Communication

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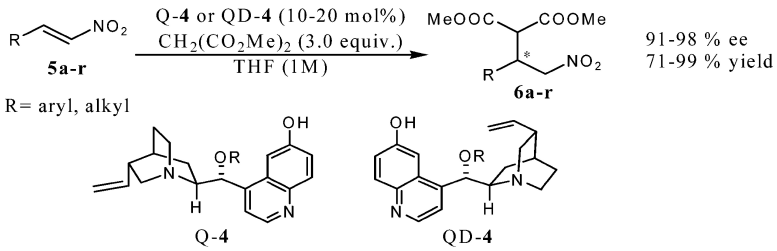

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Highly Enantioselective Conjugate Addition of Malonate and β-Ketoester to Nitroalkenes: Asymmetric C−C Bond Formation with New Bifunctional Organic Catalysts Based on Cinchona Alkaloids

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Chiral metallic and organic catalysts that possess both an acidic and a basic/nucleophilic structural moiety constitute an increasingly powerful platform for the development of asymmetric catalysis.[1,2] The design and development of such bifunctional chiral catalysts that are efficient, yet easily accessible, continues to be a major challenge. Wynberg and co-workers demonstrated that natural cinchona alkaloids such as quinidine (QD-**1**) and quinine (Q-**1**), with a C-9 alcohol and a quinuclidine, serve as bifunctional chiral organic catalysts by activating the nucleophile and electrophile, respectively (Figure 1).[3] However, the enantioselectivity of various reactions catalyzed by natural cinchona alkaloids as chiral organic catalysts is usually modest. Hatakeyama and co-workers reported that the rigid modified cinchona alkaloid **2**, which is readily accessible from quinidine, efficiently catalyzes an enantioselective Morita−Baylis−Hillman reaction.[4] Both the quinoline phenol (C6′-OH) and the quinuclidine of **2** were postulated to be involved in stabilization of the transition state.[4] With a cagelike structure that prevents rotation of the C8−C9 bond, catalyst **2** is conformationally rigid, a common feature of many efficient chiral catalysts or ligands. However, an enantiomer or pseudoenantiomer of **2** is not yet accessible.

Recent extensive studies using C-9 alcohol-modified cinchona alkaloids **3** demonstrated that cinchona alkaloids with rotational freedom around C8−C9 and C4′−C9 bonds are broadly effective chiral organic catalysts.[5,6] With an interest in developing efficient bifunctional chiral organic catalysts, we became interested in the asymmetric catalysis of cinchona alkaloids **4**, which bear a 6′-hydroxyquinoline in place of a 6′-methoxyquinoline or quinoline ring.[7] Although previously not shown to be effective catalyst for any asymmetric reaction,[7] cinchona alkaloids QD-**4** and Q-**4** are attractive to us due to their easy accessibility from quinine and quinidine, respectively. Importantly, they could therefore serve as bifunctional chiral catalysts that provide straightforward access to either enantiomer of a given chiral product. Furthermore, with an easily modified C9−OR group, **4** are more amenable than **1** or **2** toward structural variation for optimization of catalyst activity and selectivity. In this communication, we report the first successful use of cinchona alkaloids **4** as a catalyst for a highly enantioselective reaction.

Our investigations began with the preparation of catalysts QD-**4a**−**c** from quinidine (QD-**1**) via high-yielding and experimentally simple one- or two-step protocols in 60−92% overall yield.[8] These catalysts and other readily accessible natural and modified cinchona alkaloids were then examined for their ability to mediate enantioselective 1,4-addition of malonates to nitroalkenes, a synthetically important C−C bond-forming reaction employing readily available starting materials.[9] Although high enantioselectivity for this 1,4-addition is achieved with chiral Mg-bis(oxazoline) complexes[10a,b] and bifunctional organic catalysts derived from chiral 1,2-diaminocyclohexane,[10c] there is substantial room for improvement in terms of both enantioselectivity and substrate scope.

