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Direct organocatalytic aldol reactions in buffered aqueous media†

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Received (in Corvallis, OR, USA) 6th August 2002, Accepted 7th October 2002
First published as an Advance Article on the web 14th November 2002

Organocatalytic cross-aldol reactions catalyzed by cyclic secondary amines in aqueous media provide a direct route to a variety of aldols including carbohydrate derivatives and may warrant consideration as a prebiotic route to sugars.

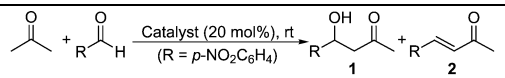
The aldol reaction is a key carbon–carbon bond-forming reaction in nature and in the repertoire of the synthetic chemist. In nature, this reaction is typically catalyzed by enzymes that utilize either an enamine mechanism (Class I aldolases) or a zinc cofactor (Class II aldolases), to effect the coupling of unmodified substrates in aqueous media while achieving absolute stereocontrol. These features have been particularly difficult to mimic chemically,[1] despite the plethora of methodologies available for the stereoselective construction of virtually any desired aldol product.[2] In fact, synthetically useful aldol reactions in aqueous media are rare and mostly involve enzymes[3] or catalytic antibodies[4] that exhibit broad substrate specificity for the aldehyde acceptor substrate. The study of amines, amino acids and small peptides as biomimetic catalysts of a variety of reactions has long intrigued chemists.[5,6] There are, however, very few reports based on this concept that are of synthetic utility.[7] Recently, it has been reported that primary and secondary amines are capable of catalyzing intermolecular aldol reactions with acetone as the donor under physiological conditions.[8] Furthermore, we and others have reported that cyclic secondary amines catalyze direct intermolecular aldol reactions with high regio-, diastereo- and enantioselectivities in organic solvents.[9] We therefore sought to extend this concept to aqueous reaction media providing for the synthesis of polyhydroxylated products under environmentally benign reaction conditions.[10] We were also interested in examining the efficiency of this approach from the perspective of its potential as a prebiotic route to carbohydrates.[11]

We initially studied the reaction of acetone with *p*-nitrobenzaldehyde (Table 1). As compared to water, aldol reactions in PBS buffer[12] alone were significantly accelerated in the presence or absence of proline (Table 1, entries 1,2, 4, and 5). We found that addition of sodium dodecyl sulfate (SDS, 0.1 equivalents) as an additive to PBS-buffer was beneficial. Under these conditions, aldol product **1** was formed smoothly in a clean reaction. The addition of SDS to the mixture completely suppressed the uncatalyzed reaction (Table 1, entries 1 and 3) and also enhanced the solubility of hydrophobic substrates.[13]

Under the conditions studied, minimal formation of aldol condensation product **2** was observed.[14] Further, the proline-catalyzed reaction in PBS/SDS completely inhibited by addition of sodium cyanide (Table 1, entry 7), indicating that proline is the catalyst in this reaction and supporting the role of an imine as an intermediate in the catalytic mechanism.[9b]

We then turned our attention to further assessing the most promising catalysts[14] in cross-aldol reactions of a variety of ketones with *p*-nitrobenzaldehyde (Table 2). Proline-catalysis was effective for 2-butanone affording aldol adducts **3** and **4** in good yield with modest regio- and diastereoselectivity (Entry 1) but provided **5** with no diastereoselectivity when cyclohexanone was used as the donor ketone (Entry 2). Furthermore, 3-pentanone was not a donor under L-proline catalysis but **7** was could be obtained under catalysis with (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **6** instead (Entry 3). The proline-catalyzed reaction with hydroxyacetone as the donor afforded diol **8** in high yield as the sole reaction product (Entry 4). This transformation was also catalyzed by **6** and pyrrolidine itself to provide **8** as the only observed regioisomer (Entries 5 and 6).

