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Nonenzymatic kinetic resolution of *racemic* α-hydroxyalkanephosphonates with chiral copper catalyst

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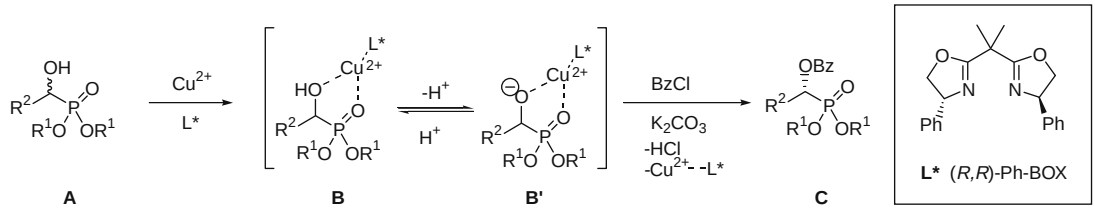
ABSTRACT

Kinetic resolution of α-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.

Optically active α-hydroxyalkanephosphonic acid derivatives are important precursors for biologically active compounds such as HIV-protease inhibitors.[1] Furthermore, they are also important precursors of α-amino phosphonates.[2] Although a multitude of enzymatic kinetic resolution methods has been developed for preparation of optically pure α-hydroxyalkanephosphonic acid derivatives,[3] 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,[4] *vic*-amino alcohols,[5] and α- or β-hydroxyalkanamides[6] with copper(II) ion associated with chiral ligand (*R*,*R*)-Ph-BOX by acylation to obtain optically active alcohols with excellent enantioselectivity.[7] In this communication, we apply our methodology to kinetic resolution of α-hydroxyalkanephosphonates **A** to afford optically active α-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.[8] 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.[4a]



Scheme 1. Kinetic resolution of α-hydroxyalkanephosphonates with chiral copper catalyst.

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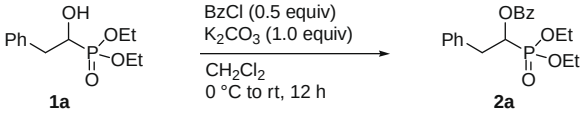


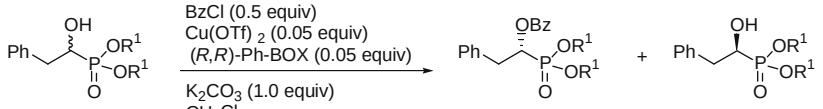
in the absence of $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX	10% yield
in the presence of $Cu(OTf)_2$ (0.05 equiv)	20% yield
in the presence of $Cu(OTf)_2$ (0.05 equiv), and (*R*,*R*)-Ph-BOX (0.05 equiv)	39% yield (83% *ee*)

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

Next, we surveyed the effect of ester substituents of α-hydroxyalkanephosphonates **1** to optimize their effect. The results are shown in Table 1. The selectivity *s* values[9] for substrates **1b–d** substituted with methyl, isopropyl, and benzyl ester were slightly lower than that of **1a** with ethyl ester (entries 1–4).[10] 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 Li_2CO_3, Na_2CO_3, K_2CO_3, $CaCO_3$, and $ZnCO_3$ as base gave benzoylated products (*R*)-**2a**[12] with moderate *s* values (entries 1–5). Although diisopropylethylamine (DIPEA) did not work at all (entry 6), $BaCO_3$ worked well to give (*R*)-**2a** with high *s* value of 24 (entry 7). Consequently, using $BaCO_3$ 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).

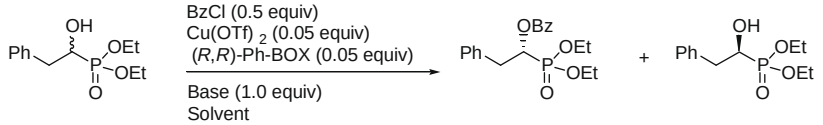
Table 1
Effect of ester group of DL-**1a–d**[a]



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

[a] DL-**1a–d** (0.5 mmol), $Cu(OTf)_2$ (0.025 mmol), (*R*,*R*)-Ph-BOX (0.025 mmol), BzCl (0.25 mmol), K_2CO_3 (0.5 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C to rt for 12 h.
[b] Determined by HPLC.

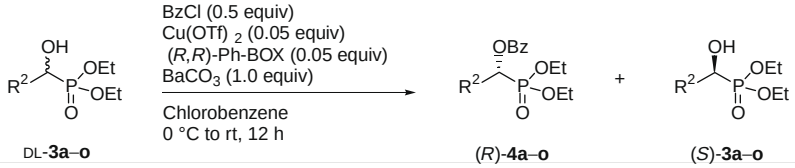
Table 2
Effect of bases and solvents on the kinetic resolution[a]



