A One Carbon Linchpin for Rh(III)-Catalyzed, C(sp^3)-Directed C–H Annulation

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C–H activation, C–C coupling, rhodium, annulation, heterocycles, quinolines

ABSTRACT: We disclose a new platform for C(sp^3)-directed C–H annulations to generate valuable heterocycles from readily available starting materials. A commercially available one carbon linchpin is leveraged to access alkyl boron species from simple anilines. Rhodium-catalyzed C(sp^3) transmetallation from this key intermediate provides a C–Rh bond appropriately positioned for *ortho*-C–H activation, enabling formation of *C,C*-rhodacycles. With the addition of a variety of alkyne coupling partners, diverse dihydroquinolines are synthesized.

Introduction

C–H functionalization is a straightforward and effective method to generate complexity in organic molecules. The ubiquity of C–H bonds allows for a uniquely broad scope of potential transformations but also presents a challenge in selectivity due to similarity in the chemical environments of various C–H bonds in the substrate. One method to overcome this challenge is to utilize the coordination of a nearby functional group to position the metal close to the desired C–H bond. The majority of directing groups are heteroatom based, requiring appropriately positioned native functionality or the installation and removal of the directing group.[1-4] A less-explored alternative to this paradigm is direct utilization of carbon atoms to position the metal. These directing groups then form the carbon skeleton of the products, providing access to novel C–C bond forming reactions and offering significant promise to expand the scope of directed C–H functionalization.

Carbon-directed C–H functionalization was pioneered by Baudoin, Cramer, Kündig, and others,[5–12] who first accessed these directing C–M bonds via palladium-catalyzed oxidative addition from a C–X species (Figure 1a). Subsequent activation of a nearby C–H bond generates a metallocycle, and reductive elimination furnishes the cyclic products. More recently, Ackermann and coworkers developed a carbon-directed C–H activation reaction utilizing transmetallation from an aryl boronic acid (Figure 1b).[13] In this electrochemical rhodium-catalyzed reaction, one equivalent of alkyne is introduced through migratory insertion to position the metal appropriately for *ortho* C–H activation, generating a 5-membered metallocycle. Migratory insertion of a second equivalent of alkyne followed by reductive elimination gives the tetraphenylnaphthalene products. Currently, carbon-directed C–H annulation chemistry remains underdeveloped. Few examples of C(sp^3)-directed annulations exist,[14,15] and coupling partners are limited.

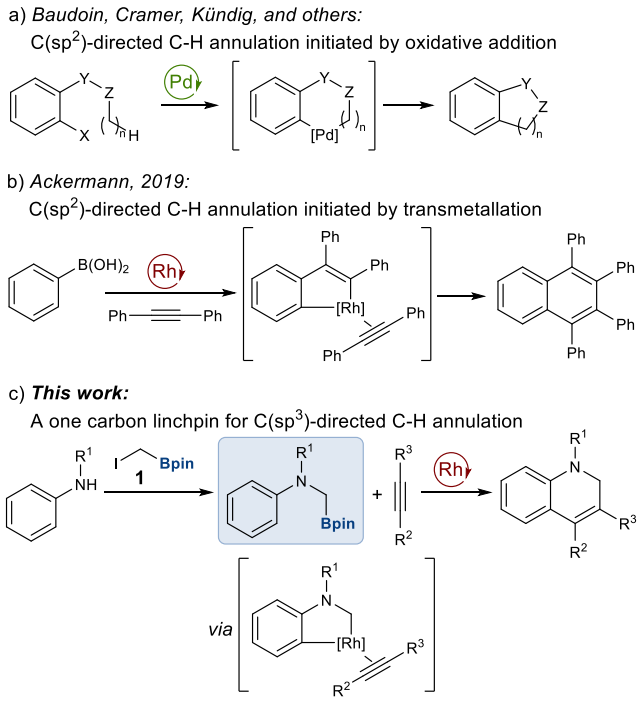


Figure 1. Background and overview of this work.

