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A synthetic route to chiral $C_{(3)}$-functionalized phthalides via a Ag(I)-catalyzed allylation/transesterification sequence

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ABSTRACT

A Ag(I)-catalyzed synthesis of chiral $C_{(3)}$-substituted phthalides (**8a**–**f**) via a Sakurai–Hosomi allylation/transesterification reaction is described (ee ≤86%). A notable feature of this reaction is that it utilizes *ortho*-substituted aldehydes, which are a class of compounds that generally afford poor levels of stereoinduction when applying most known catalytic asymmetric allylation approaches. It was also found that elongation of the *n*-alkyl chain length (R^1, up to *n*=6; R^2=H) of the starting alkyl 2-formylbenzoates (**7g**–**i**) improved the enantiomeric excess (ee) of the product.

1. Introduction

Catalytic asymmetric reaction methodologies mediated by chiral Ag(I)-complexes, have provided chemists with a rich portfolio of C–C bond-forming strategies over the last two-decades. In this regard, the Ag(I)-catalyzed asymmetric Sakurai–Hosomi allylation methodologies of Yamamoto et al. have found considerable use as key synthetic routes to chiral homoallylic alcohols.[1] For instance, Rodríguez-García et al. employed Yamamoto's (*R*)-*p*-tol-BINAP·Ag^{I}OTf (*p*-tol-BINAP=2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl) catalyzed allylation approach as a pivotal disconnection in the reported synthesis of the antifungal agents (−)-*trans*-pterocarpin (**1**) and (−)-*cis*-pterocarpin.[2] Similarly, Kanai et al. in route to the natural antibiotic fostriecin (**2**) and 8-*epi*-fostriecin (**3**) employed a (*R*)-*p*-tol-BINAP·Ag^{I}F catalyzed allylation as a strategic stereochemical setting step (Scheme 1).[3]

In a related context, our group has recently discovered an overlooked strength of these Ag(I)-catalyzed allylation procedures in terms of their operational compatibility with *ortho*-substituted arylaldehydes, which are a class of compounds that generally afford poor levels of stereoinduction when applying most known catalytic asymmetric allylation approaches.[4] More specifically, while developing synthetic methodology for preparing $C_{(1)}$-chiral 3-methylene-indan-1-ols, we found that under the Ag(I)-catalyzed allylation conditions of Yamamoto, *ortho*-halogenated benzaldehydes provided chiral homoallylic alcohol intermediates with respectable levels of enantiomeric excess (ee).[5] In following up on this advancement and our ongoing interest in developing catalytic asymmetric methodologies as well as our recent report of a stoichiometric in-mediated approach for preparing C(3)-substituted phthalides, we report herein a catalytic Ag(I)-catalyzed approach to chiral C(3)-substituted phthalides **8a**–**f** (ee ≤86%) from alkyl 2-formylbenzoates **7a**–**m** (Table 1).[6] Additionally, the somewhat counterintuitive discovery, based upon steric factors (*inter alia*), was the finding that a marked improvement in product ee occurred, up to a point, with elongation of the *n*-alkyl chain (R^1, up to *n*=6; R^2=H) of the starting alkyl 2-formylbenzoate (**7g**–**i**).

As for the existing synthetic methodologies to C(3)-chiral phthalides, over the past two-decades a number of chiral auxiliary[7] and organometallic[8] approaches have been reported.[6] In contrast, however, only a few catalytic asymmetric methods have been published, including enantioselective ketone hydroacylation,[9] enantioselective transfer hydrogenation, and transesterification sequences,[10] chiral β-amino alcohol mediated additions of zinc reagents to aldehydes,[11] and a tandem enantioselective Ni(II)/(*S*)-BINAP complex catalyzed process.[12] Furthermore, an enantioselective Rh(I)-catalyzed transesterification/[2+2+2] cycloaddition sequence,[13] propenol-promoted enantioselective alkylation process,[14] enantioselective CoI_2(*S*,*S*)dipamp-catalyzed cyclization,[15] and L-prolinamide organocatalyzed enantioselective aldol-lactonization reaction have been reported.[16] It is also noteworthy that $C_{(3)}$-substituted phthalides are prevalent throughout nature in medicinally useful compounds, such as the *Sporotrichum laxum* metabolite spirolaxine (**4**) that possesses specific activity against the microaerophilic Gram-negative bacterium *Helicobacter pylori*, and has been the target of many recent total syntheses (Scheme 2).[17a–c] Moreover, Kittakoop et al. have recently isolated from a culture of *Colletotrichum* sp. CRI53502 the phthalide containing natural product Colletorialide (**5**), which has oxygen radical absorbance capacity against peroxy radicals.[17d,e] Furthermore, the *Apium* seed

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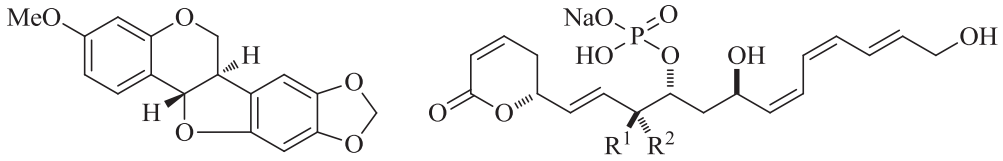


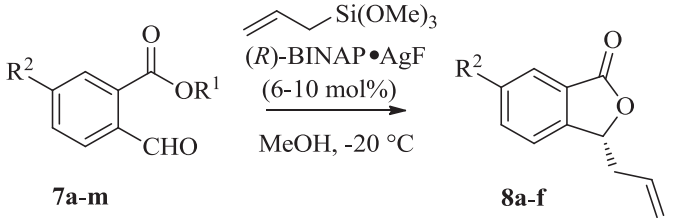
1

R^1 = Me, R^2 = OH ; **2**

R^1 = OH, R^2 = Me ; **3**

Scheme 1. Structure of (−)-*trans*-pterocarpin (**1**), fostriecin (**2**), and 8-*epi*-fostriecin (**3**).

