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Catalytic Enantioselective Halolactonization of Enynes and Alkenes

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Abstract: New organocatalysts have been developed for the enantioselective halolactonization of (*Z*)-1,3-enynes and 1,1-disubstituted alkenes. In the case of 1,3-enynes, the carboxylate nucleophile and halogen electrophile were added to the conjugated π-system from the same face. Up to 99% *ee* was achieved for the 1,4-*syn*-bromolactonization of conjugated (*Z*)-1,3-enynes. Based on the results from the enyne halolactonization, a second generation of catalysts was designed for simple olefins. Up to 91% *ee* was observed for chlorolactonization of 1,1-disubstituted alkenes. The catalysts developed for the enantioselective halolactonization of both enynes and alkenes are composed of a cinchona alkaloid skeleton tethered to a urea group.

Keywords: alkenes · allenes · enynes · halogens · halolactonization · organocatalysts

Introduction

Halogen-promoted addition of nucleophiles to alkenes is one of the most important and versatile reactions in organic chemistry and has been widely used in synthesis.[1] However, reagent-controlled enantioselective addition of halogen and various other nucleophiles to alkenes has remained elusive until recently.[2] In 2003, Kang's group reported a highly enantioselective iodocyclization of γ-hydroxy-*cis*-alkenes by using Salen–Co or Salen–Cr catalysts.[3] In 2007, Ishihara's group achieved up to 99% *ee* for the iodocyclization of polyprenoids by using a stoichiometric amount of chiral phosphoramidites.[4] One example of enantioselective dichlorination of olefins by employing a stoichiometric amount of a chiral reagent was described in the total synthesis of napyradiomycin A1 by Snyder's group.[5] In 2011, Nicolaou's group reported a catalytic method for the dichlorination of alkenes with up to 81% *ee*.[6] It is also worth mentioning that a chiral peptide-catalyst-mediated highly enantioselective bromination was recently developed by Miller's group for dynamic kinetic resolution of biaryl atropisomers.[7]

Among all halocyclizations, halolactonization is arguably the most versatile because the resulting lactone can be easily elaborated.[8] In 1992, Taguchi's group reported the first reagent-controlled enantioselective halolactonization and achieved 65% *ee* by using a stoichiometric amount of a chiral titanium complex.[9] Numerous efforts have been devoted to this area since then.[10] Low selectivity, however, was observed in these early studies. In 2009, Gao's group achieved up to 83% *ee* for the iodolactonization of 4-arylpent-4-enoic acids by using a Salen–Co complex.[11] In 2010, several highly enantioselective halolactonizations of 1,1-disubstituted olefins appeared. Borhan's group first found that up to 90% *ee* could be obtained for the chlorolactonization of 4-arylpent-4-enoic acids by using hydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2PHAL$)[12] as the catalyst.[13,14] The groups of Jacobsen,[15] Yeung,[16] and Fujioka[17] developed three different chiral catalysts for the enantioselective iodo- and bromolactonization of 1,1-disubstituted alkenes. The scope of the bromolactonization was expanded to 6-*endo*-cyclization of 1,2-disubstituted olefins in one of the above catalytic systems.[18] Various other enantioselective additions of halogens and nucleophiles to alkenes have also been developed recently.[19]

In 2009, we reported a catalyst-mediated diastereoselective 1,4-bromolactonization of conjugated 1,3-enynes [Eq. (1); NBS = *N*-bromosuccinimide].[20] Unlike the well-known *anti*-halolactonization of simple alkenes, the carboxylic acid nucleophile and bromine electrophile were added to the conjugated enyne from the same face in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst. High *syn*-diastereoselectivity (d.r. = 10:1 to 20:1) was observed for most basic amine catalysts (e.g., 4-dimethylaminopyridine (DMAP), Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and DABCO), whereas neutral nucleophilic catalysts (for example, Ph_3P, DMF, hexamethylphosphoramide (HMPA), and hexamethylphosphorous triamide (HMPT)) generally yielded poor selectivity (d.r. = 1:1 to 3:1). This novel DABCO-catalyzed *syn*-1,4-bromolactoniza-

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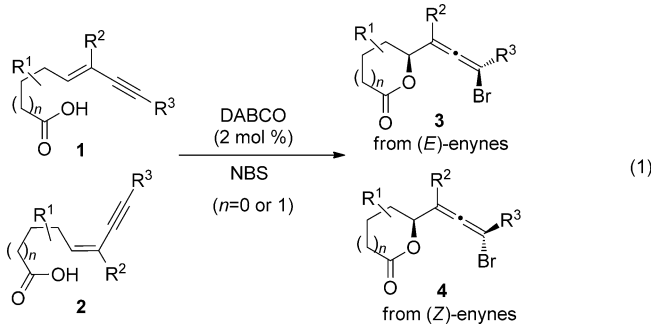
tion worked for both (*E*)- and (*Z*)-1,3-enynes **1** and **2**. It provided bromoallene products **3** and **4**, respectively, with complementary stereochemistry.[21] Over 20:1 diastereomeric ratios were obtained for almost all substrates (with one exception: d.r. = 10:1 when $R^3 = t$Bu) by using just 2 mol% of the DABCO catalyst. Di-, tri-, and tetrasubstituted allenes were prepared stereoselectively and efficiently under very mild conditions. We also found that chlorolactonization of 1,3-enynes did not occur in the presence of *N*-chlorosuccinimide (NCS) and DABCO. The iodolactonization of 1,3-enynes worked in the absence of any catalyst. The iodoallenyl lactone products, however, were not very stable. Interestingly, the bromoallene moiety is present in dozens of natural products, whereas neither chloroallene nor iodoallene has been found in naturally occurring compounds.[1j,21a,b]

