Direct Aldol Reaction

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Base-Catalyzed Direct Aldolization of α-Alkyl-α-Hydroxy Trialkyl Phosphonoacetates**

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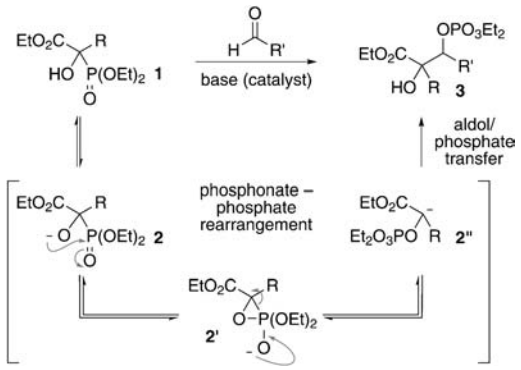
Catalytic direct aldol reactions offer a convenient method for the rapid construction of β-hydroxy carbonyl compounds through the coupling of carbonyl donors and aldehyde acceptors.[1] The generation of the reactive enolate by a basic or nucleophilic catalyst obviates the need to preform an enolate equivalent. Reaction subtypes can be broadly categorized by the oxidation state of the pronucleophile. Ketones and aldehydes can be used in direct aldolization because of their relatively high acidity (by Brønsted base catalysis) or their ability to form an enamine (by Lewis base catalysis).[2] Catalytic direct aldol and Mannich reactions involving donors in the carboxylic acid oxidation state are considerably more elusive.[3] Mechanistic nuances of these reactions are more diverse and reactions that give products that are fully substituted at the α carbon atom are difficult to achieve. We report herein a new base-catalyzed direct glycolate aldol addition that relies upon the strategic use of a [1,2] phosphonate–phosphate rearrangement (Scheme 1). This strategy was deployed in the development of highly enantio- and diastereoselective variants through the application of chiral iminophosphorane catalysts. A consequence of the reaction design is that products containing a leaving group are directly produced by the aldolization, a circumstance that is favorable for subsequent nucleophilic displacement reactions.

Although analogous to the well-studied isoelectronic [1,2] Brook rearrangement,[4] the [1,2] phosphonate–phosphate rearrangement of α-hydroxy phosphonates is comparatively underutilized.[5,6] Incorporation of an adjacent electron-withdrawing group facilitates C→O dialkoxyphosphinyl migration (**2**→**2′**→**2″**; Scheme 1) through stabilization of the incipient negative charge. The [1,2] phosphonate–phosphate rearrangement of α-hydroxy phosphonates has been employed in the formal racemic and enantioselective reduction of α-keto esters;[7] however, it has seldom been used for C–C bond construction through umpolung reactivity.[6,8] The fully substituted glycolic acid derivatives that would result from productive trapping of **2″** feature a β-phosphonyloxy moiety that can serve as an electrophile in secondary transformations,[9] and can be used as intermediates in the synthesis of biologically active compounds such as tagetitoxin, leustroducsin B, and phoslactomycin A.[10] The generation and electrophilic trapping of glycolate enolates through a base-catalyzed C→O dialkoxyphosphinyl migration was accordingly undertaken.



Scheme 1. Base-catalyzed direct-aldolization employing phosphonate–phosphate rearrangement.

Initially, we examined the reaction of α-hydroxy phosphonate **1a**[11] with an aryl aldehyde in the presence of a variety of bases (Table 1). The temperature of the reaction determined the product identity. When the reaction was conducted at room temperature, epoxide **5** was isolated in 23% yield with 2:1 d.r. (Table 1, entry 1); however, at −78 °C, under otherwise identical reaction conditions, α-hydroxy-β-phosphonyloxy ester **3a** was isolated in 97% yield and 2:1 d.r. (Table 1, entry 2). We propose that both products arise from the same reaction pathway (see below): at elevated temperature, the aldolate of **3a** can react to give epoxide **5** through an intramolecular Darzens-type S_N2 displacement of the vicinal phosphate.[12] At cryogenic temperatures, epoxide formation is completely suppressed. The identity of the counterion of the base affected diastereoselectivity, with Li*O*t*Bu (Table 1, entry 5) giving a slightly lower diastereoselectivity than K*O*t*Bu (Table 1, entry 2) and Na*O*t*Bu giving the lowest diastereoselectivity (Table 1, entry 3). A higher reaction temperature was required for Cs_2CO_3 to initiate the

