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Broadly Applicable Ion Pair-Assisted Nucleophilic Substitution of sp^3-Carbon Electrophiles with Alkynyltrifluoroborates

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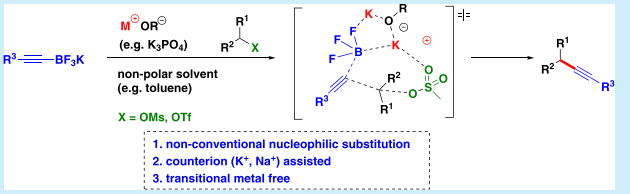
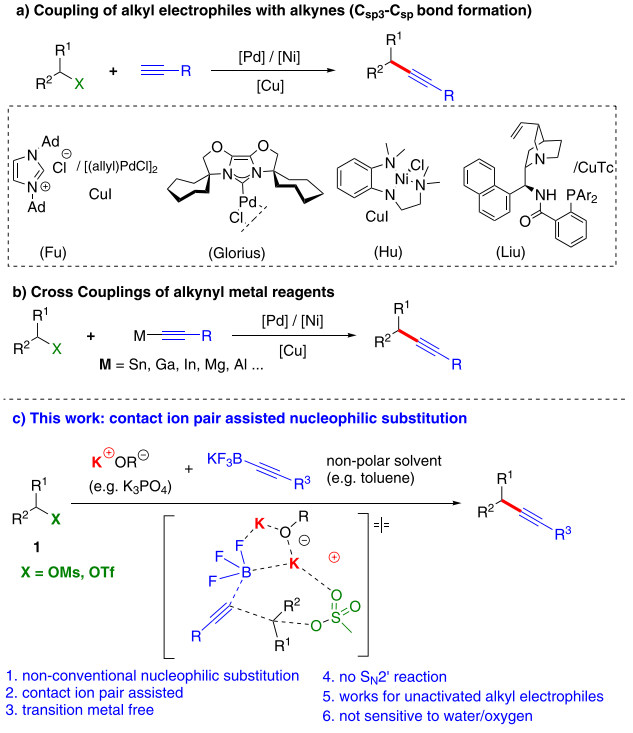
ABSTRACT: Alkynyltrifluoroborate nucleophiles react smoothly with a wide range of sp^3-carbon electrophiles, including propargyl methanesulfonates and unactivated alkyl triflates, to give Sonogashira-type products, via a novel ion pair-assisted nucleophilic substitution mechanism. An ion pair−organic complex, investigated using computational chemistry and in situ NMR experiments, may play a crucial role in this reaction.



Alkynes are important targets and versatile building blocks in organic synthesis.[1] The Sonogashira cross-coupling[2] is one of the most common methods of preparing alkynes. In the past decade, the groups of Fu,[3] Glorius,[4] Hu,[5,6] and Liu[7] have made significant inroads on Pd or Ni catalyzed cross-couplings of terminal alkynes with sp^3-carbon electrophiles, employing customized metal/ligand systems (Scheme 1a). Recently, Liu's group has developed a general asymmetric copper-catalyzed Sonogashira C(sp^3)−C(sp) coupling (Scheme 1a).[8−11]

Scheme 1. Literature Background



Alkynes have also been prepared via transition-metal-catalyzed reactions of alkynyl metal reagents and alkyl electrophiles (Scheme 1b)[12−15] or via transition-metal-catalyzed decarboxylative alkynylations.[16,17] More recently, Li and co-workers reported an innovative transition-metal-free coupling between an alkyne and an alkyl iodide using UV light in water via a radical pathway.[18] Despite these significant advances, the cross-coupling of sp^3-carbon electrophiles with terminal alkynes is still hindered by low reactivity or competing side reactions such as β-hydride elimination. On the other hand, the transition metal catalysts commonly used in this transformation is problematic and environmentally unfriendly, especially for the pharmaceutical industry. Furthermore, complex reaction systems usually increase the difficulty of separation and purification, as well as the generation of waste. Because of these shortcomings, the development of a transition-metal-free reaction system[19−21] with a minimum of additives, easy workup, mild reaction conditions, and environmental compatibility is a high-priority pursuit. Inspired by the pioneering works on metal-free Suzuki type cross-coupling[22] of alkenyl or aryl boronic acids reported by the groups of Tang,[23,24] Wang,[25] Huang,[26] Ryu,[27] and our recent work on the reactions of alkenyl or aryl boronic acids with unactivated alkyl triflate,[28] we pondered whether a nucleophilic substitution reaction of an sp^3-carbon electrophile could bring about a transition-metal-free Sonogashira type cross-coupling.

