## Hydrogen-Bond-Directed Enantioselective Decarboxylative Mannich Reaction of β-Ketoacids with Ketimines: Application to the Synthesis of Anti-HIV Drug DPC 083\*\*

Hai-Na Yuan, Shuai Wang, Jing Nie, Wei Meng, Qingwei Yao, and Jun-An Ma\*

The decarboxylative Mannich reaction (DMR) of β-ketoacids with imines has emerged as a very important tool for the synthesis of natural products and biologically active compounds. The elegant work of Robinson on the total synthesis of  $(\pm)$ -tropinone represents the first practical example of utilizing the DMR as a key step in organic synthesis.<sup>[1]</sup> Herbert and co-workers<sup>[2]</sup> and Mangla and Bhakuni<sup>[3]</sup> then developed a similar decarboxylative Mannich condensations of  $\beta$ -ketoacids with  $\Delta^1$ -pyrroline and  $\Delta^1$ -piperideine for the synthesis of biologically relevant alkaloids, such as septicine, phenanthroindolizidines, and cryptopleurine. Despite these notable achievements, little progress has been made in the development of an asymmetric version for this important reaction. Recently, the group of Tian developed a chiralauxiliary-based method in which  $\beta$ -ketoacids undergo highly diastereoselective decarboxylative Mannich transformation with optically active 2-(tert-butanesulfinyl-imino)glyoxylates,<sup>[4a]</sup> and Lu and co-workers described a catalytic asymmetric DMR of β-ketoacids with aldimines to afford β-amino ketones with a maximum of ee value of 83 %. [4b] However, all such studies have focused on the aldimine-based electrophiles. In contrast, the use of ketimines as the electrophilic acceptors for the decarboxylative Mannich reactions of βketoacids still remains a formidable challenge and there has been no report in the literature, to date, of such a potentially useful transformation.<sup>[5]</sup>

The obvious benefits that hydrogen-bonding catalysis can offer in asymmetric synthesis have been recognized in recent years.<sup>[6]</sup> A unique characteristic of hydrogen-bonding catalysis is that the catalyst not only activates the reaction partners through hydrogen-bond interactions, but also positions them in close proximity with the desired relative geometry, and as such, the reaction is often facilitated in a synergistic manner, a manner similar to that of enzymatic catalysis. Herein, we report the results of our efforts in developing a hydrogenbond-directed enantioselective decarboxylative Mannich

[*]	HN. Yuan, S. Wang, J. Nie, W. Meng, Prof. JA. Ma
	Department of Chemistry, Tianjin University
	Tianjin 300072 (China)
	E-mail: majun_an68@tju.edu.cn
	Dr. Q. Yao
	Sphinx Scientific Laboratory Corporation
	Sycamore, IL 60178 (USA)
[**]	This work was supported financially by the NSFC (No. 21172170 and 21225208).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201210361. reaction of  $\beta$ -ketoacids by employing cyclic N-acyl ketimines as the electrophilic acceptor (Figure 1). This new reaction was cooperatively promoted by saccharide-based bifunctional organocatalysts. The catalysts contain a tertiary amine and thiourea moieties which simultaneously activate the substrates and are responsible for excellent overall stereochemical control. The potential application of this catalytic asymmetric decarboxylative Mannich reaction was further exemplified in a highly enantioselective synthesis of the anti-HIV drug DPC 083.



Figure 1. Hydrogen-bond-directed enantioselective Mannich reaction of  $\beta$ -ketoacids with ketimines.

Our initial investigation began with the enantioselective decarboxylative Mannich condensation of model substrates 3oxo-3-phenylpropanoic acid (1a) and ketimine 2a (Table 1) in the presence of the saccharide-derived amino thioureas Aa-c (Figure 2), which were developed previously in our laboratory<sup>[7]</sup> as chiral catalysts. To drive the reaction to completion, the  $\beta$ -ketoacid was used in excess as significant amounts of acetophenone, formed from a competing decarboxylation pathway, was recovered during the course of the reaction.<sup>[8]</sup> Under these reaction conditions, the Mannich adduct 3a was obtained in high yield with moderate to good enantioselectivity (Table 1, entries 1-3), with catalyst Ab giving the best performance. Mindful of a detrimental background reaction which could lead to the observed low enantioselectivity, the reaction was performed at a lower temperature, and as expected, the enantioselectivity was improved from 80% ee to 89% ee at 0°C and to 92% ee at

