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Ruthenium-Catalyzed Intramolecular Arene C(sp^2)−H Amidation for Synthesis of 3,4-Dihydroquinolin-2(1*H*)-ones

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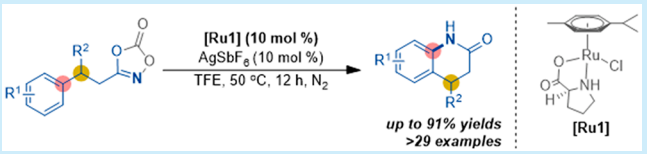
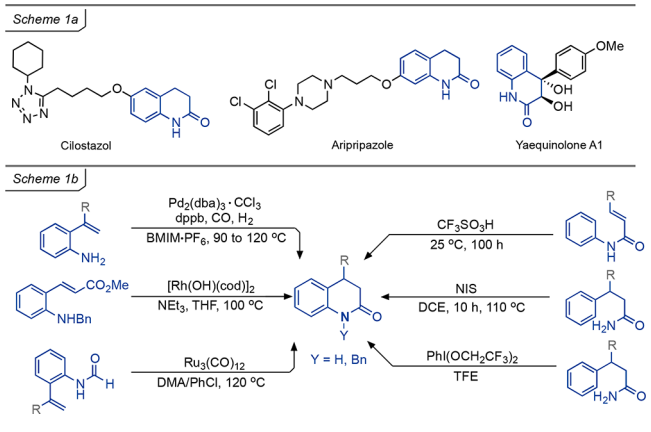
ABSTRACT: We report the [Ru(*p*-cymene)(L-proline)Cl] ([**Ru1**])-catalyzed cyclization of 1,4,2-dioxazol-5-ones to form dihydroquinoline-2-ones in excellent yields with excellent regioselectivity via a formal intramolecular arene C(sp^2)−H amidation. The reactions of the 2- and 4-substituted aryl dioxazolones proceeds initially through spirolactamization via electrophilic amidation at the arene site, which is para or ortho to the substituent. A Hammett correlation study showed that the spirolactamization is likely to occur by electrophilic nitrenoid attack at the arene, which is characterized by a negative ρ value of −0.73.



3,4-Dihydroquinolin-2(1*H*)-ones are privileged skeletons found in many bioactive compounds;[1a,b] some notable examples are cilostazol,[1c] aripripazole,[1d] and Yaequinolone A1 (isolated from *Penicillium* sp. FKI-2140;[1e] Scheme 1a).

Scheme 1. Examples of Dihydroquinolin-2-one Formation

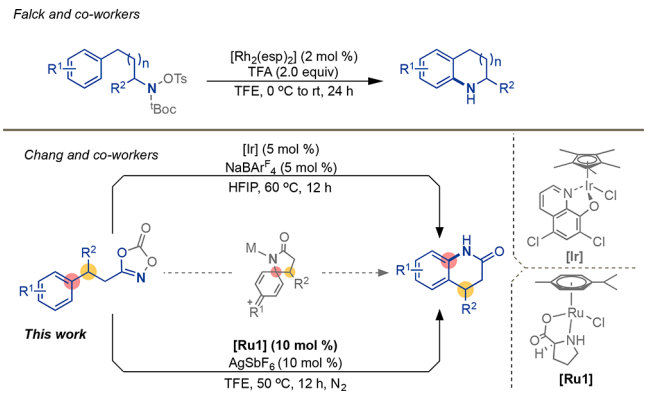


Apart from Friedel−Crafts cyclization, classical routes to the dihydroquinolin-2-one skeletons include the acid-mediated cyclization of *N*-phenylcinnamamides,[2] the oxidative cyclization of aryl methoxyamides by hypervalent iodine reagents,[3] and the *N*-iodosuccinimide (NIS)-initiated free -radical cyclization of 3-phenylpropanamides.[4]

