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trans-Diastereoselective Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of α-Acetamido Benzocyclic Ketones via Dynamic Kinetic Resolution

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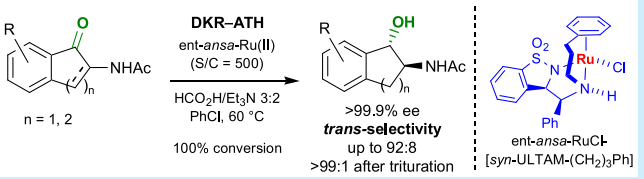
Supporting Information

ABSTRACT: A highly efficient enantio- and diastereoselective catalyzed asymmetric transfer hydrogenation via dynamic kinetic resolution (DKR−ATH) of α,β-dehydro-α-acetamido and α-acetamido benzocyclic ketones to *ent-trans*-β-amido alcohols is disclosed employing a new *ansa*-Ru(II) complex of an enantiomerically pure *syn*-*N*,*N*-ligand, i.e. *ent-syn*-ULTAM-$(CH_2)_3$Ph. DFT calculations of the transition state structures revealed an atypical two-pronged substrate attractive stabilization engaging the commonly encountered CH/π electrostatic interaction and a new additional O═S═O···HNAc H-bond hence favoring the *trans*-configured products.



Asymmetric transformations comprising a dynamic kinetic resolution (DKR) step are practically very attractive since both involved enantiomers of the stereolabile racemic substrate would ideally converge to a diastereo- and enantiomerically pure product.[1,2] In particular, the DKR encountered in transition-metal-catalyzed reduction of ketones, such as in asymmetric transfer hydrogenation (ATH), is a powerful one-pot protocol for "deracemization" of substrates which possess a stereolabile α-carbon by converting them into alcohols having two contiguous stereogenic centers.[2] A large number of these reductions are catalyzed by enantiomerically pure *ansa*-Ru(II)−[*ent-trans*-RSO_2DPEN-(η^6-arene)] complexes[3] (Figure 1) in the HCO_2H/Et_3N binary mixture, which acts as both the H-source and an adequate "racemization medium" for the intermediate en route to the final product. The substrates scope for such DKR−ATH encompasses aryl,[4] perfluoroalkyl,[5] or acetylenic[6] ketones as well as α-substituted benzocyclic ketones. Relevant to our present work are 2-Z-1-indanones and -tetralones wherein Z = alkyl, (het)aryl, F, Cl, CO_2R', SO_2Ph, C(O)Ph, SO_2NHPh, and CH(OH)CF_3, which furnish predominantly the corresponding enantiomeric *cis*-configured products under these reaction conditions.[7]

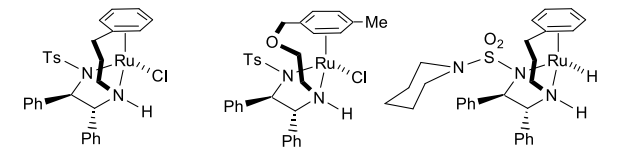


Figure 1. Representative ATH-efficient *ansa*-Ru(II) complexes of tethered (*R*,*R*)-RSO_2DPEN and η^6-arene ligands.

Herein we present the exceptional highly *trans*-selective DKR−ATH of α,β-dehydro-α-acetamido and α-acetamido benzocyclic ketones using a new chiral *ansa*-Ru(II) complex based on *ent-syn*-ULTAM *N*,*N*-ligand[8] (Scheme 1). Such a complex has enhanced thermal stability compared to its nontethered-type version.[9] In addition, the origin of the unexpected stereochemical outcome is investigated.

