ORGANIC LETTERS

2005
Vol. 7, No. 2
167−169

Highly Enantioselective Amination of α-Substituted α-Cyanoacetates with Chiral Catalysts Accessible from Both Quinine and Quinidine

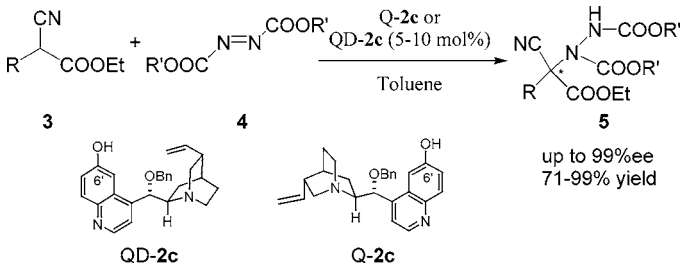
Xiaofeng Liu, Hongming Li, and Li Deng*

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110

deng@brandeis.edu

Received September 7, 2004

ABSTRACT



The catalytic construction of nitrogen-substituted quaternary stereocenters is an important and challenging task in asymmetric synthesis. In this paper, we describe the use of 6′-OH-modified cinchona alkaloids that are accessible from either quinine or quinidine for the development of a highly enantioselective amination of α,α-disubstituted carbonyl compounds that is suitable for the creation of nitrogen-substituted quaternary stereocenters in either the *R* or *S* configuration.

The catalytic enantioselective construction of nitrogen-substituted quaternary stereocenters is an important yet challenging task in asymmetric synthesis. Highly enantioselective cyanation of prochiral ketimines (Strecker reaction)[1,2] and electrophilic alkylations[3,4] and acylations[5] of α-nitrogen-substituted carbonyl compounds have been developed to provide valuable solutions to this problem. Recently, catalytic enantioselective electrophilic α-amination of carbonyl compounds, pioneered by Evans,[6a] has emerged as an important new approach for the direct creation of nitrogen-substituted stereogenic centers from readily accessible racemic or prochiral precursors.[6] These exciting advances point to highly electrophilic amination of α,α-disubstituted carbonyl compounds as a particularly attractive

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10.1021/ol048190w CCC: $30.25
Published on Web 12/22/2004

strategy to address the challenging problem of constructing nitrogen-substituted quaternary stereocenters. Jørgensen and co-workers reported highly enantioselective aminations of α-substituted β-ketoesters catalyzed by chiral Cu-bis-oxazoline complexes[7a] and, more recently, of α-substituted α-cyanoacetates by dialkyl azodicarboxylates catalyzed by a conformationally rigid cinchona alkaloid derivative (**1**).[7b] However, catalyst **1** can only be derived from quinidine. Consequently, the enantioselective amination with **1** provides a useful access to a nitrogen-substituted quaternary stereocenter in only one of the two possible absolute configurations.

We recently disclosed a new class of bifunctional organic catalysts **(**QD-**2** and Q-**2**) and provided the first demonstration of 6′-OH cinchona alkaloids **2** as highly efficient chiral catalysts for the promotion of enantioselective reactions.[8] In contrast to **1**, catalysts **2** can be readily prepared from both quinidine and quinine. Reactions catalyzed efficiently by **2** could provide access to either of the two enantiomers of a chiral product of interest. These considerations prompted us to investigate the use of **2** to catalyze an electrophilic amination of α,α-disubstituted carbonyl compounds. We wish to describe in this letter a highly enantioselective amination of α-substituted α-cyanoacetates by dialkyl azodicarboxylates with either QD-**2** or Q-**2**, which offers a catalytic method for facile enantioselective access to nitrogen-substituted quaternary stereocenters in either the *R* or *S* configuration.