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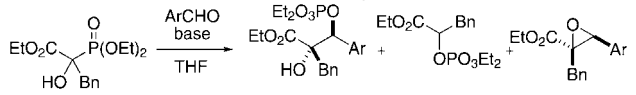
Table 1: Direct aldol addition: reaction optimization.[a]

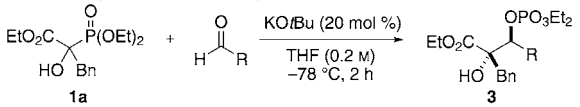


1a **3a** **4** **5**

Entry	Base [mol%]	Yield [%][b]			d.r.[b]
		3a	**4**	**5**	(*anti*/*syn*)
1[c]	KO*t*Bu (120)	–	–	23	2.0:1.0
2	KO*t*Bu (120)	97	–	–	2.0:1.0
3	NaO*t*Bu (120)	88	–	–	1.2:1.0
4[d]	Cs_2CO_3 (120)	41	58	–	1.9:1.0
5	LiO*t*Bu (120)	81	–	–	1.8:1.0
6	KHMDS (20)	74	19	–	2.2:1.0
7	*t*Bu-P4[e] (20)	97	–	–	1.0:3.3
8[f]	KO*t*Bu (20)	98	–	–	1.9:1.0

[a] Reactions were performed on 0.10 mmol scale, using 1.5 equiv of aldehyde in THF (1.0 mL) at −78 °C for 1 h. [b] Yields and diastereoselectivities were determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [c] Ar = Ph, T = 25 °C; [d] The reaction was warmed to room temperature. [e] *t*Bu-P4 ≡ ((Me$_2$N)$_3$P=N)$_3$P=N*t*Bu. [f] $[\mathbf{1}]_0$ = 0.20 M, 2.0 equiv aldehyde. Bn = benzyl, KHMDS = potassium hexamethyldisilazide.

Table 2: Aldehyde substrate scope.[a]

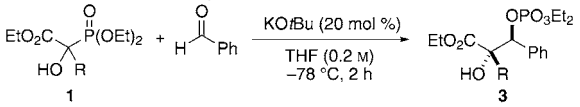


1a **3**

Entry	R	Product	Yield [%][b]	*anti*/*syn*[c]
1	4-ClC_6H_4	**3a**	95	2.0:1.0
2	2-FC_6H_4	**3b**	91	2.3:1.0
3	2-N$O_2C_6H_4$	**3c**	87	1.5:1.0
4	3-N$O_2C_6H_4$	**3d**	92	2.4:1.0
5	4-N$O_2C_6H_4$	**3e**	95	2.8:1.0
6	4-$CF_3C_6H_4$	**3f**	91	2.1:1.0
7	4-CNC_6H_4	**3g**	93	2.4:1.0
8	C_6H_5	**3h**	97	2.1:1.0
9	4-FC_6H_4	**3i**	98	2.1:1.0
10	4-MeC_6H_4	**3j**	97	2.0:1.0
11[d]	4-MeOC_6H_4	**3k**	89	4.9:1.0
12	2-thienyl	**3l**	81[e]	6.7:1.0
13[d]	(*E*)-CH=CHPh	**3m**	89	4.4:1.0
14[d]	CH_2CH_2Ph	**3n**	78	5.8:1.0

[a] Unless noted, reactions were performed on 0.20 mmol scale, using 2.0 equiv of aldehyde in THF (1.0 mL) at −78 °C for 2 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] With 5.0 equiv of aldehyde. [e] Product isolated as the *anti* diol following column chromatography.

Table 3: α Substituent scope.[a]



1 **3**

Entry	R	Product	Yield [%][b]	*anti*/*syn*[c]
1	H (**1f**)	**3o**	trace	–
2	Me (**1b**)	**3p**	81	1.9:1.0
3	$CH_2CH{=}CH_2$ (**1c**)	**3q**	89	1.2:1.0
4	$CH_2C{\equiv}CH$ (**1d**)	**3r**	93	2.9:1.0
5	CH_2Ph (**1a**)	**3h**	97	2.1:1.0

[a] Reactions were performed on 0.20 mmol scale, using 2.0 equiv of aldehyde in THF (1.0 mL) at −78 °C for 2 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture.

