ORGANIC LETTERS

1999
Vol. 1, No. 1
59−61

Enantioselective Aldol Cyclodehydrations Catalyzed by Antibody 38C2

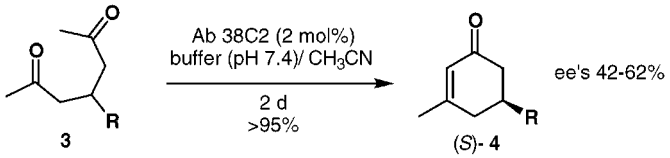
Benjamin List, Richard A. Lerner,* and Carlos F. Barbas III*

Skaggs Institute for Chemical Biology and the Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

carlos@scripps.edu

Received March 26, 1999

ABSTRACT



Aldolase antibody 38C2 catalyzes the enantioselective aldol cyclodehydration of 4-substituted-2,6-heptanediones (3) to give enantiomerically enriched 5-substituted-3-methyl-2-cyclohexen-1-ones (4). Yields, enantioselectivities, and product purities are markedly increased compared to the L-proline-catalyzed reactions.

Enantioselective reactions typically rely on the differentiation between the two enantiotopic faces of an sp^2 carbon center. Most often this center is connected to an oxygen, a nitrogen, or another carbon atom via a double bond. Examples include the asymmetric dihydroxylation (AD)[1] and the catalytic enantioselective hydrogenation of olefins.[2] A different type of enantioselectivity is observed in reactions where two enantiotopic groups are differentiated (Figure 1). Despite a few known small molecule catalysts,[3] natural enzymes dominate this reaction class. Examples include the esterase-catalyzed *meso*-diesters and the reverse reaction, the lipase-catalyzed desymmetrization of *meso*-diols.[4]

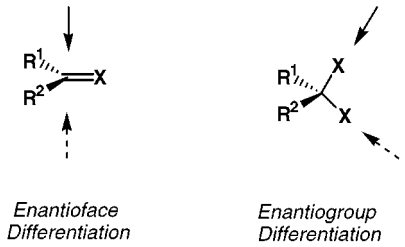


Figure 1.

While catalytic antibodies have been shown to be efficient catalysts for the enantioface-differentiating reactions[5] and enantiomer-differentiating kinetic resolutions,[6] enantiogroup-differentiating reactions with catalytic antibodies have rarely been reported.[7] In this paper we demonstrate the use of aldolase antibody 38C2 for the enantiogroup-differentiating aldol cyclodehydration of 4-substituted-2,6-heptanediones (**3**) to give enantiomerically enriched 5-substituted-3-methyl-2-cyclohexen-1-ones (**4**).

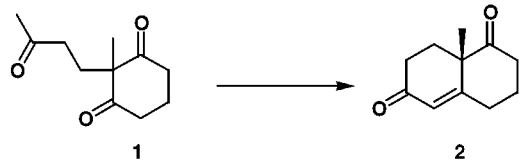
Aldolase antibody 38C2 (Aldrich no. 47,995-0) has been shown to be a highly efficient *and* enantioselective catalyst

(1) Johnson, R. A.,; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCA: Weinheim, 1993; pp 227−272.
(2) Takaya, H.; Ohta, T.; Noyori, R., ref 1, pp 1−39.
(3) For example, see: Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809−1810.
(4) Wallace, J. S.; Baldwin, B. W.; Morrow, C. J. *J. Org. Chem.* **1992**, *57*, 5231−5239.
(5) See, for example: (a) Hsieh, L. C.; Yonkovich, S.; Kochersperger, L.; Schultz, P. G. *Science* **1993**, *260*, 337. (b) Reymond, J.-L.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 2257. See ref 9a.
(6) Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490. See also ref 9b.
(7) Ikeda, S.; Weinhouse, M. I.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 7763−7764. See also ref 13.

