



# Nonenzymatic kinetic resolution of *racemic* $\alpha$ -hydroxyalkanephosphonates with chiral copper catalyst

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## ABSTRACT

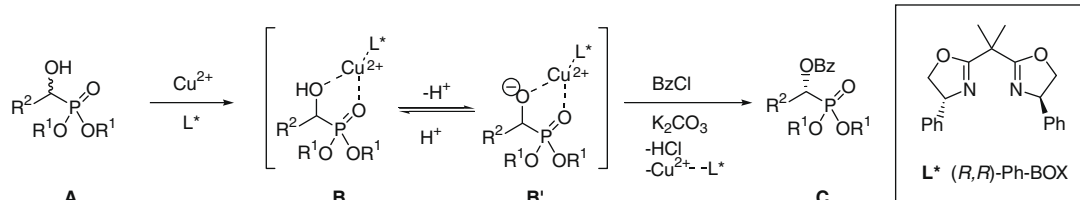
Kinetic resolution of  $\alpha$ -hydroxyalkanephosphonates was efficiently performed by benzoylation in the presence of copper(II) triflate and (*R,R*)-Ph-BOX as a catalyst with excellent *s* value of up to 286.

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Optically active  $\alpha$ -hydroxyalkanephosphonic acid derivatives are important precursors for biologically active compounds such as HIV-protease inhibitors.<sup>1</sup> Furthermore, they are also important precursors of  $\alpha$ -amino phosphonates.<sup>2</sup> Although a multitude of enzymatic kinetic resolution methods has been developed for preparation of optically pure  $\alpha$ -hydroxyalkanephosphonic acid derivatives,<sup>3</sup> to the best of our knowledge, nonenzymatic methods have not been reported. We recently reported an efficient method for kinetic resolution of 1,2-diols,<sup>4</sup> *vic*-amino alcohols,<sup>5</sup> and  $\alpha$ - or  $\beta$ -hydroxyalkanamides<sup>6</sup> with copper(II) ion associated with chiral ligand (*R,R*)-Ph-BOX by acylation to obtain optically active alcohols with excellent enantioselectivity.<sup>7</sup> In this communication, we apply our methodology to kinetic resolution of  $\alpha$ -hydroxyalkanephosphonates **A** to afford optically active  $\alpha$ -benzoyloxyalkanephosphonates **C** in high yields and enantioselectivities. This

is based on molecular recognition by Cu(II)–(*R,R*)-Ph-BOX complex to form the activated intermediates **B** or **B'** followed by benzoylation (Scheme 1).

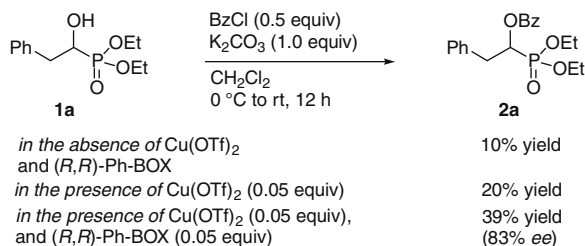
We began by examining the benzoylation of diethyl 1-hydroxy-2-phenylethylphosphonate (DL-**1a**) as a model compound to see whether it could be accelerated by chiral copper(II) complex (Scheme 2). The result showed that in the absence of copper(II) triflate and (*R,R*)-Ph-BOX the reaction of DL-**1a** with BzCl was slow, while in the presence of copper(II) triflate, the yield of benzoylated compound **2a** was somewhat improved. Further improvement was accomplished by using a combination of copper(II) triflate and (*R,R*)-Ph-BOX to afford **2a** in 39% yield with 83% ee.<sup>8</sup> These results suggest that DL-**1a** is recognized by Cu(II)–(*R,R*)-Ph-BOX complex in the same way as in kinetic resolution of 1,2-diols.<sup>4a</sup>



**Scheme 1.** Kinetic resolution of  $\alpha$ -hydroxyalkanephosphonates with chiral copper catalyst.

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**Scheme 2.** Benzoylation of DL-**1a** with or without a catalyst.

Next, we surveyed the effect of ester substituents of  $\alpha$ -hydroxyalkane phosphonates **1** to optimize their effect. The results are shown in Table 1. The selectivity  $s$  values<sup>9</sup> for substrates **1b–d**

substituted with methyl, isopropyl, and benzyl ester were slightly lower than that of **1a** with ethyl ester (entries 1–4).<sup>10</sup> We then set to investigate the effect of the base and solvent used.

