Asymmetric Synthesis

Direct Organocatalytic and Highly Enantio- and Diastereoselective Mannich Reactions of α-Substituted α-Cyanoacetates**

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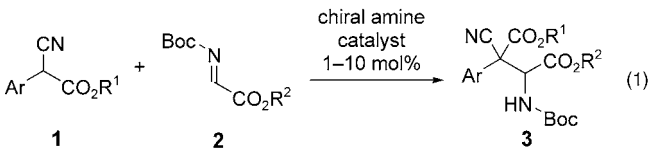

The Mannich reaction is a fundamental C–C bond-forming reaction in synthetic organic chemistry.[1] The development of an asymmetric version of this reaction is of great importance, and would allow chemists to control the configuration of the new stereocenters formed. Several catalytic enantioselective versions of the Mannich reaction have emerged that are based on chiral metal complexes.[2] Recently, metal-free (organocatalytic) systems have complemented and occasionally challenged established metal-based systems.[3] In particular, the use of chiral secondary amines as organocatalysts has been successful for a range of transformations, including the asymmetric Mannich reaction.[4] The latter takes place via a chiral enamine intermediate which undergoes nucleophilic addition to the imine in an enantioselective manner.

Alternatively, chiral tertiary amines have also been successfully applied in various organocatalytic transformations,[3,5] acting as nucleophilic,[6] phase-transfer,[7] and chiral-base catalysts.[8] However, this concept has not yet been applied to the Mannich reaction, despite the potential for the straightforward formation of highly functionalized products that contain attractive structural features.[9]

Recently, we described a highly enantioselective procedure for the direct amination of α-aryl-substituted cyanoacetates and β-dicarbonyl compounds with the chiral tertiary amine catalyst β-isocupreidine, derived in one step from inexpensive and commercially available quinidine.[8d] As the use of α-substituted cyanoacetates as nucleophiles in catalytic asymmetric reactions has been limited so far,[10] we were interested in expanding the methodology to encompass C–C bond-forming reactions. Herein we report the development of a new organocatalytic approach to the direct Mannich reaction, which affords highly functionalized products with two consecutive stereogenic carbon atoms, one of which is quaternary by all-carbon substitution [Eq. (1)].[11] Furthermore, this approach employs an α-imino ester with the readily removable *tert*-butoxycarbonyl (Boc) protecting group on the nitrogen atom.

Owing to the structural similarity of *N*-Boc-protected α-imino esters and dialkyl azodicarboxylates, we first attempted the conditions previously developed for the amination reaction.[8d] The Mannich reaction of a *tert*-butyl cyanoester with β-isocupreidine as the catalyst in toluene gave a high product yield, but with an unexpectedly poor enantioselectivity (< 20 % *ee*) and a negligible diastereoselectivity as well.

Therefore, an extensive screen of reaction conditions was undertaken, and some of the results are listed in Table 1. Variation of the catalyst (entries 1–6) showed the commercially available $(DHQD)_2PYR$ to be the most effective in both enantio- and diastereoselectivity. The nature of the cyanoacetate ester group is critical for the stereochemical outcome of the reaction. A decrease in size from *n*-propyl to methyl caused a slight decrease in the enantioselectivity of the major diastereomer (entries 6 and 7). The bulkier isopropyl group had a beneficial effect (entry 8) but a larger group was less effective (entry 9). Finally, the benzyl group gave optimal results, and the Mannich product was obtained with considerable preference for one of the two possible diastereomers, and with excellent enantioselectivity (96 % *ee*, entry 10). The influence of the structure of the α-imino ester **2** was also evaluated, but was found to be less significant when benzyl cyanoacetates were applied.[12] An increase in temperature caused a decrease in reaction selectivity (entries 11 and 12).

A further optimization of the reaction conditions (entries 13 and 14) showed that CH_2Cl_2 is a better solvent than Et_2O and surprisingly, better than toluene as well. The latter observation differs from what is intuitively expected in asymmetric reactions involving ion pair intermediates—namely that the highest selectivities are obtained in nonpolar, noncoordinating media.[13]

A decrease in catalyst loading is clearly desirable for a catalytic reaction. Although organocatalysis has proven successful in many respects, most of these processes require 10 mol % or more of the catalyst for sufficient product formation and maintenance of stereoselectivity. The reaction reported herein can be performed without notable loss of selectivity even with a catalyst loading of 1 mol % (entries 15 and 16). Finally, a controlled slow addition of the imine electrophile was found to be beneficial (entry 17).

