Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 5954

Pd-catalyzed reaction of aryl halides and propargyl furylmethyl ethers: a novel pathway to functionalized dihydroisobenzofurans†

Lingzhu Chen,[a] Ruwei Shen,[a] Luling Wu*[a] and Xian Huang‡[a,b]

Received 27th December 2012,
Accepted 12th July 2013

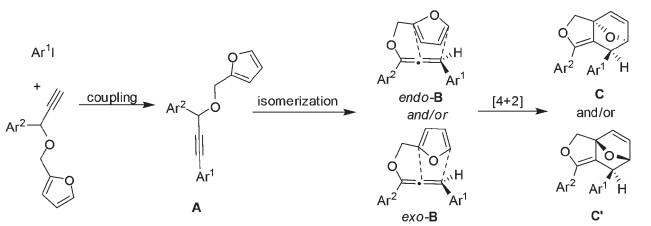
DOI: 10.1039/c3ob27503e

www.rsc.org/obc

An interesting sequential reaction involving Sonogashira coupling, propargyl–allenyl isomerization, intramolecular [4 + 2] cycloaddition, and bridged oxa-ring opening has been realized, providing a facile method for the synthesis of functionalized dihydroisobenzofurans from easily accessible starting materials with a decent diastereoselectivity.

Introduction

Cascade reactions are highly efficient in organic synthesis to access complex molecular frameworks.[1] In the early 2000s, Müller *et al.* developed a Sonogashira coupling and propargyl–allenyl isomerization sequence, upon which several heterocyclic scaffolds were further constructed.[2] We have also been developing a series of palladium-catalyzed sequential reactions from electron-deficient vinyl iodides and propargyl ethers, wherein an allene intermediate is generated *in situ* under mild conditions. These reactions provide efficient synthesis of structurally complex polycycles with 2,3-dihydrofuran units,[3a,d] dihydroisobenzofuran units,[3b] pyrrole units,[3c] and fluorene units.[3e] Along these lines, we envisaged that in the presence of a base, the Sonogashira-coupling product **A** of aryl iodides with furylmethyl propoargyl ethers may undergo a propargyl–allenyl isomerization to furnish allenyl furylmethyl ether **B**,[3] which would be followed by a [4 + 2] cycloaddition to afford cycloadduct **C** or **C′** *via* an *endo* or *exo* transition state (Scheme 1).[4]

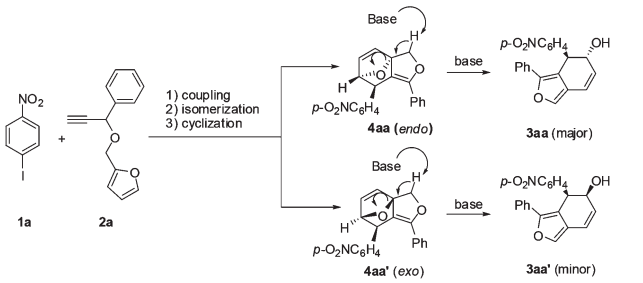


Scheme 1 Concept for the synthesis of tricyclic products with an oxa-bridge.

Results and discussion

To commence our studies, we carried out the reaction of 4-iodonitrobenzene **1a** with propargyl furylmethyl ether **2a** as a model. Instead of obtaining **C**-type products, interestingly, a pair of bicyclic diastereomers **3aa** and **3aa′** with a furan unit were isolated as the products, which must have formed from the base-induced cleavage of the oxa-bridge in **4** (Scheme 2). The typical results of optimization of the reaction conditions are summarized in Table 1. The screening of solvents and bases proved that both had a significant influence on the yield and diastereoselectivity. Among some commonly used solvents, PhMe was the best (Table 1, entries 1–4).

Amine affected the diastereoselectivity slightly (Table 1, entries 4–9). Further studies showed that **3aa** was achieved with up to 83% yield with a 93 : 7 diastereomeric ratio in 1 mL of PhMe by using i-Pr_2NH as the base (Table 1, entry 11). Here it should be noted that the predominant formation of **3aa** indicates that the allenyl



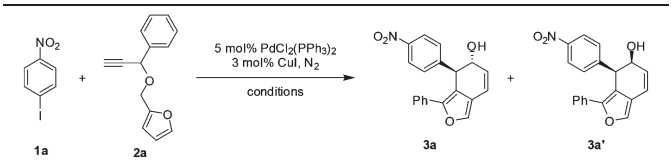
Scheme 2 The rationale for the stereoselective formation of the final bicyclic products **3aa** and **3aa′**.

[a]*Department of Chemistry, Zhejiang University, Hangzhou 310028, P. R. China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China.*
E-mail: Wululing@zju.edu.cn

†Electronic supplementary information (ESI) available. CCDC 902935. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob27503e

‡Professor Huang passed away on March 6, 2010. He was fully in charge of this project. Professor Luling Wu is helping to finish all the projects with assistance from Professor Shengming Ma.

Table 1 Effects of solvent and amine on the sequential reaction of 4-nitrophenyl iodide **2a** and propargylic 2-furylmethyl ether **1a**[a]



Entry	Solvent	Base	T (°C)/ t (h)	Yield of **3aa**[b] (%)	**3aa** : **3aa′**[c]
1	THF	NEt_3	65/3	48	84 : 16[d]
2	EtOH	NEt_3	65/2	56	78 : 22[d]
3	MeCN	NEt_3	65/2	58	78 : 22[d]
4	PhMe	NEt_3	65/3.5	62	91 : 9
5	PhMe	i-Pr_2EtN	65/18.5	58	93 : 7
6	PhMe	TMEDA	65/3.5	42	92 : 8
7	PhMe	$(n\text{-}C_4H_9)_2NH$	65/3	78	91 : 9
8	PhMe	Cy_2NH	65/10	58	94 : 6
9	PhMe	i-Pr_2NH	65/12	67	94 : 6
10	PhMe	i-Pr_2NH	85/7	64	93 : 7
11[e]	**PhMe**	**i-Pr_2NH**	**65/11**	**83**	**93 : 7**
12[f]	PhMe	i-Pr_2NH	65/35	55	95 : 5

[a] Reactions were carried out using **1a** (0.25 mmol), **2a** (0.3 mmol), $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (3 mol%) in 2 mL of solvent and 0.6 mL of amine. [b] Isolated yields. [c] Deduced from ^{1}H NMR analysis. [d] Based on isolation. [e] In 1 mL of solvent. [f] In 5 mL of solvent.

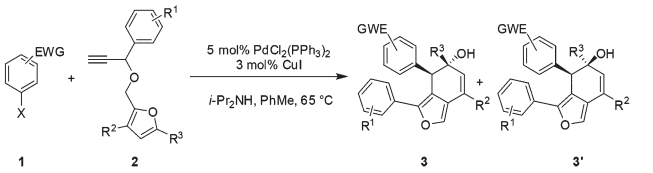
furylmethyl ether favors to adopt an *endo* transition state to undergo the intramolecular [4 + 2] cycloaddition, producing **4aa** as the major intermediate in this reaction sequence (Scheme 2).

With the optimized conditions in hand, the scope of this reaction was investigated. The results are summarized in Table 2. The reaction proceeded well with several substituted propargyl furylmethyl ethers (Table 2, entries 2–4) and different types of functionalities such as 2-nitro (**1b**), 4-cyano (**1d**), and 4-formyl (**1e**) in the substrates of **1** (Table 2, entries 5–7), yielding **3** from moderate to excellent yields with good selectivity. We also tested the reactivity of some substituted furans. To our delight, when the propargyl furylmethyl ether incorporated with a 3-methyl substituted furan ring (**2e**) and **1a** were employed as the substrates, **3ae** was synthesized with a decent yield while **3ae′** was contaminated with some unknown impurities (Table 2, entry 8). However, the reaction of the ether **2f** bearing a 2-methyl on the furan ring failed to give any identifiable product (Table 2, entry 9).

In order to further confirm the structures of the newly synthesized products, **3ab** was transformed to its acylated compound **5**§ (Scheme 3). The structure of **5** was unambiguously confirmed by X-ray diffraction analysis (Fig. 1).

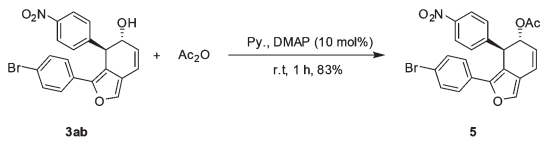
§ Crystal data for compound **5**: $C_{22}H_{16}BrNO_5$, MW = 454.27; crystal system: monoclinic; space group: $C2/c$; final R indices ($I > 2\sigma(I)$) R_1 = 0.0381, wR_2 = 0.0841, R indices (all data) R_1 = 0.0573, wR_2 = 0.0931; a = 18.9332(7) Å, b = 7.6655(2) Å, c = 27.1733(11) Å; α = 90°, β = 90.302°, γ = 90°, V = 3943.7(2) Å^3, T = 293(2) K, Z = 8; reflections collected/unique: 13 830/3605 (R(int) = 0.0284); number of observations ($I > 2\sigma(I)$): 2774; parameters: 263. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 902935.

