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COMMUNICATION

Novel chiral tetramic acid–derived diols: organocatalytic facile synthesis and unique structural properties†

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Organocatalytic tandem reactions of L–phenylalanine–derived tetramic acid with aldehydes allow a one–pot and high–yielding access to a diverse range of the novel chiral diols in enantiomerically pure forms. In addition, a new entry of the diols, featuring their unique structures associated with C_2– and pseudo C_2–symmetric chiral motifs, is reported.

Chiral diols have been extensively used as effective ligands for chiral catalysts, which are involved in a multitude of powerful applications in asymmetric organic synthesis, and therefore belong to an important class of privileged molecules.[1–6] In general, these chiral diols are designed to have the C_2–symmetry element in conformationally rigid systems, featuring two spacially close pairs of hydroxyl groups asymmetrically disposed across the mirror planes of their entire structures to create chiral environment for expressing enantiomeric recognition. Over the past few decades, impressive progress has been made in the development of enantioselective synthetic methods promoted by asymmetric catalysis of metals and/or prochiral molecules under the influence of the chiral diols, such as diethyl tartrate (DET),[2] hydrobenzoin,[3] α,α,α′,α′–tetraaryl–1,3–dioxolan–4,5–dimethanol (TADDOL),[4] 1,1′–bi–2–naphthol (BINOL),[5] and 1,1′–biaryl–2,2′–dimethanol (BAMOL)[6] (Figure 1). Currently available chiral diols fulfilling the structural and functional requirements for efficient use as ligands are generally limited to just a few simple compounds. Hence, it is a subject of great importance to develop a new alternative series of chiral diols for future progress in stereocontrolled syntheses of complex target molecules, which will be beneficial for chemical, biological, and medicinal applications. In the present communication, we report a new entry of chiral tetramic acid–derived diols possessing C_2– and pseudo C_2–symmetric elements, which are easily available on a gram scale by simple organocatalytic procedures and can be custom–designed with respect to their steric and conformational properties according to structural and functional attributes of the composition.

Our initial synthetic efforts have been made to exploit an interesting finding of unique reactivity of simple cyclic β–diketones toward one–pot synthesis of structurally analogous racemic diols,[7] which can be understood to arise from the base–catalyzed tandem reactions of Knoevenagel condensation[8] followed by Michael addition. Applying this method to biologically attractive chiral tetramic acids **1**,[9] which can be

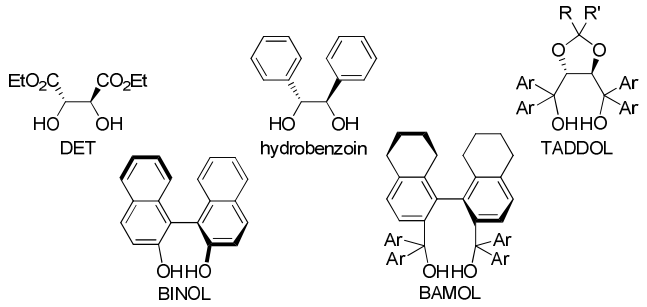
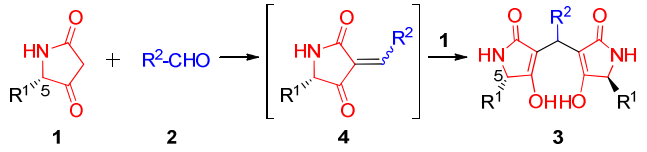


Fig. 1 Structures of representative chiral diols.



Scheme 1 Pathway for diols **3**.

expected to react with aldehydes **2** to give a new type of chiral diols **3** via the intermediacy of α,β–unsaturated 1,3–diketones (ene–diones) **4** as illustrated in Scheme 1, one may encounter difficulties in controlling the stereochemistry of reaction products, largely due to high susceptibility of the tetramic acid cores to suffer troublesome epimerization even under mild conditions.[10] In fact, when a 2:1 mixture of L–phenylalanine–derived tetramic acid **1a** and formaldehyde **2a** (37% aqueous solution) was subjected to the analogous reaction conditions with 20 mol % of piperidine (relative to **2a**) in ethanol, a smooth reaction occurred at r.t. to reach completion after 3 h and the chiral diol **3a** was obtained in 73% isolated yield (Table 1, entry 1). To our disappointment, the ^{1}H NMR analysis of this product ensured detectable loss of the stereochemical integrity, being contaminated with about 6% of its C5 epimeric isomer. Such a behavior was reproduced using the catalytic amount of pyrrolidine, which gave a 90:10 epimeric mixture of **3a** in 78% yield after 2 h (Table 1, entry 2). For both cases, we also found that the stereochemical quality seriously suffered with prolonged reaction times, thereby resulting in considerable decrease of the diastereomeric purity of the product (see Supporting Information).

