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# Metal-Reductant-Free Electrochemical Nickel-Catalyzed Couplings of Aryl and Alkyl Bromides in Acetonitrile

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*Supporting Information*

**ABSTRACT:** While reductive cross-electrochemical coupling is an attractive approach for the synthesis of complex molecules at both small and large scale, two barriers for large-scale applications have remained: the use of stoichiometric metal reductants and a need for amide solvents. In this communication, new conditions that address these challenges are reported. The nickel-catalyzed reductive cross-coupling of aryl bromides with alkyl bromides can be conducted in a divided electrochemical cell using acetonitrile as the solvent and diisopropylamine as the sacrificial reductant to afford coupling products in synthetically useful yields (22−80%). Additionally, the use of a combination of the ligands 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2′-terpyridine and 4,4′-di-*tert*-butyl-2,2′-bipyridine is essential to achieve high yields.

**KEYWORDS:** *electrochemistry, electrosynthesis, nickel catalysis, reductive coupling, cross-coupling*

Nickel-catalyzed reductive cross-coupling has been demonstrated in recent years to be a versatile method for the formation of C(sp$^2$)−C(sp$^3$) bonds (Scheme 1).[1,2] The general methods detailed several years ago[3] have been extended to a wide variety of substrates, including heterocycles,[4,5] fluorobromoalkanes,[6] amino acids,[7] enantioconvergent couplings,[8] unhindered vinyl bromides,[9] tertiary alkyls,[10] alcohol derivatives,[11] and decarboxylative couplings of redox-active esters.[12]

**Scheme 1. Cross-Electrophile Coupling in Industry**

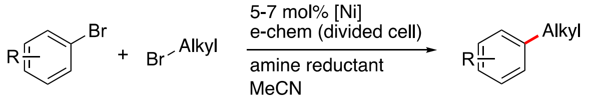
Advantages of Cross-Electrophile Coupling

- Avoids pre-activation of substrates
- Simple conditions are tolerant of moisture and $O_2$
- Broad functional-group compatibility

Challenges to Implementation on Scale

- Concentration of metal salts ($ZnX_2$, $MnX_2$, $NiX_2$)
- Amide solvents are problematic
- Workarounds to date require organic iodides

This Work



While uptake in both academia and medicinal chemistry has been rapid, uptake of cross-electrophile coupling in process chemistry has been slowed by several challenges. Although these cross-electrophile coupling reactions avoid the need to preform organometallic reagents (Scheme 1), stoichiometric metals such as Zn or Mn are generally used as terminal reductants. This is undesirable because inconsistencies in the purity and activation state of commercial metal reductants could lead to reproducibility problems.[3,13] At larger scales, the generation of stoichiometric metal waste can lead to complications in waste disposal, even for relatively nontoxic metals like zinc.[14] Finally, amide solvents have particular environmental and regulatory concerns,[15,16] but most cross-electrophile couplings require them.[17] If these limitations could be addressed, cross-electrophile coupling could become a more important tool in chemical development.

Electrochemical methods would be ideal for reductive coupling[18,19] because the reduction potential and the rate of reduction can be easily adjusted without designing a new catalyst or reagent.[20] Such tuning is more challenging with other approaches, such as the use of organic reductants[17] or photoredox cocatalysis.[21] However, significant challenges exist for realizing the promise of electrochemical methods. The most well-developed electrochemical method for nickel-catalyzed reductive C−C bond-forming chemistry uses a sacrificial metal anode in an undivided cell.[20a,e,g,22] Because of the ease of oxidation of the anode, this approach avoids problems of incompatibility and unproductive oxidation of the catalyst or substrate that can plague reactions with soluble sacrificial reductants.[22a] Pioneered by the group of Perichón,[22] it has also recently been applied successfully to the coupling of aryl bromides with alkyl bromides[18b] and aryl iodides with *N*-hydroxyphthalimide (NHP) esters.[18d] While this approach avoids the use of metal powders, stoichiometric metal salts are still generated, and amide solvents appear to be required.