Entry	Solvent	Base	Product (*R*)-**2a**		Recovered (*S*)-**1a**		*s*
			Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	
1	CH_2Cl_2	Li_2CO_3	11	89	84	8	19
2	CH_2Cl_2	Na_2CO_3	47	74	43	70	14
3	CH_2Cl_2	K_2CO_3	39	83	48	52	18
4	CH_2Cl_2	$CaCO_3$	14	88	79	4	16
5	CH_2Cl_2	$ZnCO_3$	30	74	49	48	11
6	CH_2Cl_2	DIPEA	0	—	>99	—	—
7	CH_2Cl_2	$BaCO_3$	40	84	51	71	24
8	$CHCl_3$	$BaCO_3$	19	92	73	36	34
9	$ClCH_2CH_2Cl$	$BaCO_3$	44	76	48	76	17
10	THF	$BaCO_3$	Trace	—	97	—	—
11	*i*-PrOH	$BaCO_3$	Trace	—	98	—	—
12	AcOEt	$BaCO_3$	12	87	86	17	17
13	MeCN	$BaCO_3$	11	78	65	25	10
14	Benzene	$BaCO_3$	30	92	65	48	39
15	Toluene	$BaCO_3$	34	88	60	61	29
16	Chlorobenzene	$BaCO_3$	38	90	55	79	46
17[c]	Chlorobenzene	$BaCO_3$	17	91	72	25	27
18	Fluorobenzene	$BaCO_3$	37	91	54	71	45

[a] DL-**1a** (0.5 mmol), $Cu(OTf)_2$ (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.
[b] Determined by HPLC.
[c] (*R*,*R*)-Bn-BOX was used instead of (*R*,*R*)-Ph-BOX.

Table 3
Kinetic resolution of various α-hydroxyalkanephosphonates DL-**3a**–**o**[a]



DL-**3a**–**o** (*R*)-**4a**–**o** (*S*)-**3a**–**o**

Entry	Substrate		Product (*R*)-**4a**–**o**			Recovered (*S*)-**3a**–**o**			*s*
		R^2		Yield (%)	ee[b] (%)		Yield (%)	ee[b] (%)	
1	**3a**	Me	(*R*)-**4a**	37	80	(*S*)-**3a**	47	65	18
2	**3b**	Et	(*R*)-**4b**	26	88	(*S*)-**3b**	56	47	25
3	**3c**	*n*-Pr	(*R*)-**4c**	28	>99	(*S*)-**3c**	68	37	286
4	**3d**	(*E*)-MeCH=CH	(*R*)-**4d**	18	>99	(*S*)-**3d**	73	27	259
5	**3e**	Ph–C≡C	(*R*)-**4e**	45	42	(*S*)-**3e**	47	41	4
6	**3f**	*i*-Pr	(*R*)-**4f**	40	84	(*S*)-**3f**	60	50	19
7[c]	**3f**	*i*-Pr	(*R*)-**4f**	52	74	(*S*)-**3f**	47	87	32
8	**3g**	*i*-Bu	(*R*)-**4g**	20	94	(*S*)-**3g**	64	32	44
9	**3h**	Cyclohexyl	(*R*)-**4h**	32	88	(*S*)-**3h**	67	42	24
10	**3i**	Ph	(*R*)-**4i**	Trace	—	(*S*)-**3i**	>99	—	—
11	**3j**	$ClCH_2$	(*R*)-**4j**	35	92	(*S*)-**3j**	63	55	42
12	**3k**	BnO–$(CH_2)_2$	(*R*)-**4k**	30	95	(*S*)-**3k**	65	39	57
13	**3l**	Cbz-NH–$(CH_2)_2$	(*R*)-**4l**	13	81	(*S*)-**3l**	71	7	10
14	**3m**	Boc-NH–$(CH_2)_2$	(*R*)-**4m**	29	94	(*S*)-**3m**	55	40	48
15	**3n**	BnO–$(CH_2)_3$	(*R*)-**4n**	27	88	(*S*)-**3n**	53	46	25
16	**3o**	2-Furyl	(*R*)-**4o**	38	66	(*S*)-**3o**	56	24	6

[a] DL-**3a**–**o** (0.5 mmol), $Cu(OTf)_2$ (0.025 mmol), (*R*,*R*)-Ph-BOX (0.025 mmol), BzCl (0.25 mmol), $BaCO_3$ (0.5 mmol) in chlorobenzene (3.0 mL) at 0 °C to rt for 12 h.
[b] Determined by HPLC.
[c] BzCl (0.35 mmol) was used.

Kinetic resolution of various α-hydroxyalkanephosphonates DL-**3a**–**o** by benzoylation under the optimized reaction conditions[14] is summarized in Table 3.[15] Straight-chained α-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 α-hydroxyalkanephosphonate (*S*)-**3f** (entry 7).

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

Acknowledgments

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until it warmed to room temperature and stirred for 12 h. The solution was poured into water and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over $MgSO_4$ 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, $CHCl_3$, 90% ee); IR(neat) 2984, 1732, 1273, 1111, 1061, 974, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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-EI] calcd for $C_{19}H_{23}O_5P$ 362.1283 found 362.1247. HPLC chiralcel OJ-H column (4.6 mmφ, 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**,[3a] (*S*)-**3b**,[3a] (*S*)-**3c**,[3b] (*S*)-**3j**[3c], and (*S*)-**3n**[16] 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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