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To be cited as: *ChemCatChem* 10.1002/cctc.201700695

Link to VoR: http://dx.doi.org/10.1002/cctc.201700695

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10.1002/cctc.201700695

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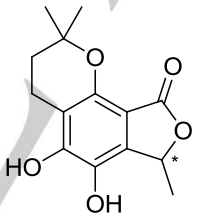
Ruthenium-Catalyzed Enantioselective Hydrogenation/Lactonization of 2-Acylarylcarboxylates：Direct Access to Chiral 3-Substituted Phthalides

Bin Lu,[a] Mengmeng Zhao,[a] Guangni Ding,[a] Xiaomin Xie,[a] Lili Jiang,[a] Virginie Ratovelomanana-Vidal,[c] and Zhaoguo Zhang*[a,b]

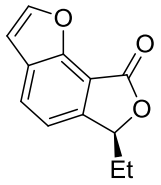
Abstract: Highly enantioselective tandem hydrogenation/lactonization of various 2-acylarylcarboxylates including 2-aroylarylcarboxylates were realized using [RuCl(benzene)(*S*)-SunPhos]Cl as catalyst under mild reaction conditions. Excellent enantioselectivities (up to 99.6% *ee*) and activities (S/C = 1000) were obtained. This convenient and practical method enables a direct access to a series of highly optically pure 3-substituted phthalides that are very important molecules as valuable pharmacological compounds and diversified synthons for medicinal chemistry. Moreover, a gram-scale reaction was performed to further demonstrate the practicality of this approach.

Introduction

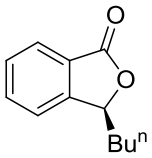
Optically active 3-substituted phthalides (1(3*H*)-isobenzofuranones) are not only very useful molecules as precious pharmacological compounds, but also key structural motif in many natural products and biologically active compounds (Figure 1).[1] Over the past decades, a variety of approaches have been developed for the asymmetric synthesis of chiral 3-substituted phthalides, including nucleophilic addition/cyclization,[2] intramolecular ketone hydroacylation,[3] asymmetric reduction/lactonization,[4] and other methods.[1g, 5] Among them, catalytic methods seem to be the most atom economic and therefore are of particular interest. Consequently, catalytic asymmetric reduction/lactonization of 2-acylarylcarboxylate compounds represents an attractive and elegant strategy for optically pure phthalide synthesis. Nevertheless to date, only a handful of relevant reports including asymmetric hydroboration,[4c, 4d] and transfer hydrogenation[4j, 4k, 4m, 4n] followed by lactonization have been realized. Among these two direct reduction/lactonization routes, the asymmetric hydroboration aforementioned suffered from limited range of substrates and poor efficiency (catalyst loading was 50 mol%). Although excellent enantioselectivity was obtained through transfer hydrogenation, the catalytic activity was need to be further improved for its practical application. Accordingly, there still remains a significant need for a more effective and highly enantioselective reduction/lactonization process to optically pure 3-substituted phthalides.



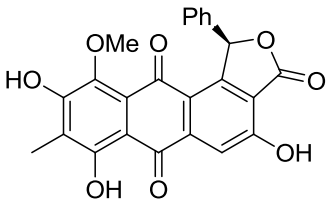
Fuscinarin



(-)-Concentricolide



(*S*)-3-n-Butylphthalide



Basidifferquinone A

Figure 1. Selected examples of natural occurring chiral 3-substituted phthalides.

Asymmetric hydrogenation of prochiral ketones using clean dihydrogen and small amount of chiral transition metal complex is considered as one of the most direct, efficient and economical strategies to produce various optically active alcohols both from academic and industrial points of view.[6] Because of its great significance, much effort has been devoted

[a] *B. Lu, M. Zhao, G. Ding, Dr. X. Xie, L, Jiang, Prof. Z. Zhang*
School of Chemistry and Chemical Engineering
Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (P.R. China)
Fax: (+86)21-5474-8925
E-mail: zhaoguo@sjtu.edu.cn
[b] *Prof. Z. Zhang*
Shanghai Institute of Organic Chemistry
Chines Academy of Sciences
345 Lingling Road, Shanghai 200032 (P.R. China)
[c] *Dr. V. Ratovelomanana-Vidal*
Institut de Recherche de Chimie Paris
PSL Research University, Chimie ParisTech–CNRS
11 rue Pierre et Marie Curie
75005 Paris, (France)

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to this important transformation and some catalytic systems have been investigated to achieve high efficiency and enantioselectivity.[7] For the Ru-catalyzed enantioselective hydrogenation of functionlized ketones, the evolutionary breakthrough was achieved by Noyori and co-workers in 1980s using the chiral Ru-BINAP catalytic system.[8] Subsequently, numerous efficient chiral ruthenium-diphosphines catalysts have been emerged for the important transformation over the last decades, which not only provide abundant choices of catalytic systems, but also improve the activity and enantioselectivity of the hydrogenation of various functionlized ketones.[7a-d, 9] Consequently, the efficiency of this transformation has promoted greatly and the substrate scope has been expanded extensively today. However, to the best of our knowledge, only three examples regarding asymmetric hydrogenation of 2-acylarylcarboxylates have been reported, which can be attributed to the much lower reactivity of *γ*-ketoacid derivatives in a hydrogenation reaction compared to that of *α*- and *β*-ketoacid derivatives.[4g-i, 10] In 1988, Noyori and co-workers firstly described the asymmetric hydrogenation of the *o*-acetylbenzoic acid using Ru-BINAP catalyst followed by lactonization in situ to afford the 3-methylisobenzofuran-1(3*H*)-one with 92% *ee*.[4g] Two years later, this group also successfully realized the enantioselective hydrogenation/lactonization of the ethyl *o*-acetylbenzoate with 97% *ee*, catalyzed by 0.4 mol% $Ru(OCOCH_3)_2$[(*S*)-BINAP] in the presence of HCl at 100 atm for 165 h.[4h] In 2011, Zhou et al. applied the Ir-SpiroPAP catalyzed highly effective enantioselective hydrogenation/cyclization of ethyl 2-pentanoylbenzoate to synthesize 3-butylisobenzofuran-1(3*H*)-one with 99% *ee* at S/C = 10000.[4i] All three above were limited to a sole substrate, so there is still no more general and effecient catalytic system reported for the asymmetric hydrogenation of various 2-acylarylcarboxylates, especially for much less reactive 2-aroylarylcarboxylates. Therefore, using asymmetric hydrogenation to synthesize diversified chiral 3-substituted phthalides is still a significant and challenging work.

Our group has been focusing on the studies of the asymmetric hydrogenation and has designed some biaryl diphosphine ligands-SunPhos family which showed high efficiency and enantioselectivity for the hydrogenation of various functionlized ketones and simple ketones.[9d, 11] Herein, we report a convenient and efficient synthetic method for the synthesis of optically pure 3-substituted phthalides by the Ru-SunPhos catalyzed asymmetric hydrogenation/lactonization of 2-acylarylcarboxylates.