In order to avoid the formation of stoichiometric metal salts, the reductive cross-electrophile coupling reaction at the cathode would have to be paired with the oxidation of a soluble sacrificial reductant at the anode. A divided cell is

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typically used to minimize side reactions.[20a,e] While this strategy has been successful in oxidative chemistry,[20] its application to metal-catalyzed reductive chemistry to form C−C bonds has been more limited.[23] Recently, the decarboxylative coupling of aryl iodides with NHP esters in a divided cell with triethylamine as a sacrificial reductant was reported.[18c] This was an important advance, but on the basis of the mechanism proposed, this approach would not work with substrates that are more difficult to reduce, such as alkyl bromides.[24,25] This mechanism also required high concentrations of the nickel catalyst (30 mol %) in order to favor radical capture by nickel over other radical side reactions.

Herein we report an electrochemically driven cross-electrophile coupling that (1) avoids high catalyst loadings, (2) uses diisopropylamine as the sacrificial reductant, (3) runs in acetonitrile[26] instead of amide solvents, and (4) works with less reactive organic bromides (Scheme 1).

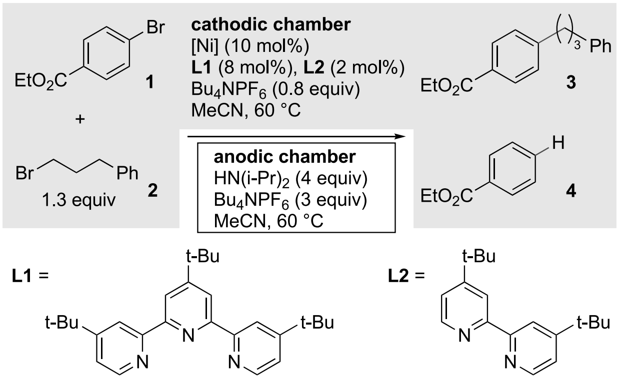
Initial optimization studies were carried out for the coupling of ethyl 4-bromobenzoate (**1**) (6.5 mmol scale, 1.5 g) and 1-bromo-3-phenylpropane (**2**) (1.3 equiv), passing 25 mA of current until the theoretical minimum charge of 2.0 *F*/mol (i.e., 2 equiv of electrons) was met (Table 1).[27] While pyridine carboxamidine ligands were found to be excellent in our previous electrochemical study[18b] in *N*,*N*-dimethylacetamide (DMA), their low solubility in MeCN forced us to examine more common bipyridine and terpyridine ligands.[21c,28] While 4,4′-di-*tert*-butyl-2,2′-bipyridine (**L2**) alone was a poor ligand (entry 3), 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (**L1**) alone (entry 2) or combined with a small amount of **L2** provided reasonable yields of the product (entries 1 and 4).[29] While combinations of **L1** with **L2** provided the same yield as pure **L1** in this case (entries 1 and 4), different ratios proved to be helpful with other substrates (Scheme 2), provided homogeneous solutions of the precatalyst,[30] and minimized the amount of relatively expensive **L1** required.

These initial reactions were selective for the product, providing a 62% yield of **3** with only a 3% yield of the hydrodehalogenation side product (**4**) and trace biaryl product, but a significant amount (36%) of ArBr starting material **1** remained (Table 1, entry 1). Consistent with reports on the use of **L1** for the homodimerization of bromoalkanes,[28c,d] more alkyl homodimer was observed in reactions run with **L1** alone (10%) than with the ligand combination (7%) (see the Supporting Information for more details). An intermediate **L1**:**L2** ratio of 2:1 led to a similar yield of product but suffered from decreased selectivity and the formation of unidentified byproducts (entry 4). The addition of a third ligand, pyridine, was not beneficial (entry 5).

