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Kinetic resolution of *d*,*l*-1,2-diols catalyzed by amine-phosphinite bifunctional organocatalysis derived from quinidine

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Abstract—Racemic C_2-symmetric 1,2-diols were kinetically resolved by the acylation reaction catalyzed by the phosphinite derivative of quinidine to afford the corresponding monoacylated product with good to high enantioselectivities.

The kinetic resolution of racemic alcohols via an acylation reaction is a convenient and powerful methodology for obtaining chiral alcohols, which are useful as chiral building blocks for the synthesis of pharmaceutical and natural compounds.[1] Many enzymatic processes[2] or non-enzymatic catalysts[3] for the kinetic resolution of racemic alcohols have been developed, and the practical levels of selectivity have been accomplished. In comparison to the many successful examples for the kinetic resolution of monools, the non-enzymatic kinetic resolution of non-protected *d*,*l*-1,2-diols has been limited to some examples in which a chiral organotin compound or a chiral Cu(II) complex was employed during the catalysis.[4]

Recently, we have demonstrated that the phosphinite derivatives of cinchona alkaloids (Fig. 1) serve as effective catalysts for the asymmetric acylation reaction of *meso*-diols.[5] For the catalytic acylation reaction, it has been postulated as a possible reaction mechanism that the phosphinite moiety activates acyl chloride as a Lewis base and the nitrogen atom of quinuclidine acts as a Brønsted base by abstracting a proton from a hydroxyl group. The successful result of the asymmetric desymmetrization of *meso*-diols prompted us to apply the chiral amine-phosphinite bifunctional organocatalysts for the kinetic resolution of racemic diols. In this letter, we describe the first organocatalytic kinetic resolution of

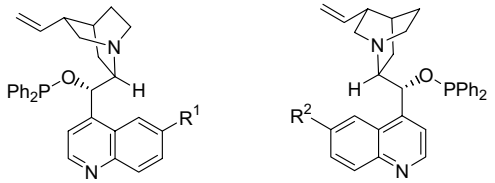

Figure 1. Phosphinite derivatives of cinchona alkaloids.

C_2-symmetric *d*,*l*-1,2-diols using the phosphinite derivative of quinidine.

Initially, the kinetic resolution of *d*,*l*-hydrobenzoin with benzoyl chloride (0.65 equiv) in the presence of 30 mol % of the phosphinite derivatives, which were obtained as a mixture with the corresponding phosphinate (phosphinite purity >90%) or the pure phosphinite via the reaction of chlorodiphenylphosphane with cinchona alkaloids followed by purification with column chromatography, was attempted. When phosphinite derivative **1a** of cinchonine was used as a catalyst, the reaction smoothly proceeded, but the selectivity was low (s[6] = 2) (Table 1, entry 1). However, the use of phosphinite derivative **1b** of quinidine led to a higher selectivity ($s = 20$) (Table 1, entry 2). The absolute configuration of the monoacylated product **3a** was determined to be the (*R*,*R*)-isomer by comparison of the chiral HPLC retention time of the recovered diol **2a** with the literature data.[7] The reactions employing other phosphinite compounds **1c** and **1d** under the same reaction conditions gave monoester **3a** with low enantioselectivities

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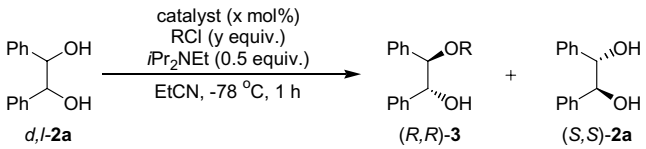
Table 1. Kinetic resolution of *d*,*l*-hydrobenzoin by the phosphinite derivatives of cinchona alkaloids



d,*l*-**2a** (*R*,*R*)-**3** (*S*,*S*)-**2a**

Entry	Catalyst	*x*	RCl	*y*	ee of **3** (%)[a]	ee of **2a** (%)[a]	*c* (%)[b]	*s*[c]
1	**1a**	30	BzCl	0.65	28 (**3a**)	32	53	2
2	**1b**	30	BzCl	0.65	72 (**3a**)	92	56	20
3	**1c**	30	BzCl	0.65	0 (**3a**)	0	—	—
4	**1d**	30	BzCl	0.65	7[d] (**3a**)	4[e]	36	1
5	**1b**	30	*p*-ClC_6H_4COCl	0.65	84 (**3b**)	99	54	59
6	**1b**	30	*p*-ClC_6H_4COCl	0.50	84 (**3b**)	67	44	23
7	**1b**	30	*p*-ClC_6H_4COCl	0.75	80 (**3b**)	99	55	46
8	**1b**	30	*o*-ClC_6H_4COCl	0.65	18 (**3c**)	5	22	2
9	**1b**	30	*p*-$CF_3C_6H_4COCl$	0.65	98 (**3d**)	99	50	525
10	**1b**	20	*p*-$CF_3C_6H_4COCl$	0.65	95 (**3d**)	99	51	206
11	**1b**	10	*p*-$CF_3C_6H_4COCl$	0.65	93 (**3d**)	95	51	103

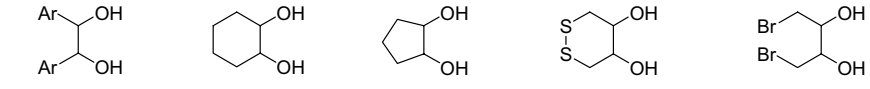
[a] Determined by chiral HPLC analysis.
[b] Conversion (%) = 100 × ee of unreacted diol/(ee of unreacted diol + ee of monoacylated product), see Ref. 6.
[c] Selectivity factor = *k*(fast-reacting enantiomer)/*k*(slow-reacting enantiomer), see Ref. 6.
[d] Absolute configuration is (*S*,*S*).
[e] Absolute configuration is (*R*,*R*).

