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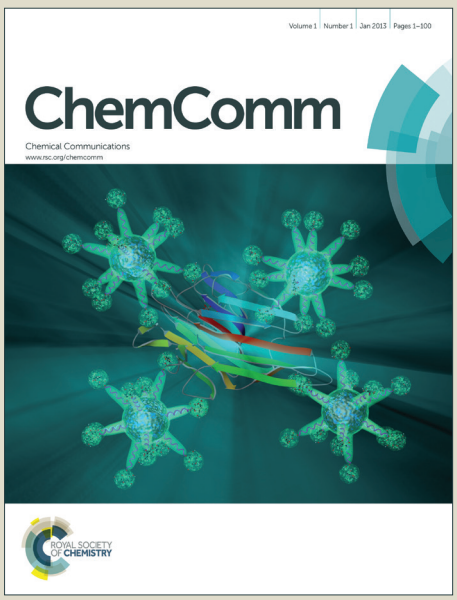

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Catalytic Enantioselective Bromoamination of Allylic Alcohols

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An enantioselective bromoamination of allylic alcohols has been developed for the first time using a newly designed cinchona-derived thiourea as the catalyst, *N,N*-dibromo-4-nitrobenzenesulfonamide as bromine and amine sources.

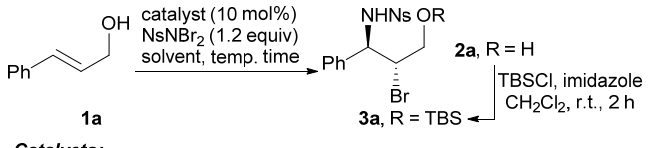
Electrophilic halogenation of alkenes is a fundamental reaction in organic chemistry, and is of great importance for the preparation of halogenated compounds.[1] Many remarkable endeavours have been made to develop the asymmetric halofunctionalization of alkenes.[2] To date, the enantioselective halocyclization reactions[3] such as halolactonization,[4] haloetherification,[5] haloaminocyclization,[6,7] and halonium ion induced reactions[8] have been developed successfully by using organocatalytic strategies. However, the intermolecular asymmetric halogenation of alkenes remains a challenging problem. Generally intermolecular reactions are entropically unfavoured compared with intramolecular reactions. Mechanistic studies demonstrate that an olefin-to-olefin transfer process occurs between a halonium ion intermediate and an olefin in an intermolecular halogenation reaction.[9] Thus, the halonium ion must be directly captured by an external nucleophile in a successful asymmetric intermolecular halogenation reaction.

Recently, important breakthroughs on the intermolecular dihalogenation of allylic alcohols have been achieved by Nicolaou and Burns groups.[10a,b] A bromoesterification of *trans*-cinnamyl alcohol with 40% ee has been observed by Tang group.[10c] Despite these advances, there is no other protocols for the asymmetric halogenation of allylic alocohols.[11] Herein we describe a catalytic enantioselective bromoamination of allylic alcohols using an aminothiourea as the catalyst, leading to the formation of enantioenriched vicinal bromoamines. Vicinal haloamines have been found widespread in natural and non-natural products, many of the vicinal haloamine derivatives displayed significant bioactivity.[12] The haloamines can serve as versatile building blocks for the synthesis of biologically active compounds.[12] Many synthetic methodologies have been developed for the production of these compounds, among them, the intermolecular haloamination (or aminohalogenation) of alkenes is the most efficient one.[13] However, the enantioselective version is still lacking,[14] aminohalogenation of α,β-unsaturated carbonyl compounds have been developed by Feng group.[15] To the best of our knowledge, this is the first report on the catalytic enantioselective bromoamination of allylic alcohols.

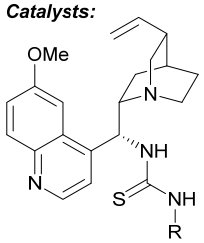
Initially, a series of cinchona alkaloids such as $(DHQD)_2PHAL$, $(DHQD)_2PYR$ as catalysts, bromine sources such as NBS, NBP, $TsNBr_2$, and amine sources such as $TsNH_2$, $NsNH_2$, $TsNBr_2$ were examined in the bromoamination of *trans*-cinnamyl alcohol (**1a**).[16] However, no positive results were obtained. Further investigation of other organocatalysts, bromine and amine sources indicated that the desired product **2a** could be obtained with moderate enantioselectivity by using quinine-derived thiourea **4a** as the catalyst and *N,N*-dibromo-4-nitrobenzenesulfonamide ($NsNBr_2$) as bromine and amine sources. Notably, 4-nitrobenzenesulfonamide ($NsNH_2$) was always observed as a side product in these reactions, which was very difficult to separate from the desired proudct **2a**.[17] Thus **2a** was transformed smoothly to **3a** using TBSCl in the presence of imidazole(Table 1, entry 1).