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**Table 1:** Screening of ligands and optimization of the reaction conditions for DMR of 1a with  $2a^{[a]}$ 

C Ph	O O CI OH +	CF <sub>3</sub> N PMB <b>2a</b> Orga s	nocatalys olvent	st ⊂	F <sub>3</sub> C	NH Ph NH O PMB <b>3a</b>
Entry	Catalyst (mol%)	Solvent	Т	t	Yield	ee
			[°C]	[h]	[%] <sup>[b]</sup>	[%] <sup>[c]</sup>
1	<b>Aa</b> (10)	THF	25	12	90	57 ( <del>+</del> )
2	<b>Ab</b> (10)	THF	25	12	96	80 (+)
3	<b>Ac</b> (10)	THF	25	12	92	63 (+)
4	<b>Ab</b> (10)	THF	0	24	90	89 (+)
5	<b>Ab</b> (10)	THF	-20	48	92	92 (+)
6	<b>Ab</b> (10)	THF	-40	120	44	90 (+)
7	Ad (10)	THF	-20	48	99	>99 (+)
8	<b>Ae</b> (10)	THF	-20	48	99	98 (+)
9	<b>Af</b> (10)	THF	-20	48	99	95 (+)
10	<b>B</b> (10)	THF	-20	48	99	98 (+)
11	<b>C</b> (10)	THF	-20	48	99	92 (+)
12	<b>Ad</b> (10)	$CH_2CI_2$	-20	48	61	79 (+)
13	<b>Ad</b> (10)	CHCl3	-20	72	97	72 (+)
14	<b>Ad</b> (10)	Et <sub>2</sub> O	-20	72	41	68 (+)
15	<b>Ad</b> (10)	1,4-dioxane	-20	72	90	85 (+)
16	<b>Ad</b> (10)	toluene	-20	72	66	90 (+)
17	Ad (5)	THF	-20	72	99	95 (+)
18	Ad (1)	THF	-20	120	92	90 (+)
19	<b>D</b> (10)	THF	-20	48	99	96 (—)

[a] General reaction conditions: **1** a (1.2 mmol for entries 1–4; 0.6 mmol for entries 5–19), **2** a (0.3 mmol), catalyst (1–10 mol%) in solvent for the stated time. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. PMB=*para*-methoxybenzyl, THF=tetrahydrofuran.



Figure 2. Structures of saccharide-derived organocatalysts tested.

-20 °C (entries 4 and 5). The amount of  $\beta$ -ketoacid can also be reduced to two equivalents at these temperatures. However, further decrease in the reaction temperature (-40 °C) led to a sluggish reaction and the yield dropped to 44 %, even after a prolonged reaction time (entry 6). Subsequently, a series of other thioureas bearing a cyclic tertiary amine moiety were designed and synthesized. To our delight, the catalysts **Ad**, **Ae**, and **Af** displayed higher catalytic activity as well as delivered a superior level of stereoselectivity (entries 7–9). Interestingly, the amino-thiourea **B**, a diastereomer of **Ad** with the opposite configuration (*R*,*R*) on the diamine moiety could also induce high enantioselectivity (entry 10) with the same sense of stereochemical induction as Ad. The same is true for the 1,2-diphenylethane-1,2-diaminebased catalyst C which gave 92% ee (entry 11). In addition, the solvent was found to have an important effect on the reactivity (entries 12-16). Among the solvents tested, THF was found to be the choice solvent for this reaction with respect to both catalytic activity and asymmetric induction. When the catalyst loading of Ad was reduced to 5 mol%, the reaction performed equally well with high enantioselectivity (entry 17). Even at a loading of 1 mol%, Ad still delivered comparable results (92% yield and 90% ee) if the reaction was run for extended reaction time (entry 18). To corroborate the activity and enantioselectivity of Ad, its enantiomer, the L-glucose-derived catalyst D was prepared and tested under similar reaction conditions. Not surprisingly, D exhibited almost identical activity and stereoselectivity with those of Ad except for the opposite sense of asymmetric induction (entry 19).

