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Note

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Dynamic Kinetic Resolution for Construction of Three Transannular Stereocenters of Dihydrobenzofuranols

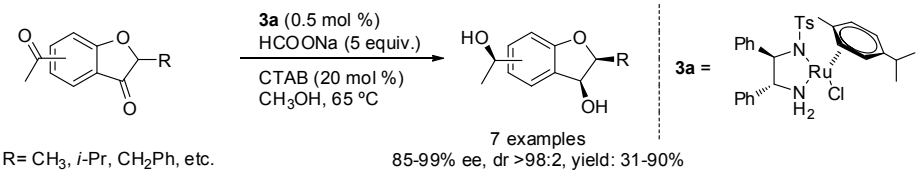
Lizhen Fang,[a,*] Fangfei Zhao,[a] Shuyu Hu,[a] Lili Han,[a] Xiaojing Hu,[b] Mingyong Wang,[c] Qianqian Sun,[a] Huipan Wu[a]

[a]School of Pharmacy, Xinxiang Medical University, Xinxiang, Henan 453003, People's Republic of China

[b]The Third Affiliated Hospital of Xinxiang Medical University, Xinxiang, Henan 453003, People's Republic of China

[c]School of Laboratory Medicine, Xinxiang Medical University, Xinxiang, Henan 453003, People's Republic of China

Supporting Information



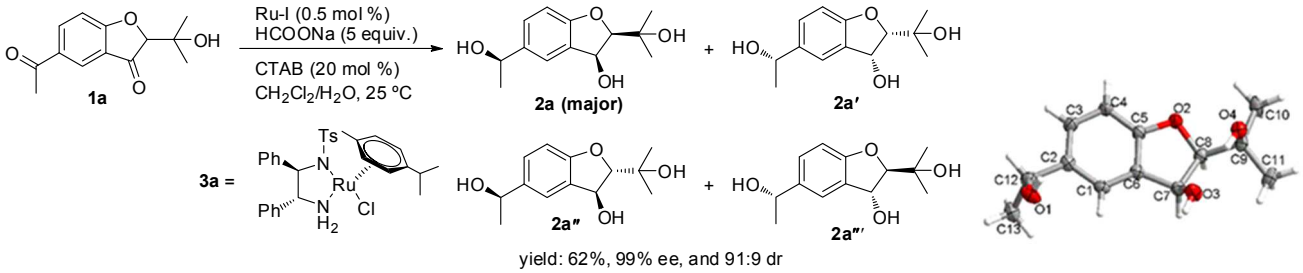
ABSTRACT: A handy and effective method was established to obtain the *cis*-2,3-dihydrobenzofuranols having three stereocenters, involving asymmetric transfer hydrogenation of benzofuranones *via* dynamic kinetic resolution. The general applicability of this method was examined with different benzofuran-3-(2*H*)-ones and stereoselectivities of 85%-99% ee and up to 98/2 dr were obtained.

Multiple stereocenters are common and important in natural products,[1] drugs[2] and organic synthesis motifs.[3] However, it is challenging to construct these chiral motifs. Methods which produce the desired multiple stereocenters in one step are highly valuable for organic synthesis; for example, the pericyclic reaction[4] and domino reactions.[5] In recent years, dynamic kinetic resolution through asymmetric transfer hydrogenation (DKR-ATH)[6] has also been used as a potent methodology to achieve various optically active compounds with 1,2 or 1,3-stereocenters.[7] Up to this date, DKR-ATH has only been used to construct two stereocenters in a chiral compound, with the stereocenters close in space and on the same side of a benzene ring. Construction of three stereocenters, specifically the transannular stereocenters, by this method has not been reported.

In our investigation of the DKR-ATH method for the preparation of dihydrobenzofuranols,[8] we obtained a unique substrate **1a** and reduced it using the catalyst RuCl(*p*-cymene)[(*R,R*)-TsDPEN] with the DKR-ATH procedure. Unexpectedly, we obtained the products with a good selectivity (**Scheme 1**). Chiral analysis showed that the reaction gave only four products (**Figure 1**), and the main product with three transannular *cis*-stereocenters was more than 99% ee after purification. Their configurations were carefully determined by x-ray crystallography and comparison of the enantiomers and racemates, respectively. We are very interested in this result and continue to explore it.

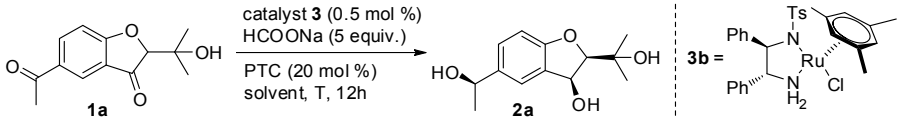
During our wide investigation of the chiral TsDPEN (*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine)-based organometal complexes in the ATH reaction, two commercially

Scheme 1. DKR-ATH of the Substrate 1a and x-ray crystal structure of 2a[a]



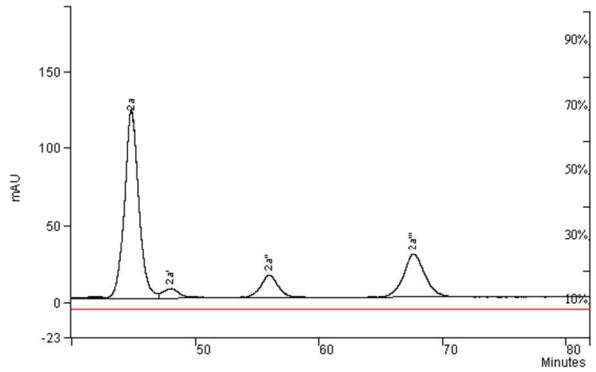
[a]Displacement ellipsoids are drawn at the 40% probability level.

Table 1. Optimization of Reaction of 1a[a]



entry	catalyst	solvent	temperature (°C)	PTC[b]	yield of **2a** (%)[c]	ee (%) of **2a**[d]	dr (**2a**+**2a'**/ **2a''**+**2a'''**)[d]
1	**3a**	CH_2Cl_2/H_2O	25	CTAB	62	99	91/9
2	**3b**	CH_2Cl_2/H_2O	25	CTAB	9	99	85/15
3	**3a**	MeOH	25	CTAB	45	99	95/5
4	**3a**	MeOH	65	CTAB	63	99	98/2
5	**3b**	CH_2Cl_2/H_2O	35	CTAB	32	90	88/12
6	**3a**	MeOH	65	none	10	99	95/5
7	**3a**	MeOH	65	TAHS	43	99	96/4
8	**3a**	MeOH	65	DTAC	63	99	95/5
9	**3a**	MeOH	65	TTAC	62	99	96/4
10	**3a**	MeOH	65	TBAC	34	99	94/6
11	**3a**	MeOH	65	β-CD	53	99	97/3
12	**3a**	MeOH	65	TBAB	26	99	94/6

[a]The reactions were run on a 1.0 mmol scale in a 25 mL sealed flask under the protection of argon. The solvent amount was 4 mL, and the ratio of the co-solvents was 1:1. [b]Abbreviations: PTC, phase transfer catalyst; CTAB, cetyltrimethylammonium bromide; TAHS, tetrabutylammonium hydrogen sulfate; DTAC, dodecyltrimethylammonium chloride; TTAC, trimethyltetradecylammonium chloride; TBAC, tetrabutylammonium chloride; β-CD, β-cyclodextrin; TBAB, tetrabutylammonium bromide. [c]Isolated yield including the minor enantiomer. [d]Determined by HPLC analysis using a chiral column.



