CATALYTIC ASYMMETRIZATION OF *CIS*-2-CYCLOPENTENE-1,4-DIOL. HIGHLY EFFICIENT AND PRACTICAL SYNTHESIS OF (*R*)-4-BENZOYLOXY-2-CYCLOPENTEN-1-ONE

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

Abstract - Highly efficient, direct, and practical synthesis of (*R*)-4-benzoyloxy-2-cyclopenten-1-one, a chiral building block for various prostaglandins, with excellent ee was performed by the catalytic asymmetric acylation of *cis*-2-cyclopentene-1,4-diol, followed by oxidation with PDC.

The preparation of optically active 4-acyloxy-2-cyclopenten-1-ol has been an important objective of synthetic organic chemistry. This compound derives much of its usefulness from the fact that it is an immediate chiral precursor to 4-acyloxy-2-cyclopenten-1-one which is a very attractive chiral building block for the synthesis of prostaglandins[1] and other cyclopentanoid natural products.[2] Although much effort has been devoted to the preparation of optically active 4-acyloxy-2-cyclopenten-1-ol, the majority of such methods involved the use of enzymes such as lipase and esterase.[3] In 1985, Duhamel reported that an optically active monobenzoate of *cis*-2-cyclopentene-1,4-diol[4] was obtained by nonenzymatic asymmetric acylation with benzoyl chloride in the presence of a tertiary chiral amine.[5] The use of a stoichiometric amount of the tertiary amine gave the corresponding monobenzoate in up to 47% ee.

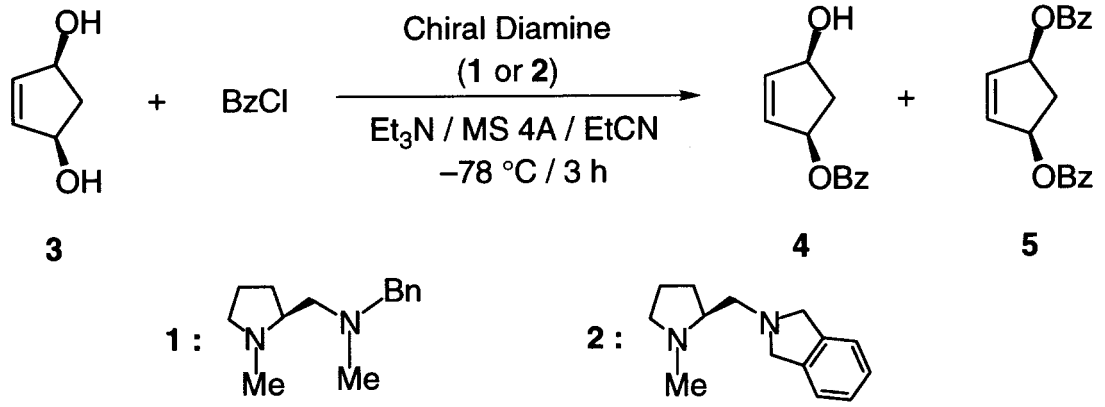
On the other hand, previous reports from our laboratory have documented the utility of chiral diamines (**1**) and (**2**), which are readily prepared from (*S*)-proline, as efficient catalysts capable of catalyzing an asymmetric acylation of racemic secondary alcohols[6] and *meso*-1,2-diols[7] with high enantioselectivities. We have more recently developed a remarkably efficient method for the catalytic asymmetric acylation of *meso*-1,2-diols[8] with achiral benzoyl chloride in the presence of a chiral diamine.[9] The use of only 0.5 mol% of chiral diamine combined with 1 equivalent of triethylamine gave the corresponding monobenzoate with excellent ee in good yield.

In this communication we wish to report a remarkably efficient procedure for the asymmetrization of *cis*-2-cyclopentene-1,4-diol (**3**) to afford (1*S*,4*R*)-4-benzoyloxy-2-cyclopenten-1-ol (**4**), which is the precursor of (*R*)-4-benzoyloxy-2-cyclopenten-1-one (**6**), with excellent ee.

The treatment of *cis*-2-cyclopentene-1,4-diol (**3**) with benzoyl chloride under the influence of the chiral

diamine combined with triethylamine gave rise to formation of chiral monobenzoate (**4**) and dibenzoate (**5**) (Table 1). The absolute configuration of 4-benzoyloxy-2-cyclopenten-1-ol (**4**) was assigned to be (1*S*,4*R*)- by the optical rotation.[1c] The optical purity was determined by HPLC analysis using a chiral column. We can not use methylene chloride as a solvent due to the very low solubility of the substrate. EtCN was an effective solvent in this asymmetric acylation. The chiral diamine (*S*)-1-methyl-2-[(1,3-dihydroisoindol-2-yl)methyl] pyrrolidine (**2**) exhibited higher ee than (*S*)-1-methyl-2-[(benzylmethylamino)methyl]pyrrolidine (**1**) (Table 1, Runs 1 and 2). When the amount of the chiral diamine (**2**) was decreased to only 0.5 mol% to the *meso*-diol in EtCN, the acylation proceeded slowly to give the monobenzoate in 17% yield (Run 3).

