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Benzaldehyde Lyase-Catalyzed Enantioselective Carboligation of Aromatic Aldehydes with Mono- and Dimethoxy Acetaldehyde

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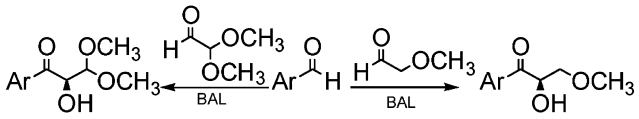
ABSTRACT

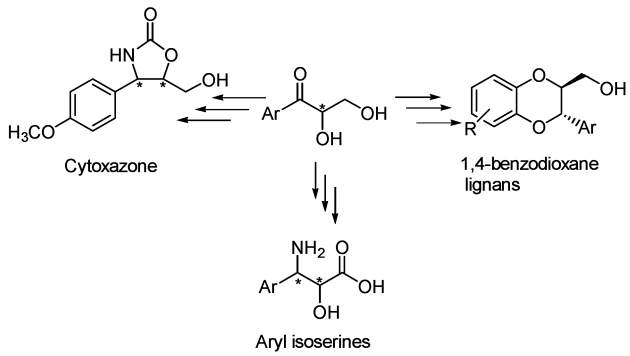


Benzaldehyde lyase from the *Pseudomonas fluorescens* catalyzes the reaction of aromatic aldehydes with methoxy and dimethoxy acetaldehyde and furnishes (*R*)-2-hydroxy-3-methoxy-1-arylpropan-1-one and (*R*)-2-hydroxy-3,3-dimethoxy-1-arylpropan-1-one in high yields and enantiomeric excess via acyloin linkage. Aromatic aldehydes and benzoins are converted into enamine-carbanion-like intermediates prior to carboligation.

Enantiopure 2,3-dioxygenated aryl propanones are highly valuable chiral synthons useful for the synthesis of various biologically active molecules such as the 1,4-benzodioxane framework, which has often been found in biologically active natural products.[1] These compounds are important starting materials for the synthesis of cytoxazone (a novel cytokine modulator),[2] the side chain of taxol, and 5′-methoxyhydnocarpin, which has multidrug pump inhibitor activity[3] (Scheme 1).

There are several methods in the literature for the synthesis of *rac*-2,3-dioxygenated aryl propanone derivatives,[4] but there are few examples of the enantioselective synthesis of these compounds. Yuen et al. synthesized (*R*)-2,3-dihydroxy-1-phenylpropan-1-one by the addition of a phenylmetallic reagent to 1,2-isopropylidene-D-glyceraldehyde followed by

Scheme 1



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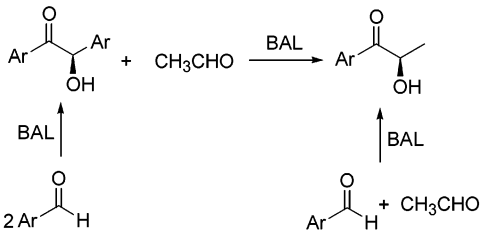
the oxidation of the newly formed hydroxy group by Moffat's reagent.[5]

In this context, the enantioselective C−C bond-forming reaction using an enzyme, i.e., a ThDP-dependent enzyme, appears to be a highly promising process. Thiamin-dependent enzymes have been used for various carbon−carbon bonding reactions.[6a] Transketolases transfer an active glycolaldehyde group from a ketose donor to an α-hydroxyaldehyde acceptor.[6b] Pyruvate decarboxylase (PDC), benzoyformate decarboxylase (BFD), and phenylpyruvate decarboxylase enzymes are capable of catalyzing acyloin-type condensation reaction leading to formation of chiral α-hydroxy ketones.[7] None of the above-mentioned enzymes are capable of catalyzing the carboligation reaction of aromatic aldehydes with derivatives of acetaldehyde.

In our ongoing studies, we reported the ability of benzaldehyde lyase (BAL), a novel thiamin diphosphate (ThDP)-dependent enzyme from *Ps. fluorescens Biovar I*, to catalyze the enantioselective formation of (*R*)- and (*S*)-benzoins and (*R*)-2-hydroxypropiophenone ((*R*)-2-HPP) derivatives via C−C bond cleavage and C−C bond formation. (*R*)-2-HPP derivatives are formed in preparative scale by benzaldehyde lyase (BAL)-catalyzed C−C bond formation from aromatic aldehydes and acetaldehyde in buffer/DMSO solution with remarkable ease in high chemical yields and high optical purity[8] (Scheme 2).

