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Monomeric cinchona alkaloid-based catalysts for highly enantioselective bromolactonisation of alkynes

Michael Wilking, Constantin G. Daniliuc and Ulrich Hennecke*[a]

Abstract: The cinchona alkaloid dimer $(DHQD)_2PHAL$ has been shown to be a broadly applicable catalyst for asymmetric halogenations. However, this catalyst does not have to be dimeric and a class of monomeric quinidine and quinine-derived catalysts was prepared which shows often superior selectivities in bromolactonisations of terminal alkynoic acids. Mechanistic investigations show that these organocatalysts act as host molecules that can bind carboxylic acid-based substrates as guests with substantial binding constants. Based on these findings it is proposed that this class of catalysts is bifunctional in nature activating the halogenating agent as well as the nucleophile in electrophilic halogenation reactions.

Introduction

The electrophilic halogenation of carbon-carbon multiple bonds is one of the fundamental reactions of organic chemistry. Dihalogenation, halolactonisation and related halofunctionalisations are often applied in organic synthesis including complex natural product synthesis.[1] However, only during the last years, reagent-controlled, enantioselective variants of this class of reactions have been developed.[2] In many cases, specific organocatalysts have been designed for one specific class of asymmetric halogenations, but their general applicability seems to be limited.[3,4] Probably the most broadly applicable catalysts in this area, are the dimeric cinchona alkaloid derivatives $(DHQD)_2PHAL$ **1** and the pseudoenantiomeric (diastereomeric) $(DHQ)_2PHAL$ **2** (Figure 1).[4,5] These catalysts, originally developed as chiral ligands for the Sharpless bishydroxylation[6], were introduced as organocatalysts for halogenation by Borhan to asymmetric chlorolactonisations.[4a] Subsequently, they were found to be efficient, enantioselective organocatalysts for a range of other halogenations including haloamidations, dichlorination, dearomatizing bromocyclizations, bromolactonizations of alkynes and other reactions.[4,5] Despite this numerous reports, the mechanistic understanding of these catalysts is limited and this limited knowledge on the role of the different components of these molecules has hindered the systematic improvement of the catalyst's properties. Borhan investigated the interaction of catalyst **1** with the stoichiometric halogenating agent and found that the quinuclidine core is acting as a Lewis base towards the halogenating agent/the electrophilic halogen and is therefore involved in catalysis.[4a,b] Nicolaou suggested a similar activation of the halogenating agent by this nitrogen, but also pointed out the important role of the bridging phthalazine moiety as hydrogen bond acceptor to orient allylic alcohol substrates.[4d] During our studies on the enantioselective bromolactonisation of dialkynoic acid we discovered the rather tight binding of the substrate carboxylic acids to the $(DHQD)_2PHAL$ catalyst **1**.[4h] However, it is currently not clear how these discoveries translate from one reaction to another and many mechanistic questions remain, including the importance of the dimeric nature of these catalyst.

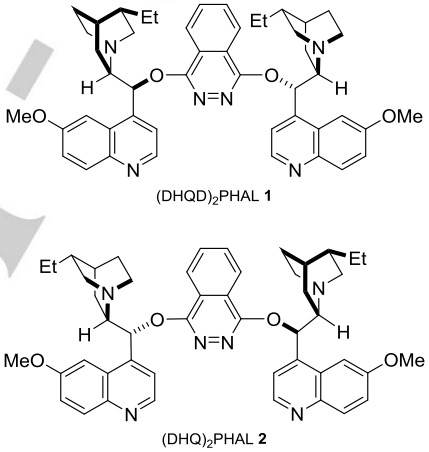

Figure 1. The pseudoenantiomeric (diastereomeric), dimeric cinchona alkaloid derivatives $(DHQD)_2PHAL$ **1** and $(DHQ)_2PHAL$ **2**.