Table 2 Palladium-catalyzed sequential reaction between electron-withdrawing aryl halides **1** and propargylic 2-furylmethyl ethers **2**[a]



Entry	EWG	X	R^1	R^2	R^3	t (h)	Yield[b] (%) of **3**	Yield[b] (%) of **3′**
1	*p*-NO_2	I (**1a**)	H	H	H (**2a**)	11	83 (**3aa**)	6 (**3aa′**)
2	*p*-NO_2	I (**1a**)	*p*-Br	H	H (**2b**)	10	60 (**3ab**)	—[c]
3	*p*-NO_2	I (**1a**)	*p*-Me	H	H (**2c**)	24	67 (**3ac**)	5 (**3ac′**)
4	*p*-NO_2	I (**1a**)	*p*-OMe	H	H (**2d**)	72	55 (**3ad**)	4 (**3ad′**)
5	*o*-NO_2	I (**1b**)	H	H	H (**2a**)	5.5	53 (**3ba**)	14 (**3ba′**)
6	*p*-CN	I (**1d**)	H	H	H (**2a**)	115	46 (**3da**)	4 (**3da′**)
7[d]	*p*-CHO	Br (**1e**)	H	H	H (**2a**)	52	37 (**3ea**)	3 (**3ea′**)
8	*p*-NO_2	I (**1a**)	H	Me	H (**2e**)	11	71 (**3ae**)	—[c]
9	*p*-NO_2	I (**1a**)	H	H	Me (**2f**)	48	—[e]	—

[a] Reactions were carried out using **1** (0.25 mmol), **2** (0.3 mmol), $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (3 mol%) in 1 mL of PhMe and 0.6 mL of i-Pr_2NH. [b] Isolated yields. [c] The pure form of **3ab′** or **3ae′** was not obtained as judged by ^{1}H NMR analysis. [d] Reaction was carried out at 100 °C with 0.5 mmol of **2a**. [e] A small amount of unidentified mixture was obtained.



Scheme 3 Establishment of the structure of **3ab**.

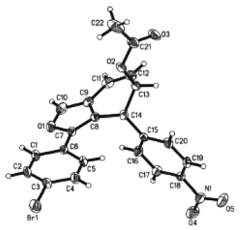
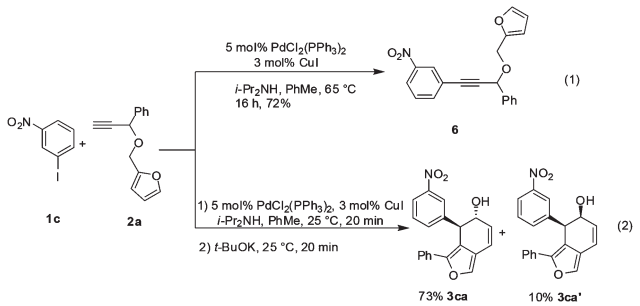


Fig. 1 ORTEP representation of **5**.

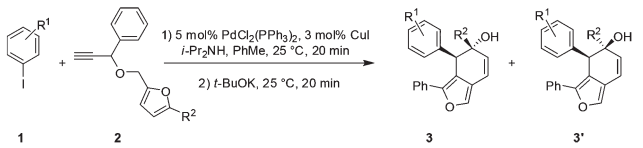
When we chose 3-iodonitrobenzene **1c** and **2a** as substrates, only 72% of direct coupling product **6** was obtained (Scheme 4, eqn (1)). However, with the extra addition of *t*-BuOK, this compound was again transformed into the final bicyclic products **3ca** and **3ca′** (Scheme 4, eqn (2)).

We also tested other iodobenzenes bearing electron-withdrawing or electron-donating substituents with this newly established two-step protocol, and the yields of the corresponding bicyclic products ranged from 62% to 77% (Table 3, entries 2–6). In the case of methyl 4-iodobenzoate (**1j**), the reaction failed to give any identifiable product under the same conditions. However, when *t*-BuOK was added at −15 °C after the first step coupling reaction at room temperature, the reaction gave **3ja** and **3ja′** in decent yields. Notably, when



Scheme 4 Palladium-catalyzed reaction of *m*-nitrophenyl iodide **1c** with **2a**.

Table 3 Palladium-catalyzed step-wise reaction between aryl halides **1** and propargylic furylmethyl ether **2a** with *t*-BuOK[a]



Entry	R^1	R^2	Yield[b] (%) of **3**	Yield[b] (%) of **3′**
1	*m*-NO_2 (**1c**)	H (**2a**)	73 (**3ca**)	10 (**3ca′**)
2	H (**1f**)	H (**2a**)	75 (**3fa**)	9 (**3fa′**)
3	*p*-Br (**1g**)	H (**2a**)	77 (**3ga**)	12 (**3ga′**)
4	*p*-F (**1h**)	H (**2a**)	73 (**3ha**)	12 (**3ha′**)
5	*p*-OMe (**1i**)	H (**2a**)	62 (**3ia**)	9 (**3ia′**)
6[c]	*p*-COOMe (**1j**)	H (**2a**)	66 (**3ja**)	12 (**3ja′**)
7	H (**1f**)	Me (**2f**)	61 (**3fb**)	9 (**3fb′**)

[a] Reactions were carried out using **1** (0.25 mmol), **2** (0.3 mmol), $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (3 mol%) in 2 mL of PhMe and 0.1 mL of i-Pr_2NH, followed by treatment with 0.75 mmol of *t*-BuOK after 20 min. [b] Isolated yields. [c] *t*-BuOK was added at −15 °C.

iodobenzene **1f** and methyl-substituted propargyl furylmethyl ether **2f** were used as substrates, the two-step reaction also proceeded well to give the corresponding products **3fb** and **3fb′** in good yield and selectivity (Table 3, entry 7).

Conclusion

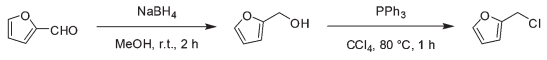
In conclusion, we developed a novel sequential palladium-catalyzed transformation of aromatic halides and propargylic 2-furylmethyl ethers involving coupling, propargyl–allenyl isomerization, intramolecular [4 + 2] cycloaddition, and bridged oxa-ring opening, affording functionalized dihydroisobenzofurans with a respectable diastereoselectivity. Further studies in this area are being pursued in our laboratory.

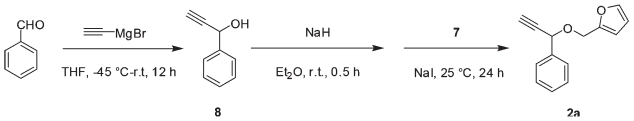
Experimental section

General

All reactions were performed under a N_2 atmosphere. Anhydrous solvents were distilled prior to use: THF and toluene were distilled from sodium-benzophenone; MeCN and pyridine were distilled from CaH_2; EtOH was filtered from $MgSO_4$. Petroleum ether refers to the fraction with boiling point in the range 60–90 °C. Unless otherwise specified, ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed in ppm and *J* values are given in Hz.

1. Procedure for the synthesis of furylmethyl propargyl ether 2a





(1) Furylmethyl chloride (7). Sodium borohydride (3.8 g, 100 mmol) was added portion-wise to a solution of furfural (19.2 g, 200 mmol) in methanol (100 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The solvent was evaporated and the residue was dissolved in ether. The organic layer was washed with water and the aqueous layer was then extracted with ether twice. The combined organic layer was dried over $MgSO_4$. The filtrate was concentrated and distilled at 68–69 °C/3–4 mmHg to give a clear oil of furylmethyl alcohol **6** (15.819 g, 81%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (s, 1 H), 6.33 (d, J = 1.6 Hz, 1 H), 6.28 (d, J = 2.8 Hz, 1 H), 4.59 (s, 2 H), 2.25 (brs, 1 H).

A mixture of carbon tetrachloride (80 mL), furylmethyl alcohol (8.22 g, 83.9 mmol) and triphenylphosphine (28.6 g, 109 mmol) was refluxed for 1 h. The mixture was allowed to cool to room temperature, which was followed by adding 80 mL of anhydrous pentane with stirring. The solution was filtered, and the precipitate was washed a few times with a total of 50 mL of anhydrous pentane. The combined filtrate was then concentrated and distilled at 41.5–42.1 °C/12–13 mmHg to yield a water-white liquid furylmethyl chloride **7** (3.734 g, 43%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1 H), 6.37–6.35 (m, 2 H), 4.60 (s, 2 H).

(2) 1-Phenylprop-2-yn-1-ol (8). Several drops of EtBr were added to a mixture of magnesium turnings (2.76 g, 115 mmol) and I_2 (a few crystals) in 120 mL of THF under a nitrogen atmosphere. Upon the initiation of the Grignard reaction, the remaining ethyl bromide (8.2 mL, 110 mmol) in 90 mL of THF was added dropwise, which was followed by stirring at room temperature for 1 h. A stream of acetylene was bubbled through the solution at −45 °C for 40 min. Then a solution of benzaldehyde (10.6 g, 100 mmol) in 20 mL of THF was added at ≤−30 °C, which was followed by a natural warming to room temperature. After 12 h, the reaction mixture was cooled with an ice bath, quenched with saturated NH_4Cl, extracted with diethyl ether (30 mL × 3), and dried over anhydrous $MgSO_4$. After filtration, evaporation and flash chromatography on silica gel (eluent: petroleum ether–ethyl acetate = 6/1) afforded **8** (11.448 g, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d,

J = 7.6 Hz, 2 H), 7.41–7.33 (m, 3 H), 5.47 (s, 1 H), 2.67 (s, 1 H), 2.18 (brs, 1 H).

