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Highly enantioselective synthesis of 1,3-mercapto alcohols from α,β-unsaturated ketones: asymmetric bifunctional group exchange reaction

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Abstract

Optically active 1,3-mercapto alcohols were synthesized from α,β-unsaturated ketones using a chiral reagent **B** and dimethylaluminum chloride in two steps. The transformation involved a tandem Michael addition–MPV reduction and a base-catalyzed elimination. The two newly created chiral carbons in *trans*-chalcone derivatives were enantioselectively controlled to a high degree. Using the above transformation, an asymmetric bifunctional group exchange reaction between the substrate and chiral reagent was developed. © 2000 Elsevier Science Ltd. All rights reserved.

The Meerwein–Ponndorf–Verley (MPV) reduction is a useful method for the chemoselective reduction of a ketone moiety among several types of carbonyl compounds.[1] Although many researchers[2] have tried to develop an asymmetric MPV reduction, high enantiomeric excess has been observed only in the intramolecular MPV reaction,[3] with the exception of the catalytic reaction by Evans and co-workers.[4] We have recently developed a tandem Michael addition–MPV reduction of α,β-unsaturated ketones using chiral mercapto alcohol **A** and Lewis acid. The resulting product **2A** was utilized in the asymmetric synthesis of secondary alcohols and allylic alcohols, as shown in equation (1) in Scheme 1.[5] The stereochemistry of the two newly created chiral carbons in the sulfide **2A** is completely controlled by dynamic kinetic resolution via a reversible Michael addition. In order to utilize the two chiral carbons effectively, we designed a new method for asymmetric synthesis of 1,3-mercapto alcohols **3** from α,β-unsaturated ketones **1** using a new chiral reagent **B**, as shown equation (2) in Scheme 1.

Chiral reagent **A** is not adequate for the strategy of the above asymmetric synthesis, because the transformation from the sulfide **2A** into the thiol **3** is not easy to carry out. Therefore, we designed a new type of chiral reagent which has a hydrogen atom on the carbon atom between the two carbon atoms bearing the thiol and hydroxyl groups, as shown in the structure **B**. The sulfides **2B** utilizing a chiral reagent **B** should be easily converted with the aid of an amine base into the 1,3-mercapto alcohols **3** and

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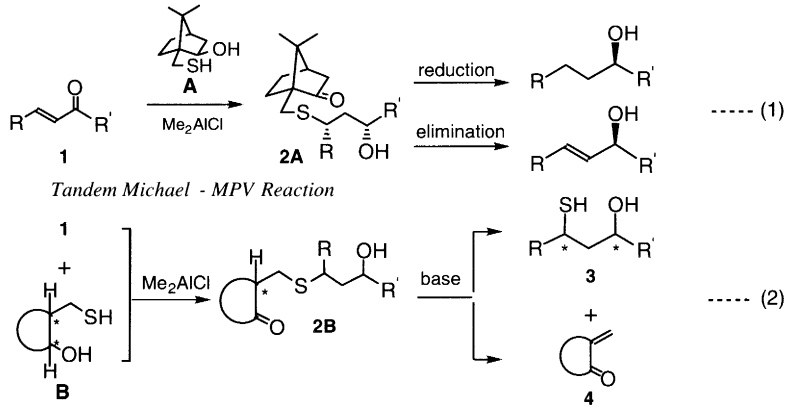
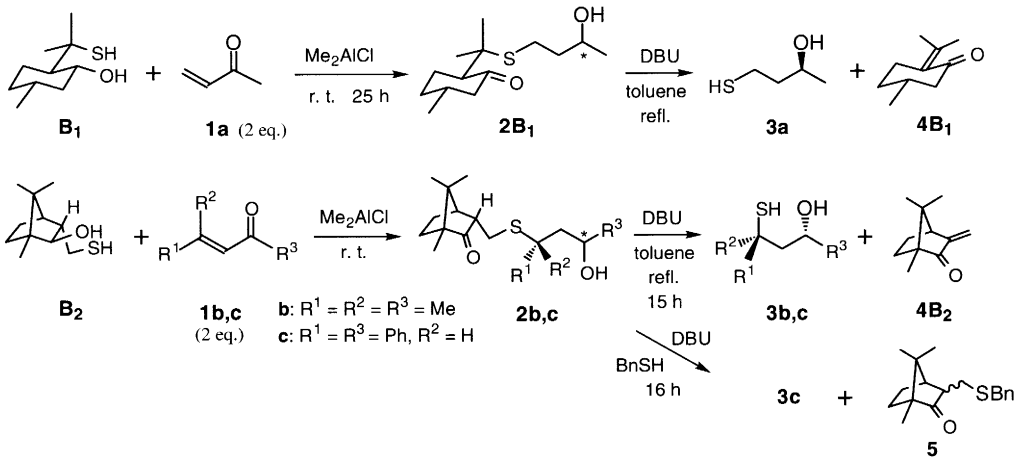


Scheme 1.

the α,β-unsaturated ketone **4**, which is the starting material used in the preparation of the reagent **B**. The product **3** should have a high de and ee if the sulfide **2B** is produced under dynamic kinetic resolution conditions.[5] The above transformation corresponds to a novel exchange reaction of bifunctional groups between the substrate and the reagent.