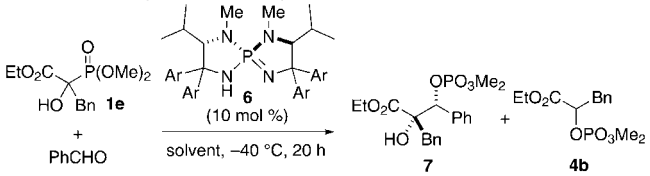
[1,2] phosphonate–phosphate rearrangement and competitive enolate quenching was observed, thus resulting in the formation of **4** (Table 1, entry 4). Attempts to render the reaction catalytic were successful because the use of 20 mol% of either KHMDS or KO*t*Bu promoted the reaction in good yield (Table 1, entries 6 and 8, respectively). The phosphazene base *t*Bu-P4 was also an effective catalyst for this reaction and gave preferentially the opposite (*syn*) diastereoisomer (Table 1, entry 7). The effect of independently increasing either the number of equivalents of aldehyde or the reaction concentration was marginal in minimizing the formation of **4**, but simultaneously increasing both provided the best ratio of desired product **3a** to quenched enolate **4**; (Table 1, entry 8). The identity of the carboxy and phosphonate ester had little impact on the diastereoselectivity of the reaction (not shown).[13]

With high-yielding reaction conditions established (Table 1, entry 8), we examined the scope of the reaction by varying the aldehydes used (Table 2). The use of electron-poor and electron-neutral aromatic aldehydes afforded products in excellent yield, albeit with marginal diastereoselectivity (Table 2, entries 1–10). The use of electron-rich aromatic, alkenyl, and alkyl aldehydes afforded product with a notable enhancement in *anti* diastereoselectivity and the use of an excess amount of aldehyde (5.0 equivalents) was optimal in these cases (Table 2, entries 11, 13, and 14). The isolation of products typically only consisted of their separation from excess aldehyde. The major byproduct formed during the reaction was the quenched glycolate enolate **4**. Bulkier aldehydes such as isobutyraldehyde and pivaldehyde were not suitable electrophiles under these reaction conditions.

The scope of the α-hydroxy phosphonate coupling partner was investigated, with benzaldehyde as the other partner, by varying the α substituent (Table 3). The presence of an α substituent was found to be critical: reactions of phosphonates in which R = H suffered from poor reactivity (< 5% conversion; Table 3, entry 1). In addition to the benzyl group, other alkyl substituents were well-tolerated under the reaction conditions, thus allowing for the incorporation of functional handles such as terminal alkenes and alkynes (Table 3, entries 3 and 4).

Having established a baseline protocol for achieving a new direct ester aldol addition reaction, we directed our efforts toward improving the modest reaction diastereoselectivity and developing an enantioselective variant of this reaction. Catalytic aldolization using *t*Bu-P4 provided the opposite major diastereomer to that obtained using alkali bases (Table 1), thus hinting at the possibility that both relative and absolute stereocontrol issues could conceivably be addressed through the use of a chiral iminophosphorane base possessing appropriate structural features and sufficient basicity.[14] Exploratory experiments to test this hypothesis are summarized in Table 4. The aldolization of **1e** did indeed take place in the presence of catalytic amounts of chiral imino-

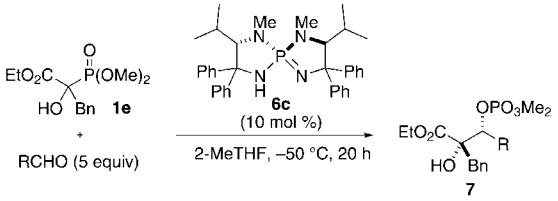
Table 4: Development of an asymmetric aldolization.[16]



Entry[a]	6	Ar	Solvent	Conv. [%][b]	7[c]/4b	e.r.[d]
1	**6a**	4-$CF_3C_6H_4$	THF	< 5	–	–
2	**6b**	4-FC_6H_4	THF	53	1:0.6	95:5
3	**6c**	C_6H_5	THF	76	1:0.8	92:8
4	**6d**	4-MeC_6H_4	THF	80	1:0.7	88:12
5	**6e**	4-$MeOC_6H_4$	THF	> 95	1:1.1	89.5:10.5
6	**6c**	C_6H_5	Et_2O	> 95	1:0.6	91:9
7	**6c**	C_6H_5	2-MeTHF	> 95	1:0.8	92.5:7.5
8[e]	**6c**	C_6H_5	2-MeTHF	> 90[f]	1:0.4	95:5

[a] Reactions were performed on 0.10 mmol scale, using 5.0 equiv of PhCHO in solvent (0.5 mL) for 20 h. [b] Conversions and diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The *syn*/*anti* ratio was > 30:1 in all cases. [d] Determined by HPLC using a CHIRALPAK AD3 column. [e] The reaction was conducted at −50 °C. [f] The product was isolated in 71% yield. Conv = conversion.

