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Catalytic asymmetric bromolactonization reactions using $(DHQD)_2PHAL$-benzoic acid combinations

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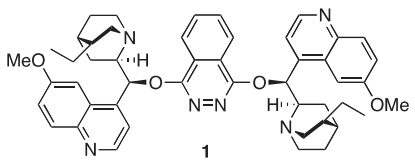
ABSTRACT

Catalytic $(DHQD)_2PHAL$ as modified by added benzoic acid, is an off-the-shelf catalyst-additive combination for effecting catalytic asymmetric bromolactonization reactions. This combination delivers bromolactones with asymmetric induction at a comparable level to bespoke catalysts previously optimized for particular substrate classes.

Catalytic asymmetric halofunctionalizations of alkenes are attracting considerable current attention.[1,2] In 2010, Borhan reported the first highly enantioselective chlorolactonization reaction using $(DHQD)_2PHAL$ (**1**) as an organocatalyst.[3] Although the corresponding asymmetric bromolactonization reaction using this catalyst gave only poor enantiomeric excess (35% ee),[3] several bespoke catalyst systems have been reported to give good to high enantiomeric excesses in bromolactonizations of selected substrates.[4] However, the substrate range for bromolactonizations is still limited, and the substrate scope for each catalyst type has not been reported. Herein, we report that the combination of $(DHQD)_2PHAL$ (**1**) and added benzoic acid is an off-the-shelf catalyst-additive combination to deliver good to high enantiomeric excesses across a range of substrate types including 5-arylhex-5-enoic,[4a,f] 4-arylpent-4-enoic,[4c,f,h,l] (*Z*)-5-arylpent-4-enoic,[4e] and 2-vinylbenzoic[4g] acids at a level of asymmetric induction comparable to that which the best bespoke catalyst system delivers, but where it is less effective for (*E*)-5-arylpent-4-enoic[4d,h] and 2-(2-ethenyl)benzoic[4g] acids. We also report on its effectiveness for some previously unexplored substrate types, and also for desymmetrization of dihydrobenzoic acids[4h,4k] and for kinetic resolution[4k,4m] reactions.

At the outset of our investigations we were drawn to the use of bis-cinchona alkaloid derivatives, such as $(DHQD)_2PHAL$ (**1**)[5] as potential catalysts for bromolactonization reactions due to their ready availability (along with its *pseudo*-enantiomer $(DHQ)_2PHAL$ in order to access either enantiomer of bromolactone). Their emergence as apparently privileged catalyst structures in a number of diverse asymmetric halogenation reactions[2l,o,q,r,3,4k,6] also provides additional impetus, although the exact modes of substrate and/or reagent activation and mode of asymmetric induction remain to be fully elucidated.[1b] Moreover, we were intrigued by the fact that multiple Lewis basic sites in such catalysts exist, which may become protonated[7] by any carboxylic acid substrate during the reaction, and once the carboxylic acid is consumed—by forming a bromolactone product—these interactions must fall away. Borhan had previously reported an improvement in $(DHQD)_2PHAL$-catalyzed chlorolactonization enantioselectivities in the presence of added benzoic acid,[3] but had not reported this effect for bromolactonizations. With the above considerations in mind we chose to investigate the bromolactonization of 4-phenyl-pent-4-enoic acid (**2**)[8] as catalyzed by $(DHQD)_2PHAL$ (**1**) in the presence of added carboxylic acids to modify the catalyst throughout the course of the reaction (Table 1).



1

Borhan and co-workers[3] had previously determined that a 1:1 hexane:chloroform mixture was the optimum solvent for their catalytic asymmetric chlorolactonization using $(DHQD)_2PHAL$, and so

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0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
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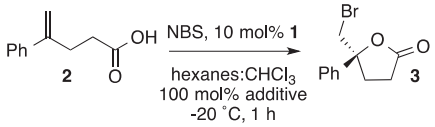
Table 1
Initial screening of additive effect in $(DHQD)_2PHAL$ (**1**) catalyzed bromolactonization



Entry[a]	Additive[b]	Additive pK_a[c]	Yield **3**[d] (%)	e.r. **3**[e]
1	—	—	92	63:37
2	CH_3CO_2H	4.76	96	67:33
3	CF_3CO_2H	0.23	92	50:50
4	$HO_2CCH_2CO_2H$	2.83	86	50:50
5	4-$MeOC_6H_4CO_2H$	3.37	94	70:30
6	4-$FC_6H_4CO_2H$	4.14	94	79:21
7	4-$NO_2C_6H_4CO_2H$	3.44	93	80:20
8	4-$NCC_6H_4CO_2H$	3.55	93	83:17
9	4-$CF_3C_6H_4CO_2H$	3.69	96	83:17
10	$C_6H_5CO_2H$	4.20	95	80:20
11	9-Anthroic acid	3.65	89	84:16
12[f]	$C_6H_5CO_2H$	4.20	95	91:9

