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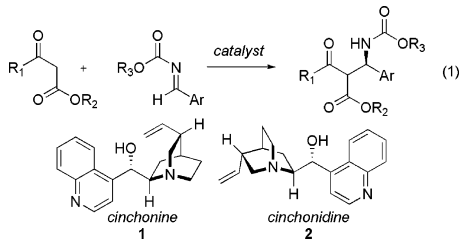
Asymmetric Mannich Reactions of β-Keto Esters with Acyl Imines Catalyzed by Cinchona Alkaloids

Sha Lou, Brandon M. Taoka, Amal Ting, and Scott E. Schaus*

Department of Chemistry and Center for Chemical Methodology and Library Development, Life Science and Engineering Building, Boston University, 24 Cummington Street, Boston, Massachusetts 02215

Received June 7, 2005; E-mail: seschaus@bu.edu

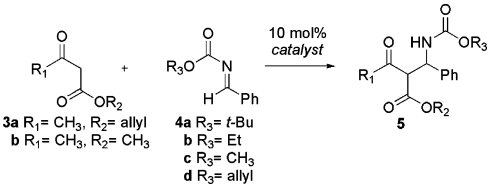
Highly functionalized amine-containing building blocks in enantioenriched form are valuable starting materials for asymmetric synthesis.[1] The asymmetric direct Mannich reaction[2] is an attractive approach toward the construction of these building blocks.[3] In particular, the direct addition of β-keto esters to imines affords multifunctional secondary amines.[4] We proposed a chiral base-mediated direct addition of β-keto esters to acyl imines.[5] The cinchona alkaloids are effective organic chiral bases capable of promoting a range of nucleophilic reactions in an asymmetric manner,[6] including alcoholysis of anhydrides,[7] cyanation of carbonyl-containing compounds,[8] aza-Henry reactions,[9] conjugate additions to ynones,[10] chalcones,[11] nitroolefins,[12] and vinyl sulfones.[13] Herein, we report the enantioselective addition of β-keto esters to acyl aryl imines catalyzed by the cinchona alkaloids cinchonine and cinchonidine.



We initially evaluated the use of cinchona alkaloids as the catalyst in the asymmetric Mannich reaction of allyl acetoacetate **3a** with acyl imines (Table 1). The reaction of **3a** with *tert*-butyl benzylidene carbamate **4a** catalyzed by cinchonine **1** in CH_2Cl_2 at −35 °C afforded the corresponding β-amino ester **5a** in 85% isolated yield of a 3:1 mixture of diastereomers (entry 1, Table 1). For purposes of analysis, the mixture of diastereomers was subjected to decarboxylation using Pd(II) and methyl acetoacetate to yield the corresponding ketone in 87 and 80% ee. In comparison, the quinine-catalyzed reaction of **3a** with **4a** afforded the product in 1:1 dr and 60% ee. Higher enantioselectivities were obtained in the reactions of **3a** with ethyl benzylidine carbamate **4b** and **3a** with methyl benzylidine carbamate **4c** (86 and 92% ee, respectively, entries 3 and 4) although in low diastereomeric ratios. The reaction of **3a** with **4c** using cinchonidine as the catalyst afforded the product in similar diastereomeric ratio and enantiomeric excess but with the opposite sense of enantioselectivity (entry 5). Other cinchona alkaloids, such as quinine and quinidine, were not as effective at promoting the reaction enantioselectively (entries 6 and 7).

The cinchonine- and cinchonidine-promoted asymmetric Mannich reaction of β-keto esters with acyl imines was also found to be equally effective with methyl acetoacetate **3b** as the nucleophile. However, the reaction was highly diastereoselective; the addition of **3b** to **4c** afforded the product **5d** in 20:1 dr and in 94% ee (entry 8). The enantiomeric excess of product derived from **3b** was determined by selective conversion to the *Z*-enamine with benzylamine

