Asymmetric 1,7-Hydride Shift: The Highly Asymmetric Reduction of α,*β*-Unsaturated Ketones to Secondary Alcohols *via* a Novel Tandem Michael Addition−Meerwein−Ponndorf−Verley Reduction

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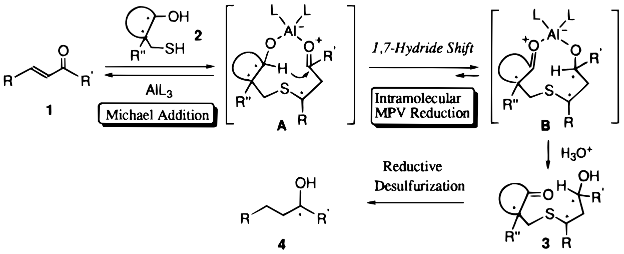
Meerwein−Ponndorf−Verley (MPV) reduction is a classical but important method for the reduction of carbonyl compounds.[1] Although asymmetric versions of the intermolecular MPV reduction of ketones have been widely studied through the use of optically active alcohols as chiral sources, high enantioselectivity has not yet been realized by this methodology.[2] On the other hand, it has been shown that intramolecular MPV reduction (1,5-hydride shift) proceeds with high stereoselectivity.[3] This latter method has a serious disadvantage in that the substrate is limited to special carbonyl compounds bearing a chiral alcohol. Recently, Evans and co-workers invented a catalytic highly enantioselective MPV reduction using a chiral samarium catalyst.[4] This reaction is also limited in that only aryl methyl ketones can be used as substrates to give products in excellent enantiomeric excess. Therefore, a new type of MPV reduction which does not have a substrate limitation is needed. We report here the asymmetric reduction of α,*β*-unsaturated ketones to saturated secondary alcohols via *a novel tandem Michael addition−MPV reduction* and subsequent reductive desulfurization.

We envisioned that a chiral alcohol with a thiol moiety could associate with an α,*β*-unsaturated ketone by Michael addition of the thiol moiety with the assistance of Lewis acid so that subsequent intramolecular MPV reduction could give an optically active saturated alcohol after subsequent reductive desulfurization, as shown in Scheme 1. Since the intramolecular MPV reduction of the Michael adduct **A** is an equilibrium reaction between complexes **A** and **B**, the chiral mercapto alcohol used must give complex **B** in a high yield. After considering several optically active mercapto alcohols, we chose (+)- or (−)-10-mercaptoisoborneol (**2**)[5] as a suitable chiral reagent for this asymmetric reduction.

Reaction of *trans*-chalcone (**1a**) with (−)-10-mercaptoisoborneol (**2**)[6] (1.2 equiv) and dimethylaluminum chloride (1.2 equiv) as a Lewis acid at *room temperature* (rt)[7] for 24 h in dichloromethane under a nitrogen atmosphere gave the desired product **3a** in 85% yield, and subsequent reductive desulfurization of the product using the Raney nickel−sodium hypophosphite combination system[8] gave (*R*)-1,3-diphenylpropanol (**4a**) with 96% ee in 96% yield (Table 1, entry 1). The results obtained with this novel reduction of various α,*β*-unsaturated ketones **1a**−**g** are summarized in Table 1. Dichloromethane was the solvent of choice for giving products with the highest enantiomeric excess. The yield of the products **3** was highest in benzene, but the ee values of the products were slightly lower (<8%) than those in dichloromethane. Dimethylaluminum chloride was the best Lewis acid among the other organoaluminums.[9] Reductions of either aromatic or aliphatic α,*β*-unsaturated ketones gave a fairly high yield, and the ee values of the resulting secondary alcohols were also excellent. The addition−reduction products **3** with an aromatic substituent at position R^1 or R^2 were subjected to reductive desulfurization to give the corresponding products **4** using the Raney nickel−sodium hypophosphite combination system, which did not produce racemization of the optically active secondary alcohol. For aliphatic α,*β*-unsaturated ketones, this desulfurization with the combination system did not proceed. Therefore, the usual Raney nickel (W2) which produces racemization of the secondary alcohol,[8] was used as a desulfurization agent after benzoylation of the hydroxyl group of **3** to prevent racemization.

