Published in final edited form as:

Chem Commun (Camb). 2016 January 04; 52(1): 108–111. doi:10.1039/c5cc07780j.

Asymmetric Synthesis of 1*H*-Pyrrol-3(2*H*)-ones from 2, 3-Diketoesters by Combination of Aldol Condensation with Benzilic Acid Rearrangement

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Abstract

An efficient two-step protocol for the asymmetric synthesis of 1*H*-pyrrol-3(2*H*)-one derivatives in 99% ee from conveniently accessed 2, 3-diketoesters has been developed.

2, 2-Disubstituted 1*H*-pyrrol-3(2*H*)-ones that possess a chiral center at the 2-position occur widely in natural products,¹ and they are also fundamental units which have been used to build molecules with significant biological activities (Figure 1).² Due to their importance, a variety of methods for their synthesis have been developed. Cycloaddition strategies are among the most efficient ways used to access the key 1*H*-pyrrol-3(2*H*)-ones.³ However, general highly enantioselective addition methods are rare: one begins with chiral starting materials,⁴ and the other employs catalytic asymmetric cycloaddition.⁵ Although progress is being made in this area, the narrow substrate scope of reported methods suggests the need for more general enantioselective processes.

Pioneering work by Wasserman and coworkers⁶ demonstrated wide applications of vicinal tricarbonyl compounds (VTCs) in the synthesis of natural products and synthetic intermediates. Our group has applied VTCs in the synthesis of functionalized furans⁷ and pyrroles⁸ and demonstrated their convenient uses as hydrates.^{8b} We also reported the first diastereoselective⁹ and enantioselective¹⁰ nucleophilic addition reactions of VTC compounds. Based on our understanding of the VTC chemistry and reported benzilic acid rearrangement reactions,¹¹ an enantioselective strategy for the synthesis of 1*H*-pyrrol-3(2*H*)-ones starting from 2, 3-diketoester hydrates was designed as shown in Scheme 1. The mixed asymmetric aldol reaction with VTCs has been unexplored. The enamine formation step is known,¹² although not in this system. To form the chiral key intermediate **3**, a chiral secondary amine-catalyzed aldol reaction was predicted to have the potential to achieve this goal.

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[†]Electronic Supplementary Information (ESI) available: Experimental procedures, optimization of reaction conditions, HPLC and spectral data for all new compounds. See DOI:10.1039/x0xx00000x

The Hajos-Parrish-Eder-Sauer-Wiechert reaction, the first example of asymmetric enamine catalysis, was reported 50 years ago.¹³ However this powerful reaction was relatively unexplored until List and coworkers¹⁴ discovered proline-catalyzed enantioselective intermolecular aldol reaction. Explosive progress ensued during which various organocatalysts were developed to realize the asymmetric aldol reaction.¹⁵ Many types of carbonyl substrates have been successfully utilized in aldol reactions, including various aromatic aldehydes, aliphatic aldehydes and activated ketones that include 2-ketoesters. However, 2, 3-diketoesters, which are unique and highly activated ketones, have not been investigated. Herein, we present the two-step asymmetric synthesis of 1*H*-pyrrol-3(2*H*)-ones that takes unique advantage of the 2, 3-diketoester framework to couple an *L*-proline catalyzed aldol reaction with the benzilic acid rearrangement.

Vicinal tricarbonyl compounds easily absorb water to form their corresponding hydrates that can be dehydrated by heating under vacuum. However, the VTC hydrates were used directly in this study due to their convenience in handling. Based on our initial hypothesis, benzyl 2, 2-dihydroxy-3-oxobutanoate hydrate **1a** and cyclohexanone **2a** were selected for the aldol reaction. Of all the organocatalysts we examined, ¹⁶*L*-proline was found to be optimal for diastereoselectivity and enantiocontrol.¹⁷ The aldol product was formed in 74:26 d.r., and the major diastereoisomer **3a** was conveniently isolated by simple chromatography in 68% yield with 99% *ee*. All attempts to increase diastereoselectivity with alternative catalysts, lowering reaction temperatures, use of **1a** in its anhydrous form, and changing solvents were unsuccessful.¹⁶ However, the good yield of the major diastereomer, its ease of isolation, and its excellent enantiomeric excess made this transformation very promising.

With the optimal reaction conditions in hand, we set out to explore the substrate generality of the *L*-proline catalyzed aldol reactions. Using hydrated 2, 3-diketoesters, the effect of different groups on the ester was investigated first (Table 1, entries 1–3). The size of the group did not significantly affect yield or stereoselectivity of products. The major diastereomers were isolated in moderate yields with 99% *ee*, and the minor diastereomers were also obtained with high *ee*'s. Then 2, 3-diketoesters with different groups on the keto side were investigated: replacing the methyl group with ethyl or benzyl gave similar results (Table 1, entries 4–5). However, changing the methyl group bound to the keto group to aryl resulted in a significant increase in the d.r. of the aldol products (Table 1, entries 6–12) up to 89:11 (Table 1, entries 7–8). The effects of different substituents on the aromatic ring were also investigated showing that electron-withdrawing groups favored this process (Table 1, entry 10). An electron-donating para-substituted methoxy group, however, strongly inhibited the aldol process (Table 1, entry 9). Dihydro-2*H*-thiopyran-4(3*H*)-one (**2b**) worked well in this process as an alternative to cyclohexanone from which the major diastereoisomer **3m** was obtained in 56% isolated yield with 99% *ee* (Table 1, entry 13).