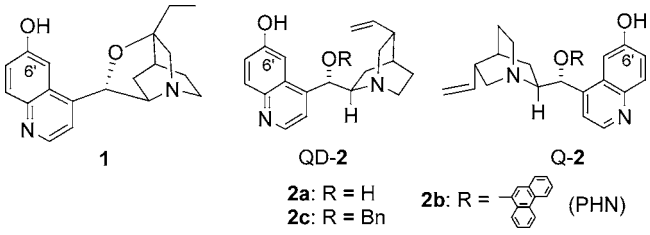

Figure 1. Structures of 6′-OH cinchona alkaloid catalysts.

Our investigation began with the amination of ethyl α-phenyl α-cyanoacetate **3a** with diethyl azodicarboxylate at room temperature in the presence of QD-**2** (Table 1). The tunable nature of **2** proved to be critical to catalyst optimization for achieving optimal enantioselectivity for the electrophilic amination.

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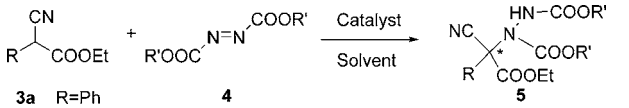
Table 1. Asymmetric Amination of Ethyl α-Phenyl α-Cyanoacetate (**3a**) with Dialkyl Azodicarboxylates (**4**)[a,b]



entry	catalyst (mol %)	conc (M)	R′	solvent	*T* (°C)	time	ee (%)
1	QD-**2a** (10)	0.5	Et	toluene	rt	1 min	11
2	QD-**2b** (10)	0.5	Et	toluene	rt	1 min	15
3	QD-**2c** (10)	0.5	Et	toluene	rt	1 min	40
4	QD-**2c** (10)	0.5	Et	toluene	−78	1 min	74
5	QD-**2c** (10)	0.08	Et	toluene	−78	1 min	85
6	QD-**2c** (10)	0.08	*iso*-propyl	toluene	−78	45 min	44
7	QD-**2c** (10)	0.08	benzyl	toluene	−78	1 min	89
8	QD-**2c** (10)	0.08	*tert*-butyl	toluene	−78	1 h	95
9	QD-**2c** (10)	0.08	*tert*-butyl	Et_2O	−78	3 h	70
10	QD-**2c** (10)	0.08	*tert*-butyl	THF	−78	12 h	10
11	QD-**2c** (10)	0.08	*tert*-butyl	CH_2Cl_2	−78	11 h	77
12	QD-**2c** (5)	0.08	*tert*-butyl	toluene	−78	3 h	95
13	QD-**2c** (2.5)	0.08	*tert*-butyl	toluene	−78	8 h	95
14	Q-**2a** (5)	0.08	*tert*-butyl	toluene	−78	4 h	97

[a] The reaction was performed with **3a** (0.1 mmol) and **4** (0.1 mmol) in the presence of **2**. [b] ee determined by HPLC analysis.

Amination of **3a** with 6′-OH cinchona alkaloids **2** bearing either a hydroxyl (QD-**2a**) or an aryl ether group (QD-**2b**) at C9 proceeded in very low enantioselectivity (entries 1 and 2). Interestingly, the enantioselectivity was improved significantly when a benzyl ether group was introduced at C9 of the 6′-OH cinchona alkaloid (QD-**2c**). The enantioselectivity of the amination was found to be also influenced considerably by temperature (entry 4 vs 3), concentration (entry 5 vs 4), solvent, and the structure of the dialkyl azodicarboxylate. Importantly, excellent enantioselectivity is obtained for amination of **3a** with di-*tert*-butyl azodicarboxylate catalyzed by QD-**2c** in toluene at −78 °C. Furthermore, the catalyst loading could be decreased to 2.5 mol % without having a negative impact on the enantioselectivity of the amination (entry 13 vs 8). The high enantioselectivity attained with dibenzyl azodicarboxylate is noteworthy (entry 7), as amination by dibenzyl azodicarboxylate with **1** was reported to proceed in a modest enantioselectivity.[7b] Most importantly, the amination catalyzed by Q-**2c** also proceeded in excellent enantioselectivity (entry 14).