Table 1 Direct catalytic aldol reaction of acetone with *p*-nitrobenzaldehyde under various aqueous conditions

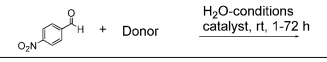


Entry	Conditions	Catalyst	*t*	**1**[a]	**2**[a]
(1)	PBS	–	48h	39%	0%
(2)	H_2O	–	48h	5%	0%
(3)	PBS[b]	–	24h	trace	0%
(4)	PBS	L-proline	24h	99%	trace
(5)	H_2O	L-proline	24h	40%	0%
(6)	PBS[b]	L-proline	24h	99%	trace
(7)	PBS[b]	L-proline[c]	24h	trace[c]	0%

[a] Conversion as determined by 1H NMR and reverse phase HPLC after extractive workup. [b] 0.1 equiv SDS used. [c] NaCN was added.

† Electronic supplementary information (ESI) available: Experimental data and full characterization of all new compounds: see http://www.rsc.org/suppdata/cc/b2/b207664k

Table 2 Amine-catalyzed aldol reactions of various ketones with *p*-nitrobenzaldehyde in PBS-buffer



Entry	Donor	Catalyst	Conditions	Products	yield[a]	de[b]
(1)	2-butanone	L-proline	PBS[c]	**3** **3**:**4** = 3:1 **4**	90%	3:1
(2)	*c*-hexanone	L-proline	PBS[c]	**5**	50%	1:1
(3)	3-pentanone	**6**	PBS[c]	**7**	5%	1:1
(4)	HA[d]	L-proline	PBS[c]	**8**	89%	1:1
(5)	HA	**6**	PBS[c]	**8**	40%	1:1
(6)	HA	Pyrrolidine	PBS[c]	**8**	65%	1:1
(7)	HA	none	PBS[c]	**8**	trace	1:1
(8)	DHA	L-proline	PBS[c]	**10**	trace	1:1
(9)	DHA	**9**	PBS	**10**	trace	1:1
(10)	DHA	**6**	PBS	**10**	90% 40%[e] 87%[f]	1:1 1:1[e] 2:1[f]
(11)	DHA	**11**	PBS	**10**	60%	1:1
(12)	DHA	Pyrrolidine	PBS	**10**	43%	1:1

[a] Yield of isolated product. [b] Determined by 1H NMR (anti/syn). [c] 0.1 equivalent SDS. [d] HA = hydroxyacetone. [e] Reaction performed in water. [f] Reaction performed in DMSO/PBS-1/1. Ar = *p*-$NO_2C_6H_4$

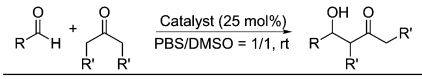
DOI: 10.1039/b207664k

Hence, all the pyrrolidine-derived catalysts activate hydroxyacetone in a highly regioselective manner providing for a facile entry to the synthesis of vicinal diols.[15] None of the chiral catalysts screened, however, provided product **8** in a diastereo- or enantioselective manner in the PBS buffer. Next we investigated whether the biologically significant substrate dihydroxyacetone (DHA) could be used as a donor in reactions catalyzed by pyrrolidine-based catalysts. Interestingly, proline and nornicotine (**9**) provided only trace amounts of **10** (Entries 8 and 9). In contrast, **6**, (*S*)-2-(methoxymethyl)pyrrolidine (**11**), and pyrrolidine were highly efficient, with **6** being the best catalyst affording polyol **10** in 90% yield within 2 h (Entries 10–14). The (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine-catalyzed reaction with dihydroxyacetone was diastereoselective in DMSO/PBS, providing **10** with a dr of 2 : 1 (Entry 11). This is the first demonstration of the use of unprotected dihydroxyacetone as a donor in an organocatalytic cross-aldol reaction. Because dihydroxyacetone dimerizes in organic solvent, none of the catalysts tested provide **10** under non-aqueous reaction conditions. The reactivity of the tested organocatalysts was in the following order: **6** > **11** > pyrrolidine > proline > **9**. As a diamine, **6** can be viewed as a mimetic of the two lysines key to the mechanism of class I aldolases.[16] In all the transformations reported in Table 2 only trace amounts of the desired products were observed in the absence of organocatalyst.

