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# Helical Multi-Coordination Anion-Binding Catalysts for the Highly Enantioselective Dearomatization of Pyrylium Derivatives

*Theresa Fischer[+], Julia Bamberger[+], Melania Gómez-Martínez, Dariusz G. Piekarski, and Olga García Mancheño**

***Abstract:*** *A general and highly enantioselective synthesis of oxygen heterocycles from readily available in situ generated pyrylium derivatives has been realized by embracing a multi-coordination approach with helical anion-binding tetrakistriazole catalysts. The high activity of the tetrakistriazole (TetraTri) catalysts, with distinct confined anion-binding pockets, allows for remarkably low catalyst loadings (down to 0.05 mol%), while providing a simple access to chiral chromanones and dihydropyrones in high enantioselectivities (up to 98:2 e.r.). Moreover, experimental and theoretical studies provide new insights into the hydrogen-donor ability and key binding interactions of the TetraTri catalysts and its host:guest complexes, suggesting the formation of a 1:3 species.*

Asymmetric anion-binding catalysis,[1] which relies on the activation of ionic substrates by catalyst binding to their counteranions and the formation of a chiral contact ion pair, has become a powerful synthetic tool in the past few years, offering new possibilities in the area of enantioselective catalysis. Despite the tremendous interest that this approach is currently evoking in the scientific community, only a limited number of catalyst motifs are available. Thus this chemistry is essentially based on chiral bidentate N–H and, more recently, O–H hydrogen-donor catalysts, such as thioureas[2] and silanediols,[3] respectively (Figure 1a, left).[4] Additionally, while anion binding offers high flexibility and tunability, the non-covalent interactions involved are more difficult to control than the covalent counterparts. All of these issues have impeded the fast development of this research area of catalysis, highlighting the need for novel catalyst structures with distinct binding pockets and/or stronger interactions with the substrate.[1,5] With this in mind, we envisioned that a C–H bond based multi-coordination catalyst would lead to a more effective fixation of the ionic substrate (Figure 1a, right), enabling efficient chirality transfer at lower catalyst loadings.

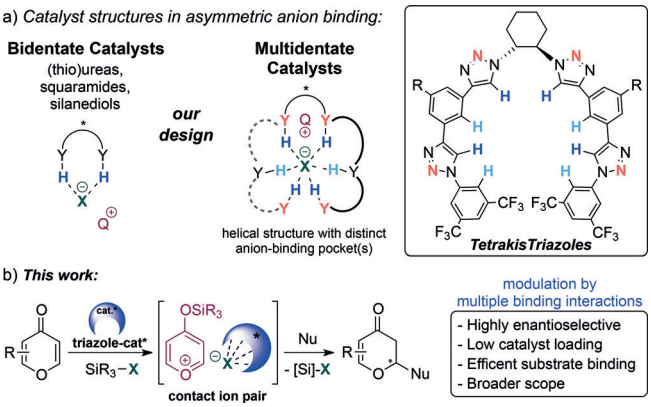


***Figure 1.*** Catalyst design in anion-binding catalysis and our multiple-binding approach with pyrylium-type substrates.

Aiming at solving some of the current limitations in this field, we focused our attention on nucleophilic dearomatization,[6] with pyrylium derivatives as well-suited, appealing substrates to test our catalyst multi-coordination approach (Figure 1b). Pyrylium salts present intrinsic reactivity and selectivity issues:[7] 1) In most cases, nucleophilic reactions with pyrylium salts lead to decomposition or ring-opening products; 2) pyrylium salts are less reactive than non-conjugated oxonium ions, and 3) it is not easy to fine-tune the stereoelectronic properties of the substrate, making enantiodifferentiation difficult.[8] As a consequence, only a few asymmetric examples embracing the anion-binding catalysis technology with this type of derivatives have been reported to date.[9] In 2011, Jacobsen and co-workers developed the first organocatalyzed highly enantioselective [5+2] cycloaddition of olefins with 3-oxopyrans bearing a carboxyl leaving group at the C6 position.[9a–b,10] However, this method relies on the use of chiral covalent aminocatalysis to form the active 3-aminopyrylium species, in combination with an achiral thiourea anion-binding co-catalyst. Later on, Mattson and co-workers reported on a silanediol-catalyzed asymmetric nucleophilic addition to chromelium salts.[9c] In this case, only moderate enantioselectivities were achieved with these bidentate hydrogen-donor catalysts. Moreover, both methods required high catalyst loadings (15–20 mol%) and remain inefficient or limited in terms of the used substrate classes. We have recently introduced chiral multidentate H-bond anion-binding tetrakistriazole (TetraTri) catalysts (Figure 1),[11,12] which have already shown outstanding catalytic activity in dearomatization reactions with demanding N-heteroarene substrates.[11b]

