

Enantioselective Nitroaldol Reaction of α -Ketoesters Catalyzed by Cinchona Alkaloids

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The nitroaldol reaction or Henry reaction constitutes an important class of C—C bond forming reactions that provide straightforward access to important synthetic intermediates from readily accessible nitroalkanes and carbonyl compounds.¹ Due to its significance in organic synthesis, considerable efforts have been devoted to the development of efficient catalytic asymmetric nitroaldol reactions.² Consequently, several chiral metal complexes and chiral phase transfer catalysts have been identified to be highly efficient catalysts for enantioselective nitroaldol reactions with aldehydes.³

In contrast to the substantial progress made with aldehydes, the development of enantioselective nitroaldol reaction with ketones has met with limited success.⁴ To date, only one catalyst system, consisting of a Cu—bisoxazoline complex and triethylamine, has been identified to afford synthetically useful enantioselectivity for the addition of nitromethane to α -ketoesters **2**.^{4a,b} However, in addition to requiring a catalyst loading of 20 mol % and the use of anhydrous conditions, both the yield and enantioselectivity of the reaction display a dependence on the structure of **2**. For example, the enantioselectivity was high for reactions with aryl α -ketoesters bearing an electron-withdrawing group on the aromatic ring, and it became moderate when the electron-withdrawing group was replaced with an electron-donating substituent. Depending on the steric bulk of the alkyl α -ketoesters, the enantioselectivity could be either high or modest. For α -ketoesters bearing an alkenyl group, synthetically useful enantioselectivity was not attainable.

On the other hand, it is especially desirable to realize a catalytic asymmetric nitroaldol reaction that affords high enantioselectivity for a wide range of α -ketoesters **2**. Such a reaction, in combination with the synthetic versatility of the ester and the nitro groups, will provide enantioselective access to a broad range of optically active tertiary carbinols (Scheme 1). In this communication, we wish to report a significant progress toward achieving this goal.

Although effective chiral organic catalysts have been reported for enantioselective aza-Henry reactions,^{5,6} no broadly effective chiral organic catalyst has been developed for the direct asymmetric Henry reaction. We recently reported C6'—OH cinchona alkaloids **1a–c** (Figure 1) as efficient catalysts for various enantioselective conjugate additions.⁷ Mechanistic studies from our laboratories indicated that catalysts **1** could serve as acid–base bifunctional catalysts via hydrogen bonding interactions with the Michael donor and acceptor through the quinuclidine nitrogen and the C6'—OH, respectively. In light of the wide range of nucleophiles and electrophiles that could engage in hydrogen bonding interactions, we envisaged that catalysts **1** might be able to effectively stabilize and organize transition states involving nucleophiles and electrophiles other than Michael donors and acceptors, thereby allowing **1** to function as efficient enantioselective catalysts for reactions that are mechanistically distinct from conjugate additions. Guided by these considerations, we began to investigate **1** as catalysts for enantioselective nitroaldol reaction with α -ketoesters **2**.

We first focused on the addition of nitromethane to alkenyl α -ketoester **2a** because high enantioselectivity had not yet been

Scheme 1. A General Approach to Optically Active Tertiary Carbinols

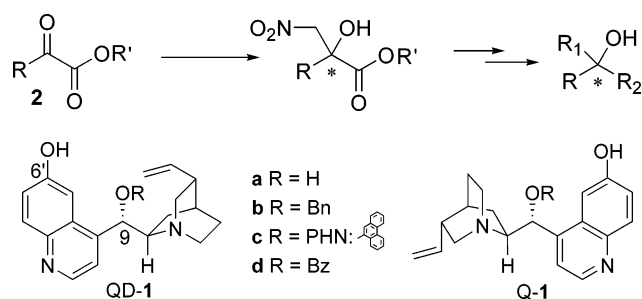


Figure 1. C6'—OH cinchona alkaloid derivatives.