The high efficiency and broad generality of the aldol reaction that gave, without exception, the major diastereomers with 99% *ee*'s was evident throughout investigations of substrate scope. A limitation that did appear was that ketone ring sizes other than six, especially cyclopentanone and cycloheptanone, gave intractable mixtures of products.

The high enantiocontrol in these aldol condensation reactions prompted us to investigate the subsequent benzilic acid rearrangement reaction. Initially, we attempted to combine the aldol reaction and the benzilic acid rearrangement reaction in one pot. As shown in Table 2, without adding any additives, **6a** was obtained in only 32% yield and 30% *ee* (Table 2, entry 1). Various additives were examined from which we discovered that by using 20 mol% trifluoroacetic acid the yield of **6a** increased significantly. However, **6a** was always obtained in only moderate enantiomeric excess no matter what solvent was used (Table 2, entries 2–6) reflecting the uniform conversions of each aldol product diastereomer (**3a** and **4a**) to 1*H*-pyrrol-3(2*H*)-one **6a** in inverse enantiomeric excesses. This result indicated that a two-step procedure to synthesize 1*H*-pyrrol-3(2*H*)-ones in which the major diastereomer from the aldol condensation is used for the benzilic acid rearrangement would be successful.

With chromatographic isolation of the major diastereomers from the asymmetric aldol reactions, we examined the benzilic acid rearrangement of these compounds with aniline. By using trifluoroacetic acid as an additive and DCM as the solvent at 65 °C for 24h, the rearrangement product **6a** was isolated in 87% yield with 99% *ee* (Table 3, 6a). Anilines with halogen atoms (F, Cl, Br, I) all gave the 1*H*-pyrrol-3(2*H*)-ones in high yield with 99% *ee* (Table 3, 6b–6e). Anilines with both electron-donating groups (Me, OMe) and electron-withdrawing groups (CN, NO₂) gave the corresponding products in good yields without loss of enantioselectivity (Table 3, 6f–6i). Hexadecylamine, which was chosen as a representative aliphatic amine, gave **6j** in 46% yield with 99% *ee* (Table 3, 6j). The presence of a sulfur atom on the cyclic aliphatic ring (**3m**), gave the benzilic acid rearrangement product **6k** in 91% yield with 99% *ee* (Table 3, 6k). Different groups on the ester all gave the corresponding 1*H*-pyrrol-3(2*H*)-one products in good yields with 99% *ee* (Table 3, 6l–6m). By changing the substituent from methyl to ethyl on the keto side, a significant decrease of the product yield was observed (Table 3, 6n) and was further limited with other alkyl substituents. However, by replacing the methyl group with phenyl, **6o** was obtained in 73% yield with 99% *ee* (Table 3, 6o). Lastly, the effects from various aryl groups were studied from which the benzilic acid rearrangement products were obtained in moderate to good yields with 99% *ee* (Table 3, 6p–6t).

The synthetic utility of the present methodology involving the *L*-proline catalyzed aldol reaction was examined on a 10 mmol scale.¹⁶ Under the optimized reaction conditions, the aldol products were formed in 74:26 d.r. The major diastereomer was isolated in 61% yield (1.86 g) with 99% *ee*. The minor diastereomer was obtained in 21% yield (0.63 g) with 98% *ee*. These separated aldol products were then used to perform the benzylic acid rearrangement. Products **6d** and **7d** were obtained in 82% yield (2.19 g) and 84% yield (0.77 g) respectively, both with excellent enantiomeric excess.

The relative and absolute configurations of **3g** and **6c** were assigned (*R*, *S*)-**3g** and *R*-**6c** based on their single-crystal X-ray diffraction analysis (Figure 2).¹⁸

Reduction of **6d** with 4.0 equiv NaBH₄ gave **8d** as the sole diastereomer in 81% yield with 99% *ee*. The configuration of **8d** was determined by NOESY experiments. In addition, **6d** is conveniently oxidized to **9d** in 65% yield with 98% *ee*, and this process provides convenient access to nearly optically pure indolin-3-ones (Scheme 3).