These are key question to be answered, which should enable rational development of catalysts for enantioselective halogenation of unsaturated carbon-carbon bonds. Therefore we set out to prepare a range of new cinchona alkaloid-based phthalazine derivatives on the one hand to study the importance of the different parts of the molecules and their relevance to catalysis. On the other hand we wanted to improve the catalysts performance and specifically address the shortcomings of the conventional $(DHQD)_2PHAL$ **1** in enantioselective bromolactonisation of alkynoic acids, e.g. lower enantioselectivity with terminal alkynes.

Results and Discussion

$(DHQD)_2PHAL$ **1** can be easily prepared from dihydroquinidine and 1,4-dichlorophthalazine in a nucleophilic aromatic substitution reaction.[6] If derivatives with only one alkaloid substituent are desired, simple adjustment of the stoichiometry

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allows the preparation of dihydroquinidine monochlorophthalazine **3b** ((DHQD)PHALCl).[7] Already Sharpless used this intermediate to prepare dihydroquinidine-based phthalazine ligands containing only one alkaloid.[7] Following this lead a small liberary of monomeric (DHQD)PHAL derivatives with (mostly alkoxy) substituents of different sterical demand was prepared (Figure 2, see Supporting Information for experimental details).

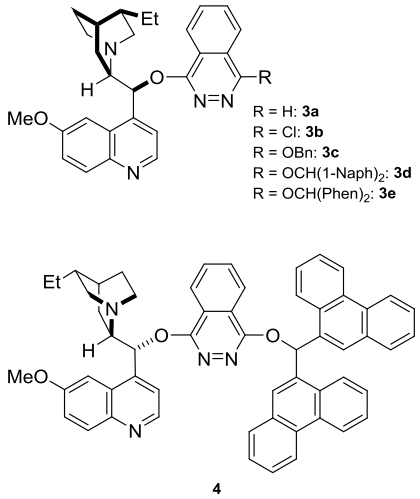
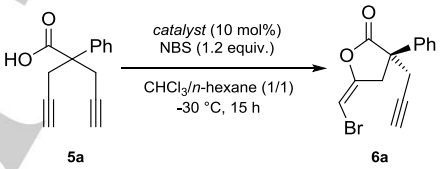


Figure 2. Phthalazine-substituted cinchona alkaloid derivatives prepared and applied as organocatalysts.

These monomeric dihydroquinidine derivatives were now investigated as catalysts in a model reaction, in this case the bromolactonisation of dialkynoic acid **5a** (Table 1). Without a catalyst present, this reaction does not proceed to a significant extent under the chosen reaction conditions (entry 1). As a reference reaction the bromolactonisation of this compound using the dimeric $(DHQD)_2PHAL$ **1** provided the bromoenol lactone **6a** in 90% yield and with an enantioselectivity of 86:14 *er* (entry 2).[4h] If instead of **1** only dihydroquinidine was used as a catalyst, the product was obtained in lower yield (74%) and as a racemate (entry 4). This showed that without the phthalazine moiety, no enantioselective catalysis was possible. If the phthalazine moiety was reintroduced to give catalyst **3a** without any further substituent, a more active catalyst was obtained (88% yield) and a moderate enantioselectivity of 67:33 *er* was observed (entry 5). Adding small substituents to the 4-position of the phthalazine led to moderate changes in activity and selectivity, depending on the nature of the substituent (entries 6,7). An electron-withdrawing chlorine substituent (catalyst **3b**) reduced the activity of the catalyst (63% yield) while retaining similar selectivity (63:37 *er*). An electron-donating benzyloxy-group on the other hand led to an increased activity (92% yield), however, the selectivity of this catalyst was rather low. This low selectivity might be due to the rather high flexibility of the benzyloxy group. Therefore catalysts **3d** and **3e** were prepared containing much more sterically demanding secondary alcohols as substituents, which should give a much more rigid catalyst (see also below). Already catalyst **3d** carrying a di(naphthyl) substituted alkoxy group was not only a highly active catalyst (92% yield), but also induced bromolactonisation with a good enantioselectivity of 85:15 *er*, very comparable to $(DHQD)_2PHAL$ **1** (entry 8). Catalyst **3e** with even larger phenantryl substituents proved to be even more selective and provided bromoenol lactone **6a** with an excellent 94:6 *er* (entry 9). This is a clear improvement over the commercial $(DHQD)_2PHAL$ **1** and enables for the first time the highly enantioselective bromolactonisation of terminal alkynes. Additionally, the pseudoenantiomeric catalyst of **3e**, catalyst **4**, was prepared based on dihydroquinine. Whereas the standard dimeric dihydroquinine derivative $(DHQ)_2PHAL$ **2** provided the product in 51% and with an enantioselectivity of 19:81 *er* (entry 3), bromolactonisation of **5a** using the monomeric derivative **4** as catalyst proceeded with excellent enantioselectivity (6:94 *er*) and the product ***ent*-6a** was obtained in moderate yield (55%, entry 10).

