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Dual Photoredox- and Titanium Catalysis-Enabled Three-Component Radical Propargylation of Aldehydes with 1,3-Enynes

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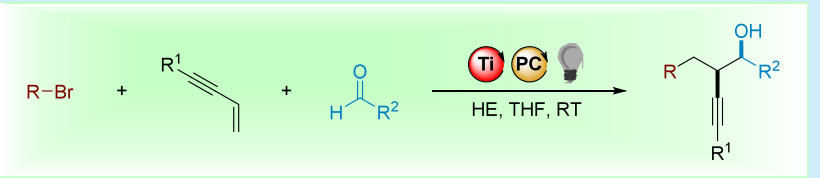

ABSTRACT: Herein, a straightforward and practical strategy involving radicals for the three-component carbonyl propargylation via dual photoredox and titanium catalysis is presented. This strategy delivers homopropargyl alcohols and includes readily available starting materials, a broad substrate scope, high functional group tolerance, and mild reaction conditions. Catalytic Cp_2TiCl_2, recognized as an inexpensive, nontoxic, and bench-stable titanium source, is employed.

Developing eco-friendly and efficient synthetic strategies has been always a fundamental pursuit in organic chemistry.[1] Propargylic compounds, such as homopropargylic alcohols/amines and their derivatives, serve as crucial building blocks for the synthesis of numerous pharmaceuticals and biologically active natural products (Figure 1a).[2] The addition of π-propargylic or allenylic metal reagents to carbonyls is recognized as an essential and straightforward approach to construct versatile homopropargylic compounds.[3−6] Propargyl halides and alcohol derivatives proved to be preeminent precursors when Pd,[7] Sn,[8] Zn,[9] In,[10] Cr,[11] and Cu[12] were employed as catalysts.

As the second most abundant transition metal in the Earth's crust, titanium stands out as an appealing option for catalytic applications due to its versatility, affordability, low toxicity, and well-established biocompatibility. Although titanium chemistry has been recognized primarily for its significant role in polyethylene production over the past two decades, its contributions to fine chemical synthesis have garnered increasing attention. Titanium catalysis has facilitated the development of a variety of catalytically active systems, allowing for substrate transformations across nearly all oxidation states of titanium and promoting the synthesis of numerous novel compounds. Titanium reagents, such as $Ti(O^iPr)_4$ and Cp_2TiCl_2, have been widely recognized as green and abundant catalysts and applied to various practical methodologies in modern synthetic chemistry.[13−32]

Addition of an allenyl−titanium complex to carbonyl was used to synthesize homopropargylic alcohol derivatives (Figure 1b). Usually, the propargyl−titanium or allenyl−titanium complexes were prepared by treating the substituted propyne derivatives with *tert*-butyllithium, forming lithio propargylic intermediates, which subsequently underwent a transmetallization of the lithium ion with $Ti(O^iPr)_4$.[33] Additionally, titanium species can be also generated through ligand exchange and subsequent elimination between divalent titanium reagent $Ti(O^iPr)_4/^iPrMgBr$ and propargyl halides or alcohol derivatives.[34] These mechanisms essentially involve a two-electron transfer process. Given that $Cp_2Ti^{III}Cl$ has been identified as a powerful one-electron reductant, we wondered whether propargyl−titanium complexes can be generated via single-electron transfer (SET) between $Cp_2Ti^{III}Cl$ and propargylic radicals from 1,3-enynes.[35,36]

1,3-Enynes and derivatives have attracted significant interest for their possibilities of preparing multifunctional substituted homopropargylic and allenylic products.[37−42] Recently, transition metals, such as Cr, Ni, and Cu, were used as high-efficiency catalysts to capture propargylic radicals by the SET process, forming propargyl− or allenyl−metal species (Figure 1c). For example, dual Cr/photoredox catalytic systems were developed by the Glorius and Wang groups via a radical-polar crossover mechanism, involving propargyl− and allenyl−Cr species and giving carbonyl propargylation and allenylation products, respectively.[43,44] The Bao and Liu groups independently reported the fascinating Cu-catalyzed enantioselective synthesis of chiral allenes via the radical 1,4-dicarbonization of 1,3-enynes.[45,46] Lu and co-workers reported a strategy for 1,4-alkylcyanation of 1,3-enynes with redox-active esters by merged photoredox and copper catalysis.[47] Besides, nickel

