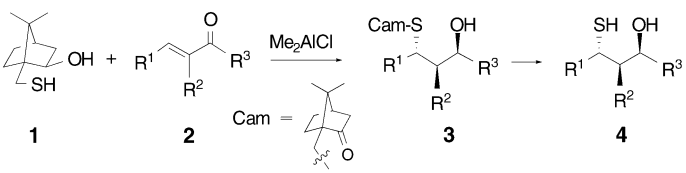
Tandem Asymmetric Reactions

One-Step Stereocontrol of Three Contiguous Stereogenic Centers in Acyclic Systems: The Tuning Effect of an Additive in a Tandem Asymmetric Michael Addition and Meerwein–Ponndorf–Verley Reduction**

*Kiyoharu Nishide, Minoru Ozeki, Hideaki Kunishige, Yukihiro Shigeta, Pranab K. Patra, Yuri Hagimoto, and Manabu Node**

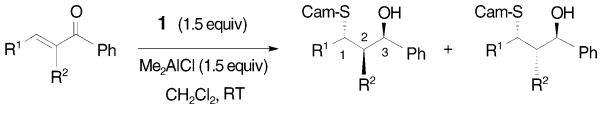
A significant amount of chemistry that involves chiral 1,3-oxathianes derived from optically active 1,3-hydroxythiols has been developed for asymmetric synthesis.[1] However, optically active 1,3-hydroxythiols are only available from natural sources,[1] for example, as 10-sulfanylisoborneol (**1**)[2] from camphor, and little attention has been focused on their synthesis.[3] The stereoselective construction of contiguous stereogenic centers in acyclic compounds is generally difficult compared to that in cyclic systems. For example, the asymmetric synthesis of cyclic systems with three contiguous stereogenic carbon centers by tandem conjugate addition to bis(α,β-unsaturated ester)s[4] and the tandem Michael–aldol cyclization of acyclic ω-oxo-α,β-unsaturated esters and ketones has been developed sufficiently.[5] Despite the sophisticated methodology of double aldol reactions[6] and of the catalytic hydrogenation of enamino ketones,[7] one-step stereocontrol of three contiguous stereogenic centers in acyclic compounds still remains a challenge for asymmetric synthesis, and the one-step asymmetric conversion of acyclic α,β-unsaturated ketones into acyclic compounds with three contiguous stereogenic carbon centers was previously unknown. We report herein the highly stereoselective construction of three contiguous stereogenic centers in a tandem Michael addition and Meerwein–Ponndorf–Verley (MPV) reduction of the α,β-unsaturated ketones **2** with (−)-**1** to give the alcohols **3**, thus allowing the asymmetric synthesis of 1,3-hydroxythiols **4** (Scheme 1).

We proposed that the tandem reaction[8] described above for the α,β-disubstituted α,β-unsaturated ketones **2** would involve asymmetric protonation[9] at the α-position in the Michael addition step and that the products **3** could be converted into the optically active 1,3-hydroxythiols **4** through a Wagner–Meerwein rearrangement followed by a thiol-exchange reaction.[9] The tandem reactions of the ketones **2** (R^1 = Ar, R^2 = alkyl, R^3 = Ph) are summarized in Table 1.



Scheme 1. Proposed tandem Michael addition–MPV reduction.

Table 1: Tandem Michael–MPV reaction of the α,β-unsaturated ketones **2**.



Entry	**2**	R^1	R^2	*t* [days][a]	Yield [%][b]	**3A**/**3B**[c]
1	**a**	Ph (*E*)	Me	3	82	92:8
2	**a**	Ph (*Z*)	Me	3	79	93:7
3	**a**	Ph (*E*/*Z* 4.7:1)	Me	2	92	94:6
4	**b**	4-MePh	Me	2	86	93:7
5	**c**	4-(MeO)Ph	Me	2	67	94:6
6	**d**	4-ClPh	Me	2	87	94:6
7	**e**	Ph	Et	2	60	97:3
8	**f**	4-MePh	Et	2	68	93:7
9	**g**	4-MeOPh	Et	2	67	94:6
10	**h**	4-ClPh	Et	2	60	96:4
11	**i**	Ph	Pr	3	44	100:0
12	**j**	Ph	Bn	3	37	100:0

[a] Reaction time. [b] Yield of isolated product. [c] Ratio determined by ^{1}H NMR spectroscopy.

The reactions of both the *E*- and the *Z*-α-methylated chalcones **2a** with (−)-**1** and Me_2AlCl at room temperature for 3 days gave mixtures of **3A** and **3B** with high diastereoselectivity (≈93:7; Table 1, entries 1 and 2). These selectivities were almost identical to that observed in the reaction of an *E*/*Z* mixture of **2a** (Table 1, entry 3). When a sample of **2a** with homogeneous stereochemistry was used and the reaction was quenched after just 1 or 2 hours, an *E*/*Z* mixture of **2a** was recovered. This isomerization might result from reversible conjugate addition of the thiol **1**.[8] The substrates **2** in entries 4–12 of Table 1 were used as an *E*/*Z* mixture (major isomer: *E*). The electronic effects of the R^1 group on the selectivity were not significant (Table 1, entries 4–6 and 8–10). With increasing bulkiness of the R^2 group the diastereomeric ratios of the products **3** increased to 100:0 and the yields decreased (Table 1, entries 3, 7, 11, and 12).

