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

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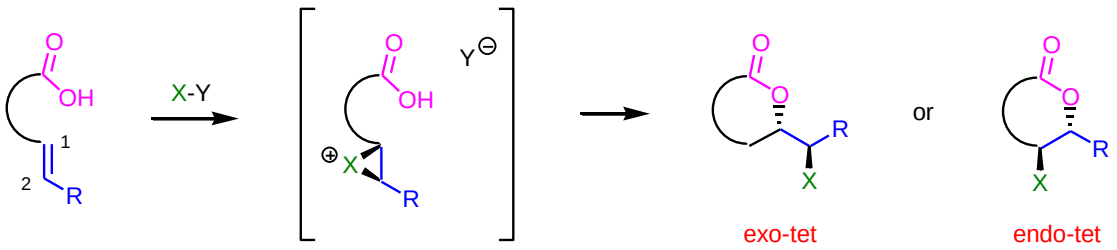
Abstract: The enantioselective synthesis of several 3-substituted isobenzofuranones has been developed through a new and flexible route. When combined with a catalytic amount of benzoic acid, quinidine thiocarbamate bifunctional catalysts have demonstrated their efficiency for the highly regioselective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

Keywords: *Asymmetric organocatalysis, Cinchona alkaloids, bromolactonization reaction, 3-substituted isobenzofuranones*

Introduction

The 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] Besides constructing lactone ring system, halolactonization reactions introduce halogen atoms into intermediates which can be utilized in further synthetic transformations. Halolactonization reactions generally consist in 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 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).



Scheme 1. General scheme of halolactonization

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 to identify a suitable catalytic system which allows 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 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 were examined in most cases. Hence, despite a huge synthetic potential, enantioselective halolactonizations of styrene-type carboxylic acids has not elicited great synthetic efforts from the scientific community and remained poorly explored. [5k,t,x,y] Moreover, halocyclization of such unsaturated compounds is challenging since the presence of an aryl ring significantly reduced the regioselectivity of the reaction, both 6-endo or 5-exo cyclization pathways being possible depending on 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] 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 (Figure 1).

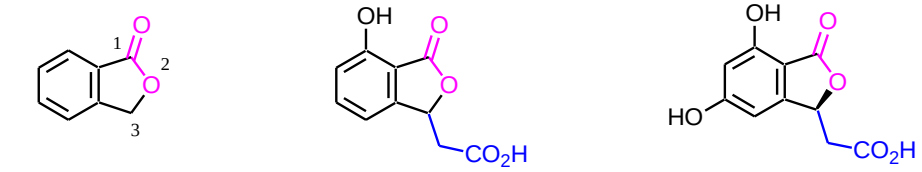
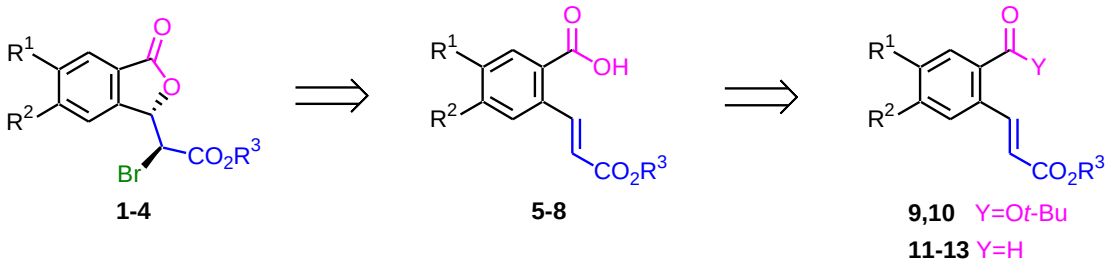


Figure 1. Natural 3-substituted bioactive isobenzofuranones

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 like 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.