Transition-metal-catalyzed cyclizations of 2-aminostyrenes are known to offer an alternative route to dihydroquinolin-2-ones (Scheme 1b). For instance, Alper and coworkers reported the Pd-catalyzed cyclocarbonylation of 2-aminostyrenes in ionic liquid medium.[5] In 2010, Youn and coworkers demonstrated the Rh(I)-catalyzed domino conjugate addition−cyclization of (*E*)-methyl 3-(2-(benzylamino)phenyl)-acrylates with organoboroxines.[6] In 2014, Chang and coworkers also reported the Ru-catalyzed olefin hydrocarbamoylation of *N*-(2-vinylphenyl)-formamides to afford dihydroquinolin-2-ones.[7] Yet these methodologies rely on the use of specially designed arylamine moieties, which often require a tedious multistep synthesis.

Regiocontrolled direct arene aminations/amidations constitute an atom- and step-economical approach for arylamine/-amide synthesis (Scheme 2). In this regard, Falck and coworkers developed dirhodium-catalyzed electrophilic C-

Scheme 2. Examples of Metal-Catalyzed Intramolecular Arene C(sp^2)−H Aminations and Amidations



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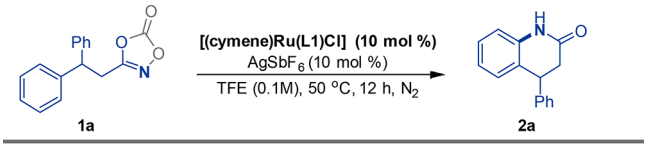
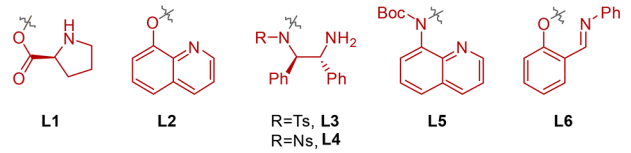
(aryl)−H amination to give tetrahydroquinolines using NH_2/NH(alkyl)-*O*-(sulfonyl)-hydroxyamines as reagents,[8] and the reaction is believed to proceed by electrophilic amination by some reactive Rh-nitrenoid species. Of particular interest, Chang and coworkers reported the Cp*Ir(III)-catalyzed intramolecular nitrenoid C(aryl)−H insertion employing dioxazolones,[9a−c] which are readily derived from carboxylic acid feedstock. Recently, we reported the Ru(II)-catalyzed enantioselective intramolecular nitrenoid C(sp^3)−H bond insertion of dioxazolones to afford γ-lactams with up to 95% *ee*.[10] Here we describe the Ru-catalyzed intramolecular C(aryl)−H amidation using dioxazolones as the nitrenoid reagents to furnish dihydroquinolin-2-ones. Analogous to the Cp*Ir(III) system, the Ru-catalyzed dihydroquinolin-2-one formation proceeds by tandem electrophilic spirocyclization and C−C migration.

In Table 1, which shows the treatment of dioxazolone **1a** (0.1 mmol) with [**Ru1**] (10 mol %) containing L-proline as a ligand and $AgSbF_6$ (10 mol %) in tetrafluoroethylene (TFE) (1 mL) at 50 °C for 12 h, 4-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**2a**) was obtained in 76% yield with 30% *ee* (entry 1). The performance of Ru catalysts bearing several ligands has been compared. The Ru catalyst with 8-hydroxyquinoline (**L2**) as a ligand was found to give comparable results as L-proline (**L1**); however, those complexes bearing ligands derived from *R*,*R*-DPEN (**L3** and **L4**) are ineffective catalysts, with the full recovery of **1a**. Analogous to **L1**, *N*-Boc-8-aminoquinoline (**L5**) is an effective ligand for productive results (**2a**: 63% yield). Yet the catalyst bearing the Schiff base ligand **L6** failed to effect significant transformation.

