ORGANIC LETTERS

2011
Vol. 13, No. 19
5248–5251

Organocatalytic Asymmetric Aldol Reaction of Hydroxyacetone with β,γ-Unsaturated α-Keto Esters: Facile Access to Chiral Tertiary Alcohols

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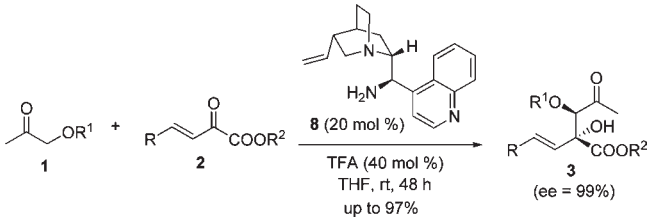
Received August 5, 2011

ABSTRACT



An efficient direct asymmetric aldol reaction between hydroxyacetone and β,γ-unsaturated α-keto esters has been successfully developed. In the presence of 9-amino-9-deoxy-*epi*-cinchonine and trifluoroacetic acid, the direct aldol reaction of *O*-protected hydroxyacetone proceeded in a highly enantioselective manner, affording the desired adducts containing a chiral tertiary alcohol in high yields and with excellent enantioselectivities. The aldol products obtained are valuable precursors for the synthesis of 2-substituted glycerol derivatives.

Creating quaternary stereogenic centers is a challenging task in organic synthesis and has drawn enormous attention in the past few decades.[1] In our continuous efforts in developing efficient asymmetric organocatalytic methods for the synthesis of chiral quaternary carbons, we had recently become interested in the efficient preparation of organic molecules containing a tertiary alcohol group.[2] Tertiary alcohols play very important roles in the pharmaceutical industry and biological sciences.[3] In this context, glycerol derivatives containing a quaternary center are key motifs in many pharmaceutical agents, as well as versatile intermediates useful in organic synthesis.[4] Despite their importance, asymmetric methods for the synthesis of glycerol derivatives bearing a quaternary center are very limited.[5] Harada and Oku described a synthesis in which

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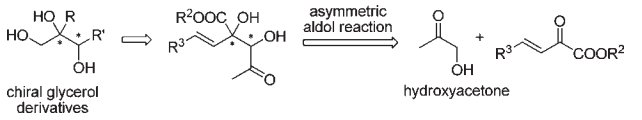
10.1021/ol2021274 © 2011 American Chemical Society
Published on Web 09/08/2011

menthone was utilized as a chiral auxiliary.[6] Recently, Kang et al. employed chiral copper complexes to achieve an enantioselective desymmetrization of *meso*-2-substituted glycerols and prepared highly enantioselective 2-substituted 1,2,3-propanetriols.[7] Very recently, our group disclosed a highly diastereoselective and enantioselective vinylogous aldol reaction of furanones with α-ketoesters, which could provide easy access to chiral glycerol derivatives containing a tertiary alcohol group.[2c] Given the importance of chiral glycerol derivatives and the limited methods for their preparation, efficient synthesis of these molecules is still highly sought.

In designing an asymmetric process to access chiral 2-substituted glycerols, we turned our attention to the direct aldol reaction between hydroxyacetone and β,γ-unsaturated α-keto esters. α-Keto esters are valuable electrophiles in organic synthesis, and they have been extensively investigated in a range of asymmetric organic transformations in recent years.[8] Yet, the utilization of β,γ-unsaturated α-keto esters in the direct asymmetric organocatalytic aldol reaction is rare. Zhao and co-workers successfully employed cyclic ketones in an organocatalytic aldol reaction with β,γ-unsaturated α-ketoesters.[9] Subsequently, Chan and Kwong developed an asymmetric aldol reaction between ketones and β,γ-unsaturated α-ketoesters; it is noteworthy that both cyclic and acyclic ketones bearing long carbon side chains were suitable substrates in their studies.[10] Hydroxyacetone is a useful donor, and its applications in the aldol reaction have been well studied.[11] For the construction of chiral glycerol derivatives, we envisioned that a direct aldol reaction between hydroxyacetone and β,γ-unsaturated α-keto esters may be utilized (Scheme 1). Given the availability of asymmetric organocatalytic synthetic methods, chiral glycerol skeletons can be readily created via the projected direct aldol reaction. Moreover, the aldol products possess rich functionalities, e.g. alkene, ester, and ketone, which would allow their ready conversion to various glycerol derivatives containing a tertiary alcohol group. Herein, we document a highly enantioselective aldol reaction between hydroxyacetone and β,γ-unsaturated α-keto esters, which provides an easy access to chiral glycerol derivatives containing a quaternary stereogenic center.

