Desymmetrizing meso*-Diols*

Asymmetric Desymmetrization of *meso*-1,2-Diols by Phosphinite Derivatives of Cinchona Alkaloids**

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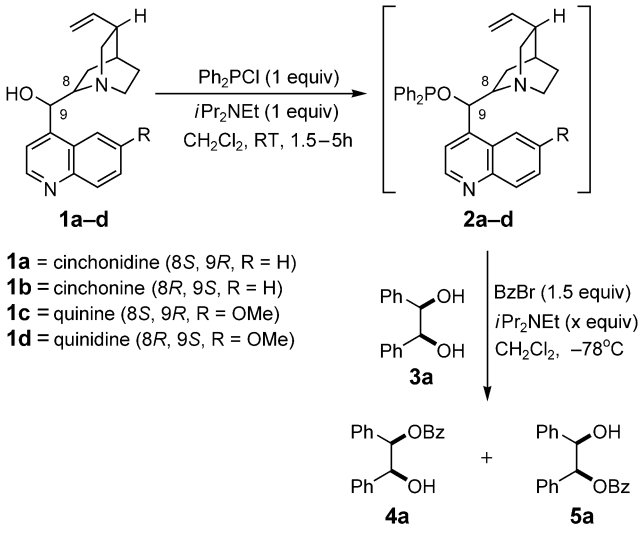
The asymmetric desymmetrization of *meso*-diols is an important and powerful methodology for obtaining optically active substances. Numerous methods for the asymmetric desymmetrization of *meso*-diols have already been developed,[1] but only a few examples of the catalytic and direct asymmetric desymmetrization reaction of *meso*-diols have been reported.[2,3c] As an efficient catalyst for the stereoselective monoacylation of *meso*-diols, we proposed a bifunctional catalyst containing a Lewis-basic trivalent phosphorus center[3] and a Brønsted-basic tertiary amino group. If these functional groups act cooperatively to activate an acylating reagent and trap a proton in the monoacylating reaction, a more effective and stereoselective desymmetrization reaction may be accomplished. On the basis of this working hypothesis we designed phosphinites derived from cinchona alkaloids as the optimal catalyst. Although phosphinite and phosphite derivatives of cinchona alkaloids have been utilized as chiral ligands in asymmetric metal complexes[4] and intermediates for the synthesis of chiral phosphanes,[5] they have not been employed as catalysts for asymmetric reactions. Herein we report the asymmetric monoacylation of *meso*-1,2-diols with high yield and with high enantioselectivity using phosphinite derivatives of cinchona alkaloids.

A phosphinite derivative generated in situ from the reaction of chlorodiphenylphosphane with cinchonidine in the presence of Hünig's base was added to the benzoylation reaction of *meso*-hydrobenzoin with benzoyl bromide (Scheme 1). As a result, the corresponding monobenzoylated diol **4a** was obtained as the major isomer in 34% yield and 74% *ee* (Table 1, entry 1). Moreover, the addition of one equivalent of Hünig's base to the acylation reaction improved the yield of the product without reducing the enantioselectivity (Table 1, entry 2). The asymmetric desymmetrization of *meso*-hydrobenzoin with other cinchona alkaloids (cincho-



Scheme 1. Generation of the catalyst and desymmetrization of *meso*-hydrobenzoin. Bz = benzoyl, RT = room temperature.

Table 1: Asymmetric monobenzoylation of *meso*-hydrobenzoin in the presence of phosphinite compounds derived from cinchona alkaloids (see Scheme 1).

Entry	Alkaloid	Hünig's base [equiv]	*t* [h]	Major product	Yield [%][a]	*ee* [%][b]
1	**1a**	0	24	**4a**	34	74
2	**1a**	1	24	**4a**[c]	83	78
3	**1b**	1	1.5	**5a**	99	82
4	**1c**	1	3.5	**4a**	58	22
5	**1d**	1	3.5	**5a**	59	29

[a] Yield of isolated product. [b] Determined by chiral HPLC analysis or by the analysis of the corresponding Mosher's ester. [c] $[\alpha]_D^{24} = +28.7°$ ($c = 1.0$, $CHCl_3$, lit: $[\alpha]_D^{25} = -21.0°$ for the corresponding enantiomer **5a** at 64% *ee*).[2b]