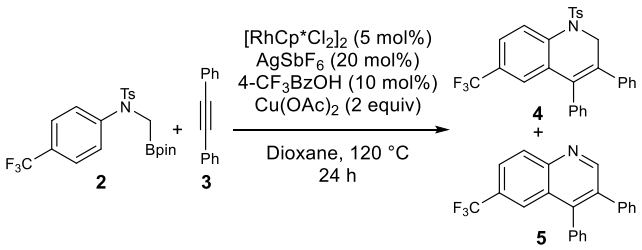
Ackermann's precedent remains one of the only reports utilizing a boron species as a precursor for carbon-directed C–H annulation reactions,[16,17] although others have used these materials in 1,4-metal migration reactions.[18] Inspired by this study, we recognized the untapped potential for boron as a traceless transmetallation agent to enable carbon-directed C–H annulation reactions. Specifically, we envisioned that commercially available **1** could act as a linchpin reagent, readily introduced to heteroatom nucleophiles to install the alkyl boron,[19] which can be used to affect a variety of annulations, yielding heterocyclic skeletons (Figure 1c). Incorporation of a carbon directing group directly into the skeleton unlocks a new scope of reactivity. Herein, we

demonstrate this platform in the context of a modular synthesis of dihydroquinolines from simple anilines and alkynes.

Results and Discussion

We began our investigation into the annulation reaction by exploring the possibility of using Cp* ligated Co, Rh, and Ir complexes to catalyze the reaction under oxidative conditions (Table 1). After investigating the reaction parameters, we found that the reaction could be successfully completed using 5 mol% $[RhCp^*Cl_2]_2$ as the catalyst, with 20 mol% $AgSbF_6$ employed as a halide scavenger under rigorously dry conditions in dioxane. We found that 2 equivalents of $Cu(OAc)_2$ were necessary as the oxidant and that 1.2 equivalents of alkyne coupling partner was optimal. We noted that the addition of an acid additive to aid in proton abstraction during the proposed concerted metalation-deprotonation (CMD) step improved yields drastically, with benzoic acid derivatives leading to fewer side products and providing an opportunity for electronic tuning. We identified 4-CF_3BzOH to be optimal and a 1:1 ratio of additive to rhodium to be necessary for higher yield. We found iridium and cobalt catalysts to be ineffective in this transformation. However, $[RhCp^{tBu}Cl_2]_2$ and $[RhInd^*Cl_2]_2$ both successfully catalyzed the reaction, albeit in diminished yields.

Table 1. Optimization of reaction for catalyst, additive, and oxidant.



Entry	Deviation from Std. Cond.	Yield of 4[a]
1	**None**	**76% (73%)[b]**
2	$[IrCp^*Cl_2]_2$ (5 mol%) as catalyst	0%
3	$[CoCp^*(CO)I_2]$ (10 mol%) as catalyst	0%
4	$[RhCp^{tBu}Cl_2]_2$ (5 mol%) as catalyst	38%
5	$[RhInd^*Cl_2]_2$ (5 mol%) as catalyst	42%
6	AcOH in place of 4-CF_3BzOH	46%
7	PivOH in place of 4-CF_3BzOH	21%
8	BzOH in place of 4-CF_3BzOH	35%
9	AgOAc in place of $Cu(OAc)_2$	>5%
10	AgOBz in place of $Cu(OAc)_2$	>5%
11	100 °C	52%
12	140 °C	40%

[a]Reactions were run on a 0.1 mmol scale. Yields were calculated by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [b]Isolated yield.

During early optimization, we observed low yields along with the formation of quinoline byproduct **5** resulting from elimination of the tosyl group from **4**. When the reaction was doped with 20 mol% of this byproduct, reactivity was completely inhibited, suggesting that the quinoline may be acting as a Lewis basic poison, coordinating with the rhodium and removing it from a productive catalytic cycle. Fortunately, our optimization efforts, and particularly the use of additive 4-CF_3BzOH, minimized the formation of this byproduct.

