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Enantioselective synthesis of unsymmetrical benzoins from (*S*)-mandelic acid enolate and aromatic aldehydes

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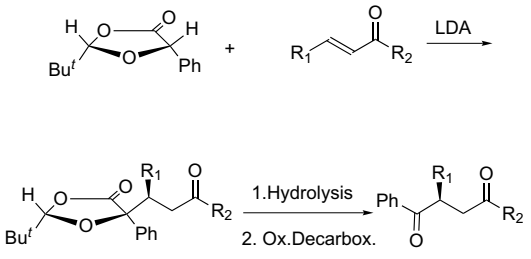
Abstract—The reaction of the lithium enolate of the 1,3-dioxolan-4-one derived from optically active (*S*)-mandelic acid and pivalaldehyde with aromatic aldehydes proceeds readily to give the corresponding aldol products in good yields and diastereoselectivities. Subsequent hydroxyl protection, basic hydrolysis of the dioxolanone, oxidative decarboxylation of the α-hydroxyacid moiety, and hydroxyl deprotection provides chiral unsymmetrical benzoins with high enantiomeric excesses.

Chiral unsymmetrically substituted benzoins constitute a valuable class of building blocks in organic and pharmaceutical chemistry due to their bifunctional nature and especially to the fact that they have a stereogenic center amenable to further synthetic manipulation.[1]

Generally the racemic compounds are prepared by cross-benzoin condensation from aromatic aldehydes in a reaction catalyzed by cyanide ions[2] or quaternary thiazolium salts ylide derived.[3] This condensation has been recognized as a reaction that involves masked acyl anion equivalents as intermediates and in fact several kinds of masked acyl anion, such as *O*-protected cyanohydrins,[4] α-(dialkylamino)nitriles,[5] cyanophosphates,[6] dithioacetals,[7] and acylsilanes[8] among other have been also used in addition reactions to carbonyl compounds to give α-hydroxyketones. However, only a few efficient enantioselective synthesis of benzoins have been described so far.[9] Recently Enders[10] and co-workers have developed a new chiral triazolium salt as precatalyst in the synthesis of symmetrical benzoins, Muller[11] and co-workers have reported the first asymmetric cross-benzoin condensation leading to a new donor–acceptor concept for enzymatic cross-coupling reactions of aldehydes and Johnson has described the enantioselective cross-silyl benzoin reaction catalyzed by metallophosphites.[12] A very interesting highlight on catalyzed reactions of acyl anion equivalents has been also published very recently by the same author.[13]

We have reported a highly diastereoselective Michael reaction of the (*S*)-mandelic acid enolate using α,β-unsaturated carbonyl compounds as acceptors and the transformation of the corresponding adducts into highly enantioenriched 2-substituted 1,4-dicarbonyl compounds[14] (Scheme 1). Formally this synthesis involves the use of (*S*)-mandelic acid as source of chiral information and as source of the benzoyl anion. In this reaction (*S*)-mandelic acid exerts the stereochemical control in the newly created stereogenic centers through its previous conversion into (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one **(2)** derived from pivalaldehyde (Seebach principle of self-regeneration of stereocenters),[15] and it acts as a masked benzoyl anion through an oxidative decarboxylation of the α-hydroxyacid moiety.[16]



Scheme 1.

Keywords: Dioxolanones; Self-regeneration of stereocenters; Aldol reaction; Oxidative decarboxylation.
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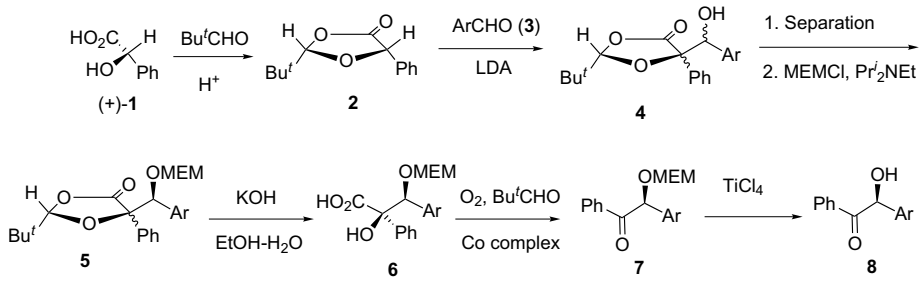

Scheme 2.

In this letter we wish to report the diastereoselective addition of the (2*S*,5*S*)-1,3-dioxolan-4-one **2** to aromatic aldehydes **3** and the transformation of the resulting aldol products **4** into highly enantioenriched unsymmetrical benzoins **8** (Scheme 2).