However, a dramatic change was observed when the catalytic amount of L–proline was used instead of the above two bases. In

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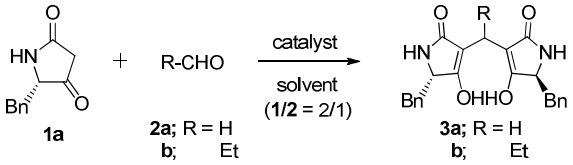
Table 1 Catalyst screening for the reaction of **1a**.



1a **2a;** R = H, **b;** Et **3a;** R = H, **b;** Et

Entry	**2**	Catalyst ([mol%])	Solvent	*T*	*t* [h]	**3**	Yield [%][a]
1	**2a**	Piperidine (20)	EtOH	r.t.	3	**3a**[b]	73
2	**2a**	Pyrrolidine (20)	EtOH	r.t.	2	**3a**[b]	78
3	**2a**	L-Proline (20)	EtOH	r.t.	5	**3a**	96
4	**2b**	L-Proline (20)	EtOH	0 ºC	2	**3b**	100
5	**2b**	Pyrrolidine/ AcOH = 1/1 (20)	EtOH	0 ºC	3	**3b**	100
6	**2b**	L-Serine (20)	EtOH	0 ºC	49	**3b**	99
7	**2b**	L-Lysine (20)	EtOH	0 ºC	20	**3b**	83
8	**2b**	L-Aspartic acid (20)	EtOH	0 ºC	291	**3b**	91
9	**2b**	L-Proline (20)	H_2O	r.t.	5	**3b**	93
10[c]	**2b**	L-Proline (1)	EtOH	r.t.	1	**3b**	100

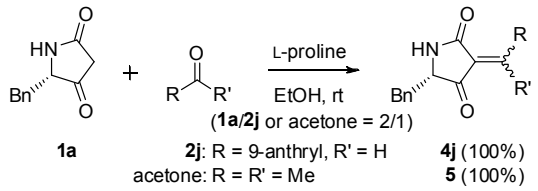
[a] Isolated yield. [b] Epimeric products were obtained in **3a**:*epi*-**3a** ratios of 94:6 (for entry 1) and 90:10 (for entry 2). See supporting Information. [c] The reaction was conducted on a gram scale (1.23 g of **3b**).

this case, the reaction proceeded smoothly at r.t. to allow efficient production of **3a** as an enantiomerically pure form in 96% yield without any other reaction products after a reaction time of 5 h (Table 1, entry 3). This catalytic system was also effective for the reaction with propanal **1b**. Indeed, the reaction proceeded very rapidly at r.t. to reach completion within 20 min with a quantitative product yield of the enantiopure diol **3b**, and still took place very efficiently over 2 h even at 0 °C to give the essentially same result (Table 1, entry 4). In order to search for a replacement of L–proline, we next explored the possibility of using neutral species as a catalyst. When an equimolar mixture of pyrrolidine and acetic acid, which represents structural components of the proline architecture, was employed for the reaction at 0 °C, closely comparable results were obtained with quantitative yield of enantiopure **3b** (Table 1, entry 5). The other amino acids such as L–serine, L–lysine, and L–aspartic acid were also found effective but underwent rather slow reactions to reach 99%, 83%, and 91% product yields for prolonged reaction periods of 49, 20, and 291 h, respectively (Table 1, entries 6–8). Obviously, the cyclic amino acid, proline, has substantial promise for the efficient catalysis of the reactions to afford the chiral diols,[11] where chemical reactivity of carbonyl electrophiles present in the reaction mixture would be enhanced through formation of proline–derived iminium intermediates.[12,13] Also worthy of note is that with the use of L–proline, the approach provided another option to use aqueous media for the reaction as well as allowed easy access in ethanolic solution at r.t. to a gram scale quantity (1.23 g, 100% isolated yield) of **3b** with a catalyst

Table 2 Scope of proline–catalyzed reaction of **1** with aldehydes **2**.[a]

Entry	**1**	**2**	R	Time [h]	**3**	Yield [%][b]
1	**1a**	**2c**	2–methylbutyl	26	**3c**	82
2	**1a**	**2d**	Ph	3	**3d**	100
3	**1a**	**2e**	4–*t*BuPh	2	**3e**	90
4	**1a**	**2f**	3–ClPh	3	**3f**	99
5	**1a**	**2g**	4–NO_2Ph	2	**3g**	99
6	**1a**	**2h**	1–naphtyl	26	**3h**	96
7	**1a**	**2i**	2–naphtyl	20	**3i**	96
8	**1b**[c]	**2b**	Et	1	**3b'**	96

[a] Conditions: aldehyde (0.12–0.30 mmol), tetramic acid (0.24–0.60 mmol), L–proline (20 mol %), EtOH (0.5–0.9 mL), r.t. [b] Isolated yield. [c] *N*-Boc derivative of **1a**.