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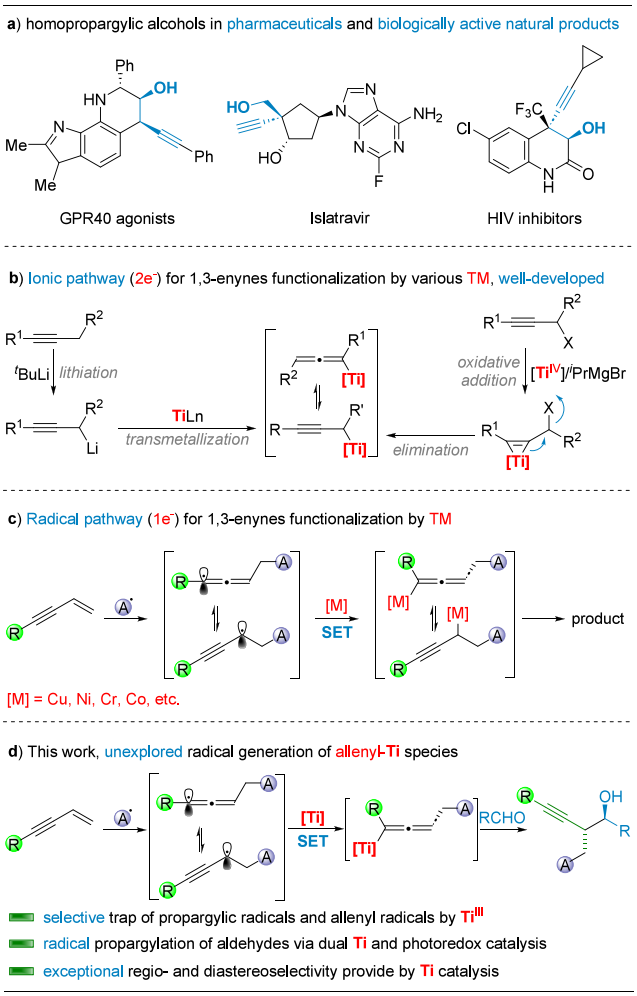


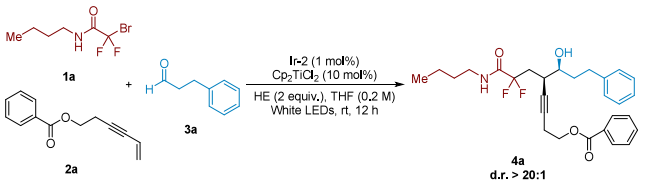
Figure 1. (a) Homopropargylic alcohols in pharmaceuticals and biologically active natural products. (b) Previously reported methods for the synthesis of propargyl−titanium or allenyl−titanium complexes. (c) Radical functionalization of 1,3-enyne and carbonyl. (d) Radical carbonyl propargylation by dual photoredox and Ti catalysis (this work).

was identified as another promising catalyst for the formation of propargyl− or allenyl−Ni species in cross-coupling reactions.[48,49] Recently, an attractive reaction system using Co/photoredox catalysts was described by the Meng group for the synthesis of homopropargylic alcohols via a propargyl−Co intermediate.[50] Although plenty of progress was made, the radical propargylation between 1,3-enyne and aldehyde, catalyzed by dual photoredox/titanium, remains undefined.

