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COMMUNICATIONS

Published on Web 12/22/2005

Enantioselective Nitroaldol Reaction of α-Ketoesters Catalyzed by Cinchona Alkaloids

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Received October 24, 2005; E-mail: deng@brandeis.edu

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]

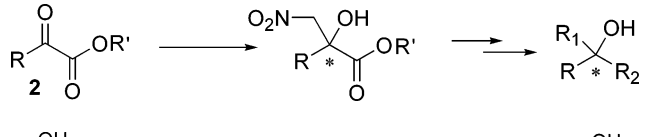
In contrast to the substantial progress made with aldehydes, the development of enantioselective nitroaldol reaction with ketones has met with limited success.[4] To date, only one catalyst system, consisting of a Cu−bisoxazoline complex and triethylamine, has been identified to afford synthetically 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 rang 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



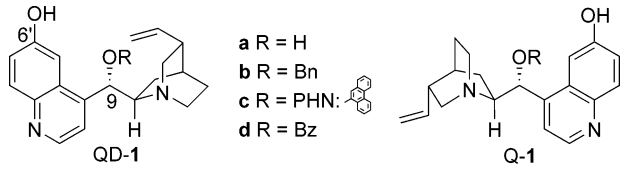
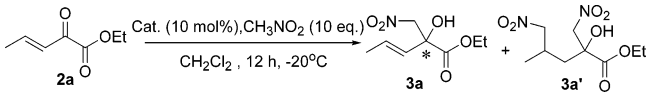


Figure 1. C6′−OH cinchona alkaloid derivatives.

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



entry	catalyst[b]	conv. (%)[c]	**3a**/**3a′**[c]	ee (%)[d]
1	Et_3N	>95	80/20	
2	QD	91	>95/5	−17
3	DHQD-PHN	74	>95/5	59
4	$(DHQD)_2AQN$	>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

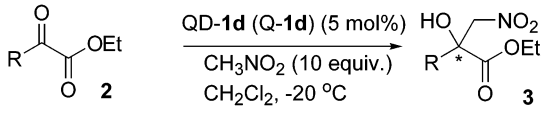
[a] Unless noted, reactions were carried out with 0.1 mmol of **2a**, 1 mmol of CH_3NO_2 in 0.1 mL of CH_2Cl_2 with 10 mol % catalyst at −20 °C for 12 h. [b] See Supporting Information for the structure of the catalysts. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis.

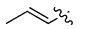
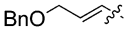
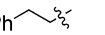
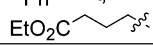
achieved for nitroaldol reactions of this important class of α-ketoesters. Furthermore, alkenyl α-ketoesters could engage in 1,2- as well as 1,4-additions with a nitroalkane, thus presenting a particularly challenging class of substrates for nitroaldol reactions. As reported previously,[4b] nitromethane reacted with **2a** in the presence of Et_3N 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

10.1021/ja057237l CCC: $33.50

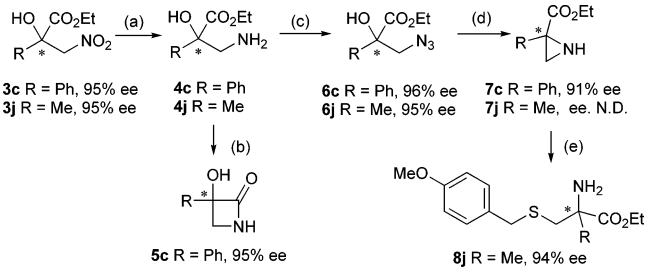
Table 2. Enantioselective Nitroaldol Addition of Nitromethane to α-Ketoester **2** Catalyzed by QD-**1d** and Q-**1d** (in parentheses)[a]



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**	Ph-	35 (46)	96 (96)	95[d] (93)
4	**2d**	4-MeO-Ph-	96 (96)	86 (84)	94 (97)
5	**2e**	4-MeS-Ph-	72 (72)	86 (86)	96 (96)
6	**2f**	4-Cl-Ph-	12 (12)	98 (96)	97[d] (96)
7	**2g**	4-CN-Ph-	9 (11)	96 (98)	94 (97)
8	**2h**	3-Cl-Ph-	11 (11)	91 (96)	95 (95)
9	**2i**	2-Naphthyl-	60 (60)	96 (97)	94 (94)
10	**2j**	Me-	12 (12)	89 (90)	95 (95)
11	**2k**	*n*-Pr-	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) TfN_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) $BF_3{\cdot}Et_2O$, *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-ketoestes **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 thiangazole.[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.

Acknowledgment. We are grateful for the generous financial support from National Institutes of Health (GM-61591).

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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(8) For preparations of Q-**1d** and QD-**1d**, see Supporting Information.

(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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JA057237L