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Regioselective organocatalyzed asymmetric bromolactonization of aryl acrylate-type carboxylic acids: a new approach towards enantioenriched 3-substituted isobenzofuranones

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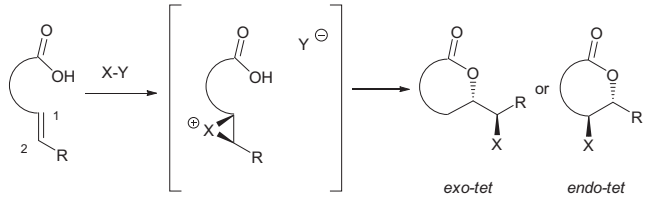
ABSTRACT

The enantioselective synthesis of several 3-substituted isobenzofuranones has been developed through a new and flexible route. When combined with a catalytic amount of benzoic acid, quinidine thiocarbamate bifunctional catalysts have demonstrated their efficiency for the highly regioselective organocatalyzed asymmetric bromolactonization reaction of aryl acrylate-type carboxylic acids.

1. Introduction

Electrophilic halocyclization reactions of unsaturated acids are versatile synthetic transformations, which represent an important class of reactions in organic synthesis.[1] In particular, halolactonizations have been widely used in organic chemistry for the synthesis of natural products and/or biologically active compounds.[2] In addition to constructing lactone ring system, halolactonization reactions introduce halogen atoms into intermediates, which can be utilized in further synthetic transformations. Halolactonization reactions generally consist of the initial formation of a halonium ion intermediate via an initial electrophilic addition of the halogen to the olefin (Scheme 1).

Subsequent antiperiplanar intramolecular cyclization through substitution by an internal oxygenated nucleophile on the carbon of the halonium ion leads to the formation of the halolactones. Halolactonization reactions usually proceed with a high degree of diastereoselectivity in a highly predictable manner. However, they can suffer from a lack of regioselectivity and they may also produce constitutional isomers arising from an *exo* or *endo* cyclization[1k,3] (Scheme 1). In comparison with the number of examples of substrate-controlled diastereoselective halolactonizations,[4] enantioselective versions under reagent or catalyst control have proven more difficult to realize and have only emerged recently (vide infra).[5] This can be attributed mainly to the difficulty in identifying



Scheme 1. General scheme of halolactonization.

a suitable catalytic system, which allows for the effective transfer of the chiral information during lactonization. Moreover, the enantiomerically enriched halonium-olefin intermediate may racemize through a rapid olefin-olefin halogen exchange.[6] Since 2010, intense research efforts have led to the development of organocatalyzed enantioselective halolactonization reactions in which the stereochemistry can be controlled by a chiral carboxylate anion and/or chiral positive halogen ion. In this context, a wide array of organocatalysts, including biscinchona alkaloids, aminoureas, aminothiocarbamates, *S*-alkylthiocarbamates, squaramides, amidine-phenol, and a trisimidazoline has been reported to induce highly enantioselective processes. On the other hand, the range of studied substrates is still limited because only alkyl and aryl-substituted pentenoic or hexenoic acid derivatives have been examined in most cases. Hence, despite the huge synthetic potential, enantioselective halolactonizations of styrene-type carboxylic acids have not elicited many synthetic efforts from the scientific community and remained poorly explored.[5k,t,x,y] Moreover, halocyclization of such unsaturated compounds is challenging

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since the presence of an aryl ring significantly reduces the regioselectivity of the reaction, with both 6-*endo* or 5-*exo* cyclization pathways being possible depending on the stereoelectronic factors. The regioselectivity of the halocyclization reaction is mainly governed by the electronic effects of the substituents connected to the styrenic carbon–carbon double bond.[5k,x] For instance, electron-rich groups connected at C2 favored the 6-*endo* product while more electron deficient groups gave higher 5-*exo* selectivity due to the destabilization of the 6-*endo* cyclization pathway.[5k] The solvent, catalyst and additives seem to have a minor impact on the regioselectivity but their roles remains unclear and are still under investigation.[7] Since considerable work has been achieved in our laboratory on the synthesis of enantioenriched isoindolinones,[8] we recently extended our interest to their oxygenated analogues i.e. isobenzofuranones **I**. These chiral bicyclic lactones display a wide array of biological activities[9] and constitute the main core of a minor group of natural products such as isoochracinic **II**[10] or herbaric acids **III**[11] bearing a carboxymethyl group at the 3 position of the lactone ring system (Fig. 1).

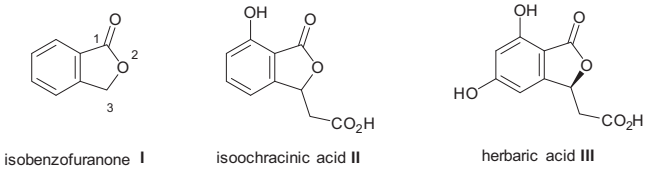


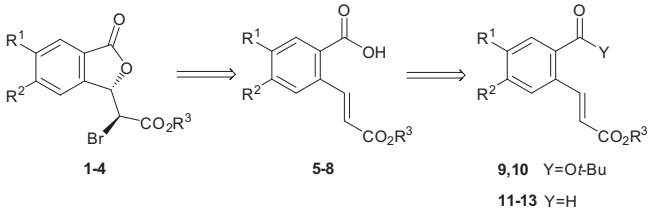
Figure 1. Natural 3-substituted bioactive isobenzofuranones.

Organic chemists have a variety of strategies at their disposal for the racemic synthesis of functionalized isobenzofuranone bearing a carboxymethyl group at C3, which are mainly based upon the lactone ring construction.[12] Otherwise, starting from racemic 3-substitued phthalides, the synthesis of enantioenriched 3,3-disubstituted benzofuranones has been reported using organocatalyzed reactions such as Mannich, allylic alkylation or Michael additions.[13] However, a few efforts have been devoted to the asymmetric synthesis of 3-carboxy isobenzofuranones and, to the best of our knowledge, only two stereoselective synthesis of such compounds have been developed so far.[14] Consequently, the development of highly regioselective organocatalyzed asymmetric synthetic methodologies for the elaboration of 3-substituted isobenzofuranones constitutes an area of current interest.

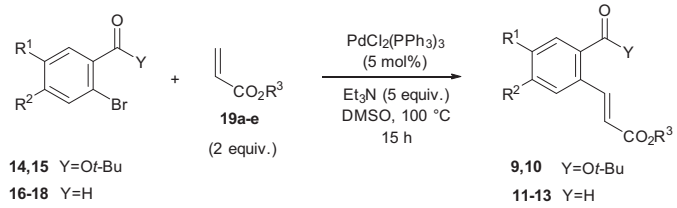
2. Results and discussion

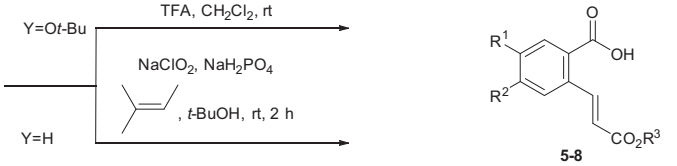
Our synthetic strategy is based upon a regio- and stereoselective organocatalyzed halolactonization reaction of aryl acrylate-type carboxylic acids **5**–**8** for the construction of the lactone ring with concomitant control of the stereogenic center at C3 (Scheme 2). In order to both increase the efficiency and control the regioselectivity of the cyclization process, we decided to incorporate an electron withdrawing group in our models on the styrenic carbon–carbon double bond. From a retrosynthetic point of view, the parent poly-substituted unsaturated benzoic acids **5**–**8** could be readily prepared from the corresponding *t*-butyl esters **9** and **10** or benzaldehydes **11**–**13** depending upon the nature and the position of the substituents connected to the aryl moiety.

t-Butyl esters **9** and **10** and benzaldehydes **11**–**13** were first readily prepared via a palladium-catalyzed Heck cross-coupling between the corresponding aryl bromides **14**–**18** and an array of acrylates **19a**–**e** (Scheme 3) (Table 1). Removal of the *t*-butyl protecting group in esters **9** and **10** by treatment with trifluoroacetic



Scheme 2. Retrosynthetic analysis.





