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Synthesis of Chiral 3-Substituted Phthalides by a Sequential Organocatalytic Enantioselective Aldol-Lactonization Reaction. Three-Step Synthesis of (*S*)-(−)-3-Butylphthalide

Haoyi Zhang,[†] Shilei Zhang,[†,§] Lu Liu,[†] Guangshun Luo,[†] Wenhu Duan,*[,†,‡] and Wei Wang*[,†,‡,§]

[†]*Department of Pharmaceutical Sciences, School of Pharmacy, East China University of Sciences & Technology, Shanghai 200237, China,* [‡]*Shanghai Institute of Materia Medica, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Shanghai 201203, China, and* [§]*Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001*

wwang@unm.edu

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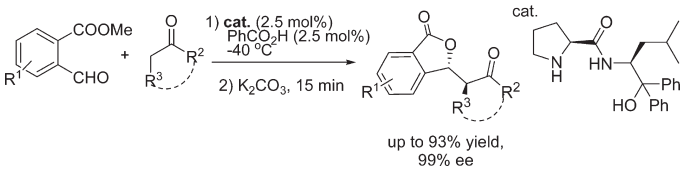

The development of efficient methods for the facile construction of important molecular frameworks is an important goal in organic synthesis. Chiral 3-substituted phthalides are widely distributed in a large collection of natural products with broad, potent, and potentially path-pointing biological activities. In this investigation, we have uncovered an unprecedented organocatalytic asymmetric aldol-lactonization reaction of 2-formylbenzoic esters with ketones/aldehydes for convenient construction of the enantioenriched "privileged" scaffold. As a result of the sensitive nature of substrate structures of an organocatalytic enantioselective aldol reaction, after extensive optimization of reaction conditions, catalyst L-prolinamide alcohol **IV** is identified as the best promoter. Interestingly, it is found that in this reaction, addition of an acid additive $PhCO_2H$ can significantly enhance reaction efficiency with use of only as low as 2.5 mol % **IV** for the process. Moreover, due to the sensitivity of reaction conditions toward a sequential aldol-lactonization process without affecting enantioselectivity and racemization, it is essential to remove the catalyst for the subsequent facile lactonization reaction in the presence of K_2CO_3. The aldol-lactonization processes serve as a powerful approach to the preparation of synthetically and biologically important 3-substitued phthalides with a high level of enantioselectivities. A 3-step catalytic asymmetric synthesis of the natural product of 3-butylphthalide is reported.

Introduction

The discovery of new synthetic methodologies for the facile construction of biologically interesting complex molecular architectures in an efficient way from readily available starting materials is of considerable significance in chemical synthesis. The importance of chiral 3-substituted phthalide (1(3*H*)-isobenzofuranone) frameworks is underscored by their wide distribution in a large collection of natural products with broad, potent, and potentially path-pointing biological activities.[1] Some representative examples are described in Figure 1. 3-Butylphthalide (**1a**), a component in the Chinese folk medicine extracted from celery seed oil,[2a] is in phase II clinical trials in China and potentially can be used for the treatment of stroke.[2b] Moreover, it is employed for

*To whom correspondence should be addressed. Phone: (505) 277-0756. Fax: (505) 277-2609.

