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Highly Diastereoselective Asymmetric Mannich Reactions of 1,3-Dicarbonyls with Acyl Imines

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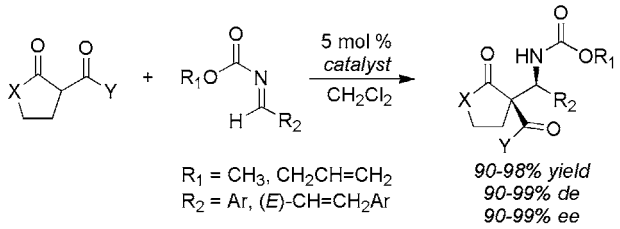
ABSTRACT



The cinchona alkaloids catalyze direct asymmetric Mannich reactions of cyclic 1,3-dicarbonyl compounds with acyl imines to afford α-quaternary carbon-bearing reaction products in yields of up to 98%, a diastereomeric excess of 90% or greater, and enantioselectivities up to 99% ee. A model is proposed that accounts for both the observed diastereoselectivities and the enantioselectivities for the reactions.

Optically active amine-containing synthons bearing quaternary carbon centers are valuable building blocks for synthesis.[1] Such chiral amine synthons have been used for the construction of pharmaceuticals and natural products.[2] In particular, cyclic derivatives of these chiral synthons have been used in the construction of peptidomimetics.[3] Incorporation of such cyclic amino acids into peptides induces conformational constraints that are pertinent to the understanding of peptide structure and function.[4] Hence, methods for their construction in diastereo- and enantioenriched form are highly desirable.[5]

The asymmetric direct Mannich reaction is an attractive method for the construction of chiral amines.[6] We recently reported the asymmetric Mannich reaction of β-keto esters

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with aryl acyl imines catalyzed by the cinchona alkaloids (Figure 1).[7] The reaction generated products in high enantio-

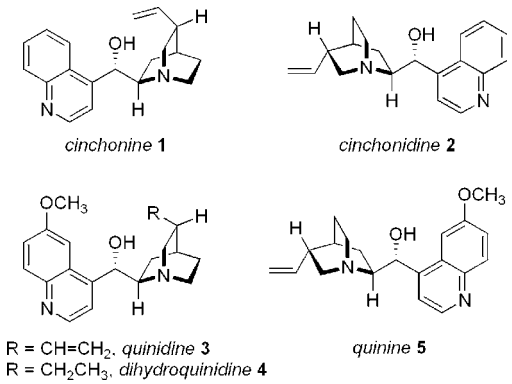
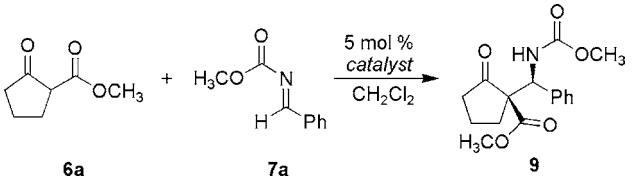


Figure 1. Cinchona alkaloids.

selectivity, and some acyl imines afforded Mannich products in high diastereoselectivity. Recently, nucleophilic additions to imines have been employed to produce quaternary carbon stereocenters.[5h−i,8] We have expanded the scope of the reaction to include cyclic α-substituted β-keto esters and β-diketones.[2f] The reaction provides a catalytic route toward the construction of cyclic β-amino esters with α-quaternary carbon centers in high diastereo- and enantiopurity.

Initially, we evaluated the reaction of methyl-2-oxocyclopentanecarboxylate **6a** with methyl benzylidene carbamate **7a** (Table 1). The reaction, catalyzed by 5 mol % of

Table 1. Asymmetric Mannich Reaction of β-Keto Esters[a]



6a **7a** **9**

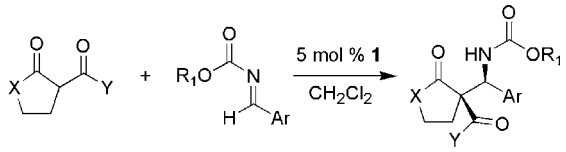
entry	catalyst	yield (%)[b]	de (%)[c]	ee (%)[c]
1	cinchonine **1**	96	93	90
2	cinchonidine **2**	96	94	−88
3	quinidine **3**	96	95	18
4	dihydroquinidine **4**	94	94	88
5	quinine **5**	95	94	−10