Peak No	Peak Name	Result (ug/ml)	Ret. Time (min)	Time Offset (min)	Width 1/2 (sec)	Area (counts)
1	2a	62.7202	44.808	0.000	73.5	99552792
2	2a'	4.4873	47.951	-0.000	135.7	7122537
3	2a''	10.5798	55.953	-0.000	102.3	16792726
4	2a'''	22.2127	67.644	0.000	116.8	35257068
	Totals	**100.0000**		**0.000**		**158725120**

Figure 1. HPLC analysis-spectra of the crude product of the reaction of **1a**[a]. [a]HPLC conditions: CHIRALPAK ®IA column; n-hexane/i-PrOH=92/8; 280 nm; 0.5 mL·min^{-1}; 35°C.

available organometallic complexes, **3a** (RuCl(*p*-cymene)[(*R,R*)-TsDPEN]) and **3b** (RuCl[(*R,R*)-TsDPEN] (mesitylene)), combined with different solvents, phase transfer catalysts, and reaction temperatures, were screened to compare their catalytic properties. The highest selectivity and yield was obtained under the conditions of entry 4 (**Table 1**). Compared to the conventional CH_2Cl_2/H_2O solvent system, the polar solvent MeOH obtained higher diastereomeric ratio (dr) values (**Table 1**, entries 2 and 3). In addition, the optimum temperature and the phase transfer catalyst are crucial to achieving high performance in the reactions.

With these optimized conditions in hand, we first wanted to find out how varying the acetyl position at the benzene ring of **1a** influences the reaction for a transannular hydrogen transfer system (**Figure 2**). So we designed the substrates **1** as in **Scheme 2**. It should be noted that these commercially unavailable substrates **1** were not easy to be obtained. Compounds **1** were prepared from the purchased starting materials **4a** and **4c**. A C-H activation method was carried out using the commercial compound **8** in order to prepare **4b** (**Scheme 2**). The substrate **1d** proved too difficult to successfully prepare which may be due to its extreme instability.

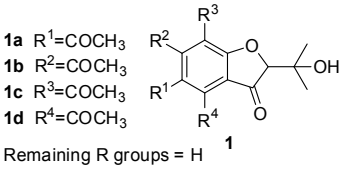
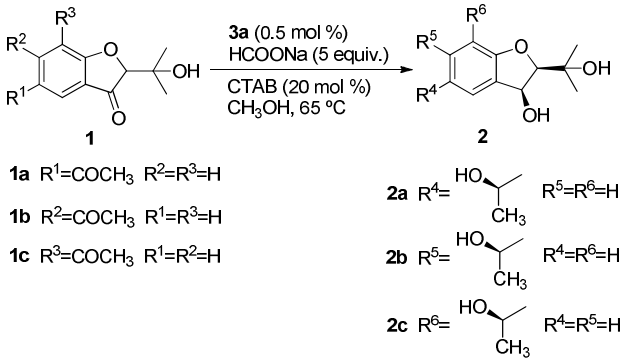


Figure 2. The designed substrates **1**.

Next, we examined the reaction with compounds **1** under the optimum conditions (**Table 1**, entry 4). Satisfactorily, all the reactions could go smoothly with the compounds **1** (**Table 2**). Regardless of where the acetyl was located, all the substrates gave high selectivities (**Table 2**, entries 1-3), but for **2b**,

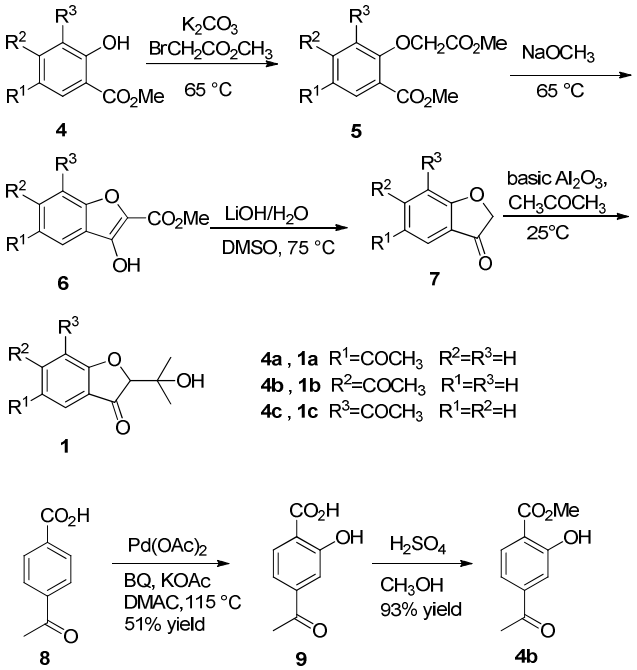
Table 2. DKR-ATH of Compounds 1



entry	substrate	yield of **2** (%)[b]	ee(%) of **2**[c]	dr[d]
1	**1a**	63	>99	98/2
2	**1b**	31	96	>99/1
3	**1c**	50	95	>99/1

[a]The reactions were run on a 1.0 mmol scale in a 25 mL sealed flask under the protection of argon. [b]Isolated yield including the minor enantiomer. [c]Determined by HPLC analysis using a chiral column. [d] The calculation method was the same as the model **2a**.

Scheme 2. Preparation of Substrates 1



the yield was modest with many by-products generated during the reaction.

Secondly, we further examined the scope of the general applicability using benzofuran-3-(2*H*)-one analogues **10a-10d** that having different alkyl groups and aromatic groups (benzyl) at the 2-position (**Figure 3**). These substrates **10** were prepared by different methods as shown in **Scheme 3**, and were subsequently reduced under the standard conditions. All the substrates were able to be reduced and afforded good selectivities (**Table 3**, entries 1-4). These results showed that this method was applicable to obtaining a wide scope of chiral 2,3-dihydrobenzofuran-3-ols containing three stereocenters.