Initial studies were carried out using benzaldehyde **(3a)**. Treatment of **2** with a freshly prepared solution of LDA (1.25 equiv) in THF at −78 °C, followed by addition of a solution of benzaldehyde (1.25 equiv) in THF at −78 °C, stirring for 1 h and quenching with aq NH_4Cl at −78 °C, gave aldol product **4a** in 84% yield.[17] A ^1H NMR analysis of the reaction mixture revealed the presence of three out of four possible diastereomers for **4a** in a ratio 14:0:76:10, one of them being strongly predominant (Table 1, entry 1). Careful flash chromatography allowed to obtain pure the two major aldols **4a-A** and **4a-C**.

The stereochemical structures of these two diastereomers were elucidated by NOE experiments, which showed that in the case of **4a-C** the phenyl group of mandelic acid remains *syn* to the *t*-Bu group whilst in the case of **4a-A** both groups are *anti*. The absolute stereochemistry of the newly formed quaternary carbon was then assigned to be *R* for aldol **4a-C** and *S* for aldol **4a-A** upon the consideration that the absolute configuration of the dioxolanone carbon bearing the *t*-Bu group in **2** is *S* and it keeps unaltered from **2** to **4**.

The absolute configuration of the hydroxyl-supporting carbon atom in the side chain could not be determined at this stage, but it was shown to be *S* in both major aldols, **4a-C** and **4a-A** after conversion of these compounds separately in (*S*)-(+)-benzoin and comparison of the specific rotations sign with that of a commercially available authentic sample.[18] Consequently, the stereochemistry of this carbon should be *R* in both minor diastereomers **4a-D** and **4a-B**, which would differ in the stereochemistry of the quaternary carbon of the dioxolanone ring.[19]

As the final objective of our synthetic sequence is the preparation of enantioenriched unsymmetrical benzoins, and since the quaternary stereogenic center in the dioxolanone ring is lost in further stages of the synthesis, the overall stereoselectivity depends exclusively on the facial diastereoselection with regards to the aldehyde carbonyl group, that is, **4a-A** and **4a-C** lead to the (*S*)-benzoin, while **4a-B** and **4a-D** would lead to the (*R*)-benzoin. This is given by the ratio **(A+C)/(B+D)** that are shown in the last column of Table 1.

Attempts to improve these results were also performed using other solvents (ethyl ether, toluene) as well as in the presence of additives (HMPA or DMPU), which modifies the enolate aggregation state.[20] However similar results were obtained in all cases regarding both the yield and facial diastereoselectivity.

On the basis of the above preliminary survey, two other aromatic aldehydes were treated with the lithium enolate derived from **2** in THF at −78 °C without additives (Table 2). The reaction of **2** with *para*-tolualdehyde **3b** gave the corresponding aldol products **4b** in goods yields and with slightly higher facial diastereoselectivity than the reaction with benzaldehyde whilst the reaction with *para*-chlorobenzaldehyde **(3c)** gave the aldol products **4c** with somewhat lower yield and facial diastereoselectivity.

Table 1. Aldol reaction of (2*S*,5*S*)-1,3-dioxolan-4-one **2** with benzaldehyde **3a** under various conditions

Entry	Solvent	Additive	Addition	**4a** Yield (%)[a]	Ratio **A**:**B**:**C**:**D**[b]	Ratio **(A+C)/(B+D)**[c]
1	THF	—	Direct	84	14:0:76:10	90:10
2	THF	—	Inverse	20	28:2:58:12	86:14
3	Diethyl ether	—	Direct	70	19:1:62:18	81:19
4	Diethyl ether–toluene	—	Direct	72	18:3:72:7	90:10
5	THF	HMPA (3 equiv)	Direct	75	26:11:55:8	81:19
6	THF	HMPA (3 equiv)	Inverse	70	13:13:68:6	81:19
7	THF	DMPU (3 equiv)	Direct	74	37:2:55:6	92:8
8	THF	HMPA (6 equiv)	Direct	70	18:8:67:7	85:15
9	THF	DMPU (6 equiv)	Direct	68	16:0:78:6	94:6

[a] Yields refer to isolated product.
[b] Ratio determined by ^1H NMR.
[c] See text. Aldols **A** and **C** lead to (*S*)-benzoin, aldols **B** and **D** would lead to (*R*)-benzoin.

