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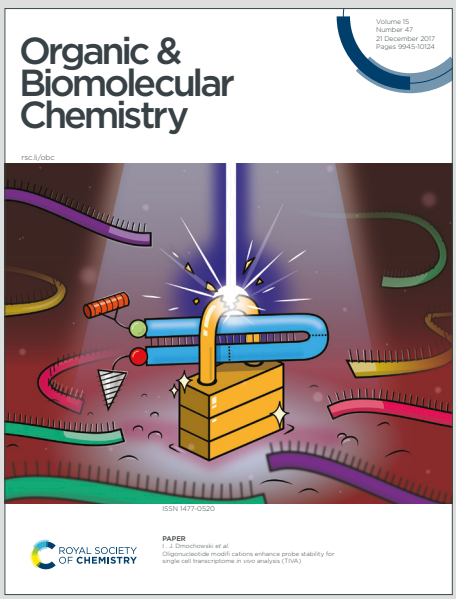

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Access to chiral α-substituted-β-hydroxy arylphosphonates enabled by biocatalytic dynamic reductive kinetic resolution

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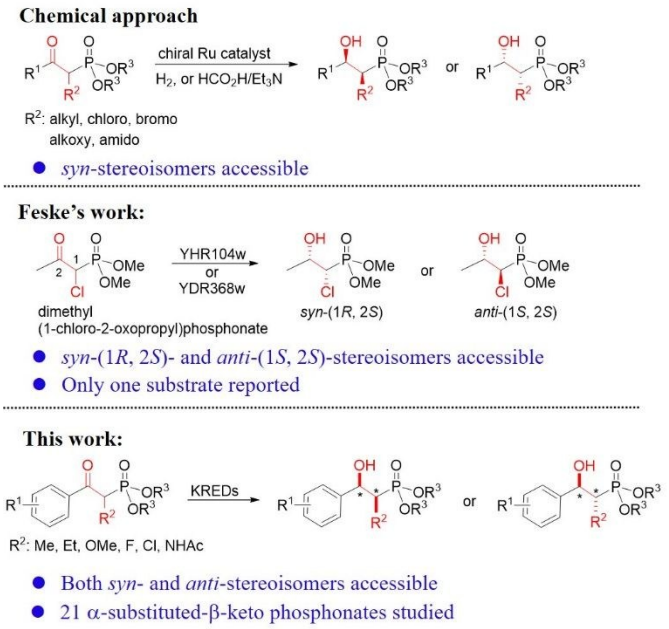
Ketoreductase (KRED)-catalyzed dynamic reductive kinetic resolution (DYRKR) of α-substituted-β-keto arylphosphonates was developed as a generic and stereoselective approach to synthesize chiral α-substituted-β-hydroxy arylphosphonates, with moderate-to-excellent isolated yield (up to 96%), good-to-excellent diastereoselectivity (up to >99:<1 dr), and excellent enantioselectivity (up to >99% ee) being achieved.

Introduction

Capable of setting up two stereogenic centers with a maximum theoretical yield of 100% renders dynamic reductive kinetic resolution (DYRKR) a step-economic process.[1] Within this context, ketoreductase (KRED)-catalyzed DYRKR in particular has drawn increasing attention in recent years, owing to intrinsic properties of enzyme catalysis, such as high stereoselectivity and environmental sustainability.[2] Among others, α-substituted-β-keto esters, nitriles, and sulfones all have been reported as effective substrates in KRED-catalyzed DYRKR, furnishing synthetically useful α-substituted-β-hydroxy esters, nitriles, and sulfones, respectively.[3]

Many α-substituted-β-hydroxy phosphonates show interesting and potent bioactivities.[4] Like other members in the phosphonate family, a class of both man-made and naturally occurring compounds containing a C-P bond, the bioactivities of α-substituted-β-hydroxy phosphonates are mainly attributed to their structural similarity to the corresponding phosphate esters and carboxylates.[4a] Enantioenriched α-substituted-β-hydroxy phosphonates also serve as versatile synthetic intermediates to other bioactive phosphonate molecules.[4b, 4d, 5]

Hence, development of an efficient and stereoselective synthesis of chiral α-substituted-β-hydroxy phosphonates is of great importance. In this regard, chiral ruthenium complex-catalyzed DYRKR has previously been employed for highly diastereo- and enantioselective preparation of a wide range of α-substituted-β-hydroxy phosphonates, including α-alkyl-, α-halo-, α-amido-, and α-alkoxy-β-hydroxy phosphonates (Scheme 1).[5, 6] Notably, only *syn*-diastereomers were accessible by using these chemical methods.