Scheme 3. Synthesis of unsaturated benzoic acids **5**–**8**.

Table 1
Compounds **5**–**8**, **9**–**13** prepared

Entry	Y	R^1	R^2	R^3	Yield (%)[a]	Yield (%)[a]
1	O*t*-Bu	H	H	Me	**9a** 73	**5a** 94
2	O*t*-Bu	H	H	Et	**9b** 91	**5b** 87
3	O*t*-Bu	H	H	Bn	**9c** 84	**5c** 88
4	O*t*-Bu	NO_2	H	Et	**10b** 81	**6b** 91
5	H	H	H	Bu	**11d** 72	**5d** 89
6	H	H	H	Ph	**11e** 34	**5e** 94
7	H	H	H	*t*-Bu	**11f** 56	**5f** 90
8	H	OBn	H	Et	**12b** 62	**7b** 91
9	H	OMe	OMe	Et	**13b** 88	**8b** 98

[a] Isolated yield.

acid and Pinnick oxidation of aldehydes **11**–**13** furnished the targeted benzoic acids **5**–**8** with good yields (87–98%) (Scheme 3) (Table 1). From these readily available aryl acrylate-type benzoic acids, a study of their stereoselective halocyclization was then initiated. The asymmetric halocyclization reaction of compound **5b** was first studied as a representative model to screen various privileged organo-catalysts[1h] (Fig. 2) (Table 2).

Since halolactonization reactions could be achieved without the use of any catalyst or additional reagent, we performed first a control experiment. If stilbene carboxylic acid derivatives were previously shown to lead mainly to 6-*endo* halolactones,[5k] the introduction of an ester electron withdrawing group in our substrates was important in controlling the 5-*exo* regioselectivity of the bromolactonization.

The reaction of **5b** with NBS as the halogen source, in toluene at −20 °C led selectively to the racemic isobenzofuranone **1b** via a 5-*exo*-*tet* cyclization pathway as a single diastereomer but in low yield (32%) (Table 2, entry 1). It is worth noting that 3,4-dihydroisocoumarin resulting from a 6-*endo*-*tet* cyclization could not be observed. According to a widely accepted mechanism, we assumed that the halolactone **1b** was obtained from the (*E*)-1,2-disubstituted olefin **5b** with an ester–halogen anti relationship.[1h]

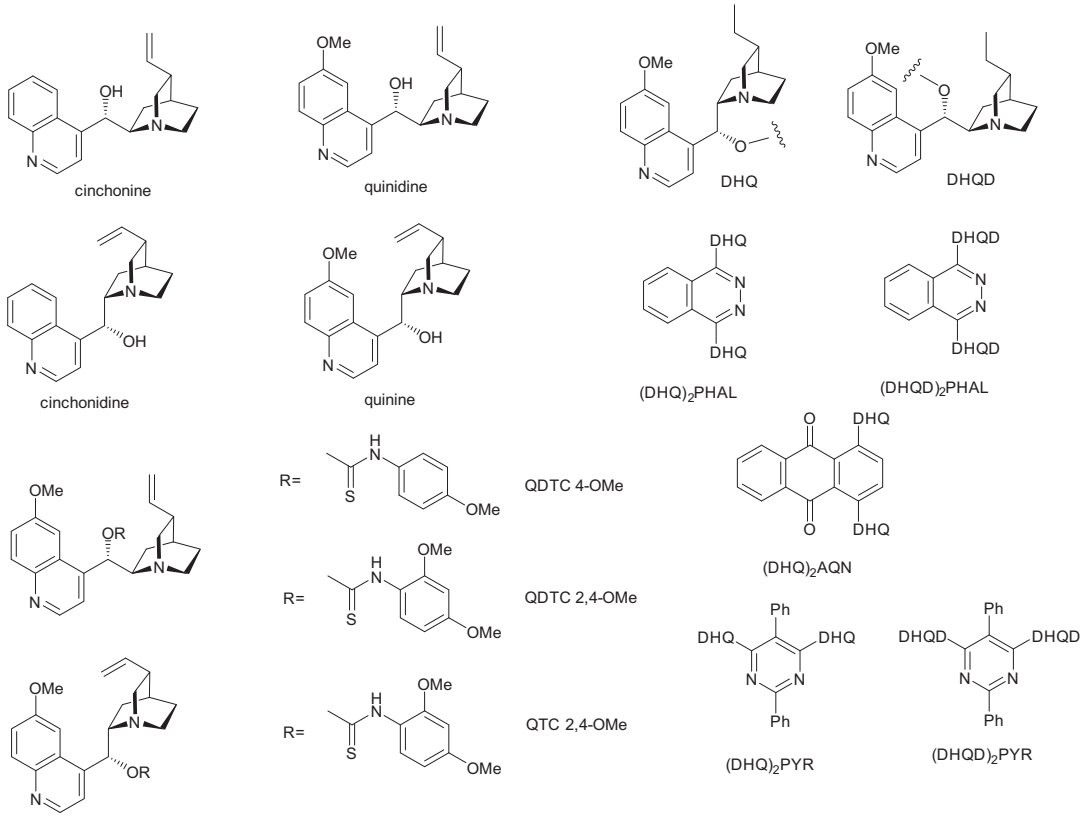
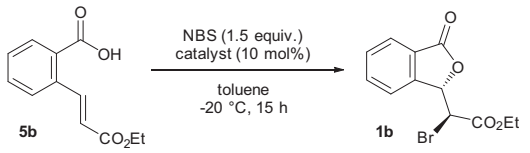


Figure 2. Organo-catalysts used in this study.

Table 2
Screening of various catalysts for enantioselective bromolactonization of **5b**[a]



Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	None	32	–
2	Cinchonine	82	5 (*R*,*R*)
3	Quinidine	79	16 (*R*,*R*)
4	Cinchonidine	84	6 (*S*,*S*)
5	Quinine	94	21 (*S*,*S*)
6	$(DHQ)_2PYR$	87	2 (*R*,*R*)
7	$(DHQD)_2PYR$	80	6 (*S*,*S*)
8	$(DHQ)_2AQN$	85	2 (*R*,*R*)
9	$(DHQD)_2PHAL$	73	12 (*S*,*S*)
10	QDTC 4-OMe	81	24 (*S*,*S*)
11	QDTC 2,4-OMe	78	18 (*S*,*S*)
12	QTC 2,4-OMe	89	15 (*R*,*R*)

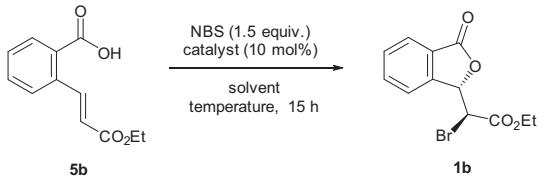
[a] Reactions were carried out with acid **5b** (0.1 mmol), catalyst (0.01 mmol) and NBS (0.15 mmol) in toluene (9 ml).
[b] Isolated yield.
[c] Measured by HPLC, absolute configurations of major enantiomer determined after the debromination reaction (see text).