With the optimized system in hand, we investigated the reactions of a variety of anilines and substituted arylalkynes. We first examined a series of *para*-substituted aniline derivatives (Figure 2a, **6a**-**6h**). These included a scale of electron-donating to electron-withdrawing substituents, all of which were well-tolerated and generated the desired products in moderate to good yields (27-78%). No clear electronic trends were observed in the data. Notably, handles for further functionalization such as an aryl halide (**6e**, 59% yield), an olefin (**6g**, 53% yield), and an ester (**6h**, 63% yield) were well-tolerated.

Substituents at the *meta*-position gave products in moderate yields (**7a**-**7d**, 36-63%), potentially due to increased steric congestion. Again, both electron-donating and electron-withdrawing substituents were tolerated. Notably, the *meta*-substitutions bearing an alkyl group (**7c** and **7d**; 36% and 54% yield) were highly regioselective at >20:1 rr for the less sterically encumbered product. However, *meta*-alkoxy substituents (**7a** and **7b**; 60% and 63% yield) resulted in more moderate regioselectivities (1.1:1 and 1.7:1 respectively). Although it is possible that the reduced regioselectivity arises from the smaller size of the alkoxy substituents (A-values: CH_3 = 1.8 kcal/mol vs CH_3O = 0.60 kcal/mol),[20] we speculate that the oxygen atom might in fact be coordinating with the Rh catalyst and guiding it to the more sterically congested site, accounting for the observed mixtures of products. Reaction with a 3,4-dioxole-containing substrate produced **13** in 41% yield and 1.6:1 rr and favored the *ortho*-substituted product regioisomer, further supporting this coordination hypothesis.

In evaluating multi-substituted aryl rings, a 3,5-methoxy-substituted substrate gave **8** in a 42% yield, and 3,4-disubstituted substrates gave **9** and **10** in yields of 75% and 74%, both with excellent regioselectivities (>20:1 rr) favoring the less sterically congested product. Importantly, several heterocyclic amines were tolerated. A 4-aminopyridine derivative gave the annulated product **11** in a 50% yield, and structure **12**, from the 3-aminopyridine derivative, was obtained in a 69% yield and 4:1 rr between the 2- and 4-positions, respectively. Finally, nosyl and mesyl groups on the nitrogen were both tolerated, giving the desired products **14** and **15** in 68% and 81% yield, respectively.

Next, we turned our attention to the effect of various alkynyl substituents on the reaction (Scheme 1b). An alkyne bearing one electron-rich aryl substituent and one electron-deficient aryl substituent reacted efficiently (**16**, 80% yield), but with limited regioselectivity (1.7:1). Alkynes that were substituted with one aryl group and one alkyl group reacted with good yields (**17**-**24**, 52-74% yield) and excellent regioselectivity; in all but one case, products in which the alkyl group was adjacent to the aromatic ring were observed in >20:1 rr. Cyclopropane **18** and amino acid derivative **19** were synthesized in 71% and 52% yields, both in excellent regioselectivities (>20:1 rr). Use of a TIPS