Table 1
A Ag(I)-catalyzed asymmetric Sakurai–Hosomi allylation/transesterification of functionalized aldehydes



7a-m **8a-f**

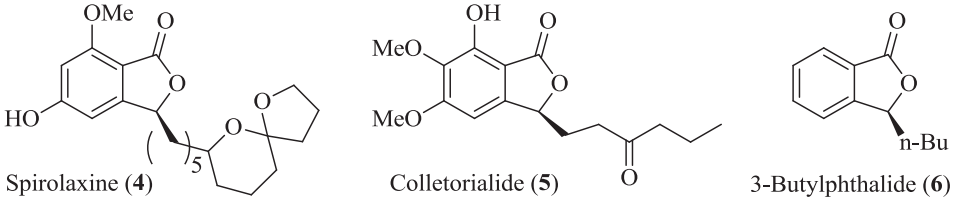
Entry	Substrate	R^1	R^2	*t* [h]	Product	Yield[b] (%)	ee[c] (%)
1	**7a**	CH_3	H	5	**8a**	68	71
2	**7b**	CH_3	Br	5	**8b**	57	39
3	**7c**	CH_3	NO_2	5	**8c**	52	33
4	**7d**	CH_3	isobutyl–CO_2NH	5	**8d**	65	43
5	**7e**	CH_3	Ph	5	**8e**	67	61
6	**7f**	CH_3	OCH_3	5	**8f**	55	86
7	**7g**	C_2H_5	H	5	**8a**	58	80
8	**7h**	C_6H_{13}	H	4	**8a**	73	86
9	**7i**	$C_{12}H_{25}$	H	4	**8a**	70	86
10	**7j**	CH_2Ph	H	10	**8a**	54	63
11	**7k**	$CH(CH_3)_2$	H	10	—	0	—[d]
12	**7l**	$C(CH_3)_3$	H	10	—	0	—
13	**7m**	Solid support[e]	H	10	**8a**	68	76

[a] Allyl trimethoxysilane, (*R*)-BINAP·AgF (6–10 mol %), in MeOH, −20 °C.
[b] Yields of isolated products after flash chromatography.
[c] Enantiomeric excess was determined by HPLC analysis.
[d] Not applicable.
[e] Merrifield resin was used.

substrates. Regardless, we were delighted to find early on that under the reported Sakurai–Hosomi allylation conditions of Yamamoto et al. that allyltrimethoxysilane reacted with methyl 2-formyl benzoate (**7a**) in the presence of (*R*)-BINAP·Ag^IF (6–10 mol %) to afford the (*R*)-$C_{(3)}$-substituted phthalide **8a** in 71% ee (Table 1, entry 1).[1] Encouraged by this result, we further explored the scope of this reaction by reacting a range of substituted methyl 2-formyl-benzoates (**7b–m**).

More specifically, the reaction of **7b** having an inductively withdrawing/resonance donating *para*-bromo substituent had a negative impact on the reaction as the target phthalide **8b** was generated with a low level of enantioinduction (Table 1, entry 2). Similarly, the incorporation of an electron withdrawing *para*-nitro substituent, which introduced the added complication of potential catalyst binding, afforded the targeted phthalide **8c** in low ee (Table 1, entry 3). Likewise, the reaction of the electron deficient *para*-carbamate substituted substrate **7d** lead to erosion in product ee (Table 1, entry 4). Having identified the limitations of this reaction toward the use of electronic deficient substrates, the more electron rich *para*-phenyl **7e** was reacted, generating phthalide **8e** with respectable yield in 61% ee (Table 1, entry 5). More encouraging, however, was the subsequent finding that the electron rich substrate methyl 2-formyl-5-methoxybenzoate (**7f**) afforded phthalide **8f** with even higher ee (Table 1, entry 6).

At that stage, our investigation shifted from an analysis of what effect the aryl substitution had on this reaction by elongating the *n*-alkyl chain length of the starting 2-formylbenzoate. In this vein, the ethyl ester functionalized **7g** was reacted, which surprisingly afforded **8a** with respectable ee, despite the slightly more sterically

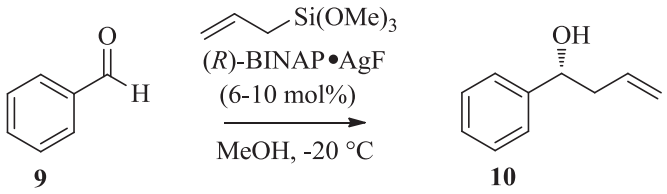


Spirolaxine (**4**) Colletorialide (**5**) 3-Butylphthalide (**6**)

Scheme 2. Examples of natural products containing $C_{(3)}$-chiral substituted phthalides.