Scheme 1. Construction of Glycerol Derivatives through Direct Aldol Reaction



The past few years have seen remarkable progress in the primary amine-based enamine catalysis.[12] In this context, our group has a keen interest in developing asymmetric catalytic processes that can be promoted by primary amine-based organic catalysts.[13] Therefore, we chose the direct aldol reaction between 1-(benzyloxy)propan-2-one **1a**[14] and methyl 2-oxo-4-phenylbut-3-enoate **2a** as a model reaction to examine the catalytic effects of various primary amine catalysts (Table 1). L-Serine-derived **4**, L-threonine-based **5**, diamine **6**, and cinchonidine-derived diamine **7** were found to be ineffective (entries 1−4). Cinchona alkaloid-derived primary amines were next investigated. 9-Amino-9-deoxy-*epi*-cinchonine **8**, in combination with trifluoroacetic acid (TFA), afforded the products in excellent yields and with high enantioselectivity, although with only a 2:1 diastereomeric ratio (entry 5). However, primary amines derived from quinidine **9**, cinchonidine **10**, or quinine **11** were less effective (entries 8−10). Therefore, cinchonine-derived **8** was chosen as the catalyst for further studies.

To further improve the stereoselectivity, we next focused on varying the ester moieties of β,γ-unsaturated α-keto esters and installing different protective groups on hydroxyacetone (Table 2). Among the different enone esters **2**, the ethyl ester offered improved diastereoselectivity and enantioselectivity, with a slighly decreased chemical yield, compared to the reaction employing

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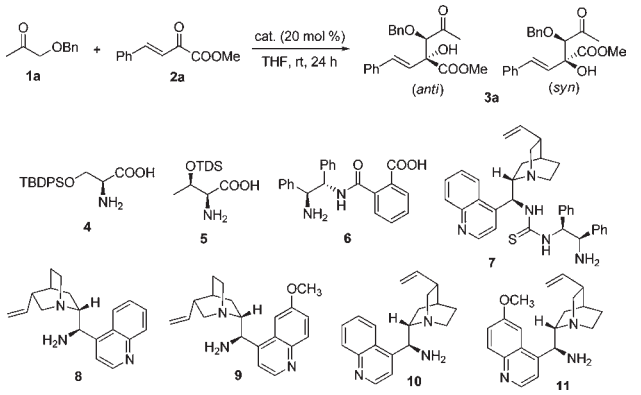
(14) When the free hydroxyacetone was used as a donor in the aldol reaction with **2a** in the presence of **8**/TFA, only < 30% conversion was observed after 48 h.

Table 1. Screening of Organocatalysts for the Aldol Reaction of 1-(Benzyloxy)propan-2-one **1a** with Methyl 2-Oxo-4-phenylbut-3-enoate **2a**[a]



entry	cat.	additive	yield (%)[b]	dr[c]	ee (%)[d]
1	**4**	none	72	1:1	−5/−9
2	**5**	none	71	1:1	33/17
3	**6**	none	77	1:1	20/31
4	**7**	TFA	79	1.5:1	−24/−30
5	**8**	TFA	97	2:1	87/64
6	**9**	TFA	98	2.5:1	66/68
7	**10**	TFA	96	2:1	−57/ −52
8	**11**	TFA	96	2:1	−17/-50