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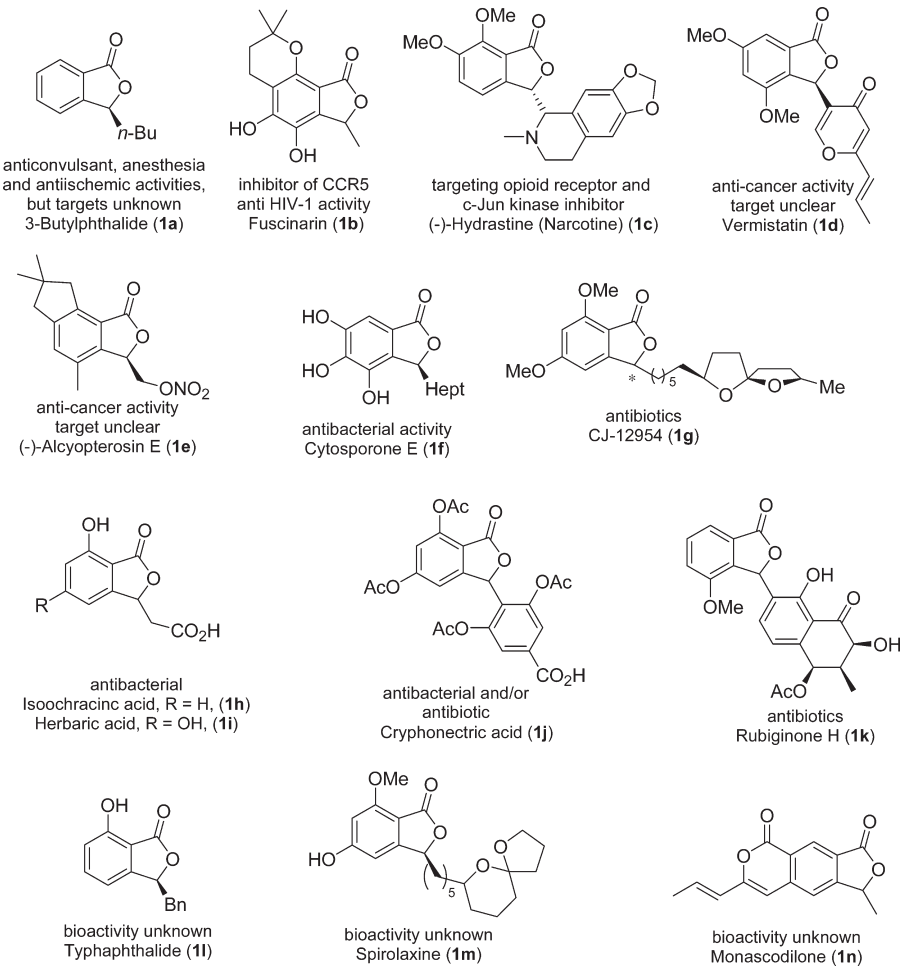

FIGURE 1. Selected examples of natural occurring chiral 3-substituted phthalides with reported biological activities.

seasoning and flavoring purposes, shows anticonvulsant action,[2c] increases the duration of anesthesia,[2d] and exhibits cerebral antiischemic action.[2e] Fuscinarin (**1b**) is a potent human CCR5 antagonist, effectively blocking HIV entry into host cells.[3] (−)-Hydrastine (**1c**) is active at the opioid receptor.[4] In addition, it possesses antipaclitaxel-resistant human ovarian cancer activity through c-Jun kinase-mediated apoptosis and it is in phase I clinical trials.[5] Vermistatin (**1d**) and alcyopterosin E (**1e**) display cytotoxic activity,[6] whereas cytosporone E (**1f**)[7] and CJ-12,954 (**1g**)[8] and isoochracinic acid (**1h**) and herbaric acid (**1i**),[9] cryphonectric acid (**1j**),[10] and (−)-rubiginone-H (**1k**)[11] are antibacterial and/or antibiotic reagents. The bioactivities of (−)-typhaphthalide (**1l**),[12] spirolaxine (**1m**),[13] and (+)-monascodilone (**1n**)[14] are unknown. Furthermore, the absolute configurations of a number of these natural products such as **1b**, **1g**, **1h**, **1i**, **1j**, **1k**, and **1n** have not been established. Accordingly, efficient asymmetric methods for the facile

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construction of the chiral 3-substituted phthalide architectures can lead to convenient approaches to these biologically intriguing natural products. Consequently their ready availability enables them to serve as effective chemical tools for the elucidation of the functions of proteins/receptors. Moreover, these asymmetric strategies will afford useful methods for establishing absolute configurations of these natural products including **1b**, **1g**, **1h**, **1i**, **1j**, **1k**, and **1n**.

Given the biological importance of the chiral 3-substituted phthalides, the molecular architectures have become a platform for new synthetic methodology development.[1] In spite of significant progress being made, asymmetric syntheses of the scaffolds are very limited.[15] Chiral auxiliaries, precursors, and resolutions have been intensively explored for such purposes.[16] Despite the fact that catalytic approaches are particularly appealing, only a handful of examples relying on the use of organometallics have been reported to date. Noyori reported the first catalytic asymmetric method using an enantioselective transfer hydrogenation reaction for the generation of the chiral 3-substituted phthalides.[17] A chiral amine alcohol mediated addition of zinc reagent to aldehydes was illustrated by Butsugan et al.[18] Lin and co-workers reported a Ni(II)/(*S*)-BINAP complex catalyzed asymmetric tandem process.[19] Tanaka[20] and Yamamoto[21] independently disclosed highly enantioselective Rh(I)-catalyzed one-pot transesterification and [2+2+2] cycloaddition to afford the chiral frameworks. Trost and Weiss described an elegant prophenol-promoted enantioselective alkynylation as a key step for the formation of enantioenriched phthalides.[22] Recently, Cheng and co-workers reported a CoI_2(*S*,*S*)dipamp-catalyzed cyclization approach to the chiral scaffold.[23]