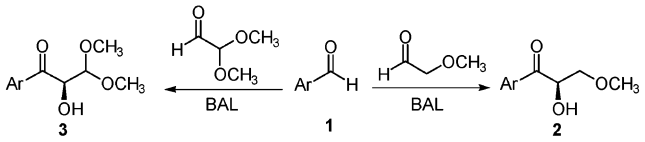
Scheme 2



In this paper, we focus on the synthetic potential of BAL with regard to its ability to catalyze C−C bond formation with aromatic aldehydes and functionalized acetaldehyde derivatives to obtain the functionalized derivatives of HPP. No such reaction was observed when using an aliphatic aldehyde other than acetaldehyde (propanal, butanal, etc.). Carboligation with functionalized acetaldehyde derivatives may be a new and efficient way to obtain important chiral polyoxo compounds.

On the basis of the preliminary information available to us from our previous work with BAL-mediated carboligation reactions of aromatic aldehydes with acetaldehyde, we tried a series of acetaldehyde derivatives for the enantioselective carboligation reaction of aromatic aldehydes (Scheme 3).

Scheme 3



Neither halogenated acetaldehyde derivatives nor glyoxal gave positive results, but methoxy and dimethoxy acetaldehydes were found to be good choices from among the readily available functionalized acetaldehyde derivatives.

Benzaldehyde (**1a**) was dissolved in potassium phosphate buffer (80 mL, 50 mM, pH 7.0, containing $MgSO_4$ (2.5 mM) and ThDP (0.15 mM)) containing 20% DMSO and methoxy acetaldehyde. After the addition of BAL, the reaction was allowed to stand at room temperature. The reaction was monitored by HPLC with a chiral column. After 48 h no more change was observed and purification of the crude product by column chromatography gave (*R*)-2-hydroxy-3-methoxy-1-phenylpropan-1-one (**2a**) in 94% yield (ee > 98%) (Table 1). A similar reaction was carried out with dimethoxy acetaldehyde, and the corresponding (*R*)-2-hydroxy-3,3-dimethoxy-1-phenylpropan-1-one (**3a**) was obtained in 91% yield and ee >98%.

This reaction was carried out with a wide range of aromatic aldehydes and heteroaromatic aldehydes, and the correspond-

Table 1. Synthetic (*R*)-2-HPP Derivatives

	ARCHO **1**	(*R*)-**2a**−**j** yield (%)[a]	(*R*)-**2a**−**j** ee (%)[b]	(*R*)-**3a**−**c** yield (%)[a]	(*R*)-**3a**−**c** ee (%)[b]
a	ph	94	>98[c]	91	>98[i]
b	2,4-$F_2C_6H_3$	81	94[c]	87	89[j]
c	4-$MeOC_6H_4$	87	92[c]	79	>98[k]
d	2-$MeOC_6H_4$	91	94[c]		
e	2-furanyl	90	95[d]		
f	4-HOC_6H_4	94	95[e]		
g	3-OH-4-$MeOC_6H_3$	72	nd[f]		
h	3,5-$F_2C_6H_3$	70	91[g]		
i	3- pyridinyl	<5[h]		<5[h]	
j	4-pyridinyl	<5[h]		<5[h]	

[a] Acetaldehyde derivatives were used in excess amounts, and yields are based on aromatic aldehydes. [b] Ee value is measured immediately after workup. [c] Chiral HPLC analysis, Chiralcel OD column, UV detection at 254 nm, 95:5 hexane/2-propanol, flow 0.6 mL/min. [d] Chiralcel OD column, UV detection at 254 nm, 90:10 hexane/2-propanol, flow 0.5 mL/min. [e] Chiralpak AD, UV detection at 254 nm, 90:10 hexane/2-propanol, flow 0.7 mL/min. [f] Not determined. [g] Chiralpak AD, UV detection at 254 nm, 80:20 hexane/2-propanol, flow 0.7 mL/min. [h] Detected by GC-MS. [i] Chiralcel OD column, UV detection at 254 nm, 85:15 hexane/2-propanol, flow 0.8 mL/min. [j] Chiralcel OD column, UV detection at 254 nm, 95:5 hexane/2-propanol, flow 0.8 mL/min. [k] Chiralcel OD column, UV detection at 254 nm, 97:3 hexane/2-propanol, flow 0.8 mL/min.

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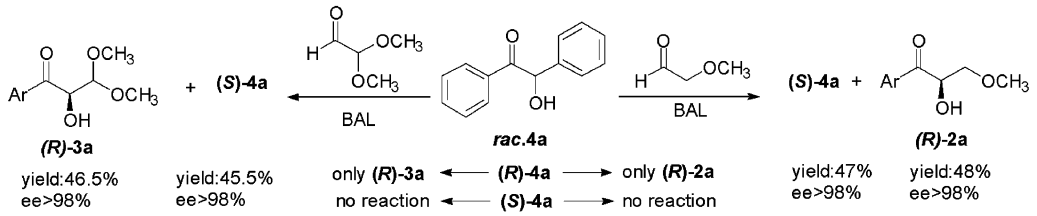
Scheme 4



