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A new synthetic route to optically active cyclomercurated ferrocenylimines

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ABSTRACT

An adaptation of Kagan's method for preparing 2-substituted ferrocenecarboxaldehydes has allowed us to directly prepare enantiopure (S_p)-2-chloromercurio-ferrocenecarboxaldehyde, (S_p)-**3**. Subsequent condensation of this aldehyde with (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine ((*R*,*R*)-**4**) yielded a novel, enantiopure bis-cyclomercurated ferrocenylimine, (S_p,S_p,R_c,R_c)-*N*,*N*-bis(2-(chloromercurio)ferrocenylidene)-1,2-diphenylethane-1,2-diimine ((S_p,S_p,R_c,R_c)-**5**). In addition to the chiroptical data collected for both (S_p)-**3** and (S_p,S_p,R_c,R_c)-**5**, the solid-state structure and absolute configuration of (S_p,S_p,R_c,R_c)-**5** were confirmed by X-ray crystallography.

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1. Introduction

Due to their propensity for transmetallation, optically active cyclomercurated ferrocenylimines represent suitable precursors for the synthesis of new organometallic compounds and new ligands for asymmetric catalysis. Current methods for preparing cyclomercurated ferrocenylimines generally proceed regioselectively, via *ortho*-mercuration of formyl- or acetyl-ferrocene, followed by condensation with a primary amine [1–3]. Alternatively, a ferrocenyl-imine may first be prepared, followed by *ortho*-mercuration of the imine to arrive at the corresponding disubstituted ferrocenylimine [1,4,5]. While the regioselectivity of these reaction schemes is controlled by the heteroatom containing substituent [1,6], the control of stereoselectivity in this context has proven to be more difficult. As a consequence of this, more indirect synthetic methods such as transmetallation of the corresponding cyclopalladated species [7] are necessary in order to prepare planar chiral cyclomercurated ferrocenylimines. Alternatively, extensive chromatographic separations may be carried out in order to isolate these products following non-selective synthetic methods such as those described above.

Precursor palladacycles may be prepared using an auxiliary [8,9] or by optical resolution [10]. Overman and co-workers reported one of the first examples of an enantiopure cyclopalladated ferrocenylimine (Scheme 1) [11] which was synthesized by condensation of (*S*)-α-iodo-ferrocenecarboxaldehyde, prepared via Kagan's method [12], and aniline. The resulting iodo-ferrocenylimine was reacted with $Pd_2(dba)_3 \cdot CHCl_3$ to yield the corresponding cyclopalladated ferrocenylimine.

It should be noted here that in addition to transmetallation of *ortho*-palladated species to prepare *ortho*-mercurated analogs, *ortho*-mercurated species may also be transmetallated with tin [13], tellurium [14], and ruthenium [15,16], and as such, they represent viable precursors for the synthesis of new organometallic compounds. One of the primary objectives of our research is the synthesis of new ligands that may be used in asymmetric, transition-metal catalyzed reactions. Further, many of the ligands that we prepare in our lab possess both planar and central chirality, and it is in this context that we saw value in working toward the expansion of existing methods for preparing planar chiral, cyclomercurated ferrocenylimines. We were recently inspired by the realization that by adapting a synthetic scheme that is used routinely in our lab, we may be able to prepare enantiopure cyclomercurated ferrocenylimines with both planar and central chirality directly, without the need for extensive isolation techniques. The use of non-selective synthetic methods [17] often necessitates accompanying preparative purification schemes in order to separate diastereomeric components of the resulting product mixtures. In addition, because of the susceptibility of many ferrocenylimines to hydrolysis when exposed to conventional chromatographing agents (silica, alumina), aromatic amines are generally used to prepare ferrocenylimines that will undergo *ortho*-metalation and can survive the chromatographic isolation. Though we realize that in practice not all *ortho*-mercurated ferrocenylimines prepared using this method would be able to be rigorously purified by re-crystallization, a stereoselective synthetic strategy such as this one, which does not