In contrast to the use of the chiral organometallics as promoters, the employment of organocatalysts for the synthesis of chiral 3-substituted phthalides has not been disclosed.[24] Moreover, there is ample room for improvement and new efficient methods are needed in this area, with respect to safety of reagents, catalysts, catalyst loadings, stereoselectivities, overall efficiency, atom economy, and methods with generation of functional diversity. Toward this end, we wish to detail a new highly efficient organocatalytic enantioselective aldol-lactonization process for the facile preparation of chiral 3-substituted phthalides from simple achiral starting materials under mild reaction conditions. We have successfully applied the powerful method for efficient synthesis of natural product (*S*) 3-butylphthalide in three steps with high yields and high enantioselectivity.

Results and Discussion

Design Plan. Aldol reactions are a cornerstone of synthetic organic chemistry.[24] A wealth of imaginative reagents, catalysts, and protocols have been devised for the synthesis of structurally diversified building blocks and targets. In recent years, considerable attention has been directed toward developing organocatalytic asymmetric aldol reactions.[25,26]

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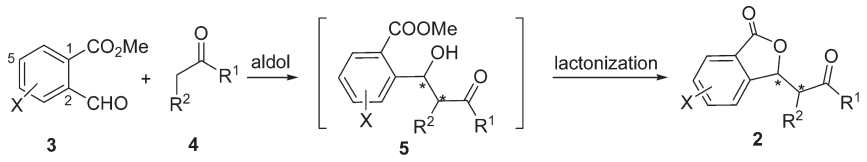
SCHEME 1. Synthesis of Chiral 3-Substituted Phthalides by a New Organocatalytic Asymmetric Aldol-Lactonization Reaction



We envision that through the design of specific substrates, a new strategy with incorporation of an unprecedented organocatalytic asymmetric aldol-initiated lactonization reaction can be implemented for the efficient preparation of biologically significant chiral 3-substituted phthalides (Figure 1 and Scheme 1).[27,28] To our knowledge, such an organocatalytic asymmetric aldol-lactonization reaction for the synthesis of the molecular architectures has not been reported.[29,30] To successfully develop an organocatalytic asymmetric aldol-lactonization reaction, we surmise that the key issue is to design a functionalized aldol acceptor. In the process, it is imaged that the use of 2-formylbenzoic esters **3** as one of the essential reactants is required. They have an amphiphilic function (Scheme 1). They serve as an aldol acceptor for the aldol reaction. They also function as the electrophile for the subsequent lactonization. It is realized that although organocatalytic asymmetric aldol reactions of aryl aldehydes with ketones or aldehydes have been intensively studied,[25,26] the asymmetric aldol reaction of 2-formylbenzoic esters **3** with ketones/aldehydes **4** has not been reported. Due to the sensitive nature of substrate structures, the enantioselectivity and reaction yield of an aldol reaction varies significantly. We speculate that the steric and electronic effect posed by the *O*-ester moiety would have a dramatic influence on the outcome of the aldol process. It is realized that 2-alkyl aryl aldehydes as substrates for organocatalytic aldol reactions have been less studied.[31] Moreover, generally poorer enantioselectivities were observed, as compared with less hindered meta- and para-substituted benzaldehydes. Therefore, seeking an optimal promoter is critical for the specific highly enantioselective aldol reaction. Furthermore, a reaction condition, which can accommodate a subsequent facile lactonization without affecting the enantioselectivity of the aldol reaction and racemization, presents another significant challenge. Finally, highly efficient organocatalytic aldol reactions with low catalyst loading (< 5 mol %) are in high demand for practical applications and such examples are rarely seen in the existing protocols.[26f,g,n,o]

