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Enantioselective Organocatalytic Aldol Reaction of Ynones and Its Synthetic Applications

Franck Silva, Marcin Sawicki, and Véronique Gouverneur*

Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, OX1 3TA Oxford, U.K.

véronique.gouverneur@chem.ox.ac.uk

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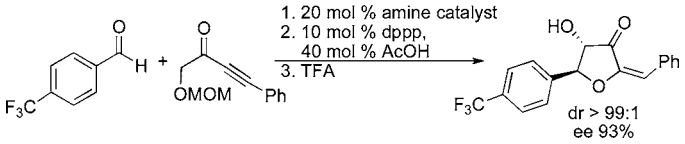
ABSTRACT



For the first time, unmodified ynones were used in organocatalytic asymmetric aldol reactions delivering monoprotected *anti*-α,*β*-dihydroxyynones in high yields, dr's up to 19:1, and ee's up to 95%. These products can be either reduced to afford enantioenriched unsaturated *anti*,*anti*-triol or cyclized using a novel intramolecular phosphine-catalyzed α-addition to the ynone. This organocatalytic sequential aldol−cyclization process provides a concise entry to unusual enantioenriched oxygenated heterocycles, which can be used for subsequent structural manipulations.

Aldol products derived from ynones are highly functionalized building blocks commonly used for the synthesis of biologically active compounds. These *β*-hydroxyynones are usually prepared from the corresponding *β*-hydroxylated Weinreb amides upon addition of the required alkynyllithium or alkynylmagnesium halide.[1] Direct catalytic asymmetric aldol reactions involving unmodified ynones are highly desirable but extremely rare due to the ability of these donors to act as Michael acceptors and the tendency of the resulting aldol products to undergo elimination or retro-aldol reactions. The use of ynones in direct catalytic asymmetric aldol reactions is virtually unknown with the exception of the additions of methyl ynones to α-ketal aldehydes in the presence of a nonracemic chiral dinuclear zinc catalyst, a process developed by Trost et al.[2] The lack of organocatalytic methods for aldolizations of ynones prompted us to investigate the efficiency of nonmetallic catalysts for the preparation of enantioenriched *β*-hydroxyynones and to study their reactivity for subsequent structural manipulations. Herein, we disclose our results in this area, which culminated in a highly concise organocatalytic route to enantioenriched five-membered oxygenated heterocycles.

A solvent, catalyst, and additive screen was performed initially for the addition of 3-hexyn-2-one (5 equiv) to *p*-nitrobenzaldehyde (1 equiv).[3] This preliminary work revealed that the presence of 20 mol % of the acyl sulfonamide **1a**[4] used in DMSO/H_2O (9:1) at room temperature afforded the aldol product **2** in low yield (39%) and moderate enantioselectivity (74% ee) after 120 h. Under these conditions, competing reaction pathways took place such as elimination coupled with Michael addition leading to the formation of significant amounts of the achiral compounds **3** and **4**, which were isolated in 15% and 11% yields, respectively (Scheme 1).

(1) For selected syntheses of *β*-hydroxyynones, see: (a) Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624. (b) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396. (c) Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587. (d) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667. (e) Marshall, J. A.; Ellis, K. *Tetrahedron Lett.* **2004**, *45*, 1351. (f) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531. (g) Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733. (h) Funel, J-A.; Prunet, J. *J. Org. Chem.* **2004**, *69*, 4555. (i) Shin, Y.; Fournier, J-H.; Balachandran, R.; Madiraju, C.; Raccor, B. S.; Zhu, G.; Edler, M. C.; Harnel, E.; Day, B. W.; Curran, D. P. *Org. Lett.* **2005**, *7*, 2873.

(2) (a) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660. (b) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666.

(3) For details, see the Supporting Information

(4) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84−96.

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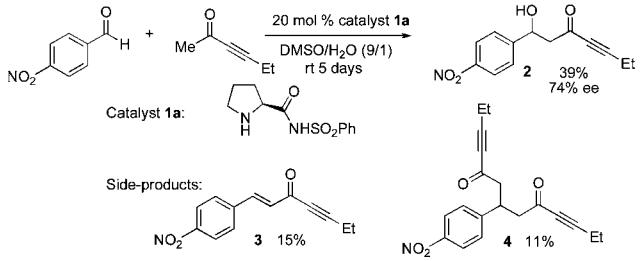
Scheme 1. Organocatalytic Aldol of 3-Hexyn-2-one