At the outset of our investigations we were drawn to the use of cinchona and bis-cinchona alkaloid derivatives as potential catalysts for bromolactonization reactions due to their availability. Cinchonine, quinidine as well as their pseudo-enantiomers cinchonidine and quinine (Fig. 2) were first engaged into the bromolactonization of benzoic acid **5b**. When compound **5b** was reacted with 10 mol % of catalyst in the presence of NBS in toluene at −20 °C, the desired bromolactone **1b** was formed in good yields but with low enantiomeric excesses (5–21% ee) (entries 2–5). Under the same reaction conditions, the use of dimeric catalysts, such as $(DHQ)_2PYR$, $(DHQD)_2PYR$, $(DHQ)_2AQN$ and $(DHQD)_2PHAL$ did not improve the enantioselectivity (entries 6–9) through their dual activation of NBS and substrate.[1e,g,h] We were encouraged by the discovery that bifunctional catalysts developed by Yeung et al.[5c] such as catalyst QDTC 4-OMe provided good conversion and improved enantioselectivity (24% ee) (entry 10). Indeed, while the NBS reagent was activated by the thiocarbamate unit of the catalyst, its protonated quinidine part may interact with the carboxylic acid fragment of the substrate.[5k,r]

Lowering the reaction temperature (Table 3, entries 1–5) led to lower enantioselectivities independently of the catalyst used, but a solvent screening (entries 6–9) subsequently revealed that $CHCl_3$/toluene (1/2) was the best solvent system and afforded the bromolactone **1b** with an improved selectivity of 35% (entry 9). An additional study confirmed that a 10 mol % catalyst loading was the best and a concentration of 0.1 M was preferred (see Supporting information Tables S1 and S2).

In order to improve the enantioselectivity of **1b**, various acidic or basic additives (Fig. 3) were screened in $CHCl_3$/toluene (1/2) with NBS as the bromine source at −20 °C in the presence of 10 mol % of a quinidine thiocarbamate catalyst (Table 4). When no catalyst or additive were used, a background reaction afforded product **1b** in a 25% yield (Entry 1 and see the Supporting information Fig. S1). The use of QDTC 4-OMe catalyst led to 88% yield and a 31% ee (Entry 2). If a stoichiometric amount of benzoic acid afforded a 29% ee (Entry 5), the switch to catalytic amounts led to similar or better results (entries 3, 4). When a 20 mol % loading of benzoic acid was combined with QDTC 4-OMe catalyst, the desired bromolactone **1b** was obtained with the highest enantios-

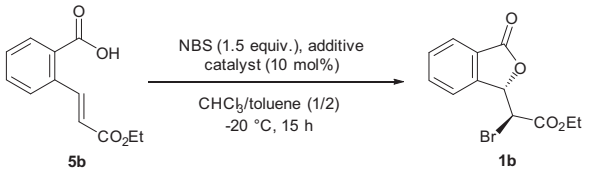
Table 3
Enantioselective bromolactonization of **5b** using different solvents[a]



Entry	Catalyst	Solvent	T (°C)	Yield (%)[b]	ee (%)[c]
1	QDTC 4-OMe	Toluene	−20	81	24
2	QDTC 4-OMe	Toluene	−40	76	22
3	QDTC 4-OMe	Toluene	−70	70	7
4	QDTC 2,4-OMe	Toluene	−20	78	18
5	QDTC 2,4-OMe	Toluene	−40	80	23
6	QDTC 4-OMe	$CHCl_3$	−20	77	13
7	QDTC 4-OMe	$CHCl_3$/toluene (1/2)	−20	89	31
8	QDTC 4-OMe	$CHCl_3$/toluene (1/2)	−30	88	25
9	QDTC 2,4-OMe	$CHCl_3$/toluene (1/2)	−20	79	35

[a] Reactions were carried out with acid **5b** (0.1 mmol), catalyst (0.01 mmol) and NBS (0.15 mmol) in solvent (9 ml).
[b] Isolated yield.
[c] Measured by HPLC.

Table 4
Enantioselective halolactonization of **5b** with various additives[a]



Entry	Catalyst	Additive	Yield (%)[b]	ee (%)[c]
1	None	None	25	—
2	QDTC 4-OMe	None	88	31
3	QDTC 4-OMe	BA (10 mol %)	84	33
4	QDTC 4-OMe	BA (20 mol %)	92	43
5	QDTC 4-OMe	BA (100 mol %)	91	29
6	QDTC 4-OMe	$NsNH_2$ (20 mol %)	77	36
7	QDTC 4-OMe	(*R*)-MA (20 mol %)	60	8
8	QDTC 4-OMe	(*S*)-MA (20 mol %)	65	6
9	QDTC 4-OMe	(*R*)-TRIP (20 mol %)	88	33
10	QDTC 4-OMe	(*S*)-TRIP (20 mol %)	74	6
11	QDTC 4-OMe	(*R*)-TIPSY (20 mol %)	88	33
12	QDTC 4-OMe	(*S*)-TIPSY (20 mol %)	74	6
13	QDTC 2,4-OMe	—	79	35
14	QDTC 2,4-OMe	BA (20 mol %)	76	38
15	QDTC 2,4-OMe	$NsNH_2$ (20 mol %)	83	36
16	QDTC 2,4-OMe	(*R*)-MA (20 mol %)	70	23
17	QDTC 2,4-OMe	(*S*)-MA (20 mol %)	77	16

[a] Reactions were carried out with acid **5b** (0.1 mmol), catalyst (0.01 mmol), additive (0.02 mmol) and NBS (0.15 mmol) in toluene (6 ml)/$CHCl_3$ (3 ml).
[b] Isolated yield.
[c] Measured by HPLC.

electivity (43% ee) (entry 4). Following the reaction course confirmed 15 h was the best reaction time for acrylate type carboxylic acids (see Supporting information, Fig. S1). Hence reactions were rather fast in comparison with the 3–7 days required for halolactonization of stilbene derivatives.[5k] It was worth to note the same trend was observed using $(DHQD)_2PHAL$ catalyst but lower enantioselectivities were obtained (see the Supporting information Table S3). By using 10 mol % of QDTC 4-OMe and 20 mol % of benzoic acid, our catalytic system was showing significant improvements. In the past, only Braddock and coworkers[5t] combined efficiently a stoichiometric amount of benzoic acid with $(DHQD)_2PHAL$ catalyst for the bromolactonization of various alkenoic acids. Moreover, if $NsNH_2$ additive had no effect on the reaction (entries 6, 15), the use of Mosher acid (entries 7, 8, 16, 17), TRIP or TIPSY (entries 9–12) had a negative effect.

We then investigated the scope of the halogen source (Table 5, Fig. 3). NBS was found to be the best brominating agent (entries 1–5). However, no reaction was observed with chlorinating agents such as *N*-chlorosuccinimide (NCS) or 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) (entries 7 and 8). Halolactonization of **5b** with NIS instead of NBS led to the targeted iodolactone in good yield and with a lower enantioselectivity (entry 6).

With the optimized reaction conditions in hand, QDTC 4-OMe catalyst was used in the asymmetric bromolactonization of several substituted benzoic acids **5**–**8** (Table 6). Overall, the desired products **1**–**4** were formed in excellent yields except for compounds **3b** and **4b** bearing electron donating alkoxy groups on the aryl moiety (entries 8 and 9). Fortunately, an increase of the reaction temperature led to compounds **3b** and **4b** with good yields without a significant loss of enantioselectivity. As it could be expected, the nature of the substrates plays an important role in this reaction in term of stereoselectivity. As highlighted in Table 6, electron donating alkoxy groups dramatically decreased the stereoselectivity of the bromolactonization process (entries 8 and 9). However, the bulkier the R^3 substituent was, the higher the enantioselectivity. Bromolactones **1a**–**e** were obtained with good yields and average enantioselectivities (entries 1–6) except for the less hindered methyl ester **1a** (entry 1). These average ee's most probably result

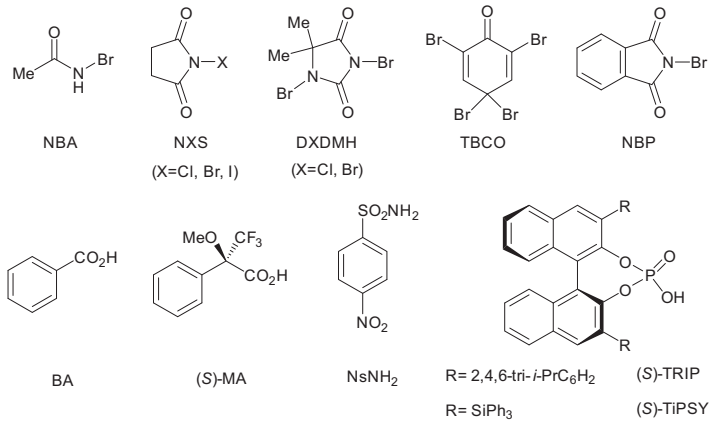
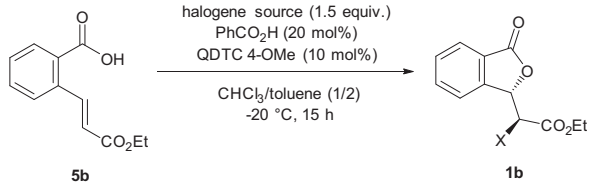


Figure 3. Halogen sources and additives used in this study.