[a] Reaction conditions: 1-(benzyloxy)propan-2-one **1a** (0.1 mmol), methyl 2-oxo-4-phenylbut-3-enoate **2a** (0.12 mmol), the catalyst (0.02 mmol), TFA (0.04 mmol), THF (0.2 mL), room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The ee values of *anti*- and *syn*-isomers, respectively, determined by HPLC analysis on a chiral stationary phase.

methyl ester (entry 2 vs 1). The aldol reaction became very slow when *tert*-butyl ester was employed, likely due to the steric hindrance induced by the bulky *tert*-butyl group (entry 3). We recently showed that the primary amine/CSA ion pair is a powerful catalytic system for the asymmetric enamine catalysis.[15] However, inclusion of CSA in our catalytic system did not prove to be beneficial (entry 4). For the hydroxyacetone donors bearing different protective groups, 1-(naphthalen-2-ylmethoxy)propan-2-one **1b** was found to be the best, affording the desired aldol products in 81% yield, with a 4:1 dr and 91% ee for the major diastereomer (entry 5). A few other protective groups on hydroxyacetone were shown to be ineffective (entries 7−9). A solvent screening revealed that THF was the best solvent, and it is interesting to note that the diastereoselectivity was reversed when $CHCl_3$ was utilized as a solvent (entry 10).

To establish the reaction scope, a number of β,γ-unsaturated α-keto esters were employed as acceptors, and the results are summarized in Table 3. Reactions were applicable to various γ-aryl-substituted β,γ-unsaturated α-keto esters, and aldol products were obtained with very high enantioselectivities and moderate diastereoselectivities (entries 1−9). Acceptors containing heterocyclic rings,

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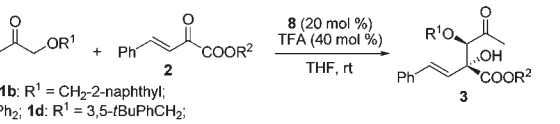
Table 2. Optimizing the Reaction Conditions[a]

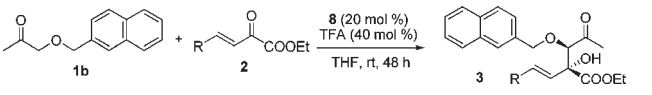


1a: R^1 = Bn; **1b**: R^1 = CH_2-2-naphthyl; **1c**: R^1 = $CHPh_2$; **1d**: R^1 = 3,5-*t*BuPhCH_2; **1e**: R^1 = TBS.

entry	1	R^2	3	*t* (d)	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	Me	**3a**	1	97	2:1	87/64
2	**1a**	Et	**3b**	1	80	3:1	91-
3	**1a**	*t*Bu	**3c**	2	57	5:1	55-
4[e]	**1a**	Et	**3b**	1	80	3:1	68/64
5	**1b**	Et	**3d**	**2**	**81**	**4:1**	**91/-**
6[f]	**1b**	Et	**3d**	2	80	2:1	92/88
7	**1c**	Et	**3e**	2	88	2:1	44/87
8	**1d**	Et	**3f**	2	—[j]	–	–
9	**1e**	Et	**3g**	2	<20	–	–
10[g]	**1b**	Et	**3d**	2	82	1:3	90/84
11[h]	**1b**	Et	**3d**	2	61	3:1	11/66
12[i]	**1b**	Et	**3d**	2	<20	3:1	32/66

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), **8** (0.02 mmol), TFA (0.04 mmol), THF (0.2 mL), room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The ee values of *anti*- and *syn*-isomers, respectively, determined by HPLC analysis on a chiral stationary phase. [e] (−)-CSA (0.04 mmol). [f] −20 °C. [g] $CHCl_3$ (0.2 mL). [h] MeOH (0.2 mL). [i] DMF (0.2 mL). [j] No reaction.