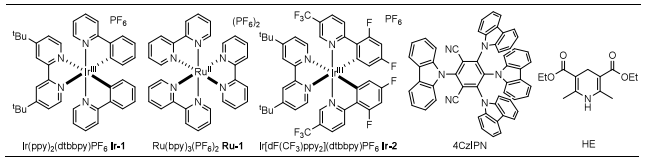
With these advancements, we anticipated that under photoreductive conditions the $Cp_2Ti^{III}Cl$ and alkyl radical would be generated via a SET process. 1,3-Enynes could act as efficient radical acceptors to trap the alkyl radicals and forge two equilibrated species, the propargylic radical and allenylic radical, which were then captured by Ti^{III} to give the nucleophilic propargyl− and allenyl−Ti^{IV} complexes, respectively (Figure 1d). This radical-based three-component approach enables two new C−C bonds to be constructed simultaneously and features a green catalyst, easily accessible starting materials, high diastereoselectivity, tolerant reaction conditions, and thus a broad substrate scope.

We began our investigation of this radical-based three-component propargylation using difluoroacetamide (**1a**), 1,3-enyne (**2a**), and benzenepropanal (**3a**) as representative substrates under photoconditions (Table 1). Initially, this

Table 1. Reaction Optimization[a]



entry	variation from the standard conditions	yield of **4a** (%)[b]	dr[c]
1	as shown	81	>20:1
2	**Ir-1** instead of **Ir-2**	70	>20:1
3	4CzIPN instead of **Ir-2**	56	>20:1
4	**Ru-1** instead of **Ir-2**	0	
5	450 nm LEDs	56	>20:1
6	400 nm LEDs	51	>20:1
7	DCE instead of THF	55	>20:1
8	DCM instead of THF	62	>20:1
9	1,4-dioxane instead of THF	69	>20:1
10	MeCN instead of THF	43	>20:1
11	DMF instead of THF	0	
12	$CpTiCl_3$ instead of Cp_2TiCl_2	37	>20:1
13	salen−Ti instead of Cp_2TiCl_2	0	
14	no Cp_2TiCl_2, PC, *hν*, or HE	0	



[a]General reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), Cp_2TiCl_2 (10 mol %), **Ir-2** (1 mol %), HE (2 equiv), THF (0.2 M), 10 W white LEDs, N_2 atmosphere, rt, 12 h. [b]Yields were determined by ^1H NMR spectroscopy vs an internal standard (1,3,5-trimethoxybenzene). [c]The diastereoselectivity was determined by ^1H NMR.

reaction was performed with **Ir-2** (1 mol %) as the photocatalyst, Cp_2TiCl_2 (10 mol %) as the metal catalyst, Hantsch ester (HE, 2 equiv) as the electron and H^+ donor, and THF (0.2 M) as the solvent under 10 W white LEDs at room temperature for 12 h. To our delight, three-component coupling product **4a** was successfully obtained in 81% yield with a >20:1 dr (entry 1). Subsequently, we proceeded with the comprehensive screening of various factors. Replacing **Ir-2** with **Ir-1** and 4CzIPN caused a markedly reduced yield (entries 2 and 3, respectively), and **Ru-1** restrained the reaction completely (entry 4). When the white LED was substituted with 450 and 400 nm blue LEDs, the yield partly decreased (entries 5 and 6, respectively). Then, several common solvents were screened, revealing a moderate (DCE, DCM, and 1,4-dioxane) to severe (MeCN and DMF) detrimental influence on the yield of product **4a** (entries 7−11, respectively). Upon substitution of Cp_2TiCl_2 with $CpTiCl_3$, a significant decrease in yield was observed (entry 12). Furthermore, when salen−Ti was used as the catalyst, the reaction did not proceed (entry 13). Control experiments demonstrated that all of the reaction parameters were necessary to achieve this carbonyl propargylation (entry 14).