Table 5
Enantioselective halolactonization of **5b** with various halogen sources[a]

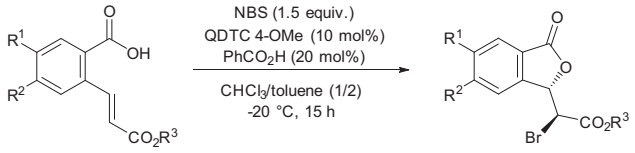


5b **1b**

Entry	Halogen source	X	Yield (%)[b]	ee (%)[c]
1	NBS	Br	89	43
2	NBP	Br	54	1
3	DBDMH	Br	88	28
4	TBCO	Br	74	37
5	NBA	Br	87	21
6	NIS	I	89	27
7	NCS	Cl	0	–
8	DCDMH	Cl	0	–

[a] Reactions were carried out with acid **5b** (0.1 mmol), QDTC 4-OMe catalyst (0.01 mmol), $PhCO_2H$ (0.02 mmol) and halogen source (0.15 mmol) in toluene (6 ml)/$CHCl_3$ (3 ml).
[b] Isolated yield.
[c] Measured by HPLC.

Table 6
Enantioselective halolactonization of **5-8**[a]



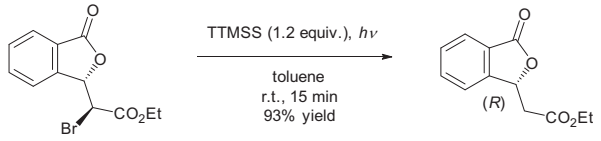
5-8 **1-4**

Entry	R^1	R^2	R^3	Yield (%)[b]	ee (%)[c]
1	H	H	Me	**1a** 93	20
2	H	H	Et	**1b** 89	43
3	H	H	Bn	**1c** 94	44
4	H	H	Bu	**1d** 91	44
5	H	H	Ph	**1e** 80	32
6	H	H	*t*-Bu	**1f** 86	53
7	NO_2	H	Et	**2b** 98[e]	49[d]
8	OBn	H	Et	**3b** 30 (68)[e]	10
9	OMe	OMe	Et	**4b** 22 (72)[e]	22

[a] Reactions were carried out with acid **5b** (0.1 mmol), QDTC 4-OMe catalyst (0.01 mmol), $PhCO_2H$ (0.02 mmol) and halogen source (0.15 mmol) in toluene (6 ml)/$CHCl_3$ (3 ml).
[b] Isolated yield.
[c] Measured by HPLC.
[d] Determined by ^1H NMR using europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate.
[e] Reaction carried out at rt.

from the combination of the uncatalyzed background reaction and the catalyzed enantioselective transformation. The kinetics of these two reactions (see Supporting information Fig. S1) are relying on the substrate electronic and steric properties on the one side (ground and catalyzed transformations) and on the efficiency and selectivity of the catalyst to assist the cyclization on the other side.

In order to determine the absolute configuration at C3, radical debromination of bromophthalide **1b** was performed by tris (trimethylsilyl)silane (TTMSS) under irradiation in toluene (Scheme 4). Bromide was cleanly removed to afford the debrominated compound **20b** in high yield (93%) without a significant loss of enantiopurity.



1b (40% e.e.) **20b** (38% e.e.)

Scheme 4. Radical debromination of bromophthalide **1b**.

The absolute configuration of **20b** was inferred by comparison of the specific rotation with the literature data, $[\alpha]_D = +6.9$ for (3*R*)-**20b** (*c* 0.92 in $CHCl_3$) (Ee 86%),[13b] +3.8 for (3*R*)-**20b** (*c* 3.3, $CHCl_3$) (Ee 38%). This debromination reaction allowed for the determination of the absolute configurations of all isolated halolactones.

3. Conclusion

In conclusion, we have developed an efficient and highly regio- and diastereoselective route to enantioenriched brominated isobenzofuranones. The key step of our methodology is based upon the first organocatalyzed enantioselective bromolactonization reaction of aryl acrylate-type carboxylic acids. When combined with a catalytic amount of benzoic acid, quinidine thiocarbamate bifunctional catalysts have demonstrated their efficiency and allowed us to obtain the target bromolactones with promising enantioselectivities (up to 53%). A more efficient catalytic system may enable a faster bromolactonization with respect to the observed background reaction. Moreover, new catalysts are required to direct and activate at once the ester fragment, the carboxylic acid unit and the NBS reagent and to achieve a complete transfer of the chiral information during the halolactonization reaction for higher enantioselectivities.

4. Experimental

4.1. General

^1H NMR spectra were recorded on a 300-MHz Bruker spectrometer. Chemical shifts for ^1H NMR spectra (in parts per million) relative to internal tetramethylsilane (Me_4Si, $\delta = 0.00$ ppm) with deuterated chloroform. ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in parts per million) relative to $CDCl_3$ ($\delta = 77.0$ ppm). Flash chromatography experiments were carried out on Silica Gel premium Rf grade (40–75 μm). Ethyl acetate/petroleum ether mixtures, dichloromethane/acetone or dichloromethane/methanol mixtures were used as the eluent for chromatographic purifications. TLC plates were visualized by UV or immersion in permanganate potassium (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% aq NaOH and 300 mL of water) followed by heating. Melting points were obtained on a capillary apparatus and are uncorrected. High resolution mass spectra (HRMS) were obtained by electrospray using a ThermoExactive spectrometer. Enantiomeric excesses were determined by chiral HPLC equipped with a photodiode array detector (200–300 nm) and one of the following Daicel CSP (4.6 5 250 mm) columns: OD, IA and IC. Optical rotations were measured at room temperature (20–23 °C) on a polarimeter using a 1 mL cell with a 1 dm path length at 589 nm (sodium D light). Dry CH_2Cl_2 and toluene were displayed by a passage down an activated alumina column. DMSO and Et_3N were distilled over molecular sieve 4 Å.

Bromobenzoic acid *tert*-butyl ester **15**, 2-Bromobenzaldehyde **16** and acrylates **19a–e** were purchased from commercial sources and used as received. Aryl bromides **14**,[15] **17**[16] and **18**[17] were pre-

pared according to reported procedures. QDTC 4-OMe, QDTC 2,4-OMe and QTC 4-OMe catalysts were prepared according to the literature.[5c] The other catalysts used herein were purchased from commercial sources.

4.2. General Heck procedure. Synthesis of compounds 9,13

A solution of aryl bromide (1 mmol, 1 equiv), acrylate (2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %) and Et_3N (5 equiv) in DMSO (2 mL) under argon was heated at 100 °C for 15 h. Water (10 mL) was then added followed by sodium chloride (until saturation) and the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified on a column of silica gel to afford the desired pure coupling product.