Table 1. Optimization of Reaction Conditions





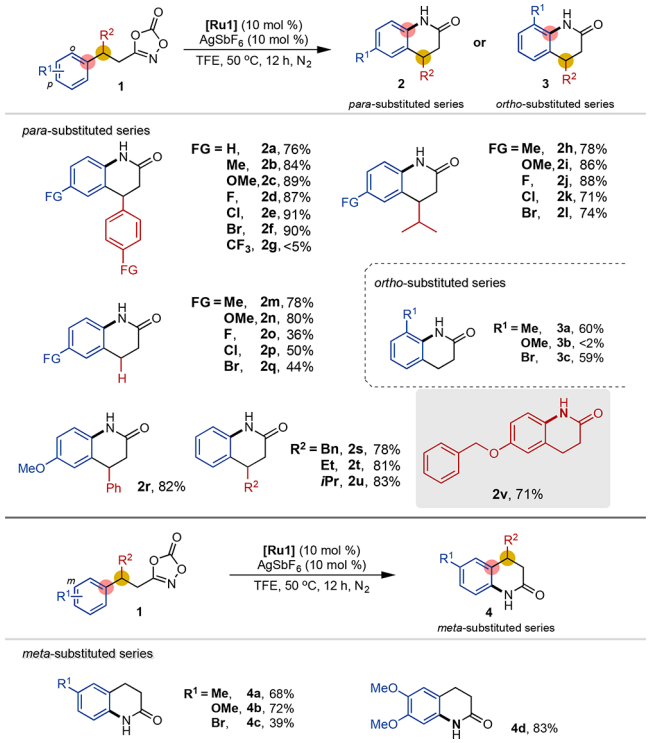
entry	deviation from standard conditions	% yield (% *ee*)[a,b]
1	none	76 (30)
2	**L2** instead of **L1**	78
3	**L3** instead of **L1**	<2
4	**L4** instead of **L1**	<2
5	**L5** instead of **L1**	63
6	**L6** instead of **L1**	<2
7	DCE instead of TFE	9 (53)
8	acetone instead of TFE	21 (63)
9	MeOH instead of TFE	13 (52)
10	EtOH instead of TFE	21 (53)
11	HFIP instead of TFE	65 (15)
12	rt instead of 50 °C	38 (29)
13	40 °C instead of 50 °C	48 (32)
14	60 °C instead of 50 °C	78 (29)

[a]Reaction conditions: **1a** (0.1 mmol), catalyst (10 mol %), $AgSbF_6$ (10 mol %), solvent (1 mL) at 50 °C for 12 h under N_2 unless other specified. Isolated yield. [b]*ee* is determined by high-performance liquid chromatography (HPLC) with a chiral column. (*S*)-**2a** is the major isomer. (See the Supporting Information for details.)

Whereas the reaction conducted in 1,2-dichloroethane (DCE) resulted in poor product yield (9%), **2a** was produced in 21% yield with 63% *ee* when acetone was the solvent. Whereas employing MeOH and EtOH as solvents produced similar results as those for acetone (entries 9 and 10), the analogous reactions conducted in hexafluoroisopropanol (HFIP) afforded **2a** in 65% yield. Performing the reaction at lower temperatures did not show significant improvement.

Table 2 depicts the intramolecular C(aryl)−H amidations for the ortho-, meta-, and para-substituted 1,4,2-dioxazol-5-ones with [**Ru1**] as the catalyst. For the para-substituted dioxazolones (**1b−1q**, **1r**, and **1v**), their dihydroquinolin-2-one products were characterized by skeletal rearrangement involving the migration of the pre-existing (aryl−alkyl) C−C bond from the position para to the substituent in the substrates to the position meta to the substituent in the products. In all cases, the anticipated products due to amidation at the position meta to the substituents were not obtained. Similar results were also reported for the analogous Cp*Ir(III)-catalyzed intramolecular C(aryl)−H amidation reactions.[9b−d]

Table 2. Substrate Scope Studies of para-, ortho-, and meta-Substituted 1,4,2-Dioxazol-5-ones



For the diaryl-substituted dioxazolones, those bearing electron-donating Me and OMe and electron-withdrawing halogen (F, Cl, and Br) groups were effectively transformed to their dihydroquinolin-2-ones **2b−2f** in up to 90% yields. Yet the reaction of **1g** bearing a 4-CF_3 substituent afforded **2g** in <5% yield. In the analogous reactions for the monoaryl-substituted series, dihydroquinolin-2-one **2h−2n** were formed in 71−88% yields. Yet those halogenated analogues **2o−2q** were formed in moderate ∼40% yields. Apparently, the amidation is preferentially directed to the more electron-rich arene moieties. For instance, the reaction of **1r** led to selective

