



Organocatalysis with endogenous compounds: Towards novel non-enzymatic reactions

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ABSTRACT

The aldol reaction of the endogenous compounds acetone and methylglyoxal has been studied using organocatalysis in relation to biologically relevant non-enzymatic reactions. Under preparative conditions, 3-hydroxy-2,5-hexadione, known as Henze's ketol, is formed in high yield and with enantioselectivities up to 88% ee. Furthermore, Henze's ketol is also formed under simulated physiological conditions at micromolar scale, indicating that this reaction might take place in living organisms.

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Organocatalysis has recently proven highly efficient in the stereoselective synthesis of a large number of α -substituted carbonyl compounds.¹ The rediscovery of the organocatalytic aldol reaction in 2000 by List, Lerner and Barbas ushered in a new field in organic synthesis,² and research in organocatalysis has since expanded exponentially. Inspired by the aldolase enzymes, the organocatalytic aldol reaction employs aminocatalysis for the activation of carbonyl compounds (aldol donors) by the formation of transient enamine species. The utility of the stereoselective organocatalytic aldol reaction has also been demonstrated in a number of total syntheses³ and the mechanism has been thoroughly studied by computational methods.⁴

Acknowledging that organocatalytic aldol reactions have been reported to proceed in aqueous environments, mediated by simple amino acid derivatives and peptides^{1,5} led us to believe that these reactions might occur in vivo.⁶ Intrigued by this possibility, we initiated a study to address the potential role of non-enzymatic organocatalytic reactions in human biochemistry. As model substrates, the endogenous compounds methylglyoxal **1** (pyruvaldehyde) and acetone **2** were chosen for our initial experiments.

Methylglyoxal **1** is a reactive endogenous α -oxoaldehyde that is known to modify biomolecules in vivo through non-enzymatic

processes.⁷ The development of complications in relation to diabetes, as well as the general aging phenomenon, has been linked to protein modifications by **1**. Although the concentration of 'free' **1** in vivo is in the high nM or low μ M regime, the bulk of **1** is bound reversibly to nucleophilic groups present in biopolymers and to reduced glutathione.⁸ The total amount of **1** in biological systems may therefore be significant; for example, up to 310 μ M of **1** in cultured CHO-cells⁹ has been measured and even concentrations in the mM range have been reported in the gingival fluid from periodontitis patients.¹⁰

Acetone **2** belongs to the class of ketone bodies that are present in elevated (millimolar) levels during prolonged starvation or poorly controlled diabetes.¹¹ To the best of our knowledge, the organocatalytic aldol reaction between **1** and **2** has not previously been studied. The product of this reaction, 3-hydroxy-2,5-hexadione **3**, also known as Henze's ketol,¹² bears an interesting history. The chemistry and biochemistry of **3** was extensively studied by Henze and his colleagues in the 1930s, and they went so far as to speculate that **3** might represent an undiscovered link between the metabolism of fatty acids and carbohydrates. This proposal was later disproved by Krebs,¹³ and no clear biological role for **3** has since emerged; however, this ketol has recently been identified in plant extracts.¹⁴ In the present work we report the enantioselective organocatalytic preparation of **3** on a synthetic scale, as well as its organocatalytic formation under simulated physiological conditions, at levels that may be biologically significant.

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Table 1

Screening of catalysts for organocatalytic formation of Henze's Ketol **3** from acetone and methylglyoxal^a

Entry	Catalyst	Solvent	Yield (%)	ee ^b (%)
1	4	Neat	<5	nd
2	4	DMSO	<10	51
3	4	H ₂ O	<5	nd
4	5	Neat	76	65
5	6	Neat	<5	33
6 ^c	7	Neat	55	88
7	8	Neat	81	62
8	9	Neat	52	0
9	10	Neat	39	–66

^a Standard conditions: To a stirred solution of the catalyst (0.05 mmol) in the specified solvent (375 μ L) and acetone (184 μ L) (total solvent volume = 559 μ L) at 4 °C was added 39 μ L methylglyoxal solution (40% in H₂O). The reaction was stirred at 4 °C for 20 h and purified using FC.

^b Determined using chiral stationary phase GC and confirmed using chiral stationary phase HPLC.

^c Reaction time was 68 h.

We explored this reaction using a number of catalysts, as shown in Table 1. (S)-Proline **4** afforded little or no conversion under preparative conditions at 4 °C (entries 1–3). Prolinamide **5** proved to be a more efficient catalyst in terms of both yield and enantioselectivity (entry 4). The dipeptide Pro-Leu **7** gave better enantioselectivity than **5** at a slightly lower yield (entry 6), while amide **8** offered yield and selectivity comparable to that observed for **5** (entry 7). Catalyst **6** was not effective for this reaction (entry 5) and the proline derivatives **9** and **10** (entries 8 and 9) offered no obvious advantages compared to catalysts **5**, **7** or **8**. Thus, **5**, **7**, and **8** all showed promise in this reaction, but we chose to focus our efforts on **5** and **7** due to the closer resemblance of these catalysts to physiological entities.