ing acyloin derivatives **2a**−**j** and **3a**−**c** were obtained in high enantiomeric excess, as summarized in Table 1. The optical purity of the products was determined using HPLC with a chiral column, and the data were compared with those from racemic products synthesized either using classical chemical synthesis methodology[4a] or by racemization of chiral compounds.[9] Since HPP generated through wild-type BAL-catalyzed reaction is of (*R*)-configuration, we assumed that HPP derivatives also possess (*R*)-configuration. To determine the absolute configurations of the products, (*R*)-2-hydroxy-3-methoxy-1-phenylpropan-1-one (**2a**) was converted chemically to the known (*R*)-2,3-dihydroxy-1-phenylpropan-1-one[5] by means of a selective cleavage of ether functionality.[10]

As shown in Table 1, BAL is able to bind a broad range of different aromatic and heteroaromatic aldehydes to C2−ThDP prior to ligation. The yield of the reaction depends on the structure of the aldehyde. Fluorine substitution on the 3,5- and 2,4-positions of the phenyl ring decreased the yield of the reaction. Pyridine carbaldehyde also furnished a low yield, but furfural and *o*-methoxy benzaldehyde gave the products in high yields. The steric and electronic demand of the substituent putatively plays a decisive role in the conversion rate.

In our previous communications,[8] we showed that BAL is also able to accept benzoin as a substrate to catalyze C−C bond cleavage followed by carboligation in the presence of acetaldehyde (Scheme 2). Accordingly, (*R*)-benzoin was reacted with BAL in the presence of methoxy and dimethoxy acetaldehyde; the reaction was monitored by HPLC. Addition of the corresponding acetaldehyde derivative resulted in the formation of (*R*)-2-hydroxy-3-methoxy-1-phenylpropan-1-one (**2a**) and (*R*)-2-hydroxy-3,3-dimethoxy-1-phenylpropan-1-one (**3a**) in high yields and almost optically pure form (Scheme 4). As anticipated, the same reaction starting from (*S*)-benzoin failed. Repeating this reaction with *rac*-benzoin afforded (*R*)-**2a**, (*R*)-**3a**, and (*S*)-benzoin in optically pure form after separation of the products by column chromatography (Scheme 4). To obtain full conversion of (*R*)-benzoin into (*R*)-HPP derivatives, methoxy and dimethoxy acetaldehydes have to be used in excess and should be added to the reaction mixture at fixed time intervals. Some representative examples of the synthesis of benzoins are shown in Table 2.

Table 2. Synthetic (*S*)-Benzoins and (*R*)-**2**-HPP Derivatives

	rac **4** Ar	(*S*)-**4a**−**e** yield (%)[a]	(*S*)-**4a**−**e** ee (%)[b]	(*R*)-**2** yield (%)[a]	(*R*)-**2** ee (%)[b]
a	ph	47	>98[c]	48	>98[f]
b	2,4-$F_2C_6H_3$	44	>98[c]	38.5	93[f]
c	4-$MeOC_6H_4$	46	>98[d]	45.5	94[f]
d	2-$MeOC_6H_4$	39	>98[e]	45	96[f]
e	2-furanyl	45.5	92[c]	44	92[g]

[a] Acetaldehyde derivatives were used in excess amounts, and yields are based on benzoin. [b] Ee value is measured immediately after workup. [c] Chiralpak AD, UV detection at 254 nm, 90:10 hexane/2-propanol, flow 0.8 mL/min. [d] Chiralpak AD, UV detection at 254 nm, 75:25 hexane/2-propanol, flow 0.95 mL/min. [e] Chiralpak AD, UV detection at 254 nm, 98:2 hexane/2-propanol, flow 0.90 mL/min. [f] Chiralcel OD column, UV detection at 254 nm, 95:5 hexane/2-propanol, flow 0.6 mL/min. [g] Chiralcel OD column, UV detection at 254 nm, 90:10 hexane/2-propanol, flow 0.5 mL/min.

The results presented here are in accord with the mechanistic investigation of other ThDP-dependent enzymes. Since structural information about BAL is still lacking, a structure-based discussion of the observed stereocontrol is not yet possible.

The method described herein presents the first enzyme-catalyzed highly enantioselective synthesis of (*R*)-2-hydroxy-3-methoxy-1-arylpropan-1-one and (*R*)-2-hydroxy-3,3-dimethoxy-1-arylpropan-1-one via acyloin linkage. The reaction works in organic-aqueous medium, overcomes the solubility problem with organic substrates, and paves the way for large-scale preparation. The products are obtained in high yields starting from simple, easily available aromatic aldehydes, benzoins, and methoxy and dimethoxy acetaldehyde via C−C bond cleavage and carboligation reactions. This

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type of polyoxygenated products in optically pure form can be used for the synthesis of many biologically active compounds.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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