Communication

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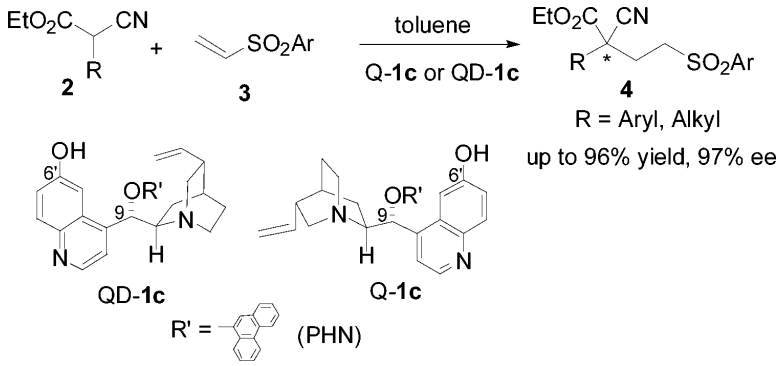
J. Am. Chem. Soc., **2005**, 127 (25), 8948-8949• DOI: 10.1021/ja0511063 • Publication Date (Web): 01 June 2005



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Catalytic Enantioselective C−C Bond Forming Conjugate Additions with Vinyl Sulfones

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Received February 21, 2005; E-mail: deng@brandeis.edu

Sulfones are widely useful intermediates of unique synthetic versatility in organic synthesis.[1] Conjugate additions of carbon nucleophiles to vinyl sulfones in parallel to those to nitroalkenes constitute a class of synthetically valuable C−C bond forming reactions. Accordingly, considerable efforts have been devoted to the development of asymmetric conjugate additions to vinyl sulfones. Although significant advancement has been made in the use of chiral auxiliary strategy, the realization of a highly enantioselective catalytic conjugate addition with vinyl sulfones remains elusive.[2−7] In this communication, we wish to report the development of the first highly enantioselective, catalytic C−C bond forming conjugate addition with vinyl sulfones.

In light of our recent discovery of cinchona alkaloid derivatives (Figure 1) as highly efficient catalysts for asymmetric conjugate additions,[8] we were attracted to the possibility of applying these readily available and tunable chiral organic catalysts to develop a highly enantioselective catalytic conjugate addition with vinyl sufones. We were particularly interested in the conjugate addition of α,α-disubstituted carbonyl Michael donors to unsubstituted vinyl sulfones, given the urgent need of efficient catalytic C−C bond forming methods for the enantioselective creation of an all-carbon substituted quaternary stereocenter.[9]

Our experiments began with a screening of a variety of cinchona alkaloid derivatives for their ability to promote enantioselective addition of α-phenyl α-cyanoacetate **2A**[10] to the commercially available phenylvinyl sulfone **3a**. As summarized in Table 1, the conjugate addition proceeded smoothly in toluene at room temperature in the presence of various natural or modified cinchona alkaloids. The enantioselectivity of the reaction was, however, found to be critically dependent on the structure of the cinchona alkaloid derivatives. Reactions with natural cinchona alkaloids such as quinidine and quinine generated the 1,4-adduct as a nearly racemic mixture (entries 1 and 2). The enantioselectivity was in general improved with cinchona alkaloids bearing a C9-substituent (entries 3−7, 9−12), among which those bearing a C6′−OH were found to be more effective than those bearing a C6′−OMe. The pronounced effect of the C9-substituent on the enantioselectivity of the C6′−OH cinchona alkaloids is also noteworthy. While modest enantioselectivity was afforded by either the C6′−OH cinchona alkaloid bearing a C9−OH (entry 8) or a rigid C6′−OH cinchona alkaloid derivative (entry 7), significantly higher enantioselectivity could be attained with C6′−OH cinchona alkaloids bearing either an aryl or alkyl ether at C9 (entries 9−12). Thus the tunable nature of cinchona alkaloids **1** provided a crucial handle for the optimization of catalytic enantioselectivity. Upon further optimization, an excellent enantioselectivity could be achieved with either QD-**1c** or Q-**1c** at −25 °C in toluene (entries 13 and 14).[11]

A substrate scope study revealed that α-cyanoacetates **2** bearing a range of aryl groups of varying electronic and steric properties underwent efficient enantioselective addition to phenylvinyl sulfone **3a**, providing the 1,4-adduct **4** bearing the all-carbon quaternary stereocenter in excellent enantioselectivity and good to excellent yield (Table 2). Notably, high enantioselectivity and yield could also be obtained with an α-heteroaryl α-cyanoacetate (Table 2, entry 9).

