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Synthesis of cinchonidinium salts containing sulfonamide functionalities and their catalytic activity in asymmetric alkylation reactions

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ABSTRACT

Various kinds of 4-(bromomethyl)benzenesulfonamides were prepared as quaternization reagent of cinchonidine. Cinchonidinium salts obtained from the quaternization of cinchonidine with 4-(bromomethyl)benzenesulfonamide showed highly enantioselective catalytic activity in the asymmetric benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester. The corresponding phenylalanine derivative was obtained in high yield with a high level of enantioselectivity, up to 98% ee.

Cinchona alkaloids have been utilized for the preparation of various types of chiral organocatalysts.[1] Particularly, the quaternary ammonium salts of cinchona alkaloids[2] are an important class of organocatalysts that have been developed for asymmetric reactions, including Michael reactions,[3] Darzen reactions,[4] cyclopropanations,[5] aldol reactions,[6] fluorinations,[7] epoxidations,[8] and alkylations.[9] Among these transformations, the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester has attracted much attention because it affords a simple synthesis of optically active α-amino acids.[10] Additionally, quinuclidine nitrogen can be easily quaternized using various reagents.[11] *N*-benzyl quaternary ammonium salts of cinchona alkaloids are most commonly used as chiral organocatalysts[12] and some of them are commercially available.[13] Chemical modification of the *N*-benzyl substituents on these cinchona alkaloids can strongly affect their catalytic activity. Incorporation of methoxy, methyl, nitro, and fluoro groups on the *N*-benzyl substituents has been examined in the literature.[11] For example, a previous study reported that a 2′-F group presumably participates in an internal hydrogen bonding interaction with C(9)*O*H via an H_2O solvent molecule, which results in a more rigid conformation.[14] However, substituent effects from other groups besides the fluoro group have not been clearly elucidated. Sulfonamide is another possible and promising functionality of the *N*-benzyl substituent. While various sulfonamide structures are available to chemically modify the *N*-benzyl substituents and thereby tune the catalytic activity of the corresponding cinchonidinium salts, sulfonamides, to our knowledge, have not been explored for use in this chemistry. Accordingly, we examined the effects of incorporating sulfonamide functionalities into the para position of the *N*-benzyl substituents in cinchonidinium catalysts and observed higher enantioselectivity in the alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester. Since para substitution of these functionalities makes them unable to participate in internal hydrogen bonding, steric factors may instead influence the observed enantioselectivity. Herein we discuss the preparation of the cinchonidinium salts possessing sulfonamide-substituted *N*-benzyl derivatives and their catalytic activity in asymmetric benzylation reactions.

Synthesis of cinchonidinium salts having sulfonamide functionality

We have synthesized a series of 4-(bromomethyl)benzenesulfonamides **3a**–**3j** as novel quaternization reagents of cinchona alkaloids from 4-(bromomethyl)benzenesulfonyl chloride **1** and amines **2a**–**2j** (Scheme 1). Since nucleophilic attack by the amine may occur both at the sulfonyl and benzyl positions of **1**, we were prompted to find suitable reaction conditions to prepare the sulfonamides **3a**–**3j** selectively. Typical reaction conditions used for sulfonamide formation were unsuccessful in our attempts to prepare the latter.[15,16] For example, the reaction of **1** with amines **2a**–**2j** in

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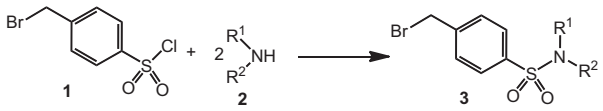
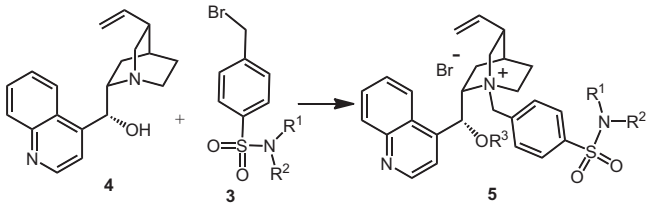