Scheme 1 Different approaches to the stereoselective DYRKR of α-substituted-β-keto phosphonates.

On the other hand, KRED-catalyzed DYRKR on α-substituted-β-keto phosphonates has been rarely studied. To the best of our knowledge, the only report was from the Feske group, who reported the KRED-catalyzed DYRKR of dimethyl(1-chloro-2-oxopropyl)phosphonate, stereoselectively generating the corresponding *syn*-(1*R*, 2*S*)-alcohol and *anti*-(1*S*, 2*S*)-alcohol for

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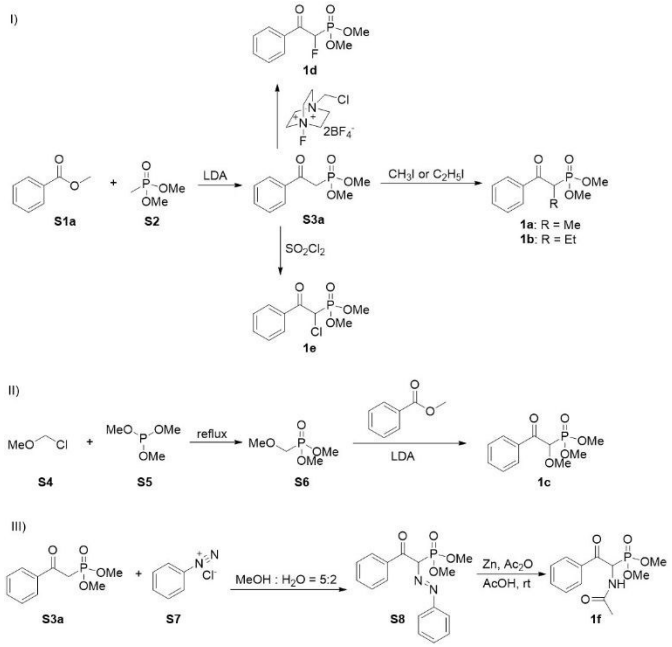
the chemo-enzymatic synthesis of fosfomycin and its diastereomer, respectively (Scheme 1).[7] Prior to our study, the generic applicability of KRED-catalyzed DYRKR to the synthesis of chiral α-substituted-β-hydroxy phosphonates, in particular the sterically demanding α-substituted-β-hydroxy arylphosphonates, had not been demonstrated. Herein, we report the first systematic study of KRED-catalyzed DYRKR of 21 β-keto arylphosphonates, and demonstrated the feasibility of this method for generic synthesis of chiral α-substituted-β-hydroxy arylphosphonates.

Results and discussion

Six β-keto arylphosphonates with different α-substituents (**1a**-**1f**) were chemically synthesized (Scheme 2, Scheme S1-S6). Briefly, the reaction between methyl benzoate **S1a** and dimethyl methylphosphonate **S2** in the presence of LDA generated dimethyl (benzoylmethyl)phosphonate **S3a**, which was used for the synthesis of **1a** and **1b** via α-alkylation, and the synthesis of **1d** and **1e** via α-halogenation, respectively. Dimethyl (methoxymethyl)phosphonate **S6**, prepared from the reaction of chloro(methoxy)methane **S4** and trimethyl phosphite **S5**, reacted with methyl benzoate to afford compound **1c**. Finally, the coupling of dimethyl (benzoylmethyl)phosphonate **S3a** and benzenediazonium chloride **S7** produced the intermediate **S8**, which was reduced and acetylated to give compound **1f**.



Scheme 2 Chemical synthesis of α-substituted-β-keto arylphosphonates **1a**-**1f**.