In each case the isomers **3A** and **3B** were the only products of the tandem reaction among the eight possible isomers, Table 1. It was suggested that this tandem reaction was controlled by dynamic kinetic resolution[8] involving the reversible Michael addition of the hydroxythiol **1** (Scheme 2). That is, the rate-determining step in the tandem reaction is the intramolecular MPV reduction of the Michael adducts **A** and

[*] Prof. Dr. M. Node, Prof. Dr. K. Nishide, M. Ozeki, H. Kunishige, Y. Shigeta, Dr. P. K. Patra, Dr. Y. Hagimoto
Department of Pharmaceutical Manufacturing Chemistry
Kyoto Pharmaceutical University
Misasagi, Yamashina, Kyoto 607-8414 (Japan)
Fax: (+81) 75-595-4775
E-mail: node@mb.kyoto-phu.ac.jp

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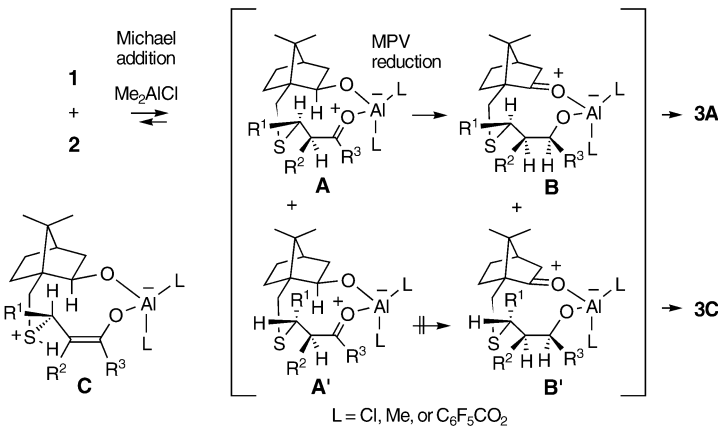
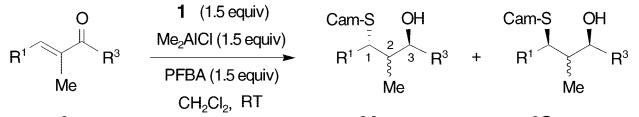


Scheme 2. A plausible mechanism.

A′. The steric congestion caused by the substituent R^1 on the chelated 10-membered ring in the adduct **A**′ results in the higher transition-state energy of **A**′ relative to that of the adduct **A** in which the R^1 group is in a more favorable orientation. Therefore, the stereoselectivity observed at C1 and C3 is based on the degree of kinetic control in the MPV reduction step, and the high stereoselectivity observed at C2 may be attributed to intramolecular protonation[9] in the aluminum enolate **C**, which bears a hydrosulfonium cation formed by the conjugate addition of the thiol **1** to the enone **2**.

Next, we examined the tandem reaction of other kinds of α,β-unsaturated ketones **2** (R^1 = Ar, R^2 = Me, R^3 = alkyl; Table 2). When the same reaction conditions were used as those for the reactions in Table 1, the products **3A** were formed with low to medium diastereomeric ratios (Table 2, entries 1, 3, and 5). To improve the diastereoselectivity, the effect of additives in the tandem reaction of **2m** was investigated. The addition of 1 equivalent of pyridine to the reaction medium improved the stereoselectivity **3m-A/3m-B** to 94:6, but the yield decreased to 6%. On the other hand, the addition[10] of trifluoroacetic acid (TFA; 1 equiv) led to an increase in both the yield (40%) and the stereoselectivity (**3m-A/3m-B** 94:6). However, in this case two additional diastereomers, **3m-C** (1.8%) and **3m-D** (2.2%), with the opposite configuration at C1, were also produced in the reaction. The relationship between the pK_a value of various acids used as additives and the yield of **3m** is plotted in Figure 1. Pentafluorobenzoic acid (PFBA; pK_a ≅2) was the most effective. From the results shown in Figure 2, the optimum amount of PFBA was determined to be 1.5 equivalents. The tandem reactions of (*E*)-**2k–q** in the presence of PFBA were investigated (Table 2, entries 2, 4, and 6–10). The reactions of the ketones **2l–q**, which have bulkier R^3 groups, exhibited higher diastereoselectivities in terms of the ratio **3A/3B** (d.r. ≥96:4) than the reaction of **2k**, which has an ethyl substituent.

Table 2: Effect of an additive in the tandem Michael–MPV reaction of the α,β-unsaturated ketones **2**.