[*] T. Fischer,[+] J. Bamberger,[+] Dr. M. Gómez-Martínez, Dr. D. G. Piekarski, Prof. Dr. O. García Mancheño
Organic Chemistry Institute, University of Münster
Corrensstraße 40, 48149 Münster (Germany)
E-mail: olga.garcia@uni-muenster.de
[+] These authors contributed equally to this work.

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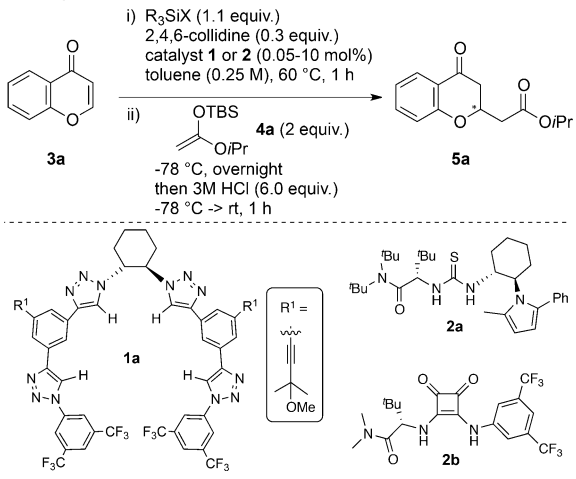
We envisioned that this type of catalysts could provide a solution to our problem and achieve high enantioselectivities in reactions with the pyrylium compounds towards a general synthesis of chiral substituted oxygen heterocycles. The TetraTri catalysts are H-bond donors that present four strongly polarized C–H bonds at the triazole units and further multiple coordination sites of neighboring C–H bonds. Moreover, they are able to form helical structures with distinct anion-binding pockets, as well as to potentially interact with cationic species through the lone pair of the nitrogen atoms in the triazole rings. All of these features should enable the formation of a chiral, three-body tight ion pair, allowing high enantio-inductions. Herein, we present a highly enantioselective nucleophilic dearomatization reaction of pyrylium salts with a rationally designed chiral multi-coordination triazole anion-binding catalyst.

To test our hypothesis, we started our studies with the one-pot reaction between commercially available 4-chromenone (**3a**) as a model substrate and silyl ketene acetal **4a** as the nucleophile at −78 °C in toluene (Table 1). The active benzopyrylium ion species was formed in situ by treatment with a silyl derivative ($R_3SiX$) in the presence of 10 mol % of the H-donor catalyst and catalytic amounts of 2,4,6-collidine at 60 °C, as previously reported.[13] The change from TMSCl to TMSOTf led to a notable increase in conversion (from 32 to 72 %) and enantioselectivity (from 64:36 to 87:13 e.r.; entries 1 and 2). Various C–H-based triazole (**1**),[11] N–H-based thiourea,[2a] and squaramide[14] (**2**) catalysts were tested (for the complete optimization see the Supporting Information), and gave product **5a** in moderate to excellent yields and a broad range of enantioselectivities from almost racemic to high e.r. (entries 2–5). As we had envisioned, the multi-coordination triazoles were clearly superior to the bidentate N–H-based catalysts **2**. Triazole **1a** showed the best performance, providing **5a** in a promising 91:9 e.r. when TBSOTf was used as the silylating reagent (entry 3).[15] A notable improvement of the enantioselectivity was achieved upon decreasing the catalyst loading to 0.1–5 mol %, reaching 96:4 to 98:2 e.r. (entries 6–8). The activity and chirality transfer of **1a** are remarkable, allowing the use of only 0.05 mol % (entry 9),[16] one of the lowest catalyst loadings reported to date in asymmetric anion-binding catalysis.[2e] Nevertheless, for practical reasons, 1 mol % of **1a** was used for further studies.