[a] Reaction conditions: 0.16 mmol **2**, 1.0 equiv NBS, 10 mol% **1**, 1:1 hexanes:$CHCl_3$ (8 mL), $[\mathbf{2}]_0$ = 21 mM, 1 h, −20 °C.
[b] 100 mol% loading of additive.
[c] Aqueous pK_a values.
[d] Isolated yield after column chromatography.
[e] e.r. determined by chiral HPLC methods (see Supplementary data); the absolute configuration of the major enantiomer was determined to be (*S*)-configured (see main text).
[f] Reaction performed in toluene as the solvent.

it was selected for our initial studies. We also selected NBS as the electrophilic bromine source. In such an initial $(DHQD)_2PHAL$ (**1**) catalyzed experiment, bromolactone **3** was rapidly produced (<1 h) in excellent isolated yield and, in agreement with Borhan, moderate% ee (Table 1, entry 1). The major enantiomer was found to be (*S*)-configured by comparison of the sign and magnitude of its optical rotation with the known (*R*)-(+)-enantiomer.[4c] Interestingly, this stands in contrast to the (*R*)-configured chlorolactones produced in Borhan's study with the same substrate and catalyst.[3] We then explored the addition of stoichiometric quantities of aliphatic and aromatic carboxylic acids to the bromolactonization reactions. The addition of acetic acid (entry 2) had little effect on the e.r., and addition of the stronger aliphatic acids, trifluoroacetic (entry 3) and malonic acids (entry 4) returned essentially racemic bromolactone **3**. On the other hand, the use of aromatic carboxylic acids as additives gave rise to significant and beneficial increases in e.r. (entries 5–11). Here, electron- deficient benzoic acids perform best (entries 6–9), but there is not a perfect correlation between e.r. and pK_a, and the use of benzoic acid itself (entry 10) as an additive provides similarly improved enantioselectivity. 9-Anthroic acid (entry 11) was the most beneficial additive in terms of e.r., but in this case small quantities of inseparable 9-bromoanthracene[9] were generated in the reaction mixture, which complicated subsequent e.r. HPLC analysis. For these reasons, inexpensive and readily available benzoic acid was selected as an additive for further study.

In a screen of reaction solvents, it was found that alcoholic solvents were not suitable since they are competitively oxidized. Solvents with lower dielectric constants gave higher enantioselectivities,[10] with toluene being the optimum solvent delivering bromolactone **3** with an e.r. of 91:9 (Table 1, entry 12).[11] Accordingly toluene became the solvent of choice, where a control experiment with no catalyst demonstrated that there was no background bromolactonization. It was also established that in toluene the e.r. was insensitive to initial substrate concentration, and that *ca.* 100 mol% benzoic acid as additive should be used at 10 mol% catalyst loading to maintain good enantioselectivity.[12] Notably, the e.r. recorded by us (91:9) for this substrate giving γ-lactone **3** is comparable to those reported by Yeung (95:5),[4c] Yeung (95:5),[4f] Martin (86:14),[4h] and Kim (88:12)[4l] with bespoke catalyst systems.

With the optimum conditions delineated[13] for the bromolactonization of 1,1-disubstituted alkene **2** with catalytic $(DHQD)_2PHAL$ **1**, we sought to examine their applicability to other substrates **4**–**14**[14] (Table 2). In each case the catalytic asymmetric bromolactonization reactions were run with and without benzoic acid as additive.[15]