Control experiments demonstrated the necessity of both the electrochemical reduction and the nickel catalyst to the reaction. No reaction occurred when no current was passed, with full recovery of the starting materials (Table 1, entry 6). Removal of the nickel catalyst led to a complex reaction mixture that contained no product **3** but significant amounts of hydrodehalogenated side product **4** and buildup of a dark-orange polymer on the cathode surface (entry 7).

Changing the nickel precatalyst and cathodic materials had little effect on the reaction. Use of $NiCl_2$(dme) instead of $NiBr_2$(dme) showed little effect on the reaction selectivity and yield (Table 1, entries 1 and 8), though 15−20% of the alkyl bromide was converted to the much less reactive alkyl chloride in this case. Changing the cathode material from reticulated vitreous carbon (RVC) to nickel foam also showed no considerable effect on the reaction outcome (entry 9).

**Table 1. Optimization of Electrochemical Ni-Catalyzed Coupling Conditions in a Divided Cell**



| entry | deviation from above conditions[a] | yields (%)[b] | | |
|---|---|---|---|---|
| | | **1** | **3** | **4** |
| 1 | none | 36 | 62 | 3 |
| 2 | **L1** only | 38 | 61 | 2 |
| 3 | **L2** only | 3 | 7 | 30[c] |
| 4 | 2:1 **L1**:**L2** | 24 | 61 | 5 |
| 5 | 0.5 equiv of pyridine added | 24 | 52 | 9 |
| 6 | no electricity | 100 | 0 | 0 |
| 7 | no $NiBr_2$(dme) | 38 | 1 | 21 |
| 8 | $NiCl_2$(dme) instead of $NiBr_2$(dme) | 39 | 59 | 3 |
| 9 | Ni foam cathode instead of RVC | 34 | 61 | 4 |
| 10 | $LiBF_4$ instead of $Bu_4NPF_6$ | 89 | 3 | 10 |
| 11 | $Bu_4NBF_4$ instead of $Bu_4NPF_6$ | 33 | 56 | 2 |
| 12[d] | 15 mA instead of 25 mA | 30 | 58 | 2 |
| 13[e] | 50 mA instead of 25 mA | 26 | 70 | 3 |
| 14[f] | 50 mA, 3.3 *F*/mol | trace | 83 (76[g]) | 7 |
| 15[h] | 5 mol % catalyst, 50 mA, 2.9 *F*/mol | trace | 77 (70[g]) | 8 |

[a] Reactions were conducted in a divided H-cell with a Nafion membrane and run on a 6.5 mmol scale (1.5 g of **1**). [Ni] = $NiBr_2$(dme). Each chamber contained an RVC electrode and 25 mL of MeCN. Reactions were run at a constant current of 25 mA until 2.0 *F*/mol was passed (14.0 h). [b] Determined by a calibrated UPLC assay with an internal standard. [c] The remainder of ArBr was converted to Ar−Ar. [d] 22.2 h. [e] 7.0 h. [f] 11.5 h. [g] Isolated yield. [h] 10.1 h.

While electrochemical conditions can avoid the need for stoichiometric metal reductants, electrolyte must still be added to both compartments to minimize the resistance of the cell to the flow of electricity. The amount of electrolyte required is cell-dependent, and the 3.8 equiv used in this study could be decreased in a cell configuration with a smaller electrode gap. In the case of an amine terminal reductant, amine oxidation would generate additional cations during the reaction, which could further diminish the amount of electrolyte required. Preliminarily, it appears that the cation $Bu_4N^+$ is essential (Table 1, entries 1 and 10), but $PF_6^-$ could be replaced with another noncoordinating counterion, $BF_4^-$ (entry 11). With $LiBF_4$, conversion of the aryl bromide was very poor, and most of the consumed aryl bromide was hydrodehalogenated rather than cross-coupled.