Table 2 summarizes the effect of bases and solvents on the kinetic resolution of DL-**1a**. Use of  $\text{Li}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{CaCO}_3$ , and  $\text{ZnCO}_3$  as base gave benzoylated products  $(R)$ -**2a**<sup>12</sup> with moderate  $s$  values (entries 1–5). Although diisopropylethylamine (DIPEA) did not work at all (entry 6),  $\text{BaCO}_3$  worked well to give  $(R)$ -**2a** with high  $s$  value of 24 (entry 7). Consequently, using  $\text{BaCO}_3$  as a base, solvent effect was investigated. Among the tested solvents (entries 8–18), aromatic solvents were suitable for the benzoylation (entries 14–18). Chlorobenzene gave the best result with  $s$  value of 46 (entry 16). Use of  $(R,R)$ -Bn-BOX de-accelerated the benzoylation of DL-**1a** compared with the use of  $(R,R)$ -Ph-BOX (entry 17).

**Table 1**  
Effect of ester group of DL-**1a–d**<sup>a</sup>

DL-**1a–d**  $\xrightarrow[\text{CH}_2\text{Cl}_2, 0^\circ\text{C to rt, 12 h}]{\text{BzCl (0.5 equiv), Cu(OTf)}_2 \text{ (0.05 equiv), (R,R)-Ph-BOX (0.05 equiv), K}_2\text{CO}_3 \text{ (1.0 equiv)}}$  (R)-**2a–d** + (S)-**1a–d**

Entry	Substrate	Product (R)- <b>2a–d</b>			Recovered (S)- <b>1a–d</b>			<i>s</i>
			Yield (%)	ee <sup>b</sup> (%)		Yield (%)	ee <sup>b</sup> (%)	
1	<b>1a</b> : R <sup>1</sup> = Et	(R)- <b>2a</b>	39	83	(S)- <b>1a</b>	48	52	18
2	<b>1b</b> : R <sup>1</sup> = Me	(R)- <b>2b</b>	45	65	(S)- <b>1b</b>	42	65	9
3	<b>1c</b> : R <sup>1</sup> = <i>i</i> -Pr	(R)- <b>2c</b>	32	68	(S)- <b>1c</b>	66	38	8
4	<b>1d</b> : R <sup>1</sup> = Bn	(R)- <b>2d</b>	38	50	(S)- <b>1d</b>	55	35	4

<sup>a</sup> DL-**1a–d** (0.5 mmol),  $\text{Cu}(\text{OTf})_2$  (0.025 mmol),  $(R,R)$ -Ph-BOX (0.025 mmol), BzCl (0.25 mmol),  $\text{K}_2\text{CO}_3$  (0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) at 0 °C to rt for 12 h.

<sup>b</sup> Determined by HPLC.

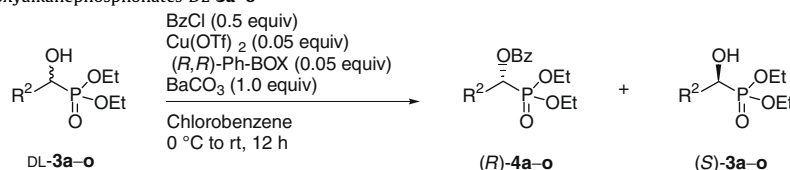
**Table 2**  
Effect of bases and solvents on the kinetic resolution<sup>a</sup>