(3) Furylmethyl propargyl ether (2a). A solution of **8** (2.64 g, 20 mmol) in dry Et_2O (5 mL) was added dropwise to a suspension of NaH (720 mg, 30 mmol) in Et_2O (5 mL) at 0 °C under a nitrogen atmosphere. After being stirred at room temperature for 0.5 h, furylmethyl chloride (1.672 g, 16 mmol) and NaI (1.2 g, 8 mmol) were added and the mixture was stirred for 24 h at 25 °C. Water (20 mL) was added and the product was extracted with Et_2O (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified with flash chromatography on silica gel (eluent: petroleum ether–ethyl acetate = 40/1) to afford **2a** (1.526 g, 45%) as a liquid.

2-((1-Phenylprop-2-ynyloxy)methyl)furan (2a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 7.2 Hz, 2 H), 7.38 (s, 1 H), 7.34–7.28 (m, 3 H), 6.34–6.31 (m, 2 H), 5.19 (s, 1 H), 4.61 (s, 2 H), 2.65 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.90, 142.85, 137.65, 128.40, 128.36, 127.32, 110.20, 109.88, 81.05, 7 6.01, 69.86, 61.75; IR (neat): 3290, 3034, 2864, 1498, 1452, 1272, 1223, 1150, 1054, 1010, 921, 817, 744, 698, 661 cm^{-1}; MS(EI) m/z (%): 212 (M^+, 1), 115 (100); HRMS: calcd for $C_{14}H_{12}O_2$ (M^+), 212.0837; found, 212.0830.

Compounds **2b–2f** were prepared according to the typical procedure for the preparation of **2a**.

2-((1-(4-Bromophenyl)prop-2-ynyloxy)methyl)furan (2b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.4 Hz, 2 H), 7.42 (m, 1 H), 7.38 (d, J = 8.8 Hz, 2 H), 6.38–6.34 (m, 2 H), 5.16 (d, J = 2.4 Hz, 1 H), 4.63 (s, 2 H), 2.68 (d, J = 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.84, 143.12, 136.93, 131.63, 129.12, 122.61, 110.36, 110.17, 80.66, 76.38, 69.30, 62.00; IR (neat): 3291, 1591, 1486, 1399, 1358, 1291, 1224, 1149, 1051, 1010, 919, 884, 814, 739, 670, 642 cm^{-1}; MS(EI) m/z (%): 292 [M^+(^{81}Br), 1], 290 [$^{79}M^+$(^{79}Br), 1], 81 (100); HRMS: calcd for $C_{14}H_{11}BrO_2$ [M^+(^{79}Br)], 289.9942; found, 289.9930.

2-((1-*p*-Tolylprop-2-ynyloxy)methyl)furan (2c). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 6.8 Hz, 3 H), 7.15 (d, J = 8.4 Hz, 2 H), 6.35–6.32 (m, 2 H), 5.17 (s, 1 H), 4.60 (s, 2 H), 2.64 (m, 1 H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.13, 142.96, 138.41, 134.84, 129.20, 127.44, 110.29, 109.93, 81.37, 75.79, 69.84, 61.73, 21.17; IR (neat): 3288, 2920, 1513, 1443, 1358, 1301, 1269, 1224, 1180, 1150, 1047, 1015, 920, 885, 810, 778, 738, 639 cm^{-1}; MS(EI) m/z (%): 226 (M^+, 1), 129 (100); HRMS: calcd for $C_{15}H_{14}O_2$ (M^+), 226.0994; found, 226.0993.

2-((1-(4-Methoxyphenyl)prop-2-ynyloxy)methyl)furan (2d). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.41 (m, 3 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.35–6.34 (m, 2 H), 5.16 (d, J = 2.4 Hz, 1 H), 4.60 (s, 2 H), 3.78 (s, 3 H), 2.67 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.78, 151.12, 142.92, 129.94, 128.87, 113.84, 110.26, 109.87, 81.35, 75.78, 69.56, 61.64, 55.23; IR (neat): 3286, 2838, 1611, 1587, 1511, 1463, 1304, 1246, 1174, 1149, 1111, 1033, 920, 885, 816, 781, 740, 637 cm^{-1}; MS(EI) m/z (%): 242 (M^+, 8), 145 (100); HRMS: calcd for $C_{15}H_{14}O_3$ (M^+), 242.0943; found, 242.0948.

3-Methyl-2-((1-phenylprop-2-ynyloxy)methyl)furan (2e). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m, 2 H), 7.38–7.25 (m, 4 H), 6.21 (d, J = 1.6 Hz, 1 H), 5.18 (d, J = 2.0 Hz, 1 H), 4.61 (dd, J_1 = 16.4 Hz, J_2 = 12.8 Hz, 2 H), 2.68 (d, J = 2.0 Hz, 1 H), 2.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.50, 142.03, 137.89, 128.48, 127.42, 119.79, 112.91, 81.38, 75.83, 69.71, 59.88, 9.81; IR (neat): 3286, 2926, 2115, 1722, 1563, 1494, 1453, 1269, 1156, 1121, 1048, 1005, 892, 846, 739, 697, 649 cm^{-1}; MS(EI) m/z (%): 226 (M^+, 6), 115 (100), 95 (100); HRMS: calcd for $C_{15}H_{14}O_2$ (M^+), 226.0994; found, 226.0999.

2-Methyl-5-((1-phenylprop-2-ynyloxy)methyl)furan (2f). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 6.4 Hz, 2 H), 7.39–7.32 (m, 3 H), 6.25 (d, J = 2.8 Hz, 1 H), 5.93 (s, 1 H), 5.22 (s, 1 H), 4.57 (s, 2 H), 2.67 (d, J = 1.2 Hz, 1 H), 2.29 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.91, 149.07, 137.85, 128.49, 127.48, 111.14, 106.25, 81.29, 75.91, 69.74, 62.02, 13.66; IR (neat): 3287, 3064, 3033, 2922, 2860, 2114, 1606, 1563, 1493, 1451, 1386, 1359, 1306, 1267, 1221, 1196, 1049, 1021, 925, 845, 789, 753, 697, 650 cm^{-1}; MS(EI) m/z (%): 226 (M^+, 3), 115 (100), 95 (95); HRMS: calcd for $C_{15}H_{14}O_2$ (M^+), 226.0994; found, 226.0998.

2. General procedure for the synthesis of 3 and 3′ in Table 2

An oven-dried Schlenk tube containing a Teflon-coated stirring bar was charged with $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%) and CuI (1 mg, 3 mol%). The Schlenk tube was sealed, and evacuated-backfilled with N_2 (3 cycles). A solution of aryl iodide **1** (0.25 mmol) and furylmethyl ether **2** (0.3 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH was subsequently injected to the Schlenk tube. The reaction mixture was stirred at 65 °C for the time specified in Table 2. After removal of the solvent *in vacuo*, the residues were purified with flash chromatography on silica gel to afford **3** and **3′**.

(1) Preparation of (4*R,5*R**)-4-(4-nitrophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3aa) and (4*R**,5*S**)-4-(4-nitrophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3aa′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1a** (62 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH afforded **3aa** (69 mg, 83%) and **3aa′** (5 mg, 6%) (eluent: petroleum ether–ethyl acetate = 3.5/1) as a liquid:

3aa ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.4 Hz, 2 H), 7.59 (s, 1 H), 7.38 (d, J = 7.6 Hz, 2 H), 7.33–7.25 (m, 4 H), 7.23–7.20 (m, 1 H), 6.75 (d, J = 9.6 Hz, 1 H), 5.93 (dd, J_1 = 9.6 Hz, J_2 = 5.2 Hz, 1 H), 4.65 (d, J = 1.2 Hz, 1 H), 4.35 (d, J = 4.0 Hz, 1 H), 2.12 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.43, 147.80, 146.86, 137.33, 130.10, 128.86, 128.60, 127.72, 125.73, 124.92, 123.89, 121.99, 121.76, 114.07, 70.68, 45.62; IR (neat): 3369, 1597, 1514, 1491, 1444, 1390, 1344, 1108, 1053, 1006, 952, 902, 836, 791, 766, 690, 631 cm^{-1}; MS (EI) m/z (%): 333 (M^+, 100), 105 (87); HRMS: calcd for $C_{20}H_{15}NO_4$ (M^+), 333.1001; found, 333.1007.

3aa′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.8 Hz, 2 H), 7.51 (s, 1 H), 7.41 (d, J = 8.8 Hz, 2 H), 7.37 (d, J = 7.6, 2 H), 7.30 (t, J = 7.6 Hz, 2 H), 7.25–7.21 (m, 1 H), 6.56 (dd, J_1 = 10.0 Hz, J_2 = 2.8 Hz, 1 H), 5.61 (dd, J_1 = 10.0 Hz, J_2 = 1.6 Hz, 1 H), 4.96

(m, 1 H), 4.59 (d, J = 6.8, 1 H), 1.67–1.61 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.96, 147.15, 145.43, 136.92, 130.81, 130.18, 128.67, 127.78, 125.03, 123.37, 122.68, 119.08, 116.36, 70.61, 43.13; IR (neat): 3433, 2918, 1703, 1595, 1513, 1492, 1445, 1344, 1222, 1182, 1129, 1109, 1071, 1050, 946, 908, 854, 814, 786, 767, 731, 692, 664, 621 cm^{-1}; MS(EI) m/z (%): 333 (M^+, 3), 84 (100); HRMS: calcd for $C_{20}H_{15}NO_4$ (M^+), 333.1001; found, 333.1002.