In summary, we have developed a two-step method for the highly enantioselective synthesis of 1*H*-pyrrol-3(2*H*)-ones. 2, 3-Diketoesters have been employed for the first time in asymmetric aldol reactions. By combining the *L*-proline catalyzed aldol reaction with the benzylic acid rearrangement, 1*H*-pyrrol-3(2*H*)-ones are obtained in moderate yields but with notably excellent enantiomeric excess (99% *ee* for all (*R*, *S*)-products). Efforts are underway to examine additional applications of 2, 3-diketoesters in highly enantioselective catalytic reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Qiang Sha acknowledges China Scholarship Council (CSC) for his financial support. We acknowledge U.S. National Science Foundation (CHE-1212446), The Welch Foundation, and the University of Texas at San Antonio for supporting this research. The HRMS used in this research was supported by a grant from the National Institutes of Health (G12MD007591).

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18. The crystal data for compound **3g** and **6c** has been deposited with the Cambridge Crystallographic Data Centre (no. CCDC1417169 for **3g** and CCDC1417170for **6c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/data_request/cif.

Fig 1.
Selected natural products containing the 1*H*-pyrrol-3(2*H*)-one unit or its analogue with a tetra substituted carbon stereocenter.

Fig 2.
X-ray structures of **3g** and **6c**.

Scheme 1.

A designed strategy for the asymmetric synthesis of 1*H*-pyrrol-3(2*H*)-ones.

Scheme 2.

L-proline catalyzed aldol reaction of benzyl 2, 2-dihydroxy-3-oxobutanoate (**1a**) with cyclohexanone (**2a**).

Scheme 3.
Reduction and oxidation of 1*H*-pyrrol-3(2*H*)-one **6d**.

Table 1

Substrate scope of *L*-proline catalyzed aldol reactions of 2, 3-diketesters with cycloketones.^a

Entry	R ¹	R ²	X	Time	Ratio 3/4 ^b	Yield ^c (e ^d) of 3	Yield ^c (e ^d) of 4
1	Me	Bn	CH ₂	24 h	74/26	3a/68% (99%)	4a/24% (97%)
2	Me	Me	CH ₂	32 h	79/21	3b/60% (99%)	4b/16% (97%)
3	Me	Cy	CH ₂	48 h	77/23	3c/67% (99%)	4c/20% (98%)
4	Et	Me	CH ₂	32 h	77/23	3d/65% (99%)	4d/19% (97%)
5	Bn	Bn	CH ₂	48 h	73/27	3e/59% (99%)	4e/21% (98%)
6	C ₆ H ₅	Et	CH ₂	32 h	81/19	3f/51% (99%)	4f/12% (98%)
7	<i>p</i> -ClC ₆ H ₄	Et	CH ₂	48 h	89/11	3g/58% (99%)	4g/7% (94%)
8	<i>p</i> -BrC ₆ H ₄	Et	CH ₂	48 h	89/11	3h/56% (99%)	4h/6% (95%)
9	<i>p</i> -OMeC ₆ H ₄	Et	CH ₂	96 h	85/15	3i/25% (99%)	4i/4% (98%)
10	<i>p</i> -CNC ₆ H ₄	Et	CH ₂	42 h	84/16	3j/70% (99%)	4j/13% (96%)
11	2-naphthyl	Et	CH ₂	54 h	79/21	3k/45% (99%)	4k/12% (97%)
12	2-thienyl	Et	CH ₂	48 h	88/12	3l/67% (99%)	4l/9% (92%)
13	Me	Bn	S	48 h	76/24	3m/56% (99%)	4m/17% (89%)

^aReaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), *L*-proline (20 mol%), DCM (5.0 mL), rt, 24–96 h.

^bDetermined by ¹H NMR spectroscopy or HPLC analysis of the reaction mixture.

^cYield of the isolated product after column chromatography.

^dThe ee value was determined by HPLC using a chiral stationary phase.

Table 2Investigation of a one-pot enantioselective synthesis of 1*H*-pyrrol-3(2*H*)-one derivatives.^a

Entry	Additive	Solvent	Yield ^b	Ee ^c
1	---	MeCN	32%	30%
2	CF ₃ COOH	MeCN	82%	31%
3	CF ₃ COOH	DCM	67%	47%
4	CF ₃ COOH	CHCl ₃	64%	41%
5	CF ₃ COOH	DCE	72%	44%
6	CF ₃ COOH	Toluene	55%	41%

^aReaction conditions: 1) **1a** (0.10 mmol), **2a** (0.20 mmol), *L*-proline (20 mol%), solvent (0.50 mL), rt, 24 h; 2) **5a** (0.11 mmol), CF₃COOH (20 mol%), 65 °C, 24 h.

^bYield of the isolated product after column chromatography.

^cThe ee value was determined by HPLC using a chiral stationary phase.

Table 3

Benzylic acid rearrangement reactions leading to 1*H*-pyrrol-3(2*H*)-ones.^a

^aReaction conditions: **3** (0.10 mmol), **5** (0.11 mmol), DCM (0.50 mL), CF₃COOH (20 mol%), 65 °C, 24 h; Yields refer to isolated yields after column chromatography; The *ee* value was determined by HPLC using a chiral stationary phase.