Asymmetric bromolactonization of homologous substrate **4** gave (*S*)-δ-lactone **4a** in 94:6 e.r. (entry 1), in a remarkable improvement from 59:41 without added benzoic acid. This level of enantioselectivity is directly comparable to that reported previously by Fujioka (94:6)[4a] and Yeung (96:4)[4f] for this substrate. 1,2-Disubstituted *Z*-alkene **5** (entry 2) gave (*S*,*S*)-γ-lactone **5a** regioselectively in 91:9 e.r., again with an improvement from 82:18 without added benzoic acid. There is a single report[4e] on the asymmetric bromolactonization of Z-alkene **5** to bromolactone **5a** (97.5:3.5 e.r.), and the off-the-shelf combination of $(DHQD)_2PHAL$ **1** and benzoic acid compares not unfavorably. For 1,2-disubstituted *E*-alkene **6**, a mixture of both *endo* **6a** and *exo* **6b** cyclization adducts were formed, each in only moderate e.r. (entry 3), where added benzoic acid was mildly detrimental for the former, and mildly beneficial for the latter. In this case, the bespoke catalysts of Yeung[4d] and Martin[4h] clearly outperform the $(DHQD)_2PHAL$ (**1**)-benzoic acid system, where *endo* **6a** was obtained regioselectively in each case with reported e.r.s of 96:4 and 98:2, respectively. However, we note that in the $(DHQD)_2PHAL$ (**1**)-benzoic acid system, the *endo:exo* ratio and the e.r. for each adduct are not constant throughout the course of the reaction.[16] A control reaction with resubmission of these products to the reaction conditions showed that they did not interconvert nor undergo a change in e.r. This implicates a change in catalyst performance as the reaction proceeds as the concentration of acid substrate decreases. Trisubstituted alkene **7**, underwent regioselective lactonization to give (*S*,*S*)-γ-lactone **7a** in 86:14 e.r., where in the reaction without benzoic acid a similar level of asymmetric induction was observed (entry 4). The bromolactonization of the trisubstituted alkene 4,5-dimethylpent-4-enoic acid has also been reported by Martin,[4h] giving a γ-lactone also in 86:14 e.r. For tetrasubstituted alkene **8** - which has not previously been reported in an asymmetric bromolactonization reaction—(*S*)-γ-lactone **8a** was formed exclusively, with a moderate level of asymmetric induction, but no significant improvement was observed with added benzoic acid (entry 5). To complete the substitution pattern in this series, the bromolactonization of terminal alkene **9** was explored. As for the tetrasubstituted substrate, an asymmetric bromolactonization has not been reported for this substrate, and in our system a moderate level of asymmetric induction was observed, both with and without benzoic acid (entry 6).

For vinyl benzoic acid **11**, bromolactonization without added benzoic acid gave the *exo* cyclization adduct **11a** exclusively, but essentially as a racemate (entry 8). With added benzoic acid the e.r. increased dramatically to 83:17 in favor of the (*S*)-configured bromolactone, and this compares with a reported e.r. of 67:33 by Yeung.[4g] The previously unreported bromolactonization of allyl benzoic acid **12** shows a similar dramatic effect on addition of benzoic acid (entry 9). The bromolactonization of stilbene carboxylic acid **10** was also explored, where Yeung had reported an optimized reaction to give *endo* **10a** and *exo* **10b** in a 2:1 ratio, with e.r.s of 86:14 and 90:10, respectively.[4g] With the $(DHQD)_2PHAL$-benzoic acid system (entry 7), the *exo* adduct **10b** is instead preferred, but the e.r. for each bromolactone is much reduced. Interestingly, and as for substrate **6** (and evidently for the same reason), the

Table 2
$(DHQD)_2PHAL$-catalyzed bromolactonizations of substrates **4**–**14** with 100 mol% added benzoic acid

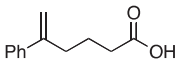
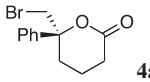
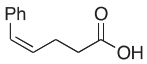
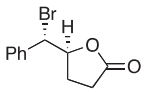
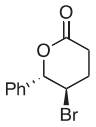
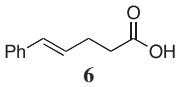
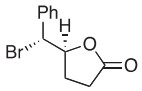
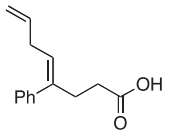
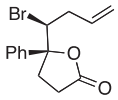
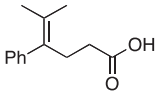
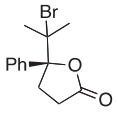
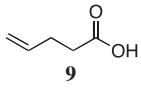
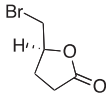
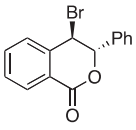
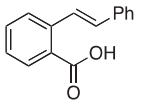
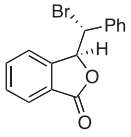
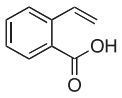
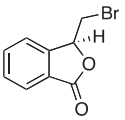
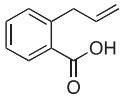
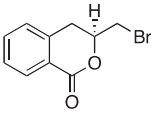
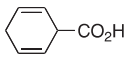
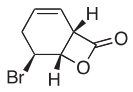
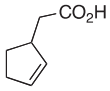
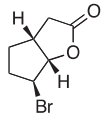
Entry[a]	Substrate[b]	Product(s)[c,d]	e.r.[e]
1	 **4**	 **4a** (94%)	94:6 (59:41)
2	 **5**	 **5a** (88%)	91:9 (82:18)
		 **6a**	74:26 (79:21)
3[f]	 **6**	 **6b** **6a:6b** 57:43 (44:56)[f]	67:33 (61:39)
4	 **7**	 **7a** (93%)	86:14 (83:17)
5	 **8**	 **8a** (95%)	69:31 (67:33)
6	 **9**	 **9a** (98%)	68:32 (63:37)
		 **10a**	63:37 (64:36)
7[f,g]	 **10**	 **10b** **10a:10b** 24:76 (22:78)[f]	57:43 (55:45)
8	 **11**	 **11a** (95%)	83:17 (50:50)
9	 **12**	 **12a** (94%)	80:20 (50:50)

