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Asymmetric Baeyer-Villiger Reaction: Diastereodifferentiating Peracid Oxidation of Chiral Acetal in the Presence of Lewis Acid

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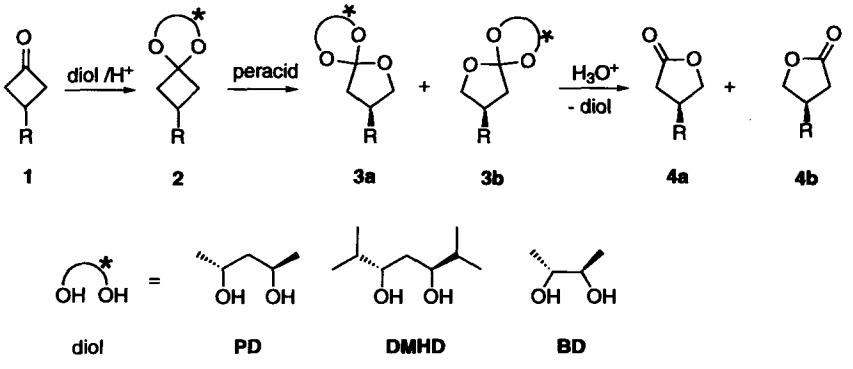
Abstract: Oxidation of **2** with *m*-chloroperbenzoic acid in the presence of $SnCl_4$ at -78 °C followed by hydrolysis afforded optically active **4** in a quantitative yield. The enantiomeric excess (ee) of **4** largely depended on the reaction solvent, the chiral diol part, the Lewis acid and its amount. The best ee was 89% when **2** (R = Ph) having 2,4-pentanediol was oxidized at -100 °C.

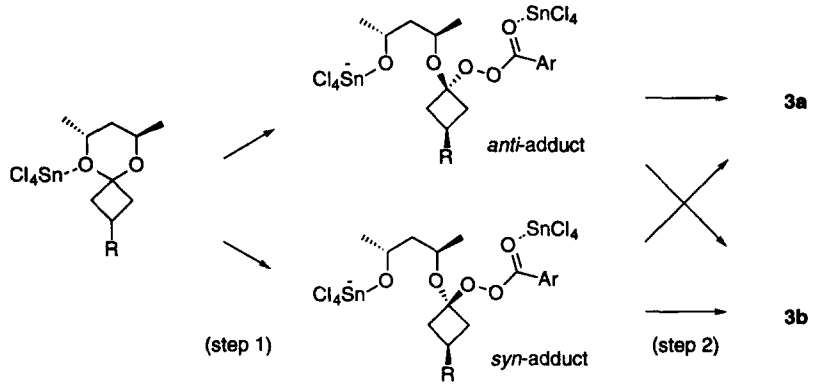
Asymmetric Baeyer-Villiger oxidation to give optically active lactones (or esters) from prochiral ketones has been well documented using enzyme catalysis,[1] but limited examples using chemical synthetic means have been reported.[2] In synthetic chemistry, Baeyer-Villiger reaction is most frequently carried out using peracid oxidation due to its easy operation and high yield of the product.[3] The reaction we designed is a diastereotopos differentiating peracid oxidation of the acetal **2** of prochiral ketone **1** with an optically active C_2 symmetric diol. Hydrolysis of the expected product **3** affords 3-substituted-γ-butyrolactone **4** which constitutes a useful class of chiral synthons. In this study, we found that a Lewis acid effectively promoted the oxidation of **2** with *m*-chloroperbenzoic acid (MCPBA) even at -100 °C. The yield of **4** from **2** was quantitative and the enantiomeric excess (ee) of **4** reached 89%.



Scheme 1

The reaction pathway from **2** to **3** by peracid oxidation is assumed to undergo two steps analogously to the reaction of a ketone (Criegee mechanism)[4] as represented in Scheme 2. To obtain **3** in high diastereomeric excess, both stereochemical courses of the addition affording *syn*- and *anti*-adducts (step 1) and the migration of one of the α-carbons in the adducts (step 2) should be controlled. The reaction of acetal and peracid is known to be sluggish and the produced orthoester is further reacted with peracid to give the orthocarbonate.[5]

Many types of nucleophiles could add to acetals by Lewis acid catalysis; therefore, we expected that a Lewis acid could also promote the present reaction by activating step 1. As expected, although the reaction of **2** with excess MCPBA in dichloromethane under reflux did not proceed at all, the reaction in the presence of strong Lewis acids such as $SnCl_4$ occurred smoothly even at -78 °C and afforded **4** in a quantitative yield after work-up with 2N hydrochloric acid.[6]