The Ru(II) complex **C4** (CCDC 1905532) and its catalyst active form (active-**C4**) were prepared starting from enantiomerically pure *syn*-(3*R*,1′*S*)-ULTAM ligand following our improved procedure[5a] of the general one introduced by Wills for **C1**.[10] Accordingly, its selective mono-*N*-alkylation at rt led to the preligand **1** (79% yield), and the shelf-stable di-μ-chlorido Ru(II) dimer **2** was readily formed (75% yield) by heating at 65 °C, in EtOH, the **1**·HCl with $RuCl_3$ hydrate. Finally, the *ansa*-Ru(II)−Cl complex **C4** was isolated in 43% yield by treatment of **2** with *i*-PrNEt_2 in CH_2Cl_2 at rt; its structure was established by single-crystal X-ray diffraction. Conveniently, the catalyst *ansa*-Ru(II)−H active-**C4** was generated *in situ* by stirring the Ru(II) dimer **2** at rt for 30 min in the HCO_2H/Et_3N medium. Alternatively, it can be generated similarly from **C4**.

We have initially surveyed the suitability of a selection of *ansa*-Ru(II) complexes (S/C = 500) for the DKR−ATH of the reference 2-acetamido-1-indenone substrate (**S1**) at 60 °C in a neat HCO_2H/Et_3N 3:2 mixture (Table1). **S1** was prepared by

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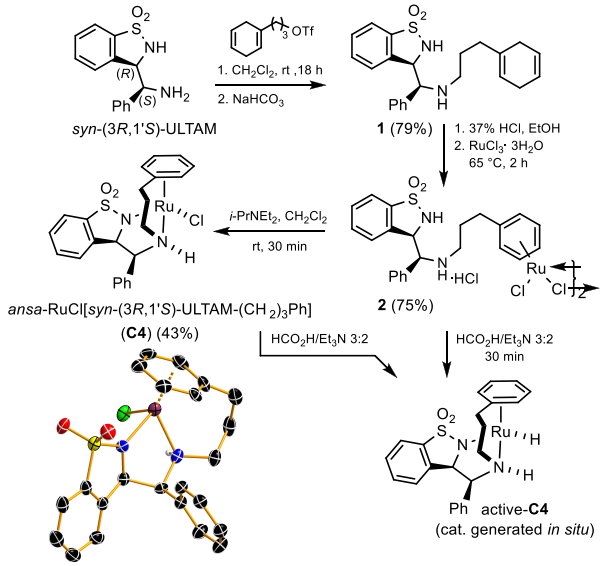
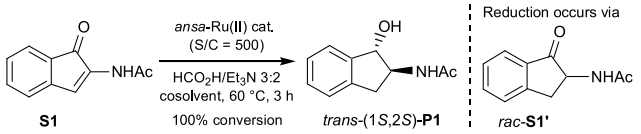
Scheme 1. Synthesis of the *ansa*-Ru(II) Complexes C4 and Active-C4 Based on the *syn*-(3*R*,1′*S*)-ULTAM Ligand



the Erlenmeyer azlactone synthesis followed by Friedel–Crafts intramolecular acylation.[11]

Table 1. Screening of *ansa*-Ru(II) Complexes in DKR–ATH of 2-Acetamido-1-indenone (S1)[a]



entry	active Ru(II) cat.	cosolvent	*trans*/*cis*	ee (%) (*trans*)
1	**C1**	–	65:35	n.d.
2	**C2**	–	54:46	n.d.
3	**C3**	–	75:25	n.d.
4	**C4**	–	84:16	>99.9
5	**C4**	DMF	82:18	n.d.
6	**C4**	EtOH	84:16	n.d.
7	**C4**	EtOAc	87:13	n.d.
8	**C4**	$(CH_2Cl)_2$	90:10	>99.9
9	**C4**	toluene	91:9	>99.9
10	**C4**	PhCl	91:9 (>99)[b]	>99.9

[a]ATH of **S1** (187 mg, 1.0 mmol) was carried out at 60 °C using the Ru(II) cat. (S/C = 500, 2 μmol) prepared *in situ* from the corresponding di-μ-chlorido Ru(II) dimer in HCO_2H/Et_3N 3:2 (1 mL); with a cosolvent (1 mL), less HCO_2H/Et_3N 3:2 (0.5 mL) was used. Conversion (100% within 3 h) and the *trans*/*cis* ratio were determined by ^1H NMR, and the ee of the *trans*-diastereomer was determined by chiral HPLC. n.d. = not determined. [b]After upgrading by trituration with MeCN of the crude (83% total yield).