10.1021/ol9905405 CCC: $18.00 © 1999 American Chemical Society
Published on Web 05/24/1999

for both aldol and *retro*-aldol reactions with rate accelerations approaching those of natural aldolase enzymes.[8] Furthermore, and in contrast to its natural counterparts, this antibody is a broad scope aldol catalyst that has been shown to work with over 200 different substrate combinations.[9] We have used antibody 38C2 in the enantioselective synthesis of naturally occurring pheromone derivatives,[10] deoxy-sugars,[11] and in a total synthesis of epothilone A.[12] Furthermore, we demonstrated its use in a preparative scale synthesis of the Wieland−Miescher ketone (**2**) from achiral triketone **1** (Scheme 1).[13] Traditionally, this reaction is catalyzed by

Scheme 1

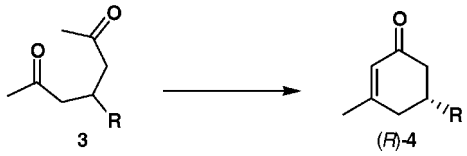


Ab 38C2 : 94%, (96% ee)

(*L*)-Proline : 83%, (71% ee)

L-proline.[14] However, here the product is obtained with an ee of 71%. A related transformation that has been catalyzed by L-proline is the enantioselective cyclodehydration of 4-substituted-2,6-heptanediones (**3**) to the 5-substituted-3-methyl-2-cyclohexen-1-ones (**4**) (Scheme 2).[15] Stereochemi-

Scheme 2



(*L*)-Proline : ~ 30%, (0-47% ee)

38C2: This work

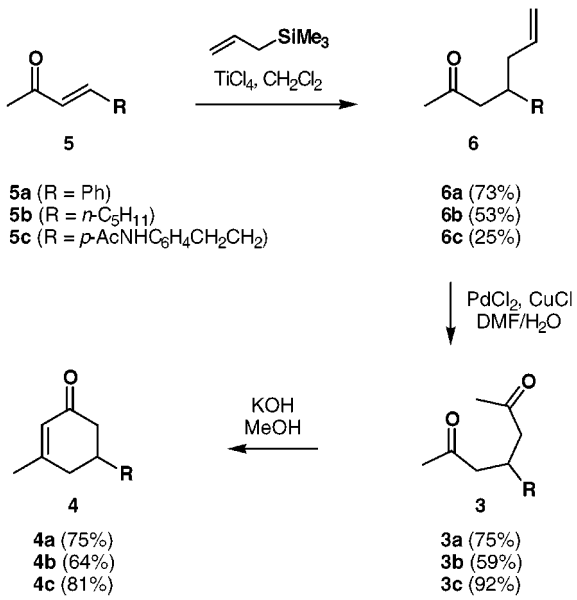
cally, both reactions are enantiogroup-differentiating and probably occur via an enamine mechanism. However, in the former case (**1** → **2**) the enantiodifferentiation follows enamine formation, while in the latter case (**3** → **4**) enantiodifferentiation occurs upon enamine formation.

In the L-proline-catalyzed reaction, typically low yields and enantioselectivities are observed.

We found that antibody 38C2 catalyzes the cyclodehydration of **3** (R = H) quite efficiently with $k_{cat} = 0.082$ min^{-1}, $K_M = 2$ mM, and $k_{cat}/k_{uncat} = 1.2 \times 10^7$.[9a] The question was whether antibody 38C2 was capable of catalyzing this transformation with enantiogroup selectivity when provided with substrates **3** where R ≠ H.

For the synthesis of the starting 1,5-diketones **3a**−**c**, we followed a route that has been developed by Sakurai and co-workers.[16] Thus, Lewis acid mediated conjugate addition of allyltrimethylsilane to α,β-unsaturated ketones **5a**−**c** gave olefins **6a**−**c**.[17] Wacker oxidation of δ,ϵ-unsaturated ketones **6a**−**c** then furnished diketones **3a**−**c**.[18] Interestingly, we found that the Wacker oxidation did not require an oxygen atmosphere. Simple stirring under air furnished the products in equivalent yield.[19] Racemic reference compounds **4a**−**c** can be prepared by base treatment (KOH/MeOH) of ketones **3a**−**c** (Scheme 3).[20]

Scheme 3



The results of the antibody-catalyzed cyclization of diketones **3** are shown in Scheme 4.

(8) (a) Wagner, J.; Lerner, R. A.; Barbas, C. F., III. *Science* **1995**, *270*, 1797. (b) Barbas, C. F., III; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Björnestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, I. A.; Lerner, R. A. *Science* **1997**, *278*, 2085−2092.

(9) (a) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768−2779. (b) Zhong, G.; Shabat, D.; List, B.; Anderson, J.; Sinha, S. C.; Lerner. R. A.; Barbas, C. F., III. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2481−2484. (c) List, B.; Barbas, C. F., III; Lerner, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, 15351−15355.