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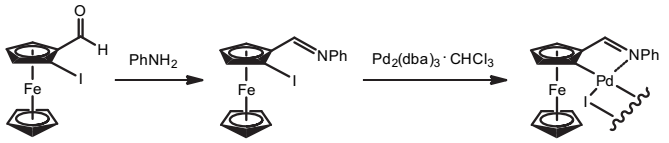
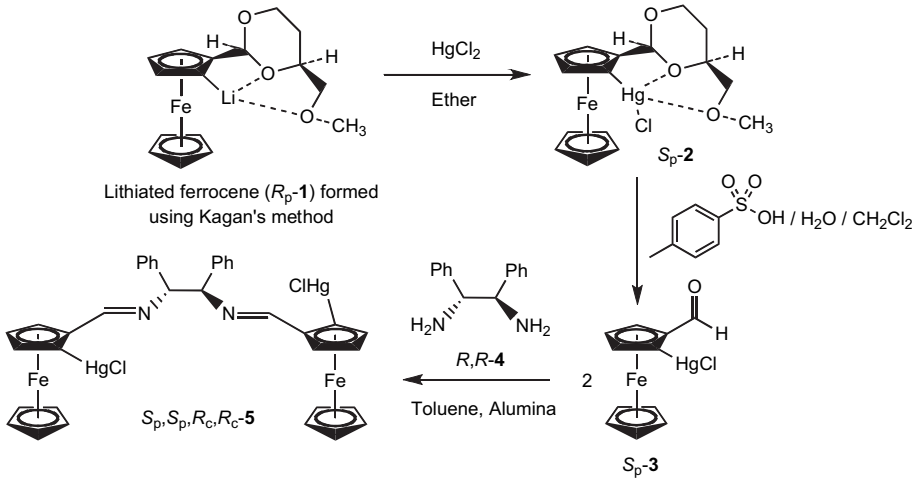


Scheme 1. Overman's preparation of an enantiopure cyclopalladated ferrocenylimine (reproduced from [11]).

directly from the method reported by Kagan and co-workers [12]. This allowed for the diastereoselective preparation of (R_p,S_c,S_c)-4-(methoxymethyl)-2-[2-(lithio)ferrocenyl]-1,3-dioxane, *Rp*-**1** (Scheme 2). Next, instead of quenching the organolithium (*Rp*-**1**) with one of the electrophiles studied previously by Kagan and co-workers, transmetallation of *Rp*-**1** using $HgCl_2$ was carried out, which yielded the cyclomercurated acetal derivative *Sp*-**2**. Subsequent deprotection of *Sp*-**2** produced (S_p)-**3**, which was subsequently reacted with (*R*,*R*)-**4** to give (S_p,S_p,R_c,R_c)-**5**. Crystalline (S_p,S_p,R_c,R_c)-**5** was obtained by layering a CH_2Cl_2 solution of the product residue with hexanes; crystal data are presented in Table 1.



Scheme 2. Preparation of an enantiopure *ortho*-mercurated ferrocenylimine.

necessitate chromatographic isolation, may expand the range of primary amines that can be used to prepare these compounds.

2. Results and discussion

2.1. Successful adaptation of Kagan's method in the direct, asymmetric preparation of (S_p,S_p,R_c,R_c)-5

Enantiopure (S_p,S_p,R_c,R_c)-**5** was prepared via the strategy outlined in Scheme 2, with the first four synthetic steps being taken

Table 1
Crystal data and structure refinement for (S_p,S_p,R_c,R_c)-**5**.

Empirical formula	$C_{36}H_{30}Cl_2Fe_2Hg_2N_2$
Formula weight	1074.40
Temperature	90(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 9.6521(5)$ Å, $\alpha = 90°$. $b = 10.6414(5)$ Å, $\beta = 90°$. $c = 32.0487(15)$ Å, $\gamma = 90°$.
Volume	3291.8(3) Å^3
Z	4
Density (calculated)	2.168 Mg/m^3
Absorption coefficient	10.354 mm^{-1}
F(000)	2024
Crystal size	0.26 × 0.17 × 0.10 mm^3
Crystal color and habit	Orange plate
θ range for data collection	1.27–27.48°.
Reflections collected	31 128
Independent reflections	7552 [R(int) = 0.0392]
Observed reflections (I > 2σ(I))	7187
Max. and min. transmission	0.424 and 0.174
Goodness-of-fit on F^2	0.965
Final R indices [I > 2σ(I)]	$R1 = 0.0210$, wR2 = 0.0427
R indices (all data)	$R1 = 0.0233$, wR2 = 0.0434
Absolute structure parameter	−0.010(4)
Largest diff. peak and hole	1.531 and −0.802 e.Å^{-3}