[a] Mannich reactions were carried out using 1.0 mmol of nucleophile **6a** and 0.5 mmol of imine in CH_2Cl_2 (0.5 M) at −35 °C for 18 h under N_2, followed by flash chromatography on silica gel. [b] Isolated yield of the Mannich reaction product. [c] Determined by chiral HPLC analysis.

cinchonine **1** in CH_2Cl_2 at −35 °C, afforded the corresponding β-amino ester **9** in 96% isolated yield and in 90% ee after 18 h (Table 1, entry 1). The use of cinchonidine **2** or quinine **5** as the catalyst afforded the product in similar diastereoselectivity but with the opposite sense of enantioselectivity (entries 2 and 5). Quinidine **3** and quinine **5** were effective at promoting the condensation but in lower enantioselectivities (entries 3 and 5). The reactions using catalysts **3** and **5** did not remain homogeneous during the course of the reaction, perhaps contributing to the observed low enantioselectivities. In contrast, the reaction using dihydroquinidine **4** did remain homogeneous.

The asymmetric Mannich reaction catalyzed by cinchonine was found to be equally effective with other nucleophiles such as ethyl-2-oxocyclopentanecarboxylate **6b**, β-diketone **6c**, and β-keto lactone **6d** (Table 2). We also investigated

Table 2. Asymmetric Mannich Reactions of β-Keto Esters and β-Diketones[a]



6a: X = CH_2, Y = OCH_3 **7a-d**: R_1 = CH_3 **10-15**
6b: X = CH_2, Y = OCH_2CH_3 **8a-b**: R_1 = allyl
6c: X = CH_2, Y = CH_3
6d: X = O, Y = CH_3

entry	Ar	nucleophile	yield (%)[b]	de (%)[c]	ee (%)[c]
1[d]	Ph (**7a**)	**6a**	**10a** (98)	98	90
2[d]	Ph (**7a**)	**6b**	**10b** (96)	96	93
3	Ph (**7a**)	**6c**	**10c** (98)	98	93
4	Ph (**8a**)	**6a**	**11a** (98)	98	90
5	Ph (**8a**)	**6b**	**11b** (98)	99	90
6	Ph (**8a**)	**6c**	**11c** (98)	99	91
7	3-CH_3−C_6H_4 (**7b**)	**6a**	**12a** (98)	93	96
8	3-CH_3−C_6H_4 (**7b**)	**6b**	**12b** (98)	98	92
9	3-CH_3−C_6H_4 (**7b**)	**6c**	**12c** (98)	94	94
10[e]	3-CH_3−C_6H_4 (**7b**)	**6d**	**12d** (88)	38	91
11	3-CH_3−C_6H_4 (**8b**)	**6a**	**13a** (96)	97	92
12	3-CH_3−C_6H_4 (**8b**)	**6b**	**13b** (98)	98	99
13	3-CH_3−C_6H_4 (**8b**)	**6c**	**13c** (92)	92	98
14	3-CH_3−C_6H_4 (**8b**)	**6d**	**13d** (78)	38	99
15[e]	2-C_4H_3O (**7c**)	**6a**	**14a** (98)	99	99
16[e]	2-C_4H_3O (**7c**)	**6b**	**14b** (98)	99	99
17[e]	2-C_4H_3O (**7c**)	**6c**	**14c** (98)	99	99
18[f]	3-F−C_6H_4 (**7d**)	**6a**	**15a** (98)	99	90
19[g]	3-F−C_6H_4 (**7d**)	**6b**	**15b** (98)	99	92
20[e]	3-F−C_6H_4 (**7d**)	**6c**	**15c** (98)	99	93

[a] Mannich reactions were carried out using 0.5 mmol of nucleophile **6a**,**b**, 0.5 mmol of acyl imines **7a**−**d** and **8a**,**b** in CH_2Cl_2 (0.5 M) for 2−6 h, at −55 °C under N_2, followed by flash chromatography on silica gel. [b] Isolated yield of the Mannich reaction product. [c] Determined by chiral HPLC analysis: see Supporting Information for details. [d] Reactions were run at −40 °C. [e] Reactions were run at −78 °C. [f] Reactions were run at −85 °C. [g] Reactions were run at −90 °C.

other acyl imines in the reaction by varying the electronic nature of the aryl substituent. Optimal conditions employed