Optimization of Reaction Conditions. As discussed above, a critical issue, which needs to be addressed in developing a catalytic asymmetric approach to the aldol-lactonization reaction, is the identification of proper organocatalysts. Consequently, our initial studies focus on screening different amine-based organocatalysts. To prove the feasibility of the proposed catalytic enantioselective aldol-lactonization process, initially an aldol reaction of methyl 2-formylbenzoate **3a** in acetone **4a** was probed in the presence of L-proline, an effective catalyst in aldol reactions (Table 1 and Figure 2).[26a] It was found that under the reaction condition, the major product was aldol adduct **5a**, which did not undergo a subsequent complete lactonization reaction in a one-pot operation. After multiple attempts, we found that by simple removal of the catalyst through a short silica gel pad, the lactonization proceeded smoothly to give phthalide **2a** in an almost quantitative yield when the intermediate **5a** was treated with K_2CO_3 (1.5 equiv) in MeOH/acetone (1:10, v/v) at rt for 15 min.

Under the reaction conditions, **2a** was obtained in 56% yield and with moderate enantioselectivity (65% ee, Table 1, entry 1). The mediocre results prompted us to screen other organocatalysts aimed at improving enantioselectivity to reach a useful level with the specific methyl 2-formylbenzoate **3a**. Although a number of chiral pyrrolidines have been used in asymmetric aldol reactions, we are particularly interested in those displaying high catalytic activity and enantioselectivity toward acetone as donor and aryl aldehydes as acceptor related reactions since such systems are close to the current one. In the first attempt with (*S*)-pyrrolidine sulfonamide **II**, surprisingly a racemic mixture was obtained (Table 1, entry 2).[26k] C_2-Symmetric bisprolinamide **III** gave a high yielding but disappointing enantiomerically enriched product (entry 3) despite the fact that it exhibited high enantioselectivity with simple aryl aldehyde aldol acceptors.[26g] These studies indicate that indeed the *O*-methyl ester moiety has a pronounced effect on the aldol reaction. Considering the steric effect of the specific substrate **3a** and high catalytic activity observed with pyrrolidine amide **III**, we reasoned that a bulky pyrrolidine amide could be a good choice for the aldol-lactonization reaction. Recently, we have successfully identified catalyst **IV** as a promoter, originally developed by Singh et al.,[26l] for the aldol reaction of acetone with α-amino aldehydes in the synthesis of antibiotic linezolid.[32] Notably, good enantioselectivity (88% ee) was achieved. With these results in mind, we examined its suitability for this reaction. To our delight, encouraging results (86% yield and 80% ee, entry 4) are seen.

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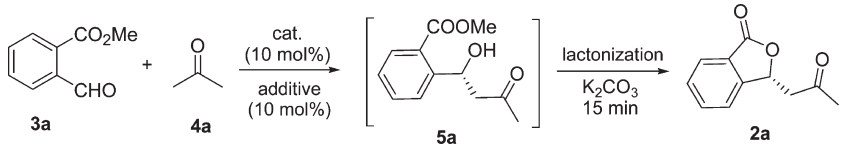
TABLE 1. Exploration of the Organocatalytic Asymmetric Aldol-Lactonization Reaction of 3a with 4a[a]



entry	cat.	additive	T (°C)	t (h)	% yield[b]	% ee[c]
1[d]	**I**	none	rt	36	56	65
2	**II**	none	rt	36	44	0
3	**III**	none	rt	24	91	40
4	**IV**	none	rt	12	86	80
5	**IV**	none	−10	12	80	85
6	**IV**	none	−40	36	71	90
7	**IV**	$PhCO_2H$	−40	6	78	94
8	**IV**	AcOH	−40	20	86	89
9	**IV**	H_3PO_4	−40	60	32	90
10	**IV**[e]	$PhCO_2H$	−40	14	81	93
11	**IV**[f]	**$PhCO_2H$**	**−40**	**24**	**81**	**96**

[a]Reaction conditions: unless specified, see the Experimental Section and the Supporting Information. [b]Isolated yields. [c]Determined by chiral HPLC analysis (Chiralcel OD-H). [d]20 mol % used. [e]5 mol % of **IV** and 5 mol % of $PhCO_2H$ used. [f]2.5 mol % of **IV** and 2.5 mol % of $PhCO_2H$ used.