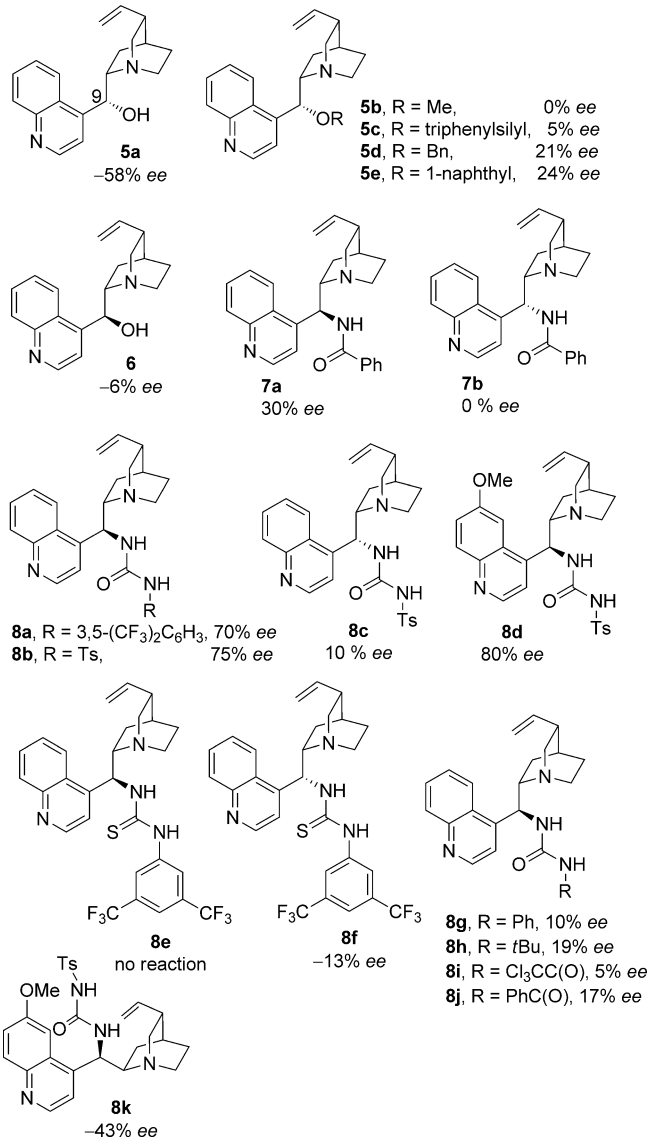


(1)

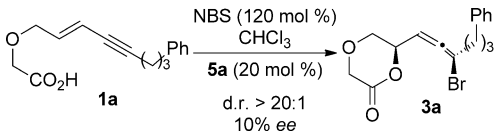
We subsequently developed a bifunctional chiral catalyst for the enantio- and diastereoselective 1,4-bromolactonization of conjugated (*Z*)-1,3-enynes.[22] This represents one of the first highly enantioselective halolactonizations.[2c] In this full account, we describe the scope, limitations, and mechanistic studies of the bifunctional-catalyst-mediated enantioselective 1,4-*syn*-bromolactonization of conjugated 1,3-enynes. We also report for the first time our efforts towards the enantioselective halolactonization of simple olefins by modifying the bifunctional catalysts that we have developed for the halolactonization of 1,3-enynes.

Results and Discussion

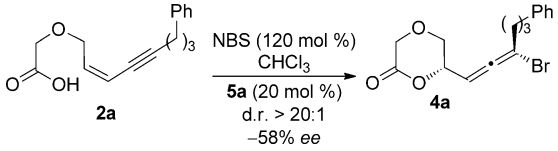
Because of the nature of *syn*-addition for the 1,4-bromolactonization of 1,3-enynes, a bifunctional chiral catalyst may easily interact with both the carboxylic acid nucleophile and the halogen electrophile in an enantioselective cyclization reaction. We first examined cinchona alkaloids as the catalyst because they are structurally similar to DABCO and might retain the high diastereoselectivity. We found that catalytic amounts of cinchonidine **5a** (Scheme 1) mediated the highly diastereoselective cyclization of both (*E*)- and (*Z*)-enynes **1a** and **2a**. Although product **3a** was isolated as a nearly racemic mixture [Eq. (2)], a moderate enantiomeric excess (58% *ee*) was obtained for lactone **4a** derived from (*Z*)-enyne **2a** [Eq. (3)].



Scheme 1. Screening of catalysts for the enantioselective bromolactonization of enyne **2a** (Bn = benzyl, Ts = tosyl).



(2)



(3)

We then prepared various derivatives of cinchona alkaloids as catalysts for the enantioselective bromolactonization of (*Z*)-enyne **2a** under the conditions shown in Equation (3). We found that the *ee* values dropped significantly with 9-alkoxy, 9-siloxy, and the 9-epimeric cinchonidines (**5b–5e** and **6**, Scheme 1). This suggests that the OH group at the 9 position in catalyst **5a** plays an important role in the induction of enantioselectivity. This 9-OH group likely served as a hydrogen-bond donor rather than an acceptor.

We then converted the 9-OH group in catalyst **5a** into different hydrogen-bond donors,[23] such as an amide group in catalyst **7** and a (thio)urea group in catalyst **8**. We observed a 30% *ee* for amide **7a**. Interestingly, the diastereomeric amide **7b** provided the racemic product, which again confirmed the importance of the stereochemistry of the C9 position. Catalysts containing a urea group (**8a**, **8b**, and **8d**) improved the enantioselectivity significantly. Notably, new urea catalysts **8b** and **8d** performed better than the known catalyst **8a**, which was first reported in 2005 by several groups.[24] Catalyst **8b** with a 9*S* configuration was much better than its 9-epimer **8c**. We were surprised that thiourea catalyst **8e**, with a 9*S* configuration, was not capable of catalyzing the reaction, whereas its 9-epimer **8f** provided a nearly racemic product. We suspected that thiourea **8e** was oxidized more readily by NBS than its epimer **8f**. However, efforts to isolate the oxidation product of these catalysts were fruitless. The tosyl group in catalysts **8b** or **8d** was proven to be critical as much lower selectivity was observed if it was replaced by other groups, as in catalysts **8g**, **8h**, **8i**, and **8j**. The corresponding pseudo-enantiomeric catalyst **8k**, derived from quinidine, yielded the other enantiomer selectively although only a 43% *ee* was obtained.

We then optimized the conditions for the enantioselective bromolactonization of (*Z*)-enyne **2a** by using urea catalyst **8d** (Table 1). The highest enantioselectivity (89% *ee*) was observed in 1,2-dichloroethane (Table 1, entry 6). The enantioselectivity dropped at lower temperatures (Table 1, entries 7 and 8). When the catalyst loading was decreased to 10 mol%, a lower *ee* was obtained (Table 1, entry 9).