Table 5: Diastereo- and enantioselective direct aldol additions.[a]

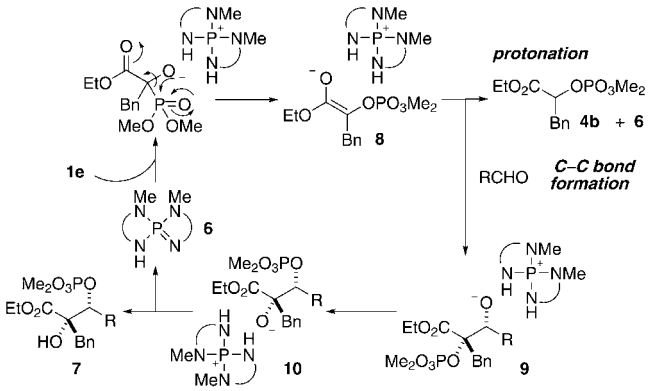


Entry	R	Product	Yield [%][b]	*syn*/*anti*[c]	e.r.[d]
1	C_6H_5	**7a**	71	> 30:1	95:5
2	2-naphthyl	**7b**	68	> 30:1	94.5:5.5
3	2-FC_6H_4	**7c**	56	> 30:1	94:6
4	2-ClC_6H_4	**7d**	64	> 30:1	95:5
5	3-NCC_6H_4	**7e**	89	> 30:1	94:6
6	3-BrC_6H_4	**7f**	87	> 30:1	95:5
7	4-ClC_6H_4	**7g**	82	> 30:1	95:5
8	4-BrC_6H_4	**7h**	91	> 30:1	95.5:4.5
9	4-$MeO_2CC_6H_4$	**7i**	89	> 30:1	97:3

[a] Reactions were performed on 0.10 mmol scale, using 5.0 equiv of aldehyde in 2-MeTHF (0.5 mL) at −50 °C for 20 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC using a CHIRALPAK AD3 column.

phosphoranes such as L-valine-derived **6** and product **7** was isolated with good enantioselectivity. Enantiocontrol could be tuned through changes of the electronics at the 4-position of the four aryl groups, but the use of electron-poor variants led to reduced reaction efficiency, presumably as a result of the reduced basicity (Table 4, entries 1–5). The identity of the solvent appeared important in terms of product distribution (ratio of aldol **7** to the quenched enolate **4b**) and stereoselectivity (Table 4, entries 6 and 7). Optimal results were obtained when using 10 mol% of **6c** in 2-MeTHF, as the reaction solvent, at −50 °C: the hydroxy phosphate adduct **7a** was isolated in 71% yield and 95:5 enantioselectivity (Table 4, entry 8). Perhaps most remarkably, the chiral iminophosphorane-catalyzed aldolization proceeded with essentially complete diastereocontrol (> 30:1 *syn*/*anti*),[15] thus revealing this strategy as a powerful method for stereoselective glycolate aldolization that give products with a fully substituted α center.

Preliminary experiments suggest that application of the optimized reaction conditions to other aldehyde electrophiles provides access to enantiomerically enriched aldol adducts. As illustrated in Table 5,[17] the use of 2-substituted aldehydes gives products in slightly reduced yields in comparison to the reaction with benzaldehyde, although complete diastereoselectivity is observed and good enantiocontrol is maintained. The structure and absolute stereochemistry of aldol adduct **7e** was determined by X-ray crystallography,[18] and other products were assigned by analogy. For electron-donating aromatic and aliphatic aldehydes, the relative rate of irreversible stereoselective C–C bond formation to afford **7** was slower than the irreversible protonation of the chiral enolate **8** to **4b** (see Scheme 2), thus resulting in diminished yields (R = 4-MeC_6H_4: 48% yield, *syn*/*anti* > 30:1, e.r. 89:11). Under proton transfer conditions, minimization of undesired protonation of the chiral enolate **8**[7d] remains a challenge despite the enhanced basicity of the chiral catalyst **6c**.[19]

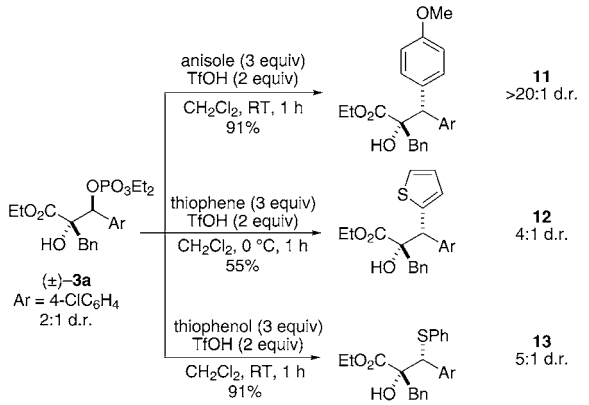


Scheme 2. Mechanistic proposal.