Results and Discussion

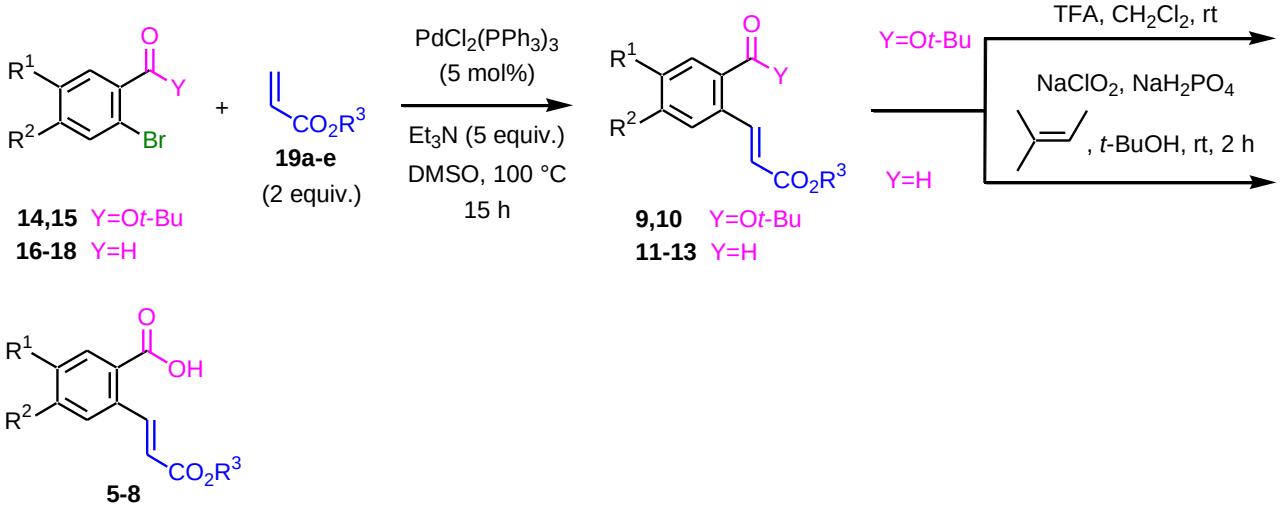
Our synthetic strategy is based upon a regio- and stereoselective organocatalyzed halolactonization reaction of aryl acrylate-type carboxylic acids **5-8** for the construction of the lactone ring with concomitant control of the stereogenic center at C3 (Scheme 2). In order to both increase the efficiency 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.



Scheme 2. Retrosynthetic analysis

1. Synthesis of unsaturated benzoic acids 5-8

t-Butyl esters **9** and **10** and benzaldehydes **11-13** were first readily prepared *via* a pallado-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 acid and Pinnick oxidation of aldehydes **11-13** furnished the targeted benzoic acids **5-8** with good yields (87-98%) (Scheme 3) (Table 1).



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

Table 1. Compounds **5-7**, **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