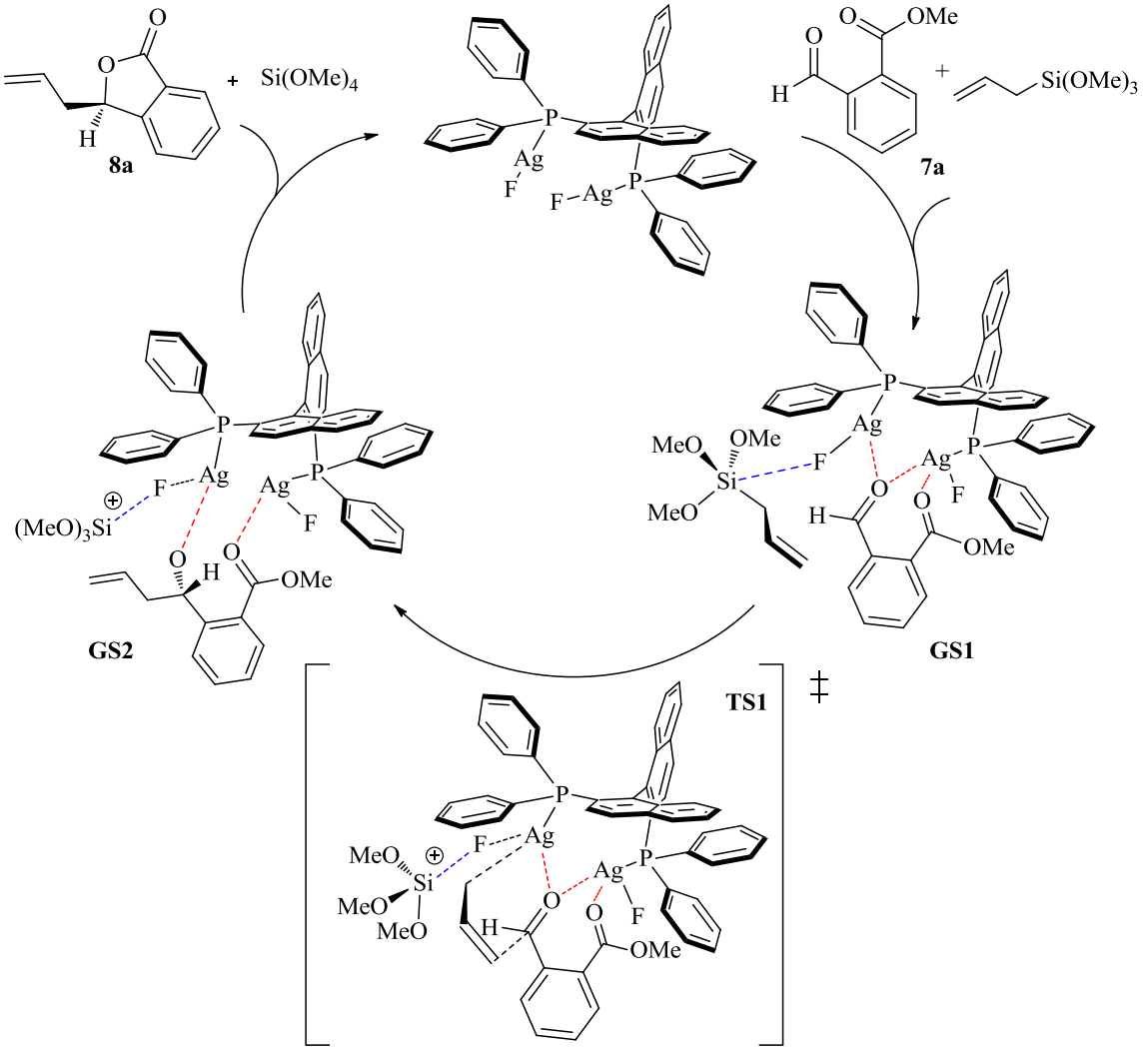
extract (*S*)-3-*n*-butylphthalide (**6**) has recognized potential as a treatment for stroke and pretreatment for Parkinson disease (PD).[17f,18]

At the outset of this study and based upon our recent report of a stoichiometric in-mediated approach to C(3)-chiral phthalides it was reasoned that the development of a mechanistically similar catalytic approach for producing these important targets would be of synthetic value.[6] However, we were somewhat concerned as to the viability of this approach considering the aforementioned challenges associated with the use of *ortho*-substituted arylaldehydes as demanding nature of this substrate (Table 1, entry 7). Intrigued by this finding, hexyl-2-formylbenzoate (**7h**) was then subjected to the reaction conditions to afford **8a** in the highest ee yet (Table 1, entry 8). Notably, the ee of phthalide **8a** derived from **7h** was almost the same as the homoallylic alcohol **10** obtained from the reaction of benzaldehyde (ee=87%, Scheme 3), which according to the proposed reaction cycle of Scheme 4 (vide infra), implied that once the stereochemical setting allylation step had occurred there was no erosion in ee and the bulky *ortho*-ester group of **7h** had no deleterious effect on the reaction outcome.



Scheme 3. Sakurai–Hosomi allylation/transesterification of benzaldehyde.

2-formyl-benzoates **7k** and **8l** were reacted, which only afforded unreacted starting materials (Table 1, entry 11, 12). In drawing on the foreseeable use of our reaction methodology within the context of 'split-and-pool', 'parallel synthesis' or other combinatorial based solid-support approaches the reaction of the Merrifield resin bound **7m** was investigated.[19] Eventfully, the desired phthalide was afforded in 76% ee, despite the heterogenous nature of this reaction (Table 1, entry 13). Furthermore, from an experimental standpoint it is noteworthy that the desired phthalide was



Scheme 4. Envisioned mechanistic cycle for the synthesis of chiral $C_{(3)}$-substituted phthalides.

