EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201500519

Tertiary Amine Promoted Asymmetric Aldol Reaction of Aldehydes

Bartosz Gut[a] and Jacek Mlynarski*[a,b]

Keywords: Aldol reactions / Organocatalysis / Enantioselectivity / Asymmetric synthesis / Aldoses

The direct asymmetric self-aldol reactions of various α-oxyaldehydes catalyzed by tertiary amines have been demonstrated. By using 10 mol-% of quinine catalyst, dimerization products have been prepared in high yields, with good *anti*-diastereocontrol, and up to 80 % *ee*. The presented enolate-mediated synthesis of protected tetrose sugars has never been accomplished before by chiral tertiary amine organocatalysts.

Introduction

Since the first example of intermolecular proline-catalyzed direct aldol reactions introduced by List and co-workers in 2000,[1] many successful examples of variants of direct aldol reactions promoted by small organic molecules have been described in the literature over the last decade.[2] As a result, various types of organocatalysts have been developed for organic transformations and substrate combinations.[3] Great progress has particularly been made in asymmetric enamine-catalyzed cross-aldol reactions between ketone donors and aldehydes by using organocatalysts based on primary or secondary amines.[4]

Aldehydes can also be used as donors for the enamine-catalyzed aldol reaction, although the range of catalysts tested is narrow and mostly limited to proline and proline-derivatives.[5] In 2002, Northrup and MacMillan reported efficient *anti*-selective cross-aldol reactions of aldehydes by using 10 mol-% of proline.[6] In this way, dimerization of the acceptor aldehyde was suppressed, which further enabled the application of this methodology to another combination of substrates.[7]

Later, MacMillan and co-workers extended the previously elaborated methodology to the dimerization of protected α-hydroxy aldehydes.[8] This particular method enabled (*S*)-proline-promoted direct and enantioselective access to protected polyols and monoprotected *anti*-1,2-diols. Dimeric aldol adducts of protected α-oxyaldehydes constituted protected forms of the naturally occurring sugar erythrose, which could be used in a subsequent Mukaiyama aldol reaction to give access to protected hexoses.[9] This exciting new field of organocatalytic synthesis of carbohydrates[10] has further been extended to direct organocatalytic cross-trimerization of aldehydes[11] leading directly to protected hexose sugars.[12] The ability of amino acids to react with aldehydes and mediate the asymmetric de novo formation of tetroses and hexoses has brought new arguments to the debate on the neogenesis of carbohydrates catalyzed by amino acids.[12b] More recently, amino acids[13] and their more hydrophobic esters have been developed as catalysts for the formation of nonprotected threose and erythrose from glycolaldehyde under aqueous and potentially more prebiotic conditions.[14] This methodology, however, has so far been limited to enamine-based organocatalysts.

We were intrigued by the question whether the asymmetric aldol reaction of aldehydes could also be accomplished by using non-enamine organocatalysts, to broaden the arsenal of known methodologies. Previously, our group had reported the first examples of cross-aldol reactions of ketones and aldehydes promoted by organocatalysts based on tertiary amines.[15] Examples of similar protocols are still rare,[16] despite the broad acceptance of cinchona alkaloids in asymmetric organocatalysis.[17] Nevertheless, we foresee that α-oxyaldehydes could also serve as good substrates in the enolate-mediated aldol reaction, because of the increased acidity of α-protons.

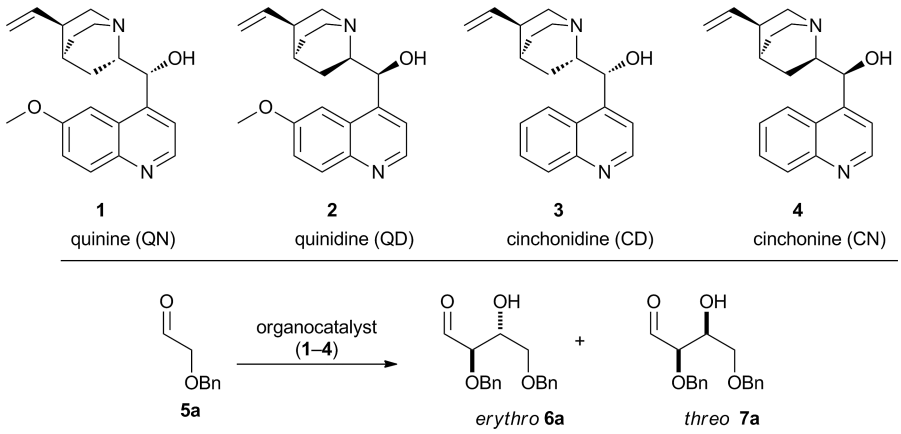
Herein, we report the unprecedented application of unmodified cinchona alkaloid-type organocatalysts for the stereoselective enolate-mediated self-aldol reaction of α-oxyaldehydes, leading to nonracemic protected tetroses isolated with up to 80% *ee*.