Table 1. Enantioselective Nitroaldol Addition of Nitromethane to α -Ketoester **2a**^a

entry	catalyst ^b	conv. (%) ^c	3a / 3a' ^c	ee (%) ^d
1	Et ₃ N	>95	80/20	
2	QD	91	>95/5	–17
3	DHQD-PHN	74	>95/5	59
4	(DHQD) ₂ AQN	>95	>95/5	40
5	β -ICD	>95	>95/5	61
6	QD-1a	>95	>95/5	86
7	QD-1b	93	>95/5	70
8	QD-1c	93	>95/5	93
9	QD-1d	>95	>95/5	97
10	Q-1d	>95	>95/5	–97

^a Unless noted, reactions were carried out with 0.1 mmol of **2a**, 1 mmol of CH₃NO₂ in 0.1 mL of CH₂Cl₂ with 10 mol % catalyst at –20 °C for 12 h. ^b See Supporting Information for the structure of the catalysts. ^c Determined by ¹H NMR analysis. ^d Determined by HPLC analysis.

achieved for nitroaldol reactions of this important class of α -ketoesters. Furthermore, alkenyl α -ketoesters could engage in 1,2- as well as 1,4-additions with a nitroalkane, thus presenting a particularly challenging class of substrates for nitroaldol reactions. As reported previously,^{4b} nitromethane reacted with **2a** in the presence of Et₃N to give products **3a** and **3a'** in 4:1 ratio (entry 1, Table 1).

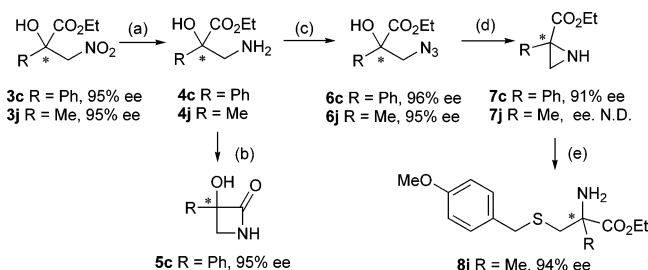
Promoted by various cinchona alkaloids, the addition of nitromethane to **2a** in methylene chloride proceeded in a highly chemoselective fashion to cleanly afford the nitroaldol product **3a** (Table 1). The enantioselectivity of the C6'—OH cinchona alkaloids **1a–c** was found to be considerably higher than that displayed by C6'—OMe cinchona alkaloids (entries 6–8 vs 2–4, Table 1). Furthermore, the significant impact of the C9 substituent (OR) on the enantioselectivity of **1** raised the possibility of finding a more effective and practical C6'—OH cinchona alkaloid for the nitroaldol reaction by modifications of this substituent. Further studies following this hypothesis led to the discovery that C6'—OH

Table 2. Enantioselective Nitroaldol Addition of Nitromethane to α -Ketoester **2** Catalyzed by QD-**1d** and Q-**1d** (in parentheses)^a

$\text{R}-\text{C}(=\text{O})-\text{C}(=\text{O})\text{OEt} \xrightarrow[\text{CH}_2\text{Cl}_2, -20^\circ\text{C}]{\text{QD-1d (Q-1d) (5 mol\%)}, \text{CH}_3\text{NO}_2 (10 \text{ equiv.})} \text{R}-\text{C}(\text{OH})(\text{NO}_2)-\text{C}(=\text{O})\text{OEt}$					
Entry	R	Time / h	yield / % ^b	ee / % ^c	
1	2a	14 (15)	92 (92)	96 (97)	
2	2b	24 (24)	98 (99)	94 (95)	
3	2c	35 (46)	96 (96)	95 ^d (93)	
4	2d	96 (96)	86 (84)	94 (97)	
5	2e	72 (72)	86 (86)	96 (96)	
6	2f	12 (12)	98 (96)	97 ^d (96)	
7	2g	9 (11)	96 (98)	94 (97)	
8	2h	11 (11)	91 (96)	95 (95)	
9	2i	60 (60)	96 (97)	94 (94)	
10	2j	12 (12)	89 (90)	95 (95)	
11	2k	17 (15)	90 (90)	93 (93)	
12	2l	14 (11)	88 (89)	95 (94)	
13	2m	15 (11)	87 (86)	94 (93)	

