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Catalytic Asymmetric Desymmetrization of Cyclic *meso*-1,3- and 1,4-Diols by a Phosphinite Derivative of Quinidine

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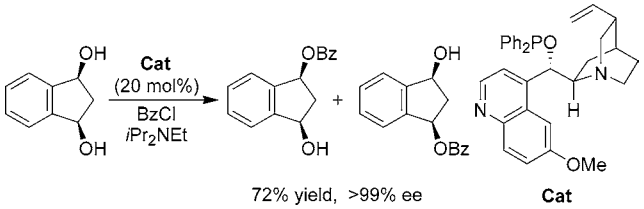
ABSTRACT



Asymmetric monobenzoylation reactions of cyclic *meso*-1,3- and 1,4-diols were catalyzed by a phosphinite derivative of quinidine to afford the corresponding monobenzoylated diol with good yield and enantioselectivity.

Enantioselective monoacylation of *meso*-diols is a powerful methodology for the preparation of useful chiral building blocks. In recent years, several successful examples of nonenzymatic catalysts for the desymmetrization of *meso*-diols by asymmetric acylation have been reported. In particular, some effective nonenzymatic catalysts for *meso*-1,2-diols have been realized.[1] However, in comparison to the promising results of the *meso*-1,2-diols, only a few examples of the nonenzymatic asymmetric acylation catalysts for 1,3- or 1,4-diols have been reported.[2] In particular, the asymmetric desymmetrization of cyclic *meso*-1,3- or 1,4-diols was mainly carried out using an enzymatic procedure,[3] and effective nonenzymatic catalysts for them have been recently reported. In 2000, Oriyama et al. reported the impressive catalytic asymmetric monobenzoylation of *cis*-4-cyclopentene-1,3-diol by chiral diamine organocatalysts.[2b] The reaction was catalyzed by only 0.5 mol % of the chiral diamines to afford the monobenzoylated product with excellent enantioselectivity (98% ee), but the yield of the product decreased because of the formation of the dibenzoylated product.

We have recently designed a bifunctional organocatalyst[4,5] bearing both Lewis basic phosphinite and Brϕnsted basic tertiary amine functional groups for asymmetric acylation

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(3) For some examples, see: (a) Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287−7290. (b) Ghorpade, S. R.; Kharul, R. K.; Joshi, R. R.; Kalkote, U. R.; Ravindranathan, T. *Tetrahedron: Asymmetry* **1999**, *10*, 891−899. (c) Hilpert, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681−694. (d) Betts, R. L.; Murphy, S. T.; Johnson, C. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2853−2860.

(4) For some recent examples of bifunctional organocatalysts, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673. (b) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 4369−4372. (c) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625−627. (d) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807−811. (e) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680−3681. (f) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603−606. (g) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898−1900.

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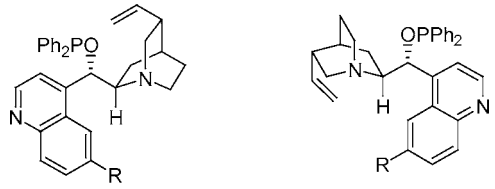
of *meso*-diols and demonstrated that a phosphinite derivative of cinchonine **1a** (Figure 1) catalyzed the reaction of *meso*-



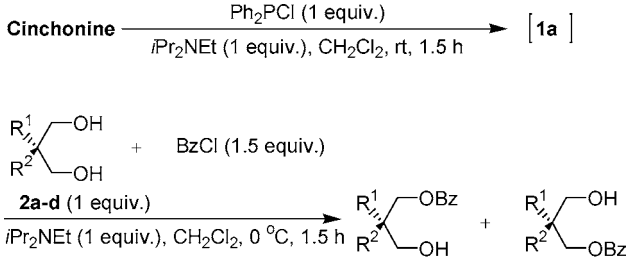
1a: R = H
1b: R = OMe
1c: R = H
1d: R = OMe

Figure 1. Phosphinite derivatives of cinchona alkaloids.

1,2-diols with benzoyl chloride to give the monobenzoylated products with high enantioselectivities and yields.[6] On the basis of these results, we examined the catalytic asymmetric acylation of 1,3-diols using the phosphinite derivatives of cinchona alkaloids as catalysts. In this communication, we report the effective enantioselective acylation of cyclic *meso*-1,3- and 1,4-diols catalyzed by the phosphinite derivative of quinidine **1b**.