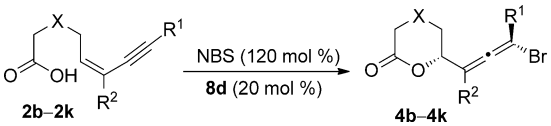
Table 1. Screening of conditions for the enantioselective bromolactonization of enyne **2a**.[a,b]

Entry	Catalyst ([mol%])	Solvent	*T* [°C]	Yield [%]	*ee* [%]
1	**8d** (20)	$CHCl_3$	RT	71	80
2	**8d** (20)	toluene	RT	55	89
3	**8d** (20)	CH_2Cl_2	RT	84	59
4	**8d** (20)	EtOAc	RT	58	87
5	**8d** (20)	CH_3CN	RT	49	85
6	**8d (20)**	**$ClCH_2CH_2Cl$**	**RT**	**72**	**89**
7	**8d** (20)	$ClCH_2CH_2Cl$	−20	60	65
8	**8d** (20)	$ClCH_2CH_2Cl$	0	67	85
9	**8d** (10)	$ClCH_2CH_2Cl$	RT	62	80

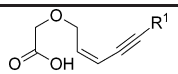
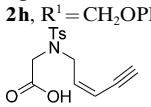
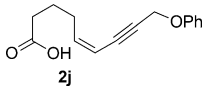
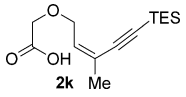
[a] Reaction conditions: NBS (120 mol%) was added to a solution of **2a** and **8d** (20 mol%) in the given solvent and the solution was stirred at the indicated temperature for 0.5 h. [b] The d.r. values of product **4a** were over 20:1.

We then prepared substrates **2b–2k** and explored the scope of this catalytic enantioselective enyne bromolactonization [Eq. (4)]. Similar results were obtained for substrates with a terminal alkyne (Table 2, entry 1). The reaction

Table 2. Scope of the enantioselective bromolactonization of (*Z*)-1,3-enynes bearing an aliphatic carboxylic acid.[a,b]



2b–2k **4b–4k** (4)

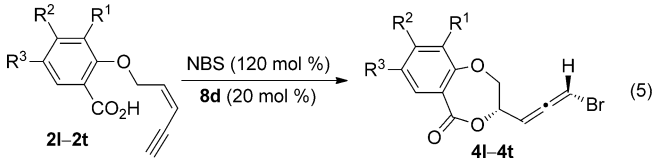
Entry	Substrate	Yield [%]	*ee* [%]
	 **2b–2h**		
1	**2b**, R^1 = H	71	90
2	**2c**, R^1 = *n*Pr	77	90
3	**2d**, R^1 = *i*Pr	72	90
4[c]	**2e**, R^1 = *t*Bu	76	90
5	**2f**, R^1 = TES	87	88
6	**2g**, R^1 = CH_2OPh	70	90
7	**2h**, R^1 = CH_2OPMB	70	92
8	 **2i**	62	93
9	 **2j**	82	80
10	 **2k** Me	86	81

[a] Reaction conditions: NBS (120 mol%) was added to a solution of **2** and **8d** (20 mol%) in $ClCH_2CH_2Cl$ and the solution was stirred at RT for 0.5–10 h. [b] The d.r. values of product **4** were over 20:1 except for compound **2e**. [c] d.r. = 10:1.

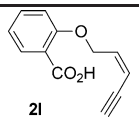
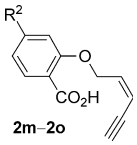
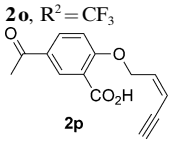
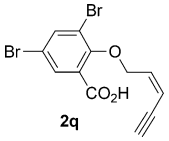
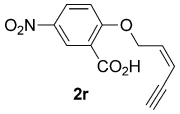
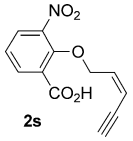
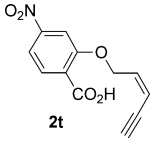
worked well for (*Z*)-enynes with various terminal substituents (Table 2, entries 2–7; PMB = *para*-methoxybenzyl), including sterically hindered *t*Bu and triethylsilyl (TES) groups (Table 2, entries 4 and 5). The observed d.r. values were >20:1 for almost all substrates except **2e** (Table 2, entry 4). A nitrogen tether could also be tolerated by the reaction (Table 2, entry 8). The *ee* dropped to 80% for a substrate with a carbon linker (Table 2, entry 9). The reaction time was longer (≈10 h) for substrates with electron-withdrawing groups on the terminal position of the enyne (Table 2, entries 6, 7, and 9). Trisubstituted olefin **2k** yielded a tetrasubstituted allene in 81% *ee* (Table 2, entry 10).

We then examined the formation of seven-membered lactones from substrates **2l–2t**, containing a benzoic acid motif [Eq. (5)]. Cyclization of enyne **2l** provided lactone **4l** in high enantioselectivity, albeit in lower conversion (Table 3, entry 1). Surprisingly, mainly 1,2-addition products were obtained for substrate **2m**, containing a methoxy-substituted benzoic acid motif (Table 3, entry 2). In contrast, electron-

Table 3. Scope of the enantioselective bromolactonization of (*Z*)-1,3-enynes, bearing a substituted benzoic acid.[a,b]



(5)

Entry	Substrate **2**	Yield [%]	*ee* [%]
1	 **2l**	44 (79)[c]	97
	 **2m–2o**		
2	**2m**, $R^2 = OMe$	0	–
3	**2n**, $R^2 = Cl$	72	98
4	**2o**, $R^2 = CF_3$	74	99
5	 **2p**	68	97
6	 **2q**	85	94
7	 **2r**	80	97
8	 **2s**	88	95
9	 **2t**	76	98

[a] Reaction conditions: NBS (120 mol %) was added to a solution of **2** and **8d** (20 mol %) in $ClCH_2CH_2Cl$ and the solution was stirred at RT for 0.5–10 h. [b] The d.r. values of product **4** were over 20:1. [c] The yield of 79% is based on recovered starting material.

withdrawing groups improved the conversion and still retained the high enantioselectivity, with *ee* values up to 99% (Table 3, entries 3–9). Ketone and nitro groups could be tolerated under the bromolactonization conditions (Table 3, entries 5 and 7–9). The *ortho*-substituent in substrates **2q** and **2s** did not interfere with the efficiency and enantioselectivity of the bromolactonization (Table 3, entries 6 and 8).