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



entry	catalyst	ester	imine	yield (%)[b]	dr[c]	% ee[d]
1	**1**	**3a**	**4a**	**5a** (85)	3:1	80
2	quinine	**3a**	**4a**	**5a** (86)	1:1	60
3	**1**	**3a**	**4b**	**5b** (91)	2:1	86
4	**1**	**3a**	**4c**	**5c** (99)	3:1	92
5	**2**	**3a**	**4c**	**5c** (96)	2:1	90
6	quinine	**3a**	**4c**	**5c** (90)	1:1	60
7	quinidine	**3a**	**4c**	**5c** (95)	1:1	65
8	**1**	**3b**	**4c**	**5d** (99)	20:1[e]	94
9	**2**	**3b**	**4c**	**5d** (95)	20:1	90
10	quinine	**3b**	**4c**	**5d** (97)	4:1	60
11	quinidine	**3b**	**4c**	**5d** (98)	5:1	65
12	**1**	**3b**	**4d**	**5e** (91)	2:1	90

[a] Reactions were carried out using 0.5 mmol ester **3**, 0.5 mmol imine **4**, and 0.05 mmol catalyst in CH_2Cl_2 (0.5 M) at −35 °C for 16 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Enantiomeric excess of diastereomeric mixture determined by chiral HPLC analysis; see Supporting Information. [e] The major isomer is (1*R*,2*S*).

using $HC(OCH_3)_3$ and cat. $Yb(OTf)_3$. The asymmetric Mannich reaction was similarly diastereo- and enantioselective using cinchonine as the catalyst (entry 9), and quinine and quinidine were not as effective at promoting the reaction (entries 10 and 11). Last, the reaction of **3b** with allyl benzylidene carbamate **4d** was not diastereoselective, but afforded the product in 90% ee.

The reaction conditions that proved optimal for β-keto ester **3a**, benzylidene carbamate **4c**, and cinchonine as the catalyst (Table 1, entry 4) were found to be general for a variety of aryl methyl carbamate imines (Table 2).[14] While most aryl imines readily formed the Mannich products with **3a** in good isolated yields (81−99%) and good enantioselectivities (80−96% ee, Table 2), the products were isolated as a mixture of diastereomers. In contrast, the direct Mannich products from the reaction of methyl acetoacetate **3b** with aryl imines were isolated in 10−20:1 diastereomeric ratios (entries 1−3 and 8, Table 3) and good enantioselectivities (81−94% ee). Neither the diastereomeric ratio nor the percent enantiomeric excess eroded when the isolated Mannich products were exposed to the reaction conditions, indicating that the observed results reflect the imine addition selectivity. However, not all electrophiles afforded the corresponding Mannich products with **3b** in diastereomeric ratios greater than 1:1, but in these cases, the mixture of diastereomers was obtained in ≥90% ee (Table 2, entries 4−7).

The asymmetric Mannich reaction provided ready access to highly functionalized building blocks, the synthetic utility of which

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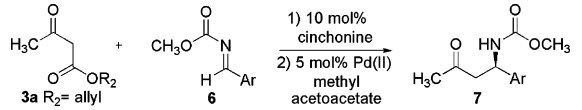
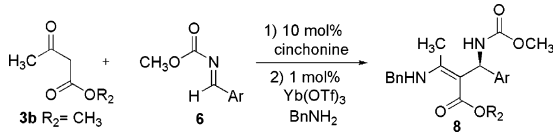
Table 2. Asymmetric Mannich Reactions of β-Keto Ester **3a**[a]



entry	Ar	% yield[b]	dr[c]	yield (%)[d]	% ee[e]
1	Ph	99	3:1	**7a** (80)	92
2	4-Cl−C_6H_4	93	1:1	**7b** (80)	83
3	4-F−C_6H_4	98	1:1	**7c** (97)	93
4	3-F−C_6H_4	98	1:1	**7d** (84)	91
5	3-CH_3−C_6H_4	96	1:1	**7e** (81)	96
6	3-CF_3−C_6H_4	99	1:1	**7f** (83)	90
7	3,4-$(OCH_2O)C_6H_3$	95	1:1	**7g** (81)	80
8	2-C_4H_3O	81	1:1	**7h** (96)	93
9	2-C_4H_3S	84	1:1	**7i** (82)	92
10	2-naphthyl	96	5:1	**7j** (83)	95

[a] Mannich reactions were carried out using 0.5 mmol ester **3**, 0.5 mmol imine **6**, and 0.05 mmol cinchonine **1** in CH_2Cl_2 (0.5 M) at −35 °C for 16 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield of Mannich reaction product. [c] Determined by ^{1}H NMR analysis. [d] Isolated yield of **7**. [e] Enantiomeric excess of **7** determined by chiral HPLC analysis.