14 KREDs were selected to test their catalytic ability against **1a**-**1f** (Table S1). Many of these KREDs, such as RasADH and CaADH, have previously been shown to catalyze DYRKR on β-keto esters.[3e-3i] YDR368w and YHR104w were revealed by the Feske group as the effective and stereo-complementary KREDs for the DYRKR of dimethyl(1-chloro-2-oxopropyl)phosphonate.[7] Two other KREDs in this list, KmCR2 and SsCR, were chosen because of their demonstrated activity on reducing 'bulky-bulky' ketones, for instance, diarylmethanones.[8] This initial screening of reactivity was performed in analytical scale using purified KREDs and glucose dehydrogenase (GDH), with the latter being used for recycling NADPH (Table 1 and Table S2-S7). For ketone with a methyl group at the α-position (**1a**), most of the KREDs tested could transform it to the corresponding alcohol **2a**. KmCR2 and RasADH produced *anti*-(1*S*, 2*S*)-**2a** and *anti*-(1*R*, 2*R*)-**2a** in 17:1 and 12:1 *dr*, respectively, and both with perfect enantiomeric purity (>99% *ee*), whereas one enantiomer of *syn*-**2a** was obtained in CaADH-catalyzed reduction reaction with excellent *dr* and *ee*, but low yield (10% conv.) (entry 1-3, Table 1). In contrast, all the KREDs tested except YNL331c failed to reduce ketone **1b** with an α-ethyl substituent, suggesting the steric effect at the α-position played an important role in reactivity (Table S3). Although YNL331c-catalyzed reduction of **1b** reached complete conversion, the diastereoselectivity was rather poor (1.6:1 *dr*). The replacement of the ethyl group by a methoxy group slightly increased the reactivity, evidenced by that all the KREDs tested could reduce ketone **1c** to some extent (Table S4). We attribute this enhanced reactivity to the stronger inductive effect of the oxygen atom relative to that of the carbon atom, which renders the carbonyl carbon of **1c** more electron-deficient and hence more susceptible to reduction by KREDs. Both α-fluoro ketone (**1d**) and α-chloro ketone (**1e**) turned out to be suitable substrates for this KRED-catalyzed DYRKR process. The use of YDL124w and YDR368w enabled the efficient access to *anti*-(1*S*, 2*R*)-**2d** and one enantiomer of *syn*-**2d**, respectively, in excellent *dr* and *ee*, whereas KRED-F42-catalyzed reduction of **1d** gave the other *syn*-isomer of **2d** with 4:1 *dr* and >99% *ee* (entry 4-6, Table 1). On the other hand, KmCR2 and RasADH were proved as the most effective enzymes for the reduction of **1e**, yielding *anti*-(1*S*, 2*S*)-**2e** and *anti*-(1*R*, 2*R*)-**2e** in 26:1 and 8:1 *dr*, respectively, and both with >99% *ee* (entry 7-8, Table 1). The reduction of **1e** to one enantiomer of *syn*-**2e** catalyzed by YDR368w also proceeded in a highly stereoselective manner (91:1 *dr* and >99% *ee*) (entry 9, Table 1). However, the reaction conversion was only 26%, much lower than that reported in the YDR368w-catalyzed reduction of dimethyl(1-chloro-2-oxopropyl)phosphonate (97%).[7] The different reaction conversions likely resulted from the distinct steric bulkinesses of these two substrates (phenyl *versus* methyl). Finally, similar as in the reduction of **1b**, YNL331c was the only KRED capable of reducing the sterically demanding ketone **1f** (entry 10, Table 1, and Table S7). Fortunately, the stereoselectivity of this reaction was excellent, furnishing one enantiomer of *anti*-**2f** in >99:<1 *dr* and >99% *ee*. In present, the origin of the unique capability of YNL331c towards the reduction of sterically demanding substrates, such as **1b** and **1f**, is unknown and deserves more detailed studies in the future. It is worth noting that we have attempted to improve the diastereoselectivity of some reactions using approaches such as lowering reaction temperature, decreasing enzyme loading, or changing the pH of the reaction buffer.[9] To our disappointment, no improvement has been achieved. The complete screening results are provided in Table S2-S7.

