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Use of Odorless Thiols: Formal Asymmetric Michael Addition of Hydrogen Sulfide to α-Substituted α,β-Unsaturated Carbonyl Compounds

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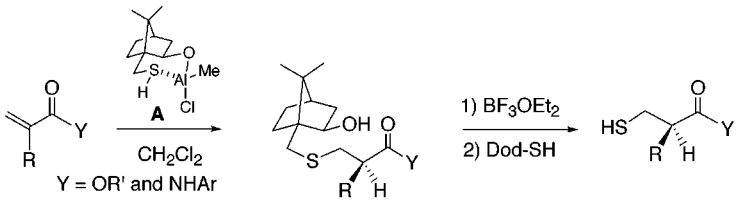
ABSTRACT



The Michael addition to α-substituted α,β-unsaturated esters and amides using complex A containing a chiral odorless thiol proceeded diastereoselectively. The Michael adducts were converted to β-mercapto esters and amides via a Wagner−Meerwein rearrangement with boron trifluoride etherate and a thiol exchange reaction using odorless 1-dodecanethiol. This conversion constitutes a formal asymmetric Michael addition of hydrogen sulfide to α,β-unsaturated carbonyl compounds using odorless thiols instead of the toxic hydrogen sulfide.

The Michael addition of a thiol to α,β-unsaturated carbonyl compounds is a fundamental reaction in organic chemistry.[1] From the standpoint of asymmetric synthesis, this reaction essentially consists of an *asymmetric 1,4-addition* and an *asymmetric protonation*. Excellent diastereoselective[2] and enantioselective[3] Michael additions of thiols to α,β-unsaturated carbonyl compounds have been extensively studied. However, the enantioselective protonation of enolates and enols has only recently been recognized as a promising method for the construction of a tertiary carbon center in asymmetric synthesis.[4] Therefore, much effort has been focused on the enantioselective protonation of the enolates derived from the parent carbonyl compounds.[4] Only a few studies have been reported on the reaction of the enolates generated by 1,4-addition of a thiolate anion to α,β-unsaturated carbonyl compounds.[3g,h,5] Thiophosphonates of 1,1′-binaphthol as chiral equivalents of hydrogen sulfide were used in radical additions to strained alkenes but with low diastereoselectivity.[6a] Recently, Palomo et al. reported an

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(4) (a) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566−2587. (b) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1−24. Also see the references therein.

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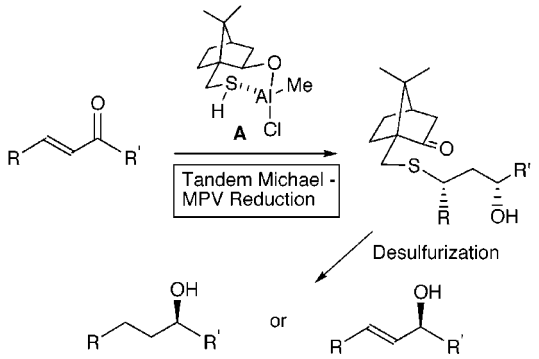
excellent asymmetric synthesis of β-mercapto carboxylic acid derivatives by intramolecular sulfur transfer reaction.[6b] However, there is no precedent for the highly asymmetric Michael addition of hydrogen sulfide to α-substituted α,β-unsaturated carbonyl compounds based on asymmetric protonation. We report herein the highly diastereoselective Michael addition of a chiral odorless thiol to α-substituted α,β-unsaturated carbonyl compounds and specific degradation of the Michael adduct using Lewis acid and an odorless thiol. This constitutes *a formal asymmetric Michael addition of hydrogen sulfide* under odorless conditions.

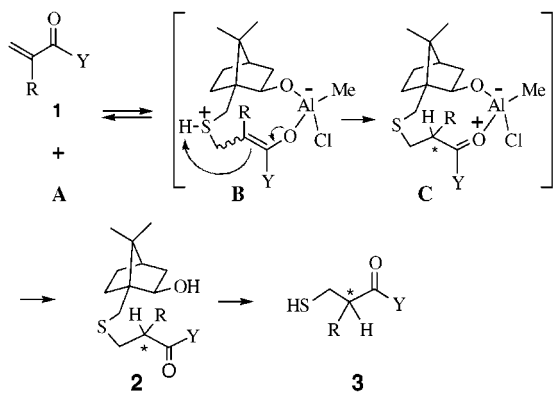
Recently, we developed *a tandem Michael addition−Meerwein−Ponndorf−Verley reduction*[7] for the asymmetric transformation of α,β-unsaturated ketones to secondary alcohols using the chiral aluminum complex **A** generated from Me_2AlCl and (−)-10-mercaptoisoborneol,[8,9] as shown in Scheme 1. On the basis of the above reaction, we planned