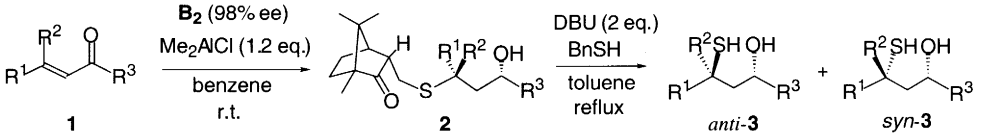
The exchange reaction using methyl vinyl ketone and a known chiral reagent $\mathbf{B_1}$[6] prepared from (−)-pulegone was carried out first (Scheme 2). The sulfide $\mathbf{2B_1}$ obtained by the tandem reaction was subjected to the elimination reaction using DBU in refluxing toluene for 24 h to give the desired 1,3-mercapto alcohol **3a** (90% ee) and (−)-pulegone ($\mathbf{4B_1}$) in 70 and 79% yields, respectively. Because of the low chemical yield (38%) of $\mathbf{2B_1}$, we further investigated the exchange reaction using a new chiral reagent $\mathbf{B_2}$[7] (98% ee), which was prepared from (+)-camphor. The tandem reactions of mesityl oxide **1b** and *trans*-chalcone **1c** with the reagent $\mathbf{B_2}$ afforded the sulfides **2b** and **2c** in 94 and 60% yields, respectively. These sulfides were next converted by base-catalyzed elimination to the 1,3-mercapto alcohols **3b** (74% yield, 82% ee) and **3c** (72% yield, 96% ee) together with the α,β-unsaturated ketone $\mathbf{4B_2}$ (≤76% yield). The mercapto alcohol **3c**, having two chiral carbons, showed an especially high optical purity and high *syn–anti* selectivity.[8] Reagent $\mathbf{B_2}$ was more effective compared to reagent $\mathbf{B_1}$, although the chemical yield was lower than that in the reaction using **A**, even given the fact that 2 equivalents of the substrate were used compared to 1 equivalent of the chiral reagent.



Scheme 2.

Although a novel asymmetric exchange reaction of bifunctional groups was demonstrated by the above reactions, nevertheless we attempted to improve the chemical yield in the base-catalyzed elimination. Since the elimination reaction is an equilibrium reaction, it is expected that the addition of a thiol would shift the equilibrium to the right. Actually, the thiol exchange reaction of **2c** proceeded smoothly using benzyl mercaptan in refluxing toluene to give the 1,3-mercapto alcohol **3c** and the sulfide **5** in 97 and 91% yields, respectively. Generalization of the asymmetric synthesis of 1,3-mercapto alcohols under the latter elimination conditions was tried. The results of the tandem reaction of α,β-unsaturated ketones using the chiral reagent $\mathbf{B_2}$ and the base-catalyzed elimination of the reaction product are summarized in Table 1.

Table 1
Asymmetric synthesis of 1,3-mercaptoalcohol from α,β-unsaturated ketone[9]

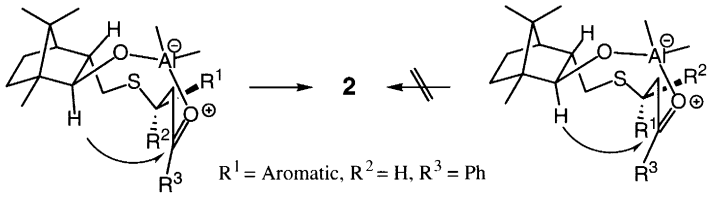


		Substrate **1**				**2**		**3**		
Entry		R^1	R^2	R^3	time(h)	yield (%)[a]	time(h)	yield (%)[a]	anti / syn	ee (%)[b]
1	**a**	H	H	CH_3	76	50	24	92[c]	—	98[d]
2	**b**	CH_3	CH_3	CH_3	21	94	14	94	—	82[d]
3	**c**	Ph	H	Ph	48	60	18	97	100/0	96[e]
4	**d**	*p*-ClPh	H	Ph	43	56	22	93	100/0	93[e]
5	**e**	*p*-MeOPh	H	Ph	48	56	18	99	100/0	94[e]
6	**f**	*p*-MePh	H	Ph	44	63	18	92	100/0	96[e]
7	**g**	Ph	H	CH_3	21	74	21	96	36/64	95[e]
8	**h**	Ph	H	*n*-C_8H_{17}	20	50	17	97	47/53	98[e]

a) Isolated yield b) Enantiomeric excesses of the alcoholic carbon; determined by HPLC analyses using Daicel CHIRALCEL OB, OD or CHIRALPAK AS.
c) The elimination was carried out after benzylation of the hydroxyl group of **2**.
d) Determined after desulfurization of the benzoate of **2** with Raney Ni (W2) in EtOH.
e) Determined after desulfurization of **2** with Raney Ni (W2)-$NaPH_2O_2$-acetate buffur-EtOH.[10]

