Enzyme-Mediated Cross-Benzoin Reaction of Highly Enolizable Aldehydes and Aryl Aldehydes for Acess to Chiral Phosphonates

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Abstract: Enzymatic catalysis has emerged as an attractive technology for organic synthesis but remains in its infancy for constructing biologically-relevant chiral phosphonates. Here, we disclose a highly chemo- and enantioselective reactions between highly enolizable 2-phosphonate aldehydes and aryl aldehydes for synthesis of chiral phosphonates. This reaction mediated by *Pf*BAL or its mutant A28G features the first example of cross-benzoin reaction involving highly enolizable aldehydes, an elusive challenge previously. Unlike the small molecule NHC-mediated process that give complex mixture of multiple adducts, our enzymatic process selectively gives biologically active hydroxyl ketone-containing phosphonate products in excellent yields and enantioselectivities. The chiral phosphonate products can be obtained on gram scales and carry rich reactivities for further downstream transformation to afford diverse molecules, which will bring more opportunity to the development of novel C-P drugs. This work opened a new avenue in the development of novel cross-benzoin reaction and will stimulate the widespread application of cross-benzoin in organic synthesis.

Chiral organophosphates are unique moieties with a large presence in medicines, agrochemicals, natural products (figure 1a). [1, 2] Not surprisingly, various chemical synthetic methods, such as asymmetric hydrogenation,[3] hydrophosphination,[4] addition to unsaturated phosphonates,[5] and transition metal-catalyzed cross-coupling reaction [6] have been well developed for preparing chiral organophosphates. However, these methods heavily depend on complex chiral ligands or organic catalysts and suffer from high costs and environmental problems. Enzymatic catalysis has emerged as an attractive technology for organic synthesis due to its high efficiency, unparalleled levels of selectivity, and environmentally-friendly nature.[7] Nevertheless, only a handful of enzymatic methods has been developed for synthetizing chiral organophosphates.[8-10] Lipase-mediated kinetic resolution of racemic alcohols or esters has been used for the synthesis of chiral phosphates, but affords products with a less than 50% yield. [8] To break through the bottleneck of yield, reductase-catalyzed reduction of ketophosphonates or vinylphosphonates has been developed.[9] Very recently, an elegant work concerning synthesis of cyclopropylphosphonates was achieved with engineered carbene transferases by Fasan and co-workers.[10] Although these progress, the synthesis of chiral phosphonates by enzyme remains largely undeveloped. A novel biocatalytic system, especially those with broad substrate scope and giving products with rich reactivities for further transformation, was still highly demanded.