Scheme 1. A Novel Asymmetric Reduction of α,β-Unsaturated Ketones via Tandem Michael Addition−MPV Reduction



to examine the diastereoselective protonation of the 1,4-adduct **B** in the Michael addition of complex **A** to α-substituted α,β-unsaturated carbonyl compounds **1** (Scheme 2). Since the 1,4-adduct **B** forms the ten-membered ring

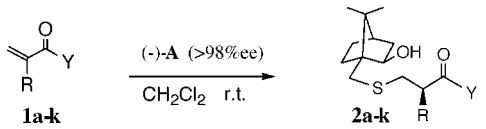
Scheme 2. A Strategy for the Synthesis of Optically Active β-Mercapto Carbonyl Compounds **3** via Asymmetric Michael Addition of **A** to **1**



aluminum enolate containing the chiral reagent, it is highly likely that the intramolecular protonation from the hydrosulfonium ion in **B** occurs diastereoselectively to give the sulfide **2** via the complex **C**. Therefore, removal of the chiral reagent moiety from the sulfide to the β-mercapto derivative **3** would serve as a novel method for an asymmetric Michael addition of hydrogen sulfide to α-substituted α,β-unsaturated carbonyl compounds.

In previous tandem reactions (Scheme 1), it is known that the Michael addition of a chiral thiol to the β-carbon of a β-substituted α,β-unsaturated ketone proceeds with no selectivity. Thus, an α-substituted α,β-unsaturated carbonyl compound without a substituent at the β-carbon would be suitable as the substrate for our strategy. Results of the asymmetric protonation in the Michael addition of a chiral thiol to α-substituted acrylic acid derivatives are summarized in Table 1. The reaction of benzyl methacrylate (**1a**) with

Table 1. Asymmetric Michael Addition of Chiral Thiol to α-Substituted Acrylic Acid Derivatives



entry	substrate R	substrate Y	Me_2AlCl (equiv)	time (h)	product	yield (%)	de (%)
1	**1a** Me	OBn	1.5	1	**2a**	90	96[a]
2	**1a**		1.5	12	**2a**	67	92[a]
3	**1b** Et	OBn	1.5	2	**2b**	82	90[b]
4	**1c** Bn	OBn	1.5	2	**2c**	90	93[c]
5	**1d** Me	OMe	1.5	2	**2d**	86	85[a]
6	**1e** Bn	OMe	1.5	2	**2e**	92	94[a]
7	**1f** Bn	OEt	1.5	2	**2d**	90	96[c]
8	**1g** Ph	OMe	1.5	1	**2g**	40	90[c]
9	**1g**		1.5	2	**2g**	89	47[c]
10	**1h** Me	NHPh	1.2	1	**2h**	100	75[c]
11	**1i** Me	NH(4-Br)Ph	1.2	1	**2i**	92	78[c]
12	**1j** Me	NH(4-Cl)Ph	1.2	1	**2j**	100	80[c]
13	**1k** Me	NH(4-F)Ph	1.2	2	**2k**	100	85[c]

[a] Determined by integrated intensity on NMR spectrum with shift reagent $Eu(fod)_3$. [b] Determined by ratio of isolated two diastereomers. [c] Determined by integrated intensity on NMR spectrum (without shift reagent).

the chiral aluminum complex **A** (1.5 equiv) generated from (−)-10-mercaptoisoborneol (98% ee) and Me_2AlCl was carried out in dichloromethane at room temperature. After

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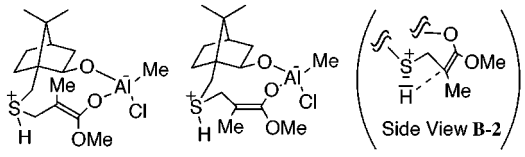
(9) (−)-10-Mercaptoisoborneol has almost no odor compared to other malodorous thiols. The syntheses and utility of other new odorless thiols and sulfides will be published elsewhere.

