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Organocatalyzed enantioselective aldol reaction of 1*H*-pyrrole-2,3-diones

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Abstract

The enantioselective cross aldol reaction of 1-benzyl 4,5-dioxo-2-aryl-4,5-dihydro-1*H*-pyrrole-3-carboxylates and ketones was studied with proline derivatives or cinchona alkaloid-derived primary amines as the catalysts for the first time. *trans*-4-Benzoyloxy-L-proline (**15**) was found to be the best catalyst for acyclic ketones. For cyclohexanone, the best results were achieved with 9-deoxy-9-*epi*-aminoquinine (**18**) as the catalyst in the presence of racemic 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (**19**) as the cocatalyst. Using these protocols, 3-alkyl-3-hydroxy-1*H*-pyrrol-2(3*H*)-one derivatives were obtained in excellent yields and good to high ee values (up to 94% ee).

Keywords

Aldol reaction; 1*H*-Pyrrole-2,3-dione; 3-Hydroxy-1*H*-pyrrol-2(3*H*)-one; Organocatalysis; Enantioselective; Proline; Cinchona alkaloid

Substituted pyrrole derivatives are very important heterocycles. Many biological active compounds, potent pharmaceuticals, and natural products contain the pyrrole structural motif.¹ Among the pyrrole derivatives, 3-hydroxy-1*H*-pyrrol-2(5*H*)-one (a tautomer of pyrrolidine-2,3-dione) shows many interesting biological activities, such as, enzyme-inhibiting, antiviral, and antibacterial activities.² For example, ethyl 1-benzyl-3-hydroxy-2(5*H*)-oxopyrrole-4-carboxylate (**EBPC**, Figure 1) is a highly specific aldose reductase inhibitor.^{2c} Since increased activity of aldose reductase is associated with increased resistance to chemotherapeutic drugs, recent studies have demonstrated that **EBPC** enhances the cytotoxic effects of the anticancer agents doxorubicin and cisplatin in HeLa cervical carcinoma cells.^{2d} In contrast, the double bond regioisomer of 3-hydroxy-1*H*-pyrrol-2(5*H*)-one, 3-hydroxy-1*H*-pyrrol-2(3*H*)-one, such as compound **1** (Figure 1), has been rarely studied. To our knowledge, only Maghsoodlou and coworkers have reported a synthesis of these derivatives using isocyanides and methyl 2-acetylacetoacetate.³ The biological relevance of these interesting pyrrole derivatives is still unknown.

Our group is interested in developing novel organocatalytic enantioselective aldol reactions⁴ for the synthesis of biologically active molecules.⁵ Previously, we and others have

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Supplementary data

Supplementary data (detailed experimental procedures, copy of NMR spectra and HPLC chromatograms for compounds **4a-l**) associated with this article can be found, in the online version at doi:.

demonstrated that activated carbonyl compounds are very good substrates for organocatalyzed aldol reactions.^{5,6} During our recent study of organocatalyzed aldol reaction of isatin derivatives,^{5f} we became interested in using 1*H*-pyrrole-2,3-dione derivatives as the substrates in an organocatalyzed aldol reaction, since the latter may also be regarded as an activated ketone compound. Herein we wish to report the first asymmetric synthesis of enantioenriched 3-alkyl-3-hydroxy-1*H*-pyrrol-2(3*H*)-one derivatives using chiral amine-catalyzed asymmetric aldol reactions.