L-Proline and **6** were also efficient catalysts in aqueous media of intermolecular aldol reactions involving nonactivated acceptors affording products **12**–**20** (Table 3).[17,18] Moreover, the results presented in Table 3 demonstrate that catalysis by small organic molecules provides a direct route to monosaccharides. For example, catalyst **6** provided benzyl-protected pentulose **17**. This sugar was isolated as a single diastereomer possessing an *anti*-configuration of the vicinal hydroxy groups (Entry 6).[19] In addition, natural sugar derivatives such as protected D-fructose (1 of 4 sugars formed in this reaction) were obtained under physiological conditions by enamine catalysis (Entry 9).

In conclusion, we have demonstrated that small organic molecules can catalyze direct intermolecular aldol reactions involving a variety of ketones, including dihydroxyacetone in aqueous media. Reactions involving hydroxyacetone were highly regioselective. Furthermore, our study suggests that naturally occurring *sec*-amines with the pyrrolidine structural motif can catalyze the synthesis of monosaccharides under physiological conditions. Moreover, the use of organocatalysts provides an inexpensive efficient route for the synthesis of polyols under environmentally benign reaction conditions and may warrant further attention as a prebiotic route to sugars.

Table 3 Amine-catalyzed aldol reactions between acetone or DHA and various aldehydes in aqueous media



Entry	R	R'	Catalyst	*t*	Product	Yield[a]	dr[b]
(1)	$BnOCH_2$	H	L-Proline	24h	**12**	55%	–
(2)		H	L-Proline	24h	**13**	65%	–
(3)	Ph	H	L-Proline	24h	**14**	63%	–
(4)	*i*-Pr	H	L-Proline	24h	**15**	45%	–
(5)	*c*-Hex	H	L-Proline	24h	**16**	67%	–
(6)	$BnOCH_2$	OH	**6**	24h	**17**	50%	>20:1
(7)	Ph	OH	**6**	48h[c]	**18**	35%[c]	1:1[c]
(8)	*c*-Hex	OH	**6**	48h	**19**	55%	>20:1
(9)		OH	**6**	24h	**20**	47%[c]	1:1[c]

[a] Isolated yield after column chromatography. [b] dr = anti/syn as determined by NMR. [c] Reaction performed in PBS-buffer at 37 °C.

This study was supported in part by the NIH (CA27489) and the Skaggs Institute for Chemical Biology.

Notes and references

1 (*a*) Y. Mori, K. Manabe and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2001, **40**, 2815; (*b*) S. Kobayashi, T. Hamada, S. Nagayam and K. Manabe, *Org. Lett.*, 2001, **3**, 165; (*c*) S. Kobayashi and H. Ishitani, *Chem. Commun.*, 1995, 1379; (*d*) S. Nagayama and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 11531.

2 D. A. Evans, J. V. Nelson and T. R. Taber, *Stereoselective Aldol Condensations*in *Topics in Stereochemistry*, ed. E. L. Eliel and S. H. Wilen, Wiley-Interscience, New York, 1982, **Vol 13**, p. 1; C. H. Heathcock, *The Aldol Addition Reaction*in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1984, **Vol. 3**, Chapter 2, p. 111.

3 J. H. M. Gijsen, W. Fitz and C.-H. Wong, *Chem. Rev.*, 1996, 443; C.-H. Wong and G. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamon Press, Oxford, 1994.

4 J. Wagner, R. A. Lerner and C. F. Barbas III, *Science*, 1995, **270**, 1797.

5 H. D. Dakin, *J. Biol. Chem.*, 1910, **7**, 49; H. S. Raper, *J. Chem. Soc.*, 1908, 1831; F. G. Fischer and A. Marschall, *Ber.*, 1931, **64**, 2825.