1 h, the reaction gave both the highest yield and diastereomeric excess of all the adducts[10] (entry 1). Prolonging the reaction time resulted in a lowering of both the yield and de of the product due to side reactions of debenzylation and enolization in the Michael adduct (entry 2). The α-substituents (Me, Et, Bn) on the benzyl esters did not affect the yields and de values of the products which were generally excellent (entries 1, 3, and 4). The diastereoselectivity in the reaction of methyl methacrylate (**1d**) (entry 5) was lower than that of benzyl methacrylate (**1a**) (entry 1), presumably because the substituents at the α-position and the alkoxy moiety in the ester group were less bulky. Methyl and ethyl α-benzyl methacrylates (**1e**,**f**) (entries 6 and 7) both gave good results. Therefore, bulkiness of either the α-substituent or the alkoxy moiety of the ester is required to give satisfactory results. The α-phenyl-substituted ester (**1g**) gave high diastereoselectivity in 1 h but afforded a low yield of the product (entry 8). When the reaction was prolonged, the yields increased but the de values decreased presumably due to the easy epimerization of the weakly acidic benzylic methine (entry 9).

Next, we examined the reactivity of the α-substituted α,*β*-unsaturated amides in the Michael addition. The reaction of the *N*-alkyl methacrylamides gave low diastereoselectivity (~60% de), while the reaction of anilide **1h** showed relatively high diastereoselectivity (75% de) (entry 10), indicating that the donating ability of the lone pair of electrons on the nitrogen atom might be related to the degree of diastereoselectivity in the adduct. Therefore, we attempted to improve the diastereoselectivity by using amides containing halogenated anilines **1i**−**k**. As a result of the weak donating ability of the nitrogen lone pair, the Michael addition reaction of these halogenated anilides showed a higher de than the reaction of **1h** (entries 11−13). On the other hand, the reaction of methacrylamides containing a secondary amine (NR_2) did not occur under the same conditions. In the case of the enolate of the above amides, significant allylic strain is generated on the nitrogen substituents and may retard the 1,4-addition of the thiol.

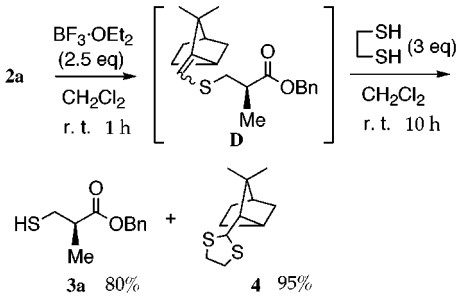
The configuration of the resulting esters and amides was determined to be *R* by chemical conversion to known compounds.[11] We initially thought that the protonation of the *E*-enolate intermediate **B-1** could occur from the *outside* of the 10-membered ring[7] as shown in Scheme 2. However, MOPAC PM3 calculations of the sulfonium enolates **B** revealed that the *Z*-enolate (**B-2**) is more stable than the *E*-enolate (**B-1**), as shown in Scheme 3. Therefore, we deduced that the protonation would occur from the *inside* of the 10-membered ring, as illustrated in Scheme 3.

Scheme 3. PM3 Calculations of the Intermediates **B**



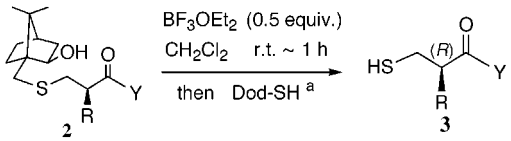
We next tried to convert the Michael adducts **2** into the *β*-mercapto esters and amides **3**. The chiral thiol reagent was specifically designed to contain an isoborneol skeleton, making it easy to remove under relatively mild conditions. Thus, the Michael adduct **2a** was subjected to boron trifluoride etherate followed by the addition of ethanedithiol to give the *β*-mercapto ester **3a**, along with the dithioacetal **4** (Scheme 4). To avoid the stench of ethanedithiol, the

Scheme 4. Synthesis of *β*-Mercapto Ester **3a** from Michael Adduct **2a**



odorless 1-dodecanethiol[9] was used in the thiol exchange of **D**. The results of the major diastereomers of the esters **2a**, **2c**, and **2f**, which were obtained by chromatographic separation, are listed in entries 1−3 of Table 2. Removal of the

Table 2. Removal of Isoborneol Moiety from Michael Adduct **2**



entry	substrate[b]	R	Y	Dod-SH (equiv)	time (h)	product	yield (%)[c]
1	**2a**	Me	OBn	30	2	**3a**	86[d]
2	**2c**	Bn	OBn	30	2	**3c**	89[d]
3	**2f**	Bn	OEt	30	2	**3f**	80[d]
4	**2h**	Me	NHPh	10	3	**3h**	74[d,f]
5	**2i**	Me	NH(4-Br)Ph	10	2.5	**3i**	77[e,f]
6	**2j**	Me	NH(4-Cl)Ph	10	3.5	**3j**	91[d,f]