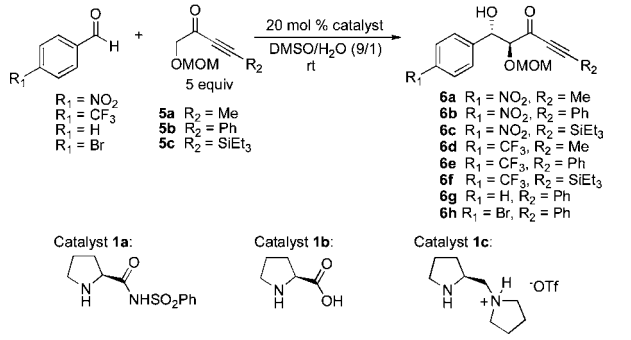
Hydroxylated ynones were selected as alternative substrates as the additional α-hydroxy group could shift the iminium−enamine equilibrium, therefore favoring the aldolization process.[5] To test this hypothesis, the aldol reaction of the MOM-protected ynone **5a** (5 equiv) with *p*-nitrobenzaldehyde to afford **6a** was investigated first varying the amine catalyst (**1a**, **1b**, or **1c**) and the reaction time (Table 1, entries 1−4).[6]

The results revealed that the sulfonamide **1a** remains the catalyst of choice leading after 120 h to **6a** in 68% yield and a diastereomeric ratio of 9:1 in favor of the anti isomer. A synthetically useful level of enantiomeric purity (93%) was observed for the *anti*-aldol product (entry 4).

Notably, no side product resulting from an elimination process and/or Michael addition was detected in the crude reaction mixture. (L)-Proline was not a suitable catalyst for this transformation as only 15% of the desired aldol product **6a** was formed after 48 h (entry 2). The diamine **1c**[7] was slightly superior but not as good as catalyst **1a** (entry 3). The tolerance of this organocatalytic enantioselective aldolization to the presence of different substituents on both the donor and the acceptor was then evaluated. Ynones **5a**−**c** with triple bonds capped with a methyl, phenyl, or triethylsilyl group were subsequently reacted in combination with four representative aldehydes (Table 1, entries 5−11).

In all cases, the reaction proceeded smoothly to give the aldol products **6a**−**h** in good yields, except when benzaldehyde was used as the acceptor (entry 10), and with a high level of stereocontrol. The higher diastereoselectivities were achieved decreasing the bulkiness of the substituent on the ynone donor in the order of R = Me > Ph > $SiEt_3$. Significantly, for ynone **5a**, one diastereomer was formed predominantly (dr > 19:1) as determined by ^{1}H NMR. For most reactions, the minor syn diastereomers could be easily separated upon purification leading to an analytically pure sample of the major *anti*-aldol products **6a**−**h**. For the anti diastereomers, enantioselectivities were ranging from 77% to 93%. The relative and absolute configurations of the aldol products were assigned by NMR after derivatization.[3] The anti selectivity arose from the preferential in situ formation

Table 1. Organocatalytic Aldol of Ynones **5a**−**c** to Aldehydes **7**−**9**



entry	catalyst	aldehyde (R_1)	ynone	product	time (h)	yield (%)[a]	anti/syn[b]	ee (%)[c]
1	**1a**	NO_2	**5a**	(−)-**6a**	48	52	9:1	89
2	**1b**	NO_2	**5a**	(−)-**6a**	48	15		56
3	**1c**	NO_2	**5a**	(−)-**6a**	48	38	3:1	84
4	**1a**	NO_2	**5a**	(−)-**6a**	120	68	9:1	93
5	**1a**	NO_2	**5b**	(−)-**6b**	120	90	9:1	94
6	**1a**	NO_2	**5c**	(−)-**6c**	120	87	4:1	77
7	**1a**	CF_3	**5a**	(−)-**6d**	120	67	19:1	95
8	**1a**	CF_3	**5b**	(−)-**6e**	120	84	9:1	93
9	**1a**	CF_3	**5c**	(−)-**6f**	120	75	3:1	—[d]
10	**1a**	H	**5a**	(−)-**6g**	120	26	13:1	90
11	**1a**	Br	**5b**	(−)-**6h**	120	65	9:1	93

[a] Isolated yields. [b] Determined by ^{1}H NMR spectroscopy of the crude product (after purification, most compounds can be isolated as the pure anti diastereomer. [c] Determined by chiral HPLC. [d] The two enantiomers could not be separated by chiral HPLC.

of the intermediate *E*-enamine leading to the aldol product via a chairlike transition state. The sense of enantiocontrol is in accordance with previously proposed transition states for (L)-proline-mediated aldol reactions with the enantiofacial selectivity (*re*) of the aldehyde being identical to that obtained using hydroxyacetone as the aldol donor.[8]

The chemistry of α,*β*-dihydroxylated derivatives such as **6a**−**h** is virtually unknown.[9] The lack of information on the synthetic usefulness of these building blocks prompted us to study their reactivity and to determine whether the stereochemical integrity of these aldol products can be propagated and preserved through further functional group manipulations. A successful diastereo- and chemoselective reduction of **6e** was carried out targeting the carbonyl group (Scheme 2).

(5) (a) Lin, J.-F.; Wu, C.-C.; Lien, M.-H. *J. Phys. Chem.* **1995**, *99*, 16903. (b) Maggiotti, V.; Bahmanyar, S.; Reiter, M.; Houk, K. N.; Gouverneur, V. *Tetrahedron* **2004**, *60*, 619.