4.2.1. 2-((*E*)-2-Methoxycarbonylvinyl)benzoic acid *tert*-butyl ester 9a

General Heck procedure using *tert*-butyl 2-bromobenzoate **14** (257 mg, 1 mmol, 1 equiv) and methyl acrylate **19a** (0.18 mL, 2 mmol, 2 equiv) affords **9a** (192 mg, 0.73 mmol, yield = 73%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43 (d, J = 15.9 Hz, 1H), 7.91–7.84 (m, 1H), 7.56–7.32 (m, 3H), 6.28 (d, J = 15.9 Hz, 1H), 3.81 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 166.0, 144.5, 135.6, 132.0, 131.7, 130.6, 129.3, 127.7, 119.9, 82.0, 51.5, 28.1 (3C); HRMS (ESI+) m/z calcd for $C_{15}H_{19}O_4$ $[MH]^+$ 263.12779, found 263.12744.

4.2.2. 2-((*E*)-2-Ethoxycarbonylvinyl)benzoic acid *tert*-butyl ester 9b[18]

General Heck procedure using *tert*-butyl 2-bromobenzoate **14** (2.56 g, 10 mmol, 1 equiv) and ethyl acrylate **19b** (2.2 mL, 20 mmol, 2 equiv) affords **9b** (2.52 g, 9.1 mmol, yield = 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, J = 15.9 Hz, 1H), 7.82–7.76 (m, 1H), 7.48–7.26 (m, 3H), 6.18 (d, J = 15.9 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 1.52 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H).

4.2.3. 2-((*E*)-2-Benzyloxycarbonylvinyl)benzoic acid *tert*-butyl ester 9c[8g]

General Heck procedure using General Heck procedure using *tert*-butyl 2-bromobenzoate **14** (500 mg, 1.95 mmol, 1 equiv) and benzyl acrylate **19c** (0.6 mL, 2 mmol, 2 equiv) affords **9c** (552 mg, 1.63 mmol, yield = 84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, J = 15.9 Hz, 1H), 7.96–7.91 (m, 1H), 7.62–7.32 (m, 8H), 6.38 (d, J = 15.9 Hz, 1H), 5.31 (s, 2H), 1.62 (s, 9H).

4.2.4. 2-((*E*)-2-Ethoxycarbonylvinyl)-5-nitro-benzoic acid *tert*-butyl ester 10b

Modified Heck procedure with *tert*-butyl 2-bromo-5-nitro-benzoate **15** (302 mg, 1 mmol, 1 equiv), ethyl acrylate **19b** (0.17 mL, 1.5 mmol, 1.5 equiv) but using $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol %) and P(*o*-Tol)$_3$ (12.2 mg, 0.04 mmol, 4 mol %) as catalyst affords **10b** (260 mg, 0.81 mmol, yield = 81%) as a yellow solid. Mp 84–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (d, J = 2.5 Hz, 1H), 8.38 (d, J = 15.9 Hz, 1H), 8.32 (dd, J = 8.6 and 2.5 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 6.37 (d, J = 15.9 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.64 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 163.9, 147.8 (2C), 141.6, 133.0, 129.0, 126.0, 125.6, 123.6, 83.5, 60.7, 27.9 (3C), 14.1; Anal. calcd (%) for $C_{16}H_{19}NO_6$: C, 59.86; H, 5.96; N, 4.36; found C, 59.80; H, 5.96; N, 4.07.

4.2.5. (*E*)-3-(2-Formylphenyl)acrylic acid butyl ester 11d[13b]

General Heck procedure using 2-bromobenzaldehyde **16** (500 mg, 2.70 mmol, 1 equiv) and *n*-butyl acrylate **19d** (0.77 mL, 5.4 mmol, 2 equiv) affords **11d** (451 mg, 1.94 mmol, yield = 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.28 (s, 1H), 8.54 (d, J = 15.9 Hz, 1H), 7.90–7.84 (m, 1H), 7.67–7.52 (m, 3H), 6.39 (d, J = 15.9 Hz, 1H), 4.23 (t, J = 6.7 Hz, 2H), 1.77–1.63 (m, 2H), 1.52–1.32 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).

4.2.6. (*E*)-3-(2-Formylphenyl)acrylic acid phenyl ester 11e

General Heck procedure using 2-bromobenzaldehyde **16** (185 mg, 1 mmol, 2 equiv) and phenyl acrylate **19e** (296 mg, 2 mmol, 2 equiv) affords **11e** (86 mg, 0.34 mmol, yield = 34%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.20 (s, 1H), 8.65 (d, J = 15.9 Hz, 1H), 7.83–7.72 (m, 1H), 7.65–7.46 (m, 3H), 7.36–7.26 (m, 2H), 7.19–7.06 (m, 3H), 6.48 (d, J = 15.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.8, 164.6, 150.8, 143.1, 136.2, 134.0 (2 signals), 132.8, 130.3, 129.5 (2C), 128.1, 125.9 (2C), 122.2, 121.6; HRMS (ESI+) m/z calcd for $C_{16}H_{13}O_3$ $[MH]^+$ 253.08592, found 253.08644.

4.2.7. (*E*)-3-(2-Formylphenyl)acrylic acid *tert*-butyl ester 11f[19]

General Heck procedure using 2-bromobenzaldehyde **16** (500 mg, 2.70 mmol, 1 equiv) and *tert*-butyl acrylate **19f** (0.79 mL, 5.4 mmol, 2 equiv) affords **11f** (351 mg, 1.51 mmol, yield = 56%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.33 (s, 1H), 8.42 (d, J = 15.8 Hz, 1H), 7.89–7.86 (m, 1H), 7.66–7.53 (m, 3H), 6.30 (d, J = 15.8 Hz, 1H), 1.55 (s, 9H, *t*Bu).

4.2.8. (*E*)-3-(4-Benzyloxy-2-formylphenyl)acrylic acid ethyl ester 12b[20]

General Heck procedure using 2-bromo-5-benzyloxybenzaldehyde **17** (500 mg, 1.72 mmol, 1 equiv) and ethyl acrylate **19b** (0.38 mL, 3.5 mmol, 2 equiv) affords **12b** (331 mg, 1.07 mmol, yield = 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.27 (s, 1H), 8.37 (d, J = 15.8 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.42–7.24 (m, 6H), 7.17–7.11 (m, 1H), 6.26 (d, J = 15.8 Hz, 1H), 5.09 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H).

4.2.9. (*E*)-3-(2-Formyl-4,5-dimethoxyphenyl)-acrylic acid ethyl ester 13b[21]

General Heck procedure General Heck procedure using 2-bromo-4,5-dimethoxybenzaldehyde **18** (245 mg, 1 mmol, 1 equiv) and ethyl acrylate **19b** (0.22 mL, 2 mmol, 2 equiv) affords **13b** (232 mg, 0.88 mmol, yield = 88%) as a white solid. Mp 113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.25 (s, 1H), 8.42 (d, J = 15.8 Hz, 1H), 7.33 (s, 1H), 7.07 (s, 1H), 6.35 (d, J = 15.8 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).

4.3. General *tert*-butyl ester cleavage procedure

To a solution of *tert*-butyl ester **9**,**10** (1 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added TFA (6 equiv). The reaction mixture was stirred at room temperature for 6 h (monitored by TLC) and concentrated to dryness to afford carboxylic acid **5** and **6**. Purification on silica gel may be applied if necessary.

4.3.1. 2-((*E*)-2-Methoxycarbonylvinyl)benzoic acid 5a[22]

General cleavage procedure using **9a** (183 mg, 0.7 mmol, 1 equiv) affords **5a** (135 mg, 0.66 mmol, yield = 94%) as a white solid. Mp 152–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (d, J = 15.9 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.66–7.52 (m, 2H), 7.53–7.43 (m, 1H), 6.34 (d, J = 15.9 Hz, 1H), 3.84 (s, 3H).