Table 1. Evaluation of new cinchona alkaloid-based organocatalysts in alkyne bromolactonisation[a]



5a **6a**

Entry	Catalyst	Yield **6a** (%)[b]	*er*[c]
1	-	< 5	50:50
2	$(DHQD)_2PHAL$ **1**	90	86:14
3	$(DHQ)_2PHAL$ **2**	51	19:81
4	Dihydroquinidine	74	50:50
5	**3a**	88	67:33
6	**3b**	63	63:37
7	**3c**	92	55:45
8	**3d**	92	85:15
9	**3e**	99	94:6
10	**4**	55	6:94

[a] Experiments were conducted on a 0.3 mmol scale, see Supporting Information for further details. [b] Isolated yields after column chromatography. [c] Determined by HPLC on chiral stationary phases.

The investigations clearly showed that a suitable catalyst for the bromolactonisation required three important moieties in the catalyst: firstly, the alkaloid, which carries the required chirality.

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Secondly the phthalazine moiety, which was required for good catalytic performances and selectivity.[8] And lastly a third group, which should be sterically demanding to achieve excellent enantioselectivity. In the commercial catalyst $(DHQD)_2PHAL$ **1** this is the second alkaloid, but our experiments show that this group can be easily replaced by simple secondary alcohols. This should allow the optimisation of this type of catalyst to achieve higher selectivities in many kinds of halogenation reactions. Nevertheless, for improving the catalyst it would be also very helpful if the precise function of the different functional groups in the catalyst and their mechanistic relevance would be known. Previous reports suggested, that the two mechanistically important functionalities should be the quinuclidine ring and the phthalazine moiety. Based on Borhans findings and similar NMR experiments under our reactions conditions, it can be postulated that the quinuclidine ring is involved in the activation of the halogenating agent.[4a,b] If this happens via formation of an *N*-bromo ammonium salt or by Lewis base activation of NBS is not yet fully clear.[4a,4b] In our case the nature of the brominating agent does not have a significant influence on the selectivity suggesting that the succinimide (or another imide/amide) is not involved in the stereo-determining step making first possibility more likely.[4h] The phthalazine moiety could be involved in the interaction of the catalyst with the substrate, in our case the diynoic acids **5**.

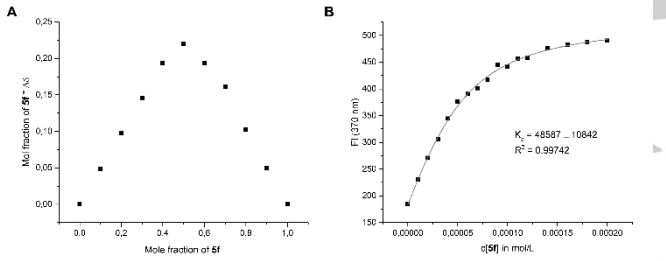

Figure 3. Titration experiments of catalyst **3e** with substrate **5f**. A: ^{1}H-NMR titration in $CDCl_3$ at 308 K with $[c]_{3e} + [c]_{5f}$ = 0.3 mmol/L. The Job plot is based on the chemical shift of the –OMe signal of **5f** (other signals provided similar plots, see Supporting Information). B: Fluorescence titration of **3e** (0.1 mmol/L in $CHCl_3$) with increasing amounts of **5f** (black data points). The fluorescence of **3e** was observed at 370 nm. The gray line shows the fitted binding isotherm.