To further explore this interesting trend between the steric size of *n*-alkyl ester chain length of the substrate and product ee, the dodecyl derivative **7i** was reacted to afford phthalide **8a** with the same ee as that obtained from **7h** (Table 1, entry 9). As to the origin of this interesting dependence of the *n*-alkyl chain length on the enantioinduction of this reaction, it is thought that micelle aggregation effects play a decided role in this respect. Nevertheless, we are currently looking into this intriguing reaction outcome in greater detail.

In branching out from an analysis of the *n*-alkyl chain length of the starting substrate, benzyl-2-formylbenzoate (**7j**) was reacted to provide **8a** in a moderate 63% ee (Table 1, entry 10). The influence of further branching at the α-carbon of the ester group was probed next. To this end, the *iso*-propyl and *tert*-butyl freed from the solid support by transesterification, thus alleviating the need for post-allylation cleavage of the product from the solid support.

Taking into consideration the above results, we tentatively propose the mechanistic cycle depicted in Scheme 4. According to this posit a short-lived complex **GS1** is initially formed from methyl-2-formylbenzoate (**7a**), allyltrimethoxysilane, and the catalyst; wherein the allyltrimethoxysilane reagent resides at the periphery of the inner coordination sphere, containing the directly bound catalyst and aldehyde assembly. From **GS1**, a fluoride assisted transmetalation occurs to form a highly reactive Ag-allyl species that rapidly undergoes enantioselective allylation via **TS1** in a *re*-stereofacial C–C bond-forming process that provides the Ag-alkoxy bound intermediate **GS2**. Thereafter, an intramolecular

transesterification (likely Ag-facilitated) follows to afford (*R*)-3-allylisobenzofuran-1(3*H*)-one (**8a**), tetramethoxysilane and turnover of the catalyst for another productive cycle.

As outlined above a unique synthetic entry-point to chiral $C_{(3)}$-phthalides, that relies upon the use of Yamamoto's variant of the Sakurai–Hosomi reaction has been described. A second unique feature of this reaction is that it utilizes *ortho*-substituted aldehydes, which in general are known to afford poor levels of stereoinduction when applying most of the catalytic asymmetric allylation technologies reported to date. As well, the counterintuitive finding that a marked improvement in product ee occurred, up to a point, upon elongation of the *n*-alkyl chain (R^1, up to n=6; R^2=H) of the starting alkyl 2-formylbenzoate was discovered.

2. Experimental

2.1. General

Materials were obtained from commercial suppliers (Sigma–Aldrich) and were used without further purification. Dry (DCM) dichloromethane, THF (tetrahydrofuran), DMF (dimethylformamide), and toluene were obtained by Puresolv MD 5 purification system. All reactions were performed under an inert atmosphere. Reactions were monitored by thin layer chromatography (TLC) using TLC silica gel 60 F_{254}, EMD Merck. Flash column chromatography was performed over Silicycle ultrapure silica gel (230–400 mesh). NMR spectra were obtained with a Bruker DPX-300 (1H 300 MHz, 13C 75.5 MHz) in CDCl3. The chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane. Enantiomeric excess was measured on an Agilent 1100 series high pressure liquid chromatography (HPLC) with (OD-H or AS-H) column, wavelength=245 nm. Mass spectra were obtained on an MSI/Kratos concept IS Mass spectrometer. Optical rotations were recorded on a Perkin Elmer 341 with sodium lamp polarimeter. FT-IR spectra were obtained on an ATI Mattson Research Series spectrometer using KBr discs and solids were mixed with Nujol.

2.2. Synthesis

2.2.1. Representative procedure A: synthesis of alkyl 2-formylbenzoate. Iodomethane (0.6 mL, 9.5 mmol) was added to a stirred solution of 2-formylbenzoic acid (0.765 g, 5.1 mmol) and potassium carbonate (0.387 g, 2.8 mmol) in DMF (4 mL). The reaction mixture was refluxed for 4 h, diluted with water (8 mL), and extracted with DCM. The combined organic phases were washed with 1 N HCl (4 mL), saturated aqueous $NaHCO_3$ (4 mL), and dried over Na_2SO_4. After filtration and evaporation of the solvents in vacuum, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 6/1) to yield **7a** as a colorless oil (0.673 g, 80.4%).

*2.2.1.1. Methyl 2-formylbenzoate (**7a**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.59 (s, 1H), 7.97–7.90 (m, 2H), 7.65–7.62 (m, 2H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=192.3, 166.9, 137.1, 134.5, 133.1, 132.5, 130.5, 128.5, 52.9. HRMS (EI): *m*/*z* calcd for $C_9H_8O_3$ (M^+): 164.0473; found: 164.0468.

2.2.2. Representative procedure B: synthesis of 5-substituted 2-formylbenzoic acid. 1,2-Dichloroethane (25 mL) was added to a mixture of 6-methoxyphthalide (670 mg, 4.5 mmol), *N*-bromosuccinimide (890 mg, 5 mmol), azobisisobutyronitrile (41 mg, 0.2 mmol), and refluxed for 1 h. The reaction mixture was kept in an ice bath for 2 h then filtered. The solvent was removed under reduced pressure. Water (10 mL) was then added and the resulting mixture refluxed for 1 h. The reaction mixture was then cooled to room temperature and extracted with EtOAc. The combined organic phases were dried and concentrated under reduced pressure.