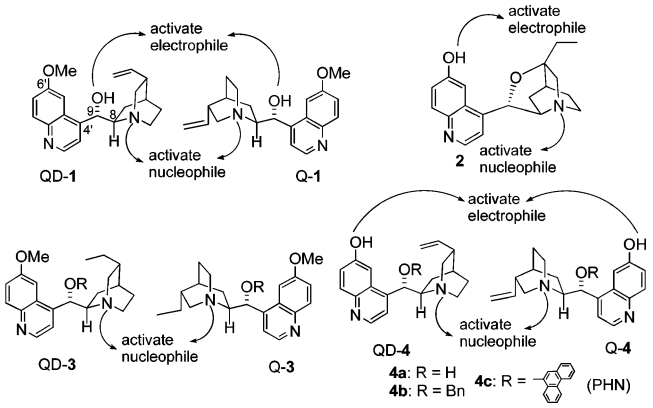
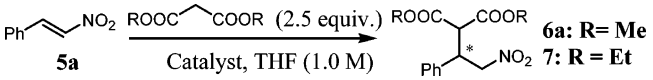


Figure 1. Mode of activation of nucleophile and electrophile by cinchona alkaloids.

Table 1. Asymmetric 1,4-Addition of Malonates to *trans*-Phenyl Nitroalkene (**5a**)[a]



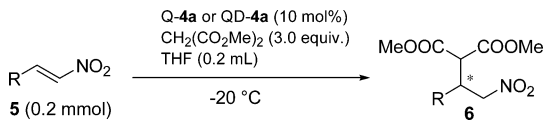
entry	catalyst[b]	R	*T* (°C)	% conversion[c]	% ee[d]
1	QD	Et	23	78	16
2	DHQD-PHN	Et	23	28	6
3	DHQD-CLB	Et	23	10	12
4	$(DHQD)_2AQN$	Et	23	38	18
5	$(DHQD)_2PYR$	Et	23	46	24
6	$(DHQD)_2PHAL$	Et	23	18	13
7	**2**	Et	23	90	75
8	QD-**4a**	Et	23	>98	79
9	QD-**4b**	Et	23	91	78
10	QD-**4c**	Et	23	84	82
11	**2**	Et[e]	−20	75	86
12	QD-**4a**	Et[e]	−20	86	90
13	QD-**4b**	Et[e]	−20	90	88
14	QD-**4c**	Et[e]	−20	73	91
15	QD-**4a**	Me[f]	−20	>98	93
16	Q-**4a**	Me[f]	−20	>98	96
17	QD-**4a**	Me[g]	−55	81	97
18	Q-**4a**	Me[g]	−55	93	99

[a] Unless noted, reactions were run with 0.1 mmol of **5** for 12 h. [b] See Supporting Information for the structure of the catalysts. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis (see Supporting Information). [e] Reaction was run for 36 h. [f] Reaction was run for 36 h using 3.0 equiv of $CH_2(CO_2Me)_2$. [g] Reaction was run for 108 h.

Additions of dimethyl and diethyl malonate to nitroalkene **5a** mediated by various cinchona alkaloids were investigated in THF (Table 1). Cinchona alkaloids bearing a 6′-hydroxyquinoline ring (**2** and **4**) were found to afford significantly higher enantioselectivity and a faster rate than those bearing a 6′-methoxyquinoline ring (entries 7−10, 75−82% ee vs entries 1−6, 6−24% ee). Catalysts

10.1021/ja047281l CCC: $27.50

Table 2. 1,4-Addition of Dimethyl Malonate to Nitroalkenes Catalyzed by Q-**4a** and QD-**4a**[a,b]



entry		R	time (h)	yield (%)[c]	ee (%)[d]
1	**5a**	Ph	36 (36)	97 (99)	96[g] (93)
2	**5b**	4-F−Ph	36 (36)	97 (97)	97 (94)
3	**5c**	4-Cl−Ph	36 (36)	97 (97)	97 (94)
4	**5d**	4-Br−Ph	36 (36)	99 (98)	96 (94)
5	**5e**	4-Me-Ph	36 (44)	97 (97)	98 (94)
6	**5f**	4-^{i}Pr−Ph	36 (39)	95 (96)	97 (93)
7	**5g**	4-MeO−Ph	44 (47)	90 (94)	97 (95)
8	**5h**	3-Me−Ph	36 (36)	97 (99)	97 (93)
9	**5i**	2-Me−Ph	36 (36)	95 (97)	98 (96)
10	**5j**	2-F−Ph	36 (36)	97 (94)	97 (95)
11	**5k**	2-NO_2−Ph[e]	69 (72)	90 (88)	97 (92)
12	**5l**	1-naphthyl	36 (36)	99 (99)	98 (92)
13	**5m**	2-thienyl	36 (44)	99 (96)	98 (95)
14	**5n**	2-furyl	36 (36)	97 (95)	98 (96)
15	**5o**	3-pyridinyl	36 (36)	98 (99)	96 (92)
16	**5p**	pentyl	72 (72)	81 (82)	94 (91)
17	**5q**	^{i}Bu	72 (72)	86 (84)	94 (92)
18	**5r**	cyclohexyl[f]	108 (108)	71 (80)	94 (91)

