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Stereoselective Mannich reactions catalyzed by Tröger's base derivatives in aqueous media

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ABSTRACT

A Tröger's base derivative (5,12-dimethyl-3,10-diphenyl-1,3,4,8,10,11-hexaazatetracyclo [6.6.1.$0^{2,6}$.$0^{9,13}$] pentadeca-2(6),4,9(13),11-tetraenes) was used as an efficient catalyst for the three-component Mannich reactions of aromatic aldehydes and aromatic amines with ketones in water at room temperature. This rapid reaction afforded the corresponding β-amino ketones in good yields with excellent stereoselectivity.

Tröger's base (TB, Fig. 1, **A**) forming from the reaction of *p*-toluidine and formaldehyde has been known since a century.[1] Recently, studies on this class of compounds have been revived due to their potential applications in many fields such as molecular recognition,[2] drug development,[3] bioorganic chemistry,[4] and supramolecular chemistry.[5] It has been used as stereoselective catalyst due to its rigid **V**-shape structure,[6–8] but has never been used in catalytic Mannich reaction.

β-Amino carbonyl compounds forming from Mannich reaction are very important intermediates in the synthesis of pharmaceuticals and natural products.[9] Therefore, much attention has been drawn to the development of new synthetic methods to prepare these compounds. One-pot Mannich reactions using the unmodified aldehydes or ketones as reactants have been reported, and a variety of acidic catalysts such as $Zn(OTf)_2$,[10,11] $H_3PW_{12}O_{40}$,[12] $ZrOCl_2{\cdot}8H_2O$,[13] (*S*)-serine,[14] DBSA,[15] SDA–HCl,[16–18] SalenZn complex,[19] SSA,[20] $HClO_4$–SiO_2,[21] and $NbCl_5$[22] have been investigated. In recent years, Mannich reaction in aqueous media has received much attention.[23,24] However, to the best of our knowledge, only few basic catalytic stereoselective Mannich reactions in water have been reported.

As a part of our interest in base-catalyzed Mannich reactions, herein we reported a TB derivative-catalyzed one-pot three-component Mannich reaction of aldehydes, amines, and ketones using water as the reaction medium (Scheme 1).

At the beginning, eight TB derivatives (Fig. 1), which were synthesized following the same procedure reported by us,[25] were tested in the Mannich reaction of benzaldehyde (2.0 mmol), aniline (2.0 mmol), and cyclohexanone (2.1 mmol).

The reaction was carried out at room temperature in water for 2 h. No product was detected in the control reaction (Table 1, entry 1), and bases including NaOH, triethylamine (TEA), pyridine (entries 2–4), or Tröger's base derivatives **A** and **B** (8*H*,16*H*-7,15-methanodinaphtho[2,1-*b*][2′,1′-*f*][1,5]diazocine) (entries 5 and 6) did not catalyze this reaction. Other six TB derivatives with substituted pyrazola or isoxazole promoted this reaction (entries 7–12). But **IIa**, **IIb**, and **IIc,** which bear three methyls at **7**, **14,** and **15** positions, gave lower yields and poor stereoselectivity than series **I** due to high steric hindrance of two bridge N atoms. This result showed that two bridge N atoms might form the catalytic active site. In the series **I**, **Ia** afforded the highest yield and better stereoselectivity because of its proper steric hindrance and conjugated system. Double catalytic loading of **Ia** from 0.02% to 0.04% improved the yield from 80% to 98%. However, the yield decreased unexpectedly when the amount of catalyst was over 0.04%, thus 0.04 mol % of **Ia** is a suitable choice for optimum yield of β-amino ketones (entries 7 and 13–16).