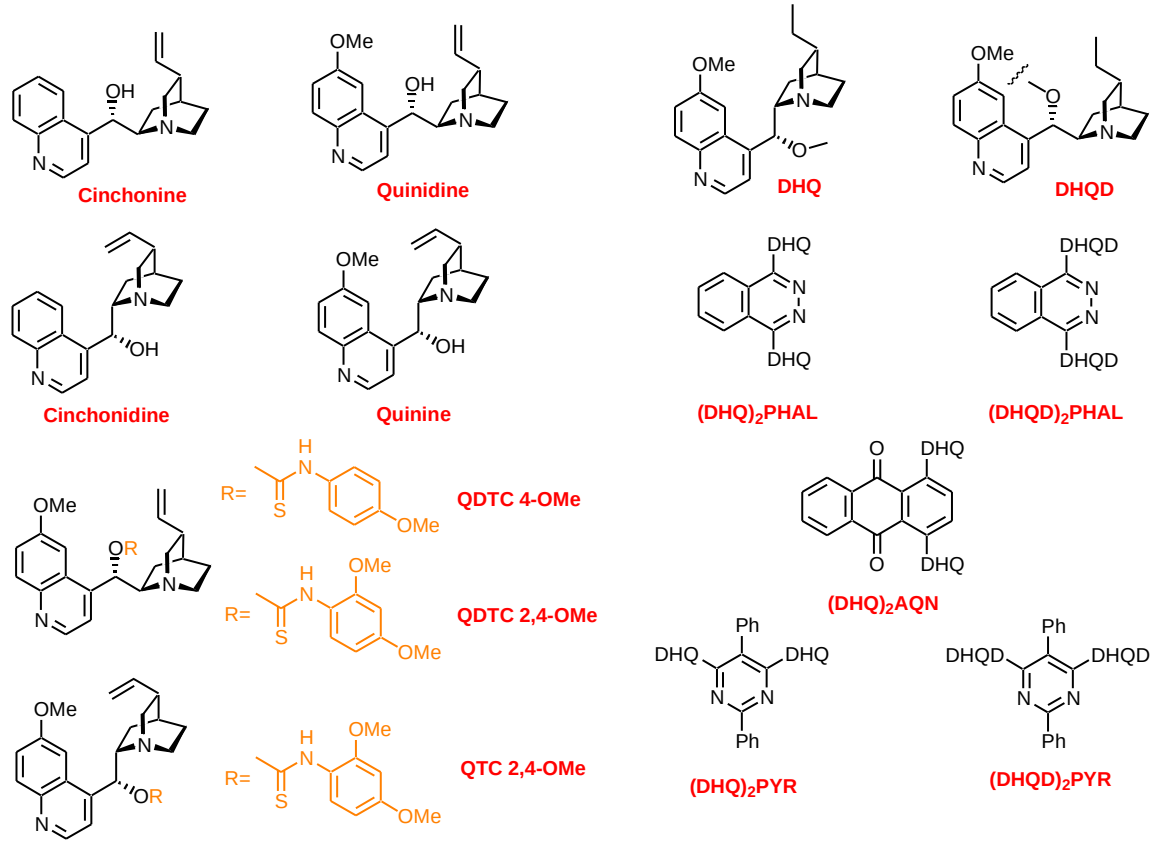


Figure 2. Organocatalysts used in this study

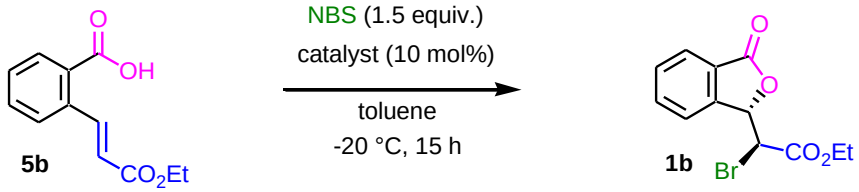
From these readily available aryl acrylate-type benzoic acids, the study of their stereoselective halocyclization was then initiated. The asymmetric halocyclization reaction of compound **5b** was first studied as a representative model to screen various privileged organo-catalysts [1h] (Figure 2) (Table 2).

2. Asymmetric intramolecular halolactonization reaction.

Because halolactonization reactions were shown to be achieved without the use of any catalyst or additional reagent, we performed first 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 decisive to control the 5-exo regioselectivity of the bromolactonization.

The reaction of **5b** with NBS as 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%) (entry 1). It was 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] 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 (Figure 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 to 21% ee) (entries 2-5). In 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) though their dual activation of NBS and substrate. [1e,g,h].

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 debromination reaction (see text).

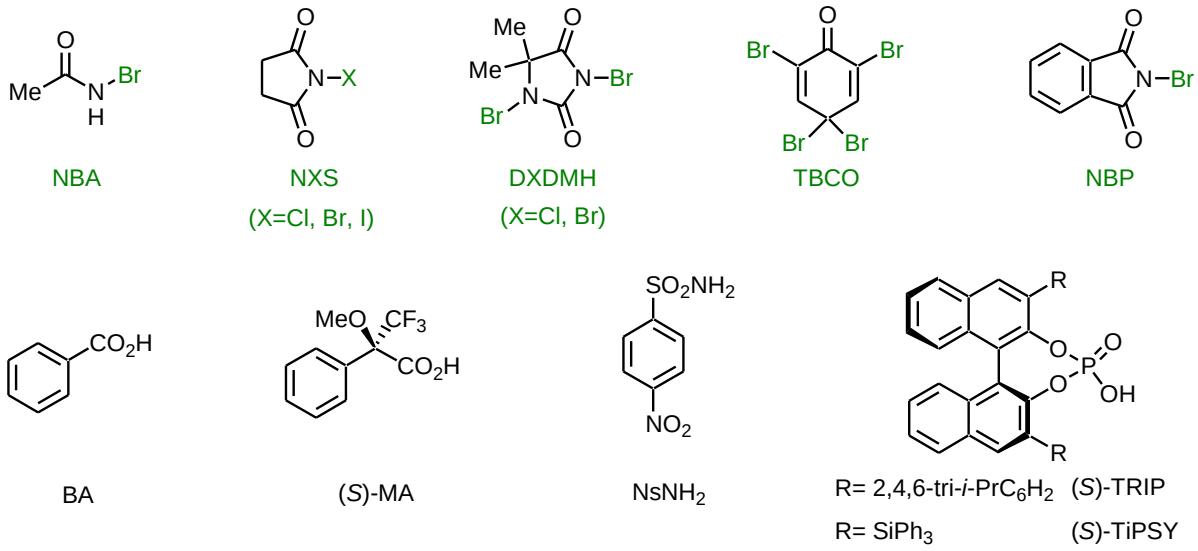
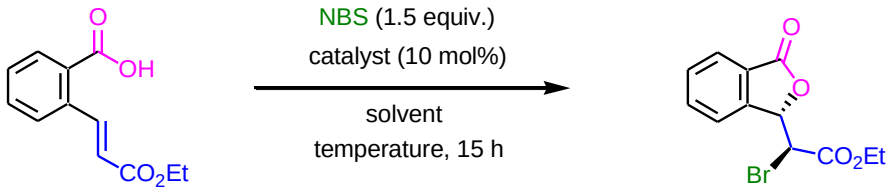


