Direct enantio- and diastereoselective Mannich reactions of malonate and β-keto esters with *N*-Boc and *N*-Cbz aldimines catalysed by a bifunctional cinchonine derivative†

A. Louise Tillman,[a] Jinxing Ye[b] and Darren J. Dixon*[b]

Received (in Cambridge, UK) 4th November 2005, Accepted 20th December 2005
First published as an Advance Article on the web 1st February 2006
DOI: 10.1039/b515725k

A highly enantioselective Mannich reaction between malonate esters and *N*-Boc and *N*-Cbz aldimines, catalysed by a bifunctional cinchonine derivative, has been developed; extension of this methodology to encompass the use of 2-substituted-1,3-dicarbonyl nucleophiles allows the formation of adjacent stereocentres, one of which is quaternary, in high relative and absolute stereocontrol.

The β-amino acid motif is found in a vast array of biologically active natural products and pharmaceutical compounds, as well as pseudopeptide materials with unusual structural properties. In addition these compounds are useful chiral starting materials in the synthesis of bioactive amine containing natural products such as those belonging to the alkaloid family.[1]

For their enantioselective synthesis, the Mannich reaction has revealed itself as an efficient and powerful method allowing the generation of up to two stereogenic centres in a single carbon–carbon bond-forming event.[2] Asymmetric, metal catalysed Mannich reactions have been shown to be highly successful and are well documented in the literature.[3,4] Lately organocatalytic approaches have been introduced[5,6] to circumvent the problems commonly associated with conventional metal catalysis.[7] For example, Uraguchi and Terada have developed a new BINOL-derived phosphoric acid to catalyse the addition of acetylacetone to *N*-Boc imines in a highly enantioselective fashion.[8] More recently, Jørgensen *et al.* have reported a highly enantio- and diastereoselective Mannich reaction using α-substituted α-cyanoacetates, catalysed by cinchonine derived catalyst $(DHQD)_2PYR$.[9a] Also Schaus *et al.* have used cinchonine itself to catalyse the highly enantioselective addition of β-keto esters to *N*-methyloxycarbonyl imines.[9b]

With the goal of creating a technically simple, scalable and metal free Mannich reaction, we became interested in the possibility of identifying an effective asymmetric organic catalyst for the addition of 1,3-dicarbonyls to *N*-acyl aldimines. The commercial availability of the nucleophilic components and the facile synthesis of *N*-Boc and *N*-Cbz arylaldimines[10] make this an ideal strategy for the synthesis of enantiomerically enriched *N*-protected β-amino carbonyl compounds. This approach also provides the potential to generate β-amino acid derivatives bearing α-quaternary centres in high relative and absolute control.

We recently reported thiourea **1** (Fig. 1) to be a highly selective catalyst for the enantioselective conjugate addition of malonate nucleophiles to nitro olefins.[11,12] This catalyst emerged from our search for new organic, asymmetric Brønsted base/Brønsted acid bifunctional catalysts based around the relatively rigid 9-amino(9-deoxy) *epi-Cinchona* alkaloid skeleton.[13] It was envisaged that the bridgehead nitrogen in **1** would activate the nucleophile whilst the thiourea moiety would simultaneously activate and organize the *N*-acyl imine through hydrogen bonding interactions. We hoped that the three dimensional spatial arrangement of the components would yield the desired products with high levels of stereocontrol.

Initially we evaluated the use of catalyst **1** in the addition of acetylacetone **2** to *N*-Boc benzaldimine **3**. When the reaction was performed in toluene at room temperature in the presence of 10 mol% **1**, product **6** was isolated in quantitative yield with an encouraging 37% ee.[14] Further tuning of the conditions found the reaction to be optimal when performed in toluene at −78 °C for 72 h, producing **6** in quantitative yield and 82% ee (Table 1). Variation of the aldimine *N*-protecting group revealed that *N*-Cbz benzaldimine **4** was also an excellent substrate, affording **7** in 73% yield and 86% ee. However a significant drop in enantioselectivity was observed when *N*-ethyloxycarbonyl imine **5** was used as the electrophile.[15]