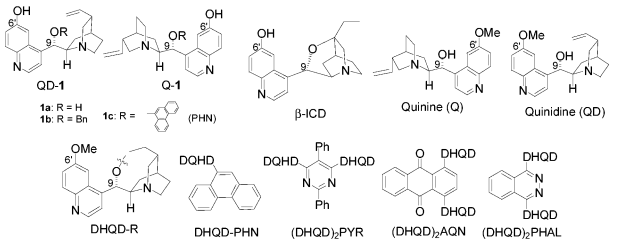
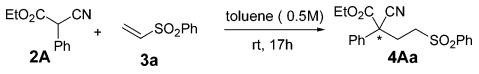


Figure 1. Structure of Cinchona Alkaloids.

Table 1. Cinchona Alkaloid-Catalyzed Addition of α-Phenyl α-Cyanoacetate (**2A**) to Vinyl Phenyl Sulfone (**3a**)[a]



entry	cat.[b]	conv/%[c]	ee/%[d]	entry	cat.	conv/%	ee/%
1	Q	>98	0	**8**	QD-**1a**	90	45
2	QD	>98	3	**9**	QD-**1b**	>98	63
3	DHQD-PHN	79	24	**10**	QD-**1c**	91	74
4	$(DHQD)_2$PYR	>98	33	**11**	Q-**1b**	65	74
5	$(DHQD)_2$PHAL	80	9	**12**	Q-**1c**	>98	84
6	$(DHQD)_2$AQN	>98	4	**13**[e]	QD-**1c**	85	91
7	*β*-lCD	>98	42	**14**[e]	Q-**1c**	95	95

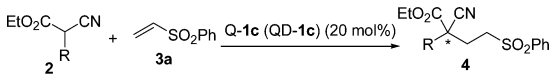
[a] Unless noted, reactions were run with 0.3 mmol of **2A**, 0.1 mmol **3a** in 0.2 mL of toluene with 20 mol % catalyst at room temperature for 17 h. [b] See Supporting Information for the structure of the catalysts. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] Reaction was run at −25 °C for 72 h.

Having established a general scope with respect to α-aryl α-cyanoacetates, we next investigated the conjugate addition with α-alkyl α-cyanoacetates. We found that, compared to their aryl congeners, α-alkyl α-cyanoacetates were significantly less active as Michael donor for the cinchona alkaloid-catalyzed conjugate addition to vinyl sulfones. While addition of α-phenyl α-cyanoacetate **2A** to phenylvinyl sulfone **3a** with Q-**1c** proceeded to completion at room temperature after 17 h (Table 1, entry 12), the addition of α-allyl α-cyanoacetate **2J** to **3a** proceeded to only 17% conversion during the same period (Table 3, entry 1).

We reasoned that the cinchona alkaloid-catalyzed conjugate addition with α-alkyl α-cyanoacetate might be accelerated considerably by enhancing the electrophilicity of the vinyl sulfone **3**, which could be implemented via the introduction of electron-withdrawing substitutents on the aromatic ring of **3**. With this consideration in mind, we investigated the conjugate addition of **2J** to 3,5-bis-(triflouromethyl)phenyl vinyl sulfone **3b**[12] with Q-**1c** at room temperature. We were pleased to see that the reaction was indeed accelerated, proceeding to 88% conversion after 17 h to afford the 1,4-adduct in 86% ee (Table 3, entry 2). Thus the ability of 6′-OH

10.1021/ja0511063 CCC: $30.25

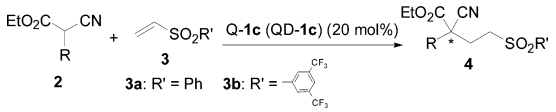
Table 2. Enantioselective Conjugate Addition of α-Aryl α-Cyanoacetate **2** to Vinyl Sulfone **3a** Catalyzed by Q-**1c** and QD-**1c** (in Parentheses)[a]



entry		R	*T*/°C	time/h	yield/%[b]	ee/%[c]
1	**2A**	Ph-	−25	72 (72)	89 (80)	95 (91)
2	**2B**	4-Me-Ph-	0	48	96	93
3	**2C**	4-MeO-Ph-	0	70	92	94
4	**2D**	4-F-Ph-	−25	72	90	94
5	**2E**	4-Cl-Ph-	−25	69 (72)	95 (94)	94 (89)
6	**2F**	4-Br-Ph-	−25	66 (72)	95 (95)	94 (88)
7	**2G**	3-Cl-Ph-	−25	60	96	93
8	**2H**	2-naphthyl-	−25	60 (60)	96 (95)	97 (90)
9	**2I**	2-thienyl-	−25	48 (48)	95 (91)	97 (88)

