Aldehyde Coupling Reactions

Enantioselective Organocatalytic Direct Aldol Reactions of α-Oxyaldehydes: Step One in a Two-Step Synthesis of Carbohydrates**

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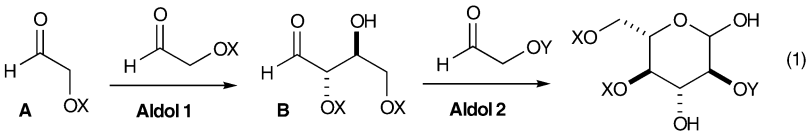
The growing study of glycobiology[1] has led to an increased focus upon carbohydrate architecture[2] as an important platform for reaction design and methodological advancement.[3] Application of the aldol reaction[4] to the synthesis of carbohydrates is well-documented;[5] however, the attendant need for protection-group manipulations and oxidation-state adjustments has thus far precluded a broadly utilizable protocol. Intriguingly, a highly expedient two-step carbohydrate synthesis can be envisioned based on an iterative aldol sequence using simple α-oxyaldehydes [Eq. (1)]. While attractive in theory, the practical execution of this carbohydrate strategy would require the invention of two new aldol technologies: a) an enantioselective aldol union of α-oxyaldehyde substrates (Aldol step 1) and b) a diastereoselective aldol coupling between tri-oxy substituted butanals and an α-oxyaldehyde enolate (Aldol step 2). Herein we report the successful development of the first enantioselective organocatalytic coupling of an α-oxyaldehyde (Aldol step 1). This new aldol reaction provides an operationally simple protocol for the stereocontrolled production of polyol architectures and sets the stage for a two-step enantioselective carbohydrate synthesis.[6]

The development of a direct, enantioselective catalytic aldol reaction between α-oxyaldehyde substrates (Aldol step 1) is dependent upon three key issues of chemical selectivity.[7] In addition to the traditional requirements of absolute and relative stereocontrol comes the chemoselective constraint that the α-oxyaldehyde reagent **A** must readily participate as both a nucleophilic and electrophilic coupling partner while the α-oxyaldehyde product **B** must be inert to in situ enolization or carbonyl addition [Eq. (1)]. Recently,

Two-Step Carbohydrate Synthesis: Iterative Aldehyde Aldol

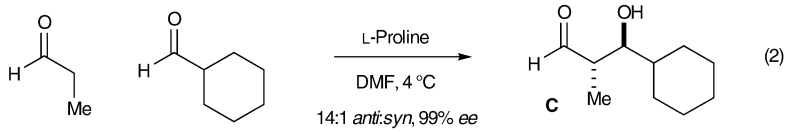


(1)

Aldol 1 requires α-oxyaldehyde **A** (reagent) is reactive in aldol union

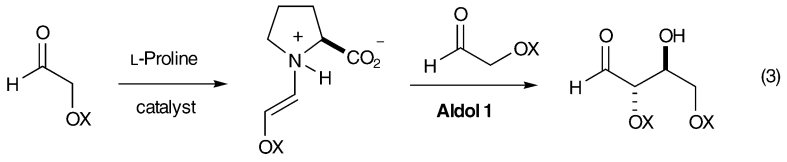
Aldol 1 requires α-oxyaldehyde **B** (product) is nonreactive in aldol union

Proline-Catalyzed Cross Aldehyde – Aldol Addition



(2)

Organocatalytic Aldol 1: Enantioselective α-Oxyaldehyde Coupling



(3)

we disclosed an organocatalytic strategy for the highly regioselective, diastereoselective, and enantioselective aldol cross-coupling of α-alkyl-bearing aldehydes [Eq. (2)].[8] An important feature of this transformation is that the enantioenriched aldehyde products **C** do not participate in further aldol reactions (by either enamine formation or carbonyl addition). With this in mind, we hoped that such remarkable catalyst-controlled stereo- and chemoselectivity might be extended to the union of α-oxygenated aldehydes [Eq. (3)], thereby allowing the first step in a two-step carbohydrate synthesis to occur [Eq. 1].

Our enantioselective organocatalytic α-oxyaldehyde coupling was first examined using L-Proline (10 mol%) and a

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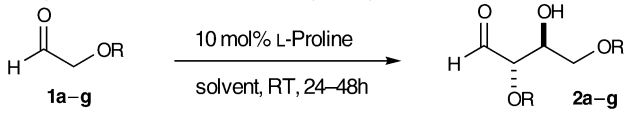
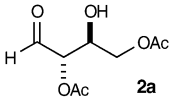
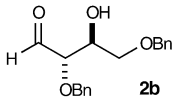
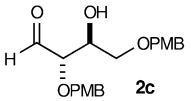
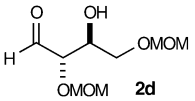
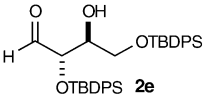
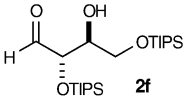
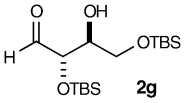
variety of glycoaldehyde substrates (Table 1). Preliminary studies revealed that the proposed enantioselective aldol union is indeed possible, however, the electronic nature of the oxyaldehyde substituent has a pronounced effect on the overall efficacy of the process. For example, substrates that possess an electron-withdrawing substituent, such as α-acetoxyacetyaldehyde **1a**, do not participate in this transformation, while aldehydes bearing relatively electron-rich oxyalkyl groups provide useful levels of enantiocontrol and reaction efficiency (entry 2, R = Bn, 73% yield, 98% *ee*; entry 3, R = PMB, 85% yield, 97% *ee*). Moreover, aldehydes bearing bulky α-silyloxy substituents can be readily utilized (entry 5, R = TBDPS, 61% yield, 96% *ee*; entry 7, PG = TBS, 50% yield, 88% *ee*), with the TIPS-protected glycoaldehyde (entry 6) affording exceptional reaction efficiency (92%), enantioselectivity (95% *ee*), and a readily separable 4:1 mixture of *anti* and *syn* diastereomers. It should be noted that all of the dimeric aldol adducts shown in Table 1 constitute protected forms of the naturally occurring sugar erythrose, a chiral synthon of established utility.[9] More importantly, the α-oxyaldehyde products of this new aldol protocol are apparently inert to further proline-catalyzed enolization or enamine addition, a central requirement for the proposed two-step iterative–aldol carbohydrate synthesis [Eq. (1)].[10]