We initially examined the reaction of 2-methyl-1,3-propanediol **2a** with benzoyl chloride in the presence of an equimolar amount of the phosphinite derivative of cinchonine **1a**, which was prepared in situ from chlorodiphenylphosphane and cinchonine in order to test the effectiveness of the catalyst for the asymmetric acylation of 1,3-diols. Although the corresponding monoacylated product **3a** was obtained in a moderate yield, no enantioselectivity was observed (Scheme 1).

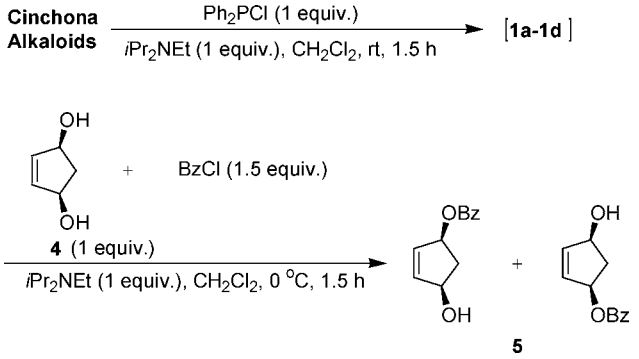
Scheme 1. Monobenzoylation Reaction of 2-Substituted 1,3-Propanediols in the Presence of **1a**



3a: R^1 = Me, R^2 = H: 56%, 3% ee
3b: R^1 = Ph, R^2 = H: 57%, 0% ee
3c: R^1 = Bn, R^2 = H: 48%, 0% ee
3d: R^1 = Ph, R^2 = Me: 62%, 2% ee

Reactions employing other acyclic 1,3-diols **2b**−**d** under the same reaction conditions were attempted, but racemic monoacylated products were isolated in all cases. However, when the cyclic *meso*-1,3-diol, *cis*-4-cyclopentene-1,3-diol **4**, was reacted with benzoyl chloride in the presence of an equimolar amount of **1a**, the corresponding 4-benzoyloxy-2-cyclopenten-1-ol **5** was obtained with 61% ee in 83% yield (Table 1, entry 1). The major product was found to be a

Table 1. Asymmetric Desymmetrization of *cis*-4-Cyclopentene-1,3-diol in the Presence of Phosphinite Derivatives of Cinchona Alkaloids



entry	phosphinite	yield (%)[a]	ee (%)[b]
1	**1a**	83	61
2	**1b**	76	80
3	**1c**	60	45
4	**1d**	57	57

[a] Yield of isolated product. [b] Determined by chiral HPLC analysis.

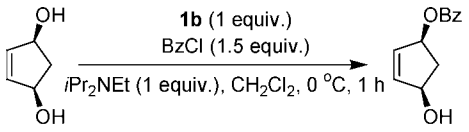
(1*R*,4*S*)-isomer by comparison with the reported optical rotation of **5**.[2b] Moreover, the reactions using other cinchona alkaloids were conducted under the same reaction conditions. As a result, when the phosphinite derivative of quinidine **1b** was employed, the corresponding monobenzoylated product was produced with the best enantioselectivity (80% ee) in 76% yield (Table 1, entry 2). The absolute configuration of the major product was the same as that for entry 1 in Table 1. On the other hand, the monobenzoylated products obtained from the derivatives of cinchonidine and quinine (**1c** and **1d**, respectively) had the opposite absolute configuration.

The phosphinite derivatives were assumed to be air-sensitive; however, the corresponding derivative of quinidine could be isolated through column chromatography with high purity (containing only 2% of phosphinate) using a neutral silica gel. In the ^{31}P NMR, the signal assigned to the trivalent phosphinite was observed at 114 ppm as almost a single peak. The reaction employing 1 equiv of the isolated phosphinite **1b** was conducted to improve the selectivity and the yield of **5**. Although **5** was obtained with a slightly increased selectivity and yield, a drastic improvement was not realized (Scheme 2). Moreover, reaction under various reaction conditions in the presence of 1 equiv of **1b** was conducted in order to optimize the asymmetric acylation reaction of **4**.

(5) For a review on bifunctional organometallic catalysts, see: (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989−1999. (b) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256.

(6) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 3383−3385.