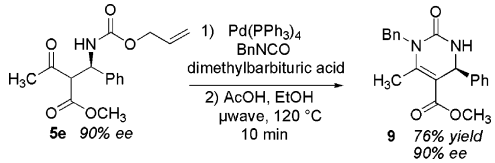
Table 3. Asymmetric Mannich Reactions of β-Keto Ester **3b**[a]



entry	Ar	% yield[b]	dr[c]	yield (%)[d]	% ee[e]
1	Ph	99	20:1[f]	**8a** (95)	94
2	4-Cl−C_6H_4	81	10:1	**8b** (83)	81
3	4-F−C_6H_4	87	10:1	**8c** (82)	91
4	3-F−C_6H_4	99	1:1	**8d** (82)	92
5	3-CH_3−C_6H_4	88	1:1	**8e** (96)	90
6	2-C_4H_3O	83	1:1	**8f** (84)	90
7	2-C_4H_3S	86	1:1	**8g** (88)	93
8	2-naphthyl	95	20:1	**8h** (96)	94

[a] Mannich reactions were carried out using 0.5 mmol ester **3**, 0.5 mmol imine **6**, and 0.05 mmol cinchonine **1** in CH_2Cl_2 (0.5 M) at −35 °C for 16 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield of Mannich reaction product. [c] Determined by ^{1}H NMR analysis. [d] Isolated yield of **8**. [e] Enantiomeric excess of **8** determined by chiral HPLC analysis. [f] The major isomer is (1*R*,2*S*).

Scheme 1. Synthesis of Enantioenriched Dihydropyrimidone



merited exploration. We first considered **5e** as starting material for the asymmetric synthesis of dihydropyrimidones (Scheme 1).[15] Although dihydropyrimidones are useful biological and pharmacological research tools, few procedures exist for their construction in enantioenriched form.[15b,16]

Treatment of **5e** with catalytic $Pd(PPh_3)_4$ and dimethyl barbituric acid as the allyl scavenger in the presence of benzyl isocyanate afforded the corresponding unsymmetrical urea in 85% isolated yield. Ring closure to the pyrimidone was promoted by AcOH in EtOH under microwave conditions to afford the 5-benzyl pyrimidone **8** in 95% yield and 90% ee.

The diastereomerically enriched Mannich product **5d** was easily converted to the corresponding β-amino alcohol using a reduction/deprotection sequence (Scheme 2). Reduction of **5d** using $Zn(BH_4)_2$ at −78 °C afforded the amino alcohol in 95% yield and >20:1 dr. The methyl carbamate was deprotected via a two-step process using

Scheme 2. Synthesis of β-Amino Alcohols

TMSI in CH_3CN followed by treatment with MeOH to yield amino alcohol **10** (86% over three steps).

In summary, we have developed a diastereo- and enantioselective direct Mannich reaction of β-keto esters to acyl aryl imines catalyzed by cinchonine and cinchonidine. We have used the products from the reaction in the synthesis of enantioenriched dihydropyrimidones and β-amino alcohols. Ongoing 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, and chiral chromatographic analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Kleinmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (c) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *113*, 4507. (d) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (e) Sewald, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5794. (f) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290.

(2) (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (c) Zhuang, W.; Sabby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476. (d) Marigo, M.; Kjaersgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem.—Eur. J.* **2003**, *9*, 2359. (e) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (f) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (g) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677. (h) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (i) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777.

(3) Reviews: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Denmark, S.; Nicaise, J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 954. (c) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, *4*, 563. (d) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.

(4) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525.

(5) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896.

(6) Reviews: (a) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (b) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (c) Tian, S.-K.; Chen, Y. G.; Hang, J. F.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.

(7) (a) Hang, J.; Tian, S.-K.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 12696. (b) Hang, J.; Li, H.; Deng, L. *Org. Lett.* **2002**, *4*, 3321. (c) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870.

(8) (a) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900. (b) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195.

(9) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.

(10) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672.

(11) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

(12) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.

(13) Li, H.; Song, J.; Liu, M.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948.

(14) Aliphatic acyl imines of this type are not readily afforded according to the literature procedure: Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem.—Eur. J.* **1997**, *3*, 1691.

(15) Prepared from the Biginelli reaction: (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360. Reviews: (b) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1. (c) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.

(16) Reviews: (a) Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630. (b) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.

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