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Roof shape chiral alcohol: auxiliary for asymmetric synthesis of α-halo acid derivatives

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ABSTRACT

Roof shape chiral enantiopure alcohol, obtained by bio-catalytic separation of isomers, was used as a new auxiliary for asymmetric synthesis of α-halo acid derivatives. Esterification reaction of roof shape chiral enantiopure alcohol and racemic α-halo acids in the presence of DCC, DMAP furnished diastereomers of ester in non-racemic manner. Diastereoselectivity up to 90% was observed, the absolute configuration of newly generated chiral center was established by the single crystal X-ray diffraction analysis.

Asymmetric synthesis of optically active products using a variety of chiral auxiliaries, natural and artificial, is an established tool in modern synthetic organic chemistry.[1] For a number of years naturally occurring chiral auxiliaries remained the preferred choice for such studies. However, due to some limitations, such as unavailability of both isomers, inability to obtain optically pure compounds in large quantities, other structural limitations. There is a continuous need to search new artificial chiral molecules to utilize as auxiliaries for asymmetric synthesis.[2] The design of molecules suitable for the use as chiral auxiliary requires some specific structural arrangement. The shape, size, and arrangement of functional groups in chiral molecules play a crucial role in the efficiency of their use as auxiliary for asymmetric synthesis. Hence, molecules with unique shape and arrangement of aromatic rings which offer stereocontrol can be examined as auxiliaries. Synthetically prepared chiral molecules have advantages over the naturally available compounds of chiral pool as their structures can be fine tuned and their both enantiomers can be easily obtained. Weber introduced a novel class of compounds resembling the shape of a roof and studied their applications as clathrate hosts with inclusion properties.[3] Such molecules also find many applications in different areas ranging from material to medicinal chemistry.[4] In our continuing work, we have presented synthesis, resolution of roof shape alcohols **1** and **2**, and their derivatives.[5,6] The roof shape alcohols were also converted to amines to be scanned as chiral solvating agents for the discrimination of the signals of optically active acids in NMR spectroscopy.[6]

Optically pure α-substituted alkanoic acids and their number of derivatives are an important class of natural and synthetic compounds. Many strategies have been developed for their enantioselective synthesis. The approach involving the selective alkylation of the enolate of chiral esters is widely investigated.[7a] This includes the use of chiral auxiliaries, utilizing hydroxy pentolactone,[7b,c] carvone derives alcohols,[7d] 2-oxoimidazolidine 4-carboxylate,[7e] cyclohexanol based auxiliaries,[7f] carbohydrate based alcohols,[7g] and sultam based amides[7h]. Besides these, other strategies including asymmetric hydrogenation of acrylates,[8] α-alkylation by phase-transfer catalysis,[9] etc. have also been investigated. Separation of enantiomers of the easily available α-substituted acids and their straightforward conversion to functionalized derivatives is another attractive option to access such molecules. This may be achieved by fractional crystallization of its salt with chiral resolving agents[10] or by enzymatic kinetic resolution methods.[11] Both these classical approaches can furnish maximum 50% yield of the desired isomer. To overcome this limitation dynamic kinetic resolution (DKR) and dynamic thermodynamic resolution (DTR) have been developed where the unreacted isomer of the starting material is interconverted to the more reactive one or stable one, hence effectively increasing the yields to acceptable level.[12] In this work we explore the roof shape chiral alcohol **1** as a new auxiliary to access optically enriched α-halo esters. These are important intermediates for the synthesis of other functionalities by suitable substitution reactions (see Fig. 1).

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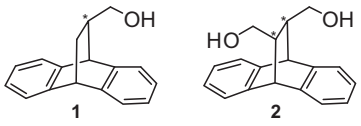


Figure 1. Roof shape chiral alcohol and diol.

In our earlier work we have reported resolution of racemic **1** by enzymatic method.[6] In our initial efforts to synthesize α-halo ester, it was condensed with phenyl acetic acid by the standard ester formation protocol[13] to access **3** in a good yield.