We next examined the ability of proline to catalyze the enantioselective cross-coupling of α-oxy- and α-alkyl-substituted aldehydes (Table 2). The principal issue in this reaction is that the nonequivalent aldehydes must selectively partition into two discrete components, a nucleophilic donor and an electrophilic acceptor. Given that most α-oxy- and α-alkyl aldehydes bear enolizable protons, we anticipated that such catalyst-controlled substrate partitioning would be mechanistically unfavorable. Remarkably, however the glycoaldehyde invariably acts as the electrophile in the presence of alkyl aldehydes that contain α-methylene protons (entries 1–4, 94–99% *ee*). Surprisingly, even the sterically demanding isovaleraldehyde assumes the role of nucleophile when exposed to proline and α-benzyloxyacetaldehyde or α-silyloxyacetaldehyde (entries 3 and 4). However, both triisopropylsilyl- and benzyl-protected oxyaldehydes can function as aldol donors in the presence of aldehydes that do not

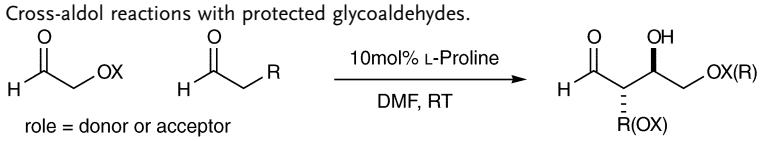
Table 1: Organocatalytic aldol dimerization of α-oxyaldehydes.

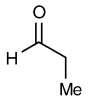
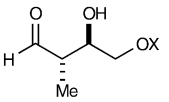
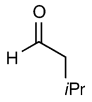
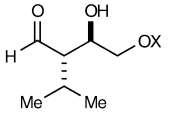
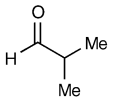
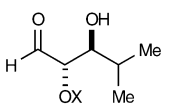


Entry	Product	Solvent	Yield [%]	*anti*:*syn*	*ee* [%][a],[b]
1	 **2a**	DMF	0	–	–
2	 **2b**	DMF	73	4:1	98
3	 **2c**	DMF	64	4:1	97
4	 **2d**	DMF	42	4:1	96
5	 **2e**	DMF/dioxane	61	9:1	96[c]
6	 **2f**	DMSO	92	4:1	95
7	 **2g**	dioxane	62	3:1	88[c]

[a] Absolute and relative stereochemistry assigned by chemical correlation. [b] Determined by chiral HPLC. [c] Using 20 mol% catalyst. Bn = benzyl, PMB = *para*-methoxybenzyl, MOM = methoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl.

Table 2: Cross-aldol reactions with protected glycoaldehydes.



Entry	Aldehyde α-alkyl	Aldehyde OX	Product	Yield [%]	*anti*:*syn*	*ee* [%][a],[b]
1		OTIPS acceptor		75	4:1	99
2	donor	OTBDPS acceptor		84	5:1	99[c]
3		OTIPS acceptor		54	4:1	99
4	donor	OBn acceptor		64	4:1	94
5		OTIPS donor		43	8:1	99
6	acceptor	OBn donor		33	7:1	96

[a] Absolute and relative stereochemistry assigned by chemical correlation. [b] Determined by chiral HPLC. [c] Determined by Mosher ester analysis.

readily participate in enamine formation (entries 5 and 6, ≥33% yield ≥7:1 *anti*:*syn*, 96–99% *ee*). It should be noted, however, that significant quantities of the homodimers **2f** and **2b** were generated in these respective cases.

These organocatalytic results stand in marked contrast to metal-mediated direct aldol technologies[11] where the increased acidity and nucleophilicity afforded by α-oxygenated aldol donors greatly enhances their effectiveness relative to their all-alkyl counterparts. We are currently investigating the mechanistic origins of such divergent reactivity between metal and organic catalysts in aldol reactions with α-oxygenated substrates.

In summary, we have documented the first direct enantioselective catalytic aldol reaction using α-oxygenated aldehydes as both the aldol donor and the aldol acceptor. Significantly, this method allows direct and enantioselective access to differentially protected polyols and monoprotected *anti*-1,2 diols. A full account of these studies will be presented in due course.

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