Using ethyl 1-benzyl-4,5-dioxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (**2a**)⁷ and acetone (**3a**) as the model substrates, we first screened some readily available primary and second amino acid-derived catalysts (Figure 2) for their ability to effect the desired aldol reaction and to control the product stereochemistry. The results are summarized in Table 1. When L-alanine (**5**) was used as the catalyst in DMSO at rt, the desired aldol product **4a** was obtained in 77% yield after 16 h; however, no enantioselectivity was observed in this reaction (entry 1). Under similar conditions, 98% of **4a** was obtained in 48% ee when L-proline (**6**) was used as the catalyst (entry 2). A higher ee value of 60% was obtained when *trans*-4-hydroxy-L-proline (**7**) was applied as the catalyst under these conditions (entry 3). In contrast, *cis*-4-hydroxy-D-proline (**8**) led to a lower ee value of 50% for the opposite enantiomer of product **4a** (entry 4). Since *trans*-4-hydroxy-L-proline (**7**) is a more effective catalyst in terms of stereocontrol, further optimization of its structure was carried out (Figure 2). Protecting the hydroxyl group in **7** with more bulky silyl groups led to enhanced stereoselectivities in this cross aldol reaction. For example, TMS-protected **9** and TBDMS-protected **10** gave **4a** in 70% and 82% ee, respectively (entries 5 and 6). Similarly, protecting the hydroxyl group in **7** with alkanoyl groups also led to more selective catalysts. For example, acetylated catalyst **11** gave an ee value of 80% for the product **4a** (entry 7). The ee value further was increased to 87% when the alkyl chain of the alkanoyl group was extended to an *n*-pentyl group (**12**, entry 8). Nonetheless, no further gain in enantioselectivity could be achieved by changing the alkyl part of the alkanoyl group to more sterically demanding ones (i.e., **13** and **14**) or to different aryl groups (i.e., **15**, **16**, and **17**) (entries 9-13). In general, these acetylated catalysts are also more reactive, since a much shorter reaction time is required to achieve a quantitative yield of the product. Thus, this screen identified that catalysts **12**, **13**, **14**, **15**, **16**, and **17** are equally efficient for the cross aldol reaction of **2a** and **3a** in terms of both the reactivity and the stereoselectivity. Since among these six catalysts, catalyst **15** is more readily available,⁸ further optimizations were conducted with catalyst **15** only. The results of these optimizations are collected in Table 2. Among those common organic solvents, DMSO (entry 1) proves to be the best one for this reaction, since much lower ee values and/or yields of **4a** were obtained in the remaining solvents (entries 2-7). On the other hand, reducing the loading of acetone (**3a**) led to slower reactions, or even lower enantioselectivities for the product (entries 8-11). Conversely, further increase of its loading from 10 to 20 equiv. (entry 12) did not provide any additional benefits, either. Increasing the catalyst loading to 15 mol % (entry 13) shortened the reaction time from 4 h to 2 h. As expected, reducing the catalyst loading led to longer reaction times (entries 14-16), but the reaction still worked well with a loading of only 2.5 mol % of catalyst **15** (entry 16).

It has been reported that water may play some beneficial role in organocatalyzed aldol reactions.⁹ Thus, water was intentionally added to the above reaction. As the results in Table 2 show, water indeed influences both the reactivity and the stereoselectivity of this cross aldol reaction. Generally, the reactions became much slower when water was added and lower yields of **4a** were obtained (entries 17-22). This may be explained by the fact that water can react with **2a** to form a hydrate. Such hydration reduces the concentration of free **2a** and leads to a slower cross aldol reaction. On the other hand, the ee values obtained for

4a increased when water was added (entries 17-22).⁹ The highest ee value of 94% was obtained with the addition of 5 equiv. of water to the reaction mixture (entry 21). To our pleasure, the loss in reactivity may be remedied by prolonging the reaction time: After 48 h of reaction, again a high yield of 98% of **4a** may be obtained (entry 23).