Table 1. Asymmetric Acylation of *cis*-2-Cyclopentene-1,4-diol [a)]



Run	Chiral Diamine (mol%)		Et_3N (equiv)	4 Yield [b)] / %	4 ee [c)] / %	5 Yield [b)] / %
1	**1**	(5)	1.0	38	74	20
2	**2**	(5)	1.0	30	93	25
3	**2**	(0.5)	1.0	17	93	20
4	**2**	(0.5)	1.5	40	94	43
5 [d)]	**2**	(0.5)	1.5	38	61	14
6 [e)]	**2**	(0.5)	1.5	32	96	48
7 [f)]	**2**	(0.5)	1.5	3	62	trace

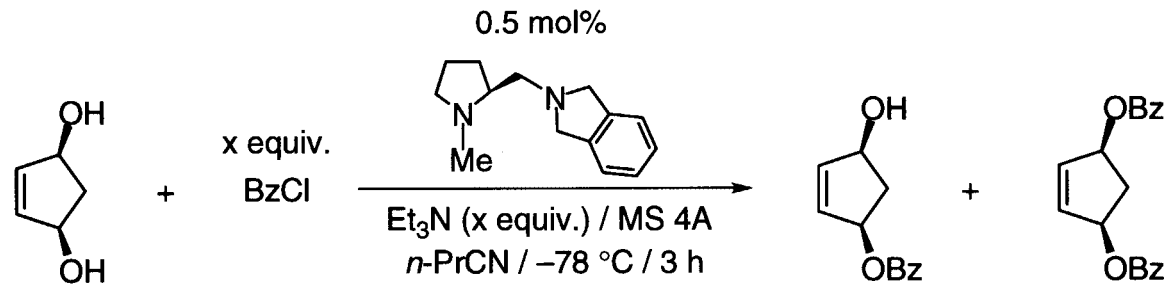
a) Unless otherwise specified, the reaction was performed using diol (0.3 mmol), BzCl (0.45 mmol), and Et_3N (0.45 mmol). b) Isolated yield of purified product. c) Determined by chiral HPLC analysis. d) BzBr was used in place of BzCl. e) The reaction was carried out in *n*-PrCN. f) The reaction was carried out in THF.

However, the use of 1.5 equivalents of triethylamine afforded the monobenzoate in 40% yield with 94% ee (Run 4). The use of butyronitrile as a solvent improved slightly the optical yield of monobenzoate (Run 6).

A significant amount of diester (**5**) was also obtained in these asymmetrizations. However, we focused our major attention on attaining higher enantioselectivity of the mono-acylation product. In fact, conversion of the undesired dibenzoate to the starting material, *cis*-2-cyclopentene-1,4-diol (**3**), was easily carried out by the methanolysis with sodium methoxide.[10]

Next, we tested the effect of the amount of benzoyl chloride and triethylamine, and we found that 1.7 equivalents of benzoyl chloride and triethylamine to the *meso*-diol (**3**) gave the best result (Table 2, Run 3)[11] This asymmetric acylation of **3** is notable not only for its excellent enantioselectivity and the synthetic utility of its product but also for its remarkable efficiency as a nonenzymatic catalytic process.

Table 2. The Effect of Equivalent of BzCl and Et_3N



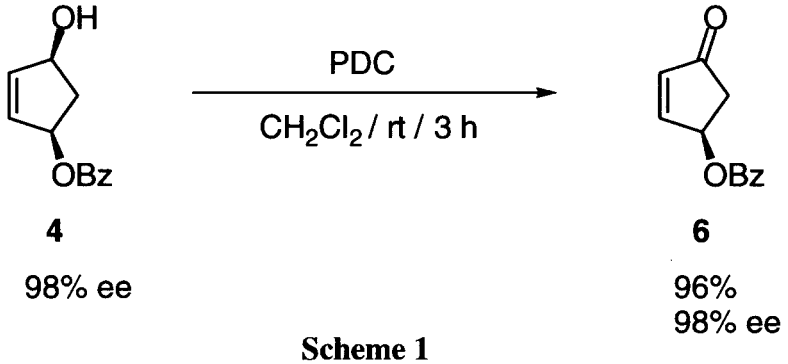
3 (0.3 mmol) **4** **5**

Run	x / equiv.	4 Yield [a] / %	4 ee [b] / %	5 Yield [a] / %
1	1.5	32	96	48
2	1.6	45	97	46
3	1.7	37	98	56
4 [c]	1.7	32	97	43
5	2.0	32	98	61

a) Isolated yield of purified product. b) Determined by chiral HPLC analysis. c) The reaction was performed in 5 mmol scale.