Results and Discussion

Considering that previous example regarding the asymmetric hydrogenation of ethyl 4-oxopentanoate using the $[NH_2Me_2][\{RuCl[(R)\text{-SegPhos}]\}_2(\mu\text{-}Cl)_3]$ catalytic system reported by Saito and co-workers, firstly we applied the $[NH_2Me_2][\{RuCl[(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl)_3]$ as catalyst for the asymmetric hydrogenation of methyl 2-acetylbenzoate (**1a**) serving as the model substrate. The reaction was initially carried out in MeOH containing 0.5 mol% of $[NH_2Me_2][\{RuCl[(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl)_3]$ under 40 atm of H_2 at 50 °C for 12 h. Unfortunately, incomplete conversion and poor yield was obtained in the reaction albeit of good enantioselectivity (Table 1 entry 1). However, when the [RuCl(benzene)(*S*)-SunPhos]Cl was employed as the catalyst, to our great delight, full reduction and subsequent in situ lactonization were realized affording optically pure **2a** with little amount of by-product **2a'** (Table 1, entry 2). The result was superior to that obtained by using other two Ru-diphosphines catalytic systems (Table 1, entry 2 vs. entries 3, 4). It is noteworthy that the reaction condition is much mild compared to that (100 atm, for 165 h) reported by Noyori using $Ru(BINAP)(OAc)_2$-HCl catalytic system. Additionally, a number of commercially available chiral diphosphines ligands (shown in Figure 2) were also tested under the same reaction conditions and the results are revealed in Table 1.

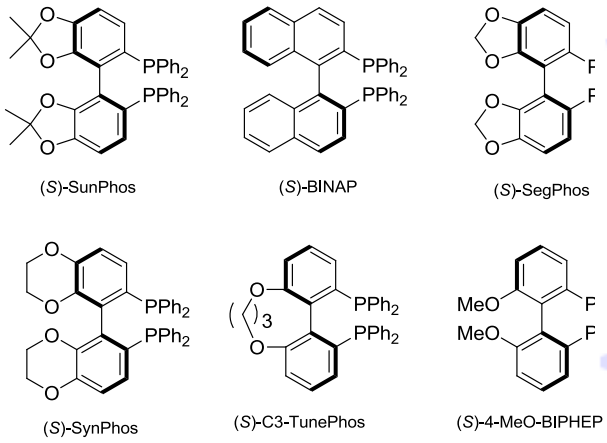
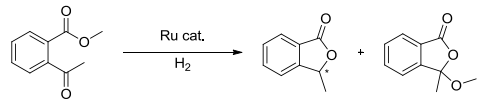


Figure 2. Structures of chiral bidentate ligands.

All the screened ligands showed excellent activity, and similar enantiomeric excess were obtained by using (*S*)-BINAP, (*S*)-SegPhos, (*S*)-SynPhos and (*S*)-4-MeO-BIPHEP as ligand (Table 1, entries 5-8, 99.0%-99.4% *ee*), which were higher than that of

(*S*)-C3-TunePhos (Table 1, entry 9, 85.8% *ee*). Based on the above results, the catalytic system [RuCl(benzene)(*S*)-SunPhos]Cl was the choice for this transformation.

Table 1. Effects of Ligands in Asymmetric Hydrogenation of 1a.[a]



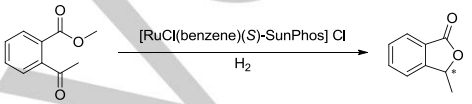
1a 2a 2a′

Entry	Ligand	**2a/2a′**[b]	*ee* [%][c]
1[d]	(*S*)-SunPhos	4/39	83.8
2[e]	(*S*)-SunPhos	99/1	99.6
3[f]	(*S*)-SunPhos	99/1	99.2
4[g]	(*S*)-SunPhos	92/8	97.0
5[e]	(*S*)-BINAP	99/1	99.0
6[e]	(*S*)-SegPhos	98/2	99.2
7[e]	(*S*)-SynPhos	99/1	99.2
8[e]	(*S*)-4-MeO-BIPHEP	99/1	99.4
9[e]	(*S*)-C3-TunePhos	98/2	85.8

[a] Unless otherwise stated, all reactions were carried out with a substrate (0.5 mmol) concentration of 0.5 M in MeOH under 40 atm of H_2 at 50°C for 12 h, substrate/catalyst = 200:1. Conversion: 100%. [b] Ratios were calculated from the NMR spectra. [c] Determined by HPLC on a Chiralpak OJ-H column. [d] $[NH_2Me_2][\{RuCl[(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl)_3]$. Conversion: 43%. [e] [RuCl(benzene)**L**]Cl. [f] [RuCl(cymene)(*S*)-SunPhos]Cl. [g] $RuCl_2[(S)\text{-SunPhos}](DMF)_n$

Next, the effect of solvent, temperature and hydrogenation pressure was explored and the results were summarized in Table 2. It has been known that solvent has a significant influence on the activity and enantioselectivity of the asymmetric hydrogenation. Changing the solvent from MeOH to other protic solvents including EtOH and *i*PrOH resulted in slightly decreased enantioselectivity (Table 2, entry 1 vs. entries 2, 3). When aprotic solvents such as CH_2Cl_2 and toluene were used, the reaction could hardly proceed (Table 2, entries 4, 5). The reactivity and enantioselectivity of the hydrogenation were also dependent on the reaction temperature. Higher reaction temperature led to a slight drop of the *ee* value (Table 2, entries 7, 8), while lower temperature dramatically reduced the reaction rate and moderately decreased the enantiomeric excess (Table 2, entry 6). Performing the reaction at a lower pressure resulted in slightly lower yields of the desired product 2a, though high enantioselectivities were remained (Table 2, entry 1 vs. entries 10, 11). On the basis of the above results, the optimized reaction conditions were using 0.5 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl as the catalyst, MeOH as the solvent with a substrate concentration of 0.5 M under 40 atm of H_2 at 50°C for 12 h.