To investigate the potential binding of **5** to phthalazine-modified cinchona alkaloids we turned to NMR titration experiments (see SI for details). These experiments strongly indicate that carboxylic acids **5** bind rather tightly to the catalysts **1** and **3e** as the NMR spectra show that the two propargyl groups of **5** become diastereotopic upon addition of a catalyst. However, with the commercially available catalyst **1** it proved difficult to establish a binding constant or binding stoichiometry based on these NMR titrations. Initial titration experiments with catalyst **3e** and carboxylic acid **5f** at room temperature (299 K) in $CDCl_3$ were also not conclusive due to line-broadening of some signals in the NMR spectra (possibly caused by host-guest exchange on the timescale of the NMR experiment). At slightly elevated temperature (308 K) this problem could be overcome and NMR spectra of mixtures of **3e** and **5f** showed significant concentration-depended shifts of most signals. This data was applied to Job plot analysis (Figure 3A), which supports the formation of a 1:1 complex between **3e** and **5f**. To determine the association constant K_a the fluorescence properties of **3e** were utilised and fluorescence titrations of **3e** with increasing amounts of **5a** or **5f** were conducted. The observed fluorescence increase upon addition of **5f** to **3e** was plotted against the concentration of **5f** (Figure 3B). To extract an association constant from the resulting binding isotherm a non-linear fitting procedure assuming 1:1 complex formation was employed.[9] This provided an association constant of approximately K_a = 48500 for the complex between **3e** and **5f**, equal to a $\Delta G_{binding}$ of 6.4 kcal/mol at room temperature. For diynoic acid **5a** similar results were obtained including an association constant of K_a = 26900 (see Supporting Information for details). These experiments clearly established that pthalazine-modified cinchona alkaloids such as compounds **1**-**4** can act as host molecules binding carboxylic acids as guests with rather substantial association constants. Currently we have no structural information on this binding event, but a key interaction should be the formation of a hydrogen bond between one of the Lewis basic nitrogens of the catalyst and the carboxylic acid group of the substrates. The rather high association constants suggest that further interactions, including for example dispersive interactions with the large aromatic groups of the catalyst, contribute to the binding of the substrate. This finding is especially interesting in the light of Borhan's and Jackson's recent proposal that chlorolactonisation of alkenoic acids proceed by an concerted Ad_E3-type mechanism including nucleophile-assisted alkene activation (NAAA).[10] Taken together with our results, this suggests that the binding of the unsaturated alkenoic or alkynoic acids to the catalyst does not only place these substrates in a chiral environment (as demonstrated by the diastereotopic propargyl groups of the carboxylic acids **5** in the NMR spectra), but that the Lewis basic organocatalysts **1** or **3** activate the carboxylic acid group (via formation of a hydrogen bond) and via NAAA also the alkene for halogenation.

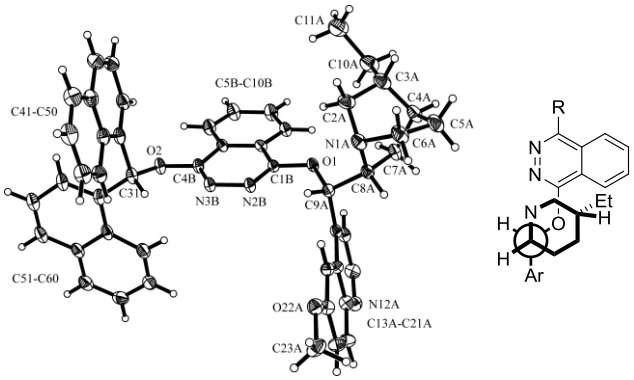

Figure 4. Crystal structure of catalyst **3d** (thermal ellipsoids are shown with 15% probability) and schematic conformation around the C8-C9-bond.