Scheme 3. Preparation of Compounds 10

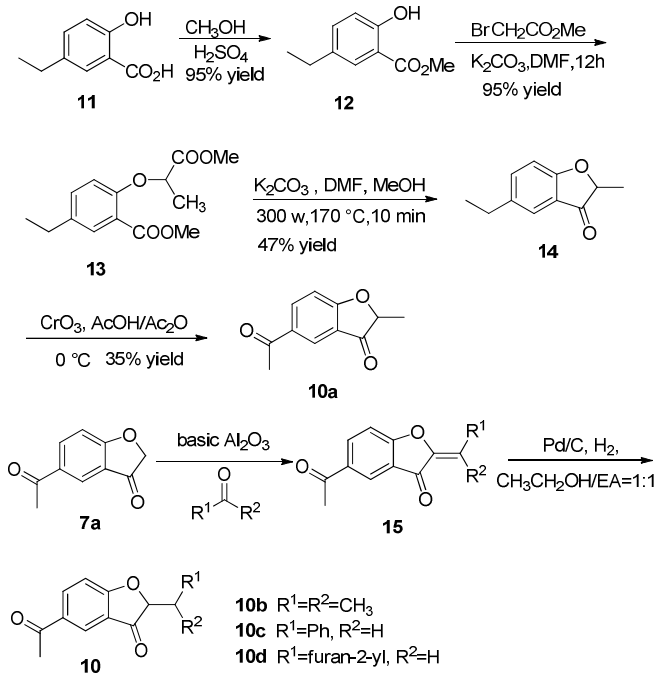
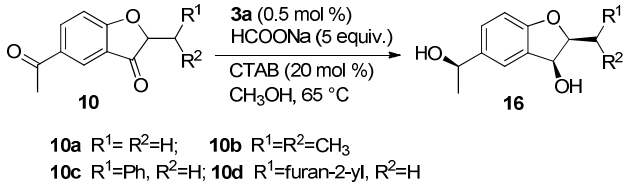


Table 3. DKR-ATH of compounds **10**[a]



entry	substrate	yield of **16** (%)[b]	ee(%) of **16**[c]	dr[d]
1	**10a**	79	91	>99/1
2	**10b**	87	94	>99/1
3	**10c**	82	85	>99/1
4	**10d**	90	92	>99/1

[a]The reactions were run on a 1.0 mmol scale in a 25 mL sealed flask under protection of argon. [b]Isolated yield including the minor enantiomer. [c]Determined by HPLC analysis using a chiral column.[d] The calculation method was the same as the model **2a**.

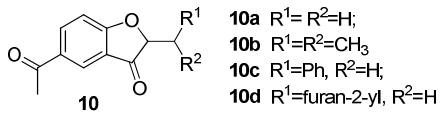


Figure 3. The designed substrates **10**.

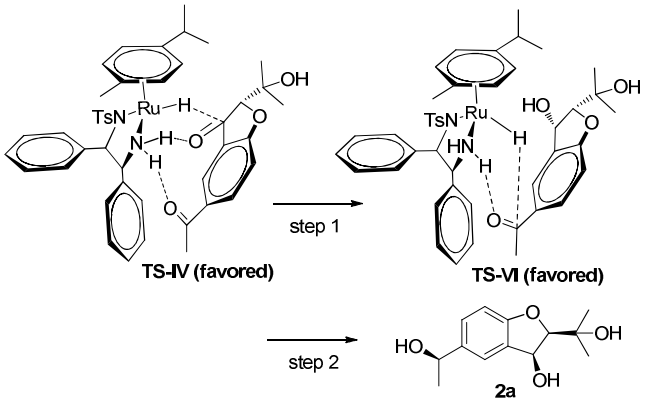


Figure 4. Proposed transition state (**TS**).

In our experiments, as an example as compound **1**, we observed that the carbonyl group at the furan ring was much easier to be reduced than the acetyl group at the benzene ring, and the intermediate compound was also obtained (see supporting information). Based on other previously reported work,[8a,9] we proposed a mechanism for the transfer hydrogenation reaction of **1a** through a catalytic cycle with two different stages (**1a** as a model). In the first stage, the substrate **1a** bonds with the catalyst, in which there is energetically favored and disfavored configurations due to the steric hindrance between **1a** and the catalyst as shown in **TS** (**Figure 4**, for the detailed explanation see supporting information). This caused the furanone part of **1a** to be reduced by a DKR-ATH process. In the second stage, the catalyst bonds to **1a** in the same configuration fixed from the first stage, and the acetophenone part of **1a** is reduced via an ATH process.[10] The absolute configurations of all products were assigned as for the model compound **1a** and rationalized using the Noyori/Ikariya (*R,R*)-I catalyst.

In summary, we developed a handy and efficient method to obtain the *cis*-2,3-dihydrobenzofuranes containing three stereocenters by the reduction of benzofuranones *via* DKR-ATH. This methodology is an efficient tool to construct the transannular multiple stereocenters of dihydrobenzofuranol motifs with excellent stereoselectivities for organic synthesis.

EXPERIMENTAL SECTION

General Information. All commercial reagents were purchased from Sigma-Aldrich, Alfa-Aesar, Acros and they were used without further purification unless specified. The progress of the reaction was monitored by TLC. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-400 spectrometers operating respectively at 400 MHz for ^{1}H, and 100 MHz for ^{13}C. The peaks were internally referenced to TMS (0.00 ppm) or residual undeuterated solvent signal. Peak multiplicities are reported as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC data were obtained on a VARIAN HPLC system using DAICEL CHIRALPAK® IA column (25 cm) at 35 °C. The Melting points were determined using WRS-1B apparatus and are uncorrected. High resolution mass spectra for new compounds were recorded on a Bruker micro TOF-Q III spectrometer. X-ray crystallographic analyses were performed at the X-ray crystallography facility, Analysis and Test Center of Zhengzhou University.

General Procedure for Preparation of Compounds 5 (5a as a model). To a solution of **4a** (388 mg, 2 mmol) in acetone (10 mL), K_2CO_3 (966 mg, 7 mmol) and $BrCH_2CO_2Me$ (367mg, 2.4 mmol) were added. After stirring under reflux for 3 h, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using petroleum ether /ethyl acetate = 3/1 as eluent to give **5a** (452 mg, 85%) as a white solid.

*Methyl 5-acetyl-2-(2-methoxy-2-oxoethoxy)benzoate (**5a**)*. White solid, 85% yield; mp 108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.0 Hz, 1H), 7.56 (dd, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 1H), 7.43 (d, J = 1.4 Hz, 1H), 4.77 (s, 2H), 3.91 (s, 3H), 3.79 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 168.8, 166.0, 157.5, 140.9, 132.3, 125.5, 121.9, 112.8, 66.4, 52.7, 52.6, 27.0; HRMS (ESI): calc. for $C_{13}H_{14}NaO_6$ $[M+Na]^+$: 289.0683; found: 289.0684.