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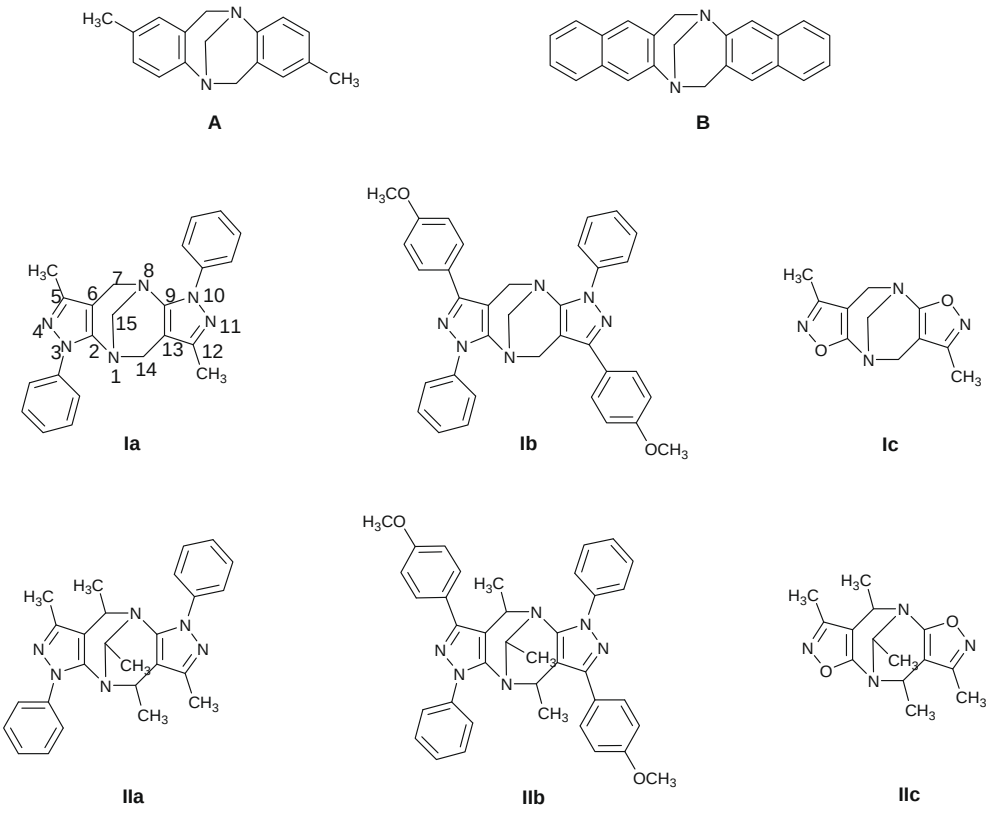
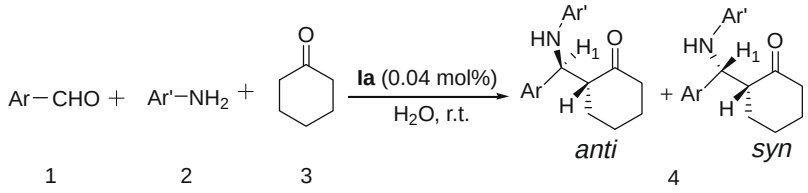


Figure 1. The Tröger's base derivatives[25] that were used in the reaction.



Scheme 1. Mannich reaction of aromatic aldehydes, arylamine, and cyclohexanone.

Table 1
One-pot Mannich reaction of benzaldehyde (2.0 mmol), aniline (2.0 mmol), and cyclohexanone (2.1 mmol) in water

Entry	Catalyst (mol %)	Isolated yields (%)	*anti*/*syn*
1	—	No reaction	—
2	NaOH (0.04)	No reaction	—
3	TEA (0.04)	No reaction	—
4	Pyridine (0.04)	No reaction	—
5	A[a] (0.04)	No reaction	—
6	B[a] (0.04)	No reaction	—
7	**Ia** (0.04)	98	85:15
8	**Ib** (0.04)	30	87:13
9	**Ic** (0.04)	40	90:10
10	**IIa** (0.04)	10	—
11	**IIb** (0.04)	5	—
12	**IIc** (0.04)	20	—
13	**Ia** (0.02)	80	83:17
14	**Ia** (0.06)	65	80:20
15	**Ia** (0.08)	60	81:19
16	**Ia** (0.10)	40	80:20

[a] A—Tröger's base, B—(8*H*,16*H*-7,15-methanodinaphtho[2,1-*b*][2′,1′-*f*][1,5]diazocine).