Having established thiourea **1** as an effective catalyst for this reaction type, a range of commercially available malonate esters was investigated as potential nucleophilic substrates. In all cases, good to excellent yields of the desired products were obtained (Table 2). However the enantioselectivity dropped when the size of the alkyl group on the ester was increased. Dimethyl and diethyl

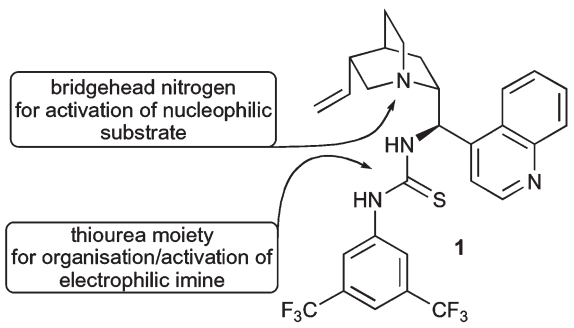
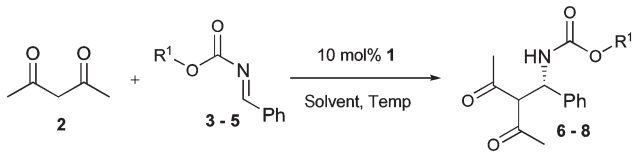


Fig. 1 Bifunctional catalyst **1**.

[a]*University of Cambridge, Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW*
[b]*School of Chemistry, The University of Manchester, Oxford Road, Manchester, UK M13 9PL. E-mail: Darren.Dixon@manchester.ac.uk; Tel: +44 (0) 161 275 1426*
† Electronic supplementary information (ESI) available: Details of the procedure and spectral data for all products and HPLC traces. See DOI: 10.1039/b515725k

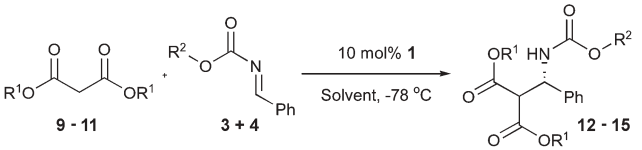
Table 1 Preliminary investigations into the addition of acetylacetone **2** to imines **3–5** in the presence of bifunctional catalyst **1**



Imine	R^1	Solvent	Temp/°C	Yield (%)[a]	ee (%)[b]	Product
3	*t*-Bu	Toluene	rt	>99	37	**6**
3	*t*-Bu	Toluene	−78	>99	82	**6**
3	*t*-Bu	DCM	−78	94	64	**6**
3	*t*-Bu	Et_2O	−78	87	76	**6**
4	Bn	Toluene	−78	73	86	**7**
5	Et	Toluene	−78	>99	ND[c]	**8**

[a] Isolated yields after column chromatography. [b] Enantiomeric excess was determined by HPLC analysis. [c] Incomplete separation was attained for this compound—the ee was estimated to be around 50%.

Table 2 Addition of malonates **9–11** to imines **3** and **5** in the presence of bifunctional catalyst **1**



Malonate	R^1	R^2	Solvent	Yield (%)[a]	ee (%)[b]	Product
9	Me	*t*-Bu	DCM	76	87	**12**
9	Me	*t*-Bu	Toluene	>99	89	**12**
10	Et	*t*-Bu	Toluene	96	78	**13**
11	*t*-Bu	*t*-Bu	Toluene	81	7	**14**
9	Me	Bn	Toluene	86	92	**15**

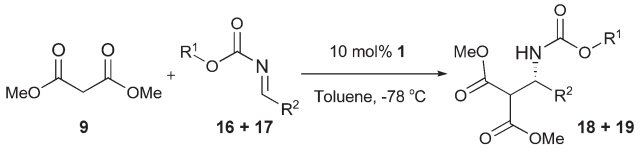
[a] Isolated yields after column chromatography. [b] Enantiomeric excess was determined by HPLC analysis.