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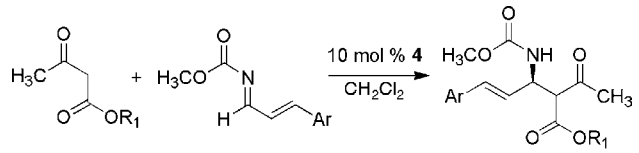
for 1,3-dicarbonyls **6a**−**d** and methyl benzylidene carbamate **7a** were applicable to a variety of acyl imines **7b**−**d** (entries 7−10 and 15−20). The reactions of both electron-rich and electron-poor aromatic acyl imines afforded products in high diastereomeric excess (92−99%) and high enantiomeric excess (90−99%). Lower temperatures were necessary to achieve high enantioselectivity for highly electrophilic acyl imines **7c** and **7d** (entries 15−20).

A selection of 1,3-dicarbonyl compounds were evaluated in the asymmetric Mannich reaction using the general reaction conditions. A cyclic six-membered ring-containing β-keto ester and α-alkyl-substituted methyl-2-methylacetoacetate were employed in the Mannich reaction with acyl imine **7a**. Although these nucleophiles reacted with high levels of diastereoselectivity (>90% de), the reaction afforded the products in low isolated yields and in essentially racemic form.

The general reaction conditions also proved effective in the asymmetric Mannich reactions of allyl benzylidene carbamate **8a**,**b** to afford the products in similar levels of selectivities (Table 2, entries 4−6, 11−13). In all cases, the reactions proceeded cleanly with nearly quantitative yields in excellent enantioselectivity.

We added a new class of electrophiles to our investigation in the Mannich reaction: aryl-propenyl acyl imines **17a**,**b** (Tables 3 and 4). This substrate class was synthesized using

Table 3. Asymmetric Mannich Reactions of β-Keto Esters[a]



16a: R_1 = allyl
16b: R_1 = CH_3

17a-b

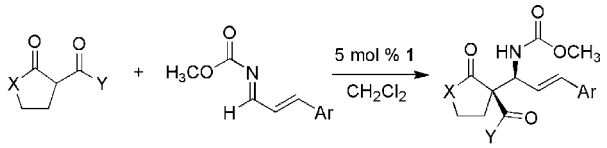
18, 19

entry	Ar	nucleophile	yield (%)[b]	de (%)[c]	ee (%)[d]
1	Ph (**17a**)	**16a**	**18a** (98)	0	95
2	Ph (**17a**)	**16b**	**18b** (97)	67	92
3	2-C_4H_3O (**17b**)	**16a**	**19a** (98)	0	90
4	2-C_4H_3O (**17b**)	**16b**	**19b** (98)	0	90

[a] Mannich reactions were carried out using 0.5 mmol of nucleophile **16a**,**b** and 0.5 mmol of acyl imines **17a**,**b** in CH_2Cl_2 (0.5 M) for 2−3 h, at −78 °C under N_2, followed by flash chromatography on silica gel. [b] Isolated yield of the Mannich reaction product. [c] Determined by NMR analysis. [d] Determined by chiral HPLC analysis: see Supporting Information for details.

procedures similar to the preparation of simple benzylidene carbamates.[9] We first investigated β-keto esters **16a**,**b** (Table

Table 4. Asymmetric Mannich Reactions of β-Keto Esters and β-Diketones[a]



6a: X = CH_2, Y = OCH_3
6b: X = CH_2, Y = OCH_2CH_3
6c: X = CH_2, Y = CH_3
6d: X = O, Y = CH_3

17a-b

20, 21

entry	Ar	nucleophile	yield (%)[b]	de (%)[c]	ee (%)[c]
1	Ph (**17a**)	**6a**	**20a** (98)	90	99
2	Ph (**17a**)	**6b**	**20b** (98)	94	98
3	Ph (**17a**)	**6c**	**20c** (98)	95	99
4	Ph (**17a**)	**6d**	**20d** (88)	38	98
5	2-C_4H_3O (**17b**)	**6a**	**21a** (98)	99	99
6[d]	2-C_4H_3O (**17b**)	**6b**	**21b** (98)	98	93
7	2-C_4H_3O (**17b**)	**6c**	**21c** (98)	94	98

[a] Mannich reactions were carried out using 0.5 mmol of nucleophile **6a**,**b** and 0.5 mmol of acyl imines **17a**,**b** in CH_2Cl_2 (0.5 M) for 2−3 h, at −78 °C under N_2, followed by flash chromatography on silica gel. [b] Isolated yield of the Mannich reaction product. [c] Determined by chiral HPLC analysis: see Supporting Information for details. [d] Reaction was run at −85 °C.