Results and Discussion

Initially, self-aldol coupling of glycolaldehyde was tested by using benzyloxyacetaldehyde **5a** when promoted by four readily available cinchona alkaloids (**1**–**4**, Scheme 1). To our delight, application of 10 mol-% of tertiary amines in $CHCl_3$ at 4 °C resulted in preferential formation of *anti*-aldol **6a** in high yields ranging from 81% for quinine (**1**) to 90% for cinchonine (**4**) (Table 1, entries 1–4). Both dimeric

[a] Faculty of Chemistry, Jagiellonian University,
Ingardena 3, 30-060 Krakow, Poland
E-mail: jacek.mlynarski@gmail.com
http://www.jacekmlynarski.pl
[b] Institute of Organic Chemistry, Polish Academy of Sciences,
Kasprzaka 44/52, 01-224 Warsaw, Poland

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500519.



Scheme 1. Self-condensation of benzyloxyacetaldehyde **5a** promoted by cinchona alkaloid catalysts **1**–**4**.

aldol adducts **6a** and **7a** constitute protected forms of the naturally occurring tetrose sugars. Application of the organocatalyst quinine (**1**) delivered protected D-erythrose **6a** accompanied by a minor amount of D-threose derivative **7a** (Table 1, entry 1). In contrast, quinidine (**2**) enabled the synthesis of L-sugars (Table 1, entry 2). In general, application of quinine/cinchonidine (QN-**1**/CD-**3**) and pseudoenantiomeric quinidine/cinchonine (QD-**2**/CN-**4**) couples delivers the expected antipodes (Table 1, entries 1–4).[18]

Table 1. Studies for catalysts and conditions in self-condensation of benzyloxyacetaldehyde.[a]

	Cat.	Time [d]	Temp. [°C]	Yield [%][b]	*anti*/*syn*	*ee anti* [%][c]
1	**1**	5	4	81	63:37	75 (2*R*,3*R*)
2	**2**	5	4	84	67:33	62 (2*S*,3*S*)
3	**3**	5	4	83	67:33	49 (2*R*,3*R*)
4	**4**	5	4	90	66:34	32 (2*S*,3*S*)
5	**1**	5	r. t.	59	71:29	47 (2*R*,3*R*)
6	**1**	3	4	81	65:35	80 (2*R*,3*R*)
7	**1**	3	–30	35[d]	60:40	69 (2*R*,3*R*)

[a] Reaction conditions: **5a** (1 mmol, catalyst 10 mol-%) in $CHCl_3$ (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC of the derivatives; details have been presented in the Supporting Information. [d] 20 mol-% of catalyst was used.

Since it is known that hydrogen bonds play an important role in reactions involving cinchona catalysts, we synthesized and tested various derivatives that were previously tested in asymmetric synthesis.[19] Such studies revealed that unmodified catalyst **1** showed the best selectivity, and for this reason it was used exclusively for the further studies.

The effect of solvents and reaction temperature were then more carefully studied with catalyst **1**, and the results are summarized in Table 1 (entries 5–7) and Table 2. When the reaction was carried out at room temp. or –30 °C, lower *ee* values and lower yields of aldols were obtained. As the data in Table 2 indicate, common organic solvents have only minimal influence on reaction selectivity. The worst enantioselectivity was noted for nonpolar hexane, and the best parameters were observed for $CHCl_3$ (Table 2, entry 1). Interestingly, the reaction carried out in the presence of water also delivered the expected tetroses, albeit with lower yield and enantioselectivity (Table 2, entry 9).

Table 2. Solvent screening for benzyloxyacetaldehyde **5a** self-condensation promoted by quinine (**1**).[a]

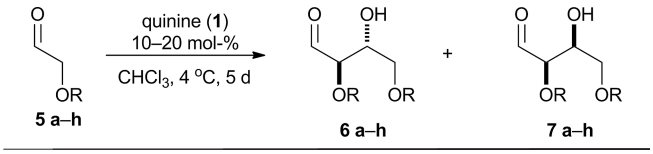
	Solvent	Yield [%][b]	*anti*/*syn*	*ee anti* [%][c]
1	$CHCl_3$	81	65:35	80
2	DCM	70	64:36	71
3	hexane	80	62:38	33
4	1,4-dioxane	76	62:38	60
5	toluene	81	65:35	63
6	Et_2O	76	63:37	61
7	MeCN	68	63:37	62
8	THF	81	61:39	56
9	THF/H_2O (9:1)	37	61:39	46
10	neat	91	63:37	55

[a] Reaction conditions: **5a** (1 mmol, catalyst 10 mol-%) in $CHCl_3$ (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC of the derivatives; details have been presented in the Supporting Information.