Several important features of (S_p,S_p,R_c,R_c)-**5** are elucidated from its crystal structure (Fig. 1 and Table 2). First, the two Hg–N distances in this diimine are seen to be 2.738(3) Å (Hg(1)-N(1)) and 2.698(3) Å (Hg(2)-N(2)), respectively. These values are below the sum (approx. 3.05 Å) of the van der Waals radii for Hg^{2+} (1.50 Å) and N (1.55 Å) [1,3,16,17], which confirm our expectation that (S_p,S_p,R_c,R_c)-**5** is cyclomercurated in the solid state. The planar chirality (S_p) of the disubstituted ferrocene, in addition to the point chirality of the ethane moiety (1*R*,2*R*) can clearly be seen in Fig. 1.

2.2. CD studies

Wu and co-workers synthesized opposing enantiomers of a particular planar chiral cyclomercurated ferrocenylimine and subsequently obtained X-ray crystallographic and chiroptical data for these compounds, thus allowing for a meaningful assignment of characteristic Cotton effects (CEs) [1,14]. Additional CD data was obtained for transmetallated analogs of Wu's compounds, which

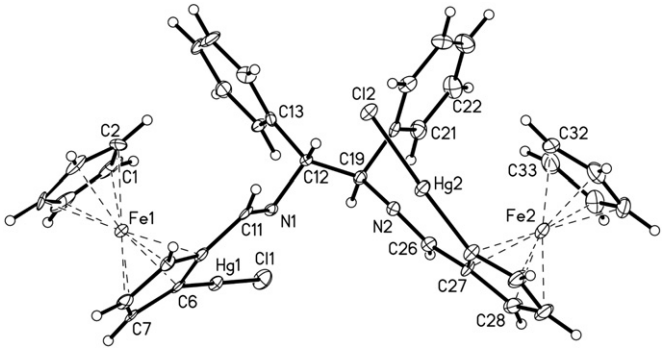


Fig. 1. Molecular structure of (S_p,S_p,R_c,R_c)-**5**.

Table 2
Selected geometric parameters for (S_p,S_p,R_c,R_c)-**5**.

Bond lengths (Å)			
Hg(1)-N(1)	2.738(3)	N(1)-C(11)	1.273(5)
Hg(2)-N(2)	2.698(3)	N(2)-C(26)	1.278(5)
Bond angles (°)			
C(10)-C(6)-Hg(1)	118.6(3)	C(27)-C(31)-Hg(2)	117.6(3)
C(7)-C(6)-Hg(1)	133.7(3)	C(30)-C(31)-Hg(2)	133.1(3)
Torsion angles (°)			
C(6)-C(10)-C(11)-N(1)	−9.6(6)	N(2)-C(26)-C(27)-C(31)	−4.3(7)
N(1)-C(12)-C(19)-N(2)	−70.9(4)		

then allowed for assertions to be made about retention of stereochemistry upon transmetallation etc [7]. Since (S_p,S_p,R_c,R_c)-**5** is an analog of Wu's compounds, and because we can also assign its absolute configuration definitively using X-ray crystallography (Fig. 1), we thought it would be advantageous to also obtain chiroptical data for (S_p,S_p,R_c,R_c)-**5**, especially in light of possible future transmetallation experiments (Figs. 2 and 3).