Although the tandem reaction of the α,β-unsaturated ketone **1** to give the sulfide **2** proceeded in moderate yield, the base-catalyzed reaction of **2** with benzyl mercaptan resulted in high yields to give the 1,3-mercapto alcohols **3** with excellent ees,[11] except for **3b**. The relatively low ee of **3b** compared with **3a** might be attributed to the restriction in the transition state of the MPV reduction due to the bulkiness of the two methyl substituents on the β-carbon. In the reaction of the *trans*-chalcone derivatives (**1c**–**f**), two chiral carbons were created to give optically active 1,3-mercapto alcohols **3c**–**f** as a single diastereomer. The controlling factor for this exceedingly high diastereoselectivity[8] for *anti* to *syn* must be dynamic kinetic resolution. On the other hand, the tandem reactions of benzalacetone **1g** and its derivative **1h** having an alkyl group at R^3 afforded a diastereomeric mixture of the sulfides **2**, which were converted to the optically active alcohols **3g** and **3h** as *anti* and *syn* mixtures. This low diastereoselectivity suggests that the tandem reaction of **1g** and **1h** proceeded without control by dynamic kinetic resolution. It is presumed that the above difference between *trans*-chalcone and benzalacetone is due to the magnitude of a 1,3-diaxial like interaction of R^1 and R^2 toward R^3 in the transition states of MPV reduction, as shown in Scheme 3. The MPV reduction of the diastereomer having a large steric interaction between the two phenyl groups does not take place and the other diastereomer is subject to the MPV reduction because of

a small steric interaction, i.e. that the reaction undergoes control by dynamic kinetic resolution. There are many papers on asymmetric Michael addition of a thiol to an α,β-unsaturated system;[12] however, there is no precedent for a synthetic method corresponding to the asymmetric Michael addition of hydrogen sulfide like the one observed in the reaction of the *trans*-chalcones.



Scheme 3. Plausible transition states for sulfide **2**

In conclusion, we have developed the first method for an asymmetric synthesis of the 1,3-mercapto alcohols **3** from the α,β-unsaturated ketones **1** through the tandem Michael addition–MPV reduction followed by elimination. An important feature of this method is that the α,β-unsaturated ketone **4** or the sulfide **5** obtained together with **3** is able to be recycled for the preparation of the chiral reagent **B**.[7] This is characteristic of an asymmetric bifunctional group exchange reaction.

Acknowledgements

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7. Chiral reagent $\mathbf{B_2}$ was prepared as follows: (1) The *exo* methylenation of (+)-camphor with phenyllithium and paraformaldehyde gave $\mathbf{4B_2}$ in 89% yield; (2) the Michael addition of benzyl mercaptan of $\mathbf{4B_2}$ gave **5** in 82% yield; (3) debenzylation with sodium metal in liquid ammonia after sodium borohydride reduction afforded $\mathbf{B_2}$ in 17% yield, along with the other diastereomers.
8. The absolute configurations of the thiolic carbon in **3c**–**f** were determined by NOE experiments, because a 1,3-mercapto alcohol formed a chair conformation of a six-membered ring by intramolecular hydrogen bonding between the oxygen atom and the hydrogen atom of the thiol.
9. A typical procedure: (Entry 3 in Table 1) To a benzene solution (4 ml) of the mercapto alcohol $\mathbf{B_2}$ (37 mg, 0.18 mmol) was added dropwise dimethylaluminum chloride (1.0 M hexane solution, 0.21 ml, 0.22 mmol). After the mixture was stirred for 15 min at room temperature, a benzene solution (2 ml) of the α,β-unsaturated ketone **1c** (75 mg, 0.36 mmol) was added, and the resulting mixture was stirred for 48 h at the same temperature. The reaction mixture was quenched with a 1N-HCl solution, and the aqueous layer extracted with chloroform. After the usual work-up, the product **2c** (36 mg, 60%) was isolated by silica gel chromatography. A mixture of **2c** (28 mg, 0.07 mmol), DBU (0.047 ml, 0.34 mmol), and benzyl mercaptan (15 μl, 0.13 mmol) in toluene (8 ml) was refluxed for 18 h. The usual work-up and purification by silica gel chromatography gave the 1,3-mercapto alcohol **3c** (16 mg, 97% yield), along with **5** (18 mg, 91% yield).
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11. The absolute configuration of the alcoholic carbon in **3** was determined by comparison of the sign of the specific rotation with that in the literature (Holt, D. A. et al. *J. Am. Chem. Soc*. **1993**, *115*, 9925–9938, and Ref. 5).
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