Once the reaction conditions were optimized, and to further demonstrate the potential of this catalytic system, the scope of the reaction was examined for various α-oxyaldehydesby using quinine (10 mol-%) in $CHCl_3$. As shown in Table 3, the reaction proceeded very well with various protected glycolaldehydes, and aldol products **6a**–**6g** were generated in good yields and good enantioselectivities favoring the formation of protected D-erythroses (Table 3, entries 1–6). We noticed that α-oxyaldehyde products **6** and **7** formed in these reactions are inert to further reaction promoted by the tertiary amine catalyst, and thus can easily be isolated as end-products without any possible side reactions.

Interestingly, dimerization of unprotected glycolaldehyde **5h** promoted by quinine also led directly to the formation of erythrose *anti*-**6h** and threose *syn*-**7h** in a 75:25 ratio (entry 8). In this case, however, application of the quinidine catalyst resulted in the best selectivity up to 45% *ee* (entry 9). The observed enantioselectivity for the formation of D-erythrose revealed an unexpected pathway for the formation of natural sugars promoted by chiral tertiary amines. In

Table 3. Different aldehydes in the asymmetric aldol reaction.[a]



	R	Product	Yield [%][b]	*anti*/*syn*	*ee anti* [%][c]
1	Bn	**6a**	81	63:37	81
2	4-MeOC_6H_4	**6b**	68	73:27	65
3	4-F–C_6H_4	**6c**	77	62:38	70
4	3,5-*t*$Bu_2C_6H_3$	**6d**	57	62:38	66
5	4-NCC_6H_4	**6e**	72	75:25	60
6	MOM	**6f**	69	66:34	67
7	TBDMS	**6g**	40	66:34	65
8	H	**6h**	45	75:25	17
9	H	**6h**	59	77:23	45[d,e]
10	H	**6h**	55	80:20	42[d,f]

[a] Reaction conditions: **5a** (1 mmol, catalyst 10 mol-%) for 5 d in $CHCl_3$ (2 mL). [b] Isolated yield. [c] Determined by chiral HPLC of the derivatives. The absolute configuration of the major product was proven to be (2*R*,3*R*) by comparison with authentic samples prepared from D-glucose. For details see Supporting Information. [d] Determined by chiral HPLC of the derivatives. The absolute configuration of the major product was proven to be (2*S*,3*S*) by comparison with authentic samples prepared from D-glucose. For details see Supporting Information. [e] Reaction conditions: 3 d, room temp. 20 mol-% of quinidine (**2**). [f] Reaction conditions: 3 d, room temp. 20 mol-% of cinchonine (**4**).

contrast to the broadly discussed amino-acid-catalyzed neogenesis of carbohydrates,[12,20] such a possibility has never been presented in the literature. Now, it is clear that alternative enolate-mediated syntheses of protected tetrose sugars may also be accomplished by using chiral tertiary amine organocatalysts.

Conclusions

In summary, we have presented the first direct enantioselective catalytic self-aldol reaction of α-oxyaldehydes promoted by tertiary amine organocatalysts. The desired aldol products are obtained in good to high enantioselectivities (up to 80% *ee*), opening new directions in metal-free enolate-mediated aldol reactions. Significantly, naturally occurring quinine generates tetroses (*anti*-aldol product) with the natural D-configuration (predominantly D-erythrose), while application of quinidine resulted in the formation of L-sugars (L-erythrose) even for unprotected glycolaldehyde.

Experimental Section

Representative Procedure for the Aldol Reaction: Benzyloxyacetaldehyde (1 mmol, 150 mg) was dissolved in $CHCl_3$ (1 mL), then quinine (32.4 mg, 10 mol-%) was added, and the resulting mixture was stirred for 5 d at 4 °C. After this time, the reaction mixture was poured directly on the silica gel. The aldol product was purified by column chromatography (DCM/Et_2O, 19:1) to give the desired product (see Table 3).

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data for new compounds, copies of ^1H NMR and ^{13}C NMR spectra, and HPLC and GC analyses.