Alkynyl metal reagents (e.g., potassium alkynyltrifluoroborate) are stable and readily available but, typically, lack the nucleophilic strength to react with an sp^3-carbon electrophile

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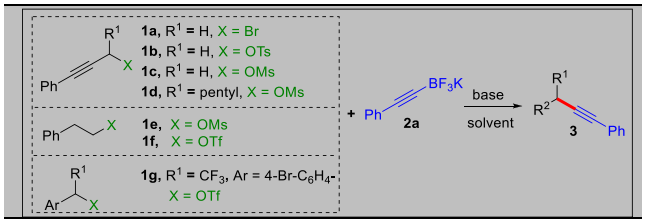
due to the high electron-withdrawing nature of fluorine.[29] Alkynyl boronic acids, unlike their alkenyl or aryl boronic counterparts, are not suitable nucleophile precursors because they are not stable. Since a mild inorganic base (e.g., K_3PO_4) can form a contact ion pair in a nonpolar solvent (e.g., toluene),[30,31] we proposed that the sp^3-carbon electrophile **1** complexed with K_3PO_4 to form a reactive ion pair-organic intermediate (Scheme 1c) that could be receptive to an attack by a relatively weak nucleophile such as potassium alkynyltrifluoroborate via a macrocyclic transition state.[32] The directing effect of the mild inorganic base may play a crucial role in the stabilization of the transition state. The resulting transformation is equivalent to a formal Sonogashira coupling without the assistance of a transition metal (Scheme 1c). We are glad to report an ion pair-assisted nucleophilic substitution of a diverse range of sp^3-carbon electrophiles, including unactivated alkyl triflates, with alkynyltrifluoroborates.

The optimization studies were carried out using the model reactions depicted in Table 1. Potassium alkynyltrifluoroborate

Table 1. Optimization of Reaction Conditions



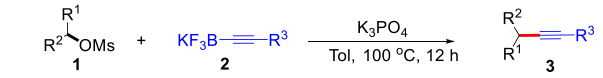
entry	1	base	temp/°C	yield (%)[b]
1	**1a**	KO*t*Bu	100	0
2	**1b**	KO*t*Bu	100	0
3	**1c**	KO*t*Bu	100	36
4	**1c**	NaOH	100	44
5	**1c**	K_2CO_3	100	33
6	**1c**	Cs_2CO_3	100	21
7	**1c**	KF	100	72
8	**1c**	K_3PO_4	100	95 (93[c])
9	**1c**	K_3PO_4	120	90
10	**1c**	K_3PO_4	80	83
11	**1d**	K_3PO_4	100	83 (77[c])
12	**1e**	K_3PO_4	100	0
13	**1f**	K_3PO_4	100	(70)[c]
14[d]	**1g**	K_3PO_4	130	(61)[c]
15	**1c**	–	100	19

[a]Conditions: **1** (0.1 mmol), **2a** (0.15 mmol), base (0.2 mmol) in solvent (1 mL), 12 h. [b]Yields were determined by GC-MS. [c]Isolated yields. [d]DCE was used as the solvent.