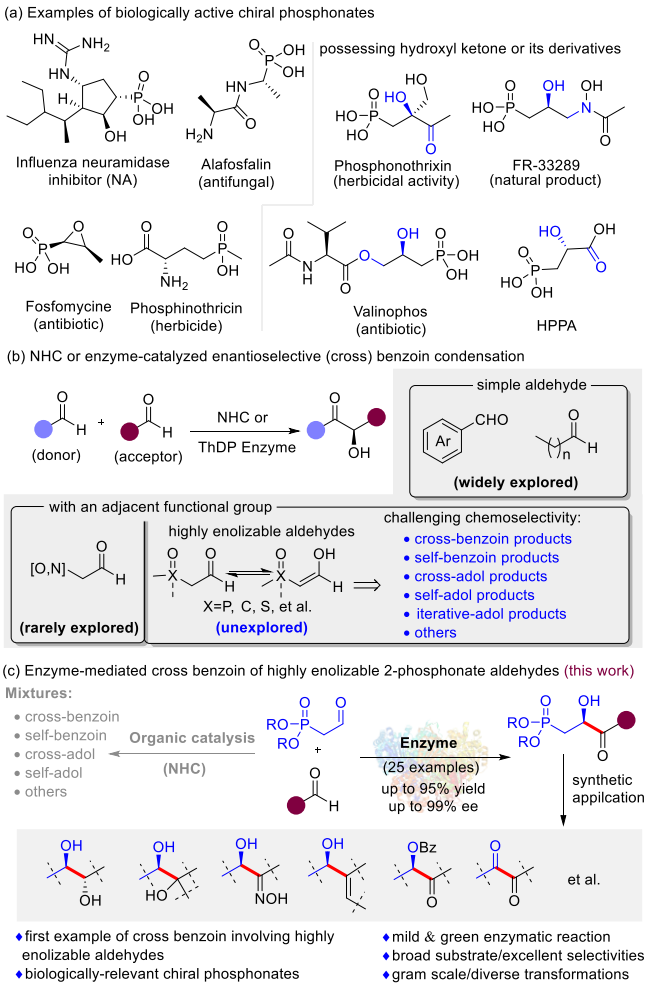


Figure 1. Chiral organophosphate-containing molecules and cross-benzoin reactions

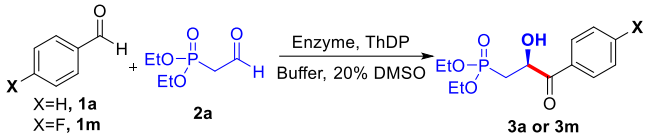
Benzoin or cross benzoin reaction of two aldehydes (electron donor and acceptor aldehydes) enabled by N-heterocyclic

carbene (NHC) organic catalysts [11] or ThDP-dependent enzymes (comprising an NHC core) [12] has emerged as one of most powerful tools to forge new C-C bond stereoselectively (figure 1b). In previous studies, the vast majority of benzoin reactions were condensation between two simple aldehydes (figure 1b).[13] The introduction of adjacent functional groups to aldehyde unit, especially the acceptor aldehyde (forming chiral hydroxyl group), will increase the complexity of the product molecules and offer more opportunity to obtain complex natural products or medicines concisely. However, the related research is largely underdeveloped (figure 1b). The only reports involving acceptor aldehydes with an adjacent N- or O- functional group, giving the ketone-neighboring chiral vicinal diol or amino alcohol compounds with a huge potential for further transformations.[14] Significantly, these work has fostered the synthesis of complex natural products via a shortened route.[15] Although these elegant progress, the introduction of other types of functional groups, especially the electron-withdrawing group (EWG) such as ester or phosphate groups, widely present in natural products or drug molecules, are still unexplored and in its urgent need. However, since such aldehydes are highly enolizable, a series of potential side reactions, such as self-/cross-benzoin, self-/cross-aldol reactions, iterative aldol reactions, and NHC-catalyzed Stetter reaction of the aldol products, will significantly complicate the chemoselectivity issue in cross benzoin. (figure 1b).[11, 12, 16] Accordingly, the development of chemoselective cross-benzoin reactions of highly enolizable aldehydes, especially those with the control of the stereochemistry simultaneously, represents a highly desirable and challenging goal.

Herein, we disclosed the ThDP-dependent benzaldehyde lyase catalyzed highly chemoselective cross benzoin of readily available 2-phosphonate aldehydes with the control of the stereochemistry simultaneously, the first success of cross benzoin reaction of highly enolizable aldehydes (figure 1c). This process enabled by enzyme (cell free lysate) is mild and green, giving the biologically active *β*-hydroxy phosphonates with high yields and excellent chemo- and enantioselectivities. In addition, this reaction exhibits broad substrate scope and can be performed on gram scales. The chiral phosphonate products carry rich reactivities and can be transformed to diverse phosphonate molecules. Notably, the phosphonates possessing hydroxyl ketones and products derivatized thereof have found wide presence in natural products and bioactive molecules such as agrochemicals and medicines (figure 1a).