With the optimized reaction conditions established, we proceeded to investigate the scope of the three-component

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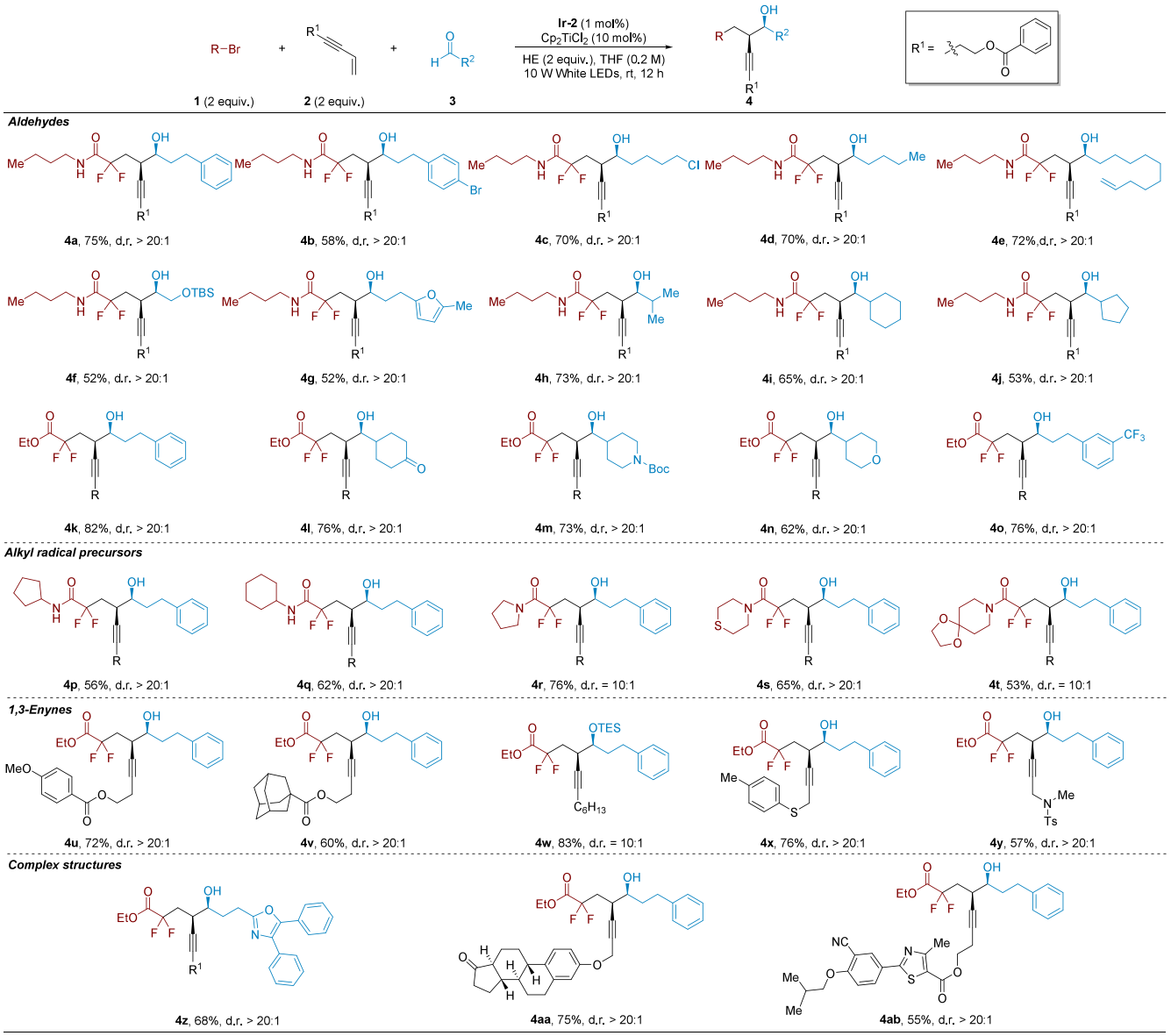
Scheme 1. Scope of Propargylation Reactions[a,b,c]