With respect to the UV-Vis spectra of (S_p)-**3** and (S_p,S_p,R_c,R_c)-**5** presented in Fig. 3, each compounds shows two strong absorption maxima that are comparable in wavelengths and molar absorptivities. These absorptions are due to the d-d electronic transitions of the Fe^{2+} chromophore within each ferrocenyl moiety. Owing to their d−d type electronic transitions and inherent planar chirality, the CD spectra of 1,2-disubstituted ferrocenes exhibit dramatic CEs [18], and those presented in this paper for (S_p)-**3** and (S_p,S_p,R_c,R_c)-**5** (Fig. 2) are no exception. With respect to planar chirality (S_p), the characteristic CD spectrum of (S_p,S_p,R_c,R_c)-**5** fully corroborates the findings of Wu and co-workers referred to above. Therefore, from right to left in the spectrum shown in Fig. 2, the signs of the CEs for (S_p,S_p,R_c,R_c)-**5** exhibit a "negative, positive, negative, positive" pattern. The same pattern was obtained by Wu and co-workers for their (S_p)-2-HgCl-ferrocenylimine, and it is opposite to that seen for their (R_p)-enantiomer. As expected, the CE profile of (S_p)-**3** (Fig. 2) is very similar to that of (S_p,S_p,R_c,R_c)-**5**, and is indicative of its *S*-planar chirality. The apparent correlation between the positions of the two positive CEs (Fig. 2) and those of the two UV-Vis absorption maxima (Fig. 3) is noted. However, one distinct difference between the CD spectrum of (S_p)-**3** and that of (S_p,S_p,R_c,R_c)-**5** is the observed red shift in the positive CE (to about 350 nm) of the latter relative to that of the former. A similar red shift is observed in the UV−Vis spectra of these two compounds, and although it may be tempting to account for such a shift in terms of the presence of central (point) chirality in (S_p,S_p,R_c,R_c)-**5**, such an assertion would be ill-advised. In this context, an analysis of point chirality is much less straightforward, and will not be attempted (Fig. 3).

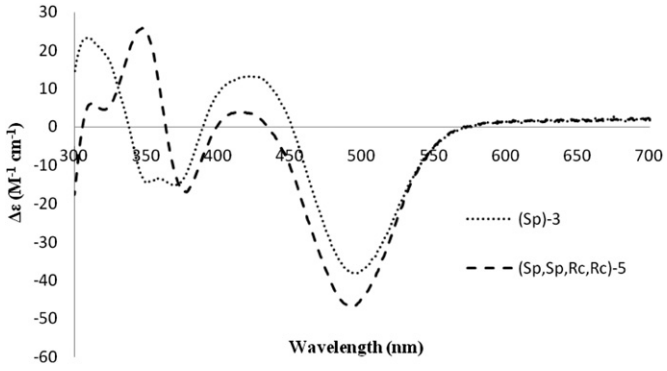


Fig. 2. CD spectra of (S_p)-**3** and (S_p,S_p,R_c,R_c)-**5**.

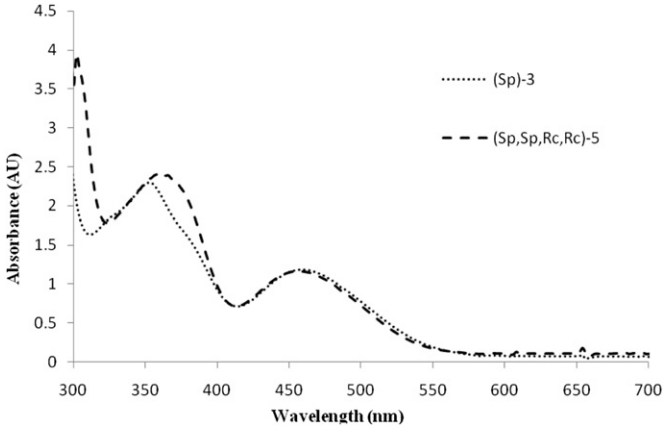


Fig. 3. UV−Vis spectra of (S_p)-**3** and (S_p,S_p,R_c,R_c)-**5**.