(2) Preparation of (4*R,5*R**)-3-(4-bromophenyl)-4-(4-nitrophenyl)-4,5-dihydroisobenzofuran-5-ol (3ab) and (4*R**,5*S**)-3-(4-bromophenyl)-4-(4-nitrophenyl)-4,5-dihydroisobenzofuran-5-ol (3ab′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (2 mg, 4 mol%), **1a** (62 mg, 0.25 mmol) and **2b** (87 mg, 0.3 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH afforded **3ab** (62 mg, 60%) (eluent: petroleum ether–ethyl acetate = 4/1) as a liquid; **3ab′** was contaminated with some unknown impurities and thus not characterized.

3ab ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.4 Hz, 2 H), 7.60 (s, 1 H), 7.42 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.8, 2 H), 7.26–7.24 (m, 2 H), 6.77 (d, J = 10.0 Hz, 1 H), 5.96 (dd, J_1 = 9.6 Hz, J_2 = 5.2 Hz, 1 H), 4.62 (d, J = 1.2 Hz, 1 H), 4.37 (dd, J_1 = 5.6 Hz, J_2 = 2.0 Hz, 1 H), 1.87 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.48, 147.41, 147.02, 137.65, 131.84, 129.02, 128.83, 126.35, 125.88, 124.03, 121.98, 121.90, 121.78, 114.76, 70.65, 45.63; IR (neat): 3433, 2918, 1595, 1513, 1492, 1445, 1344, 1222, 1182, 1129, 1109, 1071, 1050, 946, 908, 854, 814, 786, 767, 731, 692, 664, 621 cm^{-1}; MS(EI) m/z (%): 413 [M^+(^{81}Br), 4], 411 [M^+(^{79}Br), 4], 57 (100); HRMS: calcd for $C_{20}H_{14}NO_4Br$ [M^+(^{79}Br)], 411.0106; found, 411.0107.

(3) Preparation of (4*R,5*R**)-4-(4-nitrophenyl)-3-*p*-tolyl-4,5-dihydroisobenzofuran-5-ol (3ac) and (4*R**,5*S**)-4-(4-nitrophenyl)-3-*p*-tolyl-4,5-dihydroisobenzofuran-5-ol (3ac′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1a** (62 mg, 0.25 mmol) and **2c** (68 mg, 0.3 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH afforded **3ac** (58 mg, 67%) and **3ac′** (4 mg, 5%) (eluent: petroleum ether–ethyl acetate = 4/1) as a liquid:

3ac ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.4 Hz, 2 H), 7.56 (s, 1 H), 7.33–7.25 (m, 4 H), 7.09 (d, J = 8.0 Hz, 2 H), 6.75 (d, J = 9.2 Hz, 1 H), 5.93 (dd, J_1 = 9.6 Hz, J_2 = 5.6 Hz, 1 H), 4.64 (d, J = 1.2 Hz, 1 H), 4.34 (dd, J_1 = 5.6 Hz, J_2 = 2.0 Hz, 1 H), 2.29 (s, 3 H), 2.03 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.69, 147.95, 146.84, 137.71, 137.02, 129.30, 128.85, 127.39, 125.65, 124.87, 123.87, 122.06, 121.69, 113.27, 70.70, 45.65, 21.15; IR (neat): 3391, 2876, 1597, 1514, 1491, 1444, 1390, 1344, 1108, 1053, 1006, 952, 902, 836, 791, 766, 690, 631 cm^{-1}; MS(EI) m/z (%): 347 (M^+, 96), 119 (100), 84 (83); HRMS: calcd for $C_{21}H_{17}NO_4$ (M^+), 347.1158; found, 347.1151.

3ac′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.0 Hz, 2 H), 7.49 (s, 1 H), 7.41 (d, J = 8.4 Hz, 2 H), 7.27 (d, J = 6.8, 2 H), 7.11 (d, J = 7.6 Hz, 2 H), 6.57 (dd, J_1 = 10.4 Hz, J_2 = 1.6 Hz, 1 H), 5.60 (d, J = 10.0 Hz, 1 H), 4.97 (d, J = 5.6 Hz, 1 H), 4.58 (d, J = 7.6 Hz, 1 H), 2.31 (s, 3 H), 1.57 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.23, 147.18, 145.55, 137.80, 136.62, 130.80, 130.68, 129.38, 127.46, 124.98, 123.38, 122.61, 119.19, 115.62, 70.65, 43.16, 21.20; IR (neat): 3398, 2920, 1702, 1602, 1513, 1343, 1223, 1183, 1126, 1110, 1080, 1052, 1016, 946, 909, 854, 815, 784, 749, 710, 695, 666, 627 cm^{-1}; MS(EI) m/z (%): 347 (M^+, 26), 59 (100); HRMS: calcd for $C_{21}H_{17}NO_4$ (M^+), 347.1158; found, 347.1164.

(4) Preparation of (4*R,5*R**)-3-(4-methoxyphenyl)-4-(4-nitrophenyl)-4,5-dihydroisobenzo-furan-5-ol (3ad) and (4*R**,5*S**)-3-(4-methoxyphenyl)-4-(4-nitrophenyl)-4,5-dihydroisobenzofuran-5-ol (3ad′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (2 mg, 4 mol%), **1a** (62 mg, 0.25 mmol) and **2d** (73 mg, 0.3 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH afforded **3ad** (50 mg, 55%) and **3ad′** (4 mg, 4%) (eluent: petroleum ether–ethyl acetate = 4/1) as a liquid:

3ad ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.0 Hz, 2 H), 7.52 (s, 1 H), 7.29 (d, J = 7.6 Hz, 2 H), 6.80 (d, J = 8.4 Hz, 2 H), 6.72 (d, J = 10.0 Hz, 1 H), 5.88 (dd, J_1 = 9.2 Hz, J_2 = 5.2 Hz, 1 H), 4.59 (s, 1 H), 4.31 (d, J = 3.6, 1 H), 3.74, (s, 3 H), 2.43 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.98, 150.34, 148.01, 146.67, 136.65, 128.78, 126.27, 125.50, 123.79, 122.94, 121.96, 121.61, 113.97, 112.35, 70.59, 55.11, 45.49; IR (neat): 3417, 2908, 1600, 1510, 1461, 1346, 1301, 1250, 1178, 1111, 1060, 1026, 954, 904, 831, 790, 733, 699, 622 cm^{-1}; MS(EI) m/z (%): 363 (M^+, 60), 135 (100), 84 (98); HRMS: calcd for $C_{21}H_{17}NO_5$ (M^+), 363.1107; found, 363.1104.

3ad′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.4 Hz, 2 H), 7.47 (s, 1 H), 7.41 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 6.56 (dd, J_1 = 10.4 Hz, J_2 = 2.8 Hz, 1 H), 5.60 (dd, J_1 = 9.6 Hz, J_2 = 1.6 Hz, 1 H), 4.96 (m, 1 H), 4.55 (d, J = 7.2 Hz, 1 H), 3.78 (s, 3 H), 1.59 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.23, 149.07, 147.13, 145.71, 136.35, 130.78, 130.56, 126.49, 123.36, 123.08, 122.56, 119.21, 114.72, 114.14, 70.51, 55.27, 43.09; IR (neat): 3398, 2920, 1702, 1602, 1513, 1343, 1223, 1183, 1126, 1110, 1080, 1052, 1016, 946, 909, 854, 815, 784, 749, 710, 695, 666, 627 cm^{-1}; MS(EI) m/z (%): 363 (M^+, 44), 84 (100); HRMS: calcd for $C_{21}H_{17}NO_5$ (M^+), 363.1107; found, 363.1111.

(5) Preparation of (4*R,5*R**)-4-(2-nitrophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ba) and (4*R**,5*S**)-4-(2-nitrophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ba′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1b** (62 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH afforded **3ba** (44 mg, 53%) and **3ba′** (12 mg, 14%) (eluent: petroleum ether–ethyl acetate = 4/1) as a liquid:

3ba ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.57 (s, 1 H), 7.37–7.31 (m, 4 H), 7.26 (t, J = 8.0 Hz, 2 H), 7.20–7.16 (m, 1 H), 7.05–7.02 (m, 1 H), 6.78 (d, J = 9.6 Hz, 1 H), 5.93 (dd, J_1 = 10.0 Hz, J_2 = 5.6 Hz, 1 H), 5.11 (d, J = 2.0 Hz, 1 H), 4.49 (d, J = 4.0 Hz, 1 H), 2.22 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.96, 149.34, 137.05, 134.65, 133.00, 130.20, 130.06, 128.54, 127.92, 127.56, 125.95, 124.79, 124.55, 122.37, 121.66, 114.64, 69.76, 40.90; IR (neat): 3401, 2922, 1600, 1522, 1492, 1444, 1350, 1261, 1127, 1004, 952, 908, 855, 766, 734, 691, 641, 614 cm^{-1}; MS(EI) m/z (%): 333 (M^+, 13), 105 (100); HRMS: calcd for $C_{20}H_{15}NO_4$ (M^+), 333.1001; found, 333.1008.

