymmetrical C−H Alkylation and Amidation Reactions of *N*-Phenoxyacetamides. *J. Am. Chem. Soc.* **2018**, *140*, 42−45 and references cited therein. (b) Wang, X.; Lerchen, A.; Gensch, T.; Knecht, T.; Daniliuc, C. G.; Glorius, F. Combination of Cp*Rh^{III}-Catalyzed C−H Activation and a Wagner−Meerwein-Type Rearrangement. *Angew. Chem., Int. Ed.* **2017**, *56*, 1381−1384. (c) Zhou, Z.; Liu, G.; Chen, Y.; Lu, X. Cascade Synthesis of 3-Alkylidene Dihydrobenzofuran Derivatives via Rhodium(III)-Catalyzed Redox-Neutral C−H Functionalization/Cyclization. *Org. Lett.* **2015**, *17*, 5874−5877. (d) Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. Rhodium(III)-Catalyzed ortho Alkenylation of *N*-Phenoxyacetamides with *N*-Tosylhydrazones or Diazoesters through C−H Activation. *Angew. Chem., Int. Ed.* **2014**, *53*, 1364−1367 and references cited therein. (e) Zhang, X.; Qi, Z.; Li, X. Rhodium(III)-Catalyzed C−C and C−O Coupling of Quinoline *N*−Oxides with Alkynes: Combination of C−H Activation with O-Atom Transfer. *Angew. Chem., Int. Ed.* **2014**, *53*, 10794−10798. (f) Han, W.; Zhang, G.; Li, G.; Huang, H. Rh-Catalyzed Sequential Oxidative C−H and N−N Bond Activation: Conversion of Azines into Isoquinolines with Air at Room Temperature. *Org. Lett.* **2014**, *16*, 3532−3535. (g) Liu, B.; Fan, Y.; Gao, Y.; Sun, C.; Xu, C.; Zhu, J. Rhodium(III)-Catalyzed *N*-Nitroso-Directed C−H Olefination of Arenes. High-Yield, Versatile Coupling under Mild Conditions. *J. Am. Chem. Soc.* **2013**, *135*, 468−473 and references cited therein. (h) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. Rh(III)-Catalyzed Synthesis of Multisubstituted Isoquinoline and Pyridine *N*-Oxides from Oximes and Diazo Compounds. *J. Am. Chem. Soc.* **2013**, *135*, 12204−12207. (i) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. Rhodium(III)-Catalyzed Redox-Neutral Coupling of *N*-Phenoxyacetamides and Alkynes with Tunable Selectivity. *Angew. Chem., Int. Ed.* **2013**, *52*, 6033−6037.

(4) For a review: Mishra, N. K.; Sharma, S.; Park, J.; Han, S.; Kim, I. S. Recent Advances in Catalytic C(sp2)−H Allylation Reactions. *ACS Catal.* **2017**, *7*, 2821−2847.

(5) (a) Sk, M. R.; Bera, S. S.; Maji, M. S. Weakly Coordinating, Ketone-Directed Cp*Co(III)-Catalyzed C−H Allylation on Arenes and Indoles. *Org. Lett.* **2018**, *20*, 134−137 and references cited therein. (b) Kljajic, M.; Puschnig, J. G.; Weber, H.; Breinbauer, R. Additive-Free Pd-Catalyzed α-Allylation of Imine-Containing Heterocycles. *Org. Lett.* **2017**, *19*, 126−129. (c) Lee, S. Y.; Hartwig, J. F. Palladium-Catalyzed, Site-Selective Direct Allylation of Aryl C−H Bonds by Silver-Mediated C−H Activation: A Synthetic and Mechanistic Investigation. *J. Am. Chem. Soc.* **2016**, *138*, 15278−15284. (d) Dai, H.; Yu, C.; Wang, Z.; Yan, H.; Lu, C. Solvent-Controlled, Tunable β-OAc and β-H Elimination in Rh(III)-Catalyzed Allyl Acetate and Aryl Amide Coupling via C−H Activation. *Org. Lett.* **2016**, *18*, 3410−3413. (e) Wang, H.; Schröder, N.; Glorius, F. Mild Rhodium(III)-Catalyzed Direct C−H

Allylation of Arenes with Allyl Carbonates. *Angew. Chem., Int. Ed.* **2013**, *52*, 5386−5389.