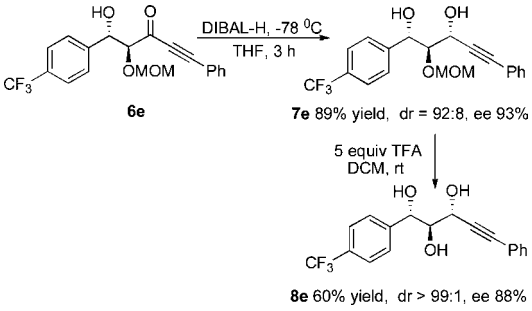
(6) Unprotected α-hydroxyynones were screened for amine-catalyzed aldolizations but led to only traces of the aldol after 24 h.

(7) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245.

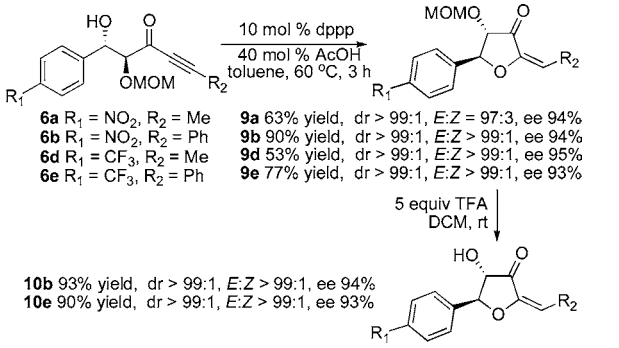
(8) (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Cordova, A.; Notz, W.; Barbas, C. F., III. *Chem. Commun.* **2002**, *24*, 3024. (d) Liu, H.; Peng, L.; Zhang, T.; Li, Y. *New J. Chem.* **2003**, *27*, 1159. (e) Pan, Q.; Zou, B.; Wang, Y.; Ma, D. *Org. Lett.* **2004**, *6*, 1009. (f) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285. (g) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752. (h) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321. (i) Guillena, G.; del Carmen, H. M.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1027. (j) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958.

(9) For a rare synthesis of a protected *syn*-α,*β*-dihydroxylated ynone, see: Paquette, L. O; Kim, H. O.; Cunière, N. *Org. Lett.* **2003**, *5*, 221.

Scheme 2. Chemoselective Reduction of **6e**



Scheme 3. Phosphine-Catalyzed Cyclization of **6a**,**b** and **6d**,**e**



The diastereoselective reduction of the carbonyl group in **6e** was feasible using DIBAL in THF and led preferentially to the monoprotected *anti*,*anti*-triol **7e** with no erosion of the enantiomeric excess (dr = 92:8, 89% yield, 93% ee). Alternative reagents such as $Me_4NBH(OAc)_3$ or Et_2BOMe/$NaBH_4$ delivered the reduced product but were not diastereoselective. Deprotection of **7e** with TFA in DCM was uneventful.

With the objective of developing novel organocatalytic routes to oxygenated heterocycles, phosphine-catalyzed cyclizations of compounds **6a**,**b** and **6d**,**e** were attempted next (Scheme 3).[10] After extensive experimentation, we found that the reaction of aldol **6b** in the presence of 10 mol % of dppp and 40 mol % of AcOH in toluene at 60 °C delivered within 3 h the five-membered cyclized product **9b** resulting from an intramolecular α-addition in 90% yield and an ee of 94% suggesting that no racemization took place upon ring closure. The product was formed as the single anti isomer. Control experiments suggested that enolization took place under these conditions delivering consistently the anti isomers independent of the relative configuration of the starting aldol. These studies also revealed that the *anti*-aldols were more reactive than the corresponding syn isomers. Using these conditions, we successfully cyclized aldols **6a** and **6d**,**e** to afford the enantioenriched **9a** and **9d**,**e** in yields ranging from 53% to 90% and with an ee up to 95%. Deprotection of the MOM group was feasible at this stage using TFA in DCM at room temperature allowing for the release of the enantioenriched hydroxylated heterocycles **10b** and **10e** as single diastereomers and with no detectable racemization.

In conclusion, for the first time, unmodified ynones were used as donors in organocatalytic asymmetric aldol reactions. Ynones featuring a MOM-protected α-hydroxyl group are better substrates than the 3-hexyn-2-one and led to the monoprotected *anti*-α,*β*-dihydroxyynones in high yields and ee's up to 95%.

These products can be transformed into enantioenriched unsaturated *anti*,*anti*-triols. An unprecedented organocatalytic phosphine-mediated cyclization featuring an intramolecular regioselective α-addition process was also developed allowing for the synthesis of a novel class of enantioenriched oxygenated heterocycles. These new compounds can be further manipulated through the ketone functionality or the activated exocyclic double bond. Further research addressing the scope and applicability of these organocatalytic reactions is currently under investigation.

Acknowledgment. We thank the European Community for their generous financial support (MRTN-CT-2003-505020 and COST Action D25).

Supporting Information Available: Complete analytical data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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