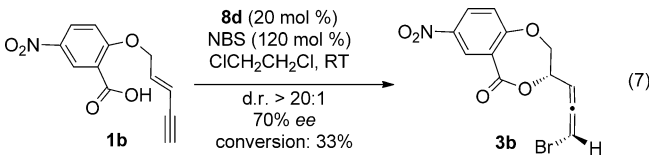
For most substrates with an aliphatic carboxylic acid, the bromolactonization was completed in about 0.5 h by using either DABCO or urea **8d** as the catalyst. In some cases (for example, **2g**, **2h**, and **2j**), however, the DABCO-mediated bromolactonization required a much longer reaction time than for the urea catalyst **8d**. Interestingly, when we tried to prepare racemic products derived from enynes bearing a benzoic acid moiety, we found no reaction occurred by using 20 mol% of either DABCO or simple urea BnNHC(O)NHTs alone. In the case of substrate **2n**, the addition of both DABCO (20 mol%) and urea BnNHC(O)NHTs (20 mol%) provided a 12% yield of racemic lactone (±)-**4n** and acid **2n** was recovered in 82% yield after 12 h. Other substrates also gave the corresponding racemic lactone products in similar yields under these conditions. For example, yields of 12% of racemic (±)-**4o**, 20% of racemic (±)-**4r**, and 9% of racemic (±)-**4t** were isolated by using the combination of DABCO and simple urea BnNHC(O)NHTs. These results suggest that cinchona alkaloid derivative **8d** might be a bifunctional catalyst, in which both the quinuclidine and urea groups are essential for the halocyclization of enynes bearing the less reactive benzoic acid nucleophile.

The relative stereochemistry of all bromoallenyl lactones was assigned based on our previous study.[20] The absolute stereochemistry of the bromoallene motif could be assigned based on Lowe's rule for allenes.[25] The X-ray structure of lactone **4n** further confirmed the assignment of both the relative and absolute stereochemistry of the bromoallenyl lactone product.[26]

In addition to six- and seven-membered lactones, we also studied the formation of five-membered lactone **4u**. Unfortunately, only 47% *ee* was observed for the bromolactonization of (*Z*)-1,3-enyne **2u** under the standard conditions [Eq. (6)].

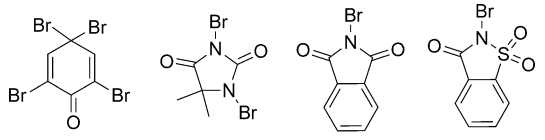
(6)

During our initial study, we obtained nearly racemic products from the cinchonidine-mediated bromolactonization of (*E*)-1,3-enyne **1a** [Eq. (2)]. With catalyst **8d** in hand, we re-examined the enantioselective bromolactonization of (*E*)-enyne **1a**. Only 37% *ee*, however, was observed for the bromoallenyl lactone product **3a** under the standard conditions. Surprisingly, 70% *ee* was obtained for (*E*)-enyne **1b** under the same conditions [Eq. (7)]. Although complete conversion was achieved for enyne **1a**, only 33% conversion could be reached after 12 h for enyne **1b**. Low or no conversion was observed for enyne **1b** when DABCO or simple urea BnNHC(O)NHTs was used alone. About 30% conversion was obtained when a mixture DABCO and urea BnNHC(O)NHTs was employed as the catalyst for substrate **1b**. We were unable to improve both the *ee* and conversion for this type of substrate under various conditions.



We also examined the effect of the halogenation reagent on the enantioselectivity. We observed significantly different *ee* values when the halogenation reagent was changed from NBS to tetrabromocyclohexadienone (TBCO), as shown in Table 4, entries 1 and 2. Slightly different enantioselectivity was obtained when NBS was replaced by unsymmetrical dibromodimethylhydantoin (DBDMH) or bulky *N*-bromophthalimide (NBP), as shown in Table 4, entries 3 and 4. NBS was chosen over NBP mainly because it was easier to remove the succinimide than the phthalimide byproduct. The nearly racemic lactone was isolated when *N*-bromosaccharin (NBSa) was employed as the brominating reagent (Table 4, entry 5).

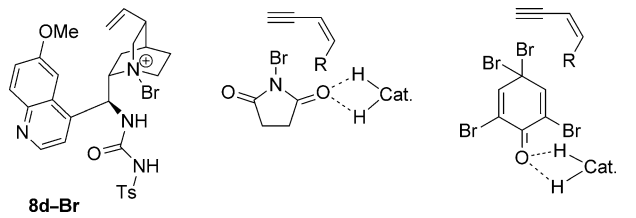
Table 4. The enantioselective bromolactonization of (*Z*)-1,3-enyne **2a** with different brominating reagents.[a]



Entry	Bromination reagent	Catalyst	Yield [%]	*ee* [%]
1	NBS	**8d**	72	89
2	TBCO	**8d**	60	35
3	DBDMH	**8d**	37	83
4	NBP	**8d**	–	91
5	NBSa	**8d**	34	4

[a] Reaction conditions: The bromination reagent (120 mol %) was added to a solution of **2a** and **8d** (20 mol %) in $ClCH_2CH_2Cl$ and the solution was stirred at RT for 0.5 h. The d.r. values of product **4a** were over 20:1.

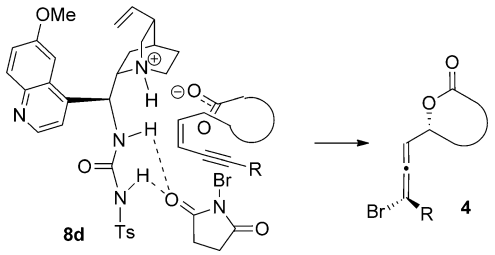
Prior to our study, it was proposed that halogenation reagents could be activated by chiral nucleophilic promoters[4] or Lewis acids.[27] For catalyst **8d**, either the quinuclidine nitrogen or urea group might activate NBS through formation of a new electrophilic brominating species **8d-Br** or through hydrogen bonding, respectively (Scheme 2). The structure of the halogenation reagent should have a minimal impact on the enantioselectivity if adduct **8d-Br** was responsible for the selectivity. Hydrogen-bond activation of NBS or TBCO by chiral catalyst **8d**, shown in Scheme 2, may explain the dramatically different enantioselectivity we observed in Table 4. In the case of NBS, the distance between the chiral catalyst and the enyne substrate was relatively small. The catalyst was placed far away from the enyne substrate when TBCO was employed as the halogenation reagent. The structures of DBDMH and NBP are similar to that of NBS and similar *ee* values were therefore observed. The sulfonamide part of NBSa clearly had a detrimental effect on the enantioselectivity.