3ba′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.82 (m, 1 H), 7.50 (s, 1 H), 7.44–7.40 (m, 3 H), 7.37–7.29 (m, 3 H), 7.35–7.19 (m,

2 H), 6.55 (dd, J_1 = 10.0 Hz, J_2 = 2.8 Hz, 1 H), 5.63 (dd, J_1 = 10.0 Hz, J_2 = 1.6 Hz, 1 H), 5.39 (d, J = 8.4 Hz, 1 H), 5.06 (dt, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 1 H), 2.88 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.15, 149.01, 136.56, 132.69, 132.58, 131.57, 130.39, 130.03, 128.68, 127.80, 127.70, 124.85, 124.05, 123.16, 118.34, 116.00, 70.43, 36.53; IR (neat): 3378, 2962, 2922, 1596, 1524, 1493, 1444, 1357, 1260, 1219, 1130, 1067, 1051, 1037, 947, 908, 885, 859, 774, 747, 721, 686, 666, 615 cm^{-1}; MS(EI) m/z (%): 333 (M^+, 13), 105 (100); HRMS: calcd for $C_{20}H_{15}NO_4$ (M^+), 333.1001; found, 333.0999.

(6) Preparation of 4-((4*R,5*R**)-5-hydroxy-3-phenyl-4,5-dihydroisobenzofuran-4-yl)benzonitrile (3da) and 4-((4*R**,5*S**)-5-hydroxy-3-phenyl-4,5-dihydroisobenzofuran-4-yl)benzonitrile (3da′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1d** (57 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH afforded **3da** (36 mg, 46%) and **3da′** (3 mg, 4%) (eluent: petroleum ether–ether = 2/1) as a liquid:

3da ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1 H), 7.52 (d, J = 8.4 Hz, 2 H), 7.39–7.36 (m, 2 H), 7.30–7.20 (m, 5 H), 6.73 (d, J = 9.6 Hz, 1 H), 5.92 (dd, J_1 = 9.6 Hz, J_2 = 5.6 Hz, 1 H), 4.59 (d, J = 2.0 Hz, 1 H), 4.32 (s, 1 H), 2.14 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.44, 145.76, 137.27, 132.50, 130.17, 128.80, 128.59, 127.69, 125.87, 124.98, 121.96, 121.85, 118.66, 114.08, 110.85, 70.79, 45.85; IR (neat): 3400, 2922, 2228, 1764, 1703, 1606, 1492, 1447, 1412, 1362, 1223, 1129, 1017, 905, 824, 792, 763, 694, 637 cm^{-1}; MS(EI) m/z (%): 313 (M^+, 98), 105 (86), 58 (100); HRMS: calcd for $C_{21}H_{15}NO_2$ (M^+), 313.1103; found, 313.1108.

3da′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.4 Hz, 2 H), 7.50 (s, 1 H), 7.38–7.24 (m, 7 H), 6.55 (dd, J_1 = 10.0 Hz, J_2 = 2.8 Hz, 1 H), 5.61 (d, J = 10.0 Hz, 1 H), 4.94 (t, J = 7.6 Hz, 1 H), 4.53 (d, J = 7.2 Hz, 1 H), 1.58 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.92, 143.25, 136.84, 132.04, 130.86, 130.74, 130.23, 128.65, 127.75, 125.04, 122.76, 119.05, 118.74, 116.41, 111.16, 70.60, 43.34; IR (neat): 3433, 2925, 2227, 1702, 1606, 1492, 1446, 1364, 1222, 1179, 1130, 1072, 1051, 1024, 946, 909, 838, 794, 767, 732, 692, 648, 614 cm^{-1}; MS(EI) m/z (%): 313 (M^+, 24), 59 (100), 84 (82); HRMS: calcd for $C_{21}H_{15}NO_2$ (M^+), 313.1103; found, 313.1103.

(7) Preparation of 4-((4*R,5*R**)-5-hydroxy-3-phenyl-4,5-dihydroisobenzofuran-4-yl)benzaldehyde (3ea) and 4-((4*R**,5*S**)-5-hydroxy-3-phenyl-4,5-dihydroisobenzofuran-4-yl)benzaldehyde (3ea′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (2 mg, 4 mol%), **1e** (46 mg, 0.25 mmol) and **2a** (106 mg, 0.5 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH at 100 °C afforded **3ea** (29 mg, 37%) and **3ea′** (2 mg, 3%) (eluent: petroleum ether–ether = 2/1) as a liquid:

3ea ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1 H), 7.77 (d, J = 8.0 Hz, 2 H), 7.59 (s, 1 H), 7.40 (d, J = 8.0 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.28 (t, J = 8.0 Hz, 2 H), 7.22–7.19 (m, 1 H), 6.76 (d, J = 10.0 Hz, 1 H), 5.96 (dd, J_1 = 9.6 Hz, J_2 = 5.6 Hz, 1 H), 4.63 (d, J = 1.2 Hz, 1 H), 4.40–4.38 (m, 1 H), 2.03 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.83, 150.39, 147.29, 137.22, 135.21, 130.24, 130.21, 128.70, 128.58, 127.60, 125.99, 124.98, 121.98, 121.93, 114.41, 70.85, 45.97; IR (neat): 3426, 1697, 1604, 1575, 1493, 1446, 1412, 1390, 1306, 1245, 1212, 1170, 1128, 1007, 951, 908, 811, 769, 733, 692, 649, 635 cm^{-1}; MS(EI) m/z (%): 316 (M^+, 18), 84 (53), 43 (100); HRMS: calcd for $C_{21}H_{16}O_3$ (M^+), 316.1099; found, 316.1107.

3ea′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1 H), 7.81 (d, J = 8.4 Hz, 2 H), 7.51 (s, 1 H), 7.44 (d, J = 8.4 Hz, 2 H), 7.40–7.38 (m, 2 H), 7.32–7.28 (m, 2 H), 7.25–7.23 (m, 1 H), 6.57 (dd, J_1 = 9.6 Hz, J_2 = 2.8 Hz, 1 H), 5.63 (dd, J_1 = 10.0 Hz, J_2 = 2.0 Hz, 1 H), 4.95 (d, J = 7.2 Hz, 1 H), 4.57 (d, J = 7.6 Hz, 1 H), 1.57 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.92, 148.81, 144.70, 136.74, 135.44, 131.06, 130.65, 130.30, 129.77, 128.63, 127.64, 125.02, 122.84, 119.00, 116.77, 70.70, 43.39; IR (neat): 3432, 2849, 1698, 1605, 1574, 1492, 1446, 1390, 1306, 1264, 1212, 1171, 1129, 1072, 1051, 946, 910, 835, 801, 782, 768, 734, 693, 664, 614 cm^{-1}; MS(EI) m/z (%): 316 (M^+, 11), 43 (100); HRMS: calcd for $C_{21}H_{16}O_3$ (M^+), 316.1099; found, 316.1096.

(8) Preparation of (4*R,5*R**)-7-methyl-4-(4-nitrophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ae) and (4*R**,5*S**)-7-methyl-4-(4-nitrophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ae′).** The reaction of $PdCl_2(PPh_3)_2$ (11 mg, 5 mol%), CuI (2 mg, 3 mol%), **1a** (75 mg, 0.3 mmol) and **2e** (81 mg, 0.36 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH afforded **3ae** (74 mg, 71%) (eluent: petroleum ether–ethyl acetate = 6/1) as a liquid. **3ae′** was contaminated with some unknown impurities and thus not characterized.

3ae ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.07 (m, 2 H), 7.61 (s, 1 H), 7.41–7.38 (m, 2 H), 7.31–7.27 (m, 4 H), 7.25–7.19 (m, 1 H), 5.65 (dd, J_1 = 5.6 Hz, J_2 = 1.6 Hz, 1 H), 4.61 (d, J = 2.0 Hz, 1 H), 4.33 (dd, J_1 = 5.6 Hz, J_2 = 1.6 Hz, 1 H), 2.09 (d, J = 1.6 Hz, 3 H), 2.01 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.48, 148.02, 146.83, 136.46, 131.14, 130.26, 128.81, 128.60, 127.66, 124.85, 124.65, 123.87, 121.71, 114.44, 71.45, 45.53, 18.91; IR (neat): 3443, 2928, 1594, 1514, 1492, 1445, 1345, 1224, 1131, 1106, 1052, 1020, 982, 935, 834, 768, 739, 696, 670, 636 cm^{-1}; MS(EI) m/z (%): 347 (M^+, 88), 105 (100); HRMS: calcd for $C_{21}H_{17}NO_4$ (M^+), 347.1158; found, 347.1151.

3. General procedure for the synthesis of 3 and 3′ in Table 3

An oven-dried Schlenk tube containing a Teflon-coated stirring bar was charged with $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%) and CuI (1 mg, 3 mol%). The Schlenk tube was sealed and then evacuated-backfilled with N_2 (3 cycles). A solution of aryl iodide **1** (0.25 mmol) and furylmethyl ether **2** (0.3 mmol) in 2 mL of toluene and 0.1 mL of i-Pr_2NH was subsequently injected to the Schlenk tube. The reaction mixture was stirred at room temperature for 20 min followed by the addition of *t*-BuOK (84 mg, 0.75 mmol). After another 20 min, the reaction was quenched by H_2O (15 mL) and the mixture was extracted with ether (10 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified with flash chromatography on silica gel to afford **3** and **3′**.