2 **3A**: 2β-Me **3B**: 2α-Me **3C**: 2β-Me **3D**: 2α-Me

Entry	**2**	R^1	R^3	*t* [days][a]	Yield[b] (ratio)[c] **3A/3B**	**3C/3D**
1[d]	**k**	Ph	Et	2.5	78 (58:42)	–
2	**k**			2	71 (73:27)	14 (100:0)
3[d]	**l**	Ph	*i*Pr	3	46 (74:26)	–
4	**l**			2	55 (98:2)	10 (53:47)
5[d]	**m**	Ph	*c*-C_6H_{11}	3	31 (80:20)	–
6	**m**			3	50 (98:2)	5 (58:42)
7	**n**	Ph	*c*-C_7H_{13}	2	55 (100:0)	7 (66:34)
8	**o**	4-(MeO)Ph	*i*Pr	2	52 (97:3)[e]	6 (47:53)[e]
9	**p**	4-ClPh	*i*Pr	2	51 (96:4)	8 (58:42)
10	**q**	4-MePh	*i*Pr	2	55 (99:1)	8 (54:46)

[a] Reaction time. [b] Yield of the mixture of isolated products. [c] Determined by ^{1}H NMR spectroscopy. [d] PFBA was not added. [e] Each diastereomer was isolated by HPLC.

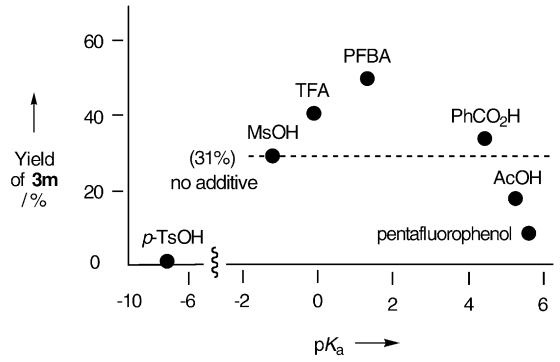


Figure 1. The relationship between pK_a of the additive and yield.

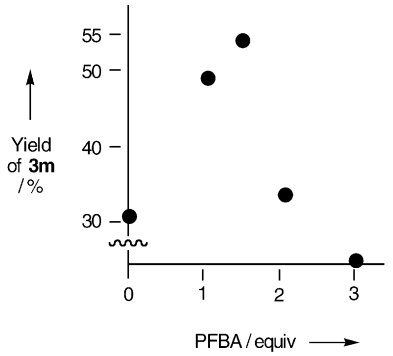
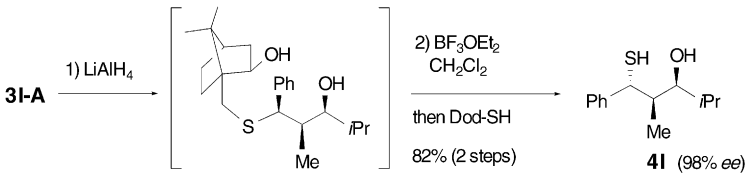


Figure 2. The relationship between yield and the amount of PFBA used.

We assume that PFBA replaces the remaining methyl group on the aluminum ate complex **A** (Scheme 2), which causes an increase in the reaction rate of the MPV reduction. Kinetic control becomes less strict at room temperature through this ligand exchange, such that the additional isomers **3C** and **3D** are produced, whereas the selectivity for **3A** over **3B** might be increased through a tighter MPV transition state favored by the resulting more reactive Al complex.

Transformation[9] of the major product **3l-A** into the 1,3-hydroxythiols **4l** could be carried out readily in good yield.

Thus, the Wagner–Meerwein rearrangement of the boron trifluoride etherate of the isoborneol derivative obtained by reduction of **3l-A**, followed by a thiol-exchange reaction in the presence of odorless 1-dodecanethiol (Dod-SH),[11] gave **4l** with 98% *ee* (Scheme 3).



Scheme 3. Synthesis of an optically active 1,3-hydroxythiol.

Although the exact role of PFBA is unclear at this stage, the discovery of PFBA as an additive with an optimum pK_a value will be helpful for the fine tuning of reactions that involve an aluminum ate complex. In conclusion, we have reported the asymmetric transformation of the acyclic α,β-unsaturated ketones **2** into the 1,3-hydroxythiols **4** through the stereocontrol of three contiguous stereogenic centers.

Experimental Section

Typical procedure: Dimethylaluminum chloride (solution in hexane, 1.05 M, 0.51 mL, 0.54 mmol) was added dropwise to a solution of (−)-10-sulfanylisoborneol ((−)-**1**; 100 mg, 0.54 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred for 0.5 h, then a solution of **2** (0.36 mmol) in dichloromethane (5 mL) was added dropwise (followed by a solution of an additive (0.54 mmol) in dichloromethane (7 mL), if used), and the mixture was stirred at room temperature under a nitrogen atmosphere for the time indicated. The reaction was then quenched with a saturated solution of ammonium chloride, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed (if an additive was used: with a saturated solution of sodium hydrogen carbonate, then with brine; in the absence of an additive: with brine), and were dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification of the residue by silica-gel column chromatography (hexane/ethyl acetate 10:1–20:1) gave **3** as a diastereomeric mixture in the yield indicated. The diastereomers of **3** were separated by recycling HPLC.

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