4.3.2. 2-((*E*)-2-Ethoxycarbonylvinyl)benzoic acid 5b[13b]

General cleavage procedure using **9b** (2.52 g, 9.1 mmol, 1 equiv) affords **5b** (1.75 g, 8.0 mmol, yield = 87%) as a white solid. Mp 68–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, J = 15.9 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.66–7.55 (m, 2H),

7.52–7.44 (m, 1H), 6.33 (d, J = 15.9 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H).

4.3.3. 2-((*E*)-2-Benzyloxycarbonylvinyl)benzoic acid 5c[8g]

General cleavage procedure using **9c** (552 mg, 1.6 mmol, 1 equiv) affords **5c** (407 mg, 1.4 mmol, yield = 88%) as a white solid. Mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (d, J = 15.9 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.66–7.55 (m, 2H), 7.52–7.28 (m, 6H), 6.39 (d, J = 15.9 Hz, 1H), 5.27 (s, 2H).

4.3.4. 2-((*E*)-2-Ethoxycarbonylvinyl)-5-nitro-benzoic acid 6b

General cleavage procedure using **10b** (240 mg, 0.75 mmol, 1 equiv) affords **6b** (180 mg, 0.68 mmol, yield = 91%) as a white solid. Mp 179–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.94 (d, J = 2.4 Hz, 1H), 8.55 (d, J = 16.0 Hz, 1H), 8.42 (dd, J = 8.6 and 2.4 Hz, 1H), 7.81 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 166.0, 148.0, 143.2, 141.4, 129.7, 129.6, 127.5, 126.8, 124.7, 61.3, 14.2; HRMS (ESI−) m/z calcd for $C_{12}H_{10}NO_6$ $[M]^-$ 264.05026, found 264.04922.

4.4. General Pinnick oxidation procedure

To a solution of aldehyde **10**–**12** (1 mmol, 1 equiv) and 2-methylbut-2-ene (10 equiv) in *tert*-butanol (30 mL) was added water (7.5 mL), followed by sodium chlorite (3 equiv) and sodium hydrogenophosphate (6 equiv). The reaction mixture was stirred at rt for 15 h (monitored by TLC), then concentrated to dryness. The residue was diluted in H_2O/ethyl acetate. The aqueous layer was saturated with NaCl, then extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and then concentrated to afford the desired carboxylic acid **5**–**8**. Purification on a column of silica gel may be applied if the purity of the material is not good enough.

4.4.1. 2-((*E*)-2-Butoxycarbonylvinyl)benzoic acid 5d[23]

General oxidation procedure using **11d** (487 mg, 2.1 mmol, 1 equiv) affords **5d** (463 mg, 1.87 mmol, yield = 89%) as a white solid. Mp 61–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (d, J = 15.9 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.67–7.55 (m, 2H), 7.52–7.43 (m, 1H), 6.34 (d, J = 15.9 Hz, 1H), 4.24 (t, J = 6.7 Hz, 2H), 1.71 (quint, J = 6.7 Hz, 2H), 1.46 (sex, J = 7.5 Hz, 2H), 0.97 (t, J = 7.5 Hz, 3H).

4.4.2. 2-((*E*)-2-Phenoxycarbonylvinyl)benzoic acid 5e

General oxidation procedure using **11e** (75 mg, 0.3 mmol, 1 equiv) affords **5e** (75 mg, 0.28 mmol, yield = 94%) as a white solid. Mp 129–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.27 (br s, 1H), 8.75 (d, J = 15.9 Hz, 1H), 8.16–8.09 (m, 1H), 7.72–7.457 (m, 2H), 7.54–7.45 (m, 1H), 7.43–7.33 (m, 2H), 7.27–7.15 (m, 3H), 6.51 (d, J = 15.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 165.0, 150.9, 145.7, 137.0, 133.3, 131.8, 129.8, 129.4 (2C), 128.8, 128.3, 125.8, 121.7 (2C), 120.5; HRMS (ESI+) m/z calcd for $C_{16}H_{13}O_4$ $[MH]^+$ 269.08084, found 269.08047.

4.4.3. 2-((*E*)-2-*tert*-Butoxycarbonylvinyl)benzoic acid 5f[24]

General oxidation procedure using **11f** (290 mg, 1.25 mmol, 1 equiv) affords **5f** (279 mg, 1.12 mmol, yield = 90%) as a white solid. Mp 125–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, J = 15.9 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.67–7.52 (m, 2H), 7.50–7.46 (m, 1H), 6.27 (d, J = 15.9 Hz, 1H), 1.55 (s, 9H, *t*Bu).

4.4.4. 5-Benzyloxy-2-((*E*)-2-ethoxycarbonylvinyl)-benzoic acid 7b

General oxidation procedure using **12b** (320 mg, 1.0 mmol, 1 equiv) affords **7b** (307 mg, 0.94 mmol, yield = 91%) as a white solid. Mp 151–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (d, J = 15.9 Hz, 1H), 7.68 (d, J = 2.7 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.48–7.33 (m, 6H), 7.18 (dd, J = 8.7 and 2.7 Hz, 1H), 6.28 (d, J = 15.9 Hz, 1H), 5.14 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 167.0, 159.6, 143.0, 136.1, 130.0, 129.7, 129.5, 128.7 (2C), 128.3, 127.6 (2C), 120.3, 119.7, 117.0, 70.4, 60.6, 14.3; HRMS (CI+) m/z calcd for $C_{19}H_{19}O_5$ $[MH]^+$ 327.12325, found 327.12271.

4.4.5. 2-((*E*)-2-Ethoxycarbonylvinyl)-4,5-dimethoxybenzoic acid 8b

General oxidation procedure using **13b** (212 mg, 0.8 mmol, 1 equiv) affords **8b** (220 mg, 0.79 mmol, yield = 98%) as a white solid. Mp 194–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (d, J = 15.9 Hz, 1H), 7.62 (s, 1H), 7.07 (s, 1H), 6.29 (d, J = 15.8 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 166.8, 152.7, 149.7, 143.7, 131.6, 121.2, 120.1, 113.9, 110.0, 60.6, 56.2, 56.1, 14.3; HRMS (ESI+) m/z calcd for $C_{14}H_{17}O_6$ $[MH]^+$ 281.10196, found 281.10153.

4.5. General procedure for the halolactonization reaction. Synthesis of 3-substituted isobenzofuranones 1–4

General procedure for the racemic version: To a solution of carboxylic acid **5**–**8** (0.1 mmol) in toluene (1 mL) was added NBS or NIS (0.15 mmol, 1.5 equiv). The reaction mixture was heated at 40 °C for 15 h. The crude mixture was directly purified by column chromatography on silica gel.

4.5.1. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid methyl ester 1a

General procedure using carboxylic acid **5a** (20.6 mg, 0.1 mmol, 1 equiv) affords **1a** (29 mg, 0.1 mmol, yield = quantitative) as white solid. Mp 81–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.90 (m, 1H), 7.87–7.81 (m,1H), 7.72 (dt, J = 1.2 and 7.4 Hz, 1H), 7.65–7.57 (m, 1H), 5.92 (d, J = 6.9 Hz, 1H), 4.52 (d, J = 6.9 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 167.4, 145.8, 134.2, 130.3, 126.6, 125.9, 124.2, 78.7, 53.6, 45.2; HRMS (ESI+) m/z calcd for $C_{11}H_{10}BrO_4$ $[MH]^+$ 284.97570, found 284.97528.

4.5.2. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid ethyl ester 1b (X = Br[25])

General procedure using carboxylic acid **5b** (22 mg, 0.1 mmol, 1 equiv) affords **1b** (30 mg, 0.1 mmol, yield = quantitative) as white solid. Mp 68–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 5.93 (d, J = 6.6 Hz, 1H), 4.55 (d, J = 6.6 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).