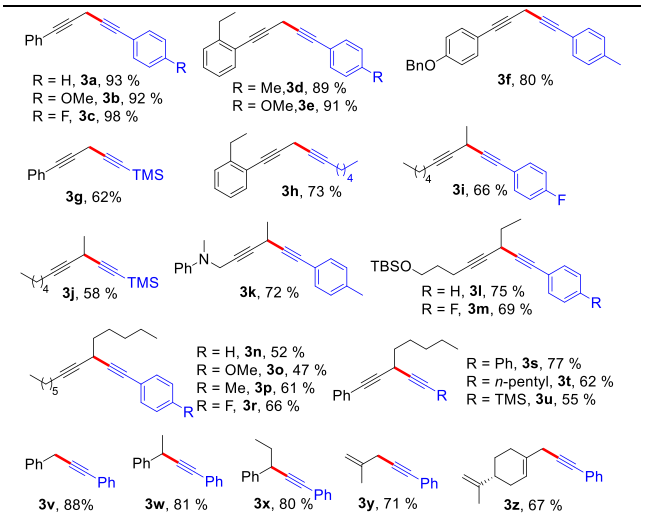
2a was chosen because it is more stable and easier to prepare than the corresponding boronic acid. The reactions of relatively reactive propargyl electrophiles containing various leaving groups (**1a**–**1c**) were investigated. In the presence of the weakly nucleophilic base KO*t*Bu, either propargyl bromide **1a** or propargyl tosylate **1b** did not yield the desired product (Table 1, entries 1, 2). To our satisfaction, the desired coupling-like product was obtained in a 36% yield when propargyl methanesulfonate **1c** was used (Table 1, entry 3). Screening bases of different strengths (Table 1, entries 4–8) revealed that a metal phosphate was better than either stronger bases (KO*t*-Bu, NaOH) or weaker bases (Cs_2CO_3, K_2CO_3). We also investigated the effect of the reaction temperature (Table 1, entries 9–10) and found that temperatures above or below 100 °C had a deleterious effect. The sterically more demanding secondary propargyl methanesulfonate **1d** was also effective (Table 1, entry 11). However, the unactivated alkyl methanesulfonate **1e** failed to furnish a coupling-type product under the optimized conditions (Table 1, entry 12). This lack of reactivity was quickly addressed by replacing the methanesulfonate with triflate, which is a better leaving group (Table 1, entries 13–14). The last entry (Table 1, entry 15) underscores the fact that the presence of an ionic base is critical if the reaction is effective.

We then turned our attention to examining the substrate scope for this transition-metal-free C_{sp3}–C_{sp} bond formation in the synthesis of 1,4-diynes (Table 2, **3a**–**3u**). 1,4-Diynes are

Table 2. Scope for the Synthesis of 1,4-Diynes



R^1 = alkynyl, aryl, alkenyl, R^2 = alkyl, H



[a]Conditions: **1** (0.1 mmol), **2** (0.15 mmol), K_3PO_4 (0.2 mmol) in toluene (1 mL), 12h, 100 °C. All yields are isolated yields.

important biomedical targets[33] and versatile synthetic building blocks,[34,35] but their preparation typically requires the cross-coupling of copper acetylides with propargylic electrophiles.[36] This approach suffers from a regioselectivity problem (S_N vs S_N'). Aryl-substituted propargylic mesylates gave good yields of the desired products (Table 2, **3a**–**3f**) when aromatic potassium alkynyltrifluoroborates containing electron-donating groups or weak electron-withdrawing groups (like fluorine) were employed. The yields were slightly decreased for the aliphatic substrates (Table 2, **3g**–**3h**). The sterically more demanding secondary propargyl methanesulfonates also worked well (Table 2, entries **3i**–**3u**). The reaction conditions also were applicable to benzyl methanesulfonates (Table 2, entries **3v**–**3x**) and allyl methanesulfonates (Table 2, entries **3y**–**3z**). Various functional groups such as amine (Table 2, **3k**), silyl ethers (Table 2, **3g, 3l, 3m**), and alkenes (Table 2, entries **3y**–**3z**) were compatible with the reaction conditions.

Next, the scope of C_{sp3}–C_{sp} bond formation using unactivated alkyl triflates (Table 3) was explored. Under the