Scheme 2. Possible activation modes for the **8d**-catalyzed enantioselective bromolactonization.

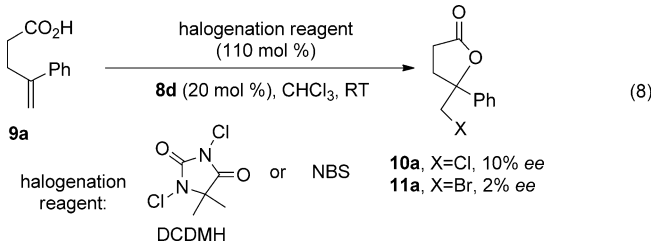
We also premixed NBS and catalyst **8d** (20 mol %) in $ClCH_2CH_2Cl$ and stirred for 20 min before the addition of enyne **2a** to encourage the formation of adduct **8d-Br**. We found that the *ee* value of product **4a** dropped to 54 % under these conditions. A longer premixing time (4 h) further reduced the selectivity to 26 % *ee*. These results indicate that the reaction between NBS and catalyst **8d** might occur in the absence of the substrate but appears to be an undesired pathway. No change in *ee* was observed when the catalyst was premixed with the substrate before the addition of NBS. Activation of NBS by catalyst **8d** through hydrogen bonding is consistent with these results. Our data in Scheme 1 also suggest that the free OH and urea groups at the C9 position in the cinchona alkaloid are likely to be a hydrogen-bond donor.

Based on previous NMR and computational investigations on cinchona alkaloid catalyzed reactions,[28] we proposed a working model for the enantioselective 1,4-*syn*-bromolactonization of (*Z*)-1,3-enynes, as shown in Scheme 3.[24] The carboxylic acid of the substrate was deprotonated by the quinuclidine nitrogen of catalyst **8d** to form an ion pair under the reaction conditions. The high *syn* diastereoselectivity could be the result of ionic interactions between the negatively charged carboxylate and the positively charged catalyst, which was associated with NBS through hydrogen bonds. Catalyst **8d** serves as a bifunctional catalyst by interacting with both the carboxylate nucleophile and the NBS electrophile. The configuration of the product derived from this model was consistent with the isolated major enantiomer.



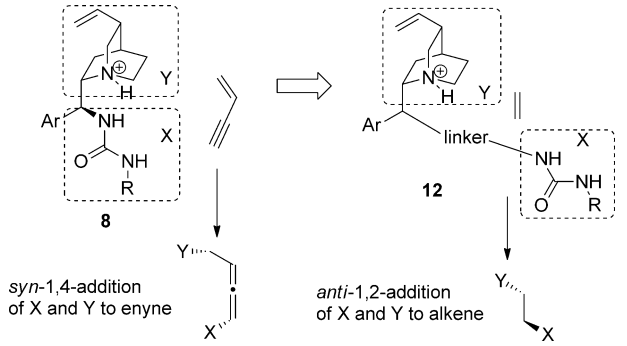
Scheme 3. A working model for bromolactonization of (*Z*)-1,3-enynes mediated by catalyst **8d**.

After the development of catalyst **8d** for the enantioselective halolactonization of 1,3-enynes, we then tried to extend the scope of the reaction with respect to the substrate from enynes to simple alkenes. Prior to our investigation, it was reported that halolactonization of 4-arylpent-4-enoic acids affords the highest enantioselectivity (83% *ee*).[11] Thus, we examined the halolactonization of alkene **9a** mediated by catalyst **8d** [Eq. (8)]. Unfortunately, nearly racemic chloro- and bromolactonization products (**10a** and **11a**) were obtained.



(8)

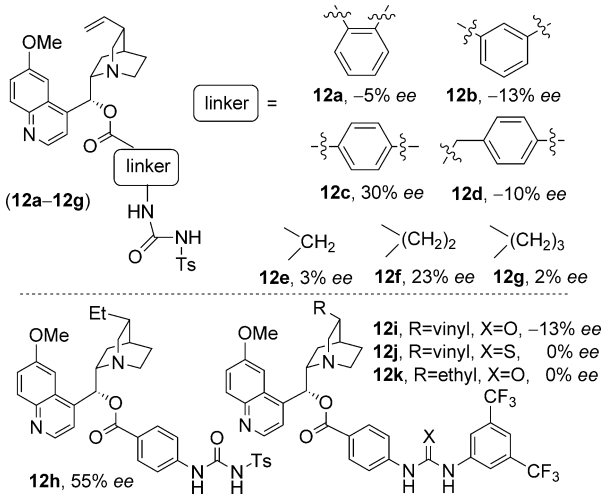
The above result was not a surprise to us considering the completely different mode of addition in the halolactonization of 1,3-enynes than in simple alkenes (Scheme 4). Based on the model that we proposed for enantioselective 1,4-*syn*-halolactonization of 1,3-enynes mediated by catalyst **8**, we



Scheme 4. Bifunctional chiral catalysts for 1,4-*syn* addition to 1,3-enynes and 1,2-*anti* addition to alkenes.

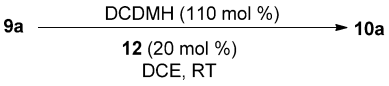
envisioned that catalyst **12**, with an appropriate linker between the quinuclidine and urea groups, might be able to accommodate the *anti*-orientation of halogenation reagent X and carboxylate nucleophile Y during their addition to simple alkenes (Scheme 4). Despite extensive investigations into (thio)urea catalysts derived from cinchona alkaloids, the (thio)urea group was, in most cases, placed either at the C9 position,[24] as shown in **8**, or at the C6′ position[29] of the aromatic quinoline ring.[30] Catalysts having a linker between the C9 position of the quinuclidine skeleton and the (thio)-urea group would represent a new class of bifunctional catalysts.[31]

To maintain the rigid scaffold of the catalyst, we decided to first examine benzoate linkers. Catalysts **12a**–**12d** (Scheme 5) were prepared in three steps—esterification of



Scheme 5. Screening of catalysts for enantioselective chlorolactonization of alkene **9a**.