The investigations suggest that catalysts **1**-**4** might very likely be bifunctional, catalyzing the addition of the electrophile (the

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bromine) and the nucleophile (the carboxylic acid group) at the same time. This idea is further corroborated by the solid state structure of catalyst **3d**, which could be determined by X-ray crystallography (Figure 4). The structure shows that the quinidine part of the catalyst adopts the *anti*-open conformation.[11] This quinidine conformation leads to an overall conformation of the catalyst, in which the quinuclidine nitrogen and the two nitrogen atoms of the phthalazine moiety point into the same direction enabling bifunctional catalysis. Furthermore, the sterically demanding secondary alcohol and the quinoline group form a type of chiral pocket, in which the substrate could bind. Taken together these findings supports a synergistic activation of electrophile and nucleophile to induce a highly enantioselective addition to the alkyne.

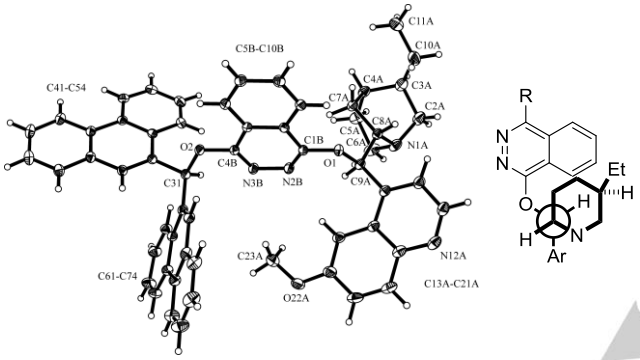
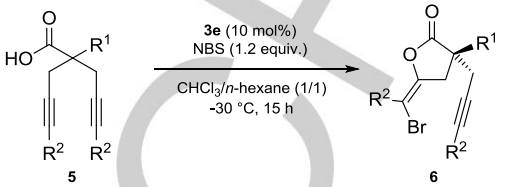


Figure 5. Crystal structure of catalyst **4** (thermal ellipsoids are shown with 15% probability) and schematic conformation around the C8-C9-bond.

What remains to be explained is the difference in catalytic activity, but not enantioselectivity between the pseudoenantiomeric catalysts **1** and **2** or **3e** and **4**. The catalysts of the quinidine series consistently led to higher yields of bromolactonisation products. A hint on a potential explanation arose when crystals of catalyst **4** were obtained and the crystal structure was determined by X-ray crystallography (Figure 5). Although the solid state structure of this catalyst is in general comparable to **3d** there are clear difference in detail. Obviously, catalyst **4** contains phenantryl- instead of naphthyl substituents, which leads to differences in the positioning of these groups. Much more remarkable is conformation of the quinine moiety including the C8-C9 bond of the alkaloid, which adopts the *anti*-closed conformation. This conformation places the catalytically relevant N1-atom of the quinuclidine moiety and the phthalazine moiety far away from each other making bifunctional catalysis impossible. This could explain, why catalyst **4** is significantly less active than its pseudoenantiomeric counterparts **3d**/**3e**. Catalyst **4** would require either a conformational reorganisation to become competent as a bifunctional catalyst or might even not be a bifunctional catalyst at all. A critical point is that this theory is based on the conformation of the alkaloid moiety in two crystal structures, e.g. in the solid state and not in solution. The different conformations of the catalysts **3d** and **4** could be also caused by crystal packing effects and further investigations are needed to establish the preferred conformation(s) of this type of organocatalysts in solution.

Table 2. Scope of bromolactonisation using DHQD-derived catalysts.[a]



Entry	Starting material	R^1, R^2	Product, yield (%)[b,d]	Er[c,d]
1	**5a**	Ph, H	**6a**, 99 (90)	94:6 (86:14)
2	**5b**	4-FC_6H_4, H	**6b**, 96 (81)	93:7 (81:19)
3	**5c**	Et, H	**6c**, 86 (58)	79:21 (63:37)
4[e]	**5d**	$CH_2OTBDPS$, H	**6d**, 80 (91)	76:24 (92:8)
5	**5e**	H, H	**6e**, 79 (65)	69:31 (78:22)
6	**5f**	COOMe, H	**6f**, 74 (79)[f]	56:44 (86:14)[f]
7	**5g**	Ph, Me	**6g**, 99 (98)[f]	95:5 (96:4)[f]
8	**5h**	3-ClC_6H_4, Me	**6h**, 93 (90)[f]	93:7 (95:5)[f]
9	**5i**	Ph, 4-ClC_6H_4	**6i**, 82 (92)[f]	85:15 (96:4)[f]

[a] Experiments were conducted on a 0.3 mmol scale, see Supporting Information for further details. [b] Isolated yields after column chromatography. [c] Determined by HPLC on chiral stationary phases. [d] Values in parenthesis provide data for reactions with $(DHQD)_2PHAL$ as catalyst. [e] 1 mol% catalyst. [f] Taken from reference 4h.