We initiated our studies by investigating a panel of structurally diverse ThDP dependent enzymes (cell free lysates) for catalyzing the cross-benzoin reaction of **1a** or **1m** with 2-phosphonate acetaldehyde **2a**, with key results summarized in Table 1 (see supporting information for details). The results show that benzaldehyde lyase from pseudomonas fluorescens (*Pf*BAL, PDB ID: 3D7K) furnish the chiral phosphonate **3a** in 90% yield and 98% ee (entry 3). However, a sharply decreased yield was observed when we used electron-withdrawing group substituted **1m** substrate (entry 3). Subsequently, we focused on the engineering of *Pf*BAL to enhance the reactivity of substrate **1m** through site saturation mutagenesis (SSM). Firstly, a molecular docking of ThDP-bound **3m** precursor with *Pf*BAL protein was performed (figure 2a). And four key residues (Y397, L112, Q113 and A28) located within 4 Å of the ThDP-bound **3m** precursor were selected as hot-spots for SSM. However, no positive mutant was identified when we performed SSM at residue Y397, L112 and Q113, and most of the mutants exhibited no catalytic activity. Surprisingly, the next round of SSM at residue A28 shows that significant improvement of yield was achieved by using the mutant A28G, giving the desired **3m** with 95% yield and 99% ee (figure 2a) (see supporting information for details). We then tested the reactivity of mutant A28G for substrate **1a** and found identical level of reactivity and enantioselectivity were achieved. Although four (cross) benzoin products can be formed, the only side product was self-benzoin product of **1a** or **1m** during the screening the reactivities of wild-type enzyme and mutants (see supporting information for details). Notably, the yield of self-benzoin side products can be decreased to below 5% under the catalysis of wild-type *Pf*BAL or its mutant A28G.

Table 1. Optimization of the Reaction Conditions.[a]



		1a⟶3a		1m⟶3m	
Entry[a]	enzyme	yield (%)[b]	ee (%)[b]	yield (%)[b]	ee (%)[b]
1	*Ss*BAL	10	98	trace	-
2	*Su*BAL	7	98	0	-
3	*Pf*BAL	**90**	**98**	**10**	**98**
4	*EcMend*	trace	-	0	-
5	*Tp*BFD	trace	-	0	-
6	KdcA	0	-	0	-
7	*Ss*PDC	0	-	0	-
8	*Ec*TK	0	-	0	-
9	*Sc*TK	0	-	0	-
10	*SeAAS*	0	-	0	-

[a] Reaction conditions: **1a** or **1n** (0.02 mmol), **2a** (0.04 mmol), cell-free extract (400 uL), ThDP (0.15 mM), $MgSO_4$ (2.5 mM), KPB buffer (50 mM, pH 7.25), DMSO (20% v/v), 1000 rpm, 20℃, 24 h; [b] Yield and ee was determined by chiral HPLC.