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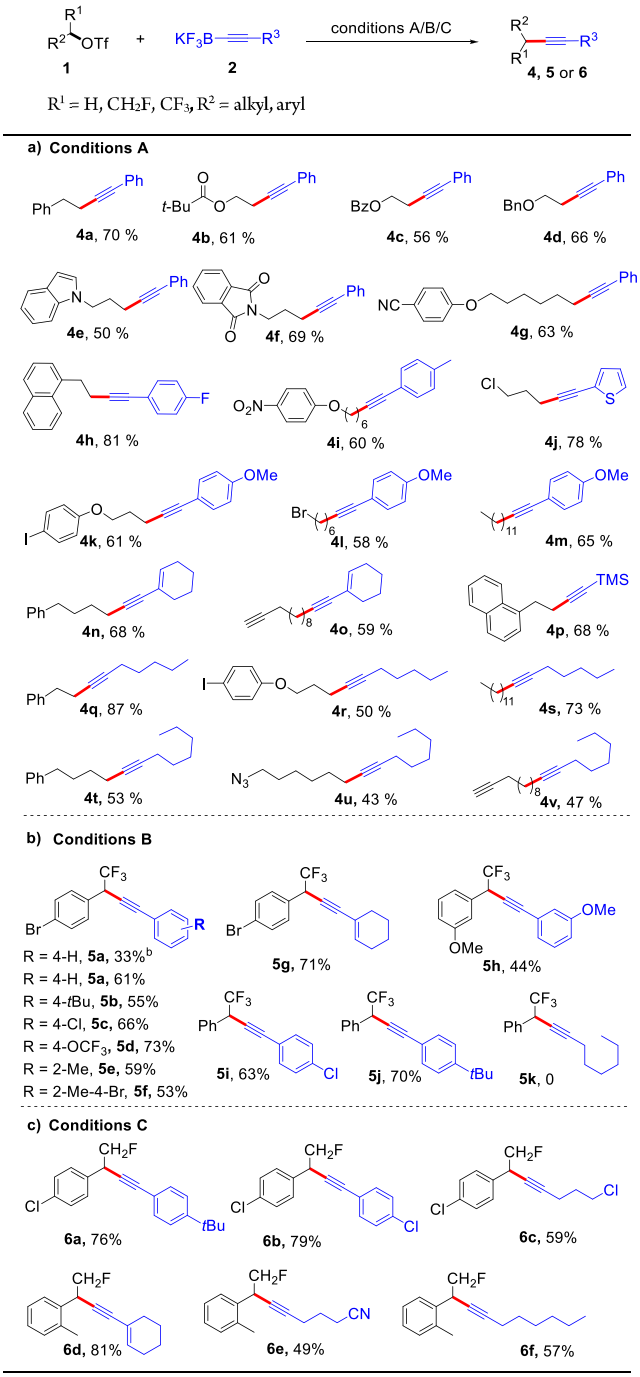
Table 3. Scope for sp^3-Carbon Triflates



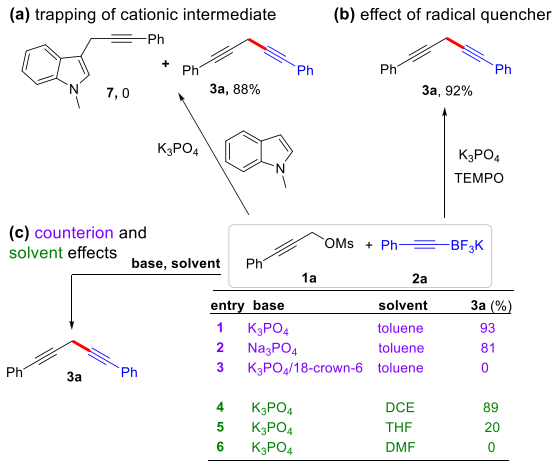
[a]Conditions A: **1** (0.1 mmol), **2** (0.15 mmol), K_3PO_4 (0.2 mmol) in toluene (1 mL), 100 °C, 12 h. Conditions B: **1** (0.2 mmol), **2** (0.3 mmol), K_3PO_4 (0.4 mmol) in DCE (1.5 mL), 130 °C, 24 h. Conditions C: **1** (0.2 mmol), **2** (0.3 mmol), K_3PO_4 (0.4 mmol) in $PhCF_3$ (1.5 mL), 110 °C, 12 h, Leaving group is OMs instead of OTf. [b]Under Conditions A. All yields are isolated yields.

optimized conditions found above, the reactions of unactivated alkyl triflates with aryl and vinyl-substituted alkynyltrifluoroborates yielded the expected products in mostly good yields (Table 3, **4a**–**4o**). However, the chemical yields were slightly lower for the alkyl-substituted alkynyltrifluoroborates (Table 3, **4p**–**4v**), probably because of their relatively weak nucleophilicity. Furthermore, the reaction conditions were compatible with a wide variety of functional groups such as esters (Table 3, **4b**, **4c**), amide (Table 3, **4f**), nitrile (Table 3, **4g**), ethers (Table 3, **4d**, **4g**, **4i**, **4k**, **4r**), nitro (Table 3, **4i**), thiophene (Table 3, **4j**), naphthalenes (Table 3, **4h**, **4p**), and azide (Table 3, **4u**).