Finally, the reaction could be driven to completion by passing additional electrons (∼3 *F*/mol), and the reaction time could be minimized by increasing the current density (∼10.5 h reaction time at 3 *F*/mol). It was initially thought that the charge inefficiency of the reaction (64% conversion at 2 *F*/

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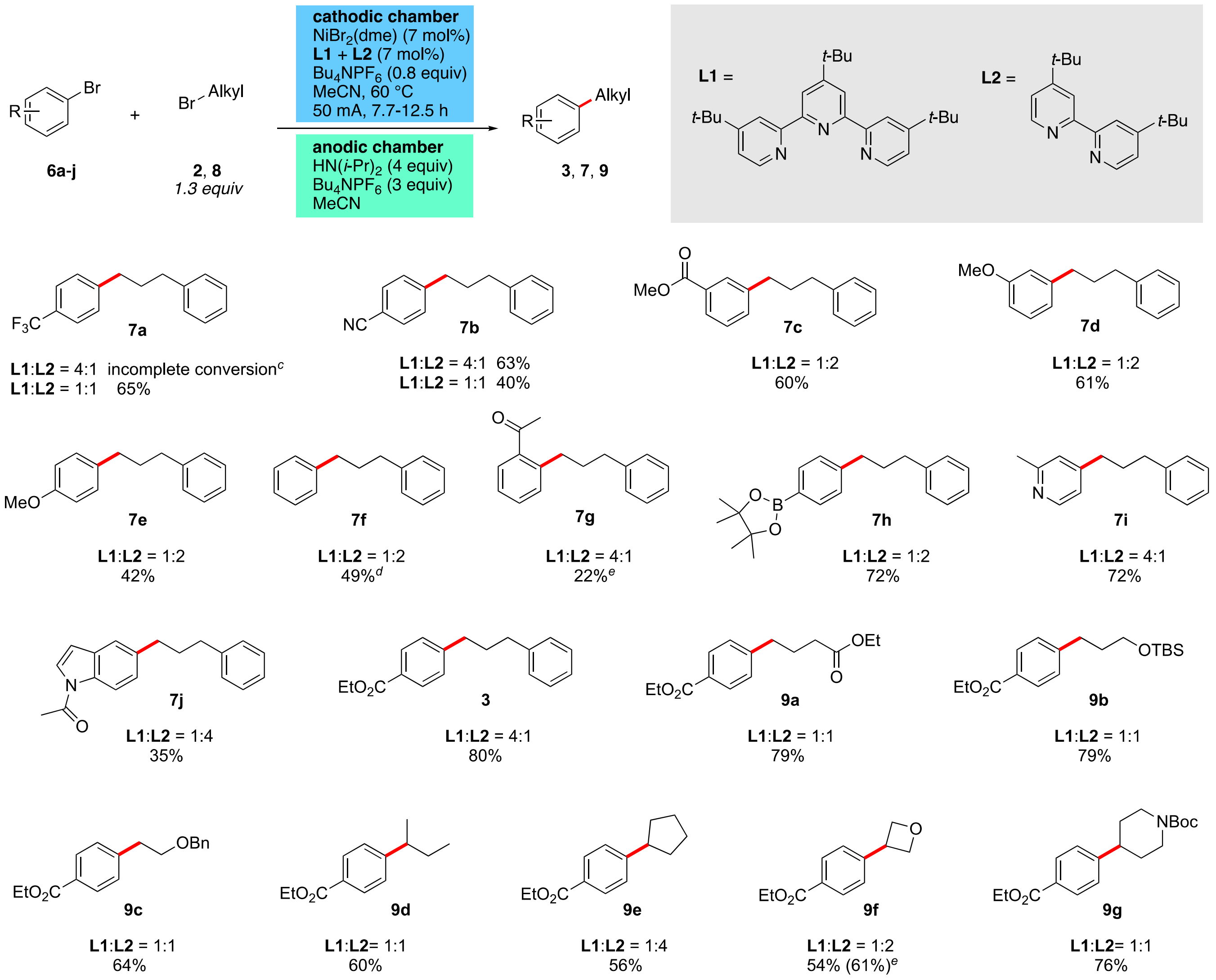
**Scheme 2. Substrate Scope of Metal-Free Electrochemical Cross-Electrophile Coupling in Acetonitrile**[a,b]