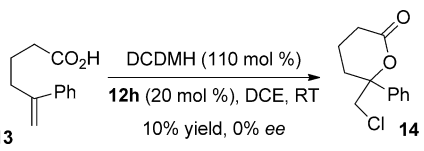
quinine with different nitrobenzoic acids, reduction of the nitro group to the amine, and formation of urea with tosylisocyanate. We then studied the above catalysts for the enantioselective chlorolactonization of 1,1-disubstituted alkene **9a** by using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as the halogen source and dichloroethane (DCE) as the solvent [Eq. (9)]. Although the enantioselectivity was low for all catalysts, it appeared that the length of the linker correlated with the *ee*. Catalyst **12c** with a *para*-substituted benzoate linker provided a higher *ee* than catalysts with shorter or longer linkers. Catalysts **12e**, **12f**, and **12g** with flexible linkers gave lower selectivity than catalyst **12c**. The *ee* of product **10a** was improved from 30 to 55% by using catalyst **12h**.



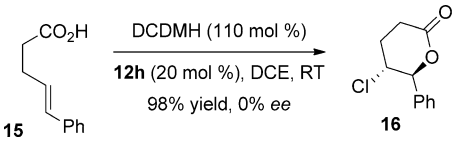
(9)

In our previous enantioselective 1,4-bromolactonization reaction, urea catalyst **8b**, containing a tosyl group, was a slightly better catalyst than **8a**, containing the more commonly used 3,5-bistrifluoromethylbenzene group (Scheme 1). We were surprised that dramatically different results were observed for the 1,2-chlorolactonization of olefin **9a** (catalysts **12c** vs. **12i** and **12h** vs. **12k**). The poor result obtained from thiourea catalyst **12j** was consistent with our previous observations (Scheme 1).

We examined the chlorolactonization of 1,1-disubstituted alkene **13** and 1,2-disubstituted alkene **15** [Eqs. (10) and (11), respectively] for the formation of six-membered lac-



(10)



(11)

tones. Completely racemic products **14** and **16**, however, were obtained.

We then focused on optimizing the enantioselective halolactonization of substrate **9a** under different conditions by varying the solvent, temperature, and catalyst loading (Table 5). The highest enantioselectivity by using a single solvent was obtained in DCE (Table 5, entries 1–8). During our investigations, several enantioselective halolactonizations of 1,1-disubstituted alkenes were reported by other groups.[13,15–17] Binary solvents were found to be beneficial or even critical in several systems.[13,16] The *ee* values were indeed improved dramatically when we used a mixture of two solvents (Table 5, entries 9–15). The highest selectivity was obtained by using a mixture of chloroform and toluene in a volume ratio of 1:1 (Table 5, entry 11) at room temperature. Lowering the temperature did not improve the enantioselectivity (Table 5, entries 16 and 17). However, lowering the catalyst loading slightly improved the selectivity (Table 5, entries 18 and 19). Even at 0.1 mol% catalyst loading, we still observed 80% *ee* for product **10a** (Table 5, entry 20).

Table 5. Screening of reaction conditions for the enantioselective chlorolactonization of substrate **9a**.[a]

Entry	Solvents	*T* [°C]	Catalyst ([mol%])	*ee* [%]
1	DCE	RT	**12h** (20)	55
2	$CHCl_3$	RT	**12h** (20)	47
3	$CHCl_3$	0	**12h** (20)	47
4	toluene	RT	**12h** (20)	47
5	THF	RT	**12h** (20)	29
6	CF_3CH_2OH	RT	**12h** (20)	−8
7	CH_3CN	RT	**12h** (20)	27
8	CH_2Cl_2	RT	**12h** (20)	51
9	CH_2Cl_2/PhMe (1:1)	RT	**12h** (20)	85
10	DCE/PhMe (1:1)	RT	**12h** (20)	80
11	$CHCl_3$/PhMe (1:1)	RT	**12h** (20)	86
12	$CHCl_3$/PhMe (2:1)	RT	**12h** (20)	83
13	$CHCl_3$/PhMe (1:2)	RT	**12h** (20)	85
14	$CHCl_3$/PhMe (1:3)	RT	**12h** (20)	82
15	$CHCl_3$/hexane (1:2)	RT	**12h** (20)	70
16	$CHCl_3$/PhMe (1:1)	−20	**12h** (20)	86
17	$CHCl_3$/PhMe (1:1)	−40	**12h** (20)	80
18	**$CHCl_3$/PhMe (1:1)**	**RT**	**12h (5)**	**91**
19	$CHCl_3$/PhMe (1:1)	RT	**12h** (1)	89
20	$CHCl_3$/PhMe (1:1)	RT	**12h** (0.1)	80
21	$CHCl_3$/PhMe (1:1)	RT	**12k** (5)	0

[a] Reaction conditions: DCDMH (110 mol%) was added to a solution of **9a** and **12h** or **12k** (20 mol%) in a given solvent and the solution was stirred at the indicated temperature until completion.

We also compared catalysts **12h** and **12k** under the optimized conditions and again observed dramatically different results (Table 5, entries 18 vs. 21). Although the exact reason for this observation is not clear, all of our data suggest that tosyl ureas should be examined in addition to the commonly used aryl ureas for asymmetric catalysis involving hydrogen-bond activation.[23] It is also worth mentioning that catalyst **12h** worked well at room temperature whereas previous enantioselective halolactonizations were generally performed at −40 to −80 °C.[13,15–17]

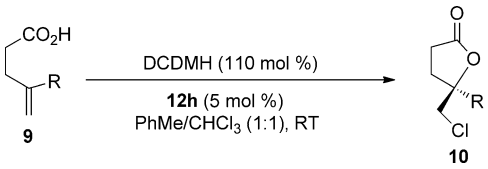
We examined the effect of halogenation reagents on the halolactonization of **9a** in the presence of catalyst **12h** (20 mol%) in $CHCl_3$/PhMe (1:1) at room temperature.[32] The *ee* dropped from 89 to 83% when DCDMH was replaced with NCS. Less than 15% *ee* values were observed for both the bromolactonization and iodolactonization of substrate **9a** by using NBS and NIS as the halogenation reagent, respectively.