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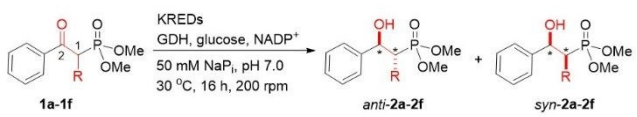
Table 1 Screen KREDs on reduction of α-substituted-β-keto arylphosphonates **1a**-**1f**.[a]



1a: R = Me; **1b**: R = Et; **1c**: R = OMe; **1d**: R = F; **1e**: R = Cl; **1f**: R = NHAc

Entry	Subs.	Enzyme	Conv. [%][b]	*dr* (*anti*:*syn*)[c]	*ee anti* [%][d]	*ee syn* [%][d]
1	**1a**	KmCR2	62	17:1	>99 (1*S*, 2*S*)	n.d.[e]
2	**1a**	RasADH	91	12:1	>99 (1*R*, 2*R*)	n.d.
3	**1a**	CaADH	10	<1:>99	n.d.	96[f]
4	**1d**	YDL124w	>99	86:1	>99 (1*S*, 2*R*)	n.d.
5	**1d**	YDR368w	69	1:27	n.d.	>99[f]
6	**1d**	KRED-F42	>99	1:4	93[f]	>99[f]
7	**1e**	KmCR2	>99	26:1	>99 (1*S*, 2*S*)	n.d.
8	**1e**	RasADH	>99	8:1	>99 (1*R*, 2*R*)	65[f]
9	**1e**	YDR368w	26	1:91	n.d.	>99[f]
10	**1f**	YNL331c	>99	>99:<1	>99[f]	n.d.

[a] Reaction conditions (1 mL): **1a**-**1f** (10 mM), glucose (20 mM), $NADP^+$ (0.2 mM), purified KREDs and GDH (1 mg/mL each) in NaP_i buffer (50 mM, pH 7.0). Reaction mixtures were incubated at 30 °C with 200 rpm shaking for 16 h. [b] The reaction conversion was determined by ^1H NMR. [c] The *dr* was determined by chiral HPLC analysis and the relative configuration of the product (*syn* or *anti*) was assigned based on the coupling constant observed in ^1H NMR. [d] The *ee* was determined by chiral HPLC analysis, and the absolute configuration was assigned by X-ray crystallography in the below section of semi-preparative scale synthesis. [e] n.d.: not determined. [f] The absolute configuration was not assigned.

To demonstrate the synthetic applicability, this KRED-catalyzed DYRKR process was then carried out at semi-preparative scale (0.45 mmol) (Table 2). α-methyl-substituted ketone **1a** and α-chloro-substituted ketone **1e** were smoothly reduced by KmCR2 and RasADH to furnish the enantiomeric pairs of *anti*-**2a** and *anti*-**2e** in 56%-to-79% isolated yields, with the diastereomeric and enantiomeric purities comparable to those observed in the analytical scale reactions (entry 1-2 and 6-7, Table 2). Similarly, α-amido-substituted alcohol *anti*-**2f** wasisolated in 83% yield along with 31:1 *dr* and >99% *ee* in YNL331c-catalyzed reduction of ketone **1f** (entry 8, Table 2). The bioreduction of the α-fluoro-substituted ketone **1d** at semi-preparative scale appeared to be less efficient. YDL124w delivered *anti*-(1*S*, 2*R*)-**2d** in 71% yield, but the diastereoselectivity and enantioselectivity (7:1 *dr* and 73% *ee*) were worse compared to those in the corresponding analytical scale reaction (entry 3, Table 2). On the other hand, although the stereoselectivity was excellent, the isolated yield of *syn*-**2d** in YDR368w-catalyzed reduction of ketone **1d** was only 36% (entry 4, Table 2). KRED-F42 produced the other *syn*-isomer of **2d** with 6:1 *dr* and >99% *ee* (entry 5, Table 2).