*2.2.2.1. Methyl 5-bromo-2-formylbenzoate (**7b**).* 6-Bromophthalide was prepared by portion wise addition of phthalide (1 g, 7.45 mmol) to a mixture of trifluoroacetic acid (TFA) (3.7 mL) and sulfuric acid (1.7 mL) at room temperature for 9 h. The reaction mixture was stirred at room temperature for 60 h, then poured onto ice and extracted with ethyl acetate. The combined organic phases were subsequently washed with a saturated solution of sodium bicarbonate and brine. After evaporation of the solvents in vacuum, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 9/1) to yield the desired product. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.01 (d, *J*=1.8 Hz, 1H), 7.80 (dd, *J*=8.4, 1.8 Hz, 1H), 7.41 (d, *J*=7.8 Hz, 1H), 5.29 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.5, 145.2, 137.2, 128.7, 127.9, 123.9, 123.1, 69.6. The representative procedures B and A outlined above were followed to prepare **7b**, which was isolated as a light yellow solid. Mp=114–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.57 (s, 1H), 8.11 (d, *J*=1.8 Hz, 1H), 7.80 (s, 1H), 7.79 (d, *J*=1.8 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=191.0, 165.4, 135.7, 133.5, 133.4, 130.0, 128.1, 53.2. HRMS (EI): *m*/*z* calcd for $C_9H_7BrO_3$ (M^+): 241.9579; found: 241.9577.

*2.2.2.2. Methyl 2-formyl-5-nitrobenzoate (**7c**).* The starting 6-nitrophthalide was prepared by the reported procedure of Wang et al.[20] Thereafter, the representative procedures B and A outlined above were followed, respectively. Mp=62–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.67 (s, 1H), 8.80 (d, *J*=2.1 Hz, 1H), 8.47–8.43 (m, 1H), 8.08 (d, *J*=8.4, 1H), 4.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.5, 164.7, 150.0, 141.5, 133.0, 130.1, 127.2, 125.8, 53.6. HRMS (EI): *m*/*z* calcd for $C_9H_7NO_5$ (M^+): 209.0324; found: 209.0326.

*2.2.2.3. Methyl 2-formyl-5-((isobutoxycarbonyl)amino)benzoate (**7d**).* 6-Aminophthalide was prepared by the reported procedure of Pokhodylo et al.[21] 4-Dimethylamino pyridine (DMAP) (0.12 g, 1 mmol) and isobutyl chloroformate (1.5 g, 11 mmol) were added to a mixture of 6-aminophthalide (1.49 g, 10 mmol) in acetonitrile (30 mL). The reaction mixture was stirred at room temperature overnight. After evaporation of the solvents in vacuum, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) to yield corresponding carbamate. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.93 (s, 1H), 7.85 (d, *J*=8.4 Hz, 1H), 7.60 (s, 1H), 7.40 (d, *J*=8.4 Hz, 1H), 5.26 (s, 2H), 3.94 (d, *J*=6.6 Hz, 2H), 1.98–1.89 (m, 1H), 0.92 (d, 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.2, 153.9, 140.9, 139.6, 126.4, 125.1, 122.7, 114.9, 71.6, 69.7, 27.94, 19.02. HRMS (EI): *m*/*z* calcd for $C_{13}H_{15}NO_4$ (M^+): 249.1001; found: 249.1006. The representative procedure B and A was followed, respectively, to yield **7d** as a light yellow solid. Mp=104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.50 (s, 1H), 8.04 (d, *J*=2.1 Hz, 1H), 7.95 (d, *J*=8.4 Hz, 1H), 7.70 (dd, *J*=8.4, 1.9 Hz, 1H), 7.45 (s, 1H), 4.00 (d, *J*=6.6 Hz, 2H), 3.95 (s, 3H), 2.04–1.89 (m, 1H), 0.95 (d, *J*=6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.9, 166.6, 153.2, 142.9, 133.7, 131.1, 130.2, 120.8, 119.2, 71.9, 52.8, 27.9, 19.0. HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}NO_5$ (M^+): 279.1107; found: 279.1110.

*2.2.2.4. Methyl 4-formyl-[1,1′-biphenyl]-3-carboxylate (**7e**).* For preparation of the intermediate 6-phenylphthalide, toluene (2.3 mL) was added to a mixture of 6-bromophthalide (280 mg, 1.3 mmol), phenylboronic acid (319.4 mg, 2.6 mmol), tetrakis(triphenylphosphine) palladium ($pd(pph_3)_4$) (75.7 mg, 0.065 mmol), and sodium carbonate solution (1.9 mL, 2 M). The reaction mixture was refluxed for 5 h followed by adding water (2 mL) and extraction with ethyl acetate (10 mL, three times). The combined organic phase was dried and concentrated under the reduced pressure. The crude product was purified by column chromatography on silica gel

(*n*-hexane/EtOAc: 1/1) to yield the desired product. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.14 (s, 1H), 7.93 (dd, *J*=8.1, 1.8 Hz, 1H), 7.65–7.60 (m, 3H), 7.50–7.43 (m, 3H), 5.38 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.2, 145.4, 142.8, 139.5, 133.3, 129.2, 128.3, 127.3, 124.1, 122.6, 69.7. HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}O_2$ (M^+): 210.0681; found: 210.0684. The representative procedures B and A outlined above were then followed, respectively, to yield **7e** as a white solid. Mp=77–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.62 (s, 1H), 8.15 (s, 1H), 7.97 (d, *J*=8.1 Hz, 1H), 7.79 (dd, *J*=8.1, 1.5 Hz, 1H), 7.60 (dd, *J*=8.4, 1.8 Hz, 2H), 7.48–7.40 (m, 3H), 3.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=191.6, 166.7, 145.7, 138.6, 130.5, 129.1, 128.9, 128.8, 127.2, 52.8. HRMS (EI): *m*/*z* calcd for $C_{15}H_{12}O_3$ (M^+): 240.0786; found: 240.0783.