The screening revealed the outperformance of the new Ru(II) catalyst active-**C4** versus the ones based on the *trans*-(*R*,*R*)-RSO_2DPEN-type *N*,*N*-ligands, leading to an increased *trans*/*cis* diastereomeric ratio (84:16) of the 2-acetamido-1-indanol product (**P1**) with a perfect enantioselectivity (>99.9% ee) for both diastereomers. A further improved diastereoselectivity of up to 91:9 was attained in the presence of less polar cosolvents such as 1,2-dichloroethane, toluene, or chlorobenzene (Table 1, entries 8–10). Noteworthy, conducting this two-step reduction process at 50 °C for 3 h led to the racemic 2-acetamido-1-indanone (*rac*-**S1′**) (by chiral HPLC) in 90% yield (by ^1H NMR). Continued reduction at 60 °C afforded the stereoenriched β-acetamido alcohol **P1**, thus clearly validating the occurrence of a DKR during the keto function reduction step. Facile trituration with MeCN of the crude product gave the stereochemically pure *trans*-(1*S*,2*S*)-**P1** (>99.9% ee) in 83% yield. The origin of this unusual and particularly high *trans*-selectivity of the Ru(II) catalyst active-**C4** is addressed below. These results are interesting relative to the Rh(I)-catalyzed hydrogenation of **S1** by the W. Zhang group.[12]

Following, the Ru(II) catalyst active-**C4** was applied to the ATH of a diverse set of α,β-dehydro-α-acetamido and α-acetamido benzocyclic ketones (**S2**–**S9**) (Figure 2). To our

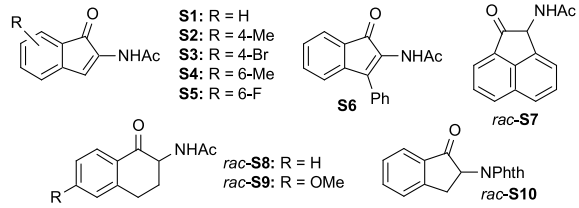


Figure 2. Benzocyclic ketones **S1**–**S10** explored in Ru(II)-catalyzed DKR–ATH.

delight, the substituted 1-indenones **S2**–**S5** were reduced quantitatively within 3 h using an S/C = 500 under our standard optimized conditions (HCO_2H/Et_3N 3:2 in chlorobenzene at 60 °C) affording high *trans*/*cis* ratios (from 87:13 up to 92:8) with >99% ee. Trituration with MeCN of the crude yielded the enantio- and diastereochemically pure products *trans*-(1*S*,2*S*)-**P2**–**P5** (Figure 3). Furthermore, the never-before-reduced 2-acetamido-3-phenyl-1-indenone (**S6**) underwent DKR–ATH with 95% conversion delivering *trans*,*trans*-**P6** in >99% ee as the major diastereomer (dr = 81:3:4:12). Interestingly, three contiguous stereogenic carbons

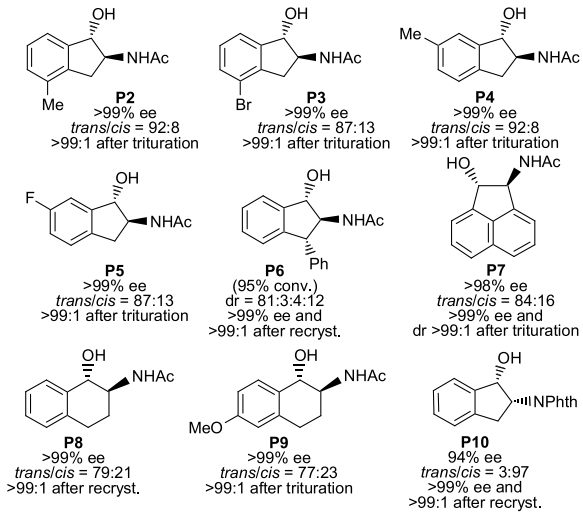


Figure 3. DKR–ATH products **P2**–**P10** derived from the corresponding benzocyclic ketones **S2**–**S10** of Figure 2. The enantio- and diastereochemically pure products (>99% ee, dr >99, 44–83% yield) were obtained by trituration with MeCN or recrystallization from EtOAc.

