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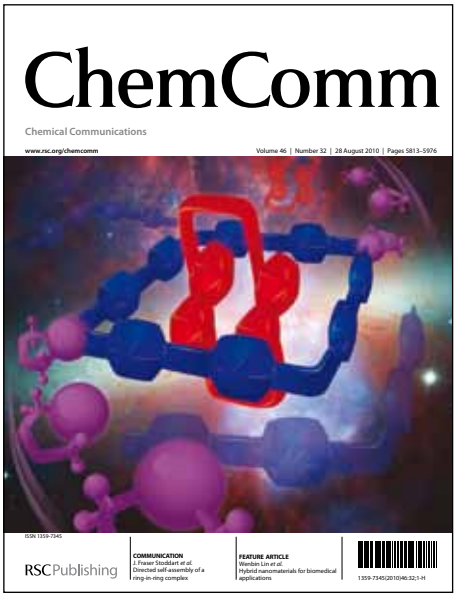

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Asymmetric 5-*endo* chloroetherification of homoallylic alcohols toward the synthesis of chiral β-chlorotetrahydrofurans

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An asymmetric 5-*endo* chloroetherification of homoallylic alcohols is successfully developed that employs an easily available quaternary ammonium salt derived from cinchonine as a conventional organocatalyst. This approach provides a ready access to β-chlorotetrahydrofurans in high enantioselectivities.

Electrophilic halocyclizations of olefins, in which electrophilichalonium ions are generated from olefins and open intramolecularly by nucleophilic functional groups, are versatile synthetic transformations with proven applications to the synthesis of halogenated heterocycles.[1,2] In this field, the use of organocatalysts including chiral ureas, amino-thiocarbamate, trisimidazolines and cinchona alkaloid derivative etc. had made significant contributions towards the halolactonization and haloaminocyclization.[2-4] Compared to the rapid development in the field of halolactonization and haloaminocyclization, the progress in asymmetric haloetherifications is limited,[2d,2e] although haloetherification is a highly valuable synthetic method that can produce tetrahydrofuran, tetrahydropyran, and even larger oxacyclic frameworks.[1e]

In 2003, pioneering work in the iodocyclization of γ-hydroxy-*cis*-alkenes catalyzed by chiral salen-Co complex has been reported by Kang et al.[5] Recently, Shi and Denmark independently reported the use of chiral phosphoric acid as catalyst for the highly enantioselective bromoetherifications of 4-alkene-1-ol substrates.[6] In addition, Hennecke et al. demonstrated chiral BINOL-derived compounds could serve as catalysts for the asymmetric haloetherification reactions on various alkenediol starting materials.[7] However, these catalyst systems generally resulted in 5-*exo* cyclization with high enantioselectivities under the optimized conditions. Through the 5-*endo* chloroetherification can directly synthetic access to β-chlorotetrahydrofurans, which are useful intermediates or important structural motifs in biologically active compounds.[8,9] As part of our ongoing interest in functionalization of olefins,[10] we herein report the discovery of highly enantioselective 5-*endo* chloroetherifications toward the synthesis of β-chlorotetrahydrofurans catalyzed by the cinchonine-derived quaternary ammonium salts.

Initially, the chloroetherification of homoallylic alcohol derivative **1a** was selected as a model reaction for screening the catalysts and reaction conditions. We were encouraged by the discovery that cinchona alkaloid *O*-ester **3a** provided good conversion and modest enantioselectivity in the chloroetherification of homoallylic alcohol **1a** in the presence of *N*-chlorosuccinimide (NCS) (Table 1, entry 1). The use of

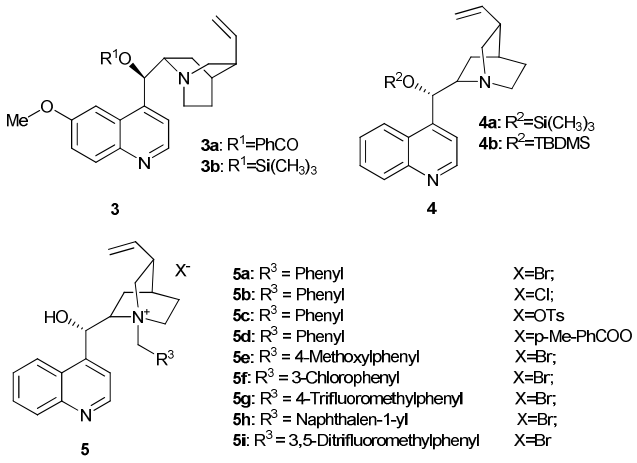
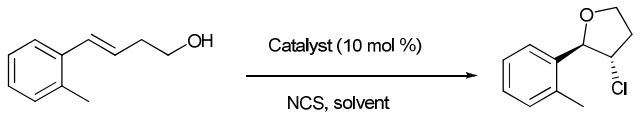


Fig. 2 The organocatalysts used in this study.