The *anti*- and *syn*-isomers were identified by the coupling constants (*J*) value between the vicinal protons adjacent to C=O and NH in ^{1}H NMR spectra.[26] The *anti*/*syn* ratio was determined by ^{1}H NMR.

Aromatic aldehydes **1**, arylamine **2,** and cyclohexanone **3** were stirred in the presence of a catalytic amount (0.04 mol %) of **Ia** at room temperature in water for 2–6 h to give the corresponding β-amino ketone compounds **4** (Scheme 1, Table 2) in good to high yield, but the benzaldehyde with strong electron-withdrawing group did not work (Table 2, **4c** and **e**). High *anti*-selectivity was obtained with various substituted benzaldehydes except for 4-chlorobenzaldehydes (Table 2, **4m**). Aliphatic aldehydes (formaldehyde, acetaldehyde, propionaldehyde, and butyraldehyde were tested) did not afford desired product **4** due to their lower reactivity.

It should be mentioned that all methods reported required excess cyclohexanone (1.7–6.0 equiv), for example, when $Zn(OTf)_2$,[10,11] $H_3PW_{12}O_{40}$,[12] and $ZrOCl_2{\cdot}8H_2O$[13] were used as catalysts. However, only stoichiometric cyclohexanone was used in our protocol. Moreover, no organic solvent was involved in our

Table 2
Direct Mannich-type reaction of aromatic aldehydes, anilines, and cyclohexanone[a]

Compound	R1	Ar'[2]	Time (h)	Isolated yield (%)	*anti*/*syn*[c]	Mp (°C)
4a	C_6H_5	C_6H_5	2	98	85:15	129.5–130.0
4b	2-BrC_6H_4	C_6H_5	4	85	99:1	130.4–131.0
4c	3-$NO_2C_6H_4$	C_6H_5	6	Nr[b]	–	–
4d	2-ClC_6H_4	C_6H_5	3	92	86:14	138.8–139.2
4e	4-CNC_6H_4	C_6H_5	6	Nr[b]	–	–
4f	4-OHC_6H_4	C_6H_5	4	85	–	191.0–191.7
4g	4-$CH_3C_6H_4$	C_6H_5	4	90	99:1	131.7–132.0
4h	2-$OCH_3C_6H_4$	C_6H_5	3	87	99:1	127.8–128.0
4i	2,3-$(OCH_3)_2C_6H_3$	C_6H_5	3	80	95:5	151.9–152.0
4j	2,5-$(OCH_3)_2C_6H_3$	C_6H_5	3.5	80	99:1	152.3–153.0
4k	3,4,5-$(OCH_3)_3C_6H_2$	C_6H_5	4	79	97:3	155.2–156.0
4l	4-$CH_3C_6H_4$	4-FC_6H_4	4	70	99:1	106.8–107.0
4m	4-$CH_3C_6H_4$	4-ClC_6H_4	4	80	75:22	105.3–105.9
4n	4-$CH_3C_6H_4$	3-Cl-4-FC_6H_3	5	80	13:87	109.4–109.7
4o	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	4	70	96:4	78.2–79.0
4p	4-$CH_3C_6H_4$	3-ClC_6H_4	4	72	96:4	159.6–160.0

[a] Reaction conditions: aldehydes (2.0 mmol), arylamine (2.0 mmol), cyclohexanone (2.1 mmol), and **Ia** (0.04 mol %).
[b] No reaction.
[c] Diastereomeric ratio measured by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

protocol. Therefore, the workup was easy. As the products were solid and insoluble in water, the pure products were obtained directly by filtration and then by recrystallization from ethanol or DMF.