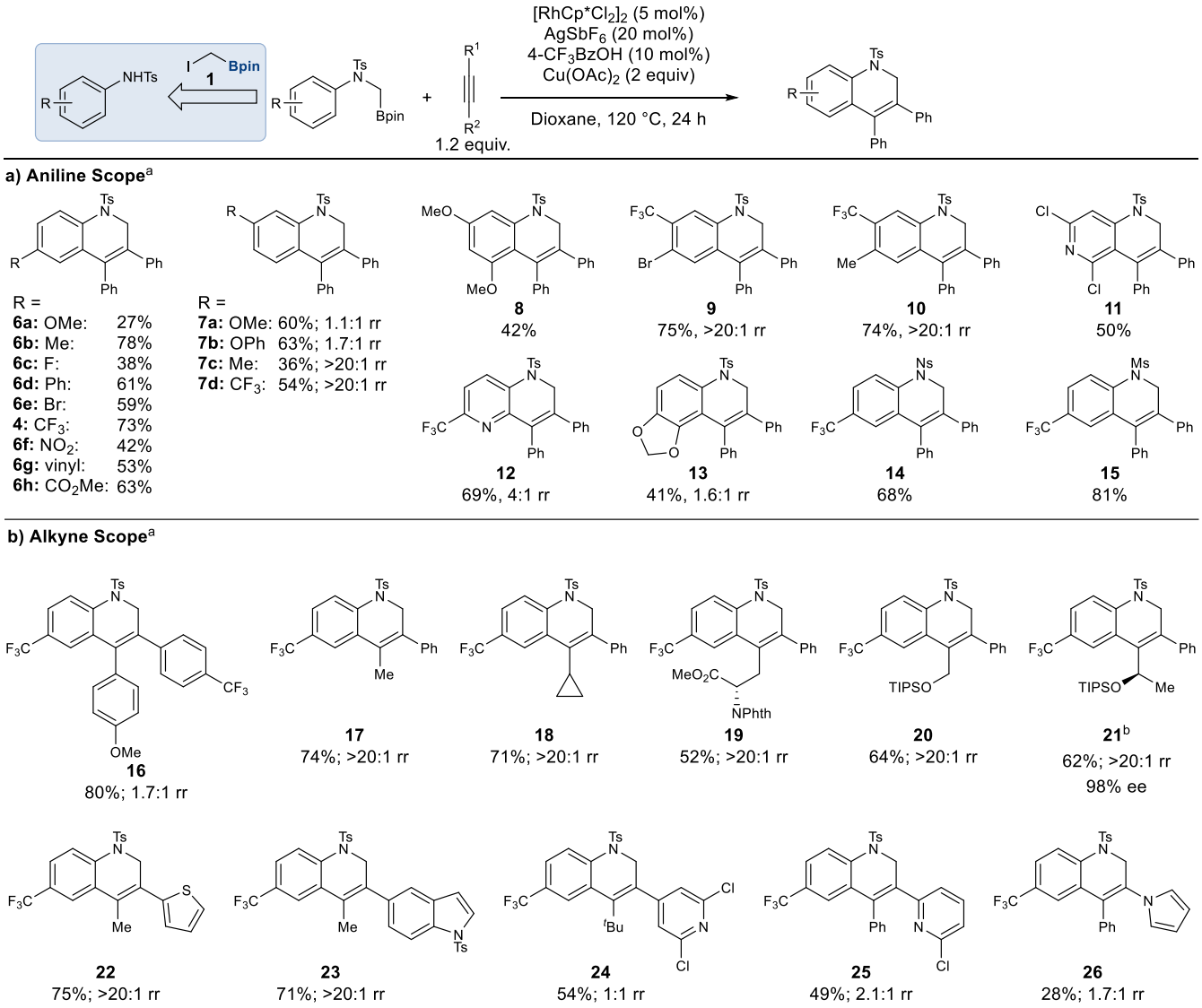


Figure 2. Scope of aniline and alkyne coupling partners. [a]Yields refer to the isolated product. Regioselectivity determined by ^{1}H NMR. Reactions were run on a 0.2 mmol scale. [b]Enantioselectivity determined by HPLC using a chiral stationary phase.

protected propargyl alcohol gave **20** in a 64% yield and >20:1 rr, and no degradation of enantiopurity was observed for secondary alcohol **21** (62% yield, >20:1 rr, 98% ee).

Alkynes containing a variety of heteroaryl substituents were also well-tolerated (**22**-**26**, 28-75% yield). Again, simple alkyl-heteroaryl disubstituted alkynes were incorporated with excellent regioselectivity (**22**-**23**, >20:1 rr). However, an alkyne substituted with a ^{t}Bu group and a pyridine provided product **24** in a 1:1 ratio of regioisomers, likely due to the similarity in size between these two substituents compared to other alkyl-aryl alkynes. Products **25** and **26**, obtained from alkynes bearing phenyl substituents and a pyridine and pyrrole respectively, were obtained in modest yields and selectivities (49% yield, 2.1:1 rr, and 28% yield, 1.7:1 rr).