[a]Standard conditions: in the cathodic chamber, 1 equiv of aryl bromide (6.2 mmol for **3** and **7**, 3.1 mmol for **9**), 1.3 equiv of alkyl bromide, 7 mol % NiBr$_2$(dme), 7 mol % ligands, 0.8 equiv of Bu$_4$NPF$_6$; in the anodic chamber, 6 equiv of NH(iPr)$_2$, 3 equiv of Bu$_4$NPF$_6$; each chamber equipped with an RVC electrode; 50 mA (6.2 mmol) or 25 mA (3.1 mmol) passed until completion. [b]Isolated yields are shown. [c]All of the alkyl bromide was consumed at roughly 50% conversion of the aryl bromide. [d]Isolated as a 73 wt % mixture with inseparable 1,3-diphenylhexane. [e]NMR yield with an internal standard.

mol; Table 1, entry 1) was due to the rate of nickel catalyst diffusion to and from the electrode along with the rate of reaction in solution being too low relative to the rate of reduction set by the current.[18b] Lowering the current from 25 to 15 mA, however, afforded little change in the conversion and yield (entry 12), suggesting that the observed charge inefficiency was not strongly correlated with reduction rate and was likely the result of an unidentified off-cycle but nondestructive pathway.

Doubling the current to 50 mA, the maximum stable current that could be achieved with this cell setup, provided a similar yield of product in half the amount of time (7 h; Table 1, entry 13). Ultimately, the reaction at 50 mA was pushed to completion with a charge of 3.3 *F*/mol being passed, again with the excess charge being nondestructive to the reactants, affording an 83% assay yield and 76% isolated yield of cross-coupled product (entry 14). A reaction run at a lower catalyst loading of 5 mol % still proceeded well, with only a slightly lower yield than with 10 mol % catalyst (entry 15). This is in contrast to the previous report in a divided cell, where 30 mol % catalyst was required for high yields.[18c] We decided to use 7 mol % catalyst for our substrate screen (Scheme 2).

With the optimized conditions for our model reaction in hand, we proceeded to test the scope of these conditions over a variety of aryl bromide coupling partners with a catalyst loading of 7 mol % (Scheme 2). While each individual reaction was not rigorously optimized, it was quickly found that the 4:1 ratio of **L1** to **L2** was not ideal for all aryl substrates. For example, for the couplings of *p*-CF$_3$-substituted aryl bromide **6a**, using an **L1**:**L2** ratio of 4:1 led to complete consumption of alkyl bromide **2** to form the alkyl homodimer before full consumption of **6a** could be achieved. Changing to a 1:1 ratio of ligands, however, allowed for full consumption of **6a** with less alkyl dimer to give a 65% yield of cross-coupled product **7a**. Conversely, as another example, *p*-CN-substituted aryl bromide **6b** cross-coupled well with the original 4:1 ligand

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ratio in 63% yield but with a 1:1 ligand ratio gave a lower yield of 40%, with the difference in yields arising from the formation of the aryl homodimer in the latter case. Thus, it was found that the **L1**:**L2** ratio could be adjusted to compensate for the relative reactivity between the aryl and alkyl bromide coupling partners. The reaction proceeded in moderate to good yields for the couplings shown in Scheme 1. In general, reactions with this catalyst system performed better with electron-poor aromatic rings. *o*-Acyl-substituted aryl bromide **6g** suffered from an especially low yield compared with other aryl bromides, giving the dehalogenated aryl as the predominant byproduct.