A catalytic cycle that accounts for the observed reactivity of the α-hydroxy phosphonate **1e** in the aldol addition is proposed in Scheme 2. After deprotonation of the alcohol **1e** by the basic catalyst, a subsequent [1,2] phosphonate–phosphate rearrangement generates the reactive glycolate enolate **8**. Consideration of frontier molecular orbital (FMO) theory[20] led us to favor the illustrated *Z* enolate as the kinetically preferred product of C→O phosphinyl migration. Enolate addition to the aldehyde would lead to the aldolate **9**. The precise structures of the enolate **8** and the aldol transition state remain open for discussion. Approximately thermoneutral O→O phosphinyl migration occurs from the tertiary alcohol to the vicinal secondary alkoxide, presumably to reduce steric strain at the fully substituted center, thus affording aldolate **10**. The reaction is rendered catalytic through proton transfer between the aldolate **10** and the α-hydroxy phosphonate starting material **1e**, either directly or via the free base **6**.

The reaction is especially attractive because the aldolization directly installs a leaving group that can be immediately

deployed in nucleophilic displacement chemistry. The OPO_3R_2 groups in benzylic phosphates are viable leaving groups in acid-promoted Friedel–Crafts alkylations.[21] Upon treatment of (±)-**3a** (d.r. 2:1) and anisole with TfOH, the α-hydroxy ester **11** was isolated in 91% yield as a single diastereomer. Heteroatom and heteroaromatic nucleophiles were also employed in this Friedel–Crafts alkylation in good to excellent yields (Scheme 3),[22] thus providing stereogenic β-diaryl glycolates in a single step with pronounced stereoconvergency. Formation of a discrete carbenium ion explains the stereoconvergence and finds precedent in the diastereoselective Friedel–Crafts alkylations pioneered by Bach and co-workers.[23]



Scheme 3. Stereoconvergent Friedel–Crafts alkylations. Tf = trifluoromethanesulfonyl.

In conclusion, a catalytic direct aldol addition of α-hydroxy trialkyl phosphonoacetates to aldehydes to afford α-hydroxy β-phosphonyloxy esters has been developed. A [1,2] phosphonate–phosphate rearrangement was utilized to generate the reactive glycolate enolate in situ. The reaction works well for a variety of alkyl, alkenyl, aryl, and heteroaryl aldehydes to afford the desired products in good to excellent yields in low to moderate diastereoselectivities. Iminophosphorane catalysts enabled positive outcomes in asymmetric versions of this reaction, providing excellent levels of stereocontrol. Stereoconvergent second stage transformations have also been developed to enhance the synthetic utility of the method. The applicability of this mechanistic framework in the context of other new reactions is the topic of ongoing investigations.

Experimental Section

A dried test tube was charged with the α-hydroxy phosphonoacetate **1e** (30.2 mg, 0.10 mmol, 1.0 equiv) and benzaldehyde (51 μL, 0.50 mmol, 5.0 equiv), and the mixture was dissolved in 2-MeTHF (500 μL, 0.2 M) under an atmosphere of argon. The solution was cooled to −50 °C. Iminophosphorane **6c** (5.8 mg, 0.01 mmol, 0.1 equiv) was added and the reaction mixture stirred at −50 °C for 20 h. The reaction was quenched at −50 °C with 0.5 M TFA in toluene (40 μL, 0.2 equiv). The resulting solution was diluted with 1 N HCl at 0 °C. The aqueous layer was extracted with $CHCl_3$ (3×). The combined organic extracts were washed with brine (1×), dried over Na_2SO_4, filtered, and concentrated in vacuo. The diastereomeric ratio was determined by ^1H NMR analysis of the crude residue. The residue was purified by column chromatography on silica gel eluting with 30% acetone/hexane to afford the aldol adduct **7a** (29.0 mg, 0.07 mmol, 71% yield, >30:1 *syn*/*anti*) as a white solid (mp 119–127 °C).

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[17] Other pronucleophiles were employed in the reaction with 4-bromobenzaldehyde; however, at our current level of reaction and catalyst optimization both **1c** (34% yield, >30:1 *syn*/*anti*, 87% *ee*) and **1d** (95% yield, >30:1 *syn*/*anti*, 70% *ee*) provided unsatisfactory levels of either reactivity or enantioselectivity despite an observed retention in absolute diastereocontrol.
[18] CCDC 854995 (**7e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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