Acknowledgments

This project is operated within the Foundation for Polish Science TEAM Programmes co-financed by the European Union European Regional Development Fund. Financial support from the Polish National Science Centre (MAESTRO Grant Nr. 2013/10/A/ST5/00233) is gratefully acknowledged.

[1] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[2] B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600–1632.
[3] a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis* Wiley-VCH, Weinheim, **2005**; b) R. R. Torres (Ed.), *Stereoselective Organocatalysis: Bond Formation Methodologies and Activation Modes*, Wiley-VCH, Weinheim, **2013**.
[4] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
[5] For an initial example of trimerization of acetaldehyde see: a) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301–303; for the reaction of aldehydes with non-enolizable α-keto-esters see: b) A. Bogevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620–624.
[6] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.
[7] a) P. M. Pihko, A. Erkkilä, *Tetrahedron Lett.* **2003**, *44*, 7607–7609; b) J. Carpenter, A. B. Northrup, D. Chung, J. J. M. Wiener, S.-G. Kim, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2008**, *47*, 3568–3572; *Angew. Chem.* **2008**, *120*, 3624; c) I. K. Mangion, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3696–3697; d) R. I. Storer, D. W. C. MacMillan, *Tetrahedron* **2004**, *60*, 7705–7714; e) R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 3541–3544; f) Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem. Int. Ed.* **2008**, *47*, 2082–2084; *Angew. Chem.* **2008**, *120*, 2112; g) S. Hu, L. Zhang, J. Li, S. Luo, J.-P. Cheng, *Eur. J. Org. Chem.* **2011**, 3347–3352; h) Y. Qiao, Q. Chen, S. Lin, B. Ni, A. D. Headley, *J. Org. Chem.* **2013**, *78*, 2693–2697.
[8] A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2004**, *43*, 2152–2154; *Angew. Chem.* **2004**, *116*, 2204.
[9] A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752–1755.
[10] J. Mlynarski, B. Gut, *Chem. Soc. Rev.* **2012**, *41*, 587–596.
[11] a) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 9591–9595; b) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Córdova, *Angew. Chem. Int. Ed.* **2005**, *44*, 1343–1345; *Angew. Chem.* **2005**, *117*, 1367.
[12] a) A. Córdova, M. Engqvist, I. Ibrahem, J. Casas, H. Sunden, *Chem. Commun.* **2005**, 2047–2049; b) A. Córdova, I. Ibrahem, J. Casas, H. Sunden, M. Engqvist, E. Reyes, *Chem. Eur. J.* **2005**, *11*, 4772–4784.
[13] S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151–1153.
[14] a) L. Burroughs, M. E. Vale, J. A. R. Gilks, H. Forintos, C. J. Hayes, P. A. Clarke, *Chem. Commun.* **2010**, *46*, 4776–4778; b) L. Burroughs, P. A. Clarke, H. Forintos, J. A. R. Gilks, C. J. Hayes, M. E. Vale, W. Wade, M. Zbytniewski, *Org. Biomol. Chem.* **2012**, *10*, 1565–1570; c) M. Markert, U. Scheffler, R. Mahrwald, *J. Am. Chem. Soc.* **2009**, *131*, 16642–16643.
[15] a) J. Paradowska, M. Rogozińska, J. Mlynarski, *Tetrahedron Lett.* **2009**, *50*, 1639–1641; b) S. Baś, Ł. Woźniak, J. Cygan, J. Mlynarski, *Eur. J. Org. Chem.* **2013**, 6917–6923.

[16] S. Konda, Q.-S. Guo, M. Abe, H. Huang, H. Arman, J. C.-G. Zhao, *J. Org. Chem.* **2015**, *80*, 806–815 and references cited therein.
[17] T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229–1279.
[18] For determining the yields diastereo-, and enantioselectivities of the tetrose products, we used a standard protocol involving reduction of the tetroses with $NaBH_4$ in MeOH followed by formation of appropriate derivatives. Details have been presented in the Supporting Information.
[19] Detailed information on applications of various modified cinchona catalysts has been presented in the Supporting Information.
[20] a) A. L. Weber, *Origins Life Evol. B* **2001**, *31*, 71–86; b) S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151–1151; c) J. Kofoed, M. Machuqueiro, J.-L. Reymond, T. Darbre, *Chem. Commun.* **2004**, 1540–1541; d) J. Kofoed, J.-L. Reymond, T. Darbre, *Org. Biomol. Chem.* **2005**, *3*, 1850–1855.

Received: April 23, 2015
Published Online: July 14, 2015