Figure 3. Halogen sources and additives used in this study

We were encouraged by the discovery that bifunctional catalysts developed by Yeung and coworkers [5c] such as catalyst (QDTC 4-OMe) provided good conversion and improved enantioselectivity (24% ee) (entry 10). Indeed, while NBS reagent shall be 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 affording the bromolactone **1b** with an improved selectivity of 35% (entry 9).

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



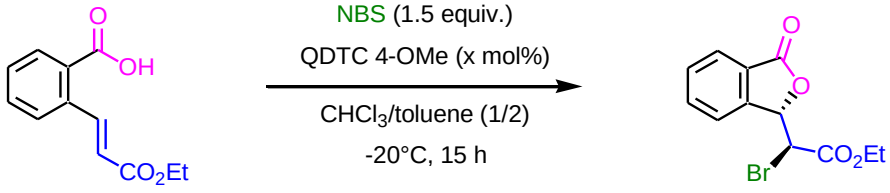
5b **1b**

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.

An additional study confirmed a 10 mol% catalyst loading was the best and a concentration of 0.1 M had to be preferred (Table 4).

Table 4. Enantioselective halolactonization of **5b** - study regarding the catalyst loading and the reaction concentration.



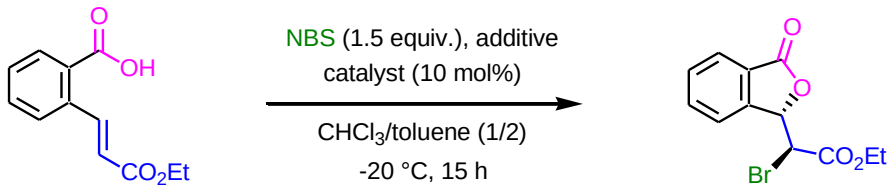
5b **1b**

Entry	Amount of catalyst (mol%)	Reaction concentration	Yield (%)[a]	Ee (%)[b]
1	5	0.1 M	99	37
2	10	0.1 M	99	36
3	20	0.1 M	99	36
4	30	0.1 M	99	37
5	40	0.1 M	99	40
6	10	0.05 M	99	36
7	10	0.2 M	99	37

[a] isolated yield. [b] measured by HPLC.

In order to improve the **1b** enantioselectivity, various acidic or basic additives (Figure 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 5). When no catalyst and additive were used, a background reaction afforded product **1b** in a 25% yield (Table 5 entry 1 and Figure 4). 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 enantioselectivity (43% ee) (entry 4).

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



5b **1b**

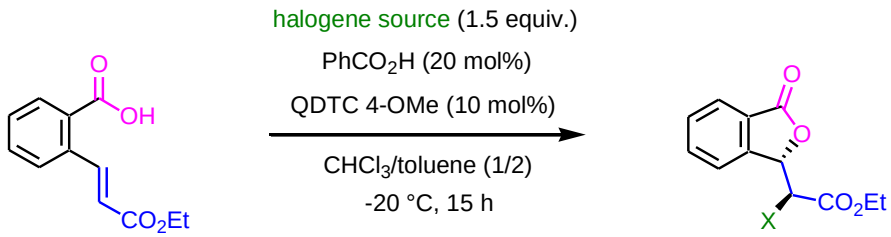
Entry	Catalyst	Additive	Yield (%)[b]	Ee (%)[c]
1	none	none	25	-
2	QDTC 4-OMe	none	88	31
3	QDTC 4-OMe	BA (10 mol%)	84	33
4	QDTC 4-OMe	BA (20 mol%)	92	43
5	QDTC 4-OMe	BA (100 mol%)	91	29
6	QDTC 4-OMe	$NsNH_2$ (20 mol%)	77	36
7	QDTC 4-OMe	(*R*)-MA (20 mol%)	60	8
8	QDTC 4-OMe	(*S*)-MA (20 mol%)	65	6
9	QDTC 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.