After identifying **3e** as an improved catalyst for the bromolactonisation of terminal alkynes, the scope of this catalyst for the bromolactonisation of terminal alkyne-containing substrates was investigated (Table 2). In all but two cases, the new catalyst **3e** performed better or at least equally well than $(DHQD)_2PHAL$ **1**. Starting materials with aryl rings as R^1 substituents were cyclised in excellent yields and with excellent enantioselectivites (94:6, 93:7 *er*, respectively, entries 1,2). A clear improvement was also observed for the sterically very challenging dialkynoic acid **5c** with an ethyl group as R^1. Using $(DHQD)_2PHAL$ **1** this cyclization proceeded to give the product **6c** in only 58% yield and with moderate enantioselectivity (63:37 *er*). Using catalyst **3e** cyclization was much more efficient (86% yield) and the selectivity was improved to 79:21 *er*. For starting material **5d** the situation was different and while catalyst **3e** led to acceptable results even with 1 mol% of catalyst (80% yield, 76:24 *er*) $DHQD_2PHAL$ **1** was this time the slightly better catalyst (91% yield, 92:8 *er*). For starting material **5e** results with $(DHQD)_2PHAL$ **1** and catalyst **3e** were roughly comparable with similar yields

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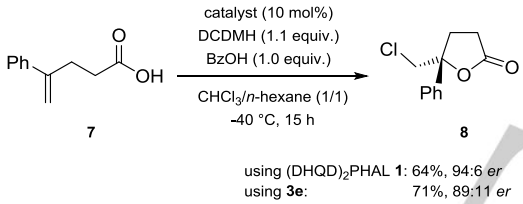
(79% vs 65%) and enantioselectivities (69:31 vs. 78:22 *er*, entry 5). Malonate-derived **5f** carrying a carboxy methyl group as R^1 was a problematic starting material for catalyst **3e**. Although yield remained high, bromolactonisation proceeded only with very low enantioselectivity. Catalyst **3e** is not only a very good catalyst for the bromlactonisation of substrates containing terminal alkenes, but is equally well applicable for bromolactonisation of substrates containing internal alkynes and for alkene bromolactonisation. Compounds **5g** and **5h** carrying a methyl substituent at the alkynes (R^2 = Me) could be cyclised to give the bromenol lactones **6g** and **6h** in excellent yield (99% and 93%) and with an enantioselectivity of 95:5 *er* and 93:7 *er*, values almost identical to those obtained with $(DHQD)_2PHAL$ **1**. For aryl substituted **5h** again a good yield of 82% was obtained, this time with a slightly reduced enantioselectivity of 85:15 *er*.

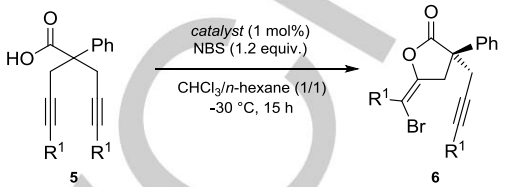
To show catalyst's **3e** broad applicability it was also used under slightly modified Borhan conditions[4a] (commercially available DCDMH was used instead of DCDPH) in the chlorolactonisation of alkenoic acid **7** (Scheme 1). Again, catalyst **3e** performed well and the product could be isolated in 71% yield and with a good enantioselectivity of 89:11 *er*. This compares well to the results of 64% yield and 94:6 *er*, obtained with $(DHQD)_2PHAL$ under identical conditions.



Scheme 1. Enantioselective chlorolactonisation of an alkenoic acid.