Table 2. Aldol reaction of (2*S*,5*S*)-1,3-dioxolan-4-one **2** with several aromatic aldehydes **3** under optimized conditions[a]

Entry	Ar	**4**	**4** Yield (%)[b]	Ratio **A**:**B**:**C**:**D**[c]	Ratio(**A**+**C**)/(**B**+**D**)[d]	**C** Yield (%)[e]
1	Ph	**4a**	84	14:0:76:10	90:10	60 (9)
2	4-MeC_6H_4	**4b**	86	22:0:70:8	92:8	57
3	4-ClC_6H_4	**4c**	60	22:0:61:17	83:17	32

[a] Optimized conditions refer to those indicated in entry 1 of Table 1.
[b] Combined yield of all four diastereomers.
[c] Ratio determined by ^{1}H NMR.
[d] See text. Aldols **A** and **C** lead to (*S*)-benzoin, aldols **B** and **D** would lead to (*R*)-benzoin.
[e] Isolated yield of pure diastereomer **C**. Entry 1, in brackets: Isolated yield of diastereomer **A**.

Table 3. Synthesis of (*S*)-benzoins[a] from aldols **4**

Entry	Starting **4**	Hydroxyl protection		Hydrolysis		Ox. decarboxylation		MEM cleavage		
		Product	Yield (%)[b]	Product	Yield (%)[b]	Product	Yield (%)[b]	Product	Yield (%)[b]	$[\alpha]_D$[c]
1	**4a-C**	**5a-C**	70	**6a-C**	97	**7a**	62	**8a**	85	+110 (*c* 1.3)
2	**4a-A**	**5a-A**	89	**6a-A**	86	**7a**	60	**8a**	85	+110 (*c* 1.3)
3	**4b-C**	**5b-C**	75	**6b-C**	96	**7b**	66	**8b**	90	+104 (*c* 1.0)
4	**4c-C**	**5c-C**	69	**6c-C**	80	**7c**	62	**8c**	80	+69 (*c* 0.6)

[a] In the case of **8a**, configuration determined by comparison with an authentic sample. In the case of **8b** and **8c**, assigned on the basis of a uniform reaction mechanism. In all the cases, higher than 95% ee were determined by ^{1}H NMR experiments with shift reagent (see text).
[b] Yields refer to isolated product.
[c] Optical rotations measured in acetone.

In the case of these two aldol products **4b** and **4c**, we performed the isolation of only the major diastereoisomers **4b-C** and **4c-C**, respectively, by silica gel flash chromatography.

With the aldol products **4** in our hands we carried out the protection of the hydroxyl group in order to avoid the retro-aldol reaction during the basic hydrolysis of the 1,3-dioxolan-4-one moiety and a possible over-oxidation[21] during the oxidative decarboxylation of the α-hydroxyacid moiety. This protection was carried out by reaction of aldols **4** with MEM-chloride and diisopropylethylamine in acetonitrile at reflux temperature to afford MEM derivatives **5**, with good yields.[22]

Once the hydroxyl group was protected as MEM derivative, we carried out the basic hydrolysis of the dioxolanone moiety to obtain the corresponding α-hydroxy acids **6** in almost quantitative yield.

The oxidative decarboxylation of the α-hydroxyacid moiety was carried out using a catalytic procedure developed in our laboratory, which employs oxygen as terminal oxidant in the presence of pivalaldehyde and of a catalytic amount of the Co(III) *ortho*-phenylene-bis(*N*′-methyloxamidate) complex (Fig. 1).[23] Under these conditions the MEM-protected benzoins **7a**, **7b**, and **7c** were obtained, respectively, with fair to good yields (Table 3). Finally the MEM-protected benzoins were treated with $TiCl_4$ in order to remove the MEM protecting group: This reaction proceeded in good yield to provide highly enantioenriched benzoins (ee > 95%) as proven by ^{1}H NMR experiments using the chiral lanthanide shift reagent $Eu(hfc)_3$ under conditions previously optimized for a racemic mixture.

The absolute configuration of **8a** was found to be *S* by comparison of the specific rotation with an authentic sample of enantiomerically pure benzoin.[18] The configuration of **8b** and **8c** was assigned as *S* on the basis of a uniform reaction mechanism.

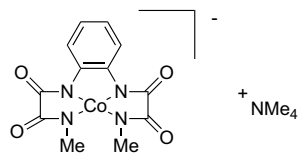

Figure 1. Co(III) *ortho*-phenylene-bis(*N*′-methyloxamidate) complex.

In summary, we have developed a strategy for the asymmetric aldol reaction of a masked benzoyl anion equivalent with aromatic aldehydes that formally involves the use of (*S*)-mandelic acid as the source of chiral information and as source of benzoyl anion. This strategy appears as a convenient method for the synthesis of highly enantioenriched unsymmetrical benzoins

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