(1) Preparation of (4*R,5*R**)-4-(3-nitrophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ca) and (4*R**,5*S**)-4-(3-nitrophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ca′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1c**

(62 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 2 mL of toluene and 0.1 mL of i-Pr_2NH followed by the addition of *t*-BuOK (84 mg, 0.75 mmol) at room temperature afforded **3ca** (61 mg, 73%) and **3ca′** (8 mg, 10%) (eluent: petroleum ether–ethyl acetate = 4/1) as a liquid:

3ca ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (t, J = 8.0 Hz, 2 H), 7.61 (s, 1 H), 7.52 (d, J = 7.6 Hz, 1 H), 7.45–7.39 (m, 3 H), 7.30 (t, J = 7.4 Hz, 2 H), 7.26–7.20 (m, 1 H), 6.79 (d, J = 10.0 Hz, 1 H), 5.95 (dd, J_1 = 9.6 Hz, J_2 = 5.6 Hz, 1 H), 4.67 (d, J = 1.6 Hz, 1 H), 4.37 (s, 1 H), 1.96 (d, J = 5.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.39, 148.46, 142.37, 137.45, 134.24, 130.14, 129.63, 128.62, 127.70, 125.66, 124.96, 122.95, 122.18, 122.14, 121.74, 114.00, 70.88, 45.35; IR (neat): 3429, 2909, 1597, 1524, 1444, 1402, 1351, 1260, 1129, 1082, 1006, 929, 866, 830, 797, 768, 733, 688, 641 cm^{-1}; MS(EI) *m*/*z* (%): 333 (M^+, 64), 105 (100); HRMS: calcd for $C_{20}H_{15}NO_4$ (M^+), 333.1001; found, 333.1002.

3ca′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12–8.10 (m, 2 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.53 (s, 1 H), 7.47 (t, J = 8.2, 1 H), 7.40–7.38 (m, 2 H), 7.31 (t, J = 7.6 Hz, 2 H), 7.26–7.24 (m, 2 H), 6.60 (dd, J_1 = 10.0 Hz, J_2 = 3.2 Hz,, 1 H), 5.62 (dd, J_1 = 10.0 Hz, J_2 = 2.0 Hz, 1 H), 4.97 (t, J = 7.2 Hz, 1 H), 4.60 (d, J = 7.6 Hz, 1 H), 1.58 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.84, 148.23, 139.74, 137.00, 136.14, 130.67, 130.21, 129.11, 128.69, 127.75, 125.01, 124.80, 12.69, 122.38, 199.22, 116.34, 70.52, 42.91; IR (neat): 3396, 2967, 1594, 1526, 1492, 1446, 1347, 1130, 1074, 1052, 1026, 948, 879, 855, 802, 767, 739, 690, 622 cm^{-1}; MS(EI) *m*/*z* (%): 333 (M^+, 51), 44 (100), 105 (75); HRMS: calcd for $C_{20}H_{15}NO_4$ (M^+), 333.1001; found, 333.1003.

(2) Preparation of (4*R,5*R**)-3,4-diphenyl-4,5-dihydro-isobenzofuran-5-ol (3fa) and (4*R**,5*S**)-3,4-diphenyl-4,5-dihydroisobenzofuran-5-ol (3fa′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1f** (51 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 2 mL of toluene and 0.1 mL of i-Pr_2NH followed by the addition of *t*-BuOK (84 mg, 0.75 mmol) at room temperature afforded **3fa** (54 mg, 75%) and **3fa′** (7 mg, 10%) (eluent: petroleum ether–ether = 4/1) as a liquid:

3fa ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 1.2 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 2 H), 7.29–7.23 (m, 4 H), 7.20–7.17 (m, 4 H), 6.73 (dd, J_1 = 10.0 Hz, J_2 = 1.2 Hz, 1 H), 5.98–5.94 (m, 1 H), 4.54 (s, 1 H), 4.39 (s, 1 H), 1.82 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.16, 140.15, 136.90, 130.55, 128.67, 128.47, 127.99, 127.30, 126.89, 126.45, 125.08, 122.25, 121.69, 115.43, 71.32, 45.82; IR (neat): 3394, 1597, 1492, 1448, 1371, 1244, 1129, 1001, 875, 848, 763, 735, 695 cm^{-1}; MS(EI) *m*/*z* (%): 288 (M^+, 100), 105 (89); HRMS: calcd for $C_{20}H_{16}O_2$ (M^+), 288.1150; found, 288.1151.

3fa′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (t, J = 8.4 Hz, 3 H), 7.33–7.19 (m, 8 H), 6.52 (dd, J_1 = 10.4 Hz, J_2 = 2.8 Hz, 1 H), 5.62 (d, J = 9.6 Hz, 1 H), 4.87 (m, 1 H), 4.47 (d, J = 7.6 Hz, 1 H), 1.55 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.46, 136.98, 136.35, 131.74, 130.58, 129.93, 128.58, 128.52, 127.45, 127.33, 125.04, 123.11, 118.60, 117.80, 70.64, 43.13; IR (neat): 3395, 3058, 1597, 1492, 1447, 1366, 1263, 1129, 1048, 946, 909, 865, 822, 764, 735, 694, 617 cm^{-1}; MS(EI) *m*/*z* (%): 288 (M^+, 76), 43 (100), 105 (87); HRMS: calcd for $C_{20}H_{16}O_2$ (M^+), 288.1150; found, 288.1145.

(3) Preparation of (4*R,5*R**)-5-methyl-3,4-diphenyl-4,5-dihydroisobenzofuran-5-ol (3fb) and (4*R**,5*S**)-5-methyl-3,4-diphenyl-4,5-dihydroisobenzofuran-5-ol (3fb′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (2 mg, 4 mol%), **1f** (51 mg, 0.25 mmol) and **2f** (68 mg, 0.3 mmol) in 2 mL of toluene and 0.1 mL of i-Pr_2NH followed by the addition of *t*-BuOK (84 mg, 0.75 mmol) at room temperature afforded **3fb** (48 mg, 61%) and **3fb′** (7 mg, 9%) (eluent: petroleum ether–ethyl acetate = 8/1) as a liquid:

3fb ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.49 (m, 3 H), 7.30 (t, J = 7.2 Hz, 2 H), 7.23–7.16 (m, 6 H), 6.69 (d, J = 9.2 Hz, 1 H), 5.78 (d, J = 9.6 Hz, 1 H), 4.29 (s, 1 H), 2.19 (s, 1 H), 1.17 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.60, 140.03, 136.61, 133.49, 130.57, 128.84, 128.41, 128.27, 127.24, 126.80, 125.06, 122.08, 120.47, 118.18, 72.08, 50.59, 26.95; IR (neat): 3509, 3033, 2926, 1700, 1640, 1542, 1489, 1439, 1372, 1334, 1182, 1124, 1087, 1049, 1027, 958, 937, 896, 846, 786, 747, 694, 641, 613 cm^{-1}; MS(EI) *m*/*z* (%): 302 (M^+, 100), 285 (63), 259 (70); HRMS: calcd for $C_{21}H_{18}O_2$ (M^+), 302.1307; found, 302.1301.

3fb′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7.2 Hz, 3 H), 7.33–7.21 (m, 8 H), 6.47 (d, J = 10.4 Hz, 1 H), 5.65 (d, J = 10.0 Hz, 1 H), 4.19 (s, 1 H), 1.60 (s, 1 H), 1.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.57, 138.31, 136.32, 136.29, 130.70, 129.85, 128.58, 128.53, 127.43, 127.25, 125.05, 122.60, 118.81, 117.35, 73.94, 49.95, 28.77; IR (neat): 3504, 2962, 1649, 1599, 1491, 1449, 1346, 1235, 1143, 1122, 1054, 1027, 930, 875, 825, 779, 750, 682, 640 cm^{-1}; MS(EI) *m*/*z* (%): 302 (M^+, 100), 259 (96), 105 (69); HRMS: calcd for $C_{21}H_{18}O_2$ (M^+), 302.1307; found, 302.1311.

(4) Preparation of (4*R,5*R**)-4-(4-bromophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ga) and (4*R**,5*S**)-4-(4-bromophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ga′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1g** (71 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 2 mL of toluene and 0.1 mL of i-Pr_2NH followed by addition of *t*-BuOK (84 mg, 0.75 mmol) at room temperature afforded **3ga** (70 mg, 77%) and **3ga′** (11 mg, 12%) (eluent: petroleum ether–ether = 2/1) as a liquid:

3ga ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1 H), 7.42–7.35 (m, 4 H), 7.30–7.26 (m, 2 H), 7.22–7.19 (m, 1 H), 7.03 (d, J = 8.4 Hz, 2 H), 6.70 (d, J = 10.0 Hz, 1 H), 5.91 (dd, J_1 = 10.0 Hz, J_2 = 6.0 Hz, 1 H), 4.49 (s, 1 H), 4.31 (d, J = 4.0 Hz, 1 H), 1.94 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.21, 139.19, 137.02, 131.75, 130.33, 129.68, 128.54, 127.48, 126.07, 124.98, 121.97, 121.78, 120.76, 114.84, 70.97, 45.16; IR (neat): 3375, 1706, 1641, 1594, 1553, 1485, 1446, 1401, 1361, 1221, 1128, 1071, 1054, 1009, 951, 907, 882, 851, 810, 788, 769, 731, 692, 661, 632 cm^{-1}; MS(EI) *m*/*z* (%): 368 [M^+(^{81}Br), 5], 366 [M^+(^{79}Br), 5], 84 (100); HRMS: calcd for $C_{20}H_{15}BrO_2$ [M^+(^{79}Br)], 366.0255; found, 366.0245.