*Methyl 4-acetyl-2-(2-methoxy-2-oxoethoxy)benzoate (**5b**)*. White solid, 82% yield; mp 69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.0 Hz, 1H), 7.47 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.34 (d, J = 1.2 Hz, 1H), 4.69 (s, 2H), 3.81 (s, 3H), 3.69 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 168.5, 165.7, 157.2, 140.7, 132.0, 125.2, 121.6, 112.6, 66.1, 52.4, 52.3, 26.7; HRMS (ESI): calc. for $C_{13}H_{14}NaO_6$ $[M+Na]^+$: 289.0683; found: 289.0684.

*Methyl 3-acetyl-2-(2-methoxy-2-oxoethoxy)benzoate (**5c**)*. Yellow oil, 89% yield; ^{1}H NMR (400 MHz, CD_3COCD_3): δ 7.95 (dd, J_1 = 1.8 Hz, J_2 = 7.7 Hz, 1H), 7.78 (dd, J_1 = 1.8 Hz, J_2 = 7.7 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 4.71 (s, 2H), 3.89 (s, 3H), 3.71 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 199.8, 169.5, 166.3, 157.3, 136.6, 135.4, 134.2, 126.3, 125.2, 72.8, 52.9, 52.1, 31.3; HRMS (ESI): calc. for $C_{13}H_{14}NaO_6$ $[M+Na]^+$: 289.0683; found: 289.0685.

General Procedure for Preparation of Compounds 6 (6a as a model). A solution of **5a** (266 mg, 1 mmol) in CH_3OH (2 mL) was added to a solution of Na (28.8 mg, 1.25 mmol) in CH_3OH (4 mL). The reaction mixture was refluxed and stirred for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was added water and adjusted pH = 3-4 with aqueous hydrochloric acid (1.0 N). The mixture was filtered and dried to afford **6a** (201 mg, 86%) as a white solid.

*Methyl 5-acetyl-3-hydroxybenzofuran-2-carboxylate (**6a**)*. White solid, 86% yield; mp 190 °C; ^{1}H NMR (400 MHz, CD_3SOCD_3): δ 8.70 (d, J = 1.6 Hz, 1H), 8.07 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 3.83 (s, 3H), 3.35 (br s, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3): δ 196.9, 159.4, 154.9, 147.6, 132.1, 128.5, 127.9, 123.5, 121.8, 112.5, 51.4, 26.8; HRMS (ESI): calc. for $C_{12}H_{10}NaO_5$ $[M+Na]^+$: 257.0420; found: 257.0424.

*Methyl 6-acetyl-3-hydroxybenzofuran-2-carboxylate (**6b**)*. White solid, 75% yield; mp 162 °C; ^{1}H NMR (400 MHz, CD_3SOCD_3): δ 11.05 (s, 1H), 8.15 (s, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 3.85 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3): δ 197.4, 159.4, 152.2, 146.5, 136.8, 129.3, 125.3, 122.2, 121.3, 112.8, 51.5, 27.0; HRMS (ESI): calc. for $C_{12}H_{10}NaO_5$ $[M+Na]^+$: 257.0420; found: 257.0425.

General Procedure for Preparation of Compounds 7 (7a as a model). A solution of **6a** (234 mg, 1 mmol), LiOH H_2O (168 mg, 4.0 mmol), DMSO (3 mL) and H_2O (2 mL) were stirred at 75 ˚C for 3 h. After being cooled to ambient temperature, the mixture was added water and adjusted pH = 1-2 with aqueous hydrochloric acid (1.0 N). The mixture was filtered and dried to give **7a** (137 mg, 78%) as a pale yellow solid.

*5-Acetylbenzofuran-3(2H)-one (**7a**)*. Pale yellow solid, 78% yield; mp 139-140 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (dd, J_1 = 1.8 Hz, J_2 = 8.8 Hz, 1H), 8.22 (d, J = 1.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 4.71 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 196.0, 176.8, 138.0, 131.9, 125.6, 121.2, 114.3, 76.0, 26.6; HRMS (ESI): calc. for $C_{10}H_8NaO_3$ $[M+Na]^+$: 199.0366; found: 199.0368.

*6-Acetylbenzofuran-3(2H)-one (**7b**)*. Pale yellow solid, 63% yield; mp 120 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 4.69 (s, 2H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 197.2, 174.0, 144.9, 124.6, 124.4, 121.9, 113.7, 75.6, 27.4; HRMS (ESI): calc. for $C_{10}H_8NaO_3$ $[M+Na]^+$: 199.0366; found: 199.0371.

*7-Acetylbenzofuran-3(2H)-one (**7c**)*. Pale yellow solid, 53% yield; mp 144 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, J_1 = 1.5 Hz, J_2 = 7.7 Hz, 1H), 7.85 (dd, J_1 = 1.5 Hz, J_2 = 7.7 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 4.74 (s, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 195.2, 172.4, 138.5, 129.4, 124.2, 123.0, 122.4, 75.1, 31.4; HRMS (ESI): calc. for $C_{10}H_8NaO_3$ $[M+Na]^+$: 199.0366; found: 199.0365.

General Procedure for Preparation of Compounds 1 (1a as a model). To a stirred solution of acetone (15 mL) and basic alumina (816 mg, 8 mmol, 10 equiv.) was added dropwise **7a** (137 mg, 1 mmol), and the resulting mixture was stirred at room temperature for about 30 min. The reaction mixture was monitored by TLC (Thin Layer Chromatography) analysis, and the reaction mixture was filtered and concentrated under reduced pressure when the substrate disappeared. Then the residue was purified by silica gel chromatography using petroleum ether /ethyl acetate = 2:1 as an eluent to give **1a** (117 mg, 50%) as a pale yellow solid.

*5-Acetyl-2-(2-hydroxypropan-2-yl)benzofuran-3(2H)-one (**1a**)*. Pale yellow solid, 50% yield; mp 139 ˚C; ^{1}H NMR (400MHz, $CDCl_3$): δ 8.28 (d, J = 8.8 Hz, 1H), 8.20 (s, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.47 (s, 1H), 2.97 (s, 1H), 2.57 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 196.0, 175.6, 138.4, 132.0, 125.8, 121.9, 114.0, 90.8, 72.7, 26.6, 25.6, 24.7; HRMS (ESI): calc. for $C_{13}H_{14}NaO_4$ $[M+Na]^+$: 257.0784; found: 257.0784.

*6-Acetyl-2-(2-hydroxypropan-2-yl)benzofuran-3(2H)-one (**1b**)*. Pale yellow solid, 47% yield; mp 84 ˚C; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 4.43 (s, 1H), 2.62 (s, 3H), 1.34 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 197.1, 172.9, 145.2, 125.0, 124.7, 122.0, 113.3, 90.3, 72.8, 27.3, 25.6, 24.7; HRMS (ESI): calc. for $C_{13}H_{14}NaO_4$ $[M+Na]^+$: 257.0784; found: 257.0783.