^a Unless noted, reactions were run with 0.5 mmol of **2**, 5 mmol of CH_3NO_2 in 0.5 mL of CH_2Cl_2 with 5 mol % QD-**1d**; the results in parentheses were obtained with Q-**1d** to give opposite enantiomer; see Supporting Information for details. ^b Isolated yield. ^c Determined by HPLC analysis. ^d The absolute configuration is determined to be *S*; see Supporting Information for details.

Scheme 2. Asymmetric Synthesis of β -Lactam, Aziridine, and α -Methylcysteine Derivatives (see Supporting Information for details)^a



^a Conditions: (a) Raney Ni, H_2 (1 atm); (b) *i*-PrMgCl, 38% yield over two steps; (c) TiN_3 , CuSO_4 (cat.), for **6c**, 84% yield over two steps; for **6j**, 63% yield over two steps; (d) PPh_3 , CH_3CN , for **7c**, 80% yield; for **7j**, 71% yield; (e) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, *p*-methoxybenzyl mercaptan, 56% yield.

cinchona alkaloid bearing a C9-OBz group (QD-**1d**) is even more effective than **1a–c**. The addition of nitromethane to **2a** with either QD-**1d** or Q-**1d** occurred in 97% ee (entries 9 and 10, Table 1). It is noteworthy that the preparation of **1d** employs significantly cheaper reagents than those required for the preparation of **1c**.⁸

With 5.0 mol % of **1d**, excellent enantioselectivity and high yield could be attained not only for alkenyl α -ketoesters **2a,b** but also for a broad range of aryl and alkyl α -ketoesters **2c–m** (Table 2).⁹ Thus, the enantioselectivity of **1d** is insensitive to either the steric or the electronic properties of **2**. The unprecedented excellent enantioselectivity obtained with α -ketoesters **2** bearing alkenyl, electron-rich aryl and sterically bulky alkyl groups is noteworthy. Among them **2a**, **2d**, and **2l** were previously reported to react with nitromethane in 57–77% ee with existing catalyst systems, and enantioselective nitroaldol reaction was not documented for **2b**, **2e**, and **2m**.^{4a,b,e}

We have applied the **1d**-catalyzed nitroaldol reaction to develop new and concise asymmetric syntheses of synthetically important chiral intermediates, such as aziridines **7** and β -lactams **5** (Scheme 2).¹⁰ As shown by the conversion of **7j** to **8j**, optically active

aziridines **7** are valuable intermediates for the synthesis of optically active α,α -disubstituted α -amino acids. It should be noted that α -methylcysteine (**8j**) was the key intermediate in the total syntheses of mirabazoles and thiagazole.¹¹ The ability of **1d** to promote highly enantioselective nitroaldol reaction for a wide range of α -ketoesters **2** should facilitate the preparations of analogues of these antitumor and anti-HIV natural products.

In conclusion, we have developed the first efficient organocatalytic enantioselective nitroaldol reaction with ketones using a new C6'-OH cinchona alkaloid **1d**. Employing a relatively low loading of an easily accessible and recyclable chiral catalyst and affording high enantioselectivity for a wide range of α -ketoesters **2**, the reaction should provide a broadly useful approach for the asymmetric synthesis of chiral compounds containing tetrasubstituted carbon stereocenters. The current study also reveals for the first time that the C6'-OH cinchona alkaloids **1** are highly efficient catalysts for enantioselective 1,2-additions to carbonyls.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) Under the same condition, the addition of nitroethane to **2c** with Q-**1d** afforded the 1,2-adducts in 4/1 dr and in 75% ee/88% ee, respectively; acetophenone was found to be inactive for the **1**-catalyzed nitroaldol reaction with nitromethane.
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