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C−H amidation at the methoxy-substituted arene (**2r**: 82%). In all cases, the dihydroquinolin-2-one formation is characterized by skeletal C−C migration, with the C−N bond being formed at the position para to the para substituent. Notably, the Ru-catalyzed cyclization of 3-(4-(benzyloxy)phenethyl)-1,4,2-dioxazol-5-one (**1v**) would afford 6-(benzyloxy)-3,4-dihydroquinolin-2(1*H*)-one (**2v**) in 71% yield. According to literature, **2v** exhibits anticonvulsant activities for treating bipolar disorder and neuropathic pain.[11]

For the ortho-substituted substrates (Table 2), the facile reaction of 3-(2-methylphenethyl)-1,4,2-dioxazol-5-one afforded **3a** in 60% yield. Again, **3a** is characterized by skeletal C−C migration, with the C−N bond being forged at the position ortho to the substituent. In this work, the transformation of 3-(2-methoxyphenethyl)-1,4,2-dioxazol-5-one to **3b** was less successful. Yet the analogous 2-bromo-substituted derivative reacted successfully to furnish **3c** in 59% yield. Compared with the current Ru-catalyzed system, the Cp*Ir catalyst would produce both the C−C migration product and the direct C−H amidation product in a ratio of 1:1.2.[9b−d]

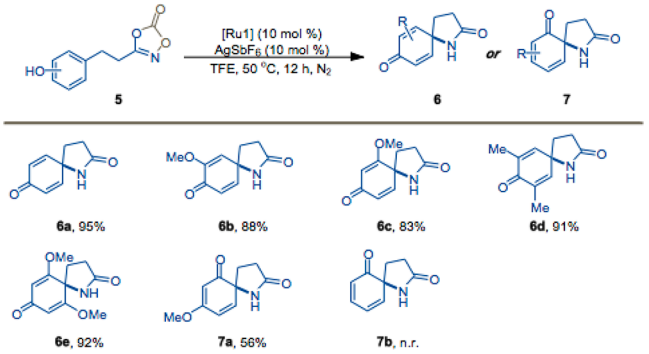
For the meta-substituted dioxazolones, the Ru-catalyzed cyclization of 3-(3-Y-substituted phenethyl)-1,4,2-dioxazol-5-one (Y = Me, OMe, and Br) furnished the corresponding dihydroquinoline-2-ones **4a**−**4c** in 39−72% yields. In all cases, the C−N bond formation occurred at the position para to the meta substituents. Apparently, skeletal C−C arrangement is not involved in the dihydroquinolin-2-one formations. The reaction of the dioxazol-5-one bearing *meta*- and *para*-OMe substituents produced **4d** exclusively in 83% yield, presumably via direct C−H amidation without skeletal rearrangement. Yet the formation of **4a**−**4d** may also occur via spirocyclization at the position meta to the substituent, followed by skeletal C−N rearrangement. The two pathways appear to be difficult to be differentiated.

Assuming Ru-nitrenoid intermediates, amidation at the benzylic C(sp^3)−H, 2° C(sp^3)−H, and 3° C(sp^3)−H sites is likely to be competitive.[10] Here the regioselectivity was assessed by reacting dioxazolones containing benzyl (**1s**), ethyl (**1t**), and isopropyl (**1u**) side arms under the Ru-catalyzed conditions. To our delight, the amidation is directed exclusively to the aryl C(sp^2)−H bond, rather than the benzylic C(sp^3)−H (**2s**), 2 °C(sp^3)−H (**2t**), and 3 °C(sp^3)−H (**2u**) bonds, and the desired amidation products were obtained in 78−83% yields.