In assessing both the practicality and applicability of this reaction, we have demonstrated that the reaction can be successfully scaled to 2.2 mmol, maintaining a similar yield and the high regioselectivity (67%; >20:1 rr) observed in the original 0.1 mmol reaction (Figure 3a). We have highlighted the value of these products by performing several one-step transformations to access other heterocycles (Figure 3b). The fully aromatized quinoline **28** was accessed from **4** in quantitative yield using potassium hydroxide in ethanol at 100 °C. Rhodium-catalyzed oxidation of **17** provided conversion to tosyl deprotected 2-quinolone **29** in 61% yield. Hydrogenation of **17** gave tetrahydroquinoline **30** in a 71% yield, and tosyl deprotection of **30** via acridine radical reduction provided **31** in 73% yield.[21]

To better understand the mechanism of this reaction, we performed several probing experiments. We investigated the reversibility of C–H activation by synthesizing deuterated analogues of our starting materials to study hydrogen incorporation at the position ortho to the amine. Under standard reaction conditions, we observed only 5% H/D exchange in product **33**, suggesting that the initial C–H activation is largely irreversible (Figure 4a). In a competitive intermolecular kinetic isotope effect (KIE) experiment, we

observed a KIE of k_H/k_D=1.0, indicating that the C–H activation step is not turnover-limiting (Figure 4b).[22]

Based on these findings and previous reports,[13,23,24] we propose a plausible mechanism for this transformation (Figure 3c). Initially, $[RhCp^*Cl_2]_2$ is dehalogenated by $AgSbF_6$. The resulting catalytic species **I** can engage the substrate and undergo transmetallation to form intermediate **II**. Subsequent carboxylate assisted CMD of the *ortho* C–H proton and alkyne coordination gives intermediate **III** as a 5-membered rhodacycle. Formal migratory insertion of the alkyne gives 7-membered *C,C*-rhodacycle intermediate **IV**, which undergoes reductive elimination to form the desired product with Rh(I) coordinated (intermediate **V**). Oxidation of the resulting Rh(I) species with copper acetate completes the catalytic cycle.

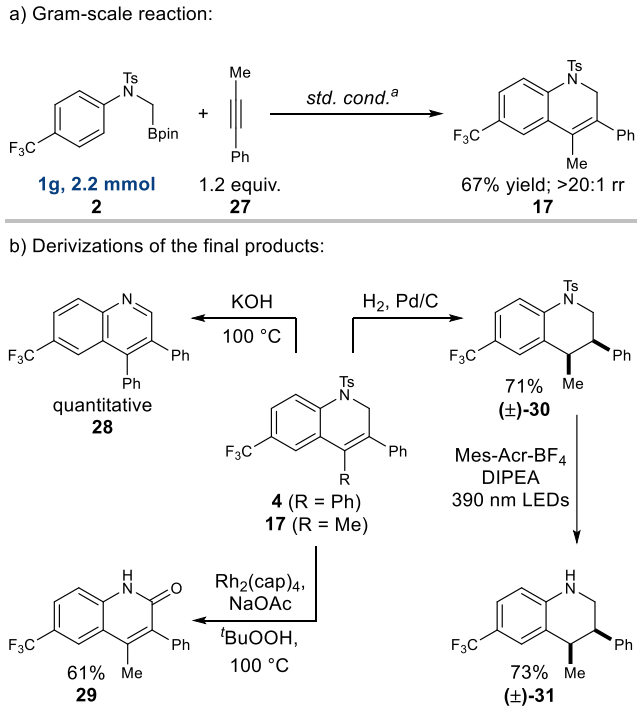


Figure 3. Representative functionalization of products. [a]Standard conditions (std. cond.): **2** (2.2 mmol), **27** (1.2 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), 4-CF_3BzOH (10 mol%), $Cu(OAc)_2$ (2 equiv), dioxane (45 mL), 120 °C, 24 h. Yield refers to the isolated product.