An important advantage of this catalytic stereoselective Mannich reaction is the use of *N*-Boc-protected imines, generated in situ by dehydrobromination of Boc-protected α-bromoglycine esters.[14] A drawback for many reactions of α-imino esters with an electron-withdrawing group (commonly tosyl) on the nitrogen atom has been the subsequent deprotection step.[15] This synthetic problem has been overcome with the present methodology, however, as the Boc protecting group is easily removed.

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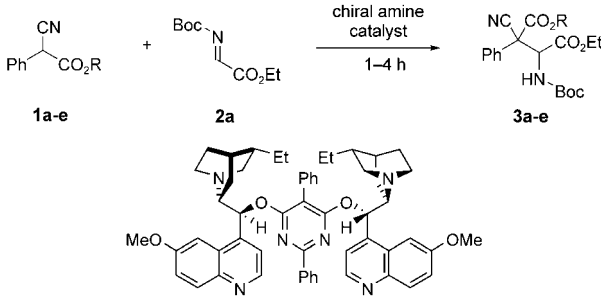
Table 1: Some screening results for the organocatalytic direct Mannich reaction.



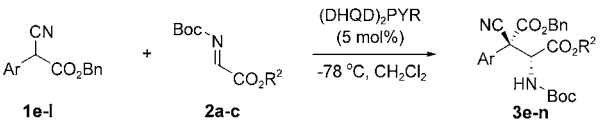
Entry	R	Cat.[a] ([mol%])	*T* [°C]	Solvent	Prod.	d.r.[b]	*ee*[c] [%]
1	*n*Pr (**1a**)	quinine (10)	−78	CH_2Cl_2	**3a**	55:45	29/46
2	*n*Pr (**1a**)	$(DHQD)_2PHAL$ (10)	−78	CH_2Cl_2	**3a**	58:42	40/18
3	*n*Pr (**1a**)	DHQ-MEQ (10)	−78	CH_2Cl_2	**3a**	58:42	41/41[d]
4	*n*Pr (**1a**)	$(DHQD)_2AQN$ (10)	−78	CH_2Cl_2	**3a**	57:43	42/13
5	*n*Pr (**1a**)	DHQD-PHN (10)	−78	CH_2Cl_2	**3a**	58:42	68/58
6	*n*Pr (**1a**)	$(DHQD)_2PYR$ (10)	−78	CH_2Cl_2	**3a**	72:28	85/41
7	Me (**1b**)	$(DHQD)_2PYR$ (10)	−78	CH_2Cl_2	**3b**	69:31	82/67
8	*i*Pr (**1c**)	$(DHQD)_2PYR$ (10)	−78	CH_2Cl_2	**3c**	74:26	90/5
9	*t*Bu (**1d**)	$(DHQD)_2PYR$ (10)	−78	CH_2Cl_2	**3d**	60:40	69/21
10	Bn (**1e**)	$(DHQD)_2PYR$ (10)	−78	CH_2Cl_2	**3e**	87:13	96/38
11	Bn (**1e**)	$(DHQD)_2PYR$ (10)	−40	CH_2Cl_2	**3e**	79:21	91/47
12	Bn (**1e**)	$(DHQD)_2PYR$ (10)	0	CH_2Cl_2	**3e**	67:33	72/29
13	Bn (**1e**)	$(DHQD)_2PYR$ (10)	−50	toluene	**3e**	66:24	90/58
14	Bn (**1e**)	$(DHQD)_2PYR$ (10)	−78	Et_2O	**3e**	73:27	93/28
15	Bn (**1e**)	$(DHQD)_2PYR$ (5)	−78	CH_2Cl_2	**3e**	85:15	93/32
16	Bn (**1e**)	$(DHQD)_2PYR$ (1)	−78	CH_2Cl_2	**3e**	84:16	94/39
17[e]	Bn (**1e**)	$(DHQD)_2PYR$ (5)	−78	CH_2Cl_2	**3e**	89:11	97/32

[a] Catalyst structures available in Supporting Information. [b] Determined by ^1H NMR spectroscopy of the crude product mixture. [c] Determined by CSP-HPLC analysis; values for both diastereomers given (CSP = chiral stationary phase). [d] The opposite enantiomers were obtained in this case. [e] Slow addition of the imine over a period of 30 min.