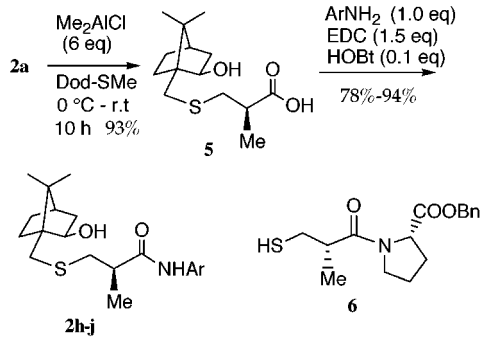
[a] 1-Dodecanethiol. [b] Substrates **2a**, **2c**, and **2f** are the major diastereomers in the reaction of Table 1, obtained by chromatographic separation (Kusano silica gel packed column Si-10 or 40). Substrates **2h**, **2i**, and **2j** were obtained by amidation of acid **5** in Scheme 5. [c] Ee of all products was detected as >98%. [d] Daicel Chiralcel OJ. [e] Shiseido Ceramospher Chiral RU-1. [f] Ee. was determined by its acetate.

chiral reagent moiety proceeded smoothly at room temperature in good yields. The configuration at the α-carbon was completely retained under the acidic conditions.

Since we could not isolate the major diastereomers of the amides **2** by chromatographic separation, we tried synthesiz-

ing β-mercapto amides utilizing the major diastereomer of the ester **2a**. Namely, the optically pure amides **2h**−**j** were synthesized from the benzyl ester **2a** (100% de) by debenzylation using Me_2AlCl in odorless 1-dodecyl methyl sulfide,[9] followed by amidation of the carboxylic acid **5** with the aniline derivatives (Scheme 5). The β-mercapto amides

Scheme 5. An Alternative Synthetic Method for Optically Pure Amides **2h**−**j**



3h−**j** with higher optical purity (>98% ee) were prepared from **2h**−**j** by degradation of the chiral reagent moiety (entries 4−6 in Table 2). This method was applied to the asymmetric synthesis of the captopril derivative **6**[12] (overall yield 74% from **2a** in three steps).

In conclusion, we have found a highly diastereoselective Michael addition of a thiol to α-substituted α,β-unsaturated esters. Subsequent cleavage of the chiral auxiliary from the Michael adduct via a Wagner−Meerwein rearrangement and a thiol exchange of the vinyl thioether intermediates furnished a formal asymmetric Michael addition of hydrogen sulfide to α-substituted α,β-unsaturated carbonyl compounds. The above synthetic method using odorless thiols instead of toxic malodorous hydrogen sulfide should be of great interest to green chemistry.

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Supporting Information Available: Typical experimental procedure and spectroscopic data for **2a**, **2h**, **3a**, **3h**, and **6** and an ORTEP drawing of the intermediate for the synthesis of the captopril derivative **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The diastereomeric excess of protonation depended on the dryness of the (−)-10-mercaptoisoborneol which was used after drying overnight over phosphorous pentoxide under high vacuum.

(11) For example, the *R*-configuration at the α-position of the ester **2f** was determined by comparison of the sign of the specific rotation of (*R*)-ethyl 2-methyl-3-phenylpropionate obtained by reductive desulfurization of **2f** with Raney nickel with that in the literature: (a) Levene, P. A.; Marker, R. E. *J. Biol. Chem.* **1935**, *110*, 299−309. (b) Cohen, S. G.; Milovanovic, A. *J. Am. Chem. Soc.* **1968**, *90*, 3495−3502. (c) Jacques, J.; Gros, C.; Bourcier, S. *Stereochemistry: Fundamentals and Methods*; Georg Thieme Publishers: Stuttgart, 1977; Vol. 4, p 84, entry l. An X-ray crystallographic analysis of (2*S*)-*N*-{3-[(1*R*,2*S*,4*S*)-2-hydroxybornane-10-sulfenyl]-2-methylpropanoyl}-L-proline benzyl ester, an intermediate for the synthesis of the captopril derivative **6**, showed the *S*-configuration at the α-position of the amide carbonyl, in which the enantiomer (+)-**A** was used (see Supporting Information).

(12) Captopril is used in clinics as an orally active antihypertensive agent having a unique inhibitory action on the angiotensin-converting enzyme. Its derivative **6** was prepared from *ent*-**5** which was obtained in this Michael addition of (+)-**A** derived from (−)-10-camphorsulfonic acid.