Entry	Solvent	Base	Product $(R)$ - <b>2a</b>		Recovered $(S)$ - <b>1a</b>		$s$
			Yield (%)	ee <sup>b</sup> (%)	Yield (%)	ee <sup>b</sup> (%)	
1	$\text{CH}_2\text{Cl}_2$	$\text{Li}_2\text{CO}_3$	11	89	84	8	19
2	$\text{CH}_2\text{Cl}_2$	$\text{Na}_2\text{CO}_3$	47	74	43	70	14
3	$\text{CH}_2\text{Cl}_2$	$\text{K}_2\text{CO}_3$	39	83	48	52	18
4	$\text{CH}_2\text{Cl}_2$	$\text{CaCO}_3$	14	88	79	4	16
5	$\text{CH}_2\text{Cl}_2$	$\text{ZnCO}_3$	30	74	49	48	11
6	$\text{CH}_2\text{Cl}_2$	DIPEA	0	—	>99	—	—
7	$\text{CH}_2\text{Cl}_2$	$\text{BaCO}_3$	40	84	51	71	24
8	$\text{CHCl}_3$	$\text{BaCO}_3$	19	92	73	36	34
9	$\text{ClCH}_2\text{CH}_2\text{Cl}$	$\text{BaCO}_3$	44	76	48	76	17
10	THF	$\text{BaCO}_3$	Trace	—	97	—	—
11	<i>i</i> -PrOH	$\text{BaCO}_3$	Trace	—	98	—	—
12	AcOEt	$\text{BaCO}_3$	12	87	86	17	17
13	MeCN	$\text{BaCO}_3$	11	78	65	25	10
14	Benzene	$\text{BaCO}_3$	30	92	65	48	39
15	Toluene	$\text{BaCO}_3$	34	88	60	61	29
16	Chlorobenzene	$\text{BaCO}_3$	38	90	55	79	46
17 <sup>c</sup>	Chlorobenzene	$\text{BaCO}_3$	17	91	72	25	27
18	Fluorobenzene	$\text{BaCO}_3$	37	91	54	71	45

<sup>a</sup> DL-**1a** (0.5 mmol),  $\text{Cu}(\text{OTf})_2$  (0.025 mmol),  $(R,R)$ -Ph-BOX (0.025 mmol), BzCl (0.25 mmol), base (0.5 mmol) in solvent (3.0 mL) at 0 °C to rt for 12 h.

<sup>b</sup> Determined by HPLC.

<sup>c</sup>  $(R,R)$ -Bn-BOX was used instead of  $(R,R)$ -Ph-BOX.

**Table 3**Kinetic resolution of various  $\alpha$ -hydroxyalkanephosphonates DL-**3a–o**<sup>a</sup>

Entry	Substrate		Product (R)- <b>4a–o</b>		Recovered (S)- <b>3a–o</b>		s		
	R <sup>2</sup>		Yield (%)	ee <sup>b</sup> (%)	Yield (%)	ee <sup>b</sup> (%)			
1	<b>3a</b>	Me	(R)- <b>4a</b>	37	80	(S)- <b>3a</b>	47	65	18
2	<b>3b</b>	Et	(R)- <b>4b</b>	26	88	(S)- <b>3b</b>	56	47	25
3	<b>3c</b>	<i>n</i> -Pr	(R)- <b>4c</b>	28	>99	(S)- <b>3c</b>	68	37	286
4	<b>3d</b>	( <i>E</i> )-MeCH=CH	(R)- <b>4d</b>	18	>99	(S)- <b>3d</b>	73	27	259
5	<b>3e</b>	Ph–C≡C	(R)- <b>4e</b>	45	42	(S)- <b>3e</b>	47	41	4
6	<b>3f</b>	<i>i</i> -Pr	(R)- <b>4f</b>	40	84	(S)- <b>3f</b>	60	50	19
7 <sup>c</sup>	<b>3f</b>	<i>i</i> -Pr	(R)- <b>4f</b>	52	74	(S)- <b>3f</b>	47	87	32
8	<b>3g</b>	<i>i</i> -Bu	(R)- <b>4g</b>	20	94	(S)- <b>3g</b>	64	32	44
9	<b>3h</b>	Cyclohexyl	(R)- <b>4h</b>	32	88	(S)- <b>3h</b>	67	42	24
10	<b>3i</b>	Ph	(R)- <b>4i</b>	Trace	—	(S)- <b>3i</b>	>99	—	—
11	<b>3j</b>	ClCH <sub>2</sub>	(R)- <b>4j</b>	35	92	(S)- <b>3j</b>	63	55	42
12	<b>3k</b>	BnO–(CH <sub>2</sub> ) <sub>2</sub>	(R)- <b>4k</b>	30	95	(S)- <b>3k</b>	65	39	57
13	<b>3l</b>	Cbz-NH–(CH <sub>2</sub> ) <sub>2</sub>	(R)- <b>4l</b>	13	81	(S)- <b>3l</b>	71	7	10
14	<b>3m</b>	Boc-NH–(CH <sub>2</sub> ) <sub>2</sub>	(R)- <b>4m</b>	29	94	(S)- <b>3m</b>	55	40	48
15	<b>3n</b>	BnO–(CH <sub>2</sub> ) <sub>3</sub>	(R)- <b>4n</b>	27	88	(S)- <b>3n</b>	53	46	25
16	<b>3o</b>	2-Furyl	(R)- <b>4o</b>	38	66	(S)- <b>3o</b>	56	24	6