6 W. Langenbeck and G. Borth, *Ber.*, 1942, **75**, 951; T. A. Spencer, H. S. Neel, T. W. Flechtner and R. A. Zayle, *Tetrahedron Lett.*, 1965, 3889; C. D. Gutsche, D. Redmore, R. S. Buriks, K. Nowotny, H. Grassner and C. W. Armbruster, *J. Am. Chem. Soc.*, 1967, **89**, 1235; F. Tanaka and C. F. Barbas III, *Chem. Commun.*, 2001, 769.

7 M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 4901; T. E. Hortstmann, D. J. Guerin and S. J. Miller, *Angew. Chem., Int. Ed.*, 2000, **39**, 3635.

8 (*a*) J.-L. Reymond and Y. Chen, *Tetrahedron Lett.*, 1995, **36**, 2575; (*b*) J.-L. Reymond and Y. Chen, *J. Org. Chem.*, 1995, **60**, 6970; (*c*) T. J. Dickerson and K. D. Janda, *J. Am. Chem. Soc.*, 2002, **124**, 3220. For an aldol reaction catalyzed by a Zn(II) complex and the ethyl ester of tyrosine in water, see: M. Nakagawa, H. Nakao and K.-I. Watanabe, *Chem. Lett.*, 1985, 391.

9 (*a*) B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395; (*b*) W. Notz and B. List, *J. Am. Chem. Soc.*, 2000, **122**, 7386; (*c*) K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc.*, 2001, **123**, 5260; (*d*) A. Córdova, W. Notz and C. F. Barbas III, *J. Org. Chem.*, 2002, **67**, 301; (*e*) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615; (*f*) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed.*, 1971, **10**, 496; (*g*) C. Agami, N. Platzer and H. Sevestre, *Bull. Soc. Chim. Fr.*, 1987, **2**, 358; (*h*) A. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 6798; (*i*) A. Bogevig, N. Kumaragurubaran and K. A. Jorgensen, *Chem. Commun.*, 2002, 620.

10 C.-J. Li and T.-H. Chan, *Organic reactions in aqueous media*, John Wiley & Sons, New York, 1997.

11 R. M. Degraaf, J. Visscher, Y. Xu, G. Arrhenius and A. W. Schwartz, *J. Mol. Evol.*, 1998, **47**, 501; R. Krishnamurthy, S. Pitsch and G. Arrhenius, *Orig. Life Evol. Biosph.*, 1999, **29**, 139.

12 0.01M Phosphate buffer, 2.7 mM KCl, 137 mM NaCl, pH = 7.4.

13 Although generally formed as a racemate, aldol product **1** can also be obtained enantiomerically enriched with ee's of up to 63% by performing the experiment in organic solvent containing 10 vol% of water. Solvents used (ee): $DMSO/H_2O$ = 9 : 1 (40%); DMF/H_2O = 10 : 1 (35%); $EtOH/H_2O$ = 9 : 1 (16%); EtOH (19%), $Dioxane/H_2O$ = 10 : 1 (63%).

14 See ESI†, Table 1S.

15 See also: S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **45**, 11273; J.-F. Lin, C.-C. Wu and M.-H. Lien, *J. Phys. Chem.*, 1995, **99**, 16903.

16 A. Heine, G. Desantis, J. G. Luz, M. Mitchell, C.-H. Wong and I. A. Wilson, *Science*, 2001, **294**, 369.

17 The reactions also proceeded in the following organic solvents: THF, dioxane, EtOH and MeOH.

18 The products were obtained as racemates in DMSO/PBS 1 : 1.

19 The ^1H and ^{13}C NMR data of the isolated 5-*O*-benzyl-D-xylulose were identical to that produced by rabbit muscle aldolase (RAMA)-catalysis. See: M. D. Bednarski, E. S. Simon, N. Bischofberger, W.-D. Fessner, M.-J. Kim, W. Lees, T. Saito, H. Waldmann and G. M. Whitesides, *J. Am. Chem. Soc.*, 1989, **111**, 627.