The optimized conditions were used to evaluate the scope of the Mannich reaction.[16] A series of benzyl α-aryl-α-cyanoacetates **1e–l** were combined with *N*-Boc-protected imines **2a–c** in reactions catalyzed by $(DHQD)_2PYR$ (5 mol%) (Table 2). Substituents present in the *meta* and *para* positions were well-tolerated (entries 2–5), providing the *N*-Boc-protected products in high yields with excellent enantioselectivities of the major diastereomer. Likewise, the polyaromatic 2-naphtyl derivative **1i** is a useful substrate (entry 6), which gave Mannich product **3i** in essentially quantitative yield with 96% *ee* in the major *u*-diastereomer, which was favored by a factor of 88:12 over the minor *l*-diastereomer.[17]

Heteroaromatic and disubstituted aromatic substrates **1j** and **1k** also afforded the Mannich products with satisfactory selectivities (entries 7, 8). Interestingly, the *ortho*-substituted bromocyanoester **1l** displayed anomalous behavior relative to the other substrates. The reaction was still very clean, but favored formation of the *l*-diastereomer instead, and the *u*-diastereomer was obtained with a disappointing 11% *ee* (entry 9). Further developments revealed that a mere change of the reaction solvent from CH_2Cl_2 to toluene drastically changed the stereochemical outcome of the reaction. With toluene as the solvent, the *u*-diastereomer was favored once more, although with low selectivity. Importantly, however, the enantiomeric excess increased to 90%. The different behavior of substrate **1l** was substantiated by the fact that the structure of the α-imino ester electrophile **2** had a significant influence on the diastereoselectivity of the reaction. A change in the ester substituent from an ethyl group in **2a** to an isopropyl group in **2b** improved the reaction selectivity to a value similar to those observed with the other substrates (entry 10). A further increase in the bulk of the ester substituent (to *t*Bu) provided the Mannich product **3n** in quantitative yield and with almost perfect stereoselectivity (entry 11). Importantly, the opposite enantiomer of the Mannich products can also be

Table 2: Direct catalytic Mannich reaction of different benzyl α-aryl cyanoacetates (**1e–l**) with α-imino esters **2a–c**[a].



Entry	Ar	R^2	Prod.	Yield[b] [%]	d.r.[c] (*u*/*l*)	*ee*[d] [%]
1[e]	C_6H_5 (**1e**)	Et (**2a**)	**3e**	98(96)	89:11(79:21)	97(89)
2	4-Cl-C_6H_4 (**1f**)	Et (**2a**)	**3f**	99	80:20	91
3[f]	4-Cl-C_6H_4 (**1f**)	Et (**2a**)	**3f**	99	83:17	94
4	3-Me-C_6H_4 (**1g**)	Et (**2a**)	**3g**	97	86:14	97
5	4-MeO-C_6H_4 (**1h**)	Et (**2a**)	**3h**	97	85:15	96
6	2-naphthyl (**1i**)	Et (**2a**)	**3i**	99	88:12	96
7	2-thienyl (**1j**)	Et (**2a**)	**3j**	89[g]	82:18	92
8	3,4-$(MeO)_2C_6H_3$ (**1k**)	Et (**2a**)	**3k**	97	85:15	97
9	2-Br-C_6H_4 (**1l**)	Et (**2a**)	**3l**	95	18:82	11
10[h]	2-Br-C_6H_4 (**1l**)	*i*Pr (**2b**)	**3m**	98	85:15	98
11[e,i]	2-Br-C_6H_4 (**1l**)	*t*Bu (**2c**)	**3n**	99(99)	98:2(95:5)	98(92)

[a] Reactions performed in CH_2Cl_2 (0.05 M) with **1** (0.1 mmol) and **2** (0.12–0.15 mmol) added by syringe pump (1 h). [b] Yield of the isolated diastereomeric mixture. [c] Determined by ^1H NMR spectroscopy. [d] Determined by CSP-HPLC for the *u*-diastereomer (Supporting Information). [e] Yield, d.r., and *ee* values in parentheses correspond to reactions catalyzed with $(DHQ)_2PYR$ (5 mol%; see text). [f] Reaction performed by slow addition of the imine over 3 h. [g] Slight decomposition of the starting cyanoester was observed. [h] Reaction carried out in toluene. [i] Reaction carried out in toluene with $(DHQ)_2PYR$ at 10 mol%.

efficiently accessed with commercially available pseudoenantiomeric $(DHQ)_2PYR$ as the catalyst (entries 1 and 11). Alkyl-substituted cyanoacetates also underwent the Mannich reaction to afford high yields of the corresponding products. However, lower enantio- and diastereoselectivities were observed.[18]

The absolute and relative configurations of the Mannich reaction products were assigned by X-ray crystallographic analysis.[19] Compound **3o** was prepared under the standard reaction conditions discussed above. Recrystallization from a mixture of TBME and hexane precipitated the minor diastereomer (TBME = *tert*-butyl methyl ether). The mother liquor was evaporated, and the compound was slowly crystallized from a mixture of EtOAc/hexane to give **3o** as a single stereoisomer (fine colorless needles, mp = 110–111 °C) with the configuration as shown in Figure 1. Through comparison of HPLC traces and NMR spectra, the same configuration for the Mannich products **3e–n** could be inferred.