Scheme 2. Asymmetric Desymmetrization of *cis*-4-Cyclopentene-1,3-diol Using **1b**

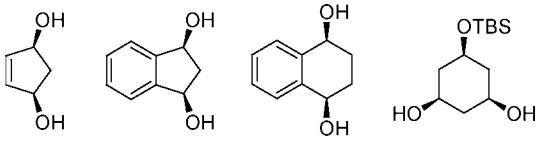


4 **5**: 84%, 83% ee

The use of other solvents ($CHCl_3$ or EtCN), a coexisting tertiary amine (triethylamine), and acylation reagents (*o*- or *p*-chlorobenzoyl chloride) did not improve the selectivity and yield of **5**. Additionally, for the reaction at lower temperature, the yield of the product decreased, and the selectivity was not constant due to the insolubility of the substrate in cold dichloromethane.

Finally, we investigated the reaction employing a catalytic amount of the isolated phosphinite **1b**. To our delight, the reaction of **4** with 1.5 equiv of benzoyl chloride proceeded smoothly in the presence of 30 mol % **1b** to afford **5** with 81% ee in 82% yield (Table 2, entry 1). The same reaction using 20 mol % **1b** resulted in a low selectivity and yield of the product. It was clarified that the dibenzoate was also formed in 11−15% yield. The optimized catalytic asymmetric benzoylation was used for the other cyclic *meso*-1,3- and 1,4-diols. When *cis*-1,3-indandiol **6** was used as a substrate, the corresponding monobenzoylated product was produced with excellent selectivity. In particular, the reaction of **6** in the presence of 20 mol % **1b** for a prolonged reaction time supplied the product with more than 99% ee in 72% yield (Table 2, entry 5). The improvement of the enantioselectivity was ascribed to the further kinetic resolution of the monobenzoylated product. However, the reaction of a racemic monobenzoylated compound **9** with 0.5 equiv of benzoyl chloride in the presence of 20 mol % **1b** gave the corresponding dibenzoylated product **10** in low yield, and the racemic monobenzoylated product **9** was recovered in 89% yield (Scheme 3). Therefore, it was suggested that the high level of the enantioselectivity (Table 2, entries 3−5) was achieved primarily in the initial step of the monobenzoylation. The functionalized cyclic *meso*-1,4-diol **7** and cyclic *meso*-1,4-diol **8** were also converted to the corresponding monobenzoates with good enantioselectivity.

Table 2. Catalytic Asymmetric Desymmetrization of Cyclic *meso*-1,3- and 1,4-Diols Using **1b**[a]

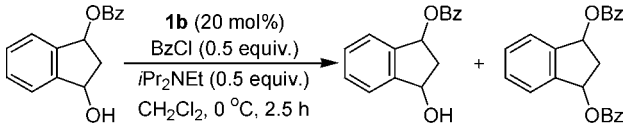


4 **6** **7** **8**

				monobenzoate		dibenzoate
entry	diol	catalyst (mol %)	time (h)	yield (%)[b]	ee (%)[c]	yield (%)[b]
1	**4**	30	4	82	81	15
2	**4**	20	2	40	71	11
3	**6**	30	2.5	71	97	7
4	**6**	20	2.5	63	96	8
5	**6**	20	7	72	>99	16
6	**6**	15	2.5	21	95	trace
7	**7**	30	4	55	82	nd[d]
8	**8**	30	6	73	70	nd[d]

[a] Reaction of *meso*-diols (1.00 mmol) with benzoyl chloride (1.50 mmol) in CH_2Cl_2 (5 mL) at 0 °C in the presence of a catalytic amount of **1b** and diisopropylethylamine (1.00 mmol). [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Not detected on TLC.

Scheme 3. Reaction of Racemic Monobenzoate **9** with Benzoyl Chloride in the Presence of **1b**



9: racemic **9**: 89%, 0% ee **10**: 5%

As described above, we demonstrated that the phosphinite **1b**, easily prepared from commercially available quinidine, was a particularly effective nonenzymatic catalyst for the asymmetric benzoylation of the cyclic *meso*-1,3- and 1,4-diols. Although the reaction mechanism in the present asymmetric benzoylation of diols remains to be elucidated, we postulate that the reaction is initiated by the activation of benzoyl chloride by the Lewis basic phosphinite. Further application of the phosphinite derivatives of the cinchona alkaloids to the asymmetric desymmetrization reaction are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic data for catalyst **1b** and monobenzolylated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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