Once the optimized reaction conditions were identified, the substrate scope of this reaction was then evaluated. The results are collected in Table 3. Besides the 2-phenyl-substituted 1-benzyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate (**2a**, entry 1), other aryl substituted **2** (**2b-f**) also participate in the aldol reaction with acetone (**3a**) to give the desired cross aldol products (**4b-4f**) in high yields and excellent ee values (entries 2-7). The electronic nature of the substituent on the phenyl ring is insignificant for the reactivity and the stereoselectivity of this reaction. Similarly, a methyl ester **2g** (entry 8) gave almost the same results as those of the ethyl ester **2a** (entry 1). On the other hand, when 2-butanone (**3b**) was employed, only the product of the kinetic enolate (**4h**) was detected (entry 9). The slower reaction rate and the lack of the other regioisomer in this case are most likely due to the sensitivity of this reaction towards the steric hindrance of the corresponding enamines. Acetaldehyde (**3c**) may also be applied in this reaction, and the desired aldol product **4j** was obtained in 73% yield and 60% ee (entry 10). However, when cyclohexanone (**3d**) and cyclopentanone were used, there was no conversion of the starting materials (data not shown). These negative results may again be due to the steric hindrance between **2a** and the enamines derived from these ketones. Since previously it was shown enamines derived from primary amine catalysts are less sterically demanding,¹⁰ some cinchona alkaloid-derived primary amine catalysts were screened for the reaction between **2a** and cyclohexanone (**3d**).¹¹ Indeed, the desired cross aldol product was obtained with these catalysts.¹¹ After extensive optimization,¹¹ it was found that the best results were achieved with quinine-derived amine **18** (Figure 2) in the presence of racemic 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (**19**, Figure 2) as a cocatalyst,¹² and the corresponding aldol product **4k** was obtained in 94% yield with a diastereoselectivity of 82:18 and an ee value of 79% for the major diastereomer (entry 11). Similar results were obtained for the methyl ester **2g**, where the product **4l** was obtained in a dr of 75:25 with 78% ee for the major diastereomer (entry 12).

In conclusion, we have developed the first enantioselective synthesis of 3-alkyl-3-hydroxy-1*H*-pyrrol-2(3*H*)-one derivatives (up to 94% ee) using a cross aldol reaction between 1-benzyl 4,5-dioxo-2-aryl-4,5-dihydro-1*H*-pyrrole-3-carboxylates and ketones. For acyclic ketones, *trans*-4-benzoyloxy-L-proline (**15**) and its analogues were found to be the best catalysts. The reaction was also found to be very sensitive towards steric hindrance and, therefore, for cyclohexanone, the best results were achieved with 9-deoxy-9-*epi*-aminoquinine (**18**) as the catalyst in the presence racemic 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (**19**) as the cocatalyst.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. For details, please see Table S-1 in the Supplementary Data.
12. When (*R*)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate [(*R*)-**19**] was used as the cocatalyst, no difference in reactivity and enantioselectivity was observed as compared with that conducted with racemic **19**.

Figure 1.
Structure of **EBPC** and compound **1**

Figure 2.
Structure of the catalysts and cocatalyst screened in the cross aldol reaction of **2a**

Table 1

Catalyst screening

Entry	Catalyst	Time (h)	Yield (%) ^b	ee (%) ^c
1	5	16	77	0
2	6	16	98	48
3	7	16	98	60
4	8	16	98	50 ^d
5	9	16	98	70
6	10	4	98	82
7	11	4	98	80
8	12	4	98	87
9	13	4	98	87
10	14	4	98	87
11	15	4	98	87
12	16	4	98	87
13	17	4	98	87

^aUnless otherwise indicated, all reactions were carried out with ethyl 1-benzyl-4,5-dioxo-2-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate (**2a**, 0.10 mmol), acetone (**3a**, 1.0 mmol), and catalysts (**5-17**, 0.010 mmol, 10 mol %) in DMSO (0.5 mL) at rt.

^bYield of isolated product after column chromatography.

^cDetermined by HPLC analysis on a ChiralPak OD-H column.

^dThe opposite enantiomer was obtained as the major product in this case.