Table 2. Optimization of Solvent, Temperature, Pressure.[a]



1a 2a

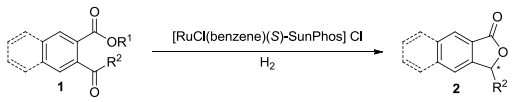
Entry	Solvent	*T*/°C	*P*/atm	Conv. [%][b]	*ee* [%][c]
1	MeOH	50	40	100	99.6
2	EtOH	50	40	100	99.2
3	*i*PrOH	50	40	100	99.0
4[d]	CH_2Cl_2	50	40	0	n.a.
5[d]	Toluene	50	40	0	n.a.
6	MeOH	30	40	57	98.4
7	MeOH	70	40	100	99.4
8	MeOH	90	40	100	99.0
9	MeOH	50	60	100	99.9
10[e]	MeOH	50	20	100	99.4
11[e]	MeOH	50	10	100	99.6

[a] All reactions were carried out with a substrate (0.5 mmol) concentration of 0.5 M in a specified solvent for 12 h, substrate/catalyst = 200:1. [b] Determined by NMR analysis and the ratio of **2a**/**2a′** = 99/1 without otherwise stated. [c] Determined by HPLC on a Chiralpak OJ-H column. [d] Starting material was recovered completely. [e] The ratio of **2a**/**2a′** = 95/5.

With the optimized reaction established, the substrate scope and limitations of the methodology were investigated and the results are depicted in Table 3. A variety of alkyl 2-acetylbenzoates and even the *o*-acetylbenzoic acid were hydrogenated smoothly followed by in situ lactonization to afford the corresponding phthalide with high yield and excellent enantioselectivity (Table 3, entries 1−4). The result

demonstrated that the bulkiness of the alcohol had no significant effect on the activity and enantioselectivity of the reaction. Moreover, it is notable that when the catalyst loading was further reduced to 0.1 mol%, the reaction also proceeded smoothly on gram-scale with excellent enantiofacial discrimination (Table 3, entries 5−6).

Table 3. Asymmetric Hydrogenation of 2-Acylarylcarboxylate.[a]



1a: R^1 = Me, R^2 = Me
1b: R^1 = Et, R^2 = Me
1c: R^1 = *i*Pr, R^2 = Me
1d: R^1 = H, R^2 = Me
1e: R^1 = Me, R^2 = Et
1f: R^1 = Me, R^2 = *n*Pr
1g: R^1 = Me, R^2 = *n*Bu
1h: R^1 = Me, R^2 = *i*Bu
1i: R^1 = Me, R^2 = *i*Pr
1j: Methyl 2-acetyl-5-methylbenzoate
1k: Methyl 2-acetyl-5-chlorobenzoate
1l: Methyl 3-acetyl-2-naphthoate
1m: R^1 = Me, R^2 = C_6H_5
1n: R^1 = H, R^2 = C_6H_5
1o: R^1 = Me, R^2 = *o*-$CH_3C_6H_5$
1p: R^1 = Me, R^2 = *p*-$OCH_3C_6H_5$
1q: R^1 = Me, R^2 = *p*-$CF_3C_6H_5$
1r: R^1 = Me, R^2 = Bn
1s: Methyl 2-benzoylcyclohexanecarboxylate

Entry	1	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	**1a**	100	95	99.6 (*S*)
2	**1b**	100	98	99.6 (*S*)
3	**1c**	100	98	99.2 (*S*)
4	**1d**	100	92	99.4 (*S*)
5[e]	**1a**	100	98	99.0 (*S*)
6[f]	**1d**	100	90	98.0 (*S*)
7	**1e**	100	94	99.6 (*S*)
8	**1f**	100	94	99.2 (*S*)
9	**1g**	100	96	99.4 (*S*)
10[g]	**1g**	100	97	98.2 (*S*)
11	**1h**	67	58	91.6
12	**1i**	0	0	n.a.
13	**1j**	100	98	99.0 (*S*)
14	**1k**	100	98	99.4 (*S*)
15	**1l**	100	98	99.4 (*S*)
16[h]	**1m**	100	95	98.2 (*S*)
17[h]	**1n**	100	95	96.2 (*S*)
18[i]	**1o**	83	75	99.2 (*S*)
19[i]	**1p**	100	89	33.8 (*S*)
20[h]	**1q**	100	98	99.4 (*S*)
21	**1r**	0	0	n.a.
22	**1s**	0	0	n.a.

[a] Unless otherwise stated, all reactions were carried out with a substrate (0.5 mmol) concentration of 0.5 M in MeOH under 40 atm of H_2 at 50°C for 12 h, substrate/catalyst = 200:1. [b] Determined by NMR analysis. [c] Isolated yield by column chromatography. [d] Determined by HPLC on a Chiralpak column. The absolute configuration was determined by comparison of the specific rotation or HPLC with reported data. [e] Substrate/catalyst = 1000:1. [f] Substrate/catalyst = 1000:1. Reaction using 1.23 g of **1d** at 40 atm of H_2 at 50 °C for 18 h. [g] Substrate/catalyst = 500:1. [h] Reaction time 15 h. [i] Under 60 atm of H_2 at 50°C for 48 h.

Additionally, almost the same enantioselectivities were obtained by the hydrogenation/cyclization of the substrates **1e**-**1g** possessing different carbon chain lengths of R^2 (Table 3, entries 7−9). This result indicated that the length of the linear alkyl carbon chain did not obviously affect the reaction activity and enantioselectivity. It is noteworthy that when the catalyst loading was lowered to 0.2 mol%, the substate **1g** could still be completely converted to the optically pure 3-*n*-butylphthalide, which was isolated from seeds of Apium graveolens and acts as a medical agent to treat brain-related neurological diseases such as cerebral ischemia (Table 3, entry 10).[1a-c] However, when R^2 was replaced by a larger alkyl group such as isobutyl, even though the asymmetric hydrogenation and subsequent in situ lactonization were still happened affording the desired product, incomplete conversion and obvious erosion of *ee* value were observed (58% yield, 91.6% *ee*, Table 3, entry 11). Moreover, the reaction failed with further increase of the steric hindrance of R^2 (Table 3, entry 12). It meant that the steric hindrance of the alkyl group R^2 plays an important role in the hydrogenation. To our delight, both of the substrates **1j** and **1k** were hydrogenated in full conversions with high enantiomeric excess, regardless of electronic properties on the 5-positions of the phenyl moiety (Table 3, entry 13 vs. entry 14). Surprisingly, the substrate **1l** containing other aromatic ring was also hydrogenated well providing the corresponding (*S*)-3-Methylnaphtho[2,3-c]furan-1(3*H*)-one (**2h**) in quantitative yield with 99.4% *ee* (Table 3, entry 15). The absolute configuration was unambiguously confirmed by X-ray analysis of **2h** (shown in Figure S1).[12]