malonate additions to **3** gave **12** and **13** in 89% and 78% ee respectively, but little stereoinduction was observed when the same reaction was performed with di-*tert*-butyl malonate; **14** was afforded in only 7% ee. Interestingly, a slightly improved enantioselectivity was observed for the addition to *N*-Cbz imine **4** (92% ee, entry 5 of Table 2) when compared to the *N*-Boc imine (89% ee, entry 2). The high level of stereoinduction obtained in both cases highlights the practical utility of the chemistry; *useful and orthogonal N-protecting groups can be installed directly into the β-amino ester products*.[16]

Investigations into the scope of this reaction showed it to be general for a wide range of *N*-Boc and *N*-Cbz protected *ortho*-, *meta*- and *para*-substituted aromatic and heteroaromatic aldimines (Table 3). In general, the products **18** and **19** were formed in high yields (81–99%) and excellent enantiomeric excess (83–97%). More specifically, entries 5, 7 and 8 highlight the power of this chemistry; *N*-Cbz imines bearing the structurally and electronically varied 2-furanyl, 1-naphthyl and *o*-chlorophenyl all yielded their respective products with 97% ee.

It was decided to extend this methodology to encompass the use of 2-alkyl-1,3-dicarbonyls as nucleophiles, leading to the formation

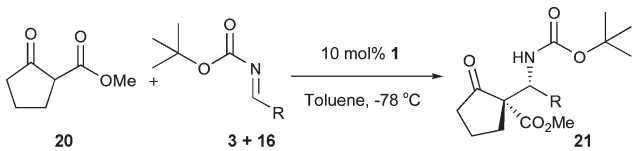
Table 3 Scope of the asymmetric addition of dimethyl malonate **9** to *N*-Boc and *N*-Cbz arylaldimines **16** and **17** catalysed by **1**



Imine	R^1	R^2	Yield (%)[a]	ee (%)[b]	Product
16a	*t*-Bu	2-Furanyl	95	94	**18a**
16b	*t*-Bu	2-Naphthyl	85	96	**18b**
16c	*t*-Bu	*p*-ClC_6H_4	85	87 (97)[c]	**18c**
16d	*t*-Bu	*m*-$MeOC_6H_4$	89	88	**18d**
17a	Bn	2-Furanyl	96	97	**19a**
17b	Bn	3-Pyridyl	81	83	**19b**
17c	Bn	1-Naphthyl	>99	97	**19c**
17d	Bn	*o*-ClC_6H_4	93	97	**19d**

[a] Isolated yields after column chromatography. [b] Enantiomeric excess was determined by HPLC analysis. [c] Enantiomeric excess after one recrystallisation from hexane.

Table 4 Enantio- and diastereoselective additions of methylcyclopentanone-2-carboxylate **20** to imines catalysed by **1**



R	Yield (%)[a]	dr	ee (%)[b]	Product
Ph	70	16 : 1	85	**21a**
2-Naphthyl	83	20 : 1	87	**21b**
2-Furanyl	97	18 : 1	84	**21c**

[a] Isolated yields after column chromatography. [b] Enantiomeric excess was determined by HPLC analysis.

of stereogenic quaternary α-centres. Accordingly, catalyst **1** was used to promote the reaction between methyl cyclopentanone-2-carboxylate **20** and a selection of imines using the optimised reaction conditions. The *N*-Boc imines were identified as the substrates of choice and in all cases products **21** were formed in good yield (70–97%) and with high levels of diastereocontrol (16 : 1 to 20 : 1 dr) (Table 4). Furthermore the enantiomeric excess of the major diastereomer was uniformly good (84–87%). The relative stereochemistry of the major diastereomer was unambiguously determined by single crystal X-ray diffraction of **21b** (Fig. 2).‡

A simple one step dealkyl, decarboxylation was performed on Mannich products **12** and **15**, to afford the corresponding β-amino esters **22** and **23** in good yield (Scheme 1) without observable

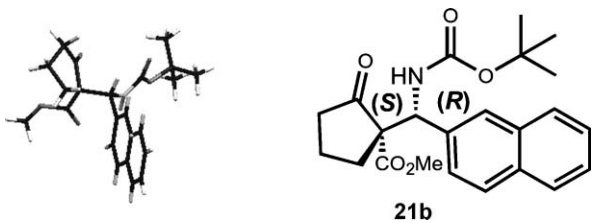
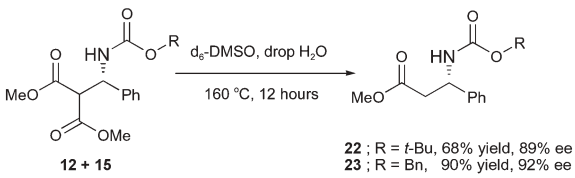


Fig. 2 Single crystal X-ray structure of **21b**.