***Table 1:*** Optimization of the reaction conditions with **3a**.[a]




| Entry | Catalyst (mol %) | $R_3SiX$ | Yield [%][b] | e.r.[c] |
|---|---|---|---|---|
| 1 | **1a** (10) | TMSCl | 32 | 64:36 |
| 2 | **1a** (10) | TMSOTf | 72 | 87:13 |
| 3 | **1a** (10) | TBSOTf | 92 | 91:9 |
| 4 | **2a** (10) | TBSOTf | 82 | 57:47 |
| 5 | **2b** (10) | TBSOTf | 59 | 51:49 |
| 6 | **1a** (5) | TBSOTf | 92 | 98:2 |
| 7 | **1a** (1) | TBSOTf | 90 | 97:3 |
| 8 | **1a** (0.1) | TBSOTf | 95 | 96:4 |
| 9 | **1a** (0.05) | TBSOTf | 82 | 88:12 |

[a] i) **3a** (1 equiv), $R_3SiX$ (1.1 equiv), 2,4,6-collidine (0.3 equiv), and catalyst (**1**–**2**) in the appropriate solvent (0.25 M) at 60 °C, 1 h; ii) at −78 °C **4a** (2 equiv) was added, and the resulting mixture was stirred overnight. [b] Yields of isolated products. [c] Enantiomeric ratios determined by HPLC analysis on a chiral stationary phase. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

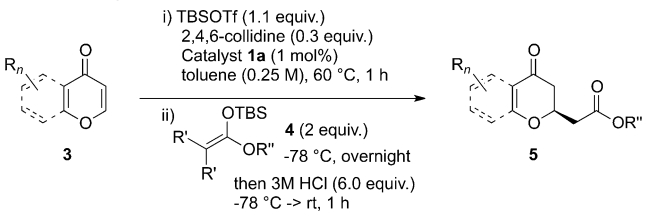
With optimized reaction conditions in hand [TBSOTf, 2,4,6-collidine, and catalyst **1a** (1 mol %) in toluene], the scope of the reaction was investigated (Table 2). It is worthy to note that the reaction could be scaled up to 1 mmol without significant changes in the yield or enantioselectivity (**5a**, 88 %, 96:4 e.r.). Various silyl ketene acetals **4** were first tested (**5b**–**e**). A slight change in the substitution of the nucleophile had a great influence on the enantioselectivity. Whereas methyl ester **4b** still provided product **5b** with high enantiopurity (90:10 e.r.), reactions with more sterically hindered nucleophiles such as **4c**–**e** proceeded smoothly but showed only moderate chirality transfer. Differently substituted 4-chromones **3** were next examined. Electron-donating (**3f**–**h**) and -withdrawing groups (**3i**–**l**) at the C6 position were well tolerated, providing high yields and good to excellent enantioselectivities (up to 97:3 e.r.). Substrates with substituents at the C7 and C8 positions gave the corresponding products **5o**–**q** in similarly high enantioselectivities (up to 94:6 e.r.). One of the best results was obtained with the 5,7-dimethyl-substituted substrate, generating **5n** in 98:2 e.r. Additionally, thiochromone was effectively enrolled in this reaction, too (**5m**, 80:20 e.r.).