The ester **3** was subjected to α-bromination using NBS, product **4** was isolated and characterized. However the diastereomer ratio (de) was quite low, established by HPLC analysis (see Schemes 1 and 2).

Optical enrichment of α-halo ester derivatives of chiral alcohols during substitution reactions has been studied.[14] In this study we also wish to examine the possibility to enrich one isomer of α-halo ester **5** prepared from α-halo acid and roof shape chiral enantiopure alcohol **1** (Scheme 3). This can take place either during the ester formation step or during the interconversion of its isolated sample under appropriate conditions.

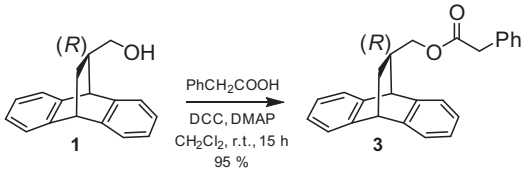
Accordingly (*R*)-**1** was subjected to ester formation with (±)-**6** (Scheme 4). The product has two possible diastereomers, (*R*,*S*)-**4** and (*R*,*R*)-**4**, and their ratio was carefully determined by HPLC analysis.

The coupling reaction was performed using DCC and DMAP at room temperature in dichloromethane (Table 1). The ratio of the two diastereomers was examined, assuming that the chiral center on the roof shape alcohol portion remains unchanged. A low diastereoselectivity was observed in the absence of DMAP in the coupling reaction. However, the presence of a base such as DMAP or DABCO may assist abstraction of acidic α-hydrogen in the ester formed resulting in the enrichment of kinetically or thermodynamically stable isomer.

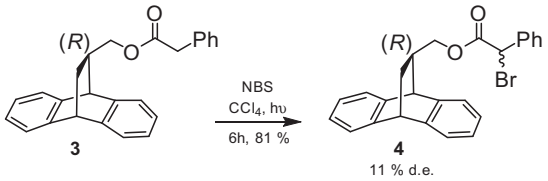
In the presence of catalytic quantity of DMAP (20 mol %) considerable improvement in the de ratio was observed, longer reaction time only improved yield, without much effect on the selectivity. Different solvents were also screened to establish the optimum conditions for selectivity and conversion (Table 2). Although toluene was found to be slightly better for selectivity, the conversion was slightly higher in dichloromethane.

It was significant to observe interesting crystallization pattern for the diastereomer of **4**. The major isomer was crystallized from acetonitrile while the minor was obtained from a mixture of ethyl acetate and hexane. Single crystal X-ray diffraction analysis of pure crystals of both isomers helped us to establish the absolute configuration of newly generated chiral center at the α-carbon of the esters. The major isomer crystallized from acetonitrile clearly indicated the configuration of the α-carbon to be '*S*', while it was '*R*' in the minor isomer (Fig. 2).

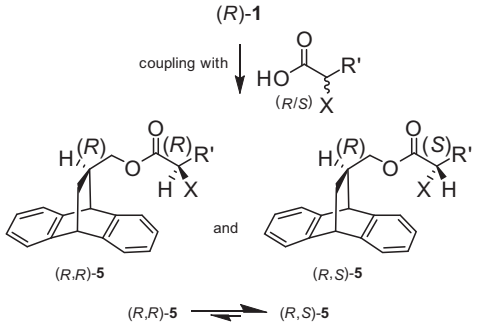
In the next set of experiments α-chloropropionic acid **7** was condensed with (*R*)-**1** in the presence of DCC-DMAP (Scheme 5). Product **8** was isolated and the diastereomer ratio was established by ^{1}H NMR analysis, where the methyl doublet for both appeared at measurable positions.