Scheme 2 Reaction of **1** with **2j** and acetone.

loading as low as 1 mol % (Table 1, entries 9 and 10).

Having identified proline as the optimal catalyst, investigation into the substrate scope of this methodology was next explored with a number of aldehydes. The results presented in Table 2 demonstrate that the proline catalyzed reaction has a high degree of functional–group tolerance with respect to the aldehyde substituents (Table 2, entries 1–7). It is remarkable to note that sterically hindered aldehydes such as **2c**, **2h**, and **2i** also reacted with **1a**, albeit sluggishly, leading to good to high yields of the corresponding diols **3c**, **3h**, and **3i**, respectively (Table 2, entries 1, 6, and 7). The versatility of this catalytic system was further enhanced by applicability of the reaction to a Boc–protected tetramic acid **1b**, a substitute for **1a**, which resulted in rapid and high–yield production of the desired Boc derivative of **3b** (denoted as **3b'**) (Table 2, entry 8). In contrast to these results, we must also note that the most sterically hindered 9–anthraldehyde **2j** exhibited exceptional reactivity, ultimately leading to exclusive formation of the ene–dione **4j**. Additionally, the reaction with acetone as a representative example of ketones in the presence of catalytic even stoichiometric amounts of L-proline also gave the relevant ene–dione **5** quantitatively in each case (Scheme 2).

Since the above result had given an indication for a reaction mechanism involving intermediacy of **4**, which would generate **3**, we next attempted to confirm this mechanistic possibility by reconsidering the reaction trajectory. In the case of entry 7, the reaction progress could be followed visually through monitoring the reaction mixtures by thin layer chromatography (TLC), which showed a spot assignable to **4h**, together with those of **1a** and **3h**. At the reaction time of 5 h, the resulting mixture allowed efficient column separation where the fraction was flushed through the silica–gel column, isolating **4h** in 62% yield as an inseparable mixture of *cis*– and *trans*–isomers.[14] With **4h** in hand, we then examined the reaction of **4h** with 1.0 equiv of **1a** at r.t. in the presence and absence of the catalytic amount (20 mol %) of L–proline. As a result, the catalytic conditions proved potentially reactive to give rise to **3h** with 83% isolated yield after a period

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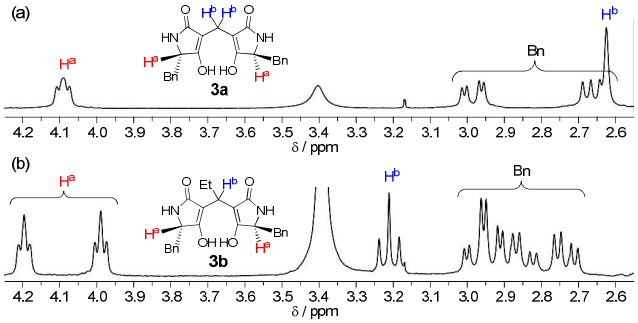

Fig. 2 ^{1}H NMR spectra (300 MHz, DMSO–d_6) for (a) **3a** and (b) **3b**.

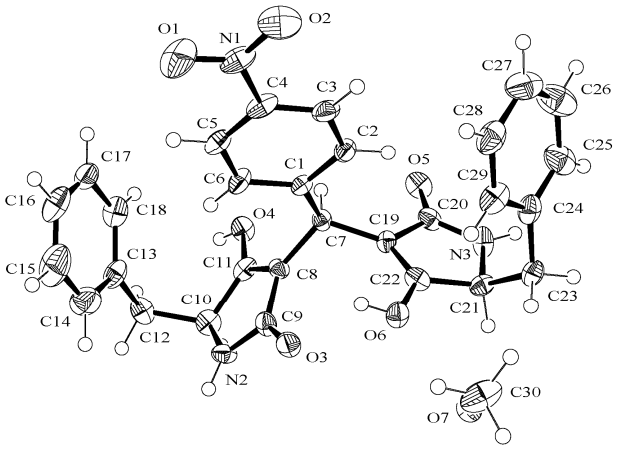

Fig. 3 ORTEP diagram for the absolute configuration of **3g** with 50% thermal ellipsoid probability.

of 50 h, whereas no reaction was found to occur without L–proline. Thus, the mechanistic pathway can be understood as the tandem Knoevenagel condensation/Michael addition sequence, in which either the *cis*– or *trans*–isomer of the resultant ene–diones equally reacts with the remaining tetramic acids to converge to form the uniform structures with the given molecular chirality.