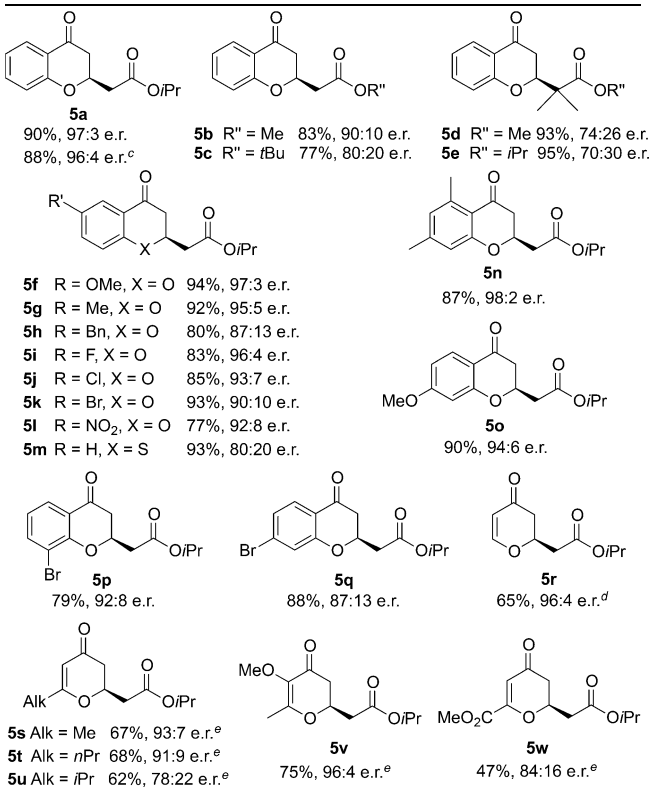
Finally, the great applicability of the catalytic system was further confirmed by the effective reaction with more challenging 4-pyrones. It is important to note that aside from our chiral multi-coordination triazoles **1**, other chiral or achiral bidentate catalysts of type **2** did not promote the reaction or generated decomposition products with these highly demanding substrates. Although it was also possible to carry out the reaction with 4-pyrone (**3r**) in the presence of 1 mol % of **1a** (**5r**, 96:4 e.r.), the use of 5 mol % of catalyst generally led to the best results with these compounds in terms of both yield and enantioselectivity. Whereas the reactions of electron-deficient (2-$CO_2$Me, **3w**) and sterically hindered (2-*i*Pr, **3u**) pyrones proceeded with moderate chirality transfer, good to excellent enantioselectivities were obtained with 2-alkyl-substituted derivatives, generating **5s**, **5t**, and **5v** with up to 96:4 e.r.

The synthetic applicability of this method was next demonstrated by derivatization of the chiral products **5**

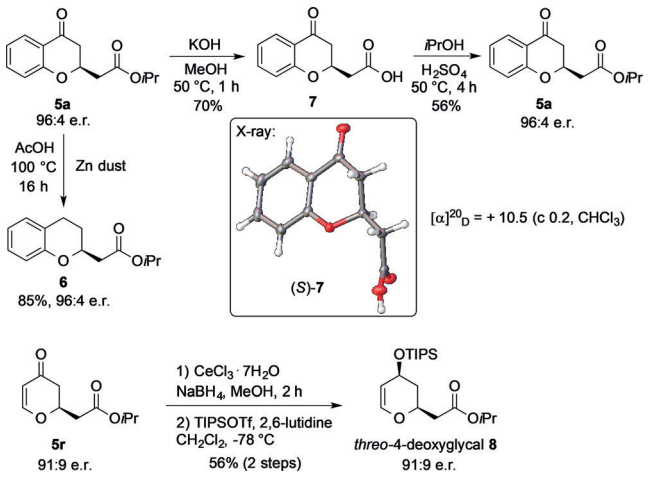
  

**Table 2:** Scope of the reaction.[a,b]




[a] i) **3** (1.0 equiv), TBSOTf (1.1 equiv), 2,4,6-collidine (0.3 equiv), and **1a** (1 mol%) in toluene, 1 h at 60 °C; ii) at −78 °C, **4** (2 equiv) was added, and the resulting mixture was stirred overnight. [b] Yields of isolated products; enantiomeric ratios determined by HPLC analysis on a chiral stationary phase. [c] Reaction conducted on a 1 mmol scale using 1.2 equiv of **4a**. [d] Reaction conducted using 1.2 equiv of **4a**. [e] Reaction conducted using 5 mol% of **1a**.




***Scheme 1.*** Derivatization of products **5**. TIPS = triisopropylsilyl.

attack (25:1 *threo*/*erythro* ratio), and subsequent alcohol protection.

