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

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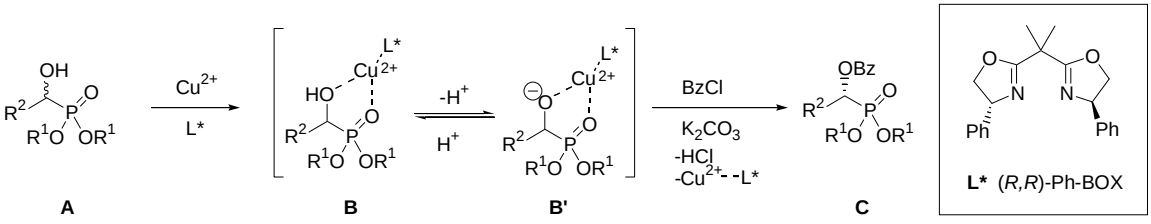
Abstract: Kinetic resolution of α-hydroxyalkanephosphonates was efficiently performed by benzoylation in the presence of copper(II) triflate and (*R*,*R*)-Ph-BOX as a catalyst with excellent *s* value of up to 286.

Keywords: Kinetic resolution; Asymmetric benzoylation; α-Hydroxyalkanephosphonates; Chiral copper complex; Molecular recognition

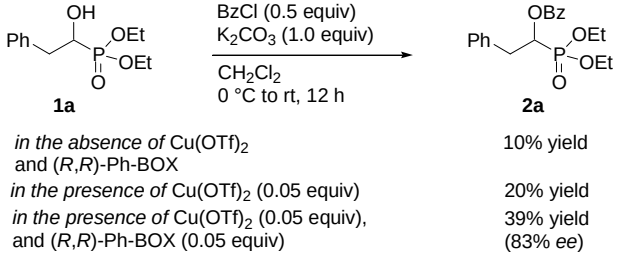
Optically active α-hydroxyalkanephosphonic acid derivatives are important precursors for biologically active compounds such as HIV-protease inhibitors.[1] Furthermore, they are also important precursors of α-amino phoshonates.[2] Although a multitude of enzymatic kinetic resolution methods have been 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).



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

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)

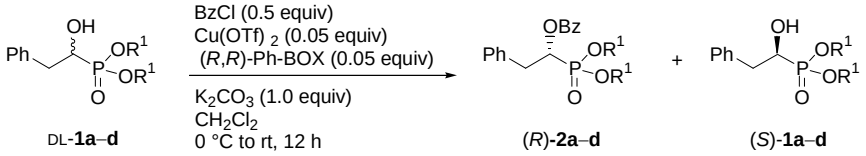
complex or not (Scheme 2). The result showed that in the absence of copper(II) triflate and (*R*,*R*)-Ph-BOX the reaction of DL-**1a** with BzCl was slow, while in the presence of copper(II) triflate, the yield of benzoylated compound **2a** was somewhat improved. Further improvement was accomplished 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 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 1.
Effect of ester group of DL-**1a**—**d**.[a]



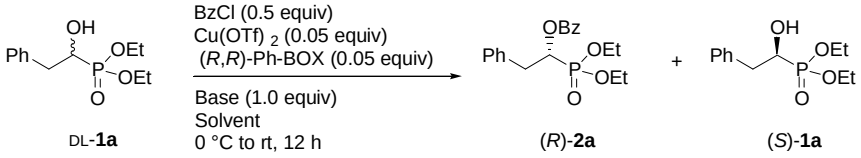
Entry	Substrate	Product (*R*)-**2a**—**d**			Recovered (*S*)-**1a**—**d**			*s*
			Yield (%)	*ee* (%)[b]		Yield (%)	*ee* (%)[b]	
1	**1a**: R^1=Et	(*R*)-**2a**	39	83	(*S*)-**1a**	48	52	18
2	**1b**: R^1=Me	(*R*)-**2b**	45	65	(*S*)-**1b**	42	65	9
3	**1c**: R^1=*i*-Pr	(*R*)-**2c**	32	68	(*S*)-**1c**	66	38	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 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 use of (*R*,*R*)-Ph-BOX (Entry 17).

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



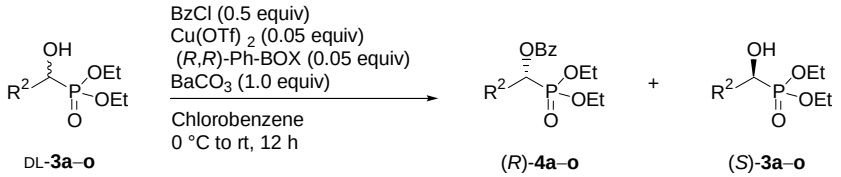
Entry	Solvent	Base	Product (*R*)-**2a**		Recovered (*S*)-**1a**		*s*
			Yield (%)	*ee* (%)[b]	Yield (%)	*ee* (%)[b]	
1	CH_2Cl_2	Li_2CO_3	11	89	84	8	19
2	CH_2Cl_2	Na_2CO_3	47	74	43	70	14
3	CH_2Cl_2	K_2CO_3	39	83	48	52	18
4	CH_2Cl_2	$CaCO_3$	14	88	79	4	16
5	CH_2Cl_2	$ZnCO_3$	30	74	49	48	11
6	CH_2Cl_2	DIPEA	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.

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 recovered α-hydroxyalkanephosphonate (*S*)-**3f** (Entry 7).

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.

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

Acknowledgements

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10. The absolute stereoconfiguration of recovered (*S*)-**1a** was determined by comparing with specific rotation of authentic sample. Compound (*S*)-**1a**: $[\alpha]^{20}_{D}$ +11.7 (*c* 1.0, $CHCl_3$, 79% ee). [lit.[11] (*S*)-**1a** (91% ee); $[\alpha]^{20}_{D}$ +21.9 (*c* 0.9, $CHCl_3$)].
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14. A typical procedure for kinetic resolution of DL-**1a**: Under an aerobic atmosphere, a solution of $Cu(OTf)_2$ (9.0 mg, 0.025 mmol) and (*R*,*R*)-Ph-BOX (8.4 mg, 0.025 mmol) in chlorobenzene (3 mL) was stirred for 10 min. Into the solution were added DL-**1a** (129 mg, 0.5 mmol), $BaCO_3$ (99 mg, 0.5 mmol) and BzCl (29 μL, 0.25 mmol) at 0 °C. The resulting mixture was allowed to stand 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 x 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. $[\alpha]^{20}_D$ —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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