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were created in a one-pot procedure.[7c] Facile single recrystallization from EtOAc afforded the virtually enantio- and diastereochemically pure *trans,trans*-(1*S*,2*S*,3*R*)-**P6** (>99% ee, dr >99); its absolute configuration was confirmed by single-crystal X-ray diffraction (CCDC 1905533). Such an attained high level of *trans,trans*-selectivity is the result of the bias efficiency of the Ru(II) catalyst active-**C4** in the reduction step giving rise to a *trans*-configuration at C(1)−C(2), while the one at C(3) is thermodynamically driven.[13]

Next, the racemic 2-acetamido-1-acenaphthenone (*rac*-**S7**), prepared from acenaphthoquinone by Pd/C-catalyzed hydrogenation in Ac_2O of the mono-oxime, was subjected to DKR−ATH. This ketone gave the *trans*-diastereomer in >98% ee with a somewhat lower *trans*/*cis* ratio (84:16). Nonetheless, trituration with MeCN yielded stereochemically pure *trans*-(*S*,*S*)-**P7**.

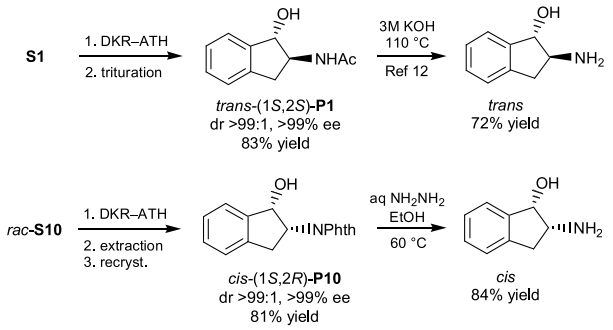
When the focus was shifted to racemic 2-acetamido-1-tetralones *rac*-**S8** and *rac*-**S9**, prepared from the corresponding α-tetralone by treatment with isoamyl nitrite/KO*t*-Bu to form the 2-oxime and then Zn in AcOH/Ac_2O reduction, their ATH resulted in >99% ee (*trans*) with 79:21 and 77:23 *trans*/*cis* ratios, respectively.[14] Gratifyingly here again, trituration with MeCN furnished the enantio- and diastereomerically pure *trans*-(*S*,*S*)-**P8** and -**P9** products.

Finally, the reason for the high *trans*-selectivity obtained in the ATH with active-**C4** was investigated. By now, it is well-established that the saturation of the keto function under [Ru(*trans*-TsDPEN)(η^6-arene)]-catalyzed ATH occurs via a six-membered pericyclic transition state (TS) involving the Ru(II)−H catalyst hydride and a proton of the *N*,*N*-ligand amino group, while the stereoselectivity is influenced by the attractive CH/π electrostatic interaction between the η^6-arene and the ketone aryl group.[15]