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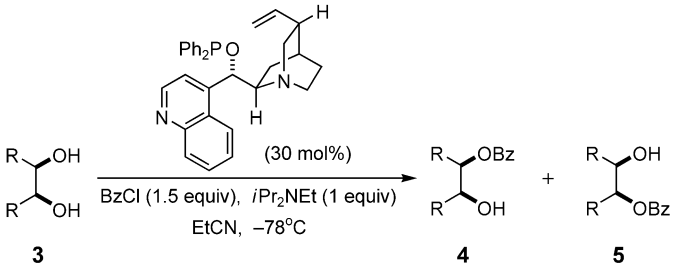
nine, quinine, quinidine) was also examined under the reaction conditions similar to those described for cinchonidine. In particular, when cinchonine, the diastereomer of cinchonidine, was employed, the corresponding enantiomeric monobenzoylated diol **5a** was obtained in nearly quantitative yield and 82% *ee* (Table 1, entry 3).

In order to optimize the reaction conditions for the desymmetrization with the phosphinite derivative of cinchonine, the reactions were conducted in different media and with various acylating reagents (Table 2). The dichloromethane solvent employed for the generation of the phosphinite derivative was removed by evaporation, and the benzoylation was carried out in propionitrile to afford the product with a higher enantioselectivity (Table 2, entry 6). When benzoyl chloride was used as the acylation reagent, an enantioselectivity of 91% ee was accomplished (Table 2, entry 7). In contrast the reactions using benzoic anhydride and pivaloyl chloride resulted in lower yields or no reaction (Table 2, entries 9 and 10).

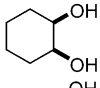
We also attempted the reaction using other cinchonidine derivatives in which the hydroxy group is protected by treatment with benzoyl chloride, pivaloyl chloride, diphenylacetyl chloride, or diphenylphosphinic chloride in place of chlorodiphenylphosphane. However, a racemic product was obtained in low yield for all cases. Consequently, the trivalent phosphinite group in the cinchonidine-based catalyst appears to play an important role in the asymmetric monobenzoylation reaction of *meso*-hydrobenzoin. Although the isolation of the pure phosphinite derivative of the cinchona alkaloid was difficult because trivalent phosphinite is susceptible to oxidation, the phosphinite derivative could be isolated as a mixture with the corresponding phosphinate.[6] The mixture of the phosphinite and phosphinate (ca. 85:15) from cinchonine was adapted for the asymmetric monobenzoylation to provide the monoacylated diol in almost quantitative yield and 91% *ee*. Moreover, the reaction in the presence of a catalytic amount (30 mol%) of the phosphinite as a mixture (containg about 15% phosphinate) afforded the corresponding monoacylated diol in 98% yield and 91% *ee* (Table 3, entry 1). Under the same reaction conditions, other *meso*-1,2-diols containg cyclic or acyclic diols were also monoacylated in good enatioselectivities (Table 3, entries 2–5).[7]

In conclusion, the phosphinite compound derived from cinchonine was found to be an effective desymmetrization catalyst for *meso*-1,2-diols. Further studies will focus on the mechanism of the catalysis and the wide array of applications for various phosphinite catalysts.

Table 3: Catalytic asymmetric acylation of *meso*-1,2-diols with the phosphinite compound derived from cinchonine.

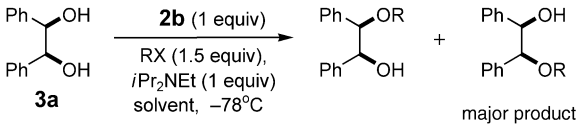


3 **4** **5**

Entry	*meso*-Diol	*t* [h]	Major product	Yield [%][a]	*ee* [%][b]
1		1.5	**5**	98	91
2		4	**4**	99	86
3		3.5	**4**	80	93
4		6	**4**	85	94
5		4.5	ND[c]	80	76

[a] Yield of isolated product. [b] Determined by chiral HPLC analysis. [c] Not determined.

Table 2: Effects of various solvents and acylation reagents on the asymmetric desymmetrization of *meso*-hydrobenzoin.