Encouraged by the promising results above, the first time we attempted to expand the methodology to the more challenging 2-aroylarylcarboxylates (R^2 = aryl group). Therefore,

the methyl 2-benzoylbenzoate (**1m**) was subjected to the hydrogenation/lactonization reaction under the same catalyst system. Pleasingly, the desired product 3-phenylisobenzofuran-1(3*H*)-one was obtained in 95% yield with 98.2% *ee* (Table 3, entry 16). It deserved to be mentioned that the enantionselectivity is much higher and the reaction time is reduced greatly compared to the result obtained by the asymmetric hydroboration of the substrate **1m** (10 day, 30% *ee* was obtained for **2i**).[4b] The 2-benzoylbenzoic acid was also reactive with excellent enantiofacial discrimination (Table 3, entry 17). Next, a variety of 2-aroylarylcarboxylates were prepared and the substituent effect was discussed. The catalytic system exhibited a good tolerance for diversified substituents with different electronic properties on the *ortho* and *para* positions of the benzene ring. The substrates **1o** possessing an *ortho* methyl substituent on the aromatic ring gave a slightly higher *ee* value, but incomplete conversion was observed even when the reaction was conducted under 60 atm of H_2 for 48 h (Table 3, entry 18). The result demonstrated that the reaction was markedly affected by the steric effect on the *ortho* position of the phenyl ring. Substrates bearing *para* substituent groups on the phenyl ring showed a distinct effect on both reactivity and enantioselectivity. Compared with the substrate**1p** containing an electron-donating methoxy group on the *para* position, substrate **1q** with an electron-withdrawing trifluoromethyl group not only was more reactive, but also gave much better enantioselectivity in the reaction (Table 3, entry 19 vs. entry 20). Electronic properties of the para substituent groups were presumed to influence the coplanarity of the phenyl rings with C=O double bond in the transition state, therefore generating an unsymmetrical bias.[13] Unfortunately, the analogues **1r** and **1s** remained inactive under the [RuCl(benzene)(*S*)-SunPhos]Cl catalyst systems (Table 3, entries 21 and 22).

Conclusions

In conclusion, we have successfully developed a highly efficient and enantioselective protocol for the synthesis of bioactive chiral 3-substituted phthalides. By means of the Ru-diphosphines catalyzed asymmetric hydrogenation and subsequent in situ lactonization, a range of 2-acylarylcarboxylates including 2-aroylarylcarboxylates were directly converted into the corresponding optically active 3-substituted phthalides (up to 99.6% *ee*, S/C = 1000) under mild reaction conditions. This convenient and practical method represents one of the most general and efficient preparation of highly optically pure 3-substituted phthalides reported to date, providing valuable pharmaceutical molecules and important building blocks for many natural products and biologically active compounds. The further investigation of the potential applications in medicinal chemistry and asymmetric catalytic synthesis is underway.

Experimental Section

General Procedures

Commercially available reagents were used throughout without further purification unless those detailed below. Both MeOH and EtOH were distilled over magnesium under nitrogen. CH_2Cl_2, MeCN and *i*PrOH were distilled from calcium hydride. Toluene was freshly distilled from Na/ benzophenone under nitrogen. All reactions were conducted under a nitrogen atmosphere using standard Schlenk techniques, unless otherwise noted. ^{1}HNMR spectra were recorded at 400 MHz using TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz and referenced to the central peak of 77.00 ppm for $CDCl_3$. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. HRMS data were collected on an ESI-TOF mass spectrometer. Flash column chromatography was performed on 300-400 mesh silica gel. $[\alpha]_D$ values were obtained in a 0.5 dm cell at 25 °C using the D-line (589 nm) of a sodium lamp. 2-Acetylbenzoic acid (**1d**) was commercially available. Racemates could be prepared by $NaBH_4$ reduction of the corresponding 2-acylarylcarboxylates.

Typical Procedure for the Preparation of 1a-1c.[4d, 14]

A mixture of *o*-acetylbenzoic acid (2.0 g, 12.2 mmol) and potassium carbonate (2.5 g, 18.3 mmol) in 10 mL *N*,*N*-dimethylformamide was stirred at room temperature. The corresponding alkyl iodine (36.6 mmol) in *N*,*N*-dimethylformamide (8 mL) was added dropwise within 10 min. Upon consumption of the starting material (monitored by TLC), DMF was removed in vacuo and the residue was extracted with CH_2Cl_2 (8 mL). Then concentration was carried out under reduced pressure. The crude product obtained was purified by column chromatography (PE/EA = 12:1) on silica gel to provide the desired compound

Methyl 2-acetylbenzoate (1a):[15] R_f = 0.32 (PE/EA = 12:1); colorless oil: 2.0 g, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.84 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.56–7.54 (m, 1H), 7.51–7.49 (m, 1H), 7.41 (dd, *J* = 7.6, 0.8 Hz, 1H), 3.89 (s, 3H), 2.53 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 202.1, 167.0, 142.00, 131.5, 129.6, 129.1, 128.4, 126.1, 52.0, 29.3.

Ethyl 2-acetylbenzoate (1b):[4k] R_f = 0.32 (PE/EA = 12:1); colorless oil: 2.2 g, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.84 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.56–7.51 (m, 1H), 7.49–7.45 (m, 1H), 7.38 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.33 (q, *J* = 7.6 Hz, 2H), 2.52 (s, 3H), 1.34 (t, *J* = 7.6 Hz, 3H);

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 202.5, 166.6, 142.3, 131.6, 129.6, 129.3, 128.7, 126.1, 61.2, 30.0, 13.6.

Isopropyl 2-acetylbenzoate (1c): R_f = 0.36 (PE/EA = 10:1); colorless oil: 2.4 g, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.85 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.56–7.52 (m, 1H), 7.49–7.45 (m, 1H), 7.37 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.22 (hept, *J* = 6.4 Hz, 1H), 2.53 (s, 3H), 1.34 (d, *J* = 6.4 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 202.4, 166.0, 142.3, 131.4, 129.5, 129.2, 129.0, 125.90, 68.9, 29.7, 21.2. HRMS-ESI (m/z): $(M + H)^+$ calcd. for $C_{12}H_{15}O_3$, 207.1021; found 207.1020.

Typical Procedure for the Preparation of 1e-1i, 1l, 1o-1q.[16]

To a stirred mixture of phthalic anhydride (6.0 g, 40.5 mmol), cuprous iodide (0.6 g, 3.2 mmol) in anhydrous THF (80 mL) under N_2 atmosphere was added dropwise the corresponding Grignard reagent (44.6 mmol in 45 mL THF) over for 1h at -10 °C. The mixture was stirred at this temperature for 2 h and then allowed to warm to room temperature. Upon completion of the reaction, the reaction was quenched with aqueous 10% HCl solution and acidified to pH = 2 at 0°C, then THF was removed in vacuum and the resulting aqueous solution was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were treated with saturated Na_2CO_3 solution and the alkaline extracted was acidified with concentrated HCl. A milky-white colloidal suspension was observed and the mixture was further kept in refrigerator for several hours. After filtration, the corresponding acid was obtained as white solid and then was dried under vacuum. Finally, the desired esterification product was prepared according to the procedure described above.