By using the optimized protocol, we explored the scope of this catalytic enantioselective decarboxylative Mannich condensation with a variety of β-ketoacids and cyclic N-acyl ketimines, and the results are summarized in Scheme 1. In the presence of 10 mol% Ad, the reaction of ortho-, meta-, and para-substituted phenyl \beta-ketoacids with trifluoromethylketimine 2a all proceeded smoothly, thus generating the desired adducts **3a-i** in consistently high yield (94–99%) and enantioselectivity (91-99% ee). 2-Naphthyl- and 2-thiophenyl-substituted \beta-ketoacids were also found to be good substrates, thus delivering the products 3j and 3k, respectively, in high yield and enantioselectivity. Additionally, it was found that linear, branched, and cyclic alkyl substituted βketoacids could also be used as the nucleophilic partners, and excellent results were obtained for the Mannich adducts 31-q. To further define the scope of our methodology, the reactions of other cyclic N-acyl trifluoromethylketimines bearing electron-withdrawing, electron-donating, or electron-neutral groups on the phenyl ring with 1a were tested. The decarboxylative Mannich condensations of these substrates all proceeded efficiently to give the products 3r-x in 92–99% yield and high enantioselectivity. It is worth noting that the presence of an N-protecting group at the ketimine substrate proved to be essential for achieving high level of asymmetric induction, as poor enantioselectivity was observed for 3y (38% ee) wherein the protecting group was absent. In addition, when the trifluoromethyl group on the quinazolin-2(1H)-one ring was replaced with a diffuoromethyl group, the decarboxylative Mannich product 3z was also obtained in 91% yield with 93% ee. However, when the trifluoromethyl group was replaced with a methyl or phenyl group, no condensation products were observed. These results indicated that the strong electron-withdrawing di- and trifluoromethyl groups are critical for this DMR to occur.<sup>[9]</sup>

To demonstrate the practical applicability of this highly efficient catalytic asymmetric DMR, the condensation of 1aand 2a was repeated on a one gram (6 mmol) scale (Scheme 2a) and the reaction delivered the desired product 3a with results almost identical to that of the model reaction. Additional synthetic transformations of the keto carbonyl moiety of 3a, through reduction with NaBH<sub>4</sub> and subsequent

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Scheme 1. Scope of Ad-catalyzed DMR of the  $\beta$ -ketoacids 1 with the ketimines 2. TMB = 2,4,6-trimethylbenzyl, Anth-M = 9-anthracenylmethyl.

reaction of the resulting diastereomeric alcohol **4** with TsCl/ KOH in THF under reflux, led to the isolation of the unique and enaniomerically pure tricyclic 5,9b-dihydro-1*H*-azeto-[1,2-*c*] quinazolin-4(2*H*)-ones **5** and **6**. X-ray crystallographic analysis of **6** allowed the absolute configuration of the two stereogenic centers to be assigned as (2R, 9bR).<sup>[10]</sup> The determination of the stereochemistry of **6** was thereafter used as the basis for the assignment of absolute configuration reported in Table 1 and Scheme 1. Compound *ent*-**6**, synthesized in a similar way in 57% overall yield and 99.9% *ee* by using **D**, was found to possess the opposite configuration through X-ray crystallographic analysis.

We next turned our attention to the application of this highly enantioselective catalytic DMR to the synthesis of the anti-HIV drug DPC 083.<sup>[11]</sup> Under the above-optimized reaction conditions, the (L, R, R)-D-catalyzed DMR of 3cyclopropyl-3-oxopropanoic acid with **2a** gave the S-configured adduct **3p'** with 90% *ee* in quantitative yield (Scheme 2b). The enantiopurity was further improved to 96% *ee* after a single recrystallization. Reduction of the carbonyl group with NaBH<sub>4</sub> gave the alcohol **7** in 98% yield as a 71:29 mixture of diastereomers. Direct dehydration of the diastereomeric mixture in HMPA and subsequent removal of the PMB group afforded (*E*)- and (*Z*)-DPC 083 in 53 and 26% yield, respectively. The optical rotation data of (*E*)-DPC 083 are in full agreement with those described in the literature.<sup>[12]</sup>