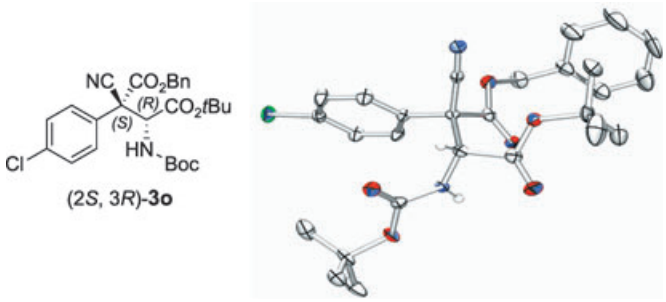
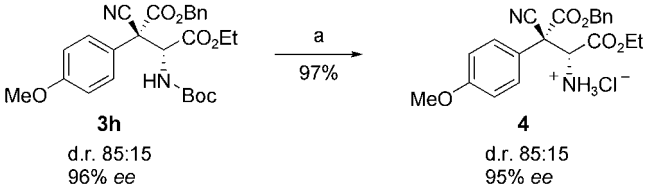


Figure 1. X-ray crystallographic structure of (2*S*,3*R*)-**3o**.

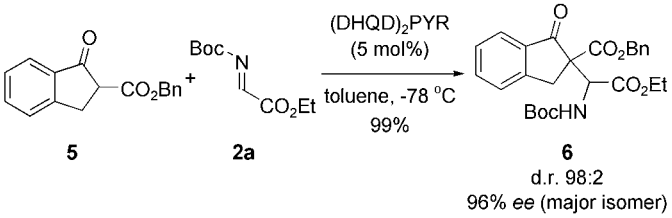
The use of *N*-Boc-protected imines **2** as electrophilic partners in the Mannich reaction allows straightforward deprotection of the products. Under standard conditions, compound **3h** was deprotected to afford the hydrochloride salt **4** in 97% yield, without affecting the diastereomeric or enantiomeric excess values (Scheme 1).



Scheme 1. Removal of the Boc protecting group: a) HCl (4 M) in 1,4-dioxane, room temperature, 5 h.

The substrate tolerance of the catalytic system was further demonstrated by the use of the β-ketoester **5** derived from 1-indanone as the nucleophilic partner in the Mannich reaction (Scheme 2). The reaction smoothly afforded the *N*-Boc-protected Mannich product **6** in high yield and essentially as a single diastereomer. We were pleased to find that the major diastereomer was obtained in 96% *ee*.

In summary, we have reported the first highly enantioselective and diastereoselective Mannich reaction of α-substituted cyanoacetates and a β-ketoester with commercially available $(DHQD)_2PYR$ as the metal-free organic chiral catalyst. An interesting solvent effect was demonstrated in reactions of an *ortho*-bromo-substituted substrate which gave dramatic changes in stereoselectivity. Work is currently underway toward a mechanistic understanding of this system and its use as a synthetic tool in asymmetric synthesis.



Scheme 2. Catalytic enantioselective Mannich reaction of β-ketoester **5** with imine **2a**.

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[16] As noted (Table 2) the reactions were performed on a 0.1-mmol scale. Compound **3h** was also prepared on a 0.5-mmol scale under the optimized conditions with similar results [95% yield, 85:15 (*u*/*l*), and 95% *ee*].

[17] The terms *u* (unlike) and *l* (like) were introduced by Seebach and Prelog as a general way of designating relative configurations in molecules with several chiral centers, particularly those in which terms like *syn*/*anti* or *erythro*/*threo* are not easily adopted; see: D. Seebach, V. Prelog, *Angew. Chem.* **1982**, *94*, 696; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654 – 660.

[18] Up to 61:39 (d.r.) and up to 51% *ee*. This fact has also been observed in other cinchona alkaloid-catalyzed reactions of α-substituted cyanoacetates; see refs. [8b,d].

[19] CCDC 260994 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