Following the optimized reaction condition, the scope of the enantioselective amination of α-substituted α-cyanoacetates with **2c** was investigated. A wide range of α-cyanoacetates bearing α-aryl substituents of various electronic and steric properties were found to undergo enantioselective amination in high enantioselectivity and excellent yield with either Q-**2c** or QD-**2c** (Table 2). Thus, this reaction allows the construction of the nitrogen-substituted quaternary stereocenter in either *R* or *S* configuration. The consistently high ee value for Q-**2c** (92−99%) or QD-**2c** (91−95%) mediated amination of cyanoacetates bearing electronically differing α-aryl groups indicates that the enantioselectivity

Table 2. Asymmetric Amination of Ethyl α-Substituted α-Cyanoacetate (**3**) Catalyzed by Q-**2c** and QD-**2c**[a−c]

entry		R	R′	catalyst (mol %)	*T* (°C)	time (h)	yield (%)	ee (%)
1	**3a**	Ph	*t*-Bu	5 (5)	−78	4 (2)	92 (92)	97 (95)
2	**3b**	*p*-F-C_6H_4	*t*-Bu	5 (5)	−78	2 (1)	95 (97)	96 (94)
3	**3c**	*p*-Cl-C_6H_4	*t*-Bu	5 (5)	−78	0.5 (0.5)	94 (96)	97 (93)[d]
4	**3d**	*p*-Br-C_6H_4	*t*-Bu	5 (5)	−78	2 (1)	97 (99)	96 (93)
5	**3e**	1-naphthyl	*t*-Bu	10 (10)	−78	12 (8)	98 (99)	99 (93)
6	**3f**	*p*-Me-C_6H_4	*t*-Bu	5 (5)	−78	8 (8)	96 (96)	96 (94)
7	**3g**	*p*-MeO-C_6H_4	*t*-Bu	10 (10)	−78	10 (5)	96 (96)	97 (94)
8	**3h**	*p*-Br−C_6H_4	Bn	5 (5)	−78	1 min (1 min)	83 (86)	92 (91)
9	**3i**	*o*-Me-C_6H_4	Bn	5 (5)	−78	3.5 (1)	72 (71)	87 (82)
10	**3j**	Me	Bn	10 (10)	rt	0.5 (0.5)	74 (75)	23 (35)

[a] The reaction was performed in toluene with **4** (0.20 mmol) and **3** (0.22 mmol) in the presence of **2c**. [b] Results in parentheses were obtained with QD-**2c**. [c] See the Supporting Information for experimental details of ee determination. [d] The QD-**2c**-catalyzed amination of **3c** gives the product in the (*S*) configuration. See the Supporting Information for experimental details of the structure determination by X-ray crystallography.

is insensitive to the electronic property of the aromatic ring. Amination of ortho-substituted α-aryl α-cyanoacetates was expected to be more challenging, since enolization of this class of cyanoacetates is relatively difficult. Indeed, a decreased but still synthetically useful enantioselectivity was observed in the amination of α-*o*-tolyl α-cyanoacetate (**3i**) by benzyl azodicarboxylate. To our knowledge, this is the first report of a synthetically useful enantioselectivity for an α-aryl α-cyanoacetate bearing an *o*-substituent that is significantly bulkier than hydrogen (entry 9). Attempts to facilitate a highly enantioselective amination of an α-alkyl α-cyanoacetate were, unfortunately, not successful (entry 10). In summary, a highly enantioselective electrophilic amination of α-aryl α-cyanoacetate was realized by using catalysts **2c** based on 6′-OH cinchona alkaloids. The similarly high enantioselectivities attained with both QD-**2c** and Q-**2c** allow this electrophilic amination to provide facile access to a nitrogen-substituted quaternary stereocenter in either the *R* or *S* configuration. This important versatility should render this reaction a useful method for the preparation of various valuable chiral building blocks containing a nitrogen-substituted quaternary stereocenter, such as α,α-disubstituted α-amino acids. Finally, these results significantly expanded the scope of the asymmetric catalysis of 6′-OH modified cinchona alkaloids.

Acknowledgment. We are grateful for the generous financial support from Daiso and an Alfred P. Sloan research fellowship (L.D.).

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.

OL048190W