At this point, we wanted to further evaluate the substrate scope of our reaction. 11 α-chloro-β-keto phosphonates with different aryl groups (**1g**-**1q**) were thus prepared. KmCR2 was able to readily transform all the 11 ketones to the corresponding *anti*-(1*S*, 2*S*)-alcohols in 43%-to-76% isolated yields, along with 10:1-to->99:<1 *dr* and 87%-to->99% *ee* (entry 9, 11, 13, 15, 17, 19, 21, 24, 27, 29, and 32, Table 2). The absolute configuration of the bromo-containing alcohol *anti*-(1*S*, 2*S*)-**2k** was established by X-ray crystallography (Figure 1), and the configuration of the other alcohols in this series was assigned in analogy. On the other hand, although highly enantioselective (all >99% ee), RasADH-catalyzed reduction of some of these ketones proceeded in a less diastereoselective manner. For instance, the diastereomeric purities of the hetero-aryl containing alcohols *anti*-(1*R*, 2*R*)-**2p** and *anti*-(1*R*, 2*R*)-**2q** were only 4:1 and 2:1 *dr*, respectively (entry 30 and 33, Table 2). To our delight, by using SyADH,[10] an KRED having the same stereoselectivity as RasADH,[11] the diastereomeric purities of these two alcohols could be improved to >99:<1 and 22:1 *dr*, respectively, with the enantiomeric purities being improved as well (entry 31 and 34, Table 2). Again, the absolute configuration of the bromo-containing alcohol *anti*-(1*R*, 2*R*)-**2k** produced by RasADH was established by X-ray crystallography (Figure 1), further supporting our stereochemical assignment. Finally, the diethyl phosphonate **1r** and the diisopropyl phosphonate **1s** were also synthesized and subjected to the KmCR2- and RasADH-catalyzed reduction reactions (entry 35-38, Table 2). Interestingly, the alcohol products **2r** and **2s** isolated from these reactions exhibited comparable, or even better diastereomeric purities than the corresponding dimethyl phosphonate **2e**. With these results, we envisioned that by replacing the dimethyl moiety with the diethyl or diisopropyl moiety, the diastereoselectivity of certain bioreduction reactions might be improved. Indeed, the diastereoselectivities of RasADH-catalyzed reduction of diethyl phosphonates **1t** and **1u** were 12:1 and 23:1 *dr*, respectively (entry 39-40, Table 2), superior to those of the same enzyme-catalyzed reduction of the dimethyl counterparts **1i** and **1j** (both 7:1 *dr*, entry 14 and 16, Table 2). Collectively, our studies suggest that the stereoselectivity of KRED-catalyzed DYRKR process could be improved both by using more selective enzymes and by using a substrate engineering strategy.

Notably, most of these synthesized phosphonates have never been reported before, we therefore were interested in examination of their bioactivity potential. Two Gram-positive strains (*Bacillus subtilis* 168 and *Staphylococcus aureus* CMCC(B) 26003), and two Gram-negative strains (*Escherichia coli* BL21 and *Pseudomonas aeruginosa* CICC10351) were employed for bioactivity tests. Our preliminary results indicated that 11 thus synthesized compounds had weak inhibitory activities against at least one of the four strains tested (Table S8). In particular, alcohol *anti*-(1*R*, 2*R*)-**2u** exhibited weak activities against all four strains. In the future, we will harness the power of the developed biocatalytic method to carry out in-depth structure-activity relationship study in order to find stereo-defined α-substituted-β-hydroxy phosphonates with more potent bioactivities.

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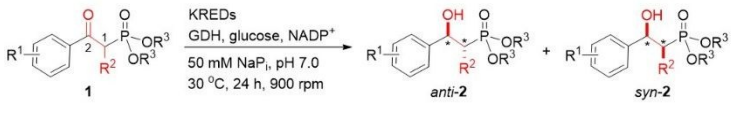
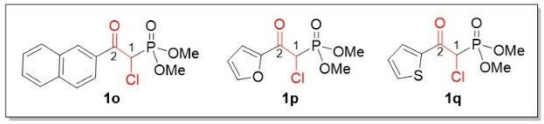
Table 2 Semi-preparative scale synthesis of α-substituted-β-hydroxy arylphosphonates. [a]