(6) Kalsi, D.; Laskar, R. A.; Barsu, N.; Premkumar, J. R.; Sundararaju, B. C-8-Selective Allylation of Quinoline: A Case Study of *β*-Hydride vs *β*-Hydroxy Elimination. *Org. Lett.* **2016**, *18*, 4198−4201.

(7) For a review: (a) Wang, F.; Yu, S.; Li, X. Transition metal-catalysed couplings between arenes and strained or reactive rings: combination of C−H activation and ring scission. *Chem. Soc. Rev.* **2016**, *45*, 6462−6477. For selected examples: (b) Lu, Q.; Klauck, F. J. R.; Glorius, F. Manganese-catalyzed allylation via sequential C−H and C−C/C−Het bond activation. *Chem. Sci.* **2017**, *8*, 3379−3383. (c) Sharma, S.; Han, S. H.; Oh, Y.; Mishra, N. K.; Han, S.; Kwak, J. H.; Lee, S.-Y.; Jung, Y. H.; Kim, I. S. Mild and Site-Selective Allylation of Enol Carbamates with Allylic Carbonates under Rhodium Catalysis. *J. Org. Chem.* **2016**, *81*, 2243−2251 and references cited therein. (d) Qi, Z.; Kong, L.; Li, X. Rhodium(III)-Catalyzed Regio- and Stereoselective C−H Allylation of Arenes with Vinyl Benzoxazinanones. *Org. Lett.* **2016**, *18*, 4392−4395 and references cited therein.

(8) (a) Sen, M.; Dahiya, P.; Premkumar, J. R.; Sundararaju, B. Dehydrative Cp*Co(III)-Catalyzed C−H Bond Allenylation. *Org. Lett.* **2017**, *19*, 3699−3702. (b) Lu, Q.; Greßies, S.; Cembellín, S.; Klauck, F. J. R.; Daniliuc, C. G.; Glorius, F. Redox-Neutral Manganese(I)-Catalyzed C−H Activation: Traceless Directing Group Enabled Regioselective Annulation. *Angew. Chem., Int. Ed.* **2017**, *56*, 12778−12782. (c) Wu, S.; Huang, X.; Wu, W.; Li, P.; Fu, C.; Ma, S. A C−H bond activation-based catalytic approach to tetrasubstituted chiral allenes. *Nat. Commun.* **2015**, *6*, 7946.

(9) (a) Wu, X.; Wang, B.; Zhou, S.; Zhou, Y.; Liu, H. Ruthenium-Catalyzed Redox-Neutral [4 + 1] Annulation of Benzamides and Propargyl Alcohols via C−H Bond Activation. *ACS Catal.* **2017**, *7*, 2494−2499. (b) Wu, X.; Wang, B.; Zhou, Y.; Liu, H. Propargyl Alcohols as One-Carbon Synthons: Redox-Neutral Rhodium(III)-Catalyzed C−H Bond Activation for the Synthesis of Isoindolinones Bearing a Quaternary Carbon. *Org. Lett.* **2017**, *19*, 1294−1297.

(10) For reviews: (a) Li, H.; Mazet, C. Iridium-Catalyzed Selective Isomerization of Primary Allylic Alcohols. *Acc. Chem. Res.* **2016**, *49*, 1232−1241. (b) Debien, L.; Quiclet-Sire, B.; Zard, S. Z. Allylic Alcohols: Ideal Radical Allylating Agents? *Acc. Chem. Res.* **2015**, *48*, 1237−1253. (c) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-directable chemical reactions. *Chem. Rev.* **1993**, *93*, 1307−1370.

(11) Li, Y.; Tang, Y.; He, X.; Shi, D.; Wu, J.; Xu, S. Rhodium(III)-Catalyzed Annulative Carbooxygenation of 1,1-Disubstituted Alkenes Triggered by C−H Activation. *Chem. - Eur. J.* **2017**, *23*, 7453−7457.

(12) CsOAc is an optimal additive for many Cp*Rh^{III}-catalyzed transformations, see: (a) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. Mild Rh(III)-Catalyzed C−H Activation and Annulation with Alkyne MIDA Boronates: Short, Efficient Synthesis of Heterocyclic Boronic Acid Derivatives. *J. Am. Chem. Soc.* **2012**, *134*, 19592−19595. (b) Guimond, N.; Gouliaras, C.; Fagnou, K. Rhodium(III)-Catalyzed Isoquinolone Synthesis: The N−O Bond as a Handle for C−N Bond Formation and Catalyst Turnover. *J. Am. Chem. Soc.* **2010**, *132*, 6908−6909.