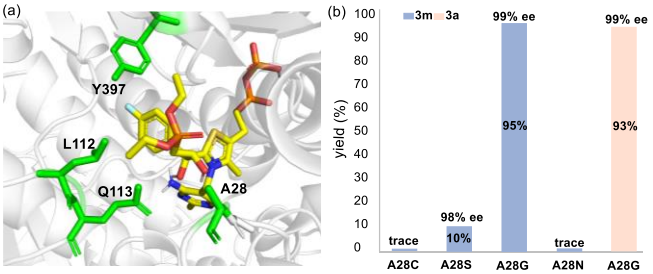
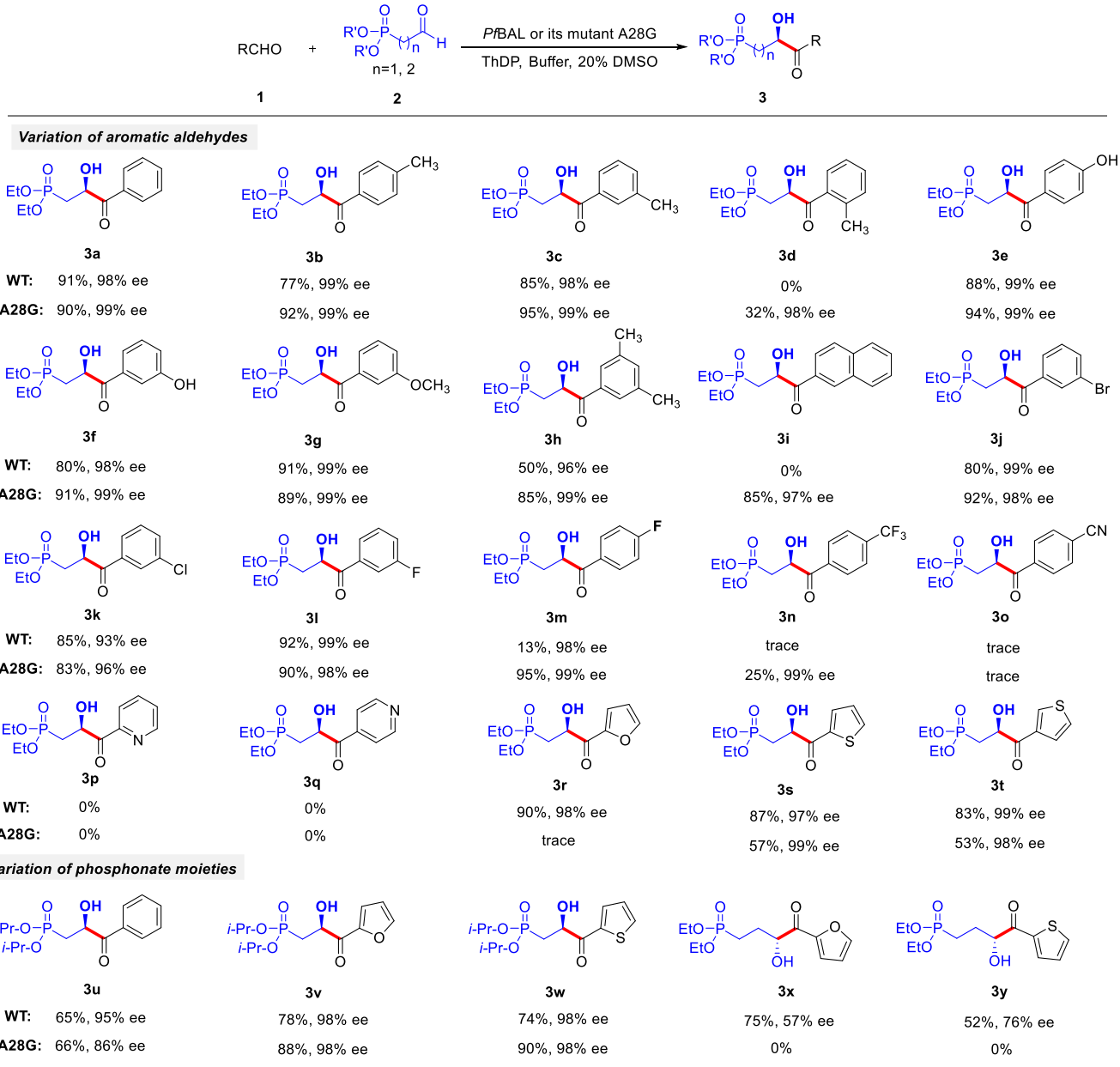


Figure 2. (a) Molecular docking of ThDP-bound **3m** precursor; (b) Screening of mutants.



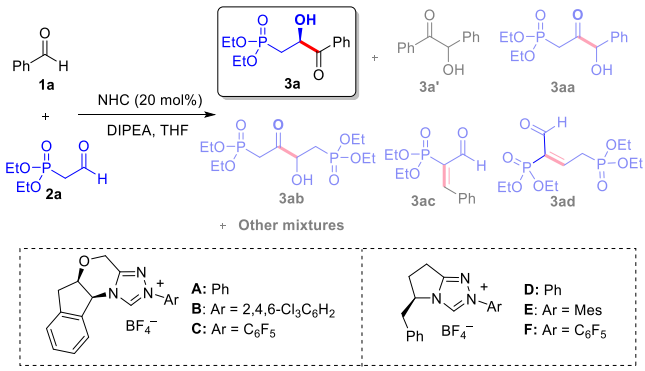
Scheme 1. Scope of BAL or its mutant A28G catalyzed enantioselective cross-benzoin reaction for synthesis of enantioenriched phosphonates. Reaction conditions: **1** (0.15 mmol), **2** (0.3 mmol), cell-free extract (55 mg/mL, 4 mL), ThDP (0.15 mM), $MgSO_4$ (2.5 mM), KPB buffer (50 mM, pH 7.25), DMSO (20% v/v), 1000 rpm, 20 ^oC, 24 h; Isolate yield.