Table 2 (*continued*)

Entry[a]	Substrate[b]	Product(s)[c,d]	e.r.[e]
10	 **13**	 **13a** (40%)	64:36 (60:40)
11[h]	 (±)-**14**	 **14a** (48%)	67:33 (63:37)

[a] Reaction conditions: 1.0 equiv NBS, 10 mol% **1**, 100 mol% BzOH, toluene (25 mM), −20 °C, 1 h.
[b] For details on substrate synthesis/availability, see the Supplementary data.
[c] The absolute configuration was determined by comparison of the sign of optical rotation of either the bromolactone (**4a–6a**, **9a–11a**, **13a**), or its desbromo derivative (**6b**, **10b**, **12a**, **14a**) with literature data or by anology (**7a**, **8a**) (see Supplementary data).
[d] Figure in parentheses is the isolated yield after column chromatography.
[e] e.r. determined by chiral HPLC or GC methods (see Supplementary data). Figures in parentheses are for parallel runs without added benzoic acid.
[f] Ratio of *endo:exo* adduct as determined by ^{1}H NMR spectroscopy at 100% conversion. The figures in parentheses are for parallel runs without added benzoic acid.
[g] 1:1 Chloroform:toluene employed as solvent.
[h] 50 mol% of NBS used.

endo:exo ratio and also the e.r. of each bromolactone were not constant throughout the course of the reaction.[17]

The desymmetrization of prochiral dienoic acid **13** by asymmetric bromolactonization to lactone **13a** in 73:27 e.r. after 4 days at −50 °C has recently been reported.[4f] The catalytic $(DHQD)_2PHAL$–$PhCO_2H$ combination returned (*S*)-β-lactone **13a** (entry 10) in 40% yield after just 1 h at −20 °C and an e.r. of 64:36 (60:40 without added benzoic acid). Kinetic resolution of acid (±)-**14** gave bromolactone **14a** in 67:33 e.r. at 50% conversion, which could be improved to 81:19 e.r. at <10% conversion (*S* factor 4.5).

Further studies on the mode of catalysis and asymmetric induction in these catalytic asymmetric bromolactonization reactions are under investigation and will be reported in due course.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, enantiomeric excess determinations and absolute stereochemical assignments) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.043.

References and notes

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9. We invoke an *ipso*-brominative decarboxylation to rationalize this.
10. $(DHQD)_2PHAL$ (**1**) catalyzed bromolactonization of alkene **2** into bromolactone **3** using NBS and 100 mol% benzoic acid additive in solvents of different dielectric constants: $ClCH_2CH_2Cl$ ($\varepsilon_0 = 10.4$; e.r. 65:35), PhCl ($\varepsilon_0 = 5.6$; e.r. 78:22), $CHCl_3$ ($\varepsilon_0 = 4.8$, e.r. 80:20).
11. It was not possible to conduct the reaction in very non-polar solvents such as hexane ($\varepsilon_0 = 1.9$) due to poor reagent and catalyst solubility, nor was it possible to use other low dielectric solvents such as benzene which is solid at −20 °C.
12. In an experiment conducted in chloroform:hexane with 100 mol% benzoic acid additive, the e.r. remained constant throughout the reaction (e.r. = 80:20). In a parallel reaction without benzoic acid as an additive, sampled over time, the e.r. *decreased* as the reaction proceeded. At 2, 5, 8 and 16 min the e.r. was 70:30, 66:34, 63:37 and 63:37, respectively.
13. NBS as the source of electrophilic bromine was preferred to N-bromoacetamide (e.r. 53:47) or dimethyldibromohydantoin (e.r. 77:23). A

screen of reaction temperature revealed −20 °C to be optimum: −78 °C (e.r. 67:33); −40 °C (e.r. 75:25); −20 °C (e.r. 80:20); 0 °C (e.r. 78:22); 20 °C (e.r. 78:22) where a balance must be struck between improved enantioselectivity at lower temperature versus decreasing solubility of benzoic acid as the temperature is reduced.
14. Details of substrate preparation can be found in the Supplementary data.
15. In these reactions, no intermolecular reaction between a bromonium ion of the substrate and the additive was observed.
16. At 21%, 49% and 65% conversions the *endo:exo* ratios were 24:76, 27:73 and 53:47, respectively. The e.r. of the *endo* adduct **6a** was 85:15, 73:27 and 68:32, respectively, and 60:40, 62:38 and 64:36 for the *exo* adduct **6b**.
17. At 23%, 53% and 78% conversions the *endo:exo* ratios were 19:81, 23:77 and 35:65, respectively. The e.r. of the *endo* adduct **10a** was 72:28, 65:35 and 62:38, respectively, and 58:42, 58:42 and 53:47 for the *exo* adduct **10b**.