*7-Acetyl-2-(2-hydroxypropan-2-yl)benzofuran-3(2H)-one (**1c**)*. Pale yellow solid, 45% yield; mp 107 ˚C; ^{1}H NMR (400MHz, $CDCl_3$): δ 8.20 (dd, J_1 = 1.5 Hz, J_2 = 7.6 Hz, 1H), 7.84 (dd, J_1 = 1.5 Hz, J_2 = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 4.49 (s, 1H), 2.72 (s, 3H), 1.43 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 195.0, 171.3, 138.8, 129.6, 123.8, 123.6, 122.6, 89.8, 72.7, 31.5, 26.0, 24.9; HRMS (ESI): calc. for $C_{13}H_{14}NaO_4$ $[M+Na]^+$: 257.0784; found: 257.0785.

Procedure for Preparation of Compounds 9. A 50 mL Schlenk-type tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) followed by **8** (0.5 mmol), benzoquinone (54.0 mg, 0.5 mmol), KOAc (98.0 mg, 1 mmol) and *N,N*-dimethylacetamide (1.5 mL). The reaction tube was evacuated and back-filled with O_2 (3 times, balloon). After the reaction mixture was stirred at 115 ˚C for 24 h, it was allowed to cool to ambient temperature. The reaction mixture was diluted with ethyl acetate and water and then filtered through a small pad of Celite. The filtrate was washed with aqueous HCl (1.0 N, 5 mL) and brine (5 mL, twice). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel flash column chromatography to give the corresponding product **9**.

*4-Acetyl-2-hydroxybenzoic acid (**9**)*. White solid, 51% yield; mp 201 ˚C; ^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (d, J = 7.3 Hz, 1H), 7.52-7.40 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 199.7, 172.9, 163.2, 144.0, 132.1, 119.4, 118.1, 117.7, 27.1; HRMS (ESI): calc. for $C_9H_7O_4$ $[M–H]^–$: 179.0350; found: 179.0354.

Procedure for Preparation of Compounds 4b. To a solution of **9** (900 mg, 5 mmol) in CH_3OH (25 mL) was added dropwise concentrated sulfuric acid (10 drops). After stirring under reflux for 12 h, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, and brine, and dried with Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether /ethyl acetate = 4/1) to afford **4b** (970 mg, 93%) as a white solid.

*Methyl 4-acetyl-2-hydroxybenzoate (**4b**)*. White solid, 93% yield; mp 86 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.74 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.40 (dd, J_1 = 1.6 Hz, J_2 = 8.3 Hz, 1H), 3.95 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 170.1, 161.7, 142.8, 130.5, 118.4, 117.9, 115.8, 52.9, 27.1; HRMS (ESI): calc. for $C_{10}H_{10}NaO_4$ $[M+Na]^+$: 217.0471; found: 217.0476.

Procedure for Preparation of Compounds 13. To a solution of **11** (830 mg, 5 mmol) in CH_3OH (25 mL) was added dropwise concentrated sulfuric acid (10 drops). After stirring under reflux for 12 h, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, and brine, and dried with Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether /ethyl acetate = 4/1) to afford **12** (855 mg, 95%) as a colorless oil.

K_2CO_3 (276 mg, 2 mmol) and methyl 2-bromopropionate (334 mg, 2 mmol) were added to a solution of **12** (360 mg, 2 mmol) in dry DMF (3 mL). After stirring at room temperature for 12 h, the mixture was diluted with ethyl acetate (5 mL), washed with 1 N HCl (5 mL), and dried (Na_2SO_4). The organic layer was then concentrated and the crude residue was puri-

fied by column chromatography using petroleum ether /ethyl acetate = 5:1 as eluent to give **13** (505 mg, 95%) as a colorless oil.

*Methyl 5-ethyl-2-((1-methoxy-1-oxopropan-2-yl)oxy) benzoate (**13**)*. Colorless oil, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 2.3 Hz, 1H), 7.20 (dd, J_1 = 2.3 Hz, J_2 = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 4.71 (q, J =6.8 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 2.57 (q, J = 7.6 Hz, 2H), 1.62 (d, J = 6.8 Hz, 3H), 1.18 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 166.9, 155.4, 137.9, 132.9, 131.2, 121.6, 116.2, 75.1, 52.5, 52.2, 28.0, 18.8, 15.7; HRMS (ESI): calc. for $C_{14}H_{18}NaO_5$ $[M+Na]^+$: 289.1046; found: 289.1045.

Procedure for Preparation of Compounds 14. K_2CO_3 (69 mg, 0.5 mmol) was added to a solution of **13** (266 mg, 1 mmol) in DMF (1.0 mL) and MeOH (0.5 mL). The mixture was heated at 170 ˚C for 10 min under stirring and 300 W microwave irradiation power. After cooling to ambient temperature, the mixture was diluted with ethyl acetate (5 mL). The resulting organic layer was washed with 1 N HCl (5 mL) and dried (Na_2SO_4). The organic layer was then concentrated and purified by column chromatography using petroleum ether /ethyl acetate = 70:1 as eluent to give **14** (82 mg, 47%) as a colorless oil.

*5-Ethyl-2-methylbenzofuran-3(2H)-one (**14**)*. Colorless oil, 47% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.42 (m, 2H), 7.02 (dd, J_1 = 1.0 Hz, J_2 = 8.1 Hz, 1H), 4.62 (q, J = 7.2 Hz, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.51 (d, J = 7.2 Hz, 3H), 1.23 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8, 171.2, 138.6, 138.1, 122.6, 120.4, 113.3, 82.2, 28.2, 16.5, 15.8; HRMS (ESI): calc. for $C_{11}H_{12}NaO_2$ $[M+Na]^+$: 199.0730; found: 199.0731.

Procedure for Preparation of Compound 10a. To a solution of CrO_3 (800 mg, 9 mmol) in Ac_2O (3 mL) and AcOH (1.5 mL) was added dropwise a suspension of the **14** (176 mg, 1 mmol) in AcOH (1.5 mL) at 0 ˚C over 10 min. The reaction mixture was stirred at 0 ˚C for 10 min, and poured into ice-water (40 mL) and then was extracted with $CHCl_3$. The combined organic layer was washed with water, saturated aqueous $NaHCO_3$ solution, and brine, and dried over Na_2SO_4. The crude mixture was purified by flash chromatography (petroleum ether /ethyl acetate = 5/1) to afford **10a** (67 mg, 35%) as a colorless solid.

*5-Acetyl-2-methylbenzofuran-3(2H)-one (**10a**)*. Colorless oil, 35% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (dd, J_1 = 1.9 Hz, J_2 = 8.8 Hz, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 4.74 (q, J = 7.2 Hz, 1H), 2.58 (s, 3H), 1.55 (d, J =7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 196.1, 175.3, 138.2, 131.8, 126.1, 120.5, 114.2, 83.5, 26.6, 16.5; HRMS (ESI): calc. for $C_{11}H_{10}NaO_3$ $[M+Na]^+$: 213.0522; found: 213.0522.