We settled on using 20 mol % prolinamide **5** or Pro-Leu **7** as our standard catalyst loading, at a concentration of methylglyoxal **1** of 0.4 M. We note that **7** has limited solubility in all solvents explored. Indeed, in all reactions run with catalyst **7**, the reaction mixture was an inhomogeneous suspension, so the precise catalyst loading when applying **7** is unknown.

The results with prolinamide **5** are shown in Table 2 and the best results with this catalyst were obtained by running the reaction in neat acetone. Interestingly, both polar protic solvents (H₂O and *i*-PrOH, entries 8 and 9) and the less polar solvents (toluene and CH₂Cl₂, entries 1 and 2) gave poorer enantioselectivity than solvents of moderate polarities (MeCN and acetone, entries 3 and 10). The very polar DMSO also gave poor enantioselectivity (entry 7). In all of our reactions, we used commercially available **1**, which is a 40% aqueous solution. Given the poor enantioselectivity observed in protic solvents, we investigated the effect of drying agents on reactions run in MeCN. The addition of Na₂SO₄ had no effect on the reaction (entry 4), while the addition of MgSO₄ did result in a small increase in enantioselectivity at a modest expense in yield (entry 5). It is possible that the increase in selectivity observed in the presence of MgSO₄ is the result of a change in

Table 2

Optimization of conditions for the prolinamide-catalyzed formation of Henze's Ketol **3**^a

Entry	Solvent	Temperature (°C)	Yield (%)	ee ^b (%)
1	Toluene	4	44	32
2	CH ₂ Cl ₂	4	49	56
3	CH ₃ CN	4	66	68
4 ^c	CH ₃ CN	4	66	68
5 ^d	CH ₃ CN	4	52	76
6	DMF	4	nd ^e	68
7	DMSO	4	47	38
8	H ₂ O	4	70	0
9	<i>i</i> -PrOH	4	74	56
10	Neat	4	76	65
11	Neat	–24	83	71

^a Standard conditions: To a stirred solution of the catalyst (0.05 mmol) in the specified solvent (375 μ L) and acetone (184 μ L) (total solvent volume = 559 μ L) at the specified temperature was added 39 μ L methylglyoxal solution (40% in H₂O). The reaction was stirred at the specified temperature for 20 h and purified using FC.

^b Determined using chiral stationary phase GC and confirmed using chiral stationary phase HPLC.

^c Na₂SO₄ added as drying agent.

^d MgSO₄ added as drying agent.

^e The DMF was not readily separated from the product by FC and given that this solvent offered no obvious advantages in enantioselectivity over others, we did not attempt further purification that would have allowed a yield determination.

mechanism to one involving chelation control by magnesium ion, but in any case, the exclusion of bulk water in the reaction mixture does not have a large effect on the stereoselectivity of the reaction. Lowering the reaction temperature to –24 °C, using neat acetone, had a small positive effect on both yield and enantioselectivity (cf. entries 10 and 11).

The results with the dipeptide Pro-Leu **7** are presented in Table 3. With the exception of water (entry 6) this catalyst consistently delivered good enantioselectivities (73–88% ee) in all solvents tested. On the other hand, the yields were generally lower than those observed with prolinamide **5**. CH₂Cl₂ offered excellent enantioselectivity, but with very poor conversion, probably as a result of the low solubility of **7** in this solvent. Of the solvents examined, neat acetone and EtOH emerged as the solvents of choice for catalyst **7**, with acetone giving the highest enantioselectivity (entry 1) and EtOH providing respectable selectivity at a higher yield (entry 5).

Table 3

Optimization of conditions for the Pro-Leu-catalyzed formation of Henze's Ketol **3**^a

Entry	Solvent	Reaction time (h)	Yield (%)	ee ^b (%)
1	Neat	68	55	88
2	<i>i</i> -PrOH	21	16	82
3	<i>i</i> -PrOH	72	30	83
4	DMF	21	51	81
5	EtOH	70	77	81
6	H ₂ O	120	27	45
7	CH ₂ Cl ₂	20	<5	88
8	DMSO	21	49	73

^a Standard conditions: To a stirred solution of the catalyst (0.05 mmol) in the specified solvent (375 μ L) and acetone (184 μ L) (total solvent volume = 559 μ L) at the specified temperature was added 39 μ L methylglyoxal solution (40% in H₂O). The reaction was stirred at 4 °C for the specified time period and purified using flash chromatography.

^b Determined using chiral stationary phase GC and confirmed using chiral stationary phase HPLC.

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