[a]Reagents and conditions: **1** (0.4 mmol), **2** (0.4 mmol), **3** (0.2 mmol), **Ir-2** (1 mol %), Cp_2TiCl_2 (10 mol %), HE (0.4 mmol), THF (1.0 mL, 0.2 M), 10 W white LEDs, rt, 12 h. Isolated yields. [b]MeCN instead of THF was used for the synthesis of compounds **4k**–**4o** and **4u**–**4ab**. [c]dr was determined by ^{1}H NMR.

propargylation under the dual photoredox/titanium catalytic system, as shown in Scheme 1. Generally, various aliphatic aldehydes could be adapted well in this radical-based process. Halides such as Cl (**4c**) and Br (**4b**) and a long chain alkyl (**4d**) were all tolerated. Potential alkyl radical acceptors such as alkenyl (**4e**) were shown to have no significant effect on this process. Acid-sensitive groups such as OTBS (**4f**) groups were easily allowed to deliver the propargylation products in good to excellent yields with high diastereoselectivity (>20:1). Aldehyde containing a heterocyclic structure is also highly compatible with the process (**4g**). The secondary (or cyclic) aldehydes (**4h**–**4j**) were also engaged in this protocol, and the results showed that most of these aldehydes were smoothly converted into the desired products in satisfactory yields and diastereoselectivity. Besides, when using MeCN as the solvent, ethyl difluorobromoacetate was also used effectively to furnish the propargylation products in good yields with impressive diastereoselectivity (>20:1) under the optimized conditions (**4k**). When using ethyl difluorobromoacetate as a radical precursor, a strong electron-withdrawing group (**4o**) can also be adapted well in the process. The cyclic aldehydes (**4l**–**4n**) were also successfully converted into the desired product.

With regard to the alkyl radical precursors, numerous difluorobromoacetamides demonstrate compatibility with this reaction system (**4p**–**4t**). In addition, numerous 1,3-enynes substituted with multiple groups were successfully used as alkyl radical acceptors to generate the corresponding radicals in situ and then participate in the following addition step with aldehyde. Ester (**4u** and **4v**)-, long chain alkyl (**4w**)-, thioether (**4x**)-, and TsN (**4y**)-substituted 1,3-enynes were all shown to be attractive coupling partners to give the desired products in moderate to excellent yields with distinguished diastereoselectivity.

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Encouraged by these successful results, we focused our attention on studying the practicability of our protocol for the late-stage modification of structurally complicated compounds that comprised marketed drug molecules and natural products. The aliphatic aldehyde derived from oxaprozin (**4z**) proved to be tolerated, as well. Moreover, estrone and febuxostat were verified to be usable, delivering potentially valuable products **4aa** and **4ab**, respectively, in favorable yields and excellent diastereoselectivity without an effect of multiple functional groups. All of the results highlighted the good functional group compatibility of our protocol, since even in the presence of an ester, a ketone, or a cyano group, only the aldehyde was selectively functionalized.

To further shed light on the possible mechanism of this process, a suite of experiments were conducted. Control experiments in the absence of Cp_2TiCl_2 were performed. In this case, the desired product was not detected and the reduction product (**5**) of the propargylic radical was isolated in 73% yield (Figure 2a), which accounted for the fact that the propargylic radical was difficult to add to carbonyl of aldehyde and easily reduced without Cp_2TiCl_2. Meanwhile, the radical clock experiment using 2-phenylcyclopropane-1-carbaldehyde (**6**) as a substrate was successfully conducted (Figure 2b). The desired three-compounent coupling products were isolated as a mixture of **7a** and **7b** in 52% yield (1.6:1 ratio), suggesting that the ketyl radical intermediates were not likely involved and the products were generated via addition between the allenyl−Ti^{IV} complex and aldehydes.