4.5.3. (*S**)-Iodo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid ethyl ester 1b (X = I)

General procedure using carboxylic acid **5b** (110 mg, 0.5 mmol, 1 equiv) affords **1b** (168 mg, 0.49 mmol, yield = 97%) as a white solid. Mp 35–36 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.90 (m, 2H), 7.72 (dt, J = 1.4 and 7.4 Hz, 1H), 7.65–7.57 (m, 1H), 5.66 (d, J = 3.1 Hz, 1H), 4.78 (d, J = 3.1 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 168.6, 147.3, 134.1, 130.3, 126.6,125.7, 124.5, 79.3, 62.6, 22.1, 13.8; HRMS (ESI+) m/z calcd for $C_{12}H_{12}IO_4$ $[MH]^+$ 346.97750, found 346.97672.

4.5.4. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid benzyl ester 1c

General procedure using carboxylic acid **5c** (28.2 mg, 0.1 mmol, 1 equiv) affords **1c** (28 mg, 0.08 mmol, yield = 77%) as a colorless

oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.5 Hz, 1H), 7.67–7.62 (m, 1H), 7.58 (dt, J = 1.2 and 7.2 Hz, 1H), 7.54–7.47 (m, 1H), 7.36–7.24 (m, 5H), 5.85 (d, J = 6.6 Hz, 1H), 5.22 (s, 2H), 4.50 (d, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 166.7, 145.8, 134.6, 134.2, 130.3, 128.8 (2 signals overlapped), 128.5, 126.6, 125.9, 124.1, 78.7, 68.5, 45.7; HRMS (ESI+) m/z calcd for $C_{17}H_{14}BrO_4$ $[MH]^+$ 361.00700, found 361.00656.

4.5.5. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid butyl ester 1d

General procedure using carboxylic acid **5d** (24.8 mg, 0.1 mmol, 1 equiv) affords **1d** (23 mg, 0.07 mmol, yield = 70%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.93 (m, 1H), 7.92–7.81 (m, 1H), 7.71 (dt, J = 1.2 and 7.4 Hz, 1H), 7.64–7.56 (m, 1H), 5.91 (d, J = 6.8 Hz, 1H), 4.51 (d, J = 6.8 Hz, 1H), 4.35–4.23 (m, 2H), 1.75–1.63 (m, 2H), 1.50–1.35 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 167.0, 145.9, 134.2, 130.3, 126.6, 125.9, 124.2, 78.8, 66.7, 45.6, 30.4, 19.0, 13.6; HRMS (ESI+) m/z calcd for $C_{14}H_{16}BrO_4$ $[MH]^+$ 327.02270, found 327.02197.

4.5.6. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid phenyl ester 1e

General procedure using carboxylic acid **5e** (24.8 mg, 0.05 mmol, 1 equiv) affords **1e** (13 mg, 0.04 mmol, yield = 75%) as a a colorless oil.; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, J = 7.6 Hz, 1H); 7.94–7.89 (m, 1H), 7.74 (dt, J = 1.2 and 7.5 Hz, 1H); 7.67–7.60 (m, 1H), 7.48–7.38 (m, 2H), 7.33–7.26 (m, 1H), 7.21–7.15 (m, 2H), 6.02 (d, J = 7.0 Hz, 1H), 4.70 (d, J = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 165.6, 150.2, 145.7, 134.3, 130.5, 129.7 (2C), 126.7, 126.6, 126.0, 124.3, 121.0 (2C), 78.7, 45.2; HRMS (ESI+) m/z calcd for $C_{16}H_{12}BrO_4$ $[MH]^+$ 346.99135, found 346.99075.

4.5.7. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid *tert*-butyl ester 1f

General procedure using carboxylic acid **5f** (24.8 mg, 0.1 mmol, 1 equiv) affords **1f** (30.4 mg, 0.093 mmol, yield = 93%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.92 (m, 1H), 7.89–7.82 (m,1H), 7.73 (dt, J = 1.2 and 7.4 Hz, 1H), 7.63–7.57 (m, 1H), 5.88 (d, J = 6.7 Hz, 1H), 4.42 (d, J = 6.7 Hz, 1H), 1.55 (s, 9H, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 165.7, 146.1, 134.1, 130.2, 126.7, 125.8, 124.1, 84.1, 79.1, 47.1, 27.7; HRMS (ESI+) m/z calcd for $C_{10}H_7BrO_4$ $[MH-C_4H_9]^+$ 270.96005, found 270.95975.

4.5.8. (*S**)-Bromo-((*S**)-5-nitro-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid ethyl ester 2b

To a solution of carboxylic acid **6b** (26.5 mg, 0.1 mmol, 1 equiv) in toluene (1 mL) was added NBS (0.5 mmol, 5 equiv). The reaction mixture was heated at 70 °C for 3 days. The crude mixture was concentrated to dryness. The residue was dissolved in ethyl acetate, washed with a saturated solution of $NaHCO_3$, water then brine to afford the desired phthalide **2b** (27 mg, 0.08 mmol, yield = 78%) as a pale yellow solid. Mp 133–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (d, J = 2.1 Hz, 1H), 8.57 (dd, J = 8.5 and 2.1 Hz, 1H), 8.11–8.06 (m, 1H), 6.04 (d, J = 5.5 Hz, 1H), 4.69 (d, J = 5.5 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 166.5, 151.1, 149.7, 128.9, 128.7, 126.0, 121.2, 78.9, 63.3, 44.8, 13.9; Anal. calcd (%) for ($C_{12}H_{10}O_6NBr$ + 1/6 CH_2Cl_2): C, 41.14; H, 2.91; N, 3.94; found C, 41.11; H, 3.53; N, 3.68.

4.5.9. (*S**)-((*S**)-5-Benzyloxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)bromoacetic acid ethyl ester 3b

General procedure using carboxylic acid General procedure using carboxylic acid **7b** (32.4 mg, 0.1 mmol, 1 equiv) affords **3b** (23 mg, 0.06 mmol, yield = 57%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.5 Hz, 1H), 7.39–7.21 (m, 7H), 5.77 (d, J = 6.8 Hz, 1H), 5.06 (s, 2H), 4.37 (d, J = 6.8 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 167.0, 160.6, 138.5, 135.9, 128.8 (2C), 128.4, 128.1, 127.6 (2C), 125.2, 123.4, 109.0, 78.7, 70.6, 62.9, 45.9, 13.9; HRMS (ESI+) m/z calcd for $C_{19}H_{18}BrO_5$ $[MH]^+$ 405.03320, found 405.03311.

4.5.10. (*S**)-Bromo-((*S**)-5,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid methyl ester 4b

General procedure using carboxylic acid **8b** (28 mg, 0.1 mmol, 1 equiv) affords **4b** (30 mg, 0.08 mmol, yield = 83%) as white solid. Mp 111–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (s, 1H), 7.29 (s, 1H), 5.79 (d, J = 6.7 Hz, 1H), 4.48 (d, J = 6.7 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2, 167.1, 154.7, 151.3, 140.5, 118.7, 106.1, 105.8, 78.2, 62.8, 56.4, 56.3, 45.8, 13.9; HRMS (ESI+) m/z calcd for $C_{14}H_{16}BrO_6$ $[MH]^+$ 359.01250, found 359.01233.

General procedure for asymmetric version: To a solution of quinine or quinidine thiocarbamate QD-thio (0.01 mmol, 10 mol %) and benzoic acid (0.02 mmol, 20 mol %) in toluene (6 mL) was added NBS or NIS (0.15 mmol, 1.5 equiv). The reaction mixture was cooled at −20 °C, then a solution of carboxylic acid 5–8 (0.1 mmol, 1 equiv) in chloroform (3 mL) was added dropwise. After 15 h at −20 °C, the crude mixture was directly purified by column chromatography on silica gel.

4.5.11. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid methyl ester 1a

General asymmetric halolactonization procedure using **5a** (20.6 mg, 0.1 mmol, 1 equiv) with **QD-thio** affords **1a** (26 mg, 0.09 mmol, yield = 93%, 20% ee) as a white solid. HPLC: rt (*R*) = 13.8 min, rt (*S*) = 15.0 min (Daicel Chiralpak™ IA CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 90:10; 25 °C, 225 nm); $[\alpha]_D^{23}$ = −11.8 (c 1.5, $CHCl_3$).