Entry	Subs. (R^1, R^2, R^3)	Enzyme	Yield [%][b]	*dr* (*anti*:*syn*)[c]	*ee anti* [%][d]	*ee syn* [%][d]
1	**1a** (H, Me, Me)	KmCR2	71	13:1	99 (1*S*, 2*S*)	n.d.[e]
2	**1a** (H, Me, Me)	RasADH	56	26:1	>99 (1*R*, 2*R*)	n.d.
3	**1d** (H, F, Me)	YDL124w	71	7:1	73 (1*S*, 2*R*)	n.d.
4	**1d** (H, F, Me)	YDR368w	36	1:19	n.d.	99[f]
5	**1d** (H, F, Me)	KRED-F42	79	1:6	n.d.	99[f]
6	**1e** (H, Cl, Me)	KmCR2	79	22:1	>99 (1*S*, 2*S*)	n.d.
7	**1e** (H, Cl, Me)	RasADH	67	10:1	>99 (1*R*, 2*R*)	n.d.
8	**1f** (H, NHAc, Me)	YNL331c	83	31:1	>99[f]	n.d.
9	**1g** (*p*-Me, Cl, Me)	KmCR2	56	47:1	99 (1*S*, 2*S*)	n.d.
10	**1g** (*p*-Me, Cl, Me)	RasADH	78	11:1	>99 (1*R*, 2*R*)	n.d.
11	**1h** (*p*-OMe, Cl, Me)	KmCR2	43	10:1	88 (1*S*, 2*S*)	n.d.
12	**1h** (*p*-OMe, Cl, Me)	RasADH	79	21:1	>99 (1*R*, 2*R*)	n.d.
13	**1i** (*p*-F, Cl, Me)	KmCR2	76	13:1	99 (1*S*, 2*S*)	n.d.
14	**1i** (*p*-F, Cl, Me)	RasADH	89	7:1	>99 (1*R*, 2*R*)	n.d.
15	**1j** (*p*-Cl, Cl, Me)	KmCR2	64	11:1	89 (1*S*, 2*S*)	n.d.
16	**1j** (*p*-Cl, Cl, Me)	RasADH	67	7:1	>99 (1*R*, 2*R*)	n.d.
17	**1k** (*p*-Br, Cl, Me)	KmCR2	51	15:1	90 (1*S*, 2*S*)	n.d.
18	**1k** (*p*-Br, Cl, Me)	RasADH	68	11:1	>99 (1*R*, 2*R*)	n.d.
19	**1l** (*p*-CF_3, Cl, Me)	KmCR2	52	12:1	87 (1*S*, 2*S*)	n.d.
20	**1l** (*p*-CF_3, Cl, Me)	RasADH	77	10:1	>99 (1*R*, 2*R*)	n.d.
21	**1m** (*m*-F, Cl, Me)	KmCR2	69	15:1	>99 (1*S*, 2*S*)	n.d.
22	**1m** (*m*-F, Cl, Me)	RasADH	74	9:1	>99 (1*R*, 2*R*)	n.d.
23	**1m** (*m*-F, Cl, Me)	SyADH	96	15:1	94 (1*R*, 2*R*)	n.d.
24	**1n** (*o*-F, Cl, Me)	KmCR2	71	>99:<1	>99 (1*S*, 2*S*)	n.d.
25	**1n** (*o*-F, Cl, Me)	RasADH	67	5:1	>99 (1*R*, 2*R*)	n.d.
26	**1n** (*o*-F, Cl, Me)	SyADH	94	23:1	97 (1*R*, 2*R*)	n.d.
27	**1o**	KmCR2	58	29:1	>99 (1*S*, 2*S*)	n.d.
28	**1o**	RasADH	68	11:1	>99 (1*R*, 2*R*)	n.d.
29	**1p**	KmCR2	72	>99:<1	>99 (1*S*, 2*S*)	n.d.
30	**1p**	RasADH	69	4:1	65 (1*R*, 2*R*)	n.d.
31	**1p**	SyADH	63	>99:<1	>99 (1*R*, 2*R*)	n.d.
32	**1q**	KmCR2	72	18:1	>99 (1*S*, 2*S*)	n.d.
33	**1q**	RasADH	78	2:1	94 (1*R*, 2*R*)	n.d.
34	**1q**	SyADH	52	22:1	96 (1*R*, 2*R*)	n.d.
35	**1r** (H, Cl, Et)	KmCR2	79	24:1	>99 (1*S*, 2*S*)	n.d.
36	**1r** (H, Cl, Et)	RasADH	92	22:1	>99 (1*R*, 2*R*)	n.d.
37	**1s** (H, Cl, *i*-Pr)	KmCR2	92	68:1	>99 (1*S*, 2*S*)	n.d.
38	**1s** (H, Cl, *i*-Pr)	RasADH	87	48:1	95 (1*R*, 2*R*)	n.d.
39	**1t** (*p*-F, Cl, Et)	RasADH	80	12:1	95 (1*R*, 2*R*)	n.d.
40	**1u** (*p*-Cl, Cl, Et)	RasADH	68	23:1	99 (1*R*, 2*R*)	n.d.