After the identification of an appropriate catalyst, bromine and amine sources, the reaction was further optimized by varying the thiourea moiety of catalyst **4a**. A catalyst analogue of **4a** with a naphthyl group (**4b**) afforded a comparable ee (Table 1, entry 2). The *ortho* substituents in this catalyst also returned comparable ees (**4c-g**, Table 1, entries 3-7). While catalyst **4h** containing two bulkier 2-*i*Pr groups resulted in a measurable decrease in ee (Table 1, entry 8). For the catalyst with a 2,4-dimethyl group (**4i**), no significant ee change was observed (Table 1, entry 9). However, when the 2,4-dimethoxy-substituted catalyst **4j** and 2,4-dichloro-substituted catalyst **4k** were used, significant difference in ee were observed (ee: 10% vs 53%; Table 1, entry 10 vs entry 11), indicating that the electronic character of the aromatic substituent in the thiourea moiety plays an important role in the enantioselectivity. A strong increase in the electron density of the phenyl group has a decreasing effect on the enantioselectivity. Meanwhile, a decrease in the electron density of the phenyl group has a little effect on the enantioselectivity (Table 1, entries 6, 11 vs entry 1). Catalysts **4l** and **4m** containing 3,5-disubstituted groups both returned measurable decrease in ees (Table 1, entries 13, 14). Following the same trend as above observed, catalyst containing *para* electron rich substituent returned clear decrease in ee (Table 1, entry 15 vs entries 16, 17), further illustrating that the electron rich substituents in catalyst proved to be detrimental to the enantioselectivity. Interestingly, a clear increase in enantioselectivity was detected when 4-phenyl-

Table 1 Catalyst optimization of enantioselective bromoamination of **1a**[a]



Catalysts:



4a, R = Ph
4b, R = 1-Naphthyl
4c, R = 2-MeC_6H_4
4d, R = 2-EtC_6H_4
4e, R = 2-*i*-PrC_6H_4
4f, R = 2-ClC_6H_4
4g, R = 2,6-$Me_2C_6H_3$
4h, R = 2,6-*i*-$Pr_2C_6H_3$
4i, R = 2,4-$Me_2C_6H_3$
4j, R = 2,4-$(MeO)_2C_6H_3$
4k, R = 2,4-$Cl_2C_6H_3$
4l, R = 3,5-$(CF_3)_2C_6H_3$
4m, R = 3,5-$Ph_2C_6H_3$
4n, R = 4-MeC_6H_4
4o, R = 4-$MeOC_6H_4$
4p, R = 4-ClC_6H_4
4q, R = 4-$CF_3C_6H_4$
4r, R = 4-PhC_6H_4
4s, R = 4-Trityl-C_6H_4
5, Quinidine-**4s**

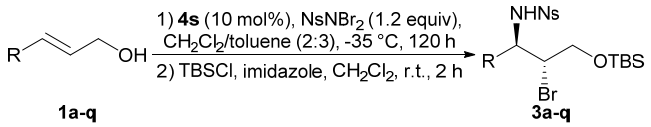
Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)
1	**4a**	72	54	51
2	**4b**	98	63	53
3	**4c**	98	63	53
4	**4d**	138	64	54
5	**4e**	96	53	54
6	**4f**	138	54	55
7	**4g**	96	61	54
8	**4h**	98	75	43
9	**4i**	96	55	51
10	**4j**	60	38	10
11	**4k**	96	44	53
12	**4l**	98	72	37
13	**4m**	98	48	42
14	**4n**	98	75	49
15	**4o**	98	72	24
16	**4p**	98	79	50
17	**4q**	138	51	58
18	**4r**	138	56	62
19	**4s**	75	54	71
20	**4s**	120	72	91[c]
21	**5**	120	67	–90[c]

[a] Reactions were carried out with **1a** (0.20 mmol), catalyst (0.02 mmol) and $NsNBr_2$ (0.24 mmol) in CH_2Cl_2 (5.0 mL) at –50 °C in the absence of light. [b] Isolated yield for **3a** by two steps, the other rgioisomer was not observed. [c] The solvent is CH_2Cl_2/toluene (2:3, 5.0 mL) and temperature is –35 °C.

substituted catalyst **4r** was used (Table 1, entry 18). It seemed that the steric bulk at the *para* position is playing an important role in the enantioinduction. With the aim of increasing the steric bulk of the aromatic substituent, we designed and synthesized a triphenylmethyl (trityl) variant (**4s**). To our surprise, a dramatic increase in enantioselectivity was observed (Table 1, entry 19). Further optimization of this reaction by varying different parameters systematically[16] allowed us to discover the optimal conditions: a 72% yield and 91% ee of **3a** was obtained when the reaction was conducted in CH_2Cl_2/toluene (2:3, 0.04 M) at –35 °C (Table 1, entry 20). Satisfactorily, enantioenriched *ent*-3a was also obtained in 67% yield and 90% ee under the same conditions using pseudoenantiomeric quinidine-derived thiourea catalyst 5 (Table 1, entry 21).