(10) List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. A. *Chem. Eur. J.* **1998**, *4*, 881−885.

(11) Shabat, D.; List, B.; Lerner, R. A.; Barbas, C. F., III. *Tetrahedron Lett.* **1999**, *40*, 1437−1440.

(12) Sinha, S. C.; Barbas, C. F., III; Lerner, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, 14603−14608.

(13) Zhong, G.; Hoffmann, T., Lerner, R. A., Danishefsky, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1997**, *119*, 8131−8132.

(14) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621.

(15) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, *2*, 358−360.

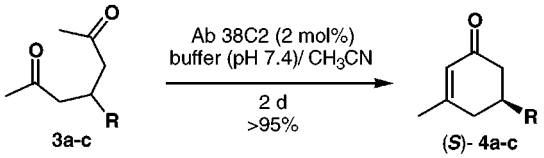
(16) Hosomi, A.; Kobayashi, H.; Sakurai, H. *Tetrahedron Lett* **1980**, *21*, 955−958.

(17) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673−1675. The yield of olefin **6c** was diminished from concurrent cyclobutane formation. A similar observation has been made by Hosomi et al. (ref 16).

(18) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2975−2976.

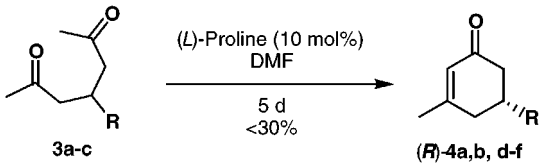
(19) Doron Shabat, The Scripps Research Institute, personal communication.

Scheme 4



(*S*)-**4**	R	ee
a	Ph	42%
b	*n*-C_5H_{11}	46%
c	*p*AcNHC$_6$H$_4$CH$_2$CH$_2$	62%

Scheme 5



(*R*)-**4**	R	ee	
a	Ph	47%	
b	*n*-C_5H_{11}	20%	
d	Me	42%	ref. 15
e	*i*-Pr	8%	
f	*t*-Bu	0%	

Antibody 38C2 (10 μM, 2 mol %) catalyzes the cyclodehydration of diketones **3a**−**c** (500 μM in phosphate buffered saline (PBS), pH 7.4, 10% CH_3CN) very efficiently to give the (*S*)-configured products **4a**−**c** with yields generally exceeding 95%.

The enantioselectivity of these reactions is moderate to good. The ee's were determined by chiral-phase HPLC analysis.[21]

To determine the absolute configuration of enones **4a**−**c**, we used the products from the L-proline-catalyzed reaction as a reference standard. This transformation is known to give the corresponding (*R*)-isomers (Scheme 5).

All products obtained from the L-proline-catalyzed reactions had a configuration opposite that of the products produced in the antibody-catalyzed reaction as determined by chiral-phase HPLC analyses.[20] Interestingly, and in contrast to these results, in the Wieland−Miescher case both L-proline and 38C2 gave the same enantiomer.

In summary, aldolase antibody 38C2 has been shown to be an efficient catalyst for the enantiogroup-differentiating cyclodehydration of 4-substituted 2,6-heptanediones. The observed enantioselectivities are modest in comparison to the exceptional high ee's that are usually obtained in aldol additions and *retro*-aldol reactions catalyzed by antibody 38C2.[9a,b] However, product yields, purities, and to some extent enantioselectivities are far better than those obtained from the corresponding L-proline-catalyzed reactions.

Acknowledgment. This study was supported in part by the NIH (CA27489). B.L. thanks the Alexander von Humboldt Stiftung, Germany, for a Feodor Lynen fellowship.

OL9905405

(20) All new compounds gave satisfactory spectroscopic data (^{1}H and ^{13}C NMR and HRMS).

(21) **4a** and **4b**: Chiracell ODR, 60% H_2O (0.1% TFA), 40% CH_3CN, 0.6 mL/min. **4c**: Chiracell ODR, 70% H_2O (0.1% TFA), 30% CH_3CN, 0.6 mL/min. (*S*)-**4a** 46.5 min, (*R*)-**4a** 49.0 min; (*S*)-**4b** 51.8 min, (*R*)-**4b** 50.7 min; (*S*)-**4c** 48.2 min, (*R*)-**4c** 45.0 min.