*2.2.2.5. Methyl 2-formyl-5-methoxybenzoate (**7f**).* Starting 6-methoxyphthalide was prepared by the reported procedure of Napoletano et al.[22] The representative procedures B and A outlined above were then followed, respectively. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.39 (s, 1H), 7.89 (d, *J*=8.7 Hz, 1H), 7.32 (d, *J*=2.4 Hz, 1H), 7.04 (dd, *J*=8.4, 2.1 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.5, 166.6, 163.2, 134.4, 130.8, 129.4, 117.4, 115.3, 55.7, 52.7. HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}O_4$ (M^+): 194.0579; found: 194.0573.

*2.2.2.6. Ethyl 2-formylbenzoate (**7g**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.90 (s, 1H), 7.96–7.88 (m, 2H), 7.63–7.60 (m, 2H), 4.41 (q, *J*=7.2 Hz, 2H), 1.40 (t, *J*=7.2, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=192.1, 166.3, 137.0, 132.9, 132.5, 132.3, 130.3, 128.3, 61.9, 14.3. HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}O_3$ (M^+): 178.0630; found: 178.0627.

*2.2.2.7. Hexyl-2-formylbenzoate (**7h**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.59 (s, 1H), 7.95–7.87 (m, 2H), 7.63–7.57 (m, 2H), 4.34 (t, *J*=3.6 Hz, 2H), 1.80–1.70 (m, 2H), 1.43–1.25 (m, 6H), 0.87 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=192.0, 166.2, 137.0, 132.8, 132.2, 130.3, 128.3, 66.0, 31.3, 28.5, 25.6, 22.5, 13.9. HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}O_3$ (M^+): 234.1256; found: 234.1250.

*2.2.2.8. Dodecyl 2-formylbenzoate (**7i**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.62 (s, 1H), 7.98–7.91 (m, 2H), 7.65–7.62 (m, 2H), 4.37 (t, *J*=6.6 Hz, 2H), 1.81–1.76 (m, 2H), 1.43–1.26 (m, 18H), 0.87 (t, *J*=6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=192.0, 166.3, 137.1, 132.9, 132.4, 132.2, 130.3, 128.3, 66.0, 31.9, 29.6, 29.5, 29.5, 29.3, 29.2, 28.6, 26.0, 24.7, 22.7, 14.1. HRMS (EI): *m*/*z* calcd for $C_{20}H_{30}O_3$ (M^+): 318.2195; found: 318.22047.

*2.2.2.9. Benzyl-2-formylbenzoate (**7j**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.62 (s, 1H), 7.97–7.87 (m, 2H), 7.58–7.55 (m, 2H), 7.46–7.33 (m, 5), 5.39 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=191.7, 165.8, 136.9, 135.2, 132.7, 132.2, 131.7.3, 130.2, 128.5, 128.3, 128.2, 128.2, 67.3, HRMS (EI): *m*/*z* calcd for $C_{15}H_{12}O_3$ (M^+): 240.0786; found: 240.0783.

*2.2.2.10. Isopropyl 2-formylbenzoate (**7k**).* Mp=77–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.45 (s, 1H), 7.81–7.67 (m, 2H), 7.51–7.41 (m, 2H), 5.20–5.05 (m, 1H), 1.24 (d, *J*=6, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=192.0, 165.7, 136.9, 132.8, 132.0, 130.2, 128.2, 69.7, 21.8. HRMS (EI): *m*/*z* calcd for $C_{11}H_{12}O_3$ (M^+): 192.0786; found: 192.0781.

*2.2.2.11. tert-Butyl 2-formylbenzoate (**7l**).* To a vigorously stirred suspension of anhydrous magnesium sulfate (3.2 g, 27 mmol) in DCM (27 mL), sulfuric acid (0.4 mL, 6.7 mmol) was added. The reaction mixture was stirred for 15 min; 2-carboxy benzaldehyde (1 g, 6.7 mmol) and *tert*-butanol (3.2 mL) were added and stirred for 18 h at room temperature followed by quenching with saturated sodium bicarbonate (75 mL). The organic phase was separated, washed with brine, and dried. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 6/1) to yield **7l** as a white solid (1.1 g, 80.0%). Mp=80–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.58 (s, 1H), 7.85 (d, *J*=7.8 Hz, 1H), 7.70–7.65 (m, 1H), 7.57–7.47 (m, 2H), 6.54 (s, 1H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=196.2, 146.5, 134.3, 130.5, 127.2, 125.2, 123.3, 98.0, 77.8, 28.7. HRMS (EI): *m*/*z* calcd for $C_{12}H_{14}O_3$ (M^+): 206.0943; found: 206.0937.

*2.2.2.12. 2-Formylphenylcarboxymethyl polystyrene (**7m**).* Compound **7m** was synthesized by following the procedure reported by Knepper et al.[4d] Spectroscopic data was in full agreement with spectral data of an authentic sample.