With the optimized reaction conditions in hand, the substrate scope of this intermolecular bromoamination reaction was explored. As shown in Table 2, a broad range of aryl allylic alcohols could be converted to the corresponding vicinal bromoamines with good yields and high to excellent ees, and the reaction was readily scalable without losing any efficiency and enantioselectivity (Table 2, entry 1). Substrates with electron-deficient substituents at the *para* or *meta* positions of the aromatic ring offered excellent ees (Table 2, entries 2-5, 7, 8). Similar to previous observation on the asymmetric halocyclization reactions,[3-8] electron-donating substituents at the *para* or *meta* positions resulted in decrease in ees (Table 2 entries 6, 9, 11), while the electron-donating methoxy group at the *meta* position was well tolerated (Table 2, entry 10). The electron-deficient 3,5- and 3,4-disubstituted substrates also returned excellent ees (Table 2, entries 12-14). However, the existence of a substituent on the *ortho* position dramatically hampered the reaction (Table 2, entries 15-17), presumably because of steric hindrance. *cis*-Cinnamyl alcohol gave a moderate enantioselectivity (59% ee) and diasteroselectivity (*syn*:*anti* = 6:1),[16] as did allyl alcohol (44% ee, major isomer) and homoallylic alcohol (52% ee, major isomer).[16] The absolute configuration of **3** was assigned on the basis of X-ray crystallographic structure of **3a**.[16]

Table 2 Substrate scope of enantioselective bromoamination[a]



1a-q **3a-q**

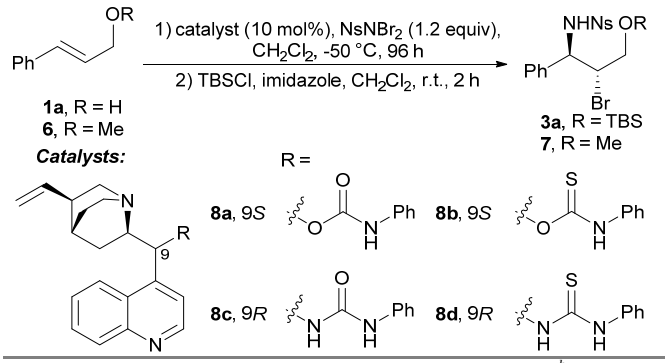
Entry	Substrate	R	Yield (%)[b]	ee (%)
1	**1a**	Ph	71	90[c] (99)[d]
2	**1b**	4-F-C_6H_4	63	88
3	**1c**	4-Cl-C_6H_4	66	93
4	**1d**	4-Br-C_6H_4	65	90
5	**1e**	4-CF_3-C_6H_4	62	92
6	**1f**	4-Me-C_6H_4	66	72
7	**1g**	3-Cl- C_6H_4	70	95
8	**1h**	3-Br-C_6H_4	64	91
9	**1i**	3-Me-C_6H_4	57	82
10	**1j**	3-MeO-C_6H_4	66	90
11	**1k**	3,5-Me_2-C_6H_3	54	72
12	**1l**	3,5-Cl_2-C_6H_3	68	95
13	**1m**	3,5-F_2-C_6H_3	62	88
14	**1n**	3,4-Cl_2-C_6H_3	64	92
15	**1o**	2-Cl-C_6H_4	19	83
16	**1p**	2-Me-C_6H_4	16	46
17	**1q**	2-naphthyl	35	79

[a] Reactions were carried out with **1** (0.20 mmol), **4s** (0.02 mmol) and $NsNBr_2$ (0.24 mmol) in CH_2Cl_2/toluene (2:3, 5.0 mL) at –35 °C for 120 h in the absence of light. [b] Isolated yield by two steps. [c] 2.00 mmol scale. [d] One crystallization.