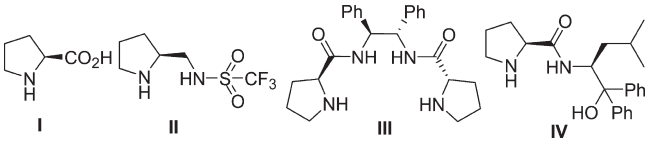


FIGURE 2. Structures of organocatalysts screened.

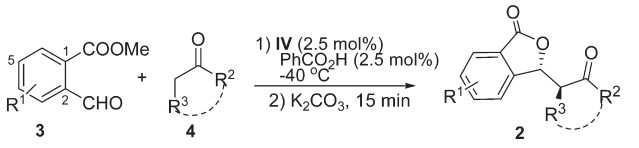
Lowering reaction temperature resulted in the enhancement of enantioselectivity (entries 5 and 6).

The general wisdom in bifunctional organocatalysis is that no additives are needed; nevertheless we found that in this reaction, addition of an acid additive could significantly augment reaction efficiency (entries 7−10). Among them probed, $PhCO_2H$ was the best one (entry 7). The reaction time was dramatically shortened (6 h) in a good yield (78%) and with high ee (94%). Remarkably, as low as 2.5 mol % of **IV** was sufficient for the highly enantioselective aldol-lactonization reaction at −40 °C (entry 11).

Scope of the Aldol-Lactonization Reactions. The optimal reaction conditions, uncovered in the exploratory effort, are exploited to probe the scope of the organocatalyst **IV** catalyzed aldol-lactonization reactions. As revealed in Table 2, the process serves as a general approach to the preparation of highly enantiomerically enriched, synthetically and biologically important 3-substituted phthalides **2** with significant structural variations for both aldol donors and acceptors. A wide range of substituted methyl *o*-formylbenzoates **3** with acetone **4a** react smoothly to give lactones **2** with high enantioselectivities ranging from 91% to 97% ee (entries 1−7). The results show that electron-neutral (entry 1), withdrawing (entries 2−5), and donating (entries 6 and 7) substituents on the aromatic have little effect on the aldol processes, providing phthalides **2** with high yields and excellent enantioselectivities except for the 5-phenyl substrate **3h** (entry 8). The steric effect is limited as well (entry 5).

The process is also applicable to a variety of aldol donors. In addition to acyclic ketones, it is possible to use cyclic ketones as well. For example, the reaction with cyclohexanone affords highly enantio- (97% ee) and diastereoselective (*anti*/*syn* > 20:1) product **2i** with generation of two new stereogenic centers

TABLE 2. The scope of IV-Catalyzed Aldol-Lactonization Reactions of Aldehydes 3 with Ketones/Aldehydes 4[a]



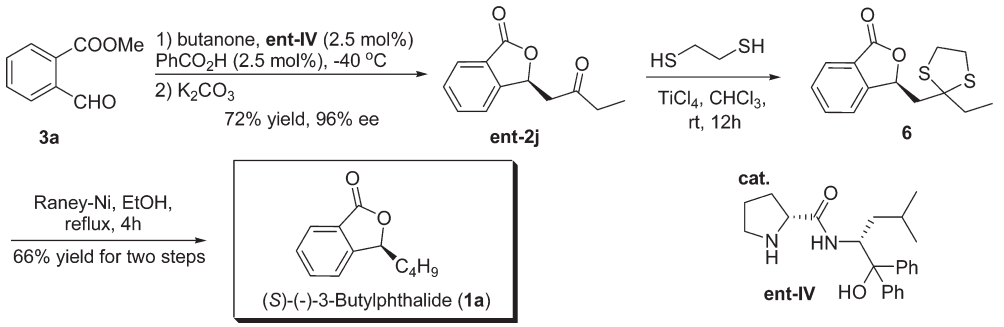
entry	R^1	R^2	R^3	**2**	t (h)	% yield[b]	% ee[c]
1	H	Me	H	**2a**	24	91	96
2	5-F	Me	H	**2b**	24	83	97
3	5-Cl	Me	H	**2c**	30	77	90
4	5-Br	Me	H	**2d**	24	84	93
5	6-NO_2	Me	H	**2e**	12	68	91[d]
6	5-MeO	Me	H	**2f**	40	70	96
7	3,5-$(MeO)_2$	Me	H	**2g**	60	53	95
8	5-Ph	Me	H	**2h**	36	78	74
9[e]	H	$(CH_2)_4$		**2i**	12	93	94[f]
10[g]	H	Et	H	**2j**	36	73	97
11[h]	H	H	Me	**2k**	12	38	99[i]