Scheme 1 Racemisation-free dealkyl, decarboxylation of Mannich products **12** and **15**.

racemisation. As well as demonstrating the synthetic utility of this methodology, synthesis of **22** and **23** allowed us to confirm the absolute stereochemistry of the products of these reactions as (*S*) by comparison of their specific rotations with literature values.[17]

In summary, a bifunctional cinchonine derived catalyst **1** has been found to efficiently promote the highly enantio- and diastereoselective addition of 1,3-dicarbonyls to *N*-Boc and *N*-Cbz aldimines. This provides an efficient synthesis of β-amino esters containing up to two adjacent stereocentres, one of which can be quaternary. Further investigations into the application of **1** in new and powerful enantioselective reactions are currently in progress and the results will be reported in due course.

We gratefully acknowledge the Sims Fund, University of Cambridge, for a scholarship (to A. L. T.) and the Royal Society & FCO Chevening China Fellowship (to J. Y.). We are also indebted to the EPSRC National Mass Spectrometry Service Centre, Swansea, UK for analysis, Dr John Davies for X-ray analysis and Dr Stuart Warren for the use of a chiral stationary phase HPLC column.

Notes and references

‡ Crystal data for **21b**. $C_{23}H_{27}N_1O_5$, M = 397.46, orthorhombic, a = 10.8665(3), b = 11.1927(3), c = 34.5493(12) Å, U = 4202.1(2) Å^3, T = 180(2) K, space group $P2(1)2(1)2(1)$, Z = 8, μ(Mo-Kα) = 0.08 8 mm^{-1}, 5309 reflections measured. The final w$R(F^2)$ was 0.1389 (all data). The Flack parameter was 0(2). CCDC 289062. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515725k

1 (*a*) E. F. Kleinmann, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Flemming, Pergamon Press, New York, 1991, vol. 2, ch. 4.1; (*b*) *Enantioselective Synthesis of β-Amino Acids*, ed. E. Juaristi, Wiley-VCH, New York, 1997; (*c*) P. A. Magriotis, *Angew. Chem., Int. Ed.*, 2001, **40**, 4377–4379; (*d*) M. Liu and M. P. Sibi, *Tetrahedron*, 2002, **58**, 7991–8035; (*e*) J. A. Ma, *Angew. Chem., Int. Ed.*, 2003, **42**, 4290–4299; (*f*) N. Sewald, *Angew. Chem., Int. Ed.*, 2003, **42**, 5794–5795.

2 (*a*) S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069–1094; (*b*) M. Benaglia, M. Cinquini and F. Cozzi, *Eur. J. Org. Chem.*, 2000, 563–572; (*c*) A. Córdova, *Acc. Chem. Res.*, 2004, **37**, 102–112.

3 Selected examples: (*a*) H. Ishitani, M. Ueno and S. Kobayashi, *J. Am. Chem. Soc.*, 1997, **119**, 7153–7154; (*b*) E. Hagiwara, A. Fujii and M. Sodeoka, *J. Am. Chem. Soc.*, 1998, **120**, 2474–2475; (*c*) D. Ferraris, B. Young, T. Dudding and T. Lectka, *J. Am. Chem. Soc.*, 1998, **120**, 4548–4549; (*d*) S. Xue, S. Yu, Y. H. Deng and W. D. Wulff, *Angew. Chem., Int. Ed.*, 2001, **40**, 2271–2274; (*e*) S. Kobayashi, T. Hamada and K. Manabe, *J. Am. Chem. Soc.*, 2002, **124**, 5640–5641; (*f*) N. S. Josephsohn, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2004, **126**, 3734–3735.