Due to the importance of fluorine-containing compounds[37−43] such as α-alkynyl benzyl trifluoromethane (e.g., Efavirenz),[44] we examined the alkynylation of α-trifluoromethyl benzyl triflates but found that lower yields were obtained under the standard conditions (**5a**). Upon further condition screening, the chemical yields could be improved. Various potassium alkynyltrifluoroborates **2** (**5a**–**5h**) reacted with electrophiles **1** smoothly, producing α-alkynyl benzyl trifluoromethanes **5** in moderate to good yields. The substitution pattern (*ortho*, *meta*, *para* or disubstitution) in **2** played only a minor role in the reaction. However, an alkyl substituted potassium alkynyltrifluoroborate (**5k**) failed to react with α-trifluoromethyl benzyl triflates (no reaction), possibly because of its weaker nucleophilicity. On the other hand, α-monofluoromethyl benzyl methanesulfonates reacted smoothly with potassium alkynyltrifluoroborates to give the coupling products in moderate to good yields (**6a**–**6f**). Alkyl substituted alkynyltrifluoroborates proved to be suitable partners but the yields were moderate (**6c**, **6e**–**6f**). The collective results suggested that the reactivity of sp^3-carbon electrophiles was impacted by nearby electron-withdrawing groups (CF_3^- vs CFH_2^-). Moreover, this transition-metal-free protocol is orthogonal to the classic transition-metal-catalyzed Sonogashira reaction. For example, reactive aryl halides (**4k**, **4r**, **5a**–**5g**) showed no reactivity toward potassium alkynyltrifluoroborates under the optimized conditions, and alkyl halides (**4j**, **4l**) remained unchanged. Our methodology could also be scaled up (Supporting Information eq 1). Because it has been reported that trace transition-metal contaminants in reagents have been able to catalyze coupling reactions,[45,46] we investigated the metal contamination using coupled plasma mass spectroscopy (ICP-MS) (see SI). The transition metal contamination was very low and not likely capable of catalyzing the coupling reaction.

To uncover the reaction mechanism, we investigated the reaction pathway of this unusual nucleophilic substitution. This reaction was not affected by either *N*-methylindole (a cation trapper) or TEMPO (a radical quencher)[23,25,47] (Scheme 2a,b), implying that it did not involve radical or

Scheme 2. Investigation of Reaction Pathways



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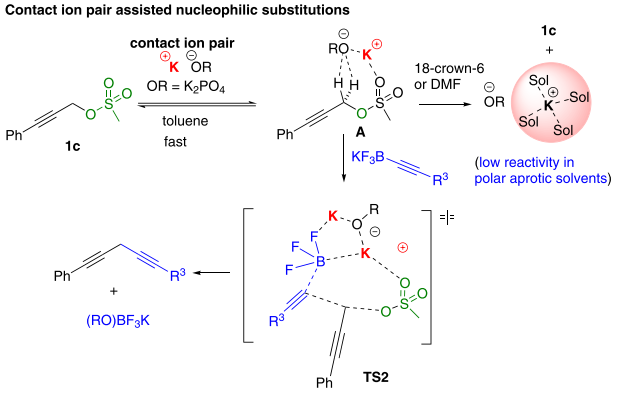
S_N1-like mechanisms. However, counterions played an essential role in this reaction: potassium or sodium gave good results, whereas a K^+ chelator inhibited the reaction (Scheme 2c). Moreover, changing the reaction solvent from less polar (DCE) to more polar (DMF, THF) resulted in a significant decrease in the yield (Scheme 2c), which indicated that this transformation is unlikely to undergo a classical nucleophilic substitution reaction. In the conventional nucleophilic substitution of ionic nucleophiles (R^-M^+), a "naked" anion displays the highest reactivity. Highly polar aprotic solvents or cation chelators, such as crown ethers, are often used to solvate or chelate the countercation in order to generate a "naked" R^-. However, the experimental results (Scheme 2c) did not fit the pattern of conventional nucleophilic substitutions. Consequently, we are suggesting a novel ion-pair-assisted nucleophilic substitution pathway, illustrated in Scheme 3. Assuming that a mild inorganic base