Attention was then turned to investigating the scope of alkyl bromide coupling partners compatible with these reaction conditions (Scheme 2). This series of substrates was run in a slightly smaller electrochemical cell on a 3.1 mmol scale at a proportionally lower current of 25 mA. The reaction conditions were compatible with alkyl bromides with various functionalities, including secondary cyclic (**8e**−**g**) and acyclic (**8d**) partners. As observed with the various aryl bromide coupling partners, changing the **L1**:**L2** ratio was found to improve the yields for reactions that provided low yields under the standard conditions. Qualitatively, we observed that the amount of the tridentate ligand **L1** was correlated with the activation of the alkyl halide. For example, reactions that generate a significant amount of alkyl dimer side product typically benefit from a decrease in the amount of **L1**. Conversely, reactions that generate aryl byproducts, leaving the alkyl bromide unreacted, typically benefit from higher levels of **L1** in the ligand ratio in order to maintain optimal cross coupling selectivity.

In summary, we have demonstrated that electrochemically reduced nickel catalysts can carry out reductive coupling between aryl and alkyl bromides in a more process-friendly solvent without the production of stoichiometric metal waste. These conditions should be more amenable to scale-up[31] than previous work while still providing synthetically useful yields across a range of coupling partners.

**Procedure** (6.5 mmol scale): To a round-bottom flask under nitrogen were added $NiBr_2$(dme) (0.20 g, 0.65 mmol, 10 mol %), **L1** (0.22 g, 0.52 mmol, 8 mol %), **L2** (0.035 g. 0.13 mmol, 2 mol %), and $Bu_4NPF_6$ (2.1 g, 5.2 mmol, 0.8 equiv) followed by acetonitrile (25 mL). The solution was degassed via sonication under light vacuum followed by sparging with nitrogen for 10 min. This light-green catalyst slurry was stirred at room temperature for 1 h under nitrogen. $Bu_4NPF_6$ (7.7 g, 19 mmol, 3 equiv) and acetonitrile (25 mL) were added to a separate round-bottom flask under nitrogen. The solution was degassed via sonication under light vacuum followed by sparging with nitrogen for 10 min. The solutions were then transferred to their respective chambers of the divided cell reactor (see the Supporting Information for details of the reactor setup) under nitrogen, first the anodic solution containing only electrolyte to the anodic chamber, followed by the nickel-containing slurry to the cathodic chamber. The cell was heated to an internal temperature of 60 °C (glycol heater temperature set to 74−77 °C, which compensated for heat losses through the transmission lines) with magnetic stirring in each chamber (400 rpm). Diisopropylamine (2.6 g, 26 mmol, 4 equiv) was then added to the anodic chamber, and 1-phenyl-3-bromopropane (1.7 g, 8.5 mmol, 1.3 equiv) and ethyl-4-bromobenzoate (1.5 g, 6.5 mmol, 1.0 equiv) were added to the cathodic chamber. Each chamber was then equipped with an RVC electrode, and the appropriate leads from the potentiostat were attached. Constant current was passed until the reaction was deemed complete on the basis of consumption of the aryl bromide.

The reaction mixture was then cooled to room temperature. The cathodic solution was transferred to a round-bottom flask, rinsing with acetonitrile. This solution was concentrated on a rotary evaporator. The solution was then diluted with 15 mL of methyl *tert*-butyl ether (MTBE) and filtered through a short pad of Celite, washing the filter cake with MTBE (2 × 15 mL). The organic solution was washed with water (2 × 15 mL). If a significant rag layer formed or solids precipitated, the mixture was filtered before the extraction was continued. The aqueous washes were then back-extracted with MTBE (1 × 20 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over sodium sulfate, and then decanted, and the solution concentrated in vacuo. The crude material was purified via silica gel chromatography to give ethyl 4-(3-phenylpropyl)benzoate (1.32 g, 76%).

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00232.

> Additional tables of optimization experiments, CV data, detailed experimental procedures, product characterization data, and copies of NMR spectra (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors.

### Notes

The authors declare no competing financial interest.

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(29) Combinations of nickel catalysts were found to be useful in early cross-electrophile coupling studies. See ref 3b.

(30) Solutions of $NiBr_2$(dme) and terpyridine **L1** were not completely homogeneous. The addition of small amounts of bipyridine **L2** resulted in a homogeneous solution.

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