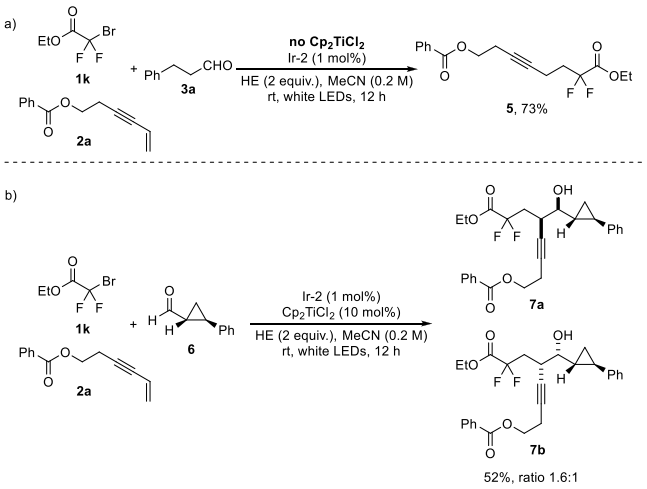

Figure 2. Control experiments.

Overall, the catalytic cycle is proposed in Figure 3. HE was oxidized by excited-state $*Ir^{III}$ to deliver $HE^{\bullet+}$ and strong reductant Ir^{II}, which was then oxidized by Cp_2TiCl_2 to give ground-state Ir^{III} and $Cp_2Ti^{III}Cl$. Meanwhile, difluoroacetamide/ethyl difluorobromoacetate was reduced by another $*Ir^{III}$ to generate related alkyl radical R•, which then added to 1,3-enyne rapidly, forming propargylic radical **I**. Immediately, species **I** was captured by Ti^{III}, producing Ti^{IV}−propargyl **II** and allenyl−Ti^{IV} **III**. The dynamic equilibrium between **II** and **III** favored the transition to intermediate **III**, which acted as a nucleophile to attack the carbonyl of aldehyde via a six-membered chelate-type ring transition state to give the titanium alkoxide species in a *syn*-selective fashion. After being hydrolyzed by PyH^+ to deliver the desired three-component propargylation product and release Ti^{IV}, the catalytic cycle reached completion.

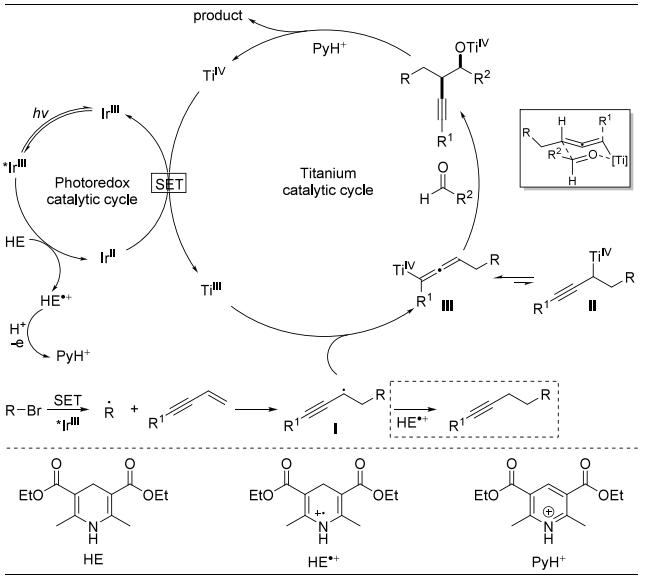

Figure 3. Proposed mechanism.

In summary, we herein successfully established a robust strategy that enables the addition of the nucleophilic allenyl−titanium complex to abundant aldehydes, delivering highly valuable homopropargylic alcohols via dual photoredox/titanium catalysis. Numerous alkyl radical precursors, 1,3-enynes, as well as broad applicability toward aliphatic aldehydes bearing multiple functional groups were presented. Preliminary mechanistic studies suggested a radical-polar crossover mechanism through the intermediary of either propargyl− or allenyl−Ti^{IV} species.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c00719.

Experimental details, characterization data of compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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