2.2.3. Representative procedure C: synthesis of substituted (R)-3-allylisobenzofuran-1(3H)-one. A round-bottomed flask wrapped in aluminum foil was charged with AgF (7.75 mg, 0.061 mmol), (*R*)-BINAP (22.8 g, 0.035 mmol), anhydrous MeOH (0.2 mL), and stirred for 10 min at room temperature. The mixture was cooled to −20 °C (dry ice/xylene bath) followed by dropwise addition of methyl 2-formylbenzoate **7a** (100 mg, 0.61 mmol) and allyltrimethoxysilane (154 μL, 0.91 mmol). After 4 h, the reaction mixture was quenched with a mixture of 1 N HCl (3 mL) and KF (ca. 0.3 g) and stirred for 30 min. The resulting precipitate was filtered and the filtrate was dried over $MgSO_4$. After evaporation of the solvents in vacuum, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) to yield **8a** as a colorless oil (72.1 mg, 68% yield).

*2.2.3.1. (R)-3-Allylisobenzofuran-1(3H)-one (**8a**).* Representative procedure C was followed to prepare **8a** from substrates **7a**, **7g**–**j**, and **7m** and the spectroscopic data was in full agreement with spectral data of an authentic sample.[6] ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.88 (d, *J*=7.8 Hz, 1H), 7.67 (t, *J*=7.6 Hz, 1H), 7.53–7.47 (m, 2H), 5.77–5.50 (m, 1H), 5.521 (t, *J*=6 Hz, 1H), 5.16–5.13 (m, 2H), 2.75–2.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.5, 149.4, 134.0, 131.3, 129.3, 126.3, 125.8, 122.1, 119.8, 80.3, 38.7. The product **8a** was obtained from substrate **7g** (61.5 mg, 58%), **7h** (77.4 mg, 73%), **7i** (74.3 mg, 70%), **7j** (57.3 mg, 54%), **7m** (72.1 mg, 68%). For **8a** prepared from **7a** $[\alpha]_D^{20}$ +50.5 (*c* 1.74, $CHCl_3$). For **8a** prepared from **7g** $[\alpha]_D^{20}$ +63.0 (*c* 2.0, $CHCl_3$). For **8a** prepared from **7h** $[\alpha]_D^{20}$ +70.1 (*c* 2.05, $CHCl_3$). For **8a** prepared from **7i** $[\alpha]_D^{20}$ +65.7 (*c* 1.5, $CHCl_3$). For **8a** prepared from **7j** $[\alpha]_D^{20}$ +62.3 (*c* 1.5, $CHCl_3$). For **8a** prepared from **7m** $[\alpha]_D^{20}$ +61.4 (*c* 1.95, $CHCl_3$). The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H, hexane/^{i}PrOH 95:5, flow rate 0.5 mL min^{-1}, wavelength=245 nm). For **8a** prepared from **7a** enantiomeric excess=71%, (t_{minor}=20.41 min (*S*), area%=14.23; t_{major}=19.00 min (*R*), area%=85.77). For **8a** prepared from **7g** enantiomeric excess=63%, (t_{minor}=18.97 min (*S*), area%=18.60; t_{major}=20.47 min (*R*), area%=81.40). For **8a** prepared from **7h** enantiomeric excess=86%, (t_{minor}=18.58 min (*S*), area%=7.24; t_{major}=19.52 min (*R*), area%=92.75. For **8a** prepared from **7i** enantiomeric excess=86%, (t_{minor}=18.72 min (*S*), area%=6.76; t_{major}=19.85 min (*R*), area%=93.24). For **8a** prepared from **7j** enantiomeric excess=63%, (t_{minor}=18.97 min (*S*), area%=18.60; t_{major}=20.47 min (*R*), area%=81.40). For **8a** prepared from **7m** enantiomeric excess=76% (racemic), (t_{minor}=19.37 min (*S*), area%=12.18; t_{major}=20.68 min (*R*), area%=87.82). Absolute configuration assigned as (*R*) by comparison of optical rotation with a literature value.[7b]

*2.2.3.2. (R)-3-Allyl-6-bromoisobenzofuran-1(3H)-one (**8b**).* Representative procedure C was followed. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) to yield **8b** (87.9 mg, 57%). The spectroscopic data was in full agreement with spectral data of an authentic sample.[6] ^{1}H NMR (300 MHz,

$CDCl_3$): δ=8.05 (d, J=1.6 Hz, 1H), 7.79 (dd, J=8.1, 1.7 Hz, 1H), 7.37 (d, J=6 Hz, 1H), 5.82–5.69 (m, 1H), 5.508 (t, J=6 Hz, 1H), 5.23–5.17 (m, 2H), 2.75–2.67 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.8, 147.0, 136.1, 131.9, 129.9, 122.7, 119.3, 79.2, 37.6. $[\alpha]_D^{20}$ +0.14 (*c* 10, $CHCl_3$). The enantioselectivity was determined by HPLC analysis on a chiral column (AS-H, hexane/^{i}PrOH 90:10, flow rate 1 mL min^{-1}, wavelength=245 nm) to be 39%: t_{minor}=7.51 min (*S*), area%=30.43, t_{major}=8.02 min (*R*), area%=69.56.