3. Conclusion

Herein we would like to report the direct, stereoselective synthesis of (S_p,S_p,R_c,R_c)-*N*,*N*-bis(2-(chloromercurio)ferrocenylidene)-1,2-diphenylethane-1,2-diimine, (S_p,S_p,R_c,R_c)-**5**. This was accomplished via an adaptation of Kagan's method [12] of preparing enantionpure 1,2-disubstituted ferrocenecarboxaldehydes, which afforded us (S_p)-2-chloromercurio-ferrocenecarboxaldehyde, (S_p)-**3**. The subsequent condensation reaction between (S_p)-**3** and (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine ((*R*,*R*)-**4**), yielded enantiopure (S_p,S_p,R_c,R_c)-**5**. A crystal structure of (S_p,S_p,R_c,R_c)-**5** was obtained and analyzed in conjunction with the chiroptical data collected for (S_p)-**3** and (S_p,S_p,R_c,R_c)-**5**.

4. Experimental Section

4.1. General

Prior to their use, toluene, THF and diethyl ether were distilled over sodium/benzophenone. Neutral alumina was activated by placing it overnight in an oven set to 120 °C. All syntheses were performed under argon unless otherwise noted. NMR spectra (^{1}H and ^{13}C) were recorded using a Bruker 300 MHz spectrometer and IR data was collected on a Nicolet Avatar 320 FT-IR spectrometer. CD spectra were recorded on a JASCO J-815 CD spectrometer and UV/Vis data was collected on an HP 8452A Diode Array spectrophotometer. The (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine, (*R*,*R*)-**4**, was purchased from Acros Organics.

4.2. (S_p)-2-(chloromercurio)-ferrocenecarboxaldehyde, (S_p)-**3**

The ferrocenyl-dioxane precursor prepared previously (4.18 g, 13.2 mmol) [12] was dissolved in 45 mL of anhydrous ether and transferred to a 250 mL three-necked flask. The flask was fitted with an addition funnel and a septum, and the system was purged with argon and maintained under static argon for the remainder of the procedure. The reaction flask was then placed in a dry ice/acetone bath to achieve a reaction temperature of approximately −78 °C. An aliquot (10.6 mL, 15.9 mmol) of a 1.5 M solution of *t*-butyl lithium in pentane was added to the addition funnel using a syringe, and then added dropwise to the reaction mixture. After 10 min of additional stirring, the flask was removed from the ice bath and allowed to warm to room temperature while stirring. The reaction mixture (containing the lithiated ferrocene **1**) was stirred for 1 h before it was again cooled in an acetonitrile/dry ice bath (−42 °C). A solution of mercuric chloride, prepared by dissolving 4.67 g (17.2 mmol) of the

white solid in 20 mL of dry THF, was then transferred to the addition funnel (via syringe) before being added dropwise to the reaction mixture. The reaction was allowed to come to room temperature and then stirred for an additional 20 h, at which point it was carefully quenched with water and extracted with ether. The ether layer was washed with water (3 × 20 mL) and dried over Na_2SO_4, and the crude *ortho*-mercurated ferrocenyl-acetal (**2**) was purified by flash chromatography (silica, 4:1 hexanes/EtOAc). Deprotection of **2** was accomplished as follows: the dark red oil (2.66 g, 4.83 mmol) in dichloromethane (70 mL) was added to a 250 round-bottomed flask, followed by the addition of DI water (30 mL) and 2.0 g of PTSA (*p*-toluenesulfonic acid monohydrate, 10.5 mmol), and the resulting mixture was stirred for 24 h. The crude product (S_p-**3**) was extracted with CH_2Cl_2 and washed with water (3 × 20 mL), and the organic layer was dried over Na_2SO_4 before the solvent was removed under reduced pressure. Further purification of S_p-**3** may be accomplished by small batch flash chromatography (silica, 4:1 hexanes:EtOAc) or via re-crystallization (by layering a CH_2Cl_2 solution of S_p-**3** with hexanes). mp 144–145 °C. ^{1}H NMR($CDCl_3$), δ: 4.32 (s, 5H, C_5H_5); 4.62 (m, 1H, C_5H_3); 4.82 (m, 1H, C_5H_3); 4.94 (m, 1H, C_5H_3); 10.13 (d, 1H, CH]O, J_{Hg-H} = 0.96 Hz). ^{13}C{^{1}H}-NMR($CDCl_3$), δ: 70.35 (C_5H_5); 73.59 (C_5H_3, *C*H); 75.92 (C_5H_3, *C*H); 78.80 (C_5H_3, *C*H); 81.94 (C_5H_3, *C*-HgCl); 83.48 (C_5H_3, *C*-CHO); 193.84 (*C*H]O). IR; ν(cm^{-1}): 3094 (w), 2844 (w), 1648 (C]O, s), 1430 (m), 1409 (m), 1361 (m), 1349 (m), 1327 (w), 1225 (m), 1106 (m), 1032 (m), 1001 (m), 827 (m), 755 (m), 734 (m).