Methyl 2-propionylbenzoate (1e):[17] R_f = 0.30 (PE/EA = 25:1); colorless oil: 3.5 g, 45% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.89 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.58–7.54 (m, 1H), 7.50–7.46 (m, 1H), 7.33 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.88 (s, 3H), 2.80 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 205.7, 166.6, 142.8, 131.7, 129.3, 129.2, 127.8, 125.7, 51.9, 35.5, 7.7.

Methyl 2-butyrylbenzoate (1f):[18] R_f = 0.32 (PE/EA = 30:1); colorless oil: 4.3 g, 51% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.89 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.59–7.55 (m, 1H), 7.51–7.47 (m, 1H), 7.36 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.89 (s, 3H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.81–1.72 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 205.3, 167.0, 143.0, 131.8, 129.5, 129.4, 128.3, 126.1, 52.2, 44.3, 17.2, 13.4.

Methyl 2-pentanoylbenzoate (1g):[19] R_f = 0.32 (PE/EA = 35:1); colorless oil: 4.6 g, 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.56–7.52 (m, 1H), 7.49–7.44 (m, 1H), 7.34 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.87 (s, 3H), 2.78 (t, *J* = 7.6 Hz, 2H), 1.75–1.66 (m, 2H), 1.43–1.32 (m, 2H),0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 205.2, 166.7, 142.9, 131.7, 129.4, 129.3, 128.1, 125.9, 52.0, 42.0, 25.7, 21.9, 13.5.

Methyl 2-(3-methylbutanoyl)benzoate (1h): R_f = 0.30 (PE/EA = 22:1); white solid: 4.1 g, 46% yield; mp 56.7-58.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.85 (dd, J = 7.6, 1.2 Hz, 1H), 7.57–7.53 (m, 1H), 7.50–7.46 (m, 1H), 7.38 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.88 (s, 3H), 2.71 (d, *J* = 6.8 Hz, 2H), 2.31–2.21 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 204.6, 167.3, 142.9, 131.8, 129.8, 129.7, 128.8, 126.4, 52.3, 51.0, 24.4, 22.5. HRMS-ESI (m/z): $(M + Na)^+$ calcd. for $C_{13}H_{16}NaO_3$, 243.0997; found 243.1000.

Methyl 2-isobutyrylbenzoate (1i): R_f = 0.34 (PE/EA = 15:1); colorless oil: 4.5 g, 54% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.93 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.58–7.54 (m, 1H), 7.50–7.46 (m, 1H), 7.30 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.88 (s, 3H), 3.11–3.00 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 209.4, 166.4, 142.6, 131.8, 129.5, 129.1, 127.9, 126.4, 52.0, 40.1, 18.0. HRMS-ESI (m/z): $(M + H)^+$ calcd. for $C_{12}H_{15}O_3$, 207.1021; found 207.1023.

Methyl 3-acetyl-2-naphthoate (1l): R_f = 0.36 (PE/EA = 15:1); colorless oil: 4.0 g, 43% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.34 (s, 1H), 7.96 (s, 1H), 7.95–7.90 (m, 2H), 7.67–7.60 (m, 2H), 3.95 (s, 3H), 2.64 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 201.4, 167.7, 137.8, 133.3, 132.6, 130.5, 128.5, 128.4, 128.2, 128.0, 127.3, 126.6, 52.2, 29.1. HRMS-ESI (m/z): $(M + Na)^+$ calcd. for $C_{14}H_{12}NaO_3$, 251.0684; found 251.0685.

Methyl 2-(2-methylbenzoyl)benzoate (1o):[20] R_f = 0.30 (PE/EA = 15:1); colorless oil: 5.1 g, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.93 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.62–7.53 (m, 2H), 7.45 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.39–7.35 (m, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 7.6, 1.2 Hz 1H), 7.12 (t, *J* = 6.8 Hz, 1H), 3.61 (s, 3H), 2.66 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 198.0, 166.5, 142.0, 139.2, 136.3, 131.5, 131.4, 131.3, 130.7, 129.6, 129.3, 128.1, 124.9, 51.7, 20.9.

Methyl 2-(4-methoxybenzoyl)benzoate (1p):[21] R_f = 0.38 (PE/EA = 7:1); colorless oil: 4.2 g, 38% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.03 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.73–7.70 (m, 2H), 7.63–7.59 (m, 1H), 7.56–7.52 (m, 1H), 7.37 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.92–6.88 (m, 2H), 3.84 (s, 3H), 3.63 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 195.5, 166.2, 163.3, 141.8, 132.1, 131.4, 130.0, 129.8, 129.1, 128.8, 127.4, 113.5, 55.2, 51.9.

Methyl 2-(4-(trifluoromethyl)benzoyl)benzoate (1q): R_f = 0.50 (PE/EA = 8:1); white solid: 3.7 g, 30% yield; mp 94.8-96.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.71–7.66 (m, 3H), 7.63–7.59 (m, 1H), 7.40 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.66 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 195.8, 166.0, 141.0, 139.9, 134.5, 134.2, 133.9, 133.6 (q, *J* = 32.4 Hz), 132.6, 130.2, 129.9, 129.3, 128.9, 127.6, 127.5, 125.52, 125.48, 125.44, 125.41 (q, *J* = 3.7 Hz), 124.9, 122.2, 119.4 (q, *J* = 271.0 Hz), 52.2. HRMS-ESI (m/z): $(M + H)^+$ calcd. for $C_{16}H_{12}F_3O_3$, 309.0739; found 309.0740.

Typical Procedure for the Preparation of 1j-1k.[22]

To a suspension of methyl 2-bromo-5-methylbenzoate (2.3 g, 10.0 mmol) $Pd(OAc)_2$ (0.18 g, 0.80 mmol) and triphenylphosphine (0.42 g, 1.6 mmol) in degassed acetonitrile (20 mL) was added *n*-butyl vinyl ether (5.0 g, 50.0 mmol), triethylamine (1.3 g, 13 mmol). The resulting mixture was heated at reflux for 24 h. After being cooled to room temperature, the mixture was diluted with water (25 mL) and EtOAc (25 mL), and then filtered over Celite®, rinsing with EtOAc (30 mL). The filtrate was concentrated under reduced pressure, then THF (60 mL) and 10% aq. HCl (60 mL) were added. The mixture was stirred at room temperature for 2 h and then THF was removed in vacuum. The resulting aqueous

solution was poured into saturated aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried by anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product obtained was purified by column chromatography (PE/EA = 8:1) on silica gel to afford the methyl 2-acetyl-5-methylbenzoate (**1j)** as yellow oil. Similarly, compounds (**1k**) were prepared from the methyl 2-bromo-5-chlorobenzoate and *n*-butyl vinyl ether. The desired product were purified by column chromatography (PE/EA = 10:1).