With the wild-type *Pf*BAL and its mutant A28G in hand, we then investigated their catalytic scope for the cross-benzoin reaction involving highly enolizable aldehydes on preparative scale (Scheme 1). The results of mutant A28G catalysis show that methyl substituents at the para-, meta-, and ortho positions are well tolerated, furnishing the corresponding products (**3b** to **3d**) with 32-95% yields and excellent ee values. However, ortho substituent proved to be unreactive for wild-type *Pf*BAL. Strong electron-donating groups, such as hydroxyl or methoxy group, are also well compatible for both the wild-type and mutant, providing the products **3e**-**3g** with excellent yields and ee values. Disubstituted aldehyde afforded product (**3h**) with an increased yield for mutant A28G compared with the wild-type. Furthermore, the larger substrate 2-naphthaldehyde failed to providing the corresponding product for wild-type enzyme. However, the mutant A28G was well tolerated and give product (**3i)** with 85% yield and 97% ee due to the expansion of the active pocket. Although the wild-type showed good compatibility with various electron-withdrawing groups (such as F, Cl, Br) on meta position (**3j** to **3l**), a sharply decreased yields were observed with electron-withdrawing groups on para position (**3m** and **3n**). However, the mutant A28G is well compatible with both meta- and para- substituted electron-withdrawing groups (**3j** to **3n**). Notably, cyano- and pyridine- containing substrates displayed no reactivity under current reaction conditions. The investigation on furan and thiofuran heterocycles shows that the mutant A28G give lower reactivities than wild-type. We next tested the compatibility of other phosphonate substrates. Diisopropoxyphosphate substrates were also well accepted as acceptor aldehydes in this cross-benzoin process for mutant A28G and the wild-type. Moreover, the products (**3x** and **3y**) were formed with moderate yields and enantioselectivities when

we extend the carbon chain of phosphate substrate. We imagine that the protein engineering could be used to further improve the reactivity and stereoselectivity with these substrates.

To demonstrate the unique advantage of enzymes in controlling chemical selectivity of cross-benzoin reaction of highly enolizable aldehydes, we conduct the same reaction by using different NHC organic catalysts to gain insights into the NHC catalyzed results (Table 2). As speculated, commonly used chiral NHC catalysts **A**-**F** were incapable to fulfil this chemoselective cross-benzoin reaction (Table 2). In addition, the insufficient conversion, low yields of benzoin related products, and unsatisfactory stereoselectivities also limited the development of chemoselective cross-benzoin reaction of highly enolizable aldehyde and aryl aldehyde in NHC organic catalysis. Self- or cross-aldol reactions also appeared in all reaction systems and accompanied with other complicated by-products. These results indicate that avoiding or minimizing the competing pathways for cross-benzoin reactions involving highly enolizable aldehyde is a daunting challenge in NHC organic catalysis. By contrast, our enzymatic approach gives an unparalleled chemoselective control for this reaction with the control of the stereochemistry simultaneously via the sophisticated non-covalent interactions and molecular recognition. Our study offers a new perspective in developing selective reactions that are otherwise difficult to achieve and will encourage further development of challenging cross reaction between two substrates that bear same reactive groups.

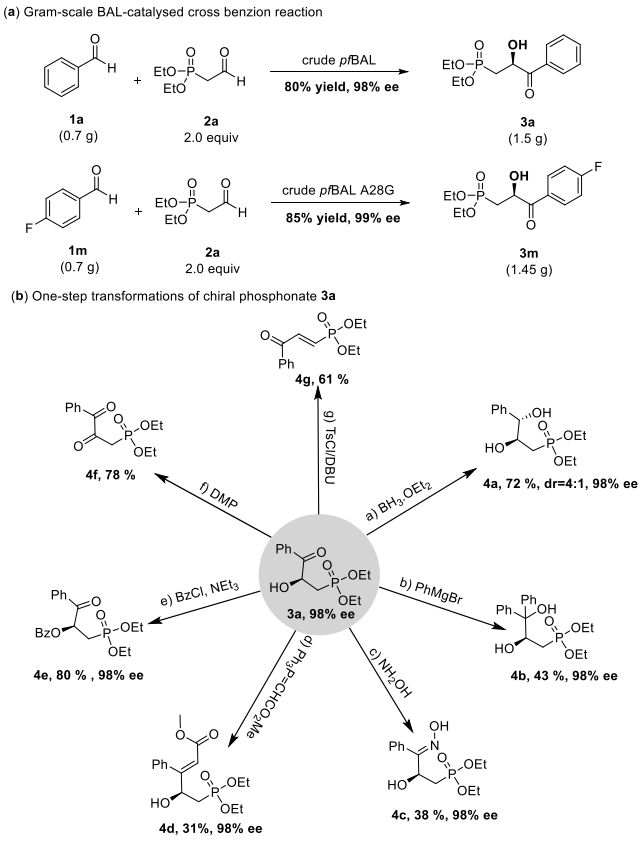
Table 2. Results of NHC-catalyzed cross-benzoin reaction involving highly enolizable aldehyde. [a]