In order to confirm our design and better understand the superior performance of catalyst **1a**, both experimental and computational studies were carried out. First, a kinetic study revealed a fast reaction at −78 °C, and almost full conversion was accomplished after only 1 h (80 vs. 90% yield after 18 h). Moreover, the chirality induction was also monitored over the course of the reaction, reaching nearly constant, high values of enantioselectivity in short times (97:3 e.r. after 2–3 h vs. 95:5 e.r. after 1 h). Second, we focused on the binding properties of the catalyst to the triflate anion and further key interactions with the ionic substrate. For feasibility and practical reasons (e.g., solubility, stability of the ionic compounds), we built a model system using an ammonium triflate salt as the substrate. The $^1$H NMR titration of catalyst **1a** with $Bu_4NOTf$ salt was performed in acetone (5 mM; Figure 2). Surprisingly, an excess of the anion (≥2 equiv) was required to detect significant binding to the catalyst. This observation explains the observed improvement in enantioselectivity upon decreasing the catalyst loading from 10 to 5 or even 0.1 mol% (Table 1), suggesting, together with a Job's plot

(Scheme 1). Thus **5a** was easily transformed into chromane **6** in one step by a Clemmensen reduction. Furthermore, alkaline hydrolysis of **5a** led to the corresponding acid **7**; upon crystallization and X-ray analysis, the absolute configuration at the new stereocenter formed during the catalytic reaction was determined as *S*.[17] Both processes proceeded without loss of enantiopurity, which was confirmed by HPLC analysis on a chiral stationary phase of **6** and compound **5a** obtained after re-esterification with *i*PrOH. Moreover, the pyrone derivative **5r** was converted into *threo*-4-deoxyglycal **8**, a valuable synthetic building block for the preparation of a large number of natural products and bioactive compounds.[18] This was accomplished by simple selective 1,2-reduction of the enone group using the $CeCl_3/NaBH_4$ reducing system; this reaction proceeded largely by axial

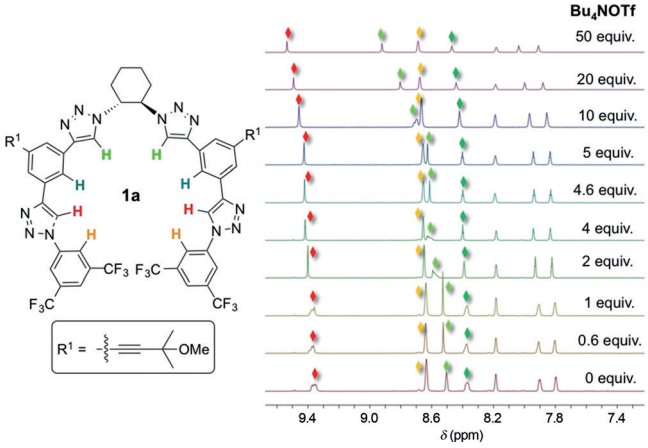



***Figure 2.*** $^1$H NMR titration of **1a** with $Bu_4NOTf$ (acetone-$d_6$, 5 mM).

(see the Supporting Information), the in situ formation of a high-order host:guest supramolecular complex.

Intrigued by these unexpected results, we optimized the geometries of catalyst **1a** and the **1a**:$n_{salt}$ host:guest complexes of the $Me_4NOTf$ salt with $n = 1$, 2, and 3 at the DFT-M06-2X/6-31G(d,p) level of theory[19] with the Gaussian 09 program.[20] Considering the temperature of the catalytic experiments (195.15 K) and the standard state in a solution of 1 mol $L^{-1}$, the quasi-rigid-rotor harmonic oscillator (quasi-RRHO) approximation was used for entropic contributions of low-frequency modes (i.e., below 100 $cm^{-1}$) using Grimme's model.[21] Relative Gibbs free energies, corrected with the quasi-RRHO method, and solvation effects calculated with the COSMOtherm software[22] (see the Supporting Information for details), were used to obtain the binding energies (BEs) of the **1a**:1, **1a**:2, and **1a**:3 complexes following an additive super-molecular approach. The conformer distribution search was performed by a first optimization at the semi-empirical AM1 level of theory,[23] implying a manual construction of a number of plausible initial structures and further possible changes in the rotation axes and binding patterns. The obtained geometries were then used for the final optimization at the DFT level of theory. We found six isomers of catalyst **1a** and various conformers of the complexes, namely ten for **1a**:1, four for **1a**:2, and seven for **1a**:3 (see the Supporting Information for all structures). In order to investigate the binding properties of these systems, we first analyzed the structures, sigma surfaces, sigma potentials, and BEs of all structures. We could distinguish four relevant complexes (see Figure 3 for their structures and corresponding sigma surfaces), where hydrogen bond donor properties were identified for the catalyst **1a** and the **1a**:1 and **1a**:2 complexes. These results are coherent with the previously shown $^1H$ NMR binding studies and suggest the formation of the **1a**:3 complex.