[a]Reaction conditions: unless specified, see the Experimental Section and the Supporting Information. [b]Isolated yields. [c]Determined by chiral HPLC analysis (Chiralcel OD-H). [d]At −20 °C. [e]The yield refers to total yields for all isomers and 10 mol % of **IV** and 10 mol % of $PhCO_2H$ at 0 °C. [f]Only *anti* isomer observed. [g]The yield refers to total yields for all isomers and regioselectivity 20:3 and less substituted as the major one. [h]Poor yield (26%) was obtained with **IV**. However, reaction was carried out with **2k** (3 mmol) and propionaldehyde (6 mmol) in the presence of 20 mol % of L-proline in DMF at 0 °C. [i]Determined by converting to a corresponding acetal for HPLC analysis.

in 93% yield (entry 9). Unsymmetric ketones can also participate in the process smoothly, as represented by butanone (97% ee and 73% yield, entry 10). It is noted that the process is complicated by regioselectivity. However, a good regioselectivity (20:3) is observed with a product formed at less substituted site dominantly. Finally, an aldehyde is also evaluated. It is found that L-proline **I** is a better promoter for the reaction of propionaldehyde affording excellent enantioselectivity (99% ee), albeit low yield (entry 11).

Three-Step Synthesis of Natural Product (*S*)-(−)-3-Butylphthalide (1a). As mentioned above, (*S*)-(−)-3-butylphthalide **1a** is a natural product isolated from celery with a broad

SCHEME 2. Total Synthesis of Natural Product 3-Butylphthalide (1a)



spectrum of intriguing pharmacological activities.[1c,2] Moreover, it is in phase II clinical trials in China and potentially can be used for the treatment of stroke. Therefore, methods for the efficient synthesis of the natural product and its analogies are of considerable synthetic and biological significance in drug discovery. Despite the significant and interesting biological activity of the simple chiral natural product, a very limited number of asymmetric total synthesis methods are available. Moreover, to our knowledge, these synthetic strategies exclusively rely on the use of chiral auxiliaries, precursors, or resolutions.[16g,h,k−m,o,33] An enantioselective catalytic approach has not been disclosed. Herein we have successfully employed the catalytic enantioselective aldol-lactonization process as a key step in the 3-step synthesis of (*S*)-(−)-3-butylphthalide **1a** for the first time (Scheme 2).

As shown in Scheme 2, we prepared 3-butylphthalide **1a** in a two-step process including simple thioacetalization[34] and desulfurization[35] in 66% overall yield from compound *ent*-**2j**, which is obtained from an *ent*-**IV**-catalyzed aldol-lactonization reaction (Scheme 2). The spectral data of **1a** are in full agreement with those described in the literature ($[\alpha]^{27}_D$ −66.2 (*c* 1.08, $CHCl_3$); lit.[16o] $[\alpha]^{26}_D$ −64.7 (*c* 1.06, $CHCl_3$, ee 99%); lit.[16m] $[\alpha]^{27}_D$ −71.3 (*c* 0.23, $CHCl_3$, ee >99%)). Moreover, this synthesis allows for the determination of the absolute configuration of the products from the new asymmetric aldol-lactonization reactions with catalyst **IV**.

Conclusion

In conclusion, a new organocatalytic, highly enantioselective aldol-lactonization process, catalyzed by chiral L-prolinamide alcohol **IV**, has been achieved. The simplicity and practical nature of the asymmetric protocols presented here is underscored by the use of simple starting materials and the generation of synthetically useful, high optically active 3-substituted phthalides under mild reaction conditions. Moreover, the value of the aldol-lactonization process is demonstrated in an efficient 3-step synthesis of natural product (*S*)-(−)3-butylphthalide in a catalytic asymmetric version for the first time. It is expected that the synthetic strategy can be explored in the total synthesis of other biologically interesting chiral 3-substituted phthalide-derived natural products. This constitutes our future plan to utilize the powerful synthetic tool in target-oriented synthesis.