*2.2.3.3. (R)-3-Allyl-6-nitroisobenzofuran-1(3H)-one (**8c**).* Representative procedure C was followed. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) to yield **8c** (69.5 mg, 52%). The spectroscopic data was in full agreement with spectral data of an authentic sample.[6] ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.72 (s, 1H), 8.54 (dd, J=8.1, 2.1 Hz, 1H), 7.67 (t, J=8.4 Hz, 1H), 5.67–5.63 (m, 2H), 5.23–5.17 (m, 2H), 2.78–2.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.8, 154.5, 149.1, 130.0, 128.8, 128.1, 123.5, 121.4, 121.4, 80.2, 38.2. $[\alpha]_D^{20}$ +10.1 (*c* 0.62, $CHCl_3$). The enantioselectivity was determined by HPLC analysis on a chiral column (AS-H, hexane/^{i}PrOH 80:20, flow rate 1 mL min^{-1}, wavelength=245 nm) to be 33%: t_{minor}=13.20 min (*S*), area%=33.33, t_{major}=17.65 min (*R*), area%=66.67.

*2.2.3.4. (R)-Isobutyl (3-allyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)carbamate (**8d**).* Representative procedure C was followed. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) to yield **8e** (114.7 mg, 65%). The spectroscopic data was in full agreement with spectral data of an authentic sample.[6] ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.87 (s, 1H), 7.86 (s, 1H), 7.41 (d, J=8.4, Hz, 1H), 7.22 (s, 1H), 5.82–5.68 (m, 1H), 5.49 (t, J=6 Hz, 1H), 5.21–5.13 (m, 2H), 3.98 (d, J=6.6 Hz, 2H), 2.77–2.58 (m, 2H), 2.05–1.94 (m, 1H), 0.98 (d, J=6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.2, 152.7, 143.0, 138.6, 130.3, 127.3, 126.3, 123.8, 121.8, 118.9, 79.3, 70.9, 37.9, 27.1, 18.2. $[\alpha]_D^{20}$ +30.3 (*c* 0.23, $CHCl_3$). The enantioselectivity was determined by HPLC analysis on a chiral column (AS-H, hexane/^{i}PrOH 90:10, flow rate 1 mL min^{-1}, wavelength=245 nm) to be 43%: t_{major}=31.31 min (*S*), area%=28.38, t_{minor}=28.28 min (*R*), area%=71.62.

*2.2.3.5. (R)-3-Allyl-6-phenylisobenzofuran-1(3H)-one (**8e**).* Representative procedure C was followed. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) to yield **8e** (102.3 mg, 67%). The spectroscopic data was in full agreement with spectral data of an authentic sample.[6] ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.13 (s, 1H), 7.92 (dd, J=6.6, 1.6 Hz, 1H), 7.65–7.63 (m, 2H), 7.67–7.43 (m, 4H), 5.90–5.76 (m, 1H), 5.59 (t, J=6 Hz, 1H), 5.27–5.19 (m, 2H), 2.83–2.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.4, 148.2, 142.9, 139.5, 133.2, 131.3, 129.2, 128.3, 127.4, 127.2, 124.1, 122.5, 119.9, 80.3, 38.9. $[\alpha]_D^{20}$ +30.1 (*c* 0.71, $CHCl_3$). The enantioselectivity was determined by HPLC analysis on a chiral column (AS-H, hexane/^{i}PrOH 90:10, flow rate 1 mL min^{-1}, wavelength=245 nm) to be 61%: t_{minor}=20.14 min (*S*), area%=19.38, t_{major}=14.88 min (*R*), area%=80.62.

*2.2.3.6. (R)-3-Allyl-6-methoxyisobenzofuran-1(3H)-one (**8f**).* Representative procedure C was followed. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 1/1) to yield **8f** (68.5 mg, 55%). The spectroscopic data was in full agreement with spectral data of an authentic sample.[6] ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36 (s, 1H), 7.33 (d, J=2.1 Hz, 1H), 7.20–7.24 (m, 1H), 5.80–5.69 (m, 1H), 5.47 (t, J=5.9 Hz, 1H), 5.21–5.14 (m, 2H), 3.87 (s, 3H), 2.71–2.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.5, 160.7, 141.8, 131.3, 127.6, 122.9, 122.9, 119.7, 107.5, 80.1, 55.8, 38.8. $[\alpha]_D^{20}$ +19.3 (*c* 0.4, $CHCl_3$). The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H, hexane/^{i}PrOH 99:1, flow rate 0.5 mL min^{-1}, wavelength=245 nm) to be 86%: t_{minor}=36.09 min (*S*), area%=7.12, t_{major}=37.59 min (*R*), area%=92.88.

*2.2.4. Preparation of the (R)-1-phenylbut-3-en-1-ol (**10**).* Representative procedure C was followed. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 6/1) to yield **10** (79.5 mg, 88%). The spectroscopic data was in full agreement with spectral data of an authentic sample.[1] ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.30–7.39 (m, 5H), 5.77–5.91 (m, 1H), 5.15–5.22 (m, 2H), 4.75 (t, J=7 Hz, 1H), 2.51–2.57 (m, 2H), 2.22 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ=144.0, 134.5, 128.5, 127.7, 125.9, 118.5, 73.4, 43.9. $[\alpha]_D^{20}$ +43.1 (*c* 0.8, $CHCl_3$). The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H, hexane/^{i}PrOH 97:3, flow rate 0.5 mL min^{-1}, wavelength=245 nm) to be 87%: t_{minor}=12.03 min (*S*), t_{major}=10.52 min (*R*).

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