Further studies revealed that the dihydroquinidine-based organocatalysts are very robust catalysts under the reaction used for bromlactonisation of dialkynoic acids. Yields and enantioselectivies observed in the model reaction of **5a** to **6a** were not influenced by water, air or impure solvents. Even more interesting was the fact that the catalyst loading could be reduced from 10 mol% to 1 mol% without any effect on the reaction yield or enantioselectivity, at least for the quinidine-based catalysts (see Supporting Information, table S1, for a table showing the connection between catalyst loading and enantioselectivity). Bromolactonisation of terminal dialkynoic acid **5a** with either catalyst **1** or **3e** delivered the product **6a** in exactly the same enantioselectivity, whether using 10 or 1 mol% catalyst (Table 3, entries 1,2). Similar behaviour was also observed for internal alkynes, which were obtained with highly similar yields and selectivities using either 10 or 1 mol% of catalyst (entries 4-7). The only exception was catalyst **4**. With 10 mol% loading of this catalyst the enantioselectivity was almost identical to the selectivity obtained with the pseudoenantiomeric catalyst **3e**, but the yield of **6a** was already significantly lower (55%, 6:94 *er*, Table 1). When only 1 mol% catalyst **4** was applied, this effect was even more pronounced and the reaction became slow. The product **6a** was obtained in only 42% yield and with a slightly reduced enantioselectivity (16:84 *er*, Table 3, entry 3). This again shows that catalysts from the quinine series are less efficient than their quinidine counterparts in this type of bromolactonisations.

Table 3. Bromolactonisation using 1 mol% catalyst loading.[a]



Entry	Starting material	R^1	Catalyst	Product, yield (%)[b]	*Er*[c]
1	**5a**	H	**1**	**6a**, 93	86:14
2	**5a**	H	**3e**	**6a**, 98	94:6
3	**5a**	H	**4**	***ent*-6a**, 42	16:84
4	**5g**	Me	**1**	**6g**, 99	95:5
5	**5g**	Me	**3e**	**6g**, 74	94:6
6	**5h**	4-ClC_6H_4	**1**	**6h**, 99	97:3
7	**5h**	4-ClC_6H_4	**3e**	**6h**, 84	82:18

[a] Experiments were conducted on a 0.3 mmol scale, see Supporting Information for further details. [b] Isolated yields after column chromatography. [c] Determined by HPLC on chiral stationary phases.

These reactions could also be conducted on gram scale without any problems (Scheme 2). Bromolactonisation of 1 g **5a** with 1 mol% catalyst **1** gave the product **6a** in 89% yield and with an enantioselectivity of 86:14 *er*. Simple fractional crystallisation from cyclohexane led to the separation of the racemate *rac*-**6a** in 17% overall yield and basically enantiopure **6a** in 71% yield. Crystals of both the racemate and the enantiopure fraction were suitable for X-ray analysis and both crystal structures were solved The absolute configuration of the major enantiomer of **6a** could be determined to be (*R*), in agreement with our previous assignment.[4h] With catalyst **3e** similar results were obtained in the bromolactonisation of **5b**. Again only 1 mol% catalyst was sufficient to obtain the product **6b** on a 3 mmol scale in excellent yield (91%) and as expected for **3e** with the same very high enantioselectivity (93:7 *er*) than in the small scale experiments. Taken together these experiments show that this method for the enantioselective bromolactonisation of alkynoic acid is very robust, efficient and applicable to large scale synthesis without any problems.