4.5.12. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid ethyl ester 1b (X = Br)

General asymmetric halolactonization procedure using **5b** (22 mg, 0.1 mmol, 1 equiv) with **QD-thio** affords **1b** (30 mg, 0.1 mmol, yield = 89%, 43% ee) as white solid. HPLC: rt (*R*) = 12.1 min, rt (*S*) = 14.7 min (Daicel Chiralpak™ IA CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 90:10; 25 °C, 225 nm); $[\alpha]_D^{23}$ = −19.6 (c 3.0, $CHCl_3$).

4.5.13. (*S**)-Iodo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid ethyl ester 1b (X = I)

General asymmetric halolactonization procedure using **5b** (22 mg, 0.1 mmol, 1 equiv) with **QD-thio** affords **1b** (35 mg, 0.1 mmol, yield = 89%, 27% ee) as a white solid. HPLC: rt (*R*) = 13.1 min, rt (*S*) = 17.8 min (Daicel Chiralpak™ IA CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 90:10; 25 °C, 225 nm); $[\alpha]_D^{23}$ = −16.8 (c 3.0, $CHCl_3$).

4.5.14. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid benzyl ester 1c

General asymmetric halolactonization procedure using **5c** (28.2 mg, 0.1 mmol, 1 equiv) with **QD-thio** affords **1c** (34 mg, 0.09 mmol, 94% yield, 44% ee) as a white solid. HPLC: rt (*R*) = 12.7 min, rt (*S*) = 31.6 min (Daicel Chiralpak™ IA CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 90:10; 25 °C; 225 nm); $[\alpha]_D^{23}$ = −11.6 (c 2.9, $CHCl_3$).

4.5.15. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid butyl ester 1d

General asymmetric halolactonization procedure using **5d** (24.8 mg, 0.1 mmol, 1 equiv) with **QD-thio** affords **1d** (30 mg, 0.09 mmol, yield = 91%, 44% ee) as a colorless oil. HPLC: rt (*R*)

= 9.8 min, rt (*S*) = 18.3 min (Daicel Chiralpak™ IA CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 90:10; 25 °C; 225 nm); $[\alpha]_D^{23}$ = −14.7 (*c* 2.5, $CHCl_3$).

4.5.16. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid phenyl ester 1e

General asymmetric halolactonization procedure using **5e** (26.8 mg, 0.1 mmol, 1 equiv) with **QD-thio** affords **1e** (28 mg, 0.08 mmol, 80% yield, 32% ee) as a white solid. HPLC: rt (*R*) = 12.0 min, rt (*S*) = 21.0 min (Daicel Chiralpak™ IA CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 90:10; 25 °C; 225 nm); $[\alpha]_D^{23}$ = −9.6 (*c* 1.0, $CHCl_3$).

4.5.17. (*S**)-Bromo-((*S**)-3-oxo-1,3-dihydroisobenzofuran-1-yl) acetic acid *tert*-butyl ester 1f

General asymmetric halolactonization procedure using **5f** (24.8 mg, 0.1 mmol, 1 equiv) with **QD-thio** affords **1f** (28.1 mg, 0.086 mmol, 86% yield, 53% ee) as a colorless oil. HPLC: rt (*R*) = 8.6 min, rt (*S*) = 12.3 min (Daicel Chiralpak™ IA CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 90:10; 25 °C; 225 nm); $[\alpha]_D^{23}$ = −15.4 (*c* 1.0, $CHCl_3$).

4.5.18. (*S**)-Bromo-((*S**)-5-nitro-3-oxo-1,3-dihydro-isobenzofuran-1-yl)acetic acid ethyl ester 2b

To a solution of quinidine thiocarbamate (4.9 mg, 0.01 mmol, 10 mol %) and benzoic acid (2.4 mg, 0.02 mmol, 20 mol %) in toluene (6 mL) was added NBS (0.15 mmol, 1.5 equiv). A solution of carboxylic acid 6b (26.5 mg, 0.1 mmol, 1 equiv) in chloroform (3 mL) was added dropwise at room temperature. After 15 h, the crude mixture was concentrated to dryness. The residue was dissolved in ethyl acetate, washed with saturated solution of $NaHCO_3$, water then brine to afford the crude phthalide **2b** (34 mg, 0.1 mmol, yield = 98%, 49% ee). Enantiomeric excess was determined by ^{1}H NMR using europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. $[\alpha]_D^{23}$ = −2.6 (*c* 1.0, $CHCl_3$).

4.5.19. (*S**)-((*S**)-5-Benzyloxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl)bromoacetic acid ethyl ester 3b

General asymmetric halolactonization procedure using **7b** (32.6 mg, 0.1 mmol, 1 equiv) with **QD-thio** affords **3b** (12 mg, 0.03 mmol, 30% yield, 10% ee) as a colorless oil. HPLC: rt (*R*) = 20.6 min, rt (*S*) = 31.7 min (Daicel Chiralpak™ IA CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 95:5; 25 °C; 212 nm); $[\alpha]_D^{23}$ = −5.6 (*c* 0.8, $CHCl_3$).

4.5.20. (*S**)-Bromo-((*S**)-5,6-dimethoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl)acetic acid methyl ester 4b

To a solution of quinidine thiocarbamate (4.9 mg, 0.01 mmol, 10 mol %) and benzoic acid (2.4 mg, 0.02 mmol, 20 mol %) in toluene (6 mL) was added NBS (0.15 mmol, 1.5 equiv). A solution of carboxylic acid **8b** (28 mg, 0.1 mmol, 1 equiv) in chloroform (3 mL) was added dropwise at room temperature. After 15 h, the crude mixture was directly purified by column chromatography on silica gel to afford **4b** (26 mg, 0.07 mmol, 72% yield, 22% ee) as a white solid. HPLC: rt (*R*) = 99.8 min, rt (*S*) = 106.4 min (Daicel Chiralpak™ IC CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 90:10; 25 °C; 221 nm); $[\alpha]_D^{23}$ = −9.7 (*c* 2.0, $CHCl_3$).

4.6. General procedure for dehalogenation reaction

A solution of halogenated compound **1b** (1 mmol, 1 equiv) in anhydrous toluene (200 mL) was bubbled with argon for 5 min in a quartz vessel. TTMSS (1.1 mmol, 1 equiv) was added and the mixture was directly irradiated in a Rayonet RPR photoreactor equipped with 254 nm lamps for 15 min. The crude was concentrated under vacuum then purified by column chromatography on silica gel to afford the pure desired dehalogenated compound **20b**.

4.6.1. ((*R*)-3-Oxo-1,3-dihydroisobenzofuran-1-yl)-acetic acid ethyl ester 20b

General procedure from bromide **1b** (73 mg, 0.24 mmol, 1 equiv, 40% ee) affords (50 mg, 0.23 mmol, 93% yield, 38% ee) as a white solid. Mp 55–56 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.89 (m, 1H), 7.73–7.65 (m, 1H), 7.60–7.48 (m, 2H), 5.89 (t, *J* = 6.5 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.94 and 2.88 (AB part of ABX system, J_{AB} = 16.5 and J_{AX} = J_{BX} = 6.5 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); HPLC: rt (*R*) = 11.0 min, rt (*S*) = 12.6 min (Daicel Chiralpak™ OD CSP; flow rate = 1.0 mL min^{-1}; heptane/2-propanol 90:10; 25 °C; 224 nm); $[\alpha]_D^{20}$ = +3.8 (*c* 3.3, $CHCl_3$), Lit.[14e] (*R*)-enantiomer (84% ee), $[\alpha]_D^{23}$ = +6.9 (0.92, $CHCl_3$).

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Supplementary data

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