<sup>a</sup> DL-**3a–o** (0.5 mmol), Cu(OTf)<sub>2</sub> (0.025 mmol), (R,R)-Ph-BOX (0.025 mmol), BzCl (0.25 mmol), BaCO<sub>3</sub> (0.5 mmol) in chlorobenzene (3.0 mL) at 0 °C to rt for 12 h.<sup>b</sup> Determined by HPLC.<sup>c</sup> BzCl (0.35 mmol) was used.

Kinetic resolution of various  $\alpha$ -hydroxyalkanephosphonates DL-**3a–o** by benzoylation under the optimized reaction conditions<sup>14</sup> is summarized in Table 3.<sup>15</sup> Straight-chained  $\alpha$ -hydroxyalkanephosphonates **3a–d** were benzoylated to afford the corresponding optically active (R)-**4a–d** in moderate yields and with good to excellent enantioselectivities (entries 1–4), while phenylethynylated alcohol **3e** gave benzoylated product **4e** with low s value of 4 (entry 5). Compounds **3f–h** with branched chained groups were kinetically resolved with good to high s values (entries 6–9), while benzoylation of phenyl-substituted alcohol **3i** did not proceed to afford the corresponding benzoate **4i** (entry 10). Straight carbon-chained compounds **3j** terminally functionalized with Cl atom, **3k** and **3n** with benzyloxy group gave high s values of 42, 57, and 25, respectively (entries 11, 12, and 15). N-Boc-aminoethylated alcohol **3m** was kinetically resolved with high s value of 48 (entry 14), while N-Cbz-protected one **3l** fell short in terms of yield and enantioselectivity (entry 13). Compound **3o** substituted with 2-furyl group gave low s value of 6 (entry 16). Using 0.7 equiv of BzCl improved the optical purity of the recovered  $\alpha$ -hydroxyalkanephosphonate (S)-**3f** (entry 7).

In conclusion, we have demonstrated a new nonenzymatic method for kinetic resolution of  $\alpha$ -hydroxyalkanephosphonates. The mechanistic study of this benzoylation and its further synthetic applications are underway.

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until it warmed to room temperature and stirred for 12 h. The solution was poured into water and extracted with  $\text{CH}_2\text{Cl}_2$  (20 mL  $\times$  3). The combined organic layer was dried over  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1: 1) to afford (*R*)-**2a** (38% yield, 90% ee) as colorless oil.  $[\alpha]_D^{20}$  –95.3 (*c* 1.2,  $\text{CHCl}_3$ , 90% ee); IR(neat) 2984, 1732, 1273, 1111, 1061, 974, 710  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.28 (t, *J* = 6.6 Hz, 6H), 3.16–3.40 (m, 2H), 4.05–4.23 (m, 4H), 5.68–5.80 (m, 1H), 7.13–7.34 (m, 5H), 7.43 (t, *J* = 8.1 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 6.9 Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  16.2 (2C), 35.6, 62.6, 67.8, 69.5, 126.6 (2C), 128.2 (3C), 129.0

(3C), 129.5 (2C), 133.1, 136.0, 164.8; MS [HR-El] calcd for  $\text{C}_{19}\text{H}_{23}\text{O}_5\text{P}$  362.1283 found 362.1247. HPLC chiralcel OJ-H column (4.6 mm $\phi$ , 250 mm), *n*-hexane/2-propanol = 100:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 24.5 min for (*S*)-**2a**, 26.7 min for (*R*)-**2a**.

15. Absolute stereoconfigurations of recovered (*S*)-**3a**,<sup>3a</sup> (*S*)-**3b**,<sup>3a</sup> (*S*)-**3c**,<sup>3b</sup> (*S*)-**3j**,<sup>3c</sup> and (*S*)-**3n**<sup>16</sup> were determined by comparing with specific rotation of authentic samples. Absolute stereoconfigurations of (*R*)-**4d–h**, **4k–m** shown in Table 3 were deduced on the basis of those of (*R*)-**4a–c**, **4l**, **4n**.
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