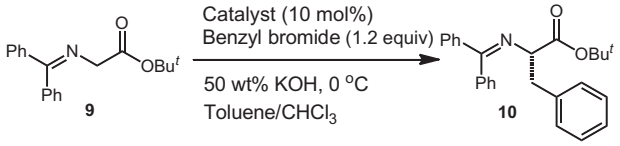
2a: R^1 = butyl, R^2 = H
2b: R^1 = *t*-butyl, R^2 = H
2c: R^1 = phenyl, R^2 = H
2d: R^1 = 1-naphthyl, R^2 = H
2e: R^1 = 4(trifluromethyl) phenyl, R^2 = H
2f: R^1 = 3,4,5-trifluorophenyl, R^2 = H
2g: R^1 = 4-methylphenyl, R^2 = H
2h: R^1 = 4-methoxyphenyl, R^2 = H
2i: R^1 = phenyl, R^2 =Me
2j: R^1 = 4-iodophenyl, R^2 = H

Scheme 1. Synthesis of sulfonamide **3**.



Scheme 2. Synthesis of cinchonidinium salt **5** having the sulfonamide group.

Table 2
Asymmetric benzylation reaction of *N*-(diphenylmethylene)glycine *tert*-butyl ester by using cinchonidinium salts[a]



Entry	Cinchonidinium salts	Time (h)	% Yield[b]	% ee[b,c]
1[d]	**6**	5	91	71 (*S*)
2	**5a**	17	80	87 (*S*)
3	**5b**	14	72	90 (*S*)
4	**5c**	20	87	93 (*S*)
5	**5d**	15	60	87 (*S*)
6	**5e**	17	73	91 (*S*)
7	**5f**	14	75	90 (*S*)
8	**5g**	17	80	91 (*S*)
9	**5h**	24	84	94 (*S*)
10	**5i**	5	53	91 (*S*)
11	**5i**	20	86	91 (*S*)
12	**5j**	20	79	91 (*S*)
13	**7**	17	75	78 (*S*)

[a] Reaction was carried out with 1.2 equiv of benzyl bromide and 50 wt % aqueous KOH in the presence of 10 mol % of the catalyst in toluene–chloroform (7:3) at 0 °C.
[b] Isolated yield.
[c] ee values were determined by HPLC using a Chiralcel OD-H column.
[d] See Ref. 23

the presence of pyridine or Na_2CO_3 gave only complex mixtures,[17,18] and we found that the use of two equivalents of amine was necessary to prepare **3a**–**3j**. Accordingly, the treatment of **1** with 2 equiv of aniline in CH_2Cl_2 at 25 °C afforded the sulfonamide **3c** in high yield. Under these conditions, the *N*-benzyl aniline side product was not obtained.

The resulting quaternization reagents **3a**–**3j** were then employed on cinchonidine **4** to afford the corresponding cinchonidinium salts **5a**–**5j**, which contain sulfonamide moieties on the *N*-benzyl substituents (Scheme 2). However, typical quaternization conditions for cinchonidine failed to synthesize **5**. Quaternization of cinchonidine usually required vigorous conditions such as reflux in toluene.[19] Many cinchonidinium salts such as *N*-benzylcinchonidinium bromide **6** were easily obtained under these reaction conditions. While Park and Jew reported that the use of a mixed solvent system consisting of ethanol/DMF/$CHCl_3$ (5:6:2 ratio) resulted in higher yields of the quaternized cinchona alkaloid derivatives,[20] these reaction conditions did not afford **5a**–**5j** as isolable products. We eventually discovered that the quaternization of cinchonidine **4** with **3a**–**3j** required only mild reaction conditions to give **5a**–**5j**, and these syntheses are summarized in Table 2. From the reaction between **3a** and cinchonidine in DMF at 25 °C for 20 h, **5a** was obtained in high yield (94%, Table 1, entry 1). All other cinchonidinium salts **5b**–**5j** were also obtained in high yields. When the reactions were conducted above 50 °C, unknown side reactions occurred, which inhibited the isolation of the desired quaternized products. The quaternization reactions also proceeded successfully in MeOH at 40 °C for several derivatives (Table 1, entries 2, 4–7). Under these mild reaction (see Fig. 1) conditions, the chiral quaternary ammonium salts **5** were selectively synthesized in high yield, as shown in Table 1. For comparison, the *ortho*-sulfonamide-substituted *N*-benzyl derivative **7** was also prepared by the same method (Table 1, entry 12). It is worth mentioning that substitution on the C(3)-position of the cinchonidinium salt can also influence the degree of enantioselectivity. The 3-ethyl derivatives **8** of the cinchonidinium salts were analogously prepared (Table 1, entries 13 and 14). Introduction of an allyl ether on the C(9)-OH position often afforded higher enantioselectivity in asymmetric alkylation