The reactions of the para- and ortho-substituted dioxazolones afforded the dihydroquinoline-2-ones involving skeletal C−C rearrangement. We postulated that the reactive Ru-nitrenoid intermediate should initiate the cyclization by electrophilic amidation at the position para/ortho to the substituent to form some spirolactam intermediates, and the subsequent skeletal C−C rearrangement should afford the observed products. A similar mechanism was reported for the analogous Cp*Ir(III)-catalyzed intramolecular aryl C−H amidation.[9b−d]

To probe the spirolactam formation, 3-(4-hydroxyphenethyl)-1,4,2-dioxazol-5-one (**5a**) was employed as a model substrate for the Ru-catalyzed amidation, and the desired azaspiro[4.5]deca-6,9-diene-2,8-dione (**6a**) was isolated in 95% yield (Table 3). Notably, replacing the 4-OMe substituent in **1n** with a hydroxyl group (**5a**) led to the successful trapping of the spirolactam intermediate. Similarly, those phenol-based dioxazolones bearing OMe and Me groups at the ortho and meta positions underwent spirolactamization in excellent yield

Table 3. Scope of the Dearomative Spirocyclization Reaction

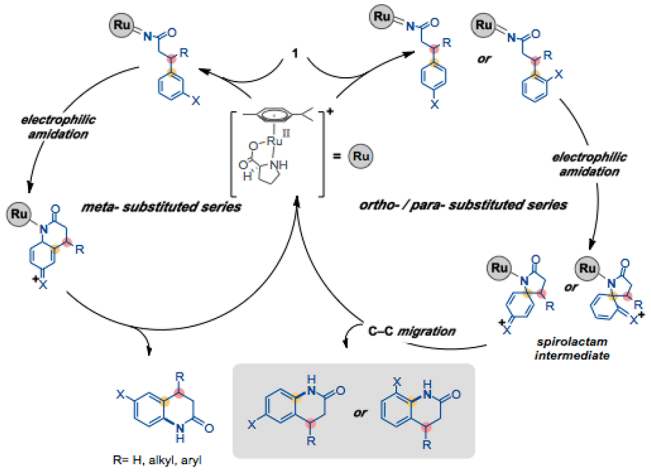


(**6b**; 88%; **6c**; 83%; **6d**: 91%; **6e**: 92%). Apparently, the nitrenoid attack at the position ortho to the hydroxy group should be facile to furnish **7a** in 56% yield. Yet the presence of a OMe group appears to be critical for an effective reaction because the production of spirolactam **7b** was unsuccessful due to the lack of a *para*-methoxy substituent.

The nature of the spirolactamization transition state has been examined by a Hammett correlation study using a series of 4-substituted dioxazolones **1-Y** (Y = OMe, Me, H, F, and Cl) as substrates. In this work, dioxazolone **1-Y** was subjected to the standard conditions: **1-Y** (0.1 mmol), [**Ru1**] (10 mol %), and $AgSbF_6$ (10 mol %) in TFE (1 mL) for 30 min. With ∼10−20% substrate conversion, the yields of the dihydroquinolin-2-ones were determined by ^{1}H NMR spectroscopy. (See the Supporting Information for details.) By plotting the log k_Y/k_H (Y = OMe, Me, H, F, and Cl) versus Hammett σ_{para} constant, a straight line (R^2 = 0.98) with slope (ρ) = −0.73. (See the Supporting Information.) The negative ρ value implies that the Ru-nitrenoid attack on the aryl ring is likely to be electrophilic in nature.

Scheme 3 depicts the proposed mechanism of the aryl C−H amidation of the 2- and 4-substituted dioxazolones. Assuming

Scheme 3. Proposed Mechanism



some Ru-nitrenoid as active intermediates, electrophilic attack of the nitrenoid moiety at the positions ortho and para to the substituents should afford the spirolactams. The regioselectivity of the amidation was probably favored by π-conjugation of the substituents, resulting in enhanced electron density at the