NHC	Conv (%)[b]	3a (%)[c]	ee (%)[d]	3a' (%)[c]	3aa (%)[c]	3ab (%)[c]	3ac	3ad
NHC A	64	0	-	5	5	13	√	√
NHC B	90	14	90	46	8	14	√	√
NHC C	90	8	65	<3	14	<3	√	√
NHC D	42	<3	-	<3	<3	6	√	√
NHC E	46	<3	-	<3	0	0	√	√
NHC F	91	10	27	16	18	17	√	√

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.3 mmol), NHC (20 mol%), DIPEA (1.0 equiv) in THF (0.75 mL) at rt for 24 h; [b] Conversion was determined by GC; [c] Yields were determined by GC; [d] ee of **3a** was determined by chiral HPLC, ee of **3a'** and **3ab** were not measured.

Next, to demonstrate the utility of the current method, gram-scale reactions and product transformations were conducted (Scheme 2). The results revealed that both the wild-type and mutant enzymes can catalyze this cross-benzoin reaction of highly enolizable aldehydes on gram scales, affording the desired products in 80% yield (1.5 grams) for **3a** and 85% yield (1.45 grams) for **3m** (Scheme 2a). Furthermore, the enantioenriched phosphonate product **3a** was easily converted to various derivatives through one-step reaction (Scheme 2b). For instance, the reduction of **3a** and Grignard reaction could provide the vicinal diol-containing phosphonates **4a** and **4b**. The ketone unit of **3a** can be transformed into imine efficiently, giving the **4c** product with hydroxyl imine. Phosphonate product **3a** could react with the Wittig reagent to give alkene **4d** without the loss of ee. In addition, the compound **3a** could also be easily acylated and oxidized, affording the corresponding products (**4e** and **4f**) with good yields. In the end, the elimination of hydroxyl group was realized by reacting with toluene sulfonyl chloride in the presence of base. Notably, all the products derived from **3a** via one-step reaction could be used as versatile synthetic precursors for further transformations, such as the reduction of imine **4c** or various functionalization of alkenes **4d** and **4g**.



Scheme 2. Gram-scale reaction and product transformation.

In summary, we disclose a novel biocatalytic system for synthesis of chiral phosphonates, giving products with broad substrate scope and rich reactivities for further transformation. This reaction features the first example of chemoselective cross-benzoin reaction of highly enolizable aldehydes with the control of the stereochemistry simultaneously. This transformation mediated by enzyme is hard to achieve by using small molecule NHC catalysts due to the complex mixture of multiple adducts. The reaction is amenable for scale-up, and various functional groups can be tolerated under mild and green condition. The hydroxyl ketone-containing chiral phosphonates from our

reactions can be readily converted to various phosphonate molecules, which will bring more opportunity to the development of novel C-P drugs[19]. Further studies on the bioactivities of these chiral phosphonates for agricultural and medical applications, and application of this method to the total synthesis of complex natural products are in progress in our laboratories. We expect this study to encourage further development of challenging cross reactions between two different substrates that bear the same reactive groups and stimulates the widespread application of cross reactions in organic synthesis.

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Keywords: Enzyme-mediated • chiral phosphonates • highly enolizable • cross benzoin

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