Table 1
Synthesis of sulfonamide containing cinchonidinium salts

Entry	Cinchonidinium salts	R^1	R^2	R^3	Solvent	Temp °C	Time (h)	% Yield
1	**5a**	Butyl	H	H	DMF	25	20	94
2	**5b**	*t*-Butyl	H	H	MeOH	40	15	97
3	**5c**	Phenyl	H	H	DMF	25	20	92
4	**5d**	1-Naphthyl	H	H	MeOH	40	18	94
5	**5e**	4-(Trifluoromethyl)phenyl	H	H	MeOH	40	12	83
6	**5f**	3,4,5-Trifluorophenyl	H	H	MeOH	40	15	90
7	**5g**	4-Methylphenyl	H	H	MeOH	40	15	97
8	**5h**	4-Methoxyphenyl	H	H	DMF	25	20	97
9	**5i**	Phenyl	Me	H	DMF	25	20	94
10	**5j**	4-Iodophenyl	H	H	DMF	25	20	94
11	**5c**(**allyl**)	Phenyl	H	Allyl	DMF	25	20	80
12	**7**	—	—	—	DMF	25	20	70
13	**8c**	Phenyl	H	H	DMF	25	20	83
14	**8h**(**allyl**)	4-Methoxyphenyl	H	Allyl	DMF	25	20	75

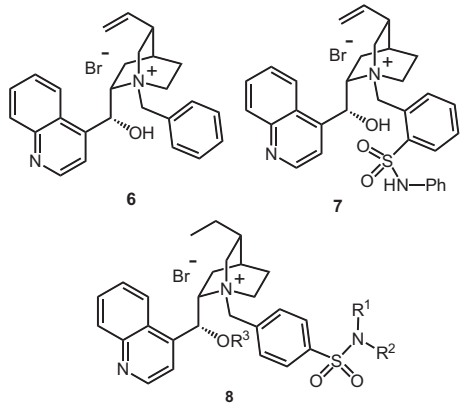


Figure 1. Cinchonidinium salts used as organocatalysts.

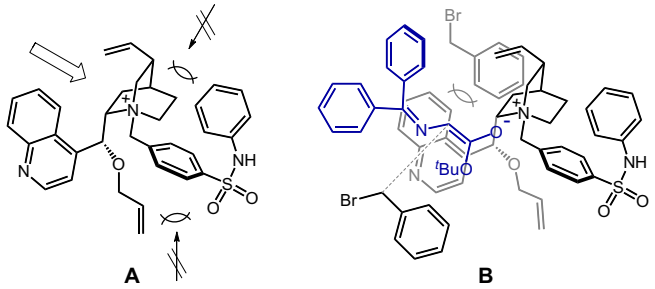


Figure 2. Plausible reaction mechanism of asymmetric benzylation with cinchonidinium salt catalyst.

reactions.[21] C(9)*O*-allyl derivatives (**5c**(**allyl**), **8h**(**allyl**)) were also synthesized (Table 1, entries 11 and 14).[22] To determine the effect of an NH group in the 4′-sulfonamide moiety, **5i** was prepared from *N*-methyl aniline using the same method (Table 1, entry 9).