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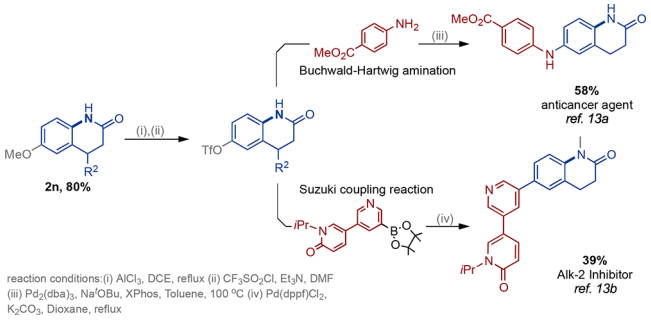
ortho and para positions of the substituent. The spirolactams should undergo skeletal C−C migration to form the dihydroquinolin-2-ones. For the 3-substituted dioxazolones, the product formation may proceed by direct electrophilic attack para to the substituent. However, a mechanism involving tandem spirocyclization and C−N skeletal rearrangement cannot be negated.[12]

To our delight, the Ru-catalyzed C(aryl)−H amidation can be performed on the gram scale. For instance, treating **1a** (2 mmol, 0.534 g) with 10 mol % [**Ru1**] and 10 mol % $AgSbF_6$ in TFE at 50 °C for 12 h gave **2a** in 61% isolated yield. (See the Supporting Information.)

Late-stage functionalization of the dihydroquinoline-2-ones can offer a convenient synthesis of methyl 4-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)amino)benzoate (anticancer agent)[13a] and 6-(1′-isopropyl-6′-oxo-1′,6′-dihydro-[3,3′-bipyridin]-5-yl)-1-methyl-3,4-dihydroquinolin-2(1*H*)-one (Alk-2 inhibitor).[13b] For instance, dihydroquinolin-2-one (**2n:** 80% yield prepared in this work) was transformed to its *O*-triflate derivative using $AlCl_3$ followed by CF_3SO_2Cl treatment.[14] Subsequent coupling to methyl 4-aminobenzoate (Buchwald−Hartwig amination) and 1-isopropyl-5′-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[3,3′-bipyridin]-6(1*H*)-one (Suzuki coupling) are known to afford the target medicinal products (Scheme 4).

Scheme 4. Late-Stage Functionalization of Dihydroquinolin-2-one 2n



In conclusion, we have developed the Ru-catalyzed cyclization of 1,4,2-dioxazol-5-ones to afford dihydroquinolin-2-ones. For the ortho- and para-substituted dioxazolones, the Ru-nitrenoid insertion occurs preferentially at the position ortho/para to the substituents, resulting in spirolactamization, followed by skeletal C−C/C−N rearrangement with remarkable regioselectivity. Because dihydroquinoline-2-ones are valuable pharmacophores, the successful development of this Ru-catalyzed reaction enables facile access to this important class of compounds from abundant hydrocarbon feedstocks. This method should be of utility to synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00781.

General information, experimental details, screening studies, and NMR spectral data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(12) With **1n** as a substrate, a careful analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed two distinct NH proton signals at δ_H 8.4 and 8.6 corresponding, respectively, to 6-methoxy-3,4-dihydroquinolin-2(1*H*)-one (**2n**; C−C migration product) and 7-methoxy-3,4-dihydroquinolin-2(1*H*)-one (C−N migration product) in a ratio of > 20:1.

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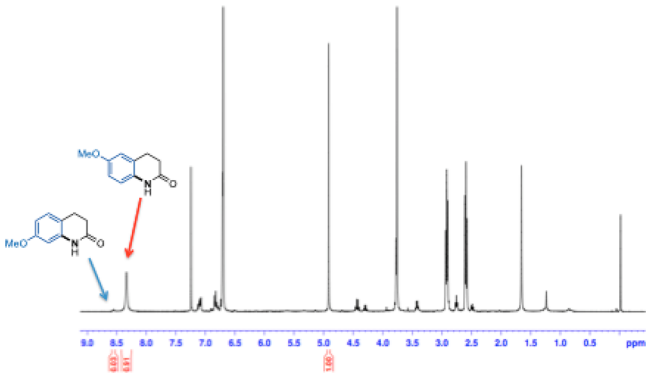

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