In order to shed light on the origin of the catalytic activity on the enantioselective bromoamination of allylic alcohols, control experiments were performed. Bromoamination of **1a** by using catalyst **4a** in the presence of an acid additive or an alcohol additive returned dramatic decrease in ees (Table 3, entries 1-4 vs Table 1, entry 1). Additionally, bromoamination of **6** by using **4a** as the catalyst resulted in product **7** in 70% yield with no enantioselectivity (Table 3, entry 5). These results suggest that the hydroxyl group play an important role in the enantioinduction. We propose the allylic alcohol OH group may form a hydrogen bond with the quinuclidine nitrogen in this enantioselective bromoamination reaction, in a manner analogous to that proposed by Deng for the enantioselective alcoholysis of *meso* cyclic anhydrides.[18]

Halogen reagents such as NBS, NBP can be activated by either Lewis bases [19] or hydrogen bonds.[3-11] We envisioned that $NsNBr_2$ can also be activated by Lewis bases directly or hydrogen bonds with sulfonyl moiety.[20] Then several catalysts were prepared, and experiments on the bromoamination of 1a were carried out. Both catalyst **8a** with phenylcarbamate moiety and 8b with phenylthiocarbamate moiety as Lewis bases were found to be ineffective in offering appreciable ee in the bromoamination of **1a** (Table 3, entries 6, 7). Urea catalyst **8c** returned almost no

Table 3 Enantioselective bromoamination of **1a** and **6**[a]



Entry	Substrate	Catalyst	Additive (equiv)	Yield (%)[b]	ee (%)
1	**1a**	**4a**	$PhCO_2H$ (0.1)	44	36
2	**1a**	**4a**	(+)-CSA (0.1)	48	11
3	**1a**	**4a**	*p*-TSA (0.1)	15	3
4	**1a**	**4a**	*n*-Butanol (0.1)	39	11
5	**6**	**4a**		70[c]	0
6	**1a**	**8a**		42	0
7	**1a**	**8b**		58	0
8	**1a**	**8c**		67	–3
9	**1a**	**8d**		69	–47

[a] Reactions were carried out with **1a** or **6** (0.20 mmol), catalyst (0.02 mmol), $NsNBr_2$ (0.24 mmol) and additive (0.02 mmol) in CH_2Cl_2 (5.0 mL) in the absence of light at –50 °C for 96 h. [b] Isolated yields. [c] Step 2 was not conducted.

enantioselectivity (Table 3, entry 8). Different with urea **8c**, thiourea **8d** resulted in 47% ee (Table 3, entry 9), this may be ascribed to thiourea leading to more stable hydrogen-bonded catalyst-$NsNBr_2$ complexes than urea.[21] We cannot rule out the possibility of sulfur center in thiourea activation of $NsNBr_2$ as a Lewis base at this stage. Taking into account the observations, an intermediate with a dual hydrogen bonding activation of $NsNBr_2$ and an interaction between the hydroxyl group and the quinuclidine nitrogen is proposed (Fig. 1).

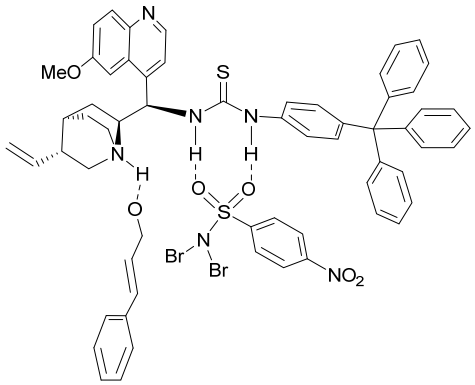
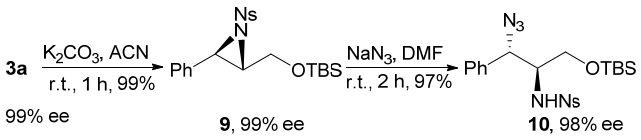


Fig. 1 Proposed working model.



Scheme 1 Synthesis of **9** and **10**.

The vicinal bromoamines are versatile chiral building blocks for further transformations. For example, treatment of **3a** with K_2CO_3 led to aziridine **9** in quantitative yield (Scheme 1), which is also a useful building block in organic and medicinal chemistry.[22] Ring opening of **9** with NaN_3 resulted in vicinal diamine[23] precursor 10 in 97% yield. All these transformations were achieved efficiently without loss of enantiopurity.

In summary, we have developed an efficient catalytic enantioselective bromoamination of allylic alcohols using a newly designed cinchona-derived thiourea catalyst for the first time. A series of enantioenriched vicinal bromoamines were prepared with good yields and high to excellent enantioselectivities. Mechanistic studies indicate that strongly electron-rich substituents in catalyst proved to be detrimental to the enantioselectivity, the steric bulk at the *para* position of the phenyl thiourea and the interaction between substrate OH group and the catalyst play important roles in the enantioinduction. A dual hydrogen-bonding activation model for this reaction has been proposed. Further investigations to better understanding the mechanism, and to extend the scope of this intermolecular bromoamination reaction are underway.

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Electronic Supplementary Information (ESI) available. CCDC 1007941. Experimental detail, CIF file of the X-ray structure, HPLC analysis, spectroscopic and analytical data for new compounds. See DOI: 10.1039/b000000x/

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Table of contents:

The first enantioselective bromoamination of allylic alcohols has been developed using a new designed quinine-thiourea catalyst.