Interestingly, the results in Table 2 show that the *anti*-isomer is much more favored than *syn* one with an exception of **4n** (*anti*/*syn* = 13:87). A possible reaction mechanism is proposed in Scheme 2. We propose that the high stereoselectivity of products may come from the characteristic rigid **V**-shape structure of TB derivatives. If hydrogen bonds are formed among **Ia**, the enol form of cyclohexanone, the aryl groups of aldimine would be *anti* to each other and there should be less steric repulsion in **III**, between the methylene groups of cyclohexanone and aryl group on the carbon atom, as well as in **Ia** and H_1. So the most stable transition state **III** would produce the *anti*-isomer **V** (Scheme 2).

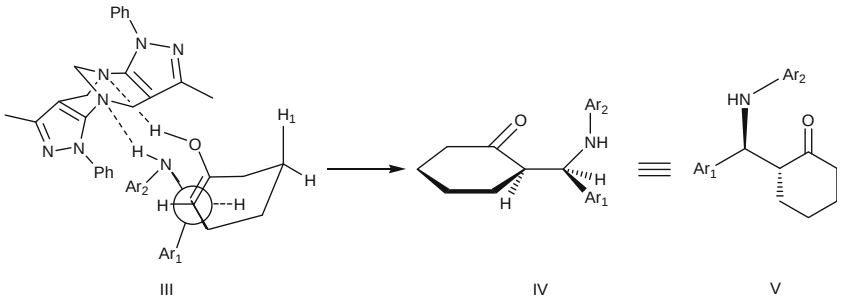
This encouraging result prompted us to test other ketones such as acetophenone (Scheme 3), and corresponding β-amino ketone **6** was obtained in high yields with 0.06% of **Ia** (Table 3). As acetophenone was less reactive than cyclohexanone, more catalyst and longer reaction time were necessary to afford the desired products. We found that the electronic effect of substitutes had some influence on the yields. For example, when there was an electron-withdrawing group on aromatic aldehyde (Table 3, **6d**), the yield was lower (60%) and the reaction time was longer (16 h).

Table 3
Mannich reaction of aromatic aldehydes, aniline, and acetophenone[a]

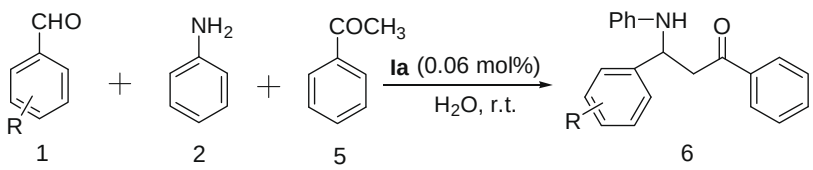
Compound	R	Time (h)	Isolated yields (%)
6a	H	9	80
6b	4-CH_3	12	75
6c	4-OCH_3	12	70
6d	4-Br	16	60
6e	2,3-OCH_3	12	75

[a] Reaction conditions: aldehydes (2.0 mmol), aniline (2.0 mmol), acetophenone (2.1 mmol), and **Ia** (0.06 mol %).

In summary, one-pot Mannich reaction in aqueous media catalyzed by TB derivative **Ia** with good *anti*-selectivity has been developed. This method has several advantages including mild reaction



Scheme 2. The proposed Mechanism for **Ia**-catalyzed Mannich reaction.



Scheme 3. Mannich-type reaction of aromatic aldehydes, anilines, and acetophenone.

conditions, low catalyst loading, and no formation of by-products such as aldol or deamination products. In addition, our process involves an environmentally benign, cheap, and easy to handle catalyst. To the best of our knowledge, this is the first report of a TB derivative-catalyzed direct-type Mannich reaction. Because of its numerous benefits, the protocol should be very useful in the synthesis of β-aminocarbonyl compounds that might have biological activities. Application of the optical pure TB derivatives in this kind of Mannich reaction is under way.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.067.

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