Procedure for Preparation of Compound 15b. To a stirred solution of acetone (10 mL) and basic alumina (816 mg, 8 mmol, 10 equiv.) was added dropwise **7a** (142 mg, 0.8 mmol) and the resulting mixture was stirred at room temperature for about 2 h. The reaction mixture was monitored by TLC analysis, and the reaction mixture was filtered and concentrated under reduced pressure when the substrate disappeared. Then the residue was purified by silica gel chromatography using petroleum ether /ethyl acetate = 3:1 as an eluent to give **15b** (113 mg, 65%) as a pale yellow solid.

*5-Acetyl-2-(propan-2-ylidene)benzofuran-3(2H)-one (**15b**)*. Pale yellow solid, 65% yield; mp 153 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 1.3 Hz, 1H), 8.23 (dd, J_1 = 1.3 Hz, J_2 = 8.7 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 2.58 (s, 3H), 2.35 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 183.2, 167.1, 145.6, 136.3, 134.3, 132.1, 125.7, 123.5, 113.2, 26.7, 20.5, 17.8; HRMS (ESI): calc. for $C_{13}H_{12}NaO_3$ $[M+Na]^+$: 239.0679; found: 239.0680.

Procedure for Preparation of Compound 10b. To a solution of Pd/C (10%) in $CHCl_3$ (5 mL) and CH_3CH_2OH (5 mL), **15b** (108 mg, 0.5 mmol) was added. The reaction was stirred at room temperature and back-filled with H_2 (3 times, balloon). After 20 min, the reaction mixture was filtered with 15 mL of ethyl acetate and concentrated under reduced pressure. Then the residue was purified by silica gel chromatography using petroleum ether /ethyl acetate = 5:1 as an eluent to give **10b** (43 mg, 20%) as a colorless oil.

*5-Acetyl-2-isopropylbenzofuran-3(2H)-one (**10b**)*. Colorless oil, 20% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, J_1 = 1.8 Hz, J_2 = 8.8 Hz, 1H), 8.19 (d, J = 1.8 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 4.50 (d, J = 3.8 Hz, 1H), 2.56 (s, 3H), 2.41-2.31 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 196.1, 176.0, 138.0, 131.6, 125.7, 121.8, 113.9, 91.2, 31.2, 26.6, 18.9, 15.8; HRMS (ESI): calc. for $C_{13}H_{14}NaO_3$ $[M+Na]^+$: 241.0835; found: 241.0839.

Procedure for Preparation of Compound 15c. Benzaldehyde (127 mg, 1.2 mmol, 1.5equiv.) and basic alumina (816 mg, 8 mmol, 10 equiv.) were added to a solution of **7a** (142 mg, 0.8 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for about 2 h. The reaction mixture was monitored by TLC analysis, and the reaction mixture was filtered and concentrated under reduced pressure when the substrate disappeared. Then the residue was purified by silica gel chromatography using CH_2Cl_2/CH_3OH/$(CH_3)_2CO$ = 200/1/1) as an eluent to give **15c** (126 mg, 60%) as a pale yellow solid.

*(Z)-5-acetyl-2-benzylidenebenzofuran-3(2H)-one(**15c**)*. Pale yellow solid, 60% yield; mp 192 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 1.7 Hz, 1H), 8.34 (dd, J_1 = 1.9 Hz, J_2 = 8.7 Hz, 1H), 7.93-7.89 (m, 2H), 7.50-7.38 (m, 4H), 6.95(s, 1H), 2.63(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 184.1, 168.7, 147.2, 137.1, 133.2, 132.0, 130.7, 129.2, 129.2, 126.0, 121.8, 114.9, 113.6, 26.8; HRMS (ESI): calc. for $C_{17}H_{12}NaO_3$ $[M+Na]^+$: 287.0679; found: 287.0682.

Procedure for Preparation of Compound 10c. To a solution of Pd/C (10%) in $CHCl_3$ (5 mL) and CH_3CH_2OH (5 mL), **15c** (106 mg, 0.4 mmol) was added. The reaction was stirred at room temperature and back-filled with H_2 (3 times, balloon). After 20 min, the reaction mixture was filtered with 15 mL of ethyl acetate and concentrated under reduced pressure. Then the residue was purified by silica gel chromatography using petroleum ether /ethyl acetate = 5:1 as an eluent to give **10c** (16 mg, 15%) as a colorless oil.

*5-Acetyl-2-benzylbenzofuran-3(2H)-one (**10c**)*. Colorless oil, 15% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, J_1 = 1.9 Hz, J_2 = 8.8 Hz, 1H), 8.18 (d, J = 1.7 Hz, 1H), 7.29-7.19 (m, 5H), 7.14 (d, J = 8.8 Hz, 1H), 4.91 (dd, J_1 = 3.8 Hz, J_2 = 8.0 Hz, 1H), 3.38 (dd, J_1 = 3.8 Hz, J_2 = 14.7 Hz, 1H), 3.06 (dd, J_1 = 8.0 Hz, J_2 = 14.7 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 196.0, 175.4, 138.1, 135.4, 131.7, 129.6, 128.7, 127.3, 125.8, 121.0, 114.0, 87.2, 37.4, 26.5;

HRMS (ESI): calc. for $C_{17}H_{14}NaO_3$ $[M+Na]^+$: 289.0835; found: 289.0833.

Procedure for Preparation of Compound 15d. Furfural (115 mg, 1.2 mmol) and basic alumina (816 mg, 8 mmol) were added to a solution of **7a** (142 mg, 0.8 mmol) in CH_2Cl_2 (10 mL). the resulting mixture was stirred at room temperature for about 2 h. The reaction mixture was monitored by TLC analysis, and the reaction mixture was filtered and concentrated under reduced pressure when the substrate disappeared. Then the residue was purified by silica gel chromatography using CH_2Cl_2/CH_3OH/$(CH_3)_2CO$) = 200/1/1) as an eluent to give **15d** (142 mg, 70%) as a pale yellow solid.

*(Z)-5-acetyl-2-(furan-2-ylmethylene)benzofuran-3(2H)-one (**15d**)*. Pale yellow solid, 70% yield; mp 194-195 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 1.7 Hz, 1H), 8.31 (dd, J_1 = 1.7 Hz, J_2 = 8.7 Hz, 1H), 7.63 (d, J = 1.7 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.14 (d, J = 3.5 Hz, 1H), 6.93 (s, 1H), 6.60 (dd, J_1 = 1.7 Hz, J_2 = 3.5 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 183.2, 168.2, 148.6, 146.2, 145.3, 136.8, 133.2, 125.8, 122.2, 118.5, 113.6, 113.5, 103.1, 26.7; HRMS (ESI): calc. for $C_{15}H_{10}NaO_4$ $[M+Na]^+$: 277.0471; found: 277.0473.

