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The Mannich Reaction of Malonates with Simple Imines Catalyzed by Bifunctional Cinchona Alkaloids: Enantioselective Synthesis of β-Amino Acids

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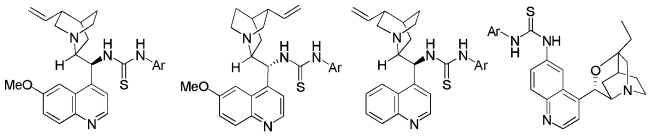
Enantioselective Mannich reactions[1] are of fundamental importance to the synthesis of optically active chiral amines. Significant progress has been made in the development of efficient chiral metal and organic catalysts for enantioselective Mannich reactions with preactivated enolate nucleophiles such as enolsilane[2] and enolizable carbonyl nucleophiles such as β-keotesters[3a−c] and 1,3-diketones.[3d] Highly enantioselective, direct Mannich reactions with aldehydes and ketones have also been accomplished with chiral secondary amines and chiral metal complexes.[4] However, a highly enantioselective Mannich reaction of malonates with simple imines[5] remains elusive; although, if successfully promoted with a practically accessible chiral catalyst under air- and moisture-tolerant conditions, it could provide a highly attractive, convergent approach toward optically active β-amino acids suitably protected for further synthetic elaborations.[6,7] The realization of such a direct Mannich reaction is particularly challenging as it involves the combination of a weakly reactive imine and a carbonyl nucleophile that is, relative to 1,3-diketones and β-ketoesters, harder to enolize and unsuitable for chiral enamine catalysis.[5] Herein, we wish to describe the application of cooperative hydrogen-bonding catalysis to develop a cinchona alkaloid-catalyzed, highly enantioselective Mannich reaction with malonates and *N*-Boc imines.

Chiral hydrogen-bond donors such as chiral thioureas and phosphoric acid have been identified as effective catalysts for the activation of simple imines toward various enantioselective nucleophilic additions[8] including Mannich reactions with enolsilane[2e,f] and 1,3-diketones.[3d] On the other hand, chiral hydrogen-bond acceptors such as cinchona alkaloids were shown to be effective for the activation of malonates for enantioselective conjugate additions.[9] These observations led us to envision that cinchona alkaloid derivatives bearing a thiourea functionality[8j,10] might act as efficient bifunctional catalysts for a Mannich reaction of malonates with simple imines.

Accordingly, we initiated a study of cinchona alkaloid derivatives bearing either a 6′- or 9-thiourea functionality (Figure 1) as catalysts for the addition of dimethyl malonate **5a** to the *N*-Boc-protected imine **4D** in dichloromethane. As summarized in Table 1, 6′- or 9-thiourea cinchona alkaloids bearing an electron-withdrawing aryl substituent emerged as the most effective catalysts. The Mannich reaction with catalysts Q-**1d** and **3** took place in 77% and 72% ee, respectively (entries 4 and 7). A study of the reaction with the synthetically more accessible Q-**1d** in various solvents identified acetonitrile and acetone as suitable alternatives to dichloromethane (entries 8 and 9). Interestingly, reactions in these solvents responded differently to temperature change. For reactions at −20 °C vs those at room temperature, the enantioselectivity was slightly increased in dichloromethane but decreased noticeably in acetonitrile. A more pronounced positive temperature effect on the enantioselectivity was observed in acetone, which led us to a highly enantioselective, completed reaction of **4D** with **5a** at −60 °C (entry 13).

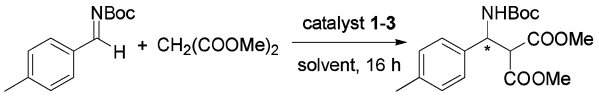


1a Ar = 4-*t*-Bu-Ph-; **1b** Ar = 2-*i*-Pr-Ph-; **1c** Ar = Ph-; **1d** Ar = 3,5-*bis*CF_3Ph-

2,3: Ar = 3,5-*bis*CF_3Ph-

Figure 1. C6′ or C9 thiourea cinchona alkaloid derivatives.

Table 1. Cinchona Alkaloid-Catalyzed Addition of Dimethyl Malonate (**5a**) to *N*-Boc-imine (**4D**)[a]



4D **5a** **6Da**

entry	cat.[b]	temp (°C)	solvent	conv./%[c]	ee/%[d]
1	Q-**1a**	RT	CH_2Cl_2	>98	57
2	Q-**1b**	RT	CH_2Cl_2	>98	43
3	Q-**1c**	RT	CH_2Cl_2	>98	62
4	Q-**1d**	RT	CH_2Cl_2	>98	77
5	QD-**1d**	RT	CH_2Cl_2	>98	-74
6	**2**	RT	CH_2Cl_2	>98	65
7	**3**	RT	CH_2Cl_2	>98	72
8	Q-**1d**	RT	CH_3CN	>98	83
9	Q-**1d**	RT	Acetone	>98	77
10	Q-**1d**	-20	CH_2Cl_2	>98	80
11	Q-**1d**	-20	CH_3CN	>98	74
12	Q-**1d**	-20	Acetone	>98	85
13[e]	Q-**1d**	-60	Acetone	>98	93

[a] Unless noted, reactions were run with 0.05 mmol of **4D**, 0.15 mmol of **5a** in 0.10 mL of solvent with 10 mol% catalyst for 16 h. [b] Cinchona alkaloids bearing no thiourea functionality afforded moderate ee, see Supporting Information for detail. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] Reaction was run with Q-**1d** (20 mol%) at −60 °C for 24 h.