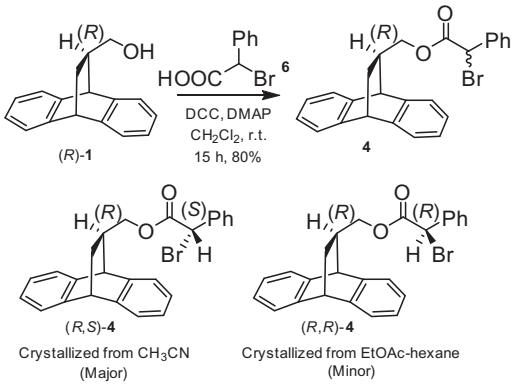
Scheme 1. Esterification of acid with roof shape alcohol.



Scheme 2. Bromination of roof shape phenyl acetate **3**.



Scheme 3. Synthesis of diastereo enriched α-halo esters.



Scheme 4. Diastereoselective ester formation with α-bromo acid.

Table 1
Diastereoselective coupling of (*R*)-**1** with (±)-**6**[a]

No	DMAP (mol %)	Reaction time (h)	Yield[b] (%)	Diastereomer ratio[c] (*R*,*S*)/(*R*,*R*)-**4**	[de]
1	0	15	40	54:46	8
2	20	15	80	76:24	52
3	20	3	60	78:22	56

[a] All reactions run in CH_2Cl_2, addition of DMAP at 0 °C, then at rt.
[b] Isolated.
[c] Determined by HPLC.

Table 2
Effect of solvent on the coupling of (*R*)-**1** with (±)-**6**[a]

No	Solvent	Yield[b] (%)	Diastereomer ratio[c] (*R*,*S*)/(*R*,*R*)-**4**	[de]
1	CH_2Cl_2	80	76:24	52
2	THF	54	78:22	56
3	CH_3CN	56	62:38	24
4	Toluene	64	80:20	60

[a] All reactions were run with DMAP (20 mol %), addition of DMAP at 0 °C, then at rt for 15 h.
[b] Isolated.
[c] Determined by HPLC.

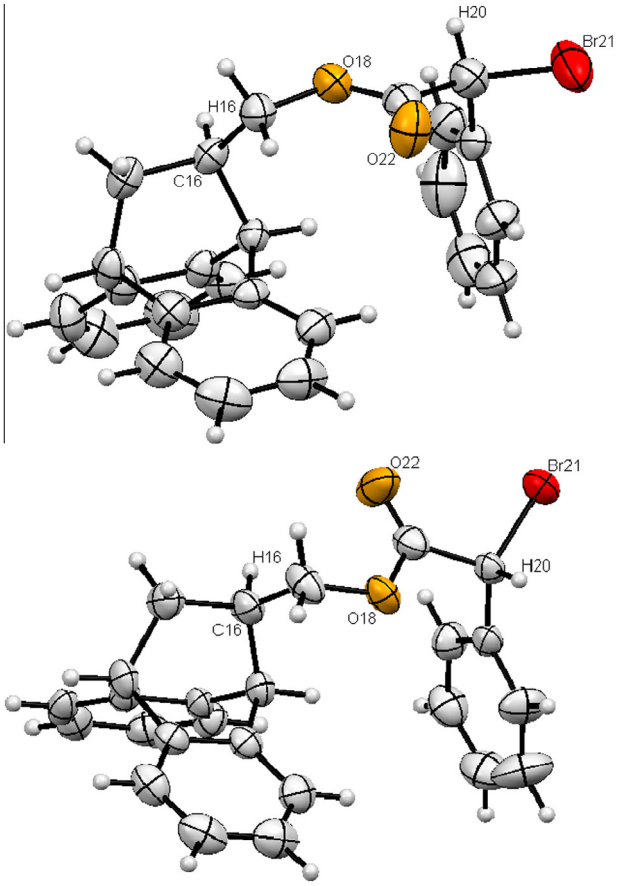
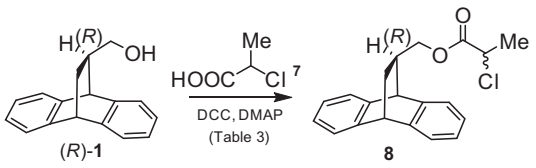


Figure 2. ORTEP diagram of (*R*,*S*)-**4** (top) [CCDC No. 1002050] and of (*R*,*R*)-**4** (bottom) [CCDC No. 1002049].