Methyl 2-acetyl-5-methylbenzoate (1j): R_f = 0.40 (PE/EA = 6:1); yellow oil: 1.7 g, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.58 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 2.52 (s, 3H), 2.41 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 201.3, 167.8, 140.6, 138.3, 131.7, 129.5, 129.4, 126.8, 52.1, 28.9, 20.7. HRMS-ESI (m/z): $(M + Na)^+$ calcd. for $C_{11}H_{12}NaO_3$, 215.0684; found 215.0690.

Methyl 2-acetyl-5-chlorobenzoate (1k): R_f = 0.36 (PE/EA = 8:1); yellow oil: 1.8 g, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.80 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 2.52 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 201.3, 166.4, 140.4, 136.4, 131.9, 130.9, 129.7, 128.1, 52.9, 29.7. HRMS-ESI (m/z): $(M + Na)^+$ calcd. for $C_{10}H_9ClNaO_3$, 235.1038; found 235.1032.

Typical Procedure for the Preparation of 1m-1n, 1s.[23]

To a stirred mixture of benzene (35 mL), phthalic anhydride (6.0 g, 40.5 mmol) was added anhydrous $AlCl_3$ (11.3 g, 85.1 mmol) in portion at 0°C. The mixture was warmed to room temperature and reacted for 12 h. The mixture was poured into aqueous 10% HCl solution to acidify to pH = 2 at 0°C. Then redundant benzene was removed in vacuum and the resulting aqueous solution was extracted with CH_2Cl_2 (15 mL×3). The combined organic layers were washed with saturated Na_2CO_3 solution and the alkaline extracted was acidified with concentrated HCl. A milky-white suspension was observed and the mixture was further kept in refrigerator for 15 h. After filtration, 2-benzoylbenzoic acid **1m** was obtained as off-white solid and then was dried under vacuum. Similarly, compound 2-benzoylcyclohexanecarboxylic acid was prepared from hexahydrophthalic anhydride and benzene. Finally, the desired esterification product was prepared according to the procedure described above.

Methyl 2-benzoylbenzoate (1m):[24] R_f = 0.42 (PE/EA = 10:1); white solid: 7.3g, 75% yield; mp 44.5-46.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.07 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.76–7.79 (m, 2H), 7.69–7.65 (m, 1H), 7.62–7.55 (m, 2H), 7.48–7.43 (m, 3H), 3.63 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 196.3, 165.8, 141.2, 136.7, 132.6, 131.9, 129.5, 129.2, 128.7, 128.0, 127.3, 51.6.

2-Benzoylbenzoic acid (1n):[25] R_f = 0.25 (PE/EA = 1:2); off-white solid: 7.6 g, 83% yield; mp 119.9-121.8 °C; ^{1}H NMR (400 MHz, DMSO, 25 °C): δ 13.19 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.68–7.62 (m, 4H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO, 25 °C): δ 197.1, 167.6, 142.0, 137.5, 133.5, 132.9, 130.3, 130.2, 129.4, 129.1, 127.8.

Methyl 2-benzoylcyclohexanecarboxylate (1s):[26] R_f = 0.40 (PE/EA = 10:1); white solid: 8.1g, 85% yield; mp 28.9-31.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ.7.87–7.85 (m, 2H), 7.51–7.55 (m, 1H), 7.47–7.43 (m, 2H), 3.89 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.62 (s, 3H), 2.75–2.71 (m, 1H), 2.24–2.17 (m, 1H), 2.10–2.05 (m,1H), 1.99–1.92 (m, 1H), 1.84–1.74 (m, 2H), 1.47–1.35 (m, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 202.3, 174.2, 136.5, 132.3, 128.3, 127.9, 51.3, 44.1, 42.6, 27.1, 25.3, 24.1, 22.5.

Preparation of Methyl 2-(2-phenylacetyl)benzoate (1r).[4k, 27]

To a mixture of benzalphthalide (2.7 g, 12.0 mmol) in 1,4-dioxane (70 mL) and water (10 ml) was added KOH (1.0 g, 18.0 mmol) with magnetic stirring and the resulting mixture reacted for 3 h at room temperature. The mixture was acidified with 3N HCl solution to pH = 2, and followed by extraction with CH_2Cl_2 (30 mL×3) and concentration. The intermediate was dissolved in 16 mL DMF directly, and then added anhydrous KF (1.1 g, 18.0 mmol) and MeI (5.1 g, 36.0 mmol). Upon completion of the reaction (monitored by TLC), DMF was removed in vacuo and the residue was extracted with CH_2Cl_2 (8 mL). Then concentration was carried out by vacuum evaporation process. The crude product obtained was purified by column chromatography (PE/EA = 15:1) on silica gel to provide the desired compound.

Methyl 2-(2-phenylacetyl)benzoate (1r): R_f = 0.30 (PE/EA = 15:1); colorless oil: 2.1 g, 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.94 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.52–7.47 (m, 2H), 7.34 – 7.30 (m, 2H), 7.27 – 7.25 (m, 3H), 7.20 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.12 (s, 2H), 3.90 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 203.1, 166.6, 142.8, 133.6, 132.0, 129.63, 129.60, 129.4, 128.2, 127.8, 126.7, 126.4, 52.3, 49.5. HRMS-ESI (m/z): $(M + Na)^+$ calcd. for $C_{16}H_{14}NaO_3$, 277.0841; found 277.0844.

Typical Procedure for the Asymmetric Hydrogenation

To a 25 mL Schlenk tube were added $[RuCl_2(benzene)]_2$ (5.0 mg, 0.01mmol) and (*S*)-SunPhos (15.0 mg, 0.022 mmol). The tube was evacuated and purged with nitrogen three times before addition of freshly distilled and freeze−thaw−degassed EtOH/CH_2Cl_2 (1.5 mL/1.5 mL). The resulting mixture was heated at 50°C for 1 h and then cooled to room temperature. The solvent was removed by vacuum evaporation process to give the catalyst as a yellow powder. The catalyst was dissolved in degassed MeOH (4 mL), and then the solution was equally charged into eight vials which contained 0.5 mmol of substrates, and 0.5 mL of MeOH. Then the vials were transferred into 300 mL autoclaves. The autoclaves were purged five times with H_2 and the required pressure of H_2 was set. The contents of autoclaves were stirred under specified reaction conditions. After being cooled to room temperature and careful release of the hydrogen, the autoclaves were opened and the solvent was evaporated. The residue was purified by a silica gel column to provide the corresponding hydrogenation products and then the enantiomeric excess was directly determined by HPLC.