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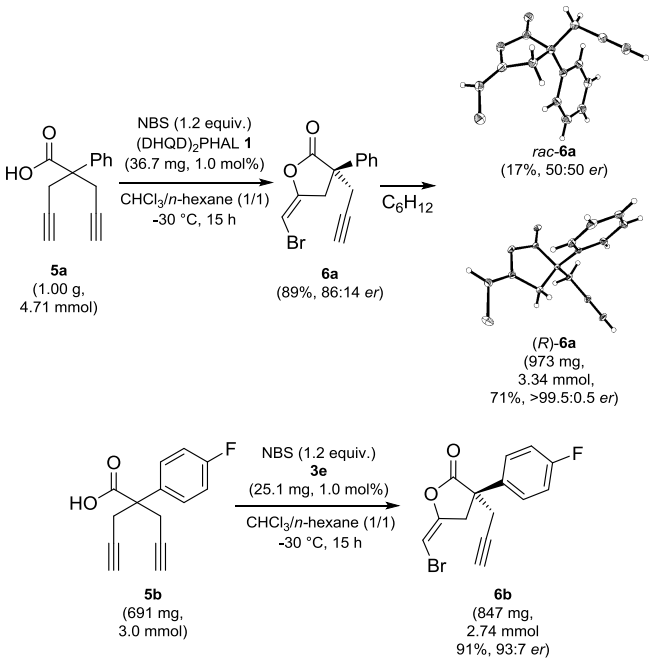

Scheme 2. Enantioselective bromolactonisation on mmol scale. Crystal structures of *rac*-**6a** and (*R*)-**6a** are shown with thermal ellipsoids 15% probability.

Conclusions

Although quinidine and quinine-based, phthalazine-containing organocatalyst have been shown to be broadly applicable in asymmetric halogenations, their mechanistic understanding is still limited. Herein, we have shown new evidence for the bifunctional nature of these catalysts including titration experiments that establish phthalzine-substituted cinchona alkaloids as efficient host molecules for carboxylic acids. By binding to unsaturated carboxylic acids such as alkenoic or alkynoic acids these catalysts provide a chiral environment in which halogenation can take place. The formation of a hydrogen bond between one of the Lewis basic nitrogens of the catalyst and the carboxylic acid could activate this group for cyclization and/or via nucleophile-assisted alkene activation also activate the alkene or alkyne for halogenation by an electophilic halogenating agent.

The monomeric cinchona alkaloid derivatives reported in this manuscript are efficient catalysts for enantioselective bromolactonisations of alkenoic and alkynoic acids. This shows that dimeric nature of compounds such as $(DHQD)_2PHAL$ is not required for high enantioselectivities in organocatalytic halogenations. For many terminal alkynes monomeric catalysts provide even significantly improved selectivities. Another advantage of the monomeric catalysts **3** and **4** is their modular design. The secondary alcohol component provides only steric bulk and could be easily replaced by other substituents. This should allow the adaption of these catalysts to a wide range of different enantioselective halogenation reactions just by the selection of suitable substituents at the phthalazine moiety.

Experimental Section

General procedure for enantioselective halolactonisation of diynoic acids

In a predried and Argon-filled Schlenk-tube the corresponding diynoic acid (0.300 mmol, 1.0 equiv.) and the catalyst (0.030 mmol, 10 mol%, or 0.003 mmol, 1 mol%) were dissolved in dry $CHCl_3$ (3 mL) and dry *n*-hexane (3 mL) and the resulting solution was stirred for 30 min at 30 °C. NBS (64.1 mg, 0.360 mmol, 1.2 equiv.) was added at -30 °C and the reaction was stirred for 15 h at this temperature. The reaction was stopped by the addition of $Na_2S_2O_3$-solution (sat. aq. sol., 6 mL) and CH_2Cl_2 (10 mL), the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude mixture by column chromatography over a short silica column provided the respective cyclization products.

For further experimental details including experimental procedures for the preparation of catalysts and starting materials, copies of NMR spectra and HPLC data and details on NMR and fluorescence titrations, see Supporting Informations. CCDC 1400023 - 1400027 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: alkynes • cyclisation • enantioselectivity • halogenation • organocatalysis

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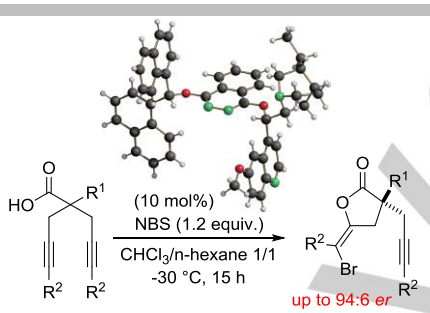

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