(Table 1, entries 3 and 4). The monoacylated product obtained from the reaction using the diastereomeric phosphinite **1d** toward **1b** was the opposite stereoisomer (*S*,*S*)-**3a**.

Next, in order to improve the selectivity, the effects of the acylation reagents were investigated. When *p*-chlorobenzoyl chloride was used as an acylation reagent, a higher selectivity ($s = 59$) was observed (Table 1, entry 5). In contrast, the treatment of *o*-chlorobenzoyl chloride resulted in a lower selectivity and the reaction slowly proceeded compared to the reaction using *p*-chlorobenzoyl chloride (Table 1, entry 8). In addition, the amount of the acylation reagent influenced the selectivity of the kinetic resolution (Table 1, entries 5–7). The addition of a slight excess of the acylation reagent (0.65 equiv) resulted in the more desirable results. The best selectivity was accomplished by the reaction using *p*-trifluoromethylbenzoyl chloride having a more electron negative functional group and the reaction in the presence of 30 mol % of phosphinite **1b** gave the corresponding monoacylated product **3d** in a 51% yield with 98% ee and the unreacted alcohol **2a** in a 43% yield with 99% ee (Table 1, entry 9). Additionally, it was noteworthy that the effective kinetic resolution was feasible even though a lower amount of catalyst (10 mol %) was used (Table 1, entry 11).

Finally, the kinetic resolution of various *d*,*l*-1,2-diols using the amine-phosphinite organocatalyst **1b** was examined (Table 2). The reaction of *p*-chloro-*d*,*l*-hydrobenzoin **2b** gave the corresponding monoacylated prod-

Table 2. Kinetic resolution of various 1,2-diols using the phosphinite **1b**[a]

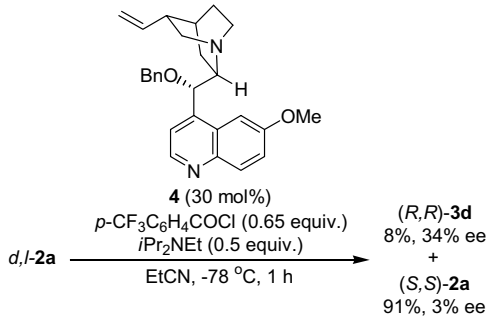


2a: Ar = Ph
2b: Ar = *p*-ClC_6H_4

2c **2d** **2e** **2f**

Entry	Diol	RCl	ee of **3** (%)[b]	ee of 2 (%)[b]	*c* (%)[c]	*s*[d]
1	**2a**	*p*-$CF_3C_6H_4COCl$	98 (**3d**)	99	50	525
2	**2b**	*p*-$CF_3C_6H_4COCl$	85 (**3e**)	90	51	38
3[e]	**2c**	*p*-$CF_3C_6H_4COCl$	89 (**3f**)	15	14	20
4	**2c**	*p*-ClC_6H_4COCl	92 (**3g**)	10	10	26
5	**2d**	*p*-$CF_3C_6H_4COCl$	81 (**3h**)	63	44	18
6	**2d**	*p*-ClC_6H_4COCl	81 (**3i**)	74	48	21
7	**2e**	*p*-$CF_3C_6H_4COCl$	74 (**3j**)	52	41	11
8	**2f**	*p*-$CF_3C_6H_4COCl$	68 (**3k**)	69	50	11

[a] Reaction of racemic diols (1.00 mmol) with acylation reagent (0.65 mmol) in EtCN (5 mL) at −78 °C for 1 h in the presence of 30 mol % of **1b** and diisopropylethylamine (0.50 mmol).
[b] Determined by chiral HPLC analysis.
[c] Conversion (%) = 100 × ee of unreacted diol/(ee of unreacted diol + ee of monoacylated product), see Ref. 6.
[d] Selectivity factor = *k*(fast-reacting enantiomer)/*k*(slow-reacting enantiomer), see Ref. 6.
[e] Reaction was performed for 3 h.



Scheme 1.

uct **3e** and unreacted alcohol **2b** with high enantioselectivities (Table 2, entry 2). In the case of the reactions of *trans*-cyclohexanediol and *trans*-cyclopentanediol, the use of *p*-chlorobenzoyl chloride as an acylation reagent resulted in slightly higher selectivity factors (Table 2, entries 4 and 6). The other diols containing heteroatoms were also kinetically resolved in moderate selectivities (Table 2, entries 7 and 8).

The kinetic resolution of *d*,*l*-hydrobenzoin using the benzylether derivative of quinidine[8] **4** in place of **1b** was attempted. The reaction under optimized reaction conditions in the presence of 30 mol % of **4** was sluggish relative to the reaction using **1b** and gave the monoacylated product with 34% ee ($s = 2$). These results indicate that the phosphinite moiety is essential for attaining a highly enantioselective monoacylation (Scheme 1).

In summary, we have demonstrated that the phosphinite derivative of quinidine catalyzed the kinetic resolution of C_2-symmetric *d*,*l*-1,2-diols to produce the monoacylated product and unreacted diol with good to excellent selectivities. Further applications of the amine-phosphinite catalyst for the kinetic resolution of other racemic compounds are under way in our laboratory.

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