(*S*)-3-Methylisobenzofuran-1(3*H*)-one (2a):[3c] R_f = 0.85 (PE/EA = 2:1); colorless oil: 70.1 mg, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.66–7.60 (m, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.44 (dd, *J* = 7.6, 0.8 Hz, 1H), 5.57 (q, *J* = 6.8 Hz, 1H), 1.64 (d, *J* = 6.8 Hz,

3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.4, 151.1, 134.0, 128.9, 125.6, 125.5, 121.5, 77.6, 20.3. HPLC (Chiralcel OJ-H column, hexane/*i*PrOH = 90/10, 0.7 mL/min, 230 nm): t_1 = 18.2 min, t_2 = 20.6 min. $[\alpha]_D^{25}$ = –33.0 (*c* = 1.4 in $CHCl_3$). Lit.[3c] $[\alpha]_D^{21}$ = +37.1 (*c* = 0.83 in $CHCl_3$) for (*R*)-enantiomer with 95% *ee*.

3-Methoxy-3-methylisobenzofuran-1(3*H*)-one (2a'):[28] R_f = 0.36 (PE/EA = 15:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.90–7.88 (m, 1H), 7.75–7.71 (m, 1H), 7.62–7.58 (m, 1H), 7.51–7.49 (m, 1H), 3.07 (s, 3H), 1.84 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 168.0, 147.4, 134.6, 130.6, 127.3, 125.5, 122.1, 108.7, 51.2, 25.2.

(*S*)-3-Ethylisobenzofuran-1(3*H*)-one (2b):[3c] R_f = 0.80 (PE/EA = 4:1); colorless oil: 76.2 mg, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.87 (d, *J* = 7.6 Hz, 1H), 7.68–7.64 (m, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 7.6, 0.8 Hz, 1H), 5.44 (dd, *J* = 7.2, 4.4 Hz, 1H), 2.16–2.06 (m, 1H), 1.86–1.75 (m, 1H), 0.98 (t, *J* = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.6, 149.7, 133.9, 129.0, 126.2, 125.6, 121.7, 82.3, 27.6, 8.8. HPLC (Chiralcel OJ-H column, hexane/*i*PrOH = 95/5, 0.7 mL/min, 210 nm): t_1 = 18.2 min, t_2 = 20.6 min. $[\alpha]_D^{25}$ = –69.9 (*c* = 1.0 in $CHCl_3$). Lit.[3c] $[\alpha]_D^{22}$ = +64.1 (*c* = 0.88 in $CHCl_3$) for (*R*)-enantiomer with 90% *ee*.

(*S*)-3-Propylisobenzofuran-1(3*H*)-one (2c):[2i] R_f = 0.82 (PE/EA = 4:1); colorless oil: 83.0 mg, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.68–7.64 (m, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 7.6, 0.8 Hz, 1H), 5.48 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.05–1.97 (m, 1H), 1.78–1.69 (m, 1H), 1.59–1.43 (m, 2H), 0.98 (t, *J* = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.7, 150.1, 133.9, 129.0, 126.1, 125.6, 121.7, 81.2, 36.8, 18.2, 13.8. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 95/5, 0.7 mL/min, 210 nm): t_1 = 15.7 min, t_2 = 17.3 min. $[\alpha]_D^{25}$ = –79.0 (*c* = 0.57 in $CHCl_3$). Lit.[2i] $[\alpha]_D^{20}$ = +49.7 (*c* = 0.23 in $CHCl_3$) for (*R*)-enantiomer with 80% *ee*.

(*S*)-3-Butylisobenzofuran-1(3*H*)-one (2d):[29] R_f = 0.78 (PE/EA = 6:1); colorless oil: 91.5 mg, 96% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.66–7.62 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.42 (dd, *J* = 7.6, 0.8 Hz, 1H), 5.44 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.06–1.97 (m, 1H), 1.77–1.67 (m, 1H), 1.50–1.26 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.5, 150.0, 133.8, 128.9, 126.0, 125.5, 121.6, 81.3, 34.3, 26.7, 22.3, 13.7. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 98/2, 1.0 mL/min, 210 nm): t_1 = 14.3 min, t_2 = 18.0 min. $[\alpha]_D^{25}$ = –64.2 (*c* = 1.2 in $CHCl_3$). Lit.[29] $[\alpha]_D^{25}$ = +63.3 (*c* = 0.495 in $CHCl_3$) for (*R*)-enantiomer with 94% *ee*.

3-Isobutylisobenzofuran-1(3*H*)-one (2e): R_f = 0.80 (PE/EA = 5:1);colorless oil: 55.1 mg, 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.68–7.64 (m, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.42 (dd, *J* = 7.6, 0.8 Hz, 1H), 5.50 (dd, *J* = 10.0, 3.2 Hz, 1H), 2.11–1.98 (m, 1H), 1.80–1.72 (m, 1H), 1.67–1.59 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.6, 150.6, 133.8, 128.9, 125.9, 125.6, 121.6, 80.0, 44.2, 25.2, 23.3, 21.8. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 98/2, 0.5 mL/min, 230 nm): t_1 = 23.4 min, t_2 = 33.8 min. $[\alpha]_D^{25}$ = –74.7 (*c* = 0.9, $CHCl_3$). HRMS-ESI (m/z): $(M + H)^+$ calcd. for $C_{12}H_{15}O_2$, 191.1072; found 191.1073.

(*S*)-3,6-Dimethylisobenzofuran-1(3*H*)-one (2f):[3a] R_f = 0.32 (PE/EA = 8:1); colorless oil: 79.5 mg, 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.64 (s, 1H), 7.46 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 5.50 (q, *J* = 6.8 Hz, 1H), 2.43 (s, 3H), 1.58 (d, *J* = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.5, 148.5, 139.2, 135.1, 125.8, 125.4, 121.2, 77.6, 21.1, 20.4. HPLC (Chiralcel AD-H column, hexane/*i*PrOH = 98/2, 1.0 mL/min, 210 nm): t_1 = 16.3 min, t_2 = 19.1 min. $[\alpha]_D^{25}$ = -45.9 (*c* = 0.90 in $CHCl_3$). Lit.[3a] $[\alpha]_D^{28}$ = -35.0 (*c* = 1.03 in $CHCl_3$) for (*S*)-enantiomer with 92% *ee*.

(*S*)-6-Chloro-3-methylisobenzofuran-1(3*H*)-one (2g):[3a] R_f = 0.42 (PE/EA = 5:1); white solid: 89.8 mg, 98% yield; mp 61.8-63.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.86 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 5.55 (q, *J* = 6.8 Hz, 1H), 1.63 (d, *J* = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 168.9, 149.2, 135.3, 134.3, 127.5, 125.5, 122.9, 77.6, 20.3. HPLC (Chiralcel OJ-H column, hexane/*i*PrOH = 99/1, 0.7 mL/min, 210 nm): t_1 = 38.9 min, t_2 = 46.5 min. $[\alpha]_D^{25}$ = -36.7 (*c* = 0.82 in $CHCl_3$). Lit.[3a] $[\alpha]_D^{28}$ = -36.1 (*c* = 0.30 in $CHCl_3$) for (*S*)-enantiomer with 95% *ee*.

