Novel CuX_2-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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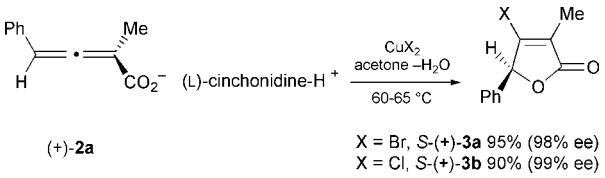
The treatment of 1:1 salts of 2,3-allenoic acid–chiral base with CuX_2 (4 equiv.) in an aqueous medium, *i.e.* acetone–H_2O (2:1), at 60–65 °C afforded β-halobutenolides with high enantiopurities in good to excellent yields.

Polysubstituted butenolides are a class of compounds of current interest due to their potential broad range of biological activities[1] 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 CuX_2-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°.[7] Release of the acid from the corresponding salt (+)-**2a** by the treatment with dilute H_2SO_4 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 $CuBr_2$ in an aqueous medium (acetone–H_2O (2:1)), at 60–65 °C for 3 h, a methodology recently developed by ourselves for the halolactonization 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 $CuCl_2$ instead of $CuBr_2$ (Scheme 2).

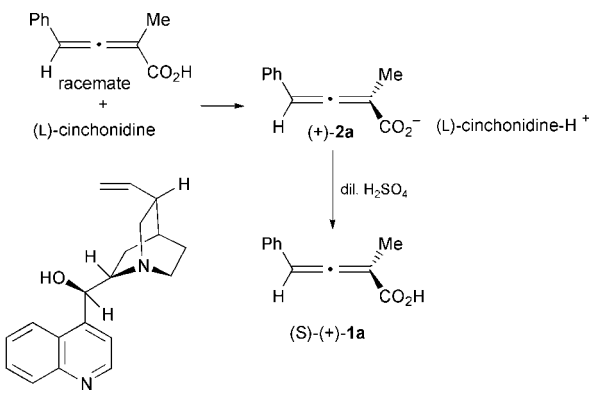


With the standard aqueous reaction conditions in hand, a series of β-bromobutenolides with high optical purity were prepared and the results are summarized in Table 1. It is obvious: (1) the yields are from good to excellent; and (2) the efficiency of the chirality transfer process is almost 100% since 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 $CuCl_2$ in place of $CuBr_2$ 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]

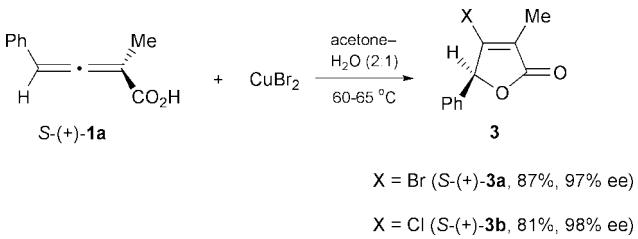
Furthermore, it is interesting to observe when we used (*S*)-(+)-α-methylbenzylamine as the resoluting agent, the salt (−)-**4a** was obtained and its treatment with $CuBr_2$ afforded the opposite enantiomers (*R*)-(−)-**3a** (98% ee) and (*R*)-(−)-**3b** (98% ee) in 90% and 93% yields, respectively (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.



Scheme 1



Scheme 3

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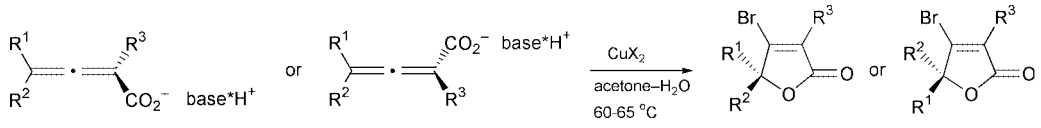
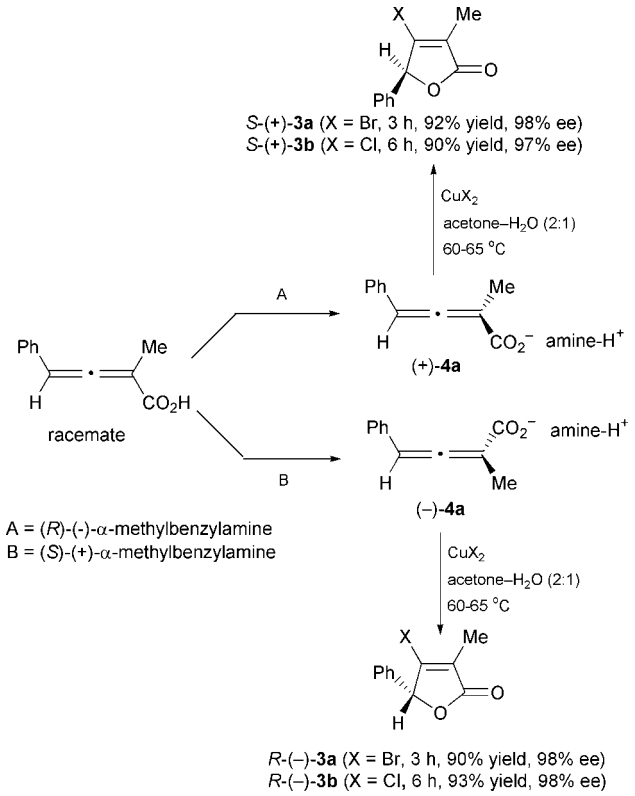
Table 1 Highly stereoselective cyclization of (L)-cinchonidine salts of 2,3-dienoic acids[a]



Entry	Acid R1	R2	R3	Optical rotation of the salt[b]	CuX_2 X =	Reaction time/h	Yield (%) (product, ee%[g])
1	C_6H_{13}	H	Me (**1b**)	−9.10	Cl	6	90 (*S*-(−)-**3c**, 94)
2	C_6H_{13}	H	Me (**1b**)	−9.10	Br	3	95 (*S*-(−)-**3d**,[c] 95)
3	$C_{10}H_7$[d]	H	Me (**1c**)	+58.3	Cl	10	88 (*S*-(+)-**3e**, 98)
4	$C_{10}H_7$[d]	H	Me (**1c**)	+58.3	Br	3	86 (*S*-(+)-**3f**,[c] 98)
5	Ph	H	C_3H_7 (**1d**)	+37.8	Cl	8	92 (*S*-(+)-**3g**, 96)
6	Ph	H	C_3H_7 (**1d**)	+37.8	Br	3	96 (*S*-(+)-**3h**, 96)

reaction was carried out using the salt and CuX_2 (4 equiv.) in acetone–H_2O (2:1) at 60–65 °C. [b] The specific optical rotation $[\alpha]_D^{20}$ (c = 1, . [c] The absolute configuration was determined by X-ray diffraction studies. [d] $C_{10}H_7$ = α-naphthyl.



Scheme 4

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10 The absolute configuration was determined using Texsan software. The Bijvoet reflections were collected and refined with Bijvoets not flagged as redundant. CCDC 152077 and 152078. See http://www.rsc.org/suppdata/cc/b0/b008818h/ for crystallographic data in .cif format.

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