(13) For selected reviews: (a) Marco-Contelles, J.; Carreiras, M.; do, C.; Rodríguez, C.; Villarroya, M.; García, A. G. Synthesis and Pharmacology of Galantamine. *Chem. Rev.* **2006**, *106*, 116−133. (b) Proksch, P.; Rodriguez, E. Chromenes and benzofurans of the asteraceae, their chemistry and biological significance. *Phytochemistry* **1983**, *22*, 2335−2348.

(14) For selected recent examples: (a) Liu, Q.-J.; Zhu, J.; Song, X.-Y.; Wang, L.; Wang, S. R.; Tang, Y. Highly Enantioselective [3 + 2] Annulation of Indoles with Quinones to Access Structurally Diverse Benzofuroindolines. *Angew. Chem., Int. Ed.* **2018**, *57*, 3810−3814. (b) Yang, J.; Mo, H.; Jin, X.; Cao, D.; Wu, H.; Chen, D.; Wang, Z. Vinylogous Elimination/Heck Coupling/Allylation Domino Reactions: Access to 2-Substituted 2,3-Dihydrobenzofurans and Indolines. *J. Org. Chem.* **2018**, *83*, 2592−2600 and references cited therein. (c) Bera, S. S.; Debbarma, S.; Jana, S.; Maji, M. S. Cobalt(III)-Catalyzed Construction of Benzofurans, Benzofuranones and One-Pot Orthogonal C−H Functionalizations to Access Polysubstituted Benzofurans. *Adv. Synth. Catal.* **2018**, *360*, 2204−2210. (d) Zhang, M.; Yu, S.; Hu, F.; Liao, Y.; Liao, L.; Xu, X.; Yuan, W.; Zhang, X. Highly enantioselective [3 + 2] coupling of cyclic enamides with quinone monoimines promoted by a chiral phosphoric acid. *Chem. Commun.* **2016**, *52*, 8757−8760.

(15) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Ligand-Accelerated C-H Activation Reactions: Evidence for a Switch of Mechanism. *J. Am. Chem. Soc.* **2010**, *132*, 14137−14151.

(16) (a) Zhou, B.; Du, J.; Yang, Y.; Li, Y. Rhodium(III)-catalyzed intramolecular redox-neutral annulation of tethered alkynes: formal total synthesis of (±)-goniomitine. *Chem. - Eur. J.* **2014**, *20*, 12768−12772. (b) Xu, X.; Liu, Y.; Park, C.-M. Rhodium(III)-Catalyzed Intramolecular Annulation through C−H Activation: Total Synthesis of (±)-Antofine, (±)-Septicine, (±)-Tylophorine, and Rosettacin. *Angew. Chem., Int. Ed.* **2012**, *51*, 9372−9376.

(17) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. The Copper-Mediated Cross-Coupling of Phenylboronic Acids and *N*-Hydroxyphthalimide at Room Temperature: Synthesis of Aryloxyamines. *Org. Lett.* **2001**, *3*, 139−142.

(18) (a) Chang, X.-H.; Liu, Z.-L.; Luo, Y.-C.; Yang, C.; Liu, X.-W.; Da, B.-C.; Li, J.-J.; Ahmad, T.; Loh, T.-P.; Xu, Y.-H. Copper-catalyzed silylation reactions of propargyl epoxides: easy access to 2,3-allenols and stereodefined alkenes. *Chem. Commun.* **2017**, *53*, 9344−9347. (b) Chenniappan, V. K.; Rahaim, R. J. Titanium-Promoted Cross-Coupling for the Selective Synthesis of Polysubstituted, Conjugated Amides. *Org. Lett.* **2016**, *18*, 5090−5093. (c) Yoshida, M.; Al-Amin, Mo.; Shishido, K. Syntheses of Substituted Furans and Pyrroles by Platinum-Catalyzed Cyclizations of Propargylic Oxiranes and Aziridines in Aqueous Media. *Synthesis* **2009**, *2009*, 2454−2466. (d) Burke, C. P.; Shi, Y. Enantioselective Epoxidation of Conjugated cis-Enynes by Chiral Dioxirane. *J. Org. Chem.* **2007**, *72*, 4093−4097.

DOI: 10.1021/acs.joc.8b01166
J. Org. Chem. 2018, 83, 9464−9470