3ga′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1 H), 7.43–7.39 (m, 4 H), 7.32–7.29 (m, 2 H), 7.25–7.23 (m, 1 H), 7.13 (d, J = 8.4 Hz, 2 H), 6.52 (dd, J_1 = 10.0 Hz, J_2 = 3.2 Hz, 1 H), 5.59 (dd, J_1 = 10.0 Hz, J_2 = 1.6 Hz, 1 H), 4.87 (t, J = 8.4 Hz, 1 H), 4.43 (d, J = 7.6 Hz, 1 H), 1.49 (d, J = 10.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.63, 136.55, 136.24, 131.61, 131.33, 130.41,

128.61, 127.54, 125.04, 122.89, 121.51, 118.81, 117.21, 70.53, 42.65; IR (neat): 3400, 2916, 1593, 1487, 1446, 1404, 1362, 1221, 1181, 1130, 1072, 1051, 1026, 1010, 943, 909, 876, 801, 786, 767, 729, 692, 665, 614 cm^{-1}; MS(EI) *m*/*z* (%): 368 [M^+(^{81}Br), 10], 366 [M^+(^{79}Br), 12], 59 (100); HRMS: calcd for $C_{20}H_{15}BrO_2$ [M^+(^{79}Br)], 366.0255; found, 366.0247.

(5) Preparation of (4*R,5*R**)-4-(4-fluorophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ha) and (4*R**,5*S**)-4-(4-fluorophenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ha′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1h** (56 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 2 mL of toluene and 0.1 mL of i-Pr_2NH followed by the addition of *t*-BuOK (84 mg, 0.75 mmol) at room temperature afforded **3ha** (56 mg, 73%) and **3ha′** (9 mg, 12%) (eluent: petroleum ether–ether = 2/1) as a liquid:

3ha ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1 H), 7.43–7.41 (m, 2 H), 7.30–7.26 (m, 2 H), 7.23–7.18 (m, 1 H), 7.14–7.10 (m, 2 H), 6.95–6.90 (m, 2 H), 6.71 (d, J = 9.2 Hz, 1 H), 5.93 (dd, J_1 = 9.6 Hz, J_2 = 5.6 Hz, 1 H), 4.51 (d, J = 2.0 Hz, 1 H), 4.33 (dd, J_1 = 5.6 Hz, J_2 = 2.0 Hz, 1 H), 1.95 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.71 (d, J = 244.0 Hz), 150.15, 136.99, 135.87 (d, J = 2.9 Hz), 130.43, 129.47 (d, J = 7.8 Hz), 128.51, 127.43, 126.23, 125.03, 122.06, 121.71, 115.49 (d, J = 21.0 Hz), 115.31, 71.24, 45.00; IR (neat): 3368, 2917, 1641, 1602, 1506, 1446, 1391, 1265, 1222, 1159, 1129, 1096, 1052, 1004, 950, 907, 861, 824, 783, 767, 735, 692, 637 cm^{-1}; MS(EI) *m*/*z* (%): 306 (M^+, 52), 105 (100); HRMS: calcd for $C_{20}H_{15}FO_2$ (M^+), 306.1056; found, 306.1047.

3ha′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1 H), 7.42–7.40 (m, 2 H), 7.33–7.21 (m, 5 H), 7.00 (t, J = 8.8 Hz, 2 H), 6.53 (dd, J_1 = 10.0 Hz, J_2 = 3.2 Hz, 1 H), 5.61 (dd, J_1 = 10.0 Hz, J_2 = 1.6 Hz, 1 H), 4.86 (d, J = 6.8 Hz, 1 H), 4.46 (d, J = 7.2 Hz, 1 H), 1.56 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.14 (d, J = 243.6 Hz), 148.47, 136.48, 132.74 (d, J = 3.4 Hz), 131.43, 131.42 (d, J = 7.5 Hz), 130.44, 128.57, 127.46, 124.99, 122.89, 118.71, 117.58, 115.41 (d, J = 21.0 Hz), 70.55, 42.34; IR (neat): 3360, 2919, 1668, 1598, 1506, 1446, 1369, 1225, 1158, 1131, 1093, 1048, 940, 806, 765, 738, 689, 660, 616 cm^{-1}; MS(EI) *m*/*z* (%): 306 (M^+, 15), 43 (100); HRMS: calcd for $C_{20}H_{15}FO_2$ (M^+), 306.1056; found, 306.1051.

(6) Preparation of (4*R,5*R**)-4-(4-methoxyphenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ia) and (4*R**,5*S**)-4-(4-methoxyphenyl)-3-phenyl-4,5-dihydroisobenzofuran-5-ol (3ia′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1i** (59 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 2 mL of toluene and 0.1 mL of i-Pr_2NH followed by the addition of *t*-BuOK (84 mg, 0.75 mmol) at room temperature afforded **3ia** (49 mg, 62%) and **3ia′** (8 mg, 10%) (eluent: petroleum ether–ether = 2/1) as a liquid:

3ia ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1 H), 7.44 (d, J = 8.0 Hz, 2 H), 7.29–7.25 (t, J = 7.6 Hz, 2 H), 7.23–7.17 (m, 1 H), 7.08 (d, J = 8.4 Hz, 2 H), 6.77 (d, J = 8.4 Hz, 2 H), 6.70 (d, J = 9.2 Hz, 1 H), 5.94 (dd, J_1 = 9.6 Hz, J_2 = 5.2 Hz, 1 H), 4.49 (s, 1 H), 4.35 (d, J = 4.8 Hz, 1 H), 3.72 (s, 3 H), 1.93 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.38, 149.99, 136.82, 132.12, 130.56, 128.92, 128.46, 127.24, 126.45, 125.03, 122.20, 121.60, 115.77, 114.01, 71.32, 55.12, 44.90; IR (neat): 3391, 2917, 1707, 1609, 1510, 1445, 1361, 1302, 1249, 1178, 1128, 1030, 951, 906, 858, 823, 766, 731, 693, 637 cm^{-1}; MS(EI) *m*/*z* (%): 318 (M^+, 32), 59 (100), 84 (95); HRMS: calcd for $C_{21}H_{18}O_3$ (M^+), 318.1256; found, 318.1257.

3ia′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 3 H), 7.32–7.17 (m, 5 H), 6.84 (d, J = 8.4 Hz, 2 H), 6.51 (dd, J_1 = 9.6 Hz, J_2 = 2.8 Hz, 1 H), 5.61 (d, J = 10.0 Hz, 1 H), 4.83 (m, 1 H), 4.42 (d, J = 7.6 Hz, 1 H), 3.77 (s, 3 H), 1.59 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.91, 148.33, 136.29, 131.89, 130.91, 130.62, 128.79, 128.53, 127.30, 125.03, 123.07, 118.51, 118.09, 114.02, 70.61, 55.18, 42.29; IR (neat): 3395, 2923, 1697, 1608, 1511, 1448, 1401, 1299, 1248, 1178, 1112, 1028, 913, 833, 799, 771, 694, 656, 618 cm^{-1}; MS(EI) *m*/*z* (%): 318 (M^+, 28), 43 (100); HRMS: calcd for $C_{21}H_{18}O_3$ (M^+), 318.1256; found, 318.1252.

(7) Preparation of methyl 4-((4*R,5*R**)-5-hydroxy-3-phenyl-4,5-dihydroisobenzo-furan-4-yl)benzoate (3ja) and methyl 4-((4*R**,5*S**)-5-hydroxy-3-phenyl-4,5-dihydroisobenzo-furan-4-yl)-benzoate (3ja′).** The reaction of $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%), CuI (1 mg, 3 mol%), **1j** (66 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 2 mL of toluene and 0.1 mL of i-Pr_2NH followed by the addition of *t*-BuOK (84 mg, 0.75 mmol) at −15 °C afforded **3ja** (57 mg, 66%) and **3ja′** (10 mg, 12%) (eluent: petroleum ether–ether = 2/1) as a liquid:

3ja ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.4 Hz, 2 H), 7.57 (s, 1 H), 7.40 (d, J = 7.2 Hz, 2 H), 7.29–7.20 (m, 5 H), 6.74 (d, J = 9.2 Hz, 1 H), 5.94 (dd, J_1 = 10.0 Hz, J_2 = 5.6 Hz, 1 H), 4.60 (s, 1 H), 4.38 (d, J = 4.0 Hz, 1 H), 3.86 (s, 3 H), 1.99 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.83, 150.29, 145.52, 137.10, 130.31, 130.00, 128.82, 128.53, 128.03, 127.49, 126.06, 124.98, 122.00, 121.85, 114.68, 70.92, 52.03, 45.78; IR (neat): 3472, 2953, 1720, 1609, 1492, 1437, 1412, 1373, 1280, 1244, 1185, 1109, 1046, 1010, 957, 842, 821, 765, 735, 693, 632, 611 cm^{-1}; MS(EI) *m*/*z* (%): 346 (M^+, 20), 43 (100); HRMS: calcd for $C_{22}H_{18}O_4$ (M^+), 346.1205; found, 346.1211.