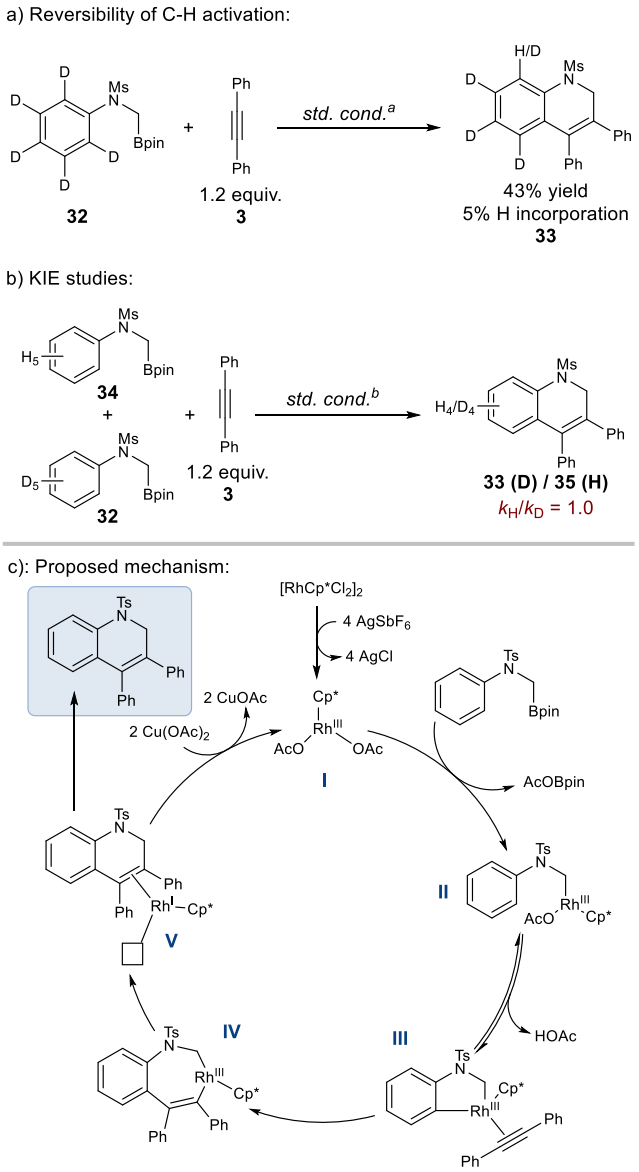


Figure 4. Mechanistic investigations and proposed mechanism. [a]Standard conditions: **32** (0.1 mmol), **3** (1.2 equiv) $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), 4-CF_3BzOH (10 mol%), $Cu(OAc)_2$ (2 equiv), dioxane (2 mL), 120 °C, 24 h. Yield refers to the isolated product. [b]Standard conditions: **34** (0.05 mmol, 0.5 equiv), **32** (0.05 mmol,0.5 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), 4-CF_3BzOH (10 mol%), $Cu(OAc)_2$ (2 equiv), dioxane (2 mL), 100 °C, 24 h.

Conclusions

In conclusion, we have developed a new platform for C(sp^3)-directed C–H annulation reactions, presenting a novel method for the generation of dihydroquinolines using a convenient commercially available linchpin reagent. Exceptional regioselectivity is observed in many cases, and a diverse array of heterocyclic coupling partners is tolerated. The dihydroquinoline products are readily transformed into a variety of valuable motifs, highlighting this as a versatile new method for medicinal chemistry campaigns. Underpinning the methodology, we have demonstrated that, through efficient access to a traceless alkyl boron species,

sp^3 transmetallation is an effective route to access carbon-based directing groups capable of affecting novel annulation reactions. We anticipate further development of this novel strategy will open up many opportunities for new carbon-directed C–H annulation reactions.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org

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ACKNOWLEDGMENT

This research was supported by the National Institutes of Health (GM136880). NMR data were collected on instruments obtained with support from the National Science Foundation (CHE-1521620).

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