Table 2

Reaction condition optimizations^a

		+
Entry	Solvent	2a (equiv.)	3a (equiv.)	H ₂ O (equiv.)	Time (h)	Yield (%) ^b	ee (%) ^c				
1	DMSO	10.0			4	98	87				
2	THF	10.0			16	91	73				
3	DMF	10.0			16	95	67				
4	EtOAc	10.0			40	35	78				
5	acetone				16	65	75				
6	CH ₂ Cl ₂	10.0			40	24	49				
7	DME	10.0			16	52	68				
8	DMSO	7.5			6	98	87				
9	DMSO	5.0			7	77	84				
10	DMSO	2.0			7	73	84				
11	DMSO	1.2			24	77	84				
12	DMSO	20.0			4	98	87				
13 ^d	DMSO	10.0			2	98	87				
14 ^e	DMSO	10.0			6	98	86				
15 ^f	DMSO	10.0			8	98	86				
16 ^g	DMSO	10.0			24	95	86				
17	DMSO	10.0		1.0	16	80	90				
18	DMSO	10.0		2.0	16	80	90				
19	DMSO	10.0		3.0	16	80	90				
20	DMSO	10.0		4.0	16	80	93				
21	DMSO	10.0		5.0	16	80	94				
22	DMSO	10.0		10.0	16	80	94

Entry	Solvent	3a (equiv.)	H ₂ O (equiv.)	Time (h)	Yield (%) ^b	ee (%) ^c
23	DMSO	10.0	5.0	48	98	94

^aUnless otherwise indicated, all reactions were carried out with ethyl 1-benzyl-4,5-dihydro-1H-pyrrole-3-carboxylate (**2a**, 0.10 mmol), acetone (**3a**, 1.0 mmol), and catalysts **15** (0.010 mmol, 10 mol %) in the specified solvent (0.5 mL) at rt.

^bYield of isolated product after column chromatography.

^cDetermined by HPLC analysis on a ChiralPak OD-H column.

^dThe catalyst loading was 15 mol %.

^eThe catalyst loading was 7.5 mol %.

^fThe catalyst loading was 5.0 mol %.

^gThe catalyst loading was 2.5 mol %.

Table 3

Substrate scope study of the cross aldol reaction^a

Entry	Ar	R ¹	R ²	R ³	Time (h)	Product	Yield (%) ^b	ee (%) ^c
1	Ph	Et	Me	H	48	4a	98	94
2	4-MeC ₆ H ₄	Et	Me	H	48	4b	95	93
3	4-MeOC ₆ H ₄	Et	Me	H	72	4c	83	94 ^d
4	4-BrC ₆ H ₄	Et	Me	H	48	4d	97	92
6	4-NO ₂ C ₆ H ₄	Et	Me	H	72	4e	95	91
7	2-Naphthyl	Et	Me	H	48	4f	90	93
8	Ph	Me	Me	H	48	4g	97	93
9	Ph	Et	Et	H	192	4h	60	80 ^d
10	Ph	Et	H	H	120	4j	73	60 ^e
11 ^f	Ph	Et	-(CH ₂) ₄	-(CH ₂) ₄	96	4k	94 ^g	79 ^d
12 ^f	Ph	Me	-(CH ₂) ₄	-(CH ₂) ₄	96	4l	90 ^h	78 ^d

^aUnless otherwise indicated, all reactions were carried out with (2, 0.10 mmol), the carbonyl compound (3a-3c, 1.0 mmol), water (0.50 mmol, 5.0 equiv.), and catalyst 15 (0.010 mmol, 10 mol %) in DMSO (0.5 mL) at rt.

^bYield of isolated product after column chromatography.

^cUnless otherwise indicated, ee values were determined by HPLC analysis on a ChiralCel OD-H column.

^dDetermined by HPLC analysis on a ChiralPak AD-H column.

^eDetermined by HPLC analysis of the corresponding alcohol on a ChiralPak AD-H column by reducing the initial product 4j with acetic acid/ NaCNBH₃.

^fCarried out with 2a or 2g (0.10 mmol), 3d (0.3 mL), catalyst 18 (0.02 mmol, 20 mol %), cocatalyst 19 under neat conditions at rt.

^gThe dr was 82:18, as determined by the ¹H NMR of the crude product.

^hThe dr was 75:25, as determined by the ¹H NMR of the crude product.