Scheme 5. Diastereoselective ester formation with α-chloro acid.

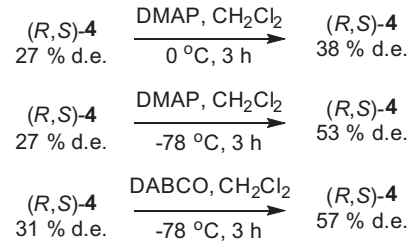
The result of the above experiment was analogous to coupling with (±)-**6**. The diastereomer ratio of the product was also found to be much higher compared to **4** (Table 3). Longer reaction time resulted in a small drop in the selectivity.

These coupling reactions were conducted with equimolar ratio of alcohol (*R*)-**1** and racemic acids **6** or **7** and the yield and the diastereomer ratios were more than 50%. This reduces the possibility of only one isomer of acid participating selectively in the reaction with chiral alcohol. The other possibility for the enrichment of diastereomer may involve interconversion of isomers of the ester to achieve the equilibrium in favor of stereochemically and thermodynamically more stable product. To test this possibility, a sample of **4** with moderate de was subjected to basic condition for some time and quenched. The product was carefully and completely recovered and analyzed to indicate some enrichment in the ratio (Scheme 6). At a slightly elevated temperature we observed almost racemization. Reaction at room temperature resulted in marginal enrichment, while at a low temperature considerable enhancement was found. The organic base DMAP and DABCO showed similar effect in this experiment.

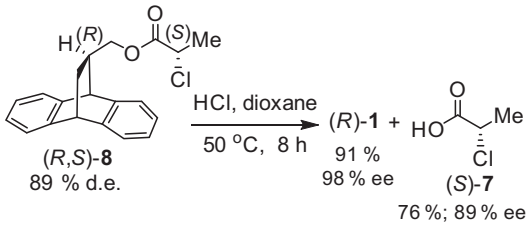
Table 3
Diastereoselective coupling of (*R*)-**1** with (±)-**7**[a]

No	DMAP (mol %)	Reaction time (h)	Yield[b] (%)	Diastereomer ratio[c] (*R*,*S*)/(*R*,*R*)-**8**	[de]
1	20	3	76	95:5	90
2	20	15	82	94:6	88
3	20	40	91	91:9	82
4	50	15	95	93:7	87

[a] All reactions were run in CH_2Cl_2, addition of DMAP at 0 °C, then at rt.
[b] Isolated.
[c] Determined by HPLC.



Scheme 6. Enrichment of diastereomeric ester (*R*,*S*)-**4**.



Scheme 7. Hydrolysis of diastereomeric ester of α-chloro acid.

When partially chiral and partially racemic sample of **4**, which is initially formed, is exposed to base, the acidic α proton can be easily abstracted. The resulting *E*-enolate intermediate[15] can selectively recapture the proton to form more stable isomer of α-halo ester. The smaller size of methyl in case of the chloro derivative **8**, probably favors the *E*-enolate even more, resulting in a better selectivity. Such dynamic kinetic resolution for substitution reactions is reported for α-halo esters attached to chiral axillaries for selective reactions,[16] including some roof shape ones.[17]

The sample of optically enriched (*R*,*S*)-**8** was subjected to acid catalyzed hydrolysis reaction (Scheme 7).[18] The recovered alcohol **1** was obtained in optically pure form and the cleaved α-chloropropionic acid was confirmed to be of '*S*' configuration by comparison of its specific rotation.

Thus we present the use of new chiral roof shape auxiliary to achieve efficient stereocontrol in the base mediated dynamic kinetic resolution of α-halo esters.

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Supplementary data

Supplementary data (Experimental procedures, characterization data and copies of the spectra are included in this section.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.003.

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