With the optimized conditions in hand, we studied the scope of the enantioselective chlorolactonization of alkene **9** [Eq. (12)]. Good yields and *ee* values were obtained for a number of aryl substituted olefins (Table 6). Among the *para*-halogen-substituted styrenes, higher enantioselectivity was observed for the substrates containing the more electron-withdrawing group (Table 6, entries 2–4). This was a general trend for several other substrates with *para*- or *meta*-substituents (Table 6, entries 5–8). Substrate **9i** with an *ortho*-fluoro substituent was less successful than its *para* counterpart **9b** (Table 6, entries 9 vs. 2). When the R group was a simple alkyl group or an electron-rich aromatic group, the enantioselectivity dropped significantly (Table 6, entries 10 and 11). Similar limitations were also observed in previous enantioselective chlorolactonization reactions.[13] The absolute stereochemistry of product **10** was determined by comparing the optical rotations of known compounds.[13]

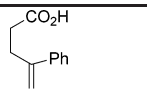
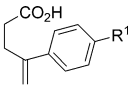
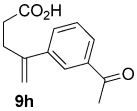
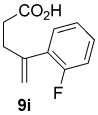
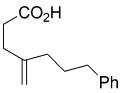
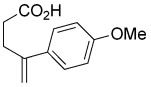
The enantioselective chlorolactonization of substrates **9a**, **9b**, **9c**, and **9g** was also studied by Borhan's group by using $(DHQD)_2PHAL$ as the catalyst. The *ee* for these substrates ranged from 80–89%.[13] For catalyst $(DHQD)_2PHAL$, the two cinchona alkaloids are linked by a phthalazine ring at the 1,4-position. The distance between the two cinchona alkaloid units in catalyst $(DHQD)_2PHAL$ is similar to that in catalyst **12h**. Borhan's group proposed that protonated $(DHQD)_2PHAL$ served as a hydrogen-bond donor to activate the halogenation reagent. It is possible that the urea moiety in catalyst **12h** has the same function as one protonated cinchona alkaloid unit in $(DHQD)_2PHAL$.

The enantioselectivity of the 1,4-bromolactonization of 1,3-enynes dropped significantly when the halogenation reagent and catalyst were premixed before the addition of enyne substrate. Similar results were observed for the catalyst-**12h**-mediated chlorolactonization of alkenes, suggesting that the reaction between catalyst **12h** and halogenation reagent DCDMH was not desired. The halogenation reagent was likely activated by urea through hydrogen bonds for enantioselective 1,2-chlorolactonization as well.

Table 6. Scope of the enantioselective chlorolactonization of 1,1-disubstituted alkenes.[a,b]



9 10 (12)

Entry	Substrate	Yield [%][b]	*ee* [%]
1	 **9a**	92	91
	 **9b–9g**		
2	**9b**, $R^1=F$	99	87
3	**9c**, $R^1=Cl$	92	84
4	**9d**, $R^1=Br$	95	80
5	**9e**, $R^1=CH_3C(O)$	87	85
6	**9f**, $R^1=BnOCH_2$	76	82
7	**9g**, $R^1=CH_3$	92	75
8	 **9h**	83	83
9	 **9i**	80	73
10	 **9j**	85	39
11	 **9k**	90	16

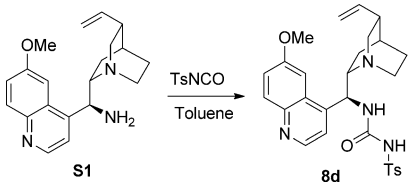
[a] Reaction conditions: DCDMH (110 mol%) was added to a solution of **9** and **12h** (5 mol%) in $CHCl_3$/PhMe (1:1) and the solution was stirred at RT until completion. [b] All yields are isolated yields.

Conclusion

We have developed two novel cinchona urea catalysts, **8d** and **12h**, and demonstrated their utility in the enantioselective halolactonization of (*Z*)-1,3-enynes and 1,1-disubstituted olefins, respectively. The modular scaffold of these catalysts should provide easy access to many new bifunctional catalysts for enantioselective halocyclizations and other (thio)urea-promoted reactions. We also found for the first time that tosyl urea **12h** worked significantly better than conventional aryl urea **12k**. This observation may have broad implications in chiral urea-mediated reactions. Despite the progress made by us and others in the area of enantioselective halolactonization, the scope of this reaction is still very limited for each catalyst. The studies that we have presented here may provide insights for further advancing this important class of reactions. The halocyclization methods that we have developed may be applied to the synthesis of halogen-containing synthetic intermediates or halogen-containing natural products directly.[1,21]

Experimental Section

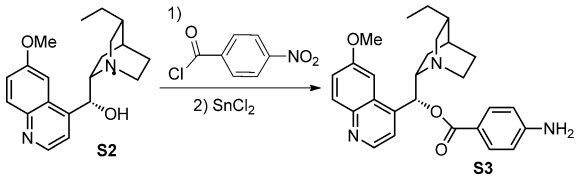
Procedure for the preparation of catalyst 8d [Eq. (13)]: A solution of 4-methylbenzenesulfonyl isocyanate (1.84 g, 6.8 mmol) in dry toluene (10 mL) was slowly added to a solution of known amine **S1**[24] (2.20 g,



S1 8d (13)

6.8 mmol) in dry toluene (20 mL) at room temperature. The mixture was stirred overnight, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (hexane/acetone/triethylamine = 40:20:1 as eluent) to afford urea **8d** (3.30 g, 81%) as an off-white amorphous solid. $[\alpha]_D^{25}=-15.8$ ($c=1.0$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta=0.95$–0.99 (m, 1H), 1.72–1.89 (m, 4H), 2.19–2.33 (m, 3H), 2.48–2.58 (m, 1H), 2.98–3.04 (m, 2H), 3.56–3.68 (m, 2H), 3.96–4.04 (m, 1H), 4.37–4.41 (m, 1H), 5.00–5.12 (m, 2H), 5.45–5.72 (m, 4H), 6.96–7.04 (m, 2H), 7.22–7.40 (m, 2H), 7.48–7.62 (m, 3H), 7.94–8.00 (m, 1H), 8.53–8.64 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.5$, 24.8, 25.5, 27.0, 37.1, 41.8, 53.3, 53.7, 55.9, 56.3, 59.1, 102.2, 117.0, 122.4, 126.4, 128.5, 129.0, 131.5, 137.8, 141.2, 141.8, 142.8, 144.7, 147.6, 158.9, 160.2 ppm; IR: $\tilde{\nu}=3300$, 2945, 1621, 1594, 1509, 1243, 1128 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{32}N_4O_4SNa$: 521.2218 [*M*+23]; found: 521.2215.