3) as nucleophiles. The optimal catalyst for these reactions was determined to be dihydroquinidine **4**. Reactions carried out using 10 mol % of **4** at −78 °C for 3 h in CH_2Cl_2 afforded the Mannich products in high yields and enantioselectivities but with no diastereoselectivity.[10] However, cinchonine **1** was found to be the optimal catalyst for Mannich reactions of 1,3-dicarbonyl compounds **6a**−**d** with this class of acyl imines. The reaction conditions required 5 mol % of **1** at −78 °C (Table 4). For the substrates we examined, the Mannich products were obtained in excellent diastereo- and enantioselectivities.

The relative stereochemistry of the products obtained from the cinchona alkaloid-catalyzed diastereoselective Mannich reactions was established by comparison to known compounds in the literature[2f] and confirmed by X-ray crystallographic analysis. Crystallographic structural determination of Mannich product **15a** confirmed the syn diastereoselectivity of the reaction. Absolute stereochemistry was assigned as (2*R*,1*S*) by comparison of optical rotations of synthetic derivatives described in the literature.[2f,11]

The high degree of selectivity observed in the reaction of methyl 2-oxocyclopentanecarboxylate **6a** with acyl imines indicates a catalyst-associated complex with specific steric requirements.[12] On the basis of the results we obtained from

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(10) Products yielded from dihydroquinidine-catalyzed reactions have the same stereochemistry to reactions catalyzed by cinchonine.

(11) Karlsson, S.; Högber, H.-E. *Eur. J. Org. Chem.* **2003**, 2782. See Supporting Information for the full analysis.

our experiments, we have developed a model that accounts for the observed diastereo- and enantioselectivity (Figure 2).

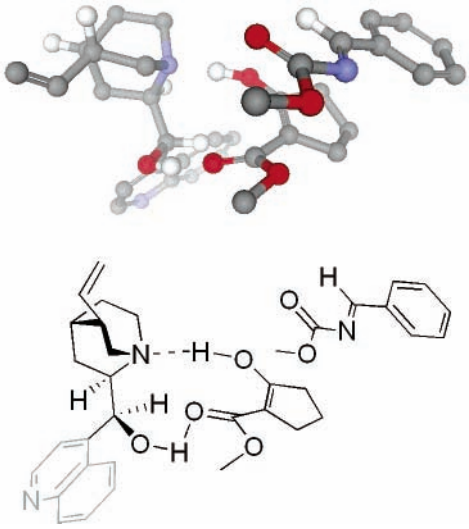

Figure 2. Proposed catalytically active cinchonine/methyl 2-oxocyclopentanecarboxylate enol tautomer complex (MMFF) approaching the *re*-face of methyl benzylidenecarbamate in the formation of (*R*,*S*)-**9**.

We first considered the enol tautomer of methyl 2-oxocyclopentanecarboxylate as the reactive intermediate in the Mannich reaction. A MMFF conformation search[13,14] identified the lowest-energy conformer of the enol form of **6a** complexed with cinchonine **1**.

The ground-state conformation of methyl benzylidene carbamate **7a** was calculated and modeled in a reactive conformation with the cinchonine/enol complex. The bifunctional nature of the catalyst as a hydrogen bond donor and acceptor is depicted by the coordination structure illustrated in Figure 2.[15,16] Consistent with this observation, use of the O-acetylated cinchonine catalyst in the reaction affords the product in lower enantioselectivity (<40% ee). Furthermore, approach of the acyl imine on the *si*-face of the enol is partially blocked by the quinoline ring. This model provides insight into the factors that result in a selective reaction.[17] Furthermore, we will use the model to design catalysts for organocatalytic Mannich reactions that have proven difficult to catalyze enantioselectively.

In summary, we have developed a highly diastereo- and enantioselective direct Mannich reaction of β-keto esters to acyl imines catalyzed by cinchonine and cinchonidine. A model has been proposed for the reaction that accounts for the observed selectivities. Continued investigations include the expansion of the current methodology and synthetic utility of the products.

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Supporting Information Available: Experimental procedures, characterization data, chiral chromatographic analysis, and crystal structure data for **15a**, **15c**, and **20c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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