The scope of the enantioselective Mannich reaction catalyzed by both Q-**1d** and QD-**1d** was investigated under the optimized condition identified above (Table 2). The enantioselectivity of catalyst **1d** was found to be nearly independent of the steric properties of the aryl imines. Reactions with *o*-, *m*-, and *p*-tolyl imines (**4B**−**D**) in the presence of QD-**1d** took place in 97−99% ee. Exceedingly high enantioselectivity could also be obtained for a variety of heteroaryl and aryl imines of varying electronic properties (**4E**−**L**), including electron-rich aryl imines.[2f] It is noteworthy that very good enantioselectivity could be attained for *N*-Boc alkyl imines, including even α-unbranched alkyl imines (**4M**−**O**).[4a] Although high loading of QD-**1d** (100 mol%) was required to sustain a useful level of enantioselectivity, QD-**1d** could be readily recycled in greater than 95% yield. To our knowledge, the results with **4M**−**N** represent the first highly enantioselective Mannich reactions with *N*-Boc α-unbranched alkyl imines (entries

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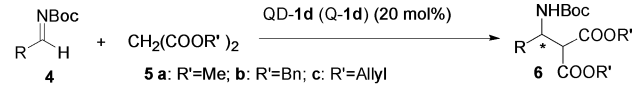
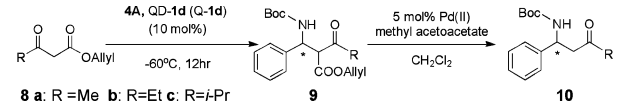
Table 2. Enantioselective Mannich Reaction of Malonate **5** to *N*-Boc-imine **4** Catalyzed by QD-**1d** and Q-**1d** (in parentheses)[a]



entry		R	5	yield/%[b]	ee/%[c,d]
1	**4B**	2-Me-Ph-	**5b**	98(96)	99(95)
2	**4C**	3-Me-Ph-	**5b**	99(99)	98(97)
3	**4D**	4-Me-Ph-	**5b**	92(96)	97(92)
4	**4E**	4-F-Ph-	**5b**	99(98)	99(94)
5	**4F**	4-Cl-Ph	**5b**	98(97)	99(91)
6	**4G**	4-CF_3-Ph-	**5b**	81(82)	97(93)
7	**4H**	2-furyl-	**5b**	99(99)	97(96)
8	**4I**	2-thienyl-	**5b**	95(96)	97(88)
9	**4J**	4-OMe-Ph-	**5b**	98(97)	97(93)
10[e]	**4J**	4-OMe-Ph-	**5b**	91	96
11	**4K**	3,4-OCH_2O-Ph-	**5b**	99(99)	98(94)
12	**4L**	3-vinyl-Ph-	**5c**	96(99)	96(95)
13[f]	**4M**	CH_3CH_2-	**5b**	63	89
14[f]	**4N**	$CH_3(CH_2)_2CH_2$-	**5b**	64	92
15[f]	**4O**	cyclohexyl-	**5b**	55	88
16	**4A**	Ph-	**5a**	90(91)	97(93)
17	**4A**	Ph-	**5b**	99(99)	96(94)
18	**4A**	Ph-	**5c**	91(86)	98(92)

[a] Unless noted, reactions were run with **4** (0.20 mmol) and **5** (0.30 mmol) in acetone (0.4 mL) at −60 °C for 36 h, and the results in parentheses were obtained with Q-**1d**. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Absolute configuration of (+)-**6Ab** prepared with a QD-**1d**-catalyzed reaction with determined to be *S*, see Supporting Information. [e] Reaction was run was 5 mol% QD-**1d** at −60 °C for 60 h. [f] Reaction was run with **4** (0.30 mmol) and **5** (0.20 mmol) in dichloromethane with high loading of **1d** (100 mol %) at 0 °C for 16−24 h with >95% recovery of QD-**1d**.

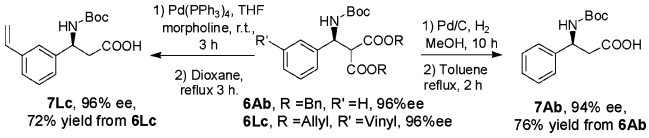
Table 3. Enantioselective Mannich Reaction of β-Ketoester **8** to *N*-Boc-imine **4A** Catalyzed by QD-**1d** and Q-**1d** (in parentheses)[a]



entry	**8**	yield of **9** /%[b]	dr of **9**[c]	yield of **10** /%[b]	ee of **10** /%[d]
1	**8a**	89	3:1	83	92
2	**8b**	79	2:1	81	91
3	**8c**	78(85)	3:1 (1:1)	66(99)	96(92)

[a] Unless noted, reactions were run with **4A** (0.20 mmol) and **8** (0.30 mmol) in acetone (0.4 mL), and the results in parentheses were obtained with Q-**1d**. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis.

Scheme 1. Synthesis of *N*-Boc-β-amino acids



13−14). Catalyst **1d** also tolerated malonates of different bulk. This allows the conversion of amine **6** to β-amino acid **7** without using strongly acidic or basic conditions (Scheme 1).

The **1d**-catalyzed Mannich reaction is also applicable to β-ketoesters (Table 3).[3a−c] Importantly, steric variations of the keto substituent are readily accepted by catalyst **1d**, thereby allowing the Mannich reaction to provide access to a wide variety of optically active β-amino ketones.

In conclusion, by exploring cooperative hydrogen-bonding catalysis with a readily accessible bifunctional cinchona alkaloid catalyst,[9−11] we have developed a highly enantioselective direct Mannich reactions of *N*-Boc aryl and alkyl imines with malonates and β-ketoesters.[12] This leads to the establishment of a convergent enantioselective synthesis of *N*-Boc β-amino acids from readily available starting materials under mild, moisture- and air-compatible conditions.

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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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