cinchona alkaloid *O*-ether **3b** as catalyst gave slightly low yield with an eroded 34% *ee* (Table 1, entry 2). Subsequent attempts to improve the enantioselectivity using cinchonine *O*-esters as catalyst were also unsuccessful (Table 1, entries 3 and 4). Interestingly, when a catalytic amount of *N*-benzyl-cinchoninium bromide **5a** was added to the reaction as a catalyst, the *ee* and yield of the resultant product were enhanced significantly (Table 1, entry 5).[3a,11] Lowering the reaction temperature to -30 °C led to the decrease of the yield and the increase of the *ee*. On the other hand, inverse results were obtained when the temperature was raised to 0 °C (Table 1, entries 6 and 7). Of the solvents surveyed, including chloroform, ethyl ether, and acetonitrile, tetrahydrofuran gave good isolated yield and *ee* (Table 1, entries 5 and 8, ESI, Table S1). This result prompted us to further pursue the reaction catalyzed by such kinds of catalysts. The chloroetherification of **1a** was examined using catalysts **5b-i** (Fig. 1) in a 10 mol % catalyst loading. The results indicated that a further improvement in the enantioselectivity of the reaction was observed when a 4-trifluoromethylbenzyl group was introduced to form the quaternary ammonium salt **5g** (Table 1, entry 14). However, *N*-benzyl-cinchoninium chloride (**5b**) completely destroyed the stereocontrol (Table 1, entry 9). In order to further improve the reaction, $TsNH_2$ was selected as an additive and the yield was increased to 88% (Table 1, entry 14 *vs* 17). TsNHCl derived from the chlorine exchange between NCS and $TsNH_2$ has been also observed by means of ^1H NMR in $CDCl_3$ with the mixture of substrate **1i** and the detailed role of the compound is not clear (Fig.

S1).[3c,12] When the solvent and additive effects were combined (ESI, Table S1), the desired β-chlorotetrahydrofuran was produced in 88% yield and 86% *ee* under the optimized conditions (Table 1, entry 17).

Table 1 Screening the reaction conditions. [a]



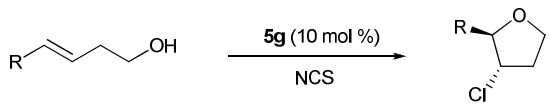
1a **2a**

Entry	Catalyst	Solvent	Temp. (°C)	Yield (%) [b]	ee (%) [c]
1	**3a**	CH_2Cl_2	-20	78	56
2	**3b**	CH_2Cl_2	-20	72	34
3	**4a**	CH_2Cl_2	-20	71	25
4	**4b**	CH_2Cl_2	-20	80	46
5	**5a**	CH_2Cl_2	-20	81	75
6	**5a**	CH_2Cl_2	0	87	70
7	**5a**	CH_2Cl_2	-30	52	81
8	**5a**	THF	-20	75	82
9	**5b**	THF	-20	70	5
10	**5c**	THF	-20	89	62
11	**5d**	THF	-20	76	10
12	**5e**	THF	-20	79	75
13	**5f**	THF	-20	84	82
14	**5g**	THF	-20	82	85
15[d]	**5h**	THF	-20	73	80
16[d]	**5i**	THF	-20	52	80
17[e]	**5g**	THF	-20	88	86
18[f]	-	THF	-20	74	-

[a] The reactions were carried out with **1a** (0.20 mmol), NCS (0.24 mmol), catalyst (0.02 mmol, 10 mol %) in solvent (1.0 mL) under argon atmosphere for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The solubility of catalyst is not good. [e] $TsNH_2$ (0.1 mmol) was used as an additive. [f] The reactions were carried out with substrate **1h** (0.2 mmol), NCS (0.24 mmol), and $TsNH_2$ (0.1 mmol) in solvent (1.0 mL) under argon atmosphere for 12 h.

After the optimized conditions were identified, other substrates were examined, and the scope of the chloroetherification is listed in Table 2. Firstly, the reactions of substituted phenylbut-3-en-1-ol were all performed smoothly with moderate to excellent yields and *ee*s. As a whole, the substrates with electron-withdrawing groups gave slightly better activity. Notably, the highest enantioselectivity of 96% *ee* was obtained employing aromatic substituted homoallylic alcohol **1k** or **1q** as the substrate (Table 2, entries 11 and 17). Homoallylic alcohols bearing mono-chloro substituted phenyl group were converted into desired β-chlorotetrahydrofuran products in good yield with > 95% *ee* (Table 2, entries 9-11). However, enantioselectivities were greatly reduced for the substrates bearing *p*-F, *p*-Br or 2,4-dichloro substituted phenyl group (Table 2, entries 12-14). In addition, substrate bearing *p*-CF_3 substituted phenyl group afforded THF product in good yield with a 92% *ee* (Table 2, entry 16). However, the yield and *ee* of *o*-CF_3 substituted substrate were only 75% and 76%, probably due to the steric hindrance (Table 2, entry 15). On the other hand, just substrates with methyl have about 90% *ee* (Table 2, entries 1-3). And other electron-rich aryl substituents gave lower enantioselectivities, which may be ascribed to the enhanced background reaction (Table 2, entries 4-7). In fact, the 5-*endo* chloroetherification occurs without any quaternary ammonium salt catalyst, such as substrate **1h** (Table *S1*, entry 12). Unfortunately, aliphatic homoallylic alcohols such as **1r** or **1s** were tested and just gave poor results (Table 2, entries 18 and 19).