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



The mechanistic aspects are as follows:

(1) For the structure of the complex of (−)-**2** and Me$_2$AlCl, the two possible structures **C** and **D** can be considered. Structure **C** can be excluded because the evolution of methane gas[10] was observed with the treatment of *s*-BuOH with dimethylaluminum chloride in dichloromethane at room temperature but not with the treatment of EtSH with dimethylaluminum chloride. Furthermore, methane gas was evolved when 1 equiv of *s*-BuOH was added to the aluminum complex generated from (−)-**2** and dimethylaluminum chloride. On the basis of the results of the above experiments, the structure of the chiral aluminum Lewis acid should be **D**. The thiol proton in structure **D** might play an important role in promoting the subsequent MPV reduction. Thus, the oxycarbenium ion **A**, which is an intermediate in the MPV reduction, could be produced by

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(6) (*S*)-(+)-Camphorsulfonic acid monohydrate and (*R*)-(−)-camphorsulfonic acid were readily available. The optical purity (98% ee) of (−)-10-mercaptoisoborneol (**2**) prepared by the Eliel procedure[5] from (*S*)-(+)-camphorsulfonic acid monohydrate purchased from Wako Pure Chemical Industries, Ltd., was determined by chiral HPLC analysis on a Daicel Chiralcel OD (hexane/*i*-PrOH = 99:1) as an *S*-benzyl ether of **2**.

(7) The reaction temperature (ca. 20 °C) was essential for this tandem Michael addition−MPV reduction. The chiral mercapto alcohol **2** was decomposed by Me$_2$AlCl at a higher temperature (ca. 35 °C), and the reaction proceeded very slowly at 0 °C and did not occur at −78 °C.

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(9) Dialkylaluminum chlorides (Me$_2$AlCl, Et$_2$AlCl, Pr$_2$AlCl) were effective for this reaction, but stronger Lewis acids such as ethylaluminum dichloride and aluminum trichloride resulted in decomposition of the chiral mercapto alcohol **2**.

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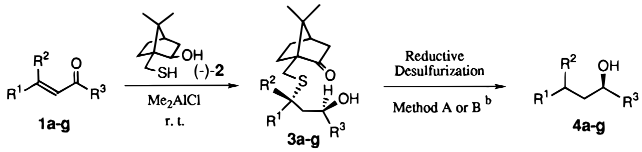
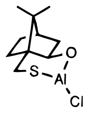
Table 1. Tandem Michael−MPV Reaction[a] and Subsequent Reductive Desulfurization



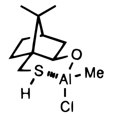
	tandem Michael-MPV reaction							reductive desulfurization					
entry	cmpd	R1	R2	R3	solvent	time (h)	yield (%)[c] of **3**	method	time (h)	yield (%)[c] of **4**	ee[d] of **4** (%)	[α]D (CHCl3)	config.
1	**1a**	Ph	H	Ph	CH_2Cl_2	24	85	A	0.33	96	96	+16.2[e]	*R*[f]
2	**1a**	Ph	H	Ph	benzene	24	94	A	0.33	99	95		*R*
3	**1b**	Ph	H	Me	CH_2Cl_2	12	83	A	0.67	89	97	+18.8	*S*[g]
4	**1b**	Ph	H	Me	benzene	12	94	A	0.67	88	89		*S*
5	**1c**	*p*-MeOPh	H	Ph	CH_2Cl_2	33	75	A	0.33	97	96[h]	+17.1	*R*[i]
6	**1c**	*p*-MeOPh	H	Ph	benzene	38	88	A	0.33	85	92[h]		*R*
7	**1d**	*p*-tolyl	H	Ph	CH_2Cl_2	16	73	A	0.33	90	98	+22.6	*R*[i]
8	**1e**	Me	Me	Me	CH_2Cl_2	16	90	B	1.5	75[j]	98[k]	+37.1	*S*[l]
9	**1e**	Me	Me	Me	benzene	15	96	B	4	73[j]	98[k]		*S*[l]
10	**1f**	H	H	Me	CH_2Cl_2	12	82	B	2[m]	73[j]	98[k]	+39.7	*S*[l]
11	**1g**	H	H	Pent	CH_2Cl_2	15	82	B	31	77[j]	97[n]	−8.0	*R*[o]

[a] See text for the reaction conditions. [b] Method A, Raney nickel (W2)−$NaPH_2O_2$−acetate buffer (pH 5.2)−EtOH, rt; Method B, (1) BzCl, pyridine, (2) Raney nickel (W2)−EtOH, rt. [c] Isolated yield. [d] HPLC analysis using a Daicel Chiralcel OD column unless otherwise noted. [e] In MeOH. [f] Lit. $[\alpha]^{27}_D = +14.8$ (0.5, MeOH) (Holt, D. A. et al. *J. Am. Chem. Soc.* **1993**, *115*, 9925−9938). [g] Determined by X-ray crystallographic analysis of the corresponding sulfone of **3b**. [h] Daicel Chiralpak AS. [i] Determined by the CD spectrum comparison with **4a**. [j] The yield of benzoate of **4**. [k] Daicel Chiralcel OB. [l] Determined by modified the Mosher method (Ohtani, I. et al. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096). [m] Reflux 2 h. [n] Daicel Chiralcel OF. [o] Lit. $[\alpha]^{20}_D = -6.2$ (2, $CHCl_3$) (Foder, G. et al. *Can. J. Chem.* **1969**, *47*, 4393−4397).