3ja′ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.8 Hz, 2 H), 7.49 (s, 1 H), 7.40–7.20 (m, 7 H), 6.55 (dd, J_1 = 10.0 Hz, J_2 = 3.2 Hz, 1 H), 5.62 (dd, J_1 = 9.6 Hz, J_2 = 1.6 Hz, 1 H), 4.92 (td, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1 H), 4.54 (d, J = 7.2 Hz, 1 H), 3.89 (s, 3 H), 1.56 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.91, 148.74, 142.78, 136.63, 131.21, 130.38, 129.99, 129.68, 129.21, 128.59, 127.55, 125.05, 122.92, 118.89, 117.04, 70.56, 52.08, 43.22; IR (neat): 3348, 2919, 2851, 1715, 1609, 1492, 1436, 1281, 1186, 1106, 1046, 1020, 910, 765, 728, 693, 619 cm^{-1}; MS (EI) *m*/*z* (%): 346 (M^+, 9), 43 (100); HRMS: calcd for $C_{22}H_{18}O_4$ (M^+), 346.1205; found, 346.11211.

4. Procedure for the synthesis of (4*R**,5*R**)-3-(4-bromophenyl)-4-(4-nitrophenyl)-4,5-dihydroisobenzofuran-5-yl acetate (5)

To a solution of **3ab** (95 mg, 0.23 mmol) in pyridine (2 mL) were added DMAP (3 mg, 10 mol%) and Ac_2O (235 mg, 2.3 mmol). The mixture was stirred for 1 h at rt. The resulting mixture was diluted by Et_2O (10 mL) and washed sequentially with HCl (2 M), a saturate of aqueous $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4.

After filtration and evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether–DCM = 2/1) to afford **5** (87 mg, 83%, m.p.: 203–204 °C) as a white solid.

5 ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 9.2 Hz, 2 H), 7.63 (s, 1 H), 7.42 (d, J = 8.4 Hz, 4 H), 7.22 (d, J = 8.4 Hz, 2 H), 6.90 (d, J = 9.2 Hz, 1 H), 5.81 (dd, J_1 = 10.0 Hz, J_2 = 6.0 Hz, 1 H), 5.47 (dd, J_1 = 6.0 Hz, J_2 = 1.6 Hz, 1 H), 4.63 (s, 1 H), 2.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.81, 148.75, 147.18, 146.61, 137.84, 131.87, 128.98, 128.90, 126.19, 124.39, 124.06, 121.98, 121.74, 121.09, 114.48, 71.69, 42.08, 21.19; IR (neat): 3402, 2921, 1605, 1523, 1492, 1445, 1351, 1128, 1055, 1006, 951, 908, 887, 855, 839, 765, 734, 692, 671, 642, 616 cm^{-1}; MS (EI) m/z (%): 455 [M^+(^{81}Br), 3], 453 [M^+(^{79}Br), 3], 395 (100); HRMS: calcd for $C_{22}H_{16}NO_5Br$ [M^+(^{79}Br)], 453.0212; found, 453.0205.

5. Procedure for the synthesis of 2-((3-(3-nitrophenyl)-1-phenylprop-2-ynyloxy)methyl)furan (6)

An oven-dried Schlenk tube containing a Teflon-coated stirring bar was charged with $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%) and CuI (1 mg, 3 mol%). The Schlenk tube was sealed and then evacuated-backfilled with N_2 (3 cycles). A solution of **1c** (62 mg, 0.25 mmol) and **2a** (64 mg, 0.3 mmol) in 1 mL of toluene and 0.6 mL of i-Pr_2NH was subsequently injected to the Schlenk tube. The reaction mixture was stirred at 65 °C for 16 h. After filtration and evaporation, the residues were purified with flash chromatography on silica gel (eluent: petroleum ether–ethyl acetate = 20/1) to afford **6** (60 mg, 72%) as a liquid:

6 ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1 H), 8.16 (d, J = 8.4 Hz, 1 H), 7.76 (d, J = 7.2 Hz, 1 H), 7.56 (d, J = 7.2 Hz, 2 H), 7.51–7.35 (m, 5 H), 6.39 (d, J = 13.6 Hz, 2 H), 5.44 (s, 1 H), 4.68 (t, J = 13.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.92, 147.99, 143.08, 137.70, 137.43, 129.31, 128.68, 128.61, 127.46, 126.58, 124.20, 123.24, 110.35, 110.08, 89.48, 85.15, 70.59, 62.17; IR (neat): 3084, 1727, 1529, 1497, 1452, 1349, 1307, 1149, 1049, 1014, 919, 883, 809, 785, 735, 698, 673 cm^{-1}; MS (EI) m/z (%): 333 (M^+, 3), 81 (100), 189 (87), 236 (85); HRMS: calcd for $C_{20}H_{15}NO_4$ (M^+), 333.1001; found, 333.1000.

Acknowledgements

We are grateful to the National Basic Research Program of China (973 Program, 2009CB825300) and the National Natural Science Foundation of China (project no. 20732005 and 20872127) for financial support.

Notes and references

1 For reviews, see: (*a*) G. H. Posner, *Chem. Rev.*, 1986, **86**, 831; (*b*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*c*) P. J. Parsons, C. S. Penkett and A. Shell, *J. Chem. Rev.*, 1996, **96**, 195; (*d*) A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223; (*e*) L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reaction in Organic Synthesis*, Wiley-VCN, Weinheim, Germany, 2006; (*f*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134.

2 For a review, see: (*a*) T. J. J. Müller, *Synthesis*, 2012, 159; For selected examples, see: (*b*) T. J. J. Müller, M. Ansorge and D. Aktah, *Angew. Chem., Int. Ed.*, 2000, **39**, 1253; (*c*) D. M. D'Souza, F. Rominger and T. J. J. Müller, *Angew. Chem., Int. Ed.*, 2005, **44**, 153; (*d*) D. M. D'Souza, F. Rominger and T. J. J. Müller, *Chem. Commun.*, 2006, 4096; (*e*) R. U. Braun, M. Ansorge and T. J. J. Müller, *Chem.–Eur. J.*, 2006, **12**, 9081; (*f*) B. U. Braun, K. Zeitler and T. J. J. Müller, *Org. Lett.*, 2001, **3**, 3297; (*g*) D. M. D'Souza, A. Kiel, D. P. Herten and T. J. J. Müller, *Chem.–Eur. J.*, 2008, **14**, 529; (*h*) B. U. Braun, K. Zeitler and T. J. J. Müller, *Org. Lett.*, 2000, **2**, 4181; (*i*) D. M. D'Souza, W. W. Liao and T. J. J. Müller, *Org. Biomol. Chem.*, 2008, **6**, 532; (*j*) J. Schönhaber and T. J. J. Müller, *Org. Biomol. Chem.*, 2011, **9**, 6169.

3 (*a*) R. W. Shen and X. Huang, *Org. Lett.*, 2008, **10**, 3283; (*b*) R. W. Shen, X. Huang and L. Z. Chen, *Adv. Synth. Catal.*, 2008, **350**, 2865; (*c*) X. Huang, S. G. Zhu and R. W. Shen, *Adv. Synth. Catal.*, 2009, **351**, 3118; (*d*) R. W. Shen, S. G. Zhu and X. Huang, *J. Org. Chem.*, 2009, **74**, 4118; (*e*) R. W. Shen, L. Z. Chen and X. Huang, *Adv. Synth. Catal.*, 2009, **351**, 2833.

4 For selected studies of intramolecular Diels–Alder reactions of propargyl furylmethyl ethers, see: (*a*) K. Hayakawa, M. Yodo, S. Ohsuki and K. Kanematsu, *J. Am. Chem. Soc.*, 1984, **106**, 6735; (*b*) K. Hayakawa, Y. Yamaguchi and K. Kanematsu, *Tetrahedron Lett.*, 1985, **26**, 2689; (*c*) Y. Yamaguchi, N. Tastsuta, K. Hayakawa and K. Kanematsu, *J. Chem. Soc., Chem. Commun.*, 1989, 470; (*d*) H. J. Wu, F. H. Ying and W. D. Shao, *J. Org. Chem.*, 1995, **60**, 6168; (*e*) H. J. Wu, C. H. Yen and C. T. Chuang, *J. Org. Chem.*, 1998, **63**, 5064; for allenamides generated *in situ*, see: (*f*) M. Lee, H. Morimoto and K. Kanematsu, *Tetrahedron*, 1996, **52**, 8169; (*g*) A. G. Lohse and R. P. Hsung, *Org. Lett.*, 2009, **11**, 3430; for a Diels–Alder reaction of furyl ketones bearing internal alkyne moieties accelerated by Grignard reagents, see: (*h*) Y. F. Chen and L. Wang, *Chem.–Eur. J.*, 2011, **17**, 12582.