Figure 2 illustrates ^{1}H NMR spectroscopic characteristics of **3a** and **3b**, obtained with DMSO–d_6 as a solvent. There is a marked difference in the spectral features between these compounds. As represented in Figure 2a, the methylene–bridged diol **3a** displays simple resonance patterns, indicating a genuine spectroscopic equivalence of the structural units. This observation is well in accordance with our assumption that **3a** should adopt the C_2–symmetric structure. In contrast to this, the ^{1}H NMR spectrum for **3b** shows more complex patterns with two sets of proton resonances for the relevant tetramic acid segments, indicating unsymmetrical nature of the tetramic acid cores (Figure 2b). This suggests that the tetramic acid units are less free to rotate at r.t. around the single bonds connecting the methine junction. To our surprise, this spectral appearance essentially remains unchanged upon changing the solvent to acetone–d_6 and methanol–d_4 as well as upon heating up to 55 °C in methanol–d_4 (see Supporting Information), indicating that energy barrier for the internal rotations is too high to allow coalescence of the separated resonances and the molecule adopts a severely restricted conformation. This behavior can be considered as a typical characteristic of the overall geometry, which should be categorized as a pseudo C_2–symmetric system.

In an attempt to have a better understanding of conformational preference of the pseudo C_2–symmetric chiral diols, a single crystal X–ray diffraction study was undertaken on *p*–nitrophenyl–substituted diol **3g**, whose X–ray quality crystals were grown by slow evaporation from a chloroform–methanol solution. Indeed, the X–ray results show that the compound adopts the chiral space group $P2_12_12_1$ where the asymmetric unit cell contains one constituent molecule with an encapsulated methanol solvent as depicted in Figure 3.[15,16] In this structure, two tetramic acid groups are oriented preferentially in the opposite direction so as to form intramolecular hydrogen bond between one of the amide oxygen atoms and enolic proton of another tetramic acid group with a short O(3)•••O(6) distance of 2.47 Å.[17] It is of interest to note that the other set of the hydrogen–bond donor and acceptor is separated by a long O(4)•••O(5) distance of 4.26 Å and is substantially in a geometry unfavorable to interact with each other. Thus, as suggested by its ^{1}H NMR spectrum, the two tetramic acid groups are shown to behave differently due to the chemical non–equivalence of the enolic functions. This symmetry breaking must be a result of deformation imposed by the *p*–nitrophenyl ring, which favors CH–π interactions with the two side phenyl groups to give a *W*–shaped conformation in the crystalline state,[18] and brings the pseudo C_2–symmetric nature along the vertical axis of the model into its structural property.

In conclusion, the results of these extensive studies have shown that the proline–catalyzed methodology allows a one–pot and high–yielding access to a diverse range of the chiral diol analogues in enantiomerically pure forms via the tandem processes, and provide an entry of novel tetramic acid–derived diols that present unique structural features associated with the C_2– and pseudo C_2–symmetric motifs. In addition, we put particular emphasis on the synthetic utility of the current reaction, offering ready availability for the preparation of custom–designed chiral diols on a gram scale, which will provide new opportunities for the future development of effective and potentially versatile chiral ligands.

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† Electronic Supplementary Information (ESI) available: Experimental details, characterization data, ^{1}H and ^{13}C NMR spectra for the compounds **3a–i**, **3b'**, **4h**, **4j** and **5**. See DOI: 10.1039/b000000x/

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15 Crystal data for **3g**: orthorhombic, space group $P2_12_12_1$, a = 10.4426(6) Å, b = 12.0149(7) Å, c = 21.1390(13) Å, V = 2652.2(3) Å^3, Z = 4, ρ = 1.359 Mgm^{-3}, μ(Cu$_{K\alpha}$) = 0.809 mm^{-1}, T = 173 K; in the final least–squares refinement cycles on F^2, the model converged at R_1 = 0.1071 ($I > 2\rho(I)$), wR_2 = 0.2861, and GOF = 1.107 for 4427 reflections and 367 parameters (CCDC deposition number 963494).

16 The elemental analysis data of **3g** (C, 65.90; H, 5.13; N, 8.12) are in good agreement with the calculated values for $C_{29}H_{25}N_3O_6 \cdot CH_3OH$ (C, 66.29; H, 5.38; N, 7.73).

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