Procedure for Preparation of Compound 10d. To a solution of Pd/C (10%) in $CHCl_3$ (5 mL) and CH_3CH_2OH (5 mL), **15d** (102 mg, 0.4 mmol) was added. The reaction was stirred at room temperature and back-filled with H_2 (3 times, balloon). After 20 min, the reaction mixture was filtered with 15 mL of ethyl acetate and concentrated under reduced pressure. Then the residue was purified by silica gel chromatography using petroleum ether /ethyl acetate = 5:1 as an eluent to give **10d** (17 mg, 17%) as a colorless oil.

*5-Acetyl-2-(furan-2-ylmethyl)benzofuran-3(2H)-one (**10d**)*. Colorless oil, 17% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, J_1 = 1.8 Hz, J_2 = 8.8 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.24 (dd, J_1 = 1.9 Hz, J_2 = 3.0 Hz, 1H), 6.13 (d, J = 3.0 Hz, 1H), 4.92 (dd, J_1 = 4.0 Hz, J_2 = 7.7 Hz, 1H), 3.39 (dd, J_1 = 4.0 Hz, J_2 = 15.8 Hz, 1H), 3.11 (dd, J_1 = 7.7 Hz, J_2 = 15.8 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 196.0, 175.5, 149.5, 142.2, 138.2, 131.9, 125.9, 120.8, 114.2, 110.6, 108.1, 85.0, 30.2, 26.6; HRMS (ESI): calc. for $C_{15}H_{12}NaO_4$ $[M+Na]^+$: 279.0628; found: 279.0629.

Optimization of Reaction Conditions for DKR-ATH of 1a. 1.0 mmol **1a**, 5.0 mmol sodium formate, 5.0 μmol catalyst and 0.2 mmol PTC were added into 4 mL CH_3OH and the mixture was stirred at 65 ˚C under argon for 12 h. During that time, the reaction was monitored constantly by TLC. After completion of the reaction, 5 mL Saturated sodium chloride solution was added to the mixture, which was extracted by CH_2Cl_2 (3 × 5.0 mL). The combined organic layer was dehydrated with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography.

General Procedure for Preparation of Compounds 2. 1.0 mmol **1a**, 5.0 mmol sodium formate, 5.0 μmol catalyst **3a** and 0.2 mmol CTAB were added into 4 mL CH_3OH and the mixture was stirred at 65 ˚C under an atmosphere of argon for 12 h. During that time, the reaction was monitored constantly by TLC analysis. After completion of the reaction, 5 mL Saturated sodium chloride solution was added to the mixture, which was extracted by CH_2Cl_2 (3 × 5.0 mL). The combined organic layer was dehydrated with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (Petroleum ether /ethyl acetate = 2/1) afforded **2a** (including the minor enantiomer). Other samples **2b-2c** were prepared as the same procedure.

*(2R,3S)-5-((S)-1-hydroxyethyl)-2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-3-ol (**2a**)*. White solid, 63% yield; mp 169-170 ˚C; 99% *ee*, 98/2 *dr*; ^{1}H NMR (400 MHz, CD_3OD): δ 7.38 (br s, 1H), 7.24 (dd, J_1 = 1.7 Hz, J_2 = 8.3 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 5.28 (d, J = 6.0 Hz, 1H), 4.79 (q, J = 6.4 Hz, 1H), 4.20 (d, J = 6.0 Hz, 1H), 3.34 (s, 1H), 1.48 (s, 3H), 1.42 (s, 3H) 1.41 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 160.6, 140.4, 131.2, 129.0, 124.0, 110.9, 91.4, 73.6, 73.4, 70.9, 27.3, 26.8, 25.8; HRMS (ESI): calc. for $C_{13}H_{18}NaO_4$ $[M+Na]^+$: 261.1097; found: 261.1097. HPLC (DAICEL CHIRALPAK® IA column, eluent: Hexanes/i-PrOH =92/8, detector: 280 nm, flow rate: 0.5 mL/min, 35 ˚C): t_R = 46.693 min.

*(2R,3S)-6-((R)-1-hydroxyethyl)-2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-3-ol (**2b**)*. White solid, 31% yield; mp 139-140 ˚C; 96% *ee*, >99/1 *dr*; ^{1}H NMR (400 MHz, CD_3OD): δ 7.30 (d, J = 7.6 Hz, 1H), 6.94-6.90 (m, 1H), 6.89 (s, 1H), 5.27 (d, J = 6.0 Hz, 1H), 4.78 (q, J = 6.5 Hz, 1H), 4.20 (d, J = 6.0 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.40 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz CD_3OD): δ 161.6, 150.9, 130.1, 126.5, 119.4, 108.3, 91.5, 73.4, 73.4, 71.0, 27.3, 26.8, 25.9; HRMS (ESI): calc. for $C_{13}H_{18}NaO_4$ $[M+Na]^+$: 261.1097; found: 261.1097. HPLC (DAICEL CHIRALPAK® IA column, eluent: Hexanes/i-PrOH =92/8, detector: 280 nm, flow rate: 0.5 mL/min, 35 ˚C): t_R = 71.917 min (major), t_R= 67.444 min (minor).

*(2R,3S)-7-((R)-1-hydroxyethyl)-2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-3-ol (**2c**)*. Colorless oil, 50% yield, 95%*ee*, >99/1 *dr*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.20 (m, 2H), 6.88 (t, J = 7.4 Hz, 1H), 5.21 (d, J = 6.0 Hz, 1H), 5.04 (q, J = 6.5 Hz, 1H), 4.08 (d, J = 6.0 Hz, 1H), 1.49-1.44 (m, 6H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 129.6, 128.0, 126.9, 124.6, 121.5, 89.2, 73.0, 72.7, 64.2, 28.0, 26.0, 22.0; HRMS (ESI): calc. for $C_{13}H_{18}NaO_4$ $[M+Na]^+$: 261.1097; found: 261.1095. HPLC (DAICEL CHIRALPAK® IA column, eluent: Hexanes/i-PrOH =92/8, detector: 280 nm, flow rate: 0.5 mL/min, 35 ˚C): t_R = 32.640 min (major), t_R= 29.140 min (minor).

General Procedure for Preparation of Compound 16. 1.0 mmol **10**, 5.0 mmol sodium formate, 5.0 μmol catalyst **3a** and 0.2 mmol CTAB were added into 4 mL CH_3OH and the mixture was stirred at 65 ˚C under an atmosphere of argon for 12 h. During that time, the reaction was monitored constantly by TLC analysis. After completion of the reaction, 5 mL Saturated sodium chloride solution was added to the mixture, which was extracted by CH_2Cl_2 (3 × 5.0 mL). The combined organic layer was dehydrated with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (Petroleum ether /ethyl acetate = 2/1) afforded **16** (including the minor enantiomer).