Scheme 3. Proposed Reaction Mechanism



such as K_3PO_4 exists as a contact ion pair in a nonpolar solvent such as toluene,[30,31] we speculated that the sp^3-carbon electrophile **1c** could complex with K_3PO_4 to form an ion pair-organic compound intermediate **A**, and that this complex reacts with a relatively weak nucleophile, like an alkynyltrifluoroborate, via a transition state **TS2** to yield the observed product. This reaction pathway accounts for the counterion and solvent effects observed in Scheme 2c, namely, that if a cation chelator or a polar aprotic solvent is present in the reaction, it will either complex with K^+ or foster the dissociation of the ion pair−organic compound−complex **A**, to shut down the reaction.

The central tenet of our proposed mechanism is the formation of the ion pair−organic compound−complex **A** (Scheme 3). To investigate whether this complex is theoretically feasible, we calculated the binding energies of various ion pair−organic complexes (see SI Figure 1). The interaction of a weakly electrophilic CH_3Cl with an ionic salt such as KF showed small bonding energy. Replacing Cl with a mesyl group (CH_3OMs) resulted in significantly higher bonding energy; the bonding energy was highest when K_3PO_4 replaced KF. Interestingly, the latter bonding energy (23.7 kcal/mol) is in the range of average bonding energies for strong hydrogen bonding interactions.[48]

The interaction of ion pairs with the sp^3-carbon electrophile **1c** was also examined utilizing an *in situ* NMR experiment. We measured the ^1H NMR of **1c** in the presence of various ionic salts employing d^3-toluene as the solvent (Figure 1). Although these ionic salts (except *n*-Bu_4NBr) were practically insoluble

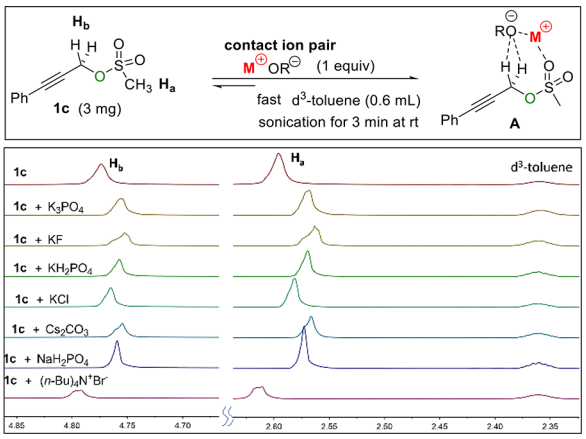


Figure 1. ^1H NMR chemical shifts of various ion pair-organic compound complexes with **1c**.

in d^3-toluene, they exerted a non-negligible influence on the chemical shifts of H_a and H_b in **1c**. We posited that these changes in the chemical shift were caused by the fast equilibrium between **1c** and the ion pair−organic complex **A** (Figure 1). We also theoretically established the transition state (see SI Figure 2) for a formal Sonogashira coupling using an S_Nip reaction, without the assistance of transition metals, and using only an ionic promoter KF (K_3PO_4 was not used due to its relatively complex structure). Clearly, the ion pair is involved in the stabilization of the macrocyclic transition state, speeding up this type of reaction.

In conclusion, we have developed a widely applicable, mild base promoted, formal Sonogashira cross-coupling protocol through a novel ion pair-assisted nucleophilic substitution mechanism. These transition-metal-free conditions are orthogonal to other transition-metal-catalyzed cross-coupling conditions, which means that our method is complementary to classic couplings for synthesizing complex molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02507.

Experimental details, characterization data, computational data, and spectra. (PDF)

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Notes

The authors declare no competing financial interest.

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