To cast some light on the mechanism, NMR and ESI/MS methods were used to study this decarboxylative Mannich reaction. <sup>19</sup>F NMR analysis of the reaction progress for  $\beta$ ketoacid 1a and 2a in CDCl<sub>3</sub> revealed the appearance of two new peaks at  $\delta = -84.4$  and -84.6 ppm, which were tentatively assigned as the addition intermediates (see the Supporting Information). However, all attempts to isolate the putative intermediate failed. Notably, an ESI/MS analysis of this reaction allowed further identification of the addition intermediate using the high-resolution mass data [HRMS (ESI) calcd for  $C_{26}H_{20}ClF_3N_2O_5Na^+$  [*M*+Na<sup>+</sup>] 555.0910, found 555.0904]. A control experiment where acetophenone was used as a surrogate of the  $\beta$ -ketoacid **1a** under otherwise identical reaction conditions did not give adduct 3a. These experimental results suggest that nucleophilic addition to the ketimine occur prior to the decarboxylation of the β-ketoacid during this decarboxylative Mannich reaction.

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**Scheme 2.** a) Additional transformations of the products and X-ray crystal structures of **6** and *ent*-**6**. b) Preparation of the anti-HIV drug DPC 083. HMPA = hexamethylphosphoramide, Ts = 4-toluenesulfonyl. F green, N blue, O red.

The interactions between substrates and catalyst were probed computationally by examining the bond critical points (BCPs) with Bader's atoms in molecules (AIM) analysis.<sup>[13]</sup> The calculations revealed that the cyclic N-acyl ketimine was activated and oriented by hydrogen bonding with the NH groups of the organocatalyst. A H– $\pi$  bonding interaction between the aromatic-substituted protecting group on the ketimine substrate and the saccharide moiety of organocatalyst may also play an important role in stabilizing the



*Figure 3.* a) Hydrogen-bonding complex between organocatalyst and ketamine. F green, N blue, O red, S yellow. b) Proposed reaction pathway.

transition state (Figure 3 a). This is in agreement with the observation that substrate **2***y*, which is lacking an aromatic protecting group on its nitrogen atom exhibited only low enenatioselectivity in forming the product **3***y*. Additionally, the tertiary amine moiety of organocatalyst electrostatically bonds to the  $\beta$ -ketoacid **1** (in its enol form<sup>[14]</sup>) through a salt bridge. Based on this analysis, the nucleophile can only be delivered to the Si face of the C=N group, thus giving predominantly the *R* enantiomer of the Mannich products **3** after decarboxylation of the initial adduct (Figure 3 b).

In summary, we have successfully developed the first hydrogen-bond-directed enantioselective decarboxylative Mannich reaction of  $\beta$ -ketoacids with ketimines. This new method affords a wide range of enantioenriched 3,4-dihydroquinazolin-2(1H)-one derivatives containing a quaternary stereogenic center in high vields and excellent enantioselectivities in the presence of saccharide-based amino-thiourea catalysts. The potential application of this catalytic asymmetric decarboxylative Mannich reaction was demonstrated as a key step in a new and efficient asymmetric synthesis of the anti-HIV drug DPC 083. Preliminary mechanistic investigations indicate that the reaction proceeds through direct addition of  $\beta$ -ketoacids to the ketimines with subsequent decarboxylation. A more systematic study on the mechanistic details and further application of the  $\beta$ -ketoacid-derived enolate synthons to other catalytic asymmetric reactions are ongoing in our laboratories.

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## **Communications**

## Organocatalysis

H.-N. Yuan, S. Wang, J. Nie, W. Meng, Q. Yao, J.-A. Ma\* \_\_\_\_\_ IIII--IIII

Hydrogen-Bond-Directed Enantioselective Decarboxylative Mannich Reaction of  $\beta$ -Ketoacids with Ketimines: Application to the Synthesis of Anti-HIV Drug DPC 083



**Key to success**: The title reaction provides facile access to enantioenriched 3,4-dihydroquinazolin-2(1*H*)-ones containing a quaternary stereogenic center in high yields with excellent enantioselec-

tivities. Subsequent transformations lead to the convenient preparation of the anti-HIV drug DPC 083 and N-fused polycyclic compounds without loss of enantiomeric excess.