The *cis*-benzoyloxycyclopentenol (**4**) was readily converted to the corresponding cyclopentenone (**6**) by the treatment of pyridinium dichromate (PDC)[12] as shown in Scheme 1.[13] In the case of *cis*-5,5-dimethyl-2-cyclopentene-1,4-diol, the corresponding monobenzoate was obtained in good yield with perfect enantioselection (87%, >99.5% ee). Oxidation of monobenzoate with PDC afforded enantiomerically pure (*S*)-4-benzoyloxy-5,5-dimethyl-2-cyclopenten-1-one as shown in Scheme 2.

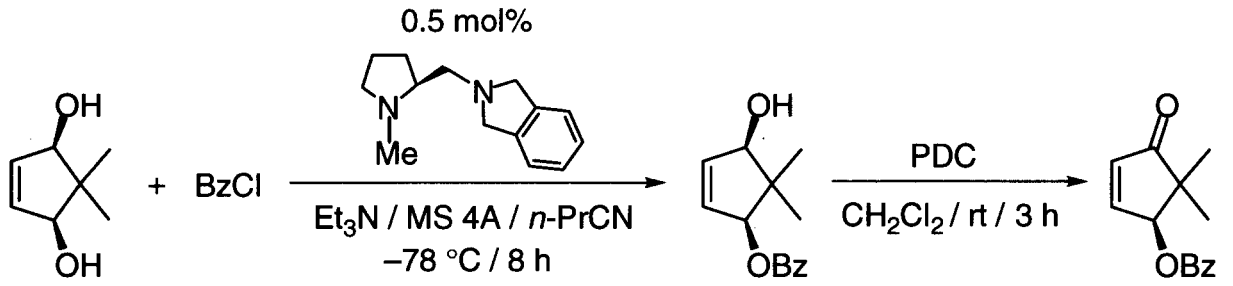
In conclusion, we have succeeded in developing a highly efficient and practical method for the synthesis of (*R*)-4-benzoyloxy-2-cyclopenten-1-one.[14,15] Further applications using this catalytic asymmetrization of *meso*-diols are under investigation in our laboratory.



4 **6**

98% ee 96%
98% ee

Scheme 1



87% 95%
>99.5% ee >99.5% ee

Scheme 2

ACKNOWLEDGEMENTS

The present work was financially supported by the Inamori Foundation, the Itoh Science Foundation, the Tokuyama Science Foundation, the Sasakawa Foundation (to T. S.) and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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4. According to the IUPAC nomenclature, *cis*-4-cyclopentene-1,3-diol.
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11. A typical experiment proceeded as follows: To molecular sieves 4A (670 mg) was added a solution of (*S*)-1-methyl-2-[(1,3-dihydroisoindol-2-yl)methyl]pyrrolidine (5.4 mg, 0.025 mmol) in *n*-PrCN (3 mL), a solution of triethylamine (858 mg, 8.48 mmol) in *n*-PrCN (30 mL), a solution of *cis*-2-cyclopentene-1,4-diol (500 mg, 4.99 mmol) in *n*-PrCN (30 mL) and a solution of benzoyl chloride (1.20 g, 8.54 mmol) in *n*-PrCN (3 mL) sequentially at –78 ℃ under an argon atmosphere. The reaction was quenched after 3 h at –78 ℃ by the addition of a phosphate buffer (pH 7). The organic materials were extracted with ether and the combined extracts were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (AcOEt : hexane = 1 : 15) to yield 326 mg (32%) of (1*S*,4*R*)-*cis*-4-benzoyloxy-2-cyclopenten-1-ol ($[\alpha]_D$ +126° (*c* 1.7, $CHCl_3$)).
12. H. Miyaoka, S. Sagawa, H. Nagaoka, and Y. Yamada, *Tetrahedron: Asymmetry*, 1995, **6**, 587.
13. To molecular sieves 4A (83.6 mg) and PDC (85.2 mg, 0.227 mmol) was added a solution of (1*S*,4*R*)-*cis*-4-benzoyloxy-2-cyclopenten-1-ol (22.6 mg, 0.111 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 3 h at rt. The reaction mixture was diluted with ether and filtered through a plug of silica gel and the filtrate was concentrated *in vacuo*. The residue was purified by thin-layer chromatography on silica gel (Et_2O : hexane = 2 : 1) to yield 21.6 mg (96%) of (*R*)-4-benzoyloxy-2-cyclopenten-1-one without loss of ee.
14. (*R*)- and (*S*)-4-Hydroxy-2-cyclopenten-1-ones were prepared by asymmetric deprotonation of *meso*-epoxide as a key reaction. M. Asami, *Tetrahedron Lett.*, 1985, **26**, 5803; M. Asami, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1402.
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Received, 6th August, 1999