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 6, Figure 2). 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 with a good yield and a lower enantioselectivity (entry 6).

Table 6. Enantioselective halolactonization of **5b** with various halogen sources[a]



5b **1b**

Entry	Halogene 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.

Following the reaction course confirmed 15 hours was the best reaction time for acrylate type carboxylic acids (Figure 4). Hence reactions were rather fast in comparison with the 3 to 7 days required for halolactonization of stilbene derivatives. [5k]

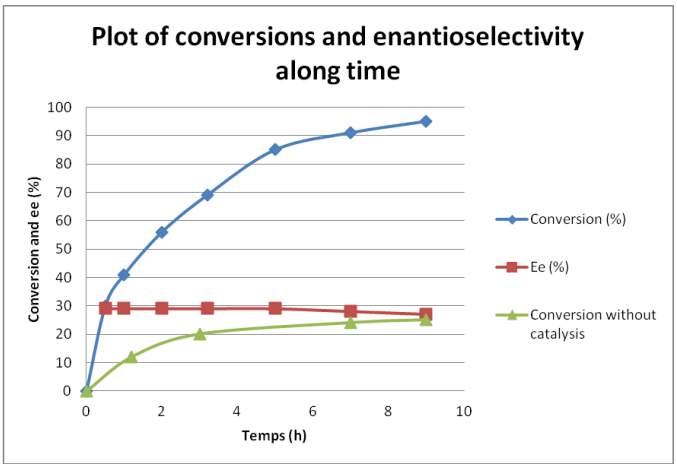
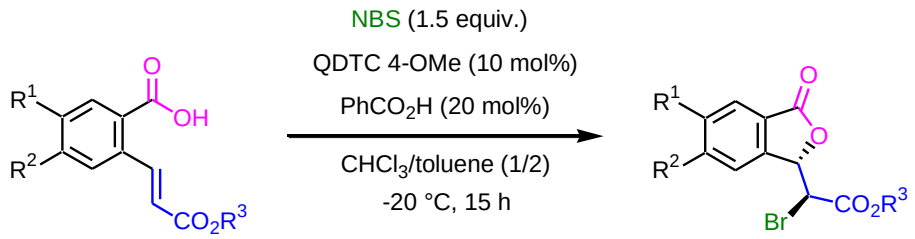


Figure 4. Plot of conversions and enantioselectivity along time.

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 7). 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 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 7, electron donating alkoxy groups decreased dramatically the stereoselectivity of the bromolactonization process (entries 8 and 9). However, the bulkier the R^3 substituent was, the higher was 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 are most probably resulting from the combination of the uncatalyzed background reaction and the catalyzed enantioselective transformation. The kinetics of these two reactions (Figure 4) 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.

Table 7. Enantioselective halolactonization of **5-8**[a]

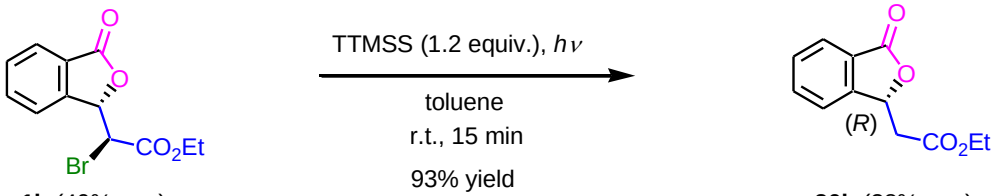


5-8 **1-4**

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	*n*-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.

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. Bromide was cleanly removed to afford the debrominated compound **20b** in high yield (93%) without significant loss of enantiopurity. 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 $CHCl_3$) (e.e. 86%), [13b] +3.8 for (3*R*)-**20b** (*c* 3.3 in $CHCl_3$) (e.e. 38%). This debromination reaction allowed the determination of the absolute configurations of all isolated halolactones.



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

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

Conclusion

In summary, 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 targeted bromolactones with promising enantioselectivities (up to 53%). A more efficient catalytic system may enable a faster bromolactonization as 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.

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