Entry	Solvent	*t* [h]	RX	Yield [%][a]	*ee* [%][b]
1	CH_2Cl_2	1.5	BzBr	99	82
2	toluene	3	BzBr	58	68
3	THF	2	BzBr	28	74
4	$CHCl_3$[c]	3	BzBr	15	65
5	MeCN[d]	1	BzBr	94	78
6	EtCN	0.5	BzBr	95	88
7	EtCN	1	BzCl	95	91
8	EtCN	2.5	*o*-MeC_6H_4COCl[e]	36	76
9	EtCN	6.5	$(PhCO)_2O$	17	4
10	EtCN	3	*t*BuCOCl	NR[f]	–

[a] Yield of isolated product. [b] Determined by chiral HPLC analysis. [c] $CHCl_3$ was also employed in the preparation of the phosphinite derivative. [d] Reaction was conducted at 0°C. [e] Absolute configuration of the major product was not determined. [f] No reaction.

Experimental Section

General procedure for the desymmetrization of *meso*-hydrobenzoin using the phosphinite compounds generated in situ (Table 2): To a suspension of cinchonine (294 mg, 1 mmol) in CH_2Cl_2 (5 mL) under an argon atmosphere were added dropwise Hünig's base (129 mg, 1 mmol) and chlorodiphenylphosphane (180 μL, 1 mmol). After the resulting solution had been stirred at room temperature for 1.5 h, the solvent was removed under reduced pressure. EtCN (5 mL) and *meso*-hydrobenzoin (214 mg, 1 mmol) were added to the residue, and Hünig's base (129 mg, 1 mmol) and benzoyl chloride (174 μL, 1.5 mmol) were added dropwise to the solution at −78°C. The mixture was stirred for 1.5 h and quenched with water. The resulting solution was

extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate 3:1 as the eluent to give the desired monoester as a white solid (302 mg, 95%). HPLC analysis (AD-H, hexane/*i*PrOH 70:30): 91% *ee*.

Preparation of the phosphinite compound derived from cinchonine: A solution of triethylamine (1.01 g, 10 mmol) in THF (2 mL) and a solution of chlorodiphenylphosphane (1.10 g, 5 mmol) in THF (2 mL) were added consecutively and dropwise to a suspension of cinchonine (1.47 g, 5 mmol) in THF (10 mL) under an argon atmosphere. The mixture was stirred at room temperature for 1.5 h, then the solvent was removed under reduced pressure. Water was added to the residue, and the resulting solution was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residual crude product was purified by flash column chromatography on basic alumina using hexane/ethyl acetate 4:1 as the eluent to give the phosphinite derivative containing the phosphinate (ca. 15%) as a white amorphous solid (1.48 g, 62%). Spectroscopic data for the phosphinite in the mixture: ^{1}H NMR (400 MHz, $CDCl_3$, TMS as an internal standard.): $\delta = 1.48$–1.59 (m, 3H), 1.78 (br s, 1H), 1.93–1.98 (m, 1H), 2.16–2.22 (m, 1H), 2.59–2.79 (m, 3H), 2.84–2.90 (m, 1H), 3.30 (br s, 1H), 4.99–5.06 (m, 2H), 5.57 (br s, 1H), 5.88–5.96 (m, 1H), 7.10–7.23 (m, 5H), 7.33–7.40 (m, 4H), 7.42–7.56 (m, 3H), 7.63–7.67 (m, 1H), 8.07 (d, $J = 7.8$ Hz, 1H), 8.14 (d, $J = 7.6$ Hz, 1H), 8.75 ppm (d, $J = 4.5$ Hz, 1H); ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4 as an external standard.): $\delta = 115.44$ ppm (33.1 for the phosphinate); HRMS calcd for $C_{31}H_{31}N_2OP$: 478.2174, found: 478.2202.

General procedure for the catalytic desymmetrization of *meso*-1,2-diols (Table 3): Hünig's base (129 mg, 1 mmol) and benzoyl chloride (174 μL, 1.5 mmol) were added to a solution of the phosphinite compound (167 mg, 0.3 mmol) and *meso*-hydrobenzoin (214 mg, 1 mmol) in EtCN (5 mL) at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 °C for 1.5 h then quenched with water. The resulting solution was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate 3:1 as the eluent to give the desired monoester as a white solid (313 mg, 98%). HPLC analysis: 91% *ee*.

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[6] The ratio of the phosphinite and the corresponding phosphinate was estimated from the ^{31}P NMR spectrum in which the peaks of the phosphinite and the phosphinate derivatives appear at $\delta =$ 115.4 and $\delta = 33.1$ ppm, respectively.

[7] When less than 30 mol% of the catalyst was used, the yields and enantioselectivities of the monoacylated products decreased except for the reaction of *meso*-hydrobenzoin (90% yield, 92% *ee* with 10 mol% catalyst).