Considering the nonclassical Ru(II) catalyst active-**C4** structure embedding a *syn*-configured *N*,*N*-ligand and the cosolvent effect observed when lowering the overall polarity of the reaction medium, we contemplated the existence of an additional attractive interaction with the substrate in the TS. Most likely, it consists of a H-bond between the AcN−*H* of the intermediate **S1′** and a proximal O atom of the sulfonamido function of active-**C4**. Thus, with the aim to validate this assumption, ATH using active-**C4** of the racemic 2-phthalimido-1-indanone (*rac*-**S10**) (an **S1′** close analog lacking the N*H*C(O) function) and of the simple basic α-acetamidoacetone (a linear nonaryl ketonic substrate) were carried out. Indeed, *rac*-**S10** converted into the expected *cis*-configured major product (1*S*,2*R*)-**P10** with a 97:3 *cis*/*trans* ratio (94% ee for *cis*) (Scheme 2);[16,17] this is due to the outward orientation of the phthalimido group in the TS thereby minimizing the sterics as with 2-Z-1-indanones of ref 7. In the case of α-acetamidoacetone, 1-acetamido-2-propanol was obtained in an er = 85:15. These findings support the presence of an additional favorable catalyst−substrate **S1′** interaction in the TS being a H-bond between O═S═O···H−NAc.

Moreover, the two most plausible TS geometries were located by applying DFT calculations in chlorobenzene: "*trans*-TS" whereby the H-transfer from active-**C4** to enantiomeric intermediate (2*S*)-**S1′** leads to *trans*-(1*S*,2*S*)-**P1**, and "*cis*-TS" whereby (2*R*)-**S1′** is transformed into *cis*-(1*S*,2*R*)-**P1** (Figure 4). These calculations predict the "*trans*-TS" to be favored over the "*cis*-TS" by Δ = 8.8 kcal mol^{-1} (E_a = 16.0 vs 24.8 kcal mol^{-1}), which is in line with the experimentally observed high

Scheme 2. Strategy for *trans*- or *cis*-β-Amino-1-indanol Using Active-C4



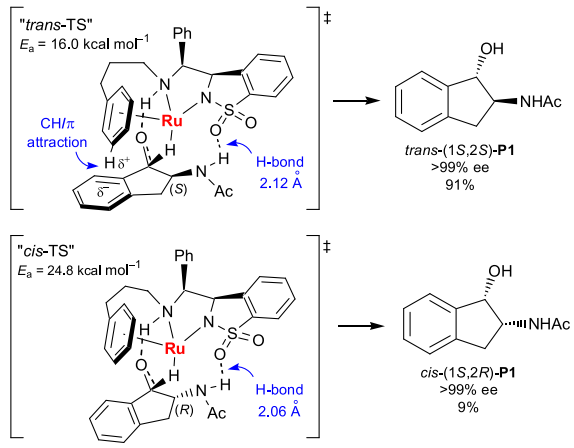


Figure 4. Schematic orientations of **S1′** enantiomers with cat. Ru(II)−H active-**C4** in their TS, and the corresponding energy level from DFT calculations in chlorobenzene.

trans-diastereoselectivity.[18] Thus, the "*trans*-TS" structure is stabilized by a two-pronged catalyst ligand−substrate attractive interaction: by the H-bond (2.12 Å) between O═S═O···H−NAc and by CH/π (T-shaped geometry) favoring the (2*S*)-configuration with an overall *trans*-selectivity. In the case of "*cis*-TS", the geometry with a H-bond of 2.06 Å but with the lack of a CH/π interaction is the lowest in energy.

The aforementioned DKR−ATH employing active-**C4** can serve to selectively prepare either of enantiomerically pure *trans*- or *cis*-β-amino-1-indanol following the deprotection of enantiomerically pure *trans*-(1*S*,2*S*)-**P1** or *cis*-(1*S*,2*R*)-**P10** (Scheme 2).

In conclusion, we have introduced a new enantiomerically pure *ansa*-RuCl[*syn*-ULTAM-$(CH_2)_3$Ph] complex **C4** and its Ru(II)−H active-**C4**. A diverse series of α,β-dehydro-α-acetamido and α-acetamido benzocyclic ketones were reduced via DKR−ATH to the corresponding *trans*-β-amido alcohols **P1**−**P9** with up to dr = 92:8 and excellent ee's. Facile trituration with MeCN yielded the enantio- and diastereochemically pure *trans*-products. DFT calculations relative to the diastereomeric TS structures revealed the existence of an atypical two-pronged attractive stabilization by CH/π interaction and by the O═S═O···H−NAc H-bond favoring the *trans*-products. These enantiomerically pure β-amido alcohols are valuable building blocks and amenable to further elaboration. In particular, either stereochemically pure *trans*- or *cis*-β-amino-1-indanol (deprotected *trans*-**P1** or deprotected

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cis-**P10**) can be selectively prepared using the same catalyst and procedure.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01069.