Scheme 2

Table 1. Enantiomeric excess of the lactones **4**.[a]

entry	R	eq. of MCPBA	eq. of $SnCl_4$	ee (%) of **4**[b]
1	Ph	2	0.1	22
2	Ph	2	0.5	34
3	Ph	2	1	63
4	Ph	2	2	75
5	Ph	2	5	79
6	Ph	2	5	89 (at -100 °C)
7	Ph	1	1	66
8	Ph	1	2	79
9	Ph	5	2	21
10	Ph	2	5	5 (in hexane)
11	Ph	2	2	48 (in toluene)
12	Ph	2	2	13 (with $TiCl_4$)
13	Ph	2	5	0 (with BF_3)
14	Ph	2	5	37 (with $SnBr_4$)
15	Ph	2	5	66 (**2** of DMHD)
16	Ph	2	5	69 (**2** of BD)
17	4-Me-Ph	2	12	76
18	4-Cl-Ph	2	12	77
19	4-MeO-Ph	2	12	75
20	2-Naphthyl	2	12	76
21	butyl	2	5	52
22	isopropyl	2	5	58
23	isobutyl	2	5	59

a. The reaction was carried out using **2** (diol = PD) and $SnCl_4$ in CH_2Cl_2 at -78 °C except as cited in parentheses.

b. **4a** was the major enantiomer in all cases.[8]

The enantiomeric excesses (ee) of the obtained **4** under the various conditions are summarized in Table 1.[7] When **2** having (2*R*,4*R*)-2,4-pentanediol (PD) as the diol and phenyl as the R-group was oxidized with 2 equivalents of MCPBA (82% pure) in the presence of less than a stoichiometric amount of $SnCl_4$, (3*R*)-(-)-**4a**[8] was obtained, but the ee stayed below 40% (entries 1 and 2). With an increasing amount of $SnCl_4$, the ee was improved; 63% ee with 1 equivalent, 75% ee with 2 equivalents and 79% ee with 5 equivalents (entries 3–5). The ee of entry 5 was improved to 89% when the reaction was carried out at -100 °C (entry 6). From the results of the additional reactions with 1 equivalent (entries 7 and 8) and 5 equivalents (entry 9) of MCPBA, it was found that the ratio of $SnCl_4$/MCPBA is responsible for the product ee and should be >1 to obtain a high ee. Because the existence of $SnCl_4$ is expected to affect, presumably reduce, the nucleophilicity of MCPBA by coordination to its carboxyl group,[9] the ee dependency on the reagent ratio could be attributed to the stereocontrol factor of step 1. Under this postulation, the *anti*/*syn* ratio of the adduct should be low with the MCPBA freed from coordination with $SnCl_4$; whereas, the *anti*/*syn* ratio of the addition should be highly controlled with the coordinated MCPBA, the weak nucleophilicity of which allows the addition to be more like the SN1 mechanism than the SN2 mechanism.[10] The mode of nucleophilic attack to **2** in the presence of $SnCl_4$ was simulated using the hydride addition with the well documented reagents.[11] When Et_3SiH was employed, the ratio of *anti*- and *syn*-additions was 70/30, while the selective *anti*-addition in a ratio of 90/10 resulted with $Me_2S{\bullet}BH_3$ having weaker nucleophilicity. Rigorous stereocontrol of the migration (step 2) by the aid of the chiralities on the PD unit afforded the product of high ee so far as step 1 was stereo-controlled.

The product ee largely depended on the reaction solvent, the Lewis acid and the chiral diol. As shown in entries 10 and 11, the use of hexane or toluene as the reaction solvent decreased the ee. A change in the Lewis acid also resulted in a drastic change in the ee. The ee's with $TiCl_4$ and $BF_3{\bullet}OEt_2$ were close to zero and with $SnBr_4$ the ee was decreased to 37% (entries 12–14). From the acetal **2** prepared with (3*S*,5*S*)-2,6-dimethyl-3,5-heptanediol (DMHD)[9], a bulky analog of PD, a 66% ee of **4a** resulted (entry 15). The five-membered ring acetal of **2** having (2*R*,3*R*)-2,3-butanediol (BD) was also converted to **4a** of lower ee than found with PD (69% ee, entry 16).

Under the reaction conditions similar to those of entry 5, the substrates **2** having different R-groups were converted to **4a** excess products[8] in a quantitative yield (entries 17–23). The ee's of **4** having an aromatic substituent were not affected by electron density or bulkiness of the aromatic group and were in a range of 75–77% . On the other hand, for **2** having different sizes of alkyl groups, the ee's were relatively low in a range of 52–59%.[13]

In this report, we presented the first example of a Lewis acid-promoted peracid Baeyer-Villiger reaction of acetal, and, by using 2,4-pentanediol as a chiral auxiliary, optically active 3-substituted-γ-butyrolactones were obtained in good enantiomeric excess.

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6. When the reaction was worked-up under basic conditions, a diastereomeric mixture of **3** with a small amount of **4** was obtained.
7. General procedure: A mixture of **1** (50 mg) and *m*-chloroperbenzoic acid (82% purity) in 10 ml of dichloromethane was cooled to -78 °C. To this, Lewis acid was added at once. After stirring for 1.5 hours at the same temperature, the mixture was warmed up to room temperature. The mixture was poured into 2N HCl solution and washed with aqueous solution of Na_2CO_3 and then Na_2SO_3. Short silica gel column afforded chemically pure **4** in 95–98% yield. The enantiomeric excess of **4** was determined by chiral capillary GLC (CP-Chirasil-β-DEX CB) or chiral HPLC analyses (CHIRALCEL OD or CHIRALPAK AD) under baseline separation.
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13. Hydride reduction of buty substituted **2** with $Me_2S{\bullet}BH_3$ and $SnCl_4$ resulted in the addition ratio of *anti/syn* = 87/13, which was lower than that from phenyl substituted **2**.

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