Table 3. Aldol Reaction of 1-(Naphthalen-2-ylmethoxy)propan-2-one **1b** with Various β,γ-Unsaturated α-Keto Esters[a]



entry	R	3	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	**3d**	81	4:1	91
2	4-$NO_2C_6H_4$	**3j**	86	3:1	99
3	4-ClC_6H_4	**3k**	82	7:2	99
4	4-$OMeC_6H_4$	**3l**	93	2:1	77
5	3-$OMeC_6H_4$	**3m**	81	3:1	99
6	3-BrC_6H_4	**3n**	87	3:1	95
7	3-MeC_6H_4	**3o**	81	3:1	91
8	2-FC_6H_4	**3p**	83	3:1	90
9	2-MeC_6H_4	**3q**	97	5:2	99
10	3-thiophenyl	**3r**	90	7:1	91
11	2-thiophenyl	**3s**	92	3:1	88
12	3-pyridinyl	**3t**	95	3:1	85
13	*i*Bu	—[e]	–	–	–
14	hexanyl	–	–	–	–

[a] Reaction conditions: **1b** (0.1 mmol), **2** (0.12 mmol), **8** (0.02 mmol), TFA (0.04 mmol), THF (0.2 mL), room temperature. [b] Isolated yield of both diastereomers. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The ee value of the major diastereomer was determined by HPLC analysis on a chiral stationary phase. [e] No reaction.

such as thiophene and pyridine, also worked well for the aldol reaction, affording the desired products in excellent yields, very

high enantioselectivities, and moderate diastereoselectivities (entries 10−12). Notably, the two diastereomers of the above aldol products can be easily separated by flash column chromatography. However, our current method is not applicable to the acceptors with aliphatic substituents on γ-positions, as no desired products were observed (entries 13−14). The absolute configurations of the aldol products were assigned unambiguously, based on a single crystal X-ray analysis of adduct **3n** (Figure 1).

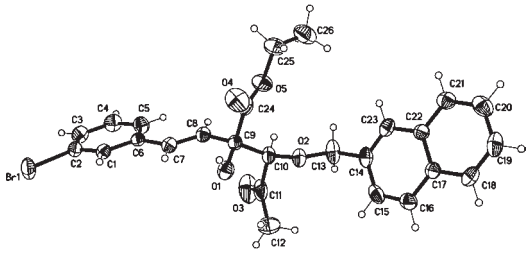
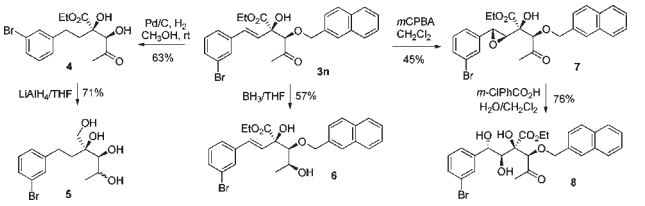


Figure 1. X-ray structure of **3n**.

The aldol products are rich in functionality, which can be readily converted to useful chiral glycerol derivatives. As illustrated in Scheme 2, the reduction of **3n** afforded chiral diol **4**, which contains a tertiary alcohol functionality. Further reduction with $LiAlH_4$ then yielded 2-substituted glycerol derivate **5**.[16] Treatment of **3n** with mCPBA yielded epoxide **7** in a diastereospecific manner, which was readily opened to generate chiral glycerol derivative **8**. Moreover, the carbonyl group in **3n** could be reduced stereoselectively to afford alcohol **6**.

(16) The products were obtained as a 1:1 diastereomeric mixture.

Scheme 2. Preparation of Various Chiral Glycerol Derivatives



In conclusion, we have developed the first highly enantioselective aldol reaction of protected hydroxyacetone with β,γ-unsaturated α-keto ester, promoted by a catalytic system comprising 9-amino-9-deoxy-*epi*-cinchonine **8** and TFA. The reported method represents a novel and practical approach to access chiral tertiary alcohol skeletons and 2-substituted glycerol derivatives. Notably, the aldol products are rich in functionalities, offering great latitude for further structural elaborations of biologically important chiral glycerol derivatives.

Acknowledgment. We thank the National University of Singapore (R-143-000-469-112) for generous financial support.

Supporting Information Available. Representative experimental procedures, HPLC chromatogram, NMR spectra of compounds, and X-ray crystallographic data of **3n**. This material is available free of charge via the Internet at http://pubs.acs.org.