4 Selected direct Mannich reaction: (*a*) S. Yamasaki, T. Iida and M. Shibasaki, *Tetrahedron Lett.*, 1999, **40**, 307–310; (*b*) K. Juhl, N. Gathergood and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 2995–2997; (*c*) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 1525–1529; (*d*) T. Yoshida, H. Morimoto, N. Kumagai, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **44**, 3470–3474; (*e*) S. Harada, S. Handa, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4365–4368.

5 Reviews on asymmetric organocatalysis: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726–3748; (*b*) B. List, *Tetrahedron*, 2002, **58**, 5573–5590; (*c*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138–5175; (*d*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719–724; (*e*) for the pioneering proline-catalysed asymmetric Mannich reaction see: B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336–9337.

6 Asymmetric organocatalysed Mannich reaction with ketene silyl acetal: (*a*) A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964–12965; (*b*) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566–1568.

7 B. Fubini and L. O. Areán, *Chem. Soc. Rev.*, 1999, **28**, 373–382.

8 D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356–5357.

9 (*a*) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 2896–2899; (*b*) S. Lou, B. M. Taoka, A. Ting and S. E. Schaus, *J. Am. Chem. Soc.*, 2005, **127**, 11256–11257.

10 All *N*-Boc imine substrates were made using the procedure reported by Wenzel and Jacobsen.[6a] *N*-Cbz substrates were synthesized using a method adapted from the Jacobsen procedure (see supporting information†).

11 (*a*) J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, 4481–4483. See also; (*b*) S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367–6370; (*c*) B. Vakulya, S. Varga, A. Csampai and T. Soós, *Org. Lett.*, 2005, **7**, 1967–1969.

12 Selected bifunctional organocatalysis: (*a*) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672–12673; (*b*) T. Okino, S. Nakamura, T. Furukawa and Y. Takemoto, *Org. Lett.*, 2004, **6**, 625–627; (*c*) Y. Hoashi, T. Okino and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 4032–4035; (*d*) T. Okino, Y. Hoashi, T. Furukawa, X. N. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119–125; (*e*) H. M. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906–9907; (*f*) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman and L. Deng, *Angew. Chem., Int. Ed.*, 2005, **44**, 105–108; (*g*) H. Li, J. Song, X. Liu and L. Deng, *J. Am. Chem. Soc.*, 2005, **127**, 8948–8949; (*h*) K. Matsui, S. Takizawa and H. Sasai, *J. Am. Chem. Soc.*, 2005, **127**, 3680–3681; (*i*) M. Shi, L. H. Chen and C. Q. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3790–3800; (*j*) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Muller and J. Lex, *Angew. Chem., Int. Ed.*, 2005, **44**, 807–811; (*k*) A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Muller and J. Lex, *Chem. Commun.*, 2005, 1898–1900; (*l*) A. Lattanzi, *Org. Lett.*, 2005, **7**, 2579–2582.

13 It has recently been reported that the unnatural 9-*epi*-*Cinchona* derived catalysts are more active than those based on the natural *Cinchona* skeleton, see ref. 11*b*.

14 Major enantiomer was (*S*). Confirmed by comparison of HPLC traces for the same compound found in ref. 8.

15 Enantiomeric excess was not determined accurately, as complete separation of enantiomers was not possible. HPLC traces using a Daicel CHIRALCEL OJ, 25 cm × 0.46 cm column indicated an ee *ca.* 50%.

16 These initial results were first disclosed on 20th July 2005 at the 19th International Symposium: Synthesis in Organic Chemistry, University of Oxford.

17 (*a*) **22**: $[\alpha]_D^{25}$ −23.3 (*c* 0.40, $CHCl_3$), Literature value for the opposite enantiomer: $[\alpha]_D^{25}$ +29.9 (*c* 1.40, $CHCl_3$), F. A. Davis and J. M. Szewczyk, *Tetrahedron Lett.*, 1998, **39**, 5951–5954; (*b*) **23**: $[\alpha]_D^{25}$ −13.7 (*c* 0.19, $CHCl_3$), Literature value for the same enantiomer: $[\alpha]_D^{25}$ −15.8 (*c* 0.55, $CHCl_3$), L. Crombie, D. Haigh, R. C. F. Jones and A. R. Mat-Zin, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2047–2054.