Asymmetric benzylation with cinchonidinium catalysts

In order to examine the catalytic activity of novel cinchonidinium salts containing sulfonamide substituents, we employed the chiral quaternary ammonium salts **5**, **7**, and **8** as catalysts in asymmetric benzylation reactions of *N*-(diphenylmethylene)glycine *tert*-butyl ester **9**. Results are summarized in Table 2. By using **5a**, which contains an aliphatic sulfonamide group on the *N*-benzyl substituent, the asymmetric reaction proceeded smoothly to afford the corresponding phenylalanine derivative **10** with 87% ee (Table 2, entry 2), which was higher than that obtained from the *N*-benzyl cinchonidinium salt **6** (74% ee, Table 2, entry 1). Compared to the *N*-benzyl cinchonidinium salt **6**, the 4′-sulfonamide-substituted *N*-benzyl derivatives exhibited greater levels of enantioselectivity. We additionally observed that the bulky *tert*-butyl sulfonamide derivative **5b** gave somewhat higher selectivity (Table 2, entry 3). Both electron-withdrawing groups (Table 2, entries 6, 7, and 12) and electron-donating groups (Table 2, entries 8 and 9) gave ee values that were greater than 90%. On the other hand, the effect of the sulfonamide NH group on the enantioselectivity was less pronounced (Table 2, entries 4 and 10), while the use of the ortho-substituted cinchonidinium salt **7** resulted in a decrease in the enantioselectivity (Table 2, entry 13). Although the relatively long reaction times were required with catalysts **5**, no racemization occurred after 20 h reaction with **5i** (entries 10 and 11).

We subsequently investigated the effect of chemically modifying the cinchonidine double bond (C10–C11) and the OH group in **5** on the observed enantioselectivity. Park and co-workers reported that the use of cinchonidinium salts hydrogenated at the C10–C11 double bond resulted in higher enantioselectivity in asymmetric alkylation reactions compared with the *N*-benzyl cinchonidinium salt **6** (Table 2, entry 1).[20] Further, Corey et al. reported that O-allylation of the 9-OH group in cinchonidinium salts provided catalysts that exhibited greater activity in asymmetric alkylation reactions.[21] Based on these findings, we synthesized both the hydrogenated and O-allylated analogues of **5c** to give **8c** and **5c**(**allyl**), respectively. As shown in Table 3 (entry 1), a slight increase in enantioselectivity was attained in the presence of **5c**(**allyl**) versus **5c**. Similarly, **8c** displayed increased enantioselectivity over **5c** (Table 3, entry 2). Since **5h** showed the highest enantioselectivity (94% ee) in the asymmetric benzylation of **9** (Table 2, entry 9), we were interested in exploring the catalytic activity of its C10–C11 hydrogenated and O-allylated analogue, **8h**(**allyl**). Indeed, greater enantioselectivity was obtained with **8h**(**allyl**) both at 0 °C (97% ee, Table 3, entry 3), and at −20 °C (98% ee, Table 3, entry 4). Some other alkylating agents also showed high enantioselectivities using **8h**(**allyl**) (entries 5 and 6).

In conclusion, we have prepared various novel cinchonidinium salt derivatives containing sulfonamide-substituted benzyl ammonium groups (**5**, **7**, and **8**). We reasoned that the presence of 4′-sulfonamide substituents provided steric protection at the right hand side of the catalyst molecule **A**, as illustrated in Figure 2. This steric protection presumably controls the approach of the enolate intermediate in the transition state **B**, thereby resulting in higher enantioselectivity in asymmetric benzylation reactions. To provide further evidence of the usefulness and effectiveness of the catalyst design explored in this study, we are investigating the catalytic activities of these ammonium salts in other asymmetric transformations.

Table 3
Asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester by using O-allylated cinchonidinium salts[a]

Entry	Cinchonidinium salts	Alkylating agent	Time (h)	% Yield[b]	% ee[b,c]
1	**5c**(**allyl**)	Benzyl bromide	18	80	95 (*S*)
2	**8c**	Benzyl bromide	16	72	94 (*S*)
3	**8h**(**allyl**)	Benzyl bromide	14	91	97 (*S*)
4[d]	**8h**(**allyl**)	Benzyl bromide	24	90	98 (*S*)
5	**8h**(**allyl**)	4-Methylbenzyl bromide	15	92	96 (*S*)
6	**8h**(**allyl**)	Allyl bromide	15	89	93 (*S*)

[a] Reaction was carried out with 1.2 equiv of alkylating agent and 50 wt% aqueous KOH in the presence of 10 mol % of the catalyst in toluene–chloroform (7:3) at 0 °C.
[b] Isolated yield.
[c] ee values were determined by HPLC using Chiralcel OD-H column.
[d] Reaction was carried out at −20 °C.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.052.

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