Finally, the host:guest interactions of the relevant complexes with the ionic substrate were investigated. The cavities presented on catalyst **1a** and its complexes were used for the interpretation of the possible docking with the ionic substrate by analyzing their sigma surfaces with opposite signs. Catalyst **1a** shows two symmetric and easily observable binding pockets. Upon binding of one substrate ($Me_4NOTf$) in one of its cavities, the **1a**:1 complex is formed, where the $OTf^-$ anion is stabilized by C–H hydrogen bonding (**A** area). Extra stabilization effects are observed for the $Me_4N^+$ cation and result from interactions of the lone pairs of both the oxygen atom of the methoxy group at one of the catalyst side chains [$R^1 = Me_2(MeO)C$-CC-] (**B** area) and the nitrogen atom of a triazole ring bonded to the cyclohexane central unit (**C** area). Owing to these interactions, the **1a**:1 structure gains 5.2 kcal $mol^{-1}$ of BE. Moreover, the **1a**:1 complex still presents a similar binding cavity as in **1a** (see the structure rotated by 180°). Interestingly, the further addition of salt to **1a**:1 results in a gain of 8.7 kcal $mol^{-1}$ of BE, leading to the **1a**:2 complex, in which the second bonded salt is differently oriented in the pocket than the first one. Although no clear binding cavity in the **1a**:2 structure could be observed, this geometry differences opens the possibility for binding a third ionic substrate through the second bound salt and form the **1a**:3 complex. This interaction is clearly seen in **1a**:3 and is also reflected in the additional gain of 3.5 kcal $mol^{-1}$ of BE. Ultimately, the **1a**:3 complex does not contain a visible cavity for subsequent substrate binding, nor H-donor properties upon analyzing its sigma potential.

In summary, we have developed a highly enantioselective nucleophilic dearomatization of pyrylium derivatives by embracing a multi-coordination triazole-based anion-binding catalysis approach. The high activity of catalyst **1a** allowed for remarkably low catalyst loadings while providing the desired chiral chromanones and dihydropyrones in high enantioselectivities of up to 98:2 e.r. Furthermore, experimental and computational studies were in line with our hypothesized distinct confined anion-binding pockets of the catalyst. They also suggest a 1:3 complexation of the triazole catalyst with the ionic substrates through interactions with both their anionic and cationic moieties.

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## Conflict of interest

The authors declare no conflict of interest.

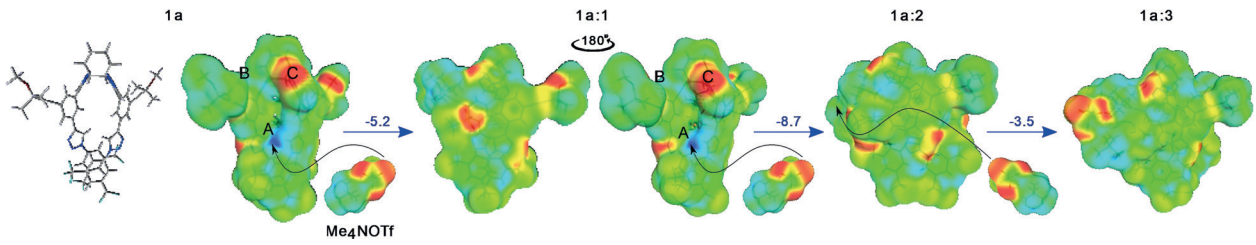


***Figure 3.*** Structures of the catalyst **1a** and its relevant **1a**:$n_{salt}$ complexes (optimized at the DFT-M06-2X/6-31G(d,p) level of theory) and their sigma surfaces (obtained at the BP86/TZVP level of theory). BEs (calculated using Gibbs free energies corrected for low-frequency modes and solvation effects of acetone) are given in kcal $mol^{-1}$.

  

**Keywords:** anion binding · asymmetric catalysis · catalyst design · chiral triazoles · pyrylium salts

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