4.3. (S_p,S_p,R_c,R_c)-N,N-bis(2-(chloromercurio)ferrocenylidene)-1,2-diphenylethane-1,2-diimine, (S_p,S_p,R_c,R_c)-**5**

To a 10 mL round-bottomed flask were added (S_p)-**3** (0.050 g, 0.11 mmol), (*R*,*R*)-**4** (0.0118 g, 0.055 mmol), and 5 mL of dry toluene. Activated alumina (0.1 g) was also added to the flask, and the mixture was heated to 50 °C and stirred at that temperature for 24 h. The reaction mixture was then filtered through celite before the solvent was removed under reduced pressure, leaving a crude red oil which was allowed to dry further under high vacuum. Recrystallization was accomplished by dissolving the crude product in a minimum of CH_2Cl_2 and layering this solution with hexanes. The resulting crystalline product, (S_p,S_p,R_c,R_c)-**5**, was harvested and washed with hexanes. d 188 °C; ^{1}H NMR($CDCl_3$), δ: 3.83 (s, 10H, C_5H_5); 4.31 (m, 2H, C_5H_3); 4.48 (m, 2H, C_5H_3); 4.63 (m, 2H, C_5H_3); 5.16 (s, 2H, NCHPh); 7.11–7.38 (m, 10H, Ph); 8.59 (d, 2H, J_{Hg-H}, 0.54 Hz). ^{13}C{^{1}H}-NMR($CDCl_3$), δ: 69.50 (C_5H_5) × 2; 71.80 (C_5H_3, *C*H) × 2; 73.20 (C_5H_3, *C*H) × 2; 75.80 (C_5H_3, *C*H) × 2; 79.37 (NCHPh) × 2; 82.32 (C_5H_3, *C*-HgCl) × 2; 84.16 (C_5H_3, *C*-CH = N) × 2; 127.52 (Ph, *C*-H) × 2; 128.09 (Ph, *C*-H) × 4; 128.81 (Ph, *C*-H) × 4; 141.33 (Ph, *C*CHN) × 2; 163.05 (HC]N) × 2. IR; ν(cm^{-1}): 3082 (w), 3028 (w), 2876 (w), 1625 (C]N, s), 1491 (w), 1452 (w), 1347 (w), 1265 (w), 1230 (w), 1105 (m), 1051 (m), 1031 (m), 1000 (m), 815 (m), 753 (m), 736 (m), 700 (s).

4.4. X-ray crystallography

Crystals suitable for single-crystal X-ray diffraction analysis were grown from a concentrated CH_2Cl_2 solution of (S_p,S_p,R_c,R_c)-**5** layered with hexanes; orange plate (0.26 × 0.17 × 0.10 mm^3). Diffraction data was collected on a Bruker SMART 1000 using graphite-monochromatized Mo Kα radiation at 90(2) K. A suitable crystal was mounted on a glass fiber with silicone grease and placed in the N_2(g) cold stream provided by a CryoIndustries apparatus. Data collection was carried out with the use of SMART software, and data reduction was done using SAINT and corrected for absorption using SADABS [19]. The structure was solved with the use of SHELXS97 and refined with SHELXL97 [20]. Hydrogen atoms were added geometrically and refined with a riding model.

4.5. CD spectroscopy

Samples analyzed via CD spectroscopy (Fig. 2) were prepared in CH_2Cl_2: (S_p)-**3**; *c* = 2 mM, (S_p,S_p,R_c,R_c)-**5**; *c* = 2 mM. The same samples were also used to obtain UV–Vis spectra for these two compounds.

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Appendix. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.jorganchem.2010.12.042.

X-ray crystallograpic data for (S_p,S_p,R_c,R_c)-**5** is available in CIF format.

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