Experimental data, chiral HPLC chromatograms, NMR spectra for prepared compounds, computational and SC-XRD details (PDF)

Accession Codes

CCDC 1905532−1905533 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(8) *syn*-ULTAM = *syn*-3-(α-aminobenzyl)-benzo-γ-sultam (accessible in both enantiomeric forms). For its preparation, see: (a) Refernce 7h. (b) Jeran, M.; Cotman, A. E.; Stephan, M.; Mohar, B. *Org. Lett.* **2017**, *19*, 2042−2045.

(9) Noteworthy, ATH of benchmark substrates 1-indanone and α-tetralone using our new tethered Ru(II)−[*syn*-(3*R*,1′*S*)-ULTAM-$(CH_2)_3$Ph] complex (active-**C4**) with an S/C = 1000 at 60 °C was complete within 4.5 h furnishing 98% ee (*R*) for both (see Supporting Information), while with the nontethered complex [Ru(*syn*-(3*R*,1′*S*)-ULTAM)(*p*-cymene)] with an S/C = 200 was required for full conversion within 4 h at 40 °C giving 99% ee (*R*) for 1-indanol or 1-tetralol.[7h] Note, this nontethered-type version has a short lifetime at 60 °C which is unsuitable for the quantitative C═C and C═O reductions of **S1**.

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(12) By contrast, asymmetric hydrogenation of **S1** catalyzed by 1% Rh(I)-(3*H*-QuinoxP*) in dioxane proceeded stereoselectively in the absence of DKR with reduction of only the C═C bond at 3 atm of H_2 (92% ee for **S1′**), or both C═C and C═O under 20 atm of H_2 (*trans*/*cis* = 93:7, 94% ee for *trans*-**P1**). For this, see: Hu, Q.; Chen, J.; Zhang, Z.; Liu, Y.; Zhang, W. *Org. Lett.* **2016**, *18*, 1290−1293.

(13) Noteworthy, under DKR−ATH (using Ru(II) cat. active-**C4**) of 2-methoxycarbonyl-3-phenyl-1-indanone (keto/enol = 88:12) and 2,3-diphenyl-1-indenone leading to dr = 57:43:0:0 (quant, 97% ee for major, >99% ee for minor) and 34:41:25:0 (quant), respectively, very

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slow epimerization at C(3) occurred. For this, see: Cotman, A. E. PhD Dissertation, University of Ljubljana, 2018.

(14) In the literature, stereochemically pure *trans*-(*R*,*R*)-**P8** was prepared through a non-racemizing intramolecular Friedel−Crafts acylation of (*R*)-homotyrosine followed by diastereoselective reduction with Red-Al. For this, see: Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143−5150.

(15) (a) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818−2821. (b) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931−7944.

(16) In the literature, *trans*-(1*R*,2*R*)-**P10** (>99% ee) was prepared via a *trans*-selective reduction of *rac*-**S10** with $NaCNBH_3$/AcOH followed by kinetic resolution with *Arthrobacter sp.* lipase. For this, see: Rouf, A.; Gupta, P.; Aga, M. A.; Kumar, B.; Parshad, R.; Taneja, S. C. *Tetrahedron: Asymmetry* **2011**, *22*, 2134−2143.

(17) Noteworthy, an identical *cis*/*trans* ratio but with a higher 98% ee was obtained employing the $PipSO_2$DPEN-based catalyst active-**C3**.

(18) Gas-phase DFT calculations similarly predicted the "*trans*-TS" to be favored over the "*cis*-TS" by Δ = 7.3 kcal mol^{-1} (E_a = 11.1 vs 18.4 kcal mol^{-1}).

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