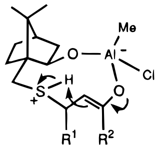
protonation of the aluminum enolate **E** formed by the Michael addition of the thiol group.



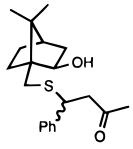
C



D



E



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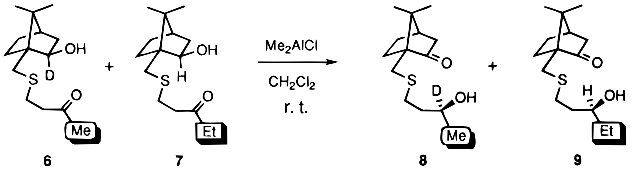
(2) To study equilibration in the tandem Michael−MPV reaction, a mixture of the two diastereomers (1:1) of the Michael adduct **5**, which were prepared from (−)-**2** and benzalacetone (**1b**) with Me_2AlCl at 0 °C, was subjected to MPV reduction with dimethylaluminum chloride (1.2 equiv) in dichloromethane at room temperature for 13 h. This reaction gave one diastereomer **3b**[11] in 86% yield, which has an *R*-configuration[12] at the chiral carbon attached to a sulfur atom, the recovered adduct **5** (8%, 1:1 diastereomers), benzalacetone (**1b**) (5%), and (−)-**2** (5%). Since these latter two compounds are the retro-Michael products of adduct **5**, the Michael addition in this tandem reaction is confirmed to be an equilibrium reaction. Therefore, the production of a single isomer (**3b**) is attributable to dynamic kinetic resolution[13] via the reversible Michael addition in this intramolecular MPV reduction.

(3) This MVP reaction was found to be a highly diastereoselective intramolecular 1,7-hydride shift[14] via a crossover experiment using Michael adducts **6** and **7**, as shown in Scheme 2. Thus, a mixture of equimolar amounts of the deuterium-labeled adduct **6** (>98% D) of methyl vinyl ketone and the unlabeled adduct **7** of ethyl vinyl ketone was treated with dimethylaluminum chloride (2.0 equiv) in dichloromethane at room temperature for 22 h to give the MPV products **8** (92%, >98% D) and **9** (91%, no deuterium incorporation).

Scheme 2. A Crossover Experiment Using Deuterated Michael Adduct



In conclusion, we have observed both *an asymmetric 1,7-hydride shift* and *dynamic kinetic resolution via the reversible Michael addition* for the first time. High diastereoselectivity was achieved at the two newly generated chiral carbons bearing the alcohol and the sulfide. The face selectivity of the oxycarbenium ion on the 10-membered-ring chelation structure **A** reached 98−100% in dichloromethane, based on the optical purity (98% ee) of the chiral alcohol used. Highly enantioselective (96−98% ee) reduction of α,*β*-unsaturated ketones to saturated secondary alcohols or their benzoates was achieved by subsequent reductive desulfurization. The range of substrates suitable for this reaction is fairly wide because of its usefulness for the reduction of both aromatic and aliphatic α,*β*-unsaturated ketones. This new method should be useful for the development of a new asymmetric reduction of bifunctional ketones. Further studies are underway in our laboratory.

Acknowledgment. We thank Nippon Aluminum Alkyls, Ltd., for the kind gift of several alkylaluminum reagents.

Supporting Information Available: Experimental procedure, spectroscopic data for all compounds, chiral HPLC analyses conditions for **4a**−**g**, the Mosher ester determination, and X-ray ORTEP drawing for **3b** derivative (12 pages). See any current masthead page for ordering and Internet access instructions.

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(11) ^1H NMR (300 MHz) of **3b** showed that it was a single diastereomer. The product **3b** gave **4b** (96% ee) by the reductive desulfurization with the Raney nickel−sodium hypophosphite combination system.[8]

(12) The *R* configuration at the carbon bearing a sulfur atom in **3b** was determined by X-ray crystallographic analysis of its sulfone derivative.

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(14) For an example of [1,7]-sigmatropic rearrangement of conjugated trienes, see: (a) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1988**, *110*, 8223−8228. (b) *Ibid.* **1987**, *109*, 8051−8056.