[a] Reaction conditions (50 mL): the semi-preparative scale reaction was carried out with **1a**-**1u** (125 mg), glucose (1 g), $NADP^+$ (50 mg), 35 mL 30% (w/v) cell-free extract (CFE) of KREDs in NaP_i buffer (50 mM, pH 7.0), 10 mL 15% (w/v) CFE of GDH in NaP_i buffer (50 mM, pH 7.0) and 0.5 mL DMSO at 30 ℃ and 900 rpm for 24 h. [b] Isolated yield. [c] The *dr* was determined by chiral HPLC analysis and the relative configuration of the product (*syn* or *anti*) was assigned based on the coupling constant observed in ^{1}H NMR. [d] The *ee* was determined by chiral HPLC analysis, and the absolute configuration was assigned by X-ray crystallography. [e] n.d.: not determined. [f] The absolute configuration was not assigned.

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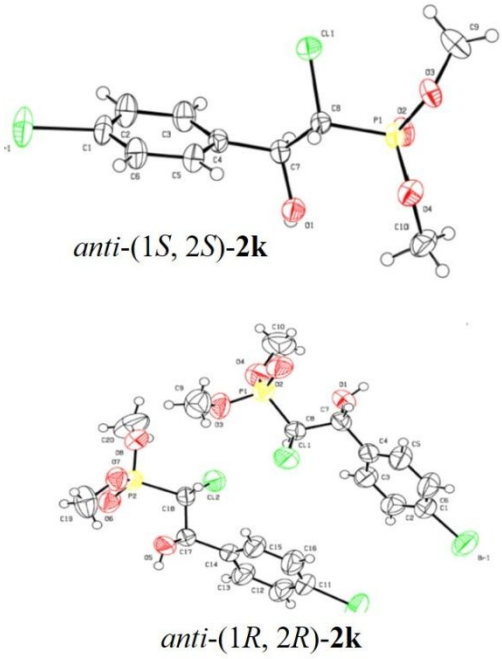

Figure 1 Crystal structures of *anti*-(1*S*, 2*S*)-**2k** and *anti*-(1*R*, 2*R*)-**2k**.

Conclusions

In summary, 14 KREDs were examined for their catalytic ability on structurally diverse α-substituted-β-keto arylphosphonates, generating the corresponding α-substituted-β-hydroxy arylphosphonates in moderate-to-excellent isolated yield (up to 96%), along with good-to-excellent diastereomeric purity (up to >99:<1 *dr*) and excellent enantiomeric purity (up to >99% *ee*). Our systematic study not only represents as the first KRED-catalyzed DYRKR of α-substituted-β-keto arylphosphonates, but also demonstrates that KRED-catalyzed DYRKR can be employed as a generic, valuable and environmentally sustainable approach, in many cases complementary to the existing chemical methods, to prepare chiral α-substituted-β-hydroxy phosphonates of synthetic importance and bioactivity potential, with the latter aspect being supported by our preliminary bioactivity test. We envision that through new enzyme discovery and protein engineering, currently problematic substrates such as α-ethyl-substituted ketone **1b** would eventually become suitable substrates for KRED-catalyzed DYRKR reaction in the future, thereby further expanding the scope of the developed biocatalytic method.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ Crystallographic data for compounds *anti*-(1*S*, 2*S*)-**2k** (CCDC-1975103) and *anti*-(1*R*, 2*R*)-**2k** (CCDC-1975107) has been deposited to the Cambridge Crystallographic Data Centre.

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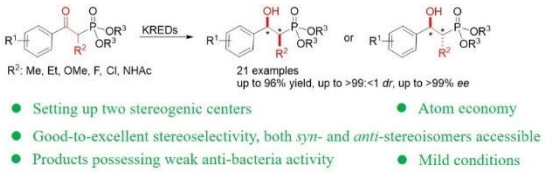

A ketoreducatse (KRED)-catalyzed dynamic reductive kinetic resolution process was developed for highly stereoselective and step-economic synthesis of chiral α-substituted-β-hydroxy arylphosphonates