Procedure for the preparation of catalyst 12h [Eqs. (14) and (15)]: Et_3N (1.2 mL) and *para*-nitrobenzoyl chloride (0.92 g, 5.8 mmol) was added to a solution of commercially available dihydroquinine hydrochloride **S2**



S2 S3 (14)

S3 —Ts-NCO→ 12h (15)

(1.79 g, 4.9 mmol) in CH_2Cl_2 (50 mL) at 0°C. The mixture was stirred at room temperature overnight. Solvent was removed under vacuum. A solution of 1 M aqueous NaOH (50 mL) was added and the mixture was extracted with EtOAc three times and dried over $MgSO_4$. The crude product was used directly in the next step without further purification. A solution of the crude product in EtOH (30 mL) was heated to 70°C. $SnCl_2$ (1.12 g) was added to the above solution and it was stirred for 1 h. The mixture was poured onto ice and quenched with saturated aqueous $NaHCO_3$ to adjust the pH to 7.0. The mixture was extracted with EtOAc and dried over $MgSO_4$. The product was purified by flash column chromatography by using EtOAc as the eluent to yield intermediate **S3** (1.68 g, 72%). A solution of TsNCO (0.663 g, 3.5 mmol) in THF (10 mL)

was added dropwise to a solution of **S3** (1.68 g, 3.5 mmol) in THF (20 mL) and the mixture was stirred at room temperature overnight. After removing the solvent under vacuum, the product was purified by flash column chromatography with 20% methanol in EtOAc to afford catalyst **12h** (1.72 g, 76%).

Compound ***S3***: $[\alpha]_D^{25} = -127$ ($c = 1.0$ in MeOH); ^{1}HNMR (400 MHz, $CDCl_3$, TMS): $\delta = 0.88$ (t, $J = 8$ Hz, 3H), 1.24 (t, $J = 8$ Hz, 1H), 1.41–1.57 (m. 2H), 1.72 (s, 1H), 1.88–1.93 (m. 1H), 2.03 (s, 1H), 2.69–2.93 (m, 4H), 3.38 (q, $J = 8$ Hz, 1H), 3.94 (s, 3H), 4.08–4.14 (q, $J = 8$ Hz, 1H), 4.35 (s, 2H), 6.58 (d, $J = 8$ Hz, 2H), 6.70 (d, $J = 8$ Hz, 1H), 7.34 (d, $J = 8$ Hz, 1H), 7.52 (s, 1H), 7.88 (d, $J = 8$ Hz, 2H), 8.00 (d, $J = 12$ Hz,1H), 8.70 ppm (d, $J = 4$ Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): $\delta = 166.0$, 158.0, 151.9, 147.7, 144.9, 144.8, 132.0, 127.4, 122.1, 119.0, 118.8, 113.9, 101.8, 73.7, 60.6, 59.8, 55.8, 51.0, 50.2, 37.6, 27.5, 26.4, 25.6, 23.8, 14.4, 12.2 ppm; IR : $\tilde{\nu} = 2360$, 1705, 1603, 1025 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{31}N_3O_3+H$: 446.2438 [M+H]; found: 446.2460.

Compound ***12h***: $[\alpha]_D^{25} = -95$ ($c = 0.25$ in $CHCl_3$); ^{1}HNMR (500 MHz, DMSO): $\delta = 0.95$ (q, $J = 4$ Hz, 3H), 1.26 (s, 1H), 1.60–1.74 (m, 2H), 1.91–1.96 (m, 3H), 2.27 (s, 1H), 2.35 (s, 3H), 2.52 (s, 1H), 3.34–3.65 (m, 6H), 3.93 (m, 1H), 4.04 (s, 3H), 7.16 (s, 1H), 7.44 (s, 2H), 7.49 (d, $J = 8$ Hz, 1H), 7.64 (d, $J = 8$ Hz, 2H), 7.72–7.77 (m, 3H), 8.01 (d, $J = 8$ Hz, 1H), 8.68 (d, $J = 4$ Hz, 1H), 9.11 ppm (s, 1H); ^{13}CNMR (125 MHz, DMSO): $\delta = 164.4$, 159.5, 158.8, 148.0, 147.8, 144.7, 144.0, 141.5, 140.6, 132.1, 130.8, 129.2, 127.0, 126.3, 123.0, 119.8, 118.8, 117.1, 102.5, 71.4, 58.2, 57.2, 51.5, 50.2, 35.1, 25.1, 24.5, 23.6, 21.6, 20.4, 12.2 ppm; IR: $\tilde{\nu} = 1726$, 1621, 1232, 1170, 769 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{38}N_4O_6S+H$: 643.2585 [M+Na]; found: 643.2594.

General procedure for bromolactionization of conjugated enynes: Catalyst **8d** (10.2 mg, 0.02 mmol) and NBS (21.4 mg, 0.12 mmol) were sequentially added to a solution of acid **2** (0.1 mmol) in 1,2-dichloroethane, directly purchased from Fisher. The reaction mixture was stirred at RT until the starting material had disappeared, as indicated by TLC. The reaction mixture was concentrated under vacuum and purified directly by flash column chromatography, eluting with ethyl acetate and hexanes.

General procedure for chlorolactonization of alkenes: Catalyst **12h** (3.3 mg, 0.005 mmol) and DCDMH (21.7 mg, 0.11 mmol) were sequentially added to a solution of acid **9** (0.10 mmol) in $CHCl_3$ and PhMe (1:1, 5 mL). The reaction mixture was stirred at RT until the starting material had disappeared, as indicated by TLC. The reaction mixture was concentrated under vacuum and purified directly by flash column chromatography, eluting with ethyl acetate and hexanes.

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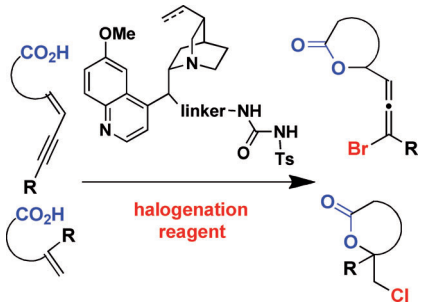
Wearing a halo: New organocatalysts have been developed for the enantioselective 1,4-*syn*-bromolactonization of conjugated (*Z*)-1,3-enynes and the 1,2-chlorolactonization of 1,1-disubstituted alkenes (see scheme). Up to 99 and 91 % *ee* values, respectively, were achieved for these two halolactonizations.



Organocatalysis

*W. Zhang, N. Liu, C. M. Schienebeck, K. Decloux, S. Zheng, J. B. Werness, W. Tang** ..... ▮▮▮▮–▮▮▮▮

Catalytic Enantioselective Halolactonization of Enynes and Alkenes