[a] Unless noted, reactions were run at −20 °C. [b] Results in parentheses were obtained with QD-**4a**. [c] Isolated yield. [d] Determined by HPLC analysis (see Supporting Information). [e] Reaction was performed at −55 °C. [f] Using 20 mol % catalyst. [g] Absolute configuration was determined to be *S*; for details, see Supporting Information.

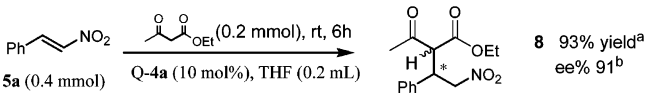
QD-**4a**−**c**, although conformationally mobile, afforded higher enantioselectivity than **2** (entries 8−10 vs 7). The simplest and most accessible member of cinchona alkaloids **4**, QD-**4a**, was found to be a highly efficient catalyst despite possessing two hydrogen-bond donors. Better conversion and enantioselectivity can be achieved with dimethyl rather than diethyl malonate (entries 15 vs 12). Importantly, Q-**4a** afforded even higher enantioselectivity with an opposite sense of asymmetric induction (entry 16) and up to 99% ee can be attained with Q-**4a** at −55 °C (entry 18).

Preliminary kinetic studies established that the addition of dimethyl malonate to **5a** with Q-**4a** followed a first-order dependence on the catalyst, the dimethyl malonate, and nitroalkene **5a**.[8] Phenol itself was found to be unable to catalyze the conjugate addition. These results and the significantly higher enantioselectivity and faster rates by QD-**4a**−**c** vs those by quinidine (QD-**1**) are consistent with the notion that **4** serves as a bifunctional catalyst that utilizes both the phenolic-OH and the quinuclidine functionalities for the stabilization and organization of the transition state assembly of the enantioselective 1,4-addition.

A wide range of nitroalkenes (**5**) bearing aryl, heteroaryl, and alkyl groups were treated with dimethyl malonate in THF at −20 °C in the presence of either QD-**4a** or Q-**4a** (Table 2). Aryl and heteroaryl nitroalkenes (**5a**−**o**) were found to be cleanly converted into the corresponding 1,4-adducts in 92−98% ee and 88−99% yield. High enantioselectivity and yield were also obtained with nitroalkenes (**5p**−**r**) bearing a wide variety of alkyl groups. The consistently excellent enantioselectivity obtained with various heteroaryl and alkyl nitroalkenes (**5m**−**r**) is noteworthy, as such nitroalkenes were shown to be relatively challenging substrates in previous studies involving chiral Mg-bis(oxazoline) complexes[10a,b] and organic catalysts.[10c] The results obtained with **5r** represent the first highly enantioselective addition of a malonate ester to a sterically hindered γ-branched nitroalkene (entry 18).

The addition of ethyl acetoacetate to **5a** catalyzed by Q-**4a** proceeded to completion in 6 h to afford 1,4-adduct **8** as a 1:1 diastereomeric mixture, but both diastereomers were formed in 91% ee. (Scheme 1). The 1:1 diastereomeric mixture is probably due to racemization at the γ-stereogenic center under the reaction conditions.

Scheme 1. Asymmetric 1,4-Addition of β-Ketoester to *trans*-Phenyl Nitroalkene (**5a**)



[a] Isolated yield as a mixture of around 1/1 diasteromer. [b]Determined by HPLC analysis (see Supporting Information).

In summary, we have developed a new class of chiral bifunctional organic catalysts based on cinchona alkaloids. These catalysts are easily accessible from either quinine or quinidine and are shown to be highly efficient for a synthetically important C−C bond-forming asymmetric conjugate addition. We are now developing these new bifunctional chiral organic catalysts for a wide range of asymmetric reactions.

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

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