(*S*)-3-Methylnaphtho[2,3-c]furan-1(3*H*)-one (2h): R_f = 0.45 (PE/EA = 10:1); white solid: 97.3 mg, 98% yield; mp 109.6-111.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.48 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.69–7.58 (m, 2H), 5.74 (q, *J* = 6.8 Hz, 1H), 1.74 (d, *J* = 6.8Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.2, 144.7, 136.1, 132.9, 129.7, 128.8, 128.0, 126.74, 126.67, 123.4, 120.3, 77.7, 20.9. HPLC (Chiralcel OD-H column, hexane/*i*PrOH = 90/10, 0.8 mL/min, 230 nm): t_1 = 16.8 min, t_2 = 20.1 min. $[\alpha]_D^{25}$ = – 90.4 (*c* = 1.5, $CHCl_3$). HRMS-ESI (m/z): $(M + H)^+$ calcd. for $C_{13}H_{11}O_2$, 199.0759; found 199.0757.

(*S*)-3-Phenylisobenzofuran-1(3*H*)-one (2i):[3c] R_f = 0.80 (PE/EA = 4:1); light yellow solid: 101.2 mg, 95% yield; mp 110.4-112.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.67–7.63 (m, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.40–7.27 (m, 6H), 6.41 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.3, 149.5, 136.2, 134.2, 129.1, 129.0, 128.7, 126.7, 125.3, 122.7, 82.5; HPLC (Chiralcel OD-H column, hexane/*i*PrOH = 85/15, 1.0 mL/min, 210 nm): t_1 = 9.1 min, t_2 = 11.2 min. $[\alpha]_D^{25}$ = + 44.5 (*c* = 1.0, $CHCl_3$). Lit.[3c] $[\alpha]_D^{22}$ = – 42.1 (*c* = 1.05, $CHCl_3$) for (*R*)-enantiomer with 91% *ee*.

(*S*)-3-(*o*-Tolyl)isobenzofuran-1(3*H*)-one (2j):[3c] R_f = 0.23 (PE/EA = 15:1); white solid: 84.5 mg, 75% yield; mp 105.3-106.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.98 (d, *J* = 7.6 Hz, 1H), 7.69–7.65 (m, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.35 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.29–7.25 (m, 2H), 7.15–7.11 (m, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.68 (s, 1H), 2.50 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.5, 149.1, 137.0, 134.1, 134.0, 131.0, 129.2, 129.2, 127.1, 126.3, 125.5, 122.9, 80.4, 19.2. HPLC (Chiralcel OD-H column, hexane/*i*PrOH = 85/15, 0.7 mL/min, 210 nm): t_1 = 12.2 min, t_2 = 15.4 min. $[\alpha]_D^{25}$ = – 69.2 (*c* 0.63 = $CHCl_3$). Lit.[3c] $[\alpha]_D^{22}$ = + 41.6 (*c* = 0.62, $CHCl_3$) for (*R*)-enantiomer with 82% *ee*.

(*S*)-3-(4-Methoxyphenyl)isobenzofuran-1(3*H*)-one (2k):[3c] R_f = 0.46 (PE/EA = 5:1); white solid: 107.6 mg, 89% yield; mp 105.8-107.3; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.67–7.63 (m,

1H), 7.58–7.53 (m, 1H), 7.32–7.30 (m, 1H), 7.19–7.16 (m, 2H), 6.90–6.88 (m, 2H), 6.37 (s, 1H), 3.81 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.5, 160.4, 149.7, 134.22, 129.3, 128.8, 128.3, 125.9, 125.5, 122.9, 114.3, 82.7, 55.3. HPLC (Chiralcel OJ-H column, hexane/*i*PrOH = 85/15, 1.0 mL/min, 230 nm): t_1 = 31.8 min, t_2 = 41.1 min. $[\alpha]_D^{25}$ = – 7.0 (*c* = 0.8, $CHCl_3$). Lit.[3c] $[\alpha]_D^{22}$ = + 31.0 (*c* = 0.42, $CHCl_3$) for (*R*)-enantiomer with 98% *ee*.

(*S*)-3-(4-(Trifluoromethyl)phenyl)isobenzofuran-1(3*H*)-one (2l):[2f] R_f = 0.38 (PE/EA = 8:1); white solid: 136.9 mg, 98% yield; mp 89.8-92.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.68–7.65 (m, 3H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.34 (dd, *J* = 7.6, 0.4 Hz, 1H), 6.45 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ 170.1, 148.9, 140.5, 134.6, 131.8, 131.5, 131.2, 130.8 (q, *J* = 32.5 Hz), 129.7, 127.8, 127.1, 126.01, 125.97, 125.93, 125.90 (q, *J* = 3.7 Hz), 125.8, 125.2, 125.1, 122.7, 122.4, 119.6 (q, *J* = 270.6 Hz), 81.5. HPLC (Chiralcel OD-H column, hexane/*i*PrOH = 98/2, 0.5 mL/min, 210 nm): t_1 = 41.6 min, t_2 = 46.3 min. $[\alpha]_D^{25}$ = + 68.0 (*c* = 0.9, $CHCl_3$). Lit.[2f] $[\alpha]_D^{27}$ = + 34.0 (*c* = 0.50, $CHCl_3$) for (*S*)-enantiomer with 70% *ee*.

Acknowledgements ((optional))

We thank the National Natural Science Foundation of China for the financial support.

Keywords: ruthenium • asymmetric hydrogenation • 3-substituted phthalides • enantioselectivity • gram-scale reaction

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[12] CCDC 1551154 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.

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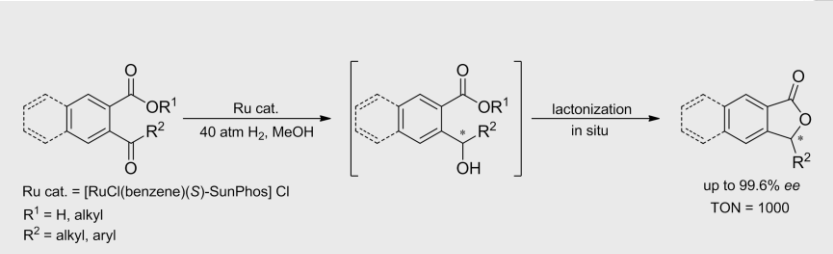

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Ruthenium-Catalyzed Enantioselective Hydrogenation/Lactonization of 2-Acylarylcarboxylates : Direct Access to Chiral 3-Substituted Phthalides

By means of the Ru-diphosphines catalyzed asymmetric hydrogenation and subsequent in situ lactonization, a series of 2-acylarylcarboxylates including 2-aroylarylcarboxylates were directly converted into the corresponding optically active 3-substituted phthalides (up to 99.6% *ee*, S/C = 1000) under mild reaction conditions.