[a] Unless noted, reactions were run with 0.5−0.6 mmol of **2**, 0.2 mmol **3a** in 0.4 mL toluene with 20 mol % Q-**1c**, the catalyst was recovered in greater than 95% yield, and the results in parentheses were obtained with QD-**1c** to give opposite enantiomer. See Supporting Information for detail. [b] Isolated yield. [c] Determined by HPLC analysis.

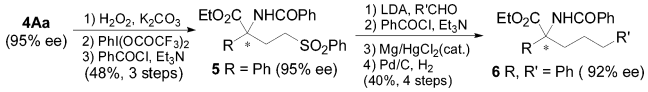
Table 3. Enantioselective Conjugate Addition of α-Alkyl α-Cyanoacetate **2** to Vinyl Sulfone 3 Catalyzed by Q-**1c** and QD-**1c** (in Parentheses)[a]



entry	**2**	R	**3**	*T*/°C	time/h	conv/%[b]	yield/%[c]	ee/%[d]
1[e]	**2J**	allyl-	**3a**	23	17	17	N. D.	87
2[e]	**2J**	allyl-	**3b**	23	17	88	N. D.	86
3	**2J**	allyl-	**3b**	0	96	100	76	94
4	**2K**	Me-	**3b**	0	96 (96)	100 (100)	85 (83)	92 (88)

[a] Unless noted, reactions were run with 0.5−0.6 mmol of **2** and 0.2 mmol **3** in 0.4 mL of toluene with 20 mol % Q-**1c**, the catalyst was recovered in greater than 95% yield, and the results in parentheses were obtained with QD-**1c** to give opposite enantiomer. See Supporting Information for detail. [b] Determined by ^{1}H NMR analysis. [c] Isolated yield. [d] Determined by HPLC analysis. [e] Reactions were run with 0.6 mmol of **2** and 0.2 mmol **3**.

Scheme 1. Synthesis of Optically Active α,α-Disubstituted Amino Acids



cinchona alkaloid catalysts to tolerate the structural change of the vinyl sulfone acceptor allowed us to significantly improve the rate of the conjugate addition of an α-alkyl α-cyanoacetate by tuning the electronic property of the vinyl sulfone acceptor. When the Michael donor and acceptor was employed in a practically attractive 1:1 stoichiometry, a conjugate addition of **2J** to **3b** in complete conversion and excellent enantioselectivity was eventually attained at 0 °C (Table 3, entry 3). Importantly, the high enantioselectivity could be readily extended to the conjugate addition of α-methyl α-cyanoacetate **2K** to **3b** (Table 3, entry 4).

We have applied the enantioselective addition with vinyl sulfones to develop a new catalytic approach for the asymmetric synthesis of the biologically significant α,α-disubstituted amino acids (Scheme 1).[13] As shown in the synthesis of **6**, an amino acid that was previously not accessible via asymmetric catalysis, our approach complements existing catalytic methods, thereby expanding the range of α,α-disubstituted amino acids accessible by catalytic asymmetric synthesis.[14]

In summary, we have developed the first highly enantioselective catalytic conjugate addition to vinyl sulfones. This reaction employs readily accessible and recyclable chiral organic catalysts and an experimentally simple protocol that avoids low temperature and high dilution and is not air- or moisture-sensitive. These attractive features in combination with its substantial scope should render it a new and valuable catalytic entry for the enantioselective construction of all-carbon quaternary stereocenters. The synthetic utility of the optically active chiral sulfones **4** is demonstrated in the development of a versatile catalytic enantioselective approach toward α,α-disubstituted amino acids.

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

Supporting Information Available: Experimental details and spectroscopic data for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Various solvents were screened under the same condition as described in entry 11 of Table 1, using Q-**1c** (20 mol %) as catalyst, at −25 °C, after 17 h: TBME (9% conv, 58% ee), $CHCl_3$ (17% conv, 79% ee), CH_2Cl_2 (17% conv, 74% ee), DCE (22% conv, 81% ee), toluene (46% conv, 95% ee).
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JA0511063