Novel CuX₂-mediated cyclization of acid–base salts of (L)-cinchonidine or (D)-/(L)- α -methylbenzylamine and 2,3-allenoic acids in an aqueous medium. An efficient entry to optically active β -halobutenolides

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The treatment of 1:1 salts of 2,3-allenoic acid–chiral base with CuX₂ (4 equiv.) in an aqueous medium, *i.e.* acetone– $H_2O(2:1)$, at 60–65 °C afforded β -halobutenolides with high enantiopurities in good to excellent yields.

Polysubstituted butenolides are a class of compounds of current interest due to their potential broad range of biological activities¹ and abundant occurrence in natural products.² However, the methods for the highly stereoselective synthesis of optically active butenolides are limited.^{3,4} In this paper, we wish to report a highly efficient CuX₂-mediated cyclization of the salts formed between chiral bases and 2,3-allenoic acids. The method provides a novel route to β -halobutenolides with high enantiopurity, important building blocks for polysubstituted butenolides.⁵

Recently, we have developed several methodologies for the synthesis of β -halobutenolides from 2,3-allenoic acids.^{5,6} The interesting point of these reactions is that the starting 2,3-allenoic acids are a class of compounds with chirality when properly substituted. Thus, it would be possible to use a cheap optically active base to resolve 2,3-allenoic acids and transfer the axial chirality in allenes into central chirality in butenolides in a highly stereoselective manner. One major issue here is the use of the salt of an optically active base with 2,3-allenoic acids *directly* as the starting point, the release of 2,3-allenoic acids from the salts would not be necessary, which makes this strategy more attractive.

The resolution of racemate 2-methyl-4-phenylbuta-2,3-dienoic acid **1a** with 0.5 equiv. of (L)-cinchonidine, a readily available and relatively cheap base, afforded a salt which could be readily recrystallized in *ethyl acetate* to afford the optically active salt (+)-**2a** in 43% yield with $[\alpha]_D^{20} = +85.4^{\circ}.7$ Release of the acid from the corresponding salt (+)-**2a** by the treatment with dilute H₂SO₄ afforded *S*-(+)-**1a**, indicating the (*S*)-configuration of the allene moiety according to the Lowe–Brewster rule (Scheme 1).⁸

Luckily, when (+)-2a was treated with CuBr₂ in an aqueous medium (acetone-H₂O (2:1)), at 60–65 °C for 3 h, a methodology recently developed by ourselves for the halolacto-

Scheme 1

nization of 2,3-allenoic acids,⁶ the reaction afforded (+)-**3a** in 95% yield with 98% ee, ⁹ the corresponding β -chlorobutenolide (+)-**3b** was also obtained in 90% yield with 99% ee by using CuCl₂ instead of CuBr₂ (Scheme 2).



With the standard aqueous reaction conditions in hand, a series of β -bromobutenolides with high optical purity were prepared and the results are summarized in Table 1. It is obvious: (1) the yields are from good to excellent; and (2) the efficiency of the chirality transfer process is almost 100% since the %ee of the products from the resolved salts are similar to those from the released free 2,3-allenoic acids (Scheme 3), indicating that the chirality of (L)-cinchonidine has almost no impact on the chirality transfer of the allene moiety. Similar results were obtained for all substrates using CuCl₂ in place of CuBr₂ to afford β -chlorobutenolides. The absolute configuration of the chiral centers in the products 3c and 3d were determined by X-ray diffraction using the bromine atoms as the reference.¹⁰ The absolute configuration of other products are based on these X-ray studies and further confirmed by the study of their CD spectra.11

Furthermore, it is interesting to observe when we used (S)-(+)- α -methylbenzylamine as the resoluting agent, the salt (-)-4**a** was obtained and its treatment with CuBr₂ afforded the opposite enantiomers (*R*)-(-)-3**a** (98% ee) and (*R*)-(-)-3**b** (98% ee) in 90% and 93% yields, respectively (Scheme 4).

By using (R)-(-)- α -methylbenzylamine instead of its *S*enantiomer, the corresponding salt (+)-**4a** afforded the same enantiomer as with (L)-cinchonidine, *i.e.* (*S*)-(+)-**3a** and (*S*)-(+)-**3b** in 92 (98% ee) and 90% yield (97% ee), respectively (Scheme 4).

In conclusion, we have developed an efficient aqueous synthesis of highly optically active β -halobutenolides. The current methodology will show its utility in organic synthesis due to the ready availability of starting materials with different substitution patterns,^{7,12} direct cyclization from the salts, and availability of both enantiomers.







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