*(2S,3S)-5-((R)-1-hydroxyethyl)-2-methyl-2,3-dihydro-benzofuran-3-ol (**16a**)*. White solid, 79% yield; mp 92-93 ˚C; 91% *ee*, >99/1 *dr*; ^{1}H NMR (400 MHz, CD_3OD, 3.1:1 mixture of rotamers): δ 7.40 (br s, 1H), 7.22 (dd, J_1 = 1.8 Hz, J_2 = 8.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 4.98 (d, J = 6.0 Hz, 1H), 4.78 (q, J = 6.5 Hz, 1H), 4.61-4.52 (m, 1H), 1.45 (d, J = 6.5 Hz, 3H), 1.41 (d, J = 6.5 Hz, 0.73H), 1.41 (d, J = 6.5 Hz, 2.26H); ^{13}C NMR (100 MHz, CD_3OD, mixture of rotamers): δ 160.7, 160.4, 140.2, 140.2, 130.9, 130.9, 129.0, 128.9, 124.5,

124.3, 110.7, 110.7, 88.6, 84.9, 79.3, 73.6, 70.9, 70.8, 25.8, 25.8, 19.6, 14.1; HRMS (ESI): calc. for $C_{11}H_{14}NaO_3$ $[M+Na]^+$: 217.0835; found: 217.0836. HPLC (DAICEL CHIRALPAK® IA column, eluent: Hexanes/i-PrOH =85/15, detector: 280 nm, flow rate: 0.5 mL/min, 35 ˚C): t_R = 16.421 min (major), t_R= 17.479 min (minor).

(2S,3S)-5-((R)-1-hydroxyethyl)-2-isopropyl-2,3-dihydro-benzofuran-3-ol ***(16b)***. White solid, 87% yield; mp: 105-106 ˚C; 94% *ee*, >99/1 *dr*; ^{1}H NMR (400 MHz, CD_3OD, 3:1 mixture of rotamers): δ 7.40 (d, *J* = 1.7 Hz, 1H), 7.22 (dd, J_1 = 1.7 Hz, J_2 = 8.3 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 4.99 (d, *J* = 5.4 Hz, 1H), 4.78 (q, *J* = 6.5 Hz, 1H), 3.87 (dd, J_1 = 5.4 Hz, J_2 = 10.2 Hz, 1H), 2.31-2.17 (m, 1H), 1.41 (d, *J* = 6.5 Hz, 0.72H), 1.41 (d, *J* = 6.5 Hz, 2.16H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD, major rotamer): δ 160.9, 140.3, 131.7, 129.1, 124.4, 110.9, 94.7, 72.6, 71.1, 28.8, 26.0, 20.6, 19.9; HRMS (ESI): calc. for $C_{13}H_{18}NaO_3$ $[M+Na]^+$: 245.1148; found: 245.1149. HPLC (DAICEL CHIRALPAK® IA column, eluent: Hexanes/i-PrOH =92/8, detector: 280 nm, flow rate: 0.5 mL/min, 35 ˚C): t_R = 25.972 min (major), t_R= 30.824 min (minor).

(2S,3S)-2-benzyl-5-((R)-1-hydroxyethyl)-2,3-dihydro-benzofuran-3-ol ***(16c)***. Colorless oil, 82% yield, 85% *ee*, >99/1 *dr*; ^{1}H NMR (400 MHz, CD_3OD, 3:1 mixture of rotamers): δ 7.42 (d, *J* = 1.6 Hz, 1H), 7.40-7.37 (m, 1H), 7.37 (s, 1H), 7.33-7.27 (m, 2H), 7.25-7.18 (m, 2H), 6.74 (d, *J* = 8.3 Hz, 1H), 5.02 (d, *J* = 5.8 Hz, 1H), 4.78 (q, *J* = 6.5 Hz, 1H), 4.63-4.55 (m, 1H), 3.21 (dd, J_1 = 5.4 Hz, J_2 = 14.3 Hz, 1H), 3.09 (dd, J_1 = 8.6 Hz, J_2 = 14.3 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 0.74H), 1.41 (d, *J* = 6.5 Hz, 2.22H); ^{13}C NMR (100 MHz, CD_3OD, major rotamer): δ 159.2, 139.0, 138.8, 129.7, 129.2, 128.1, 127.6, 126.1, 123.0, 109.5, 88.2, 71.7, 69.5, 34.5, 24.5; HRMS (ESI): calc. for $C_{17}H_{18}NaO_3$ $[M+Na]^+$: 293.1148; found: 293.1146. HPLC (DAICEL CHIRALPAK® IA column, eluent: Hexanes/i-PrOH =90/10, detector: 280 nm, flow rate: 0.5 mL/min, 35 ˚C): t_R = 32.286 min (major), t_R= 40.577 min (minor).

(2S,3S)-2-(furan-2-ylmethyl)-5-((R)-1-hydroxyethyl)-2,3-dihydrobenzofuran-3-ol ***(16d)***. Colorless oil, 90% yield, 92% *ee*, >99/1 *dr*; ^{1}H NMR (400 MHz, CD_3OD, 3:1 mixture of rotamers): δ 7.43-7.38 (m, 2H), 7.23 (dd, J_1 = 1.9 Hz, J_2 = 8.3 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.35-6.33 (m, 1H), 6.23-6.20 (m, 1H), 5.07 (d, *J* = 5.8 Hz, 1H), 4.78 (q, *J* = 6.5 Hz, 1H), 4.72-4.66 (m, 1H), 3.22 (dd, J_1 = 5.6 Hz, J_2 = 15.6 Hz, 1H), 3.13 (dd, J_1 = 8.4 Hz, J_2 = 15.6 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 0.76H), 1.41 (d, *J* = 6.5 Hz, 2.28H); ^{13}C NMR (100 MHz, CD_3OD, major rotamer): δ 158.9, 152.4, 141.1, 139.0, 129.3, 127.5, 122.9, 110.0, 109.3, 106.2, 85.1, 71.5, 69.3, 27.1, 24.3; HRMS (ESI): calc. for $C_{15}H_{16}NaO_4$ $[M+Na]^+$: 283.0941; found: 283.0941. HPLC (DAICEL CHIRALPAK® IA column, eluent: Hexanes/i-PrOH =85/15, detector: 280 nm, flow rate: 0.5 mL/min, 35 ˚C): t_R = 21.590 min (major), t_R= 24.028 min (minor).

General Procedure for Preparation of Racemic Compounds 2. To a solution of **1a** (117 mg, 0.5 mmol) in MeOH (2 mL) at 0°C was added $NaBH_4$ (37.8 mg, 1 mmol) in batches. The resulting mixture was stirred under for 2 h and then quenched with aq 1N HCl. After concentration, the mixture was extracted with ethyl acetate. The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (Petroleum ether /ethyl acetate = 2/1) afforded the racemic **2a**. Other racemic samples **2b-2c** and **16a-16d** were prepared as the same procedure.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra, HPLC chromatograms, X-ray data (PDF), X-ray crystallographic data for **2a** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: 2002flz@163.com

ORCID:

Lizhen Fang: 0000-0001-8594-4710

Notes

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