Experimental Section

General Procedure for Aldol-Lactonization Reactions (Table 2, entry 1 as an example). A mixture of **3a** (25 mg, 0.15 mmol), $PhCO_2H$ (0.46 mg, 0.00375 mmol), and catalyst **IV** (1.4 mg, 0.00375 mmol) in acetone (0.8 mL) was stirred at −40 °C for 24 h. After completion, the reaction was indicated by TLC and the reaction mixture was passed through a 3−4 cm silica gel pad quickly to remove the catalyst, eluting with acetone. The residue, after removal of solvent, was treated with K_2CO_3 (32 mg, 0.18 mmol) in acetone/methanol 10/1 (v/v, 1 mL), then stirred at rt for 15 min. The crude product was directly purified by silica gel column eluting with EtOAc/petroleum (1/10 to 1/2) and the desired product **2a** and ee and dr were determined by chiral HPLC analysis and ^{1}H NMR, respectively (see the Supporting Information for details). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.90 (d, 1H, J = 9.5 Hz, ArH), 7.67 (ddd, 1H, J = 9.5, 1.5 Hz, ArH), 7.54 (t, 1H, J = 9.5 Hz, ArH), 7.48 (dd, 1H, J = 9.5, 1 Hz, ArH), 5.93 (t,1H, J = 8.5 Hz, OCH), 3.14 (dd, 1H, J = 8.5, 22.0 Hz, CH_2), 2.92 (dd, 1H, J = 8.0, 22.0 Hz, CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 204.4, 170.0, 149.3, 134.3, 129.4, 125.8, 122.3, 76.7, 48.1, 30.6; HPLC (chiralpak OD-H column) hexanes/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 254 nm, t_R = 8.78 (major) min, 11.39 (minor) min, ee 96%; $[\alpha]^{27}_D$ −8.3 (*c* 1.10, $CHCl_3$); MS (EI) *m*/*z* (%) [M^+] 190.1, 175.0 (10), 147.0 (100), 133.0 (47), 105.0 (25), 77.0 (12); HRMS-ES *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{10}NaO_3$ 213.0528, found 213.0532.

Total Synthesis of Natural Product 3-Butylphthalide (1a). Compound *ent*-**2j** was prepared by following the general procedure of preparing 3-substituted phthalides on a 3 mmol scale except that the catalyst *ent*-**IV** was used. The product was isolated in 72% yield and with 96% ee.

To a solution of *ent*-**2j** (0.408 g, 2 mmol) in 2 mL of dry $CHCl_3$ were added 1,2-ethanedithiol (0.38 g, 4 mmol) and $TiCl_4$ (0.57 g, 3 mmol). The mixture was stirred at rt under N_2 for 12 h and then 0.5 mL of water was added at 0 °C to terminate the reaction. The reaction mixture was diluted with water (20 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and dried over Na_2SO_4. Filtration and removal of solvent under reduced pressure gave an oil. The crude product was treated with Raney-Ni (3 g) in EtOH (20 mL) under reflux for 4 h. The reaction mixture was cooled to rt, filtered, and concentrated. The residue was purified by flash silica gel column to give a colorless oil (0.25 g) in 66% overall yield. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.86 (d, 1H, J = 7.5 Hz, ArH), 7.64 (t, 1H, J = 7.5 Hz, ArH),

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7.49 (t, 1H, $J = 7.5$ Hz, ArH), 7.39 (d, 1H, $J = 7.5$ Hz, ArH), 5.44 (q, 1H, $J = 7.8$ Hz, OCH), 2.05−1.98 (m, 1H, CH_2), 1.75−1.70 (m, 1H, CH_2), 1.46−1.29 (m, 2H, CH_2), 0.87 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 170.6, 150.1, 133.9, 128.9, 125.6, 121.7, 81.4, 34.4, 26.8, 22.4, 13.8; $[\alpha]^{27}_D$ −66.2 (*c* 1.08, $CHCl_3$), lit.[16o] $[\alpha]^{26}_D$ −64.7 (*c* 1.06, $CHCl_3$, ee 99%), lit.[16m] $[\alpha]^{27}_D$ −71.3 (*c* 0.23, $CHCl_3$, ee >99%); MS (EI) *m*/*z* [M^+] (%) 190.1, 133.0 (100), 105.0 (17), 77.0 (7).

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra, and chiral HPLC analysis data for compounds **2**, **3**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.