Table 2 Scope of the asymmetric chloroetherification of homoallylic alcohols. [a]

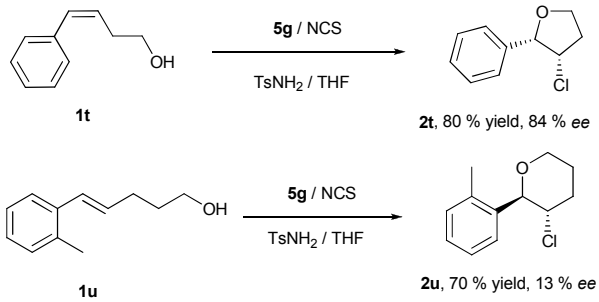


1a - s **2a - s**

Entry	Alcohol	R	Yield (%) [b]	ee (%) [c]
1	**1a**	2-Me-Ph	88	86
2	**1b**	3-Me-Ph	81	92
3	**1c**	4-Me-Ph	78	90
4	**1d**	4-OH-Ph	80	63
5	**1e**	2-MeO-Ph	87	77
6	**1f**	3-MeO-Ph	90	75
7	**1g**	4-MeO-Ph	90	61
8	**1h**	Ph	85	95
9	**1i**	2-Cl-Ph	85	95
10	**1j**	3-Cl-Ph	78	95
11	**1k**	4-Cl-Ph	80	96
12	**1l**	2,4-di-Cl-Ph	87	52
13	**1m**	4-Br-Ph	82	75
14	**1n**	4-F-Ph	83	70
15	**1o**	2-CF_3-Ph	75	76
16	**1p**	4-CF_3-Ph	85	92
17	**1q**	3-NO_2-Ph	92	96
18	**1r**	Cy	56	11
19	**1s**	*t*-Bu	NG	-

[a] The reactions were carried out with homoallylic alcohol **1a-s** (0.20 mmol), NCS (0.24 mmol), $TsNH_2$ (0.10 mmol) and **5g** (0.02 mmol, 10 mol%) in THF (1.0 mL) at -20 °C under argon atmosphere for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

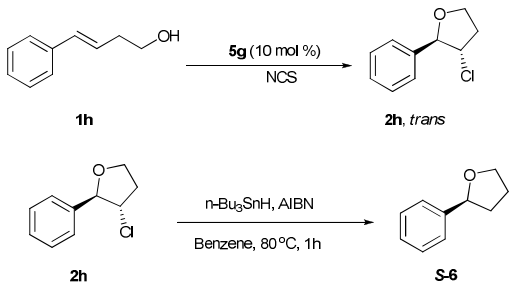
To further evaluate the preparative utility of this 5-*endo* chloroetherification, the (*Z*)-configured olefin **1t** was also investigated. More encouragingly, the 5-*endo* cyclization occurred uneventfully and enantioselectivity was only slightly reduced compared to (*E*)-configured olefin (Scheme 1 and Table 2, entry 8). Additionally, a longer-chain alcohol 5-(4-methylphenyl-4-penten-1-ol was tested to construct bigger ring system via 6-*endo* chloroetherification, while poor *ee* was obtained (Scheme 1, **1u**).



Scheme 1

For the 5-*endo* chloroetherification of (*E*)-homoallylic alcohols, it will result in a *trans*-isomer (Scheme 2).[6b] This phenomenon can be confirmed by NMR experiments (also see ESI).[13] The absolute configuration of **2h** was determined as (2*R*,3*S*), by comparing the reported optical rotation and chiral GC

analysis of **6** derived from **2h** (Scheme 2),[3f,14] and the configurations for all other β-chlorotetrahydrofurans were assigned analogously.



Scheme 2

Conclusions

In summary, we have developed an enantioselective chloroetherification of homoallylic alcohols catalyzed by the chiral quaternary ammonium salts based on cinchonine. This approach represents a successful example of a catalytic, 5-*endo* enantioselective chloroetherification toward the asymmetric synthesis of β-chlorotetrahydrofurans. In this regard, this reaction is highly practical and the products were obtained in excellent enantioselectivities. Further studies to expand the substrates scope, improve the selectivity, and understand the mechanism of this transformation are now underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Full experimental details, mechanism studies, product characterization and reproduction of NMR spectra and HPLC spectra. See DOI: 10.1039/b000000x/

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