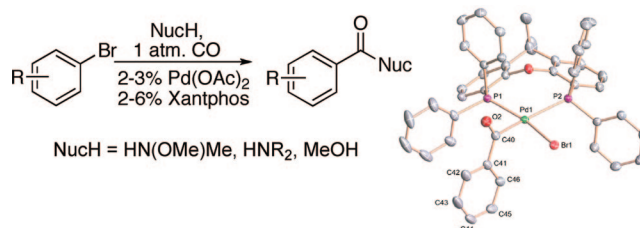# Palladium-Catalyzed Carbonylation Reactions of Aryl Bromides at Atmospheric Pressure: A General System Based on Xantphos

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A method for the Pd-catalyzed carbonylation of aryl bromides has been developed using Xantphos as the ligand. This method is effective for the direct synthesis of Weinreb amides, 1° and 2° benzamides, and methyl esters from the corresponding aryl bromides at atmospheric pressure. In addition, a putative catalytic intermediate, (Xanphos)Pd(Br)benzoyl, was prepared and an X-ray crystal structure was obtained revealing an unusual *cis*-coordination mode of Xantphos in this palladium−acyl complex.

Introduction

Carbon monoxide, CO, is a synthetically useful organic molecule and, due to its ability to act as a σ-donor and a π-acceptor, an excellent ligand for transition metals.[1] Chemists have long endeavored to utilize the unique reactivity of CO in the development of synthetic methods, and the success of these many workers is reflected by the myriad reports of highly efficient polymerization processes[2] and systems for catalytic carbonylation reactions.[3] The seminal report by Heck in 1974 details the first use of the palladium-catalyzed three-component coupling reaction of an aryl halide, CO, and an alcohol or amine (more generally, a nucleophile).[4]

The palladium-catalyzed carbonylation reaction is a very convenient method for the regioselective synthesis of carbonyl-containing compounds. The utility of this class of transforma-

tions has spurred wide interest resulting in many excellent contributions. The scope of the processes that have been developed is wide and includes many nucleophiles, enabling the efficient syntheses of numerous carbonyl derivatives,[5] including ^{11}C radio-labeled compounds used for PET studies.[6] Other interesting advances include the use of ionic liquids[7] and various surrogates for CO,[8] such as DMF[8b] or Mo(CO)$_6$.[8c] Despite the importance of each individual contribution, the ligand and the pressure of CO employed often varies from one system to another, making the development of a more general system a desirable goal.

In an effort to develop such a system, we chose three useful and representative carbonylation reactions: aminocarbonylation to form Weinreb amides, aminocarbonylation to form benzamides, and alkoxycarbonylation to form methyl esters. Additionally, for convenience (on the academic laboratory scale), we focused on reactions conducted at atmospheric pressure to obviate the need for specialized high-pressure reaction vessels. In this paper, we disclose our efforts toward arriving at a general system for these Pd-catalyzed carbonylation processes using aryl bromides as substrates and Xantphos as the supporting ligand.

Results and Discussion

As reported in a recent communication,[5d] we began our efforts to develop a general system for Pd-catalyzed carbonylation procedure by examining the formation of the Weinreb amides

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TABLE 1. Ligand Optimization for the Synthesis of Weinreb Amides via Pd-Catalyzed Aminocarbonylation[a]
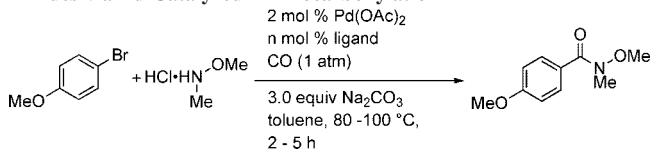
entry	n mol %	ligand	bite angle	temp (°C)	time	% conversion[b]	% yield[b]
1	8	PPh₃	145[c]	100	2 h	< 1	0
2	5	SPhos	217[c,d]	100	2 h	< 1	0
3	2.2	(*S*)-BINAP	92	100	2 h	< 1	0
4	2.2	dppp	95	100	2 h	< 1	0
5	2.2	dppb	99	100	2 h	< 1	0
6	2.2	dppf	106	100	2 h	< 1	0
7	2.2	DPEphos	108	100	2 h	< 1	0
8	2	Xantphos	110	100	2 h	36	30
9	2	Xantphos	110	100	5 h	90	87
10[e]	2	Xantphos	110	80	5 h	100	89[f]
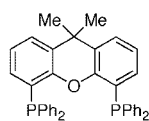
Xantphos   **DPEphos**   **dppf**
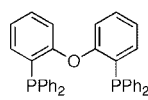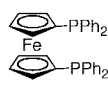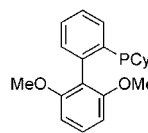
dppp: n = 1
dppb: n = 2   **SPhos**   **(*S*)-BINAP**
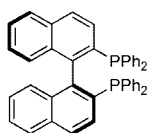
[a] Reaction conditions: 2 mol % of Pd(OAc)₂, *n* mol % of ligand, 1 mmol *para*-bromoanisole, 1.5 mmol amine, 3 mmol base in toluene (2 mL) at 100 °C. [b] Determined by GC, average of two runs. [c] Cone angles. [d] See ref 14. [e] Reaction was run at 80 °C for 5 h. [f] Isolated yield, average of two runs.

derived from *para*-bromoanisole and dimethylhydroxylamine hydrochloride (Table 1). Although numerous variables associated with the reaction conditions were examined (including Pd precatalyst, base, and solvent), the most influential proved to be the choice of ligand. Previous studies have shown that ligands employed in carbonylation chemistry must be electron-donating enough to promote oxidative addition and prevent precipitation of Pd-black or formation of Pd-carbonyl clusters.[9] Additionally, bidentate ligands are often superior to monodentate ligands in these processes,[5a−e] a fact that has been ascribed to their greater ability to prevent catalyst poisoning via ligation of multiple CO ligands. Despite these guidelines, our initial efforts in this area, which examined a wide range of electron-rich mono- and bidentate phosphine ligands, failed to provide detectable amounts of product (Table 1, entries 1−7).

Xantphos, a bidentate ligand developed by van Leeuwen for the hydroformylation reaction,[10] has been used extensively for Pd-catalyzed C−N bond forming processes.[11] The wide bite angle (110°)[12] and flexibility range (97−133°)[12] characteristic of Xantphos are believed to impart a dynamic coordination environment that may be important for catalyst activity and stability in Pd- and other transition-metal-catalyzed processes.[13]

Unlike other ligands examined, Xantphos provided a highly active catalyst, delivering significant amounts of product after only 2 h under our screening conditions (Table 1, entry 8). This result is notable as both DPEphos and dppf, which are also bidentate ligands and have similar bite angles to Xantphos,[14] did not produce active catalysts and highlights the importance of the flexible coordination environment of the Xantphos backbone.

These initial screening experiments with Xantphos were conducted with a 1:1 ratio of ligand to Pd(OAc)₂, as the literature indicated that excess Xantphos can inhibit Pd-catalyzed C−N bond forming reactions.[15] Optimization of the reaction conditions using this Pd:L ratio revealed that the reaction was best conducted at 80 °C. At 100 °C, incomplete conversion of the starting material was observed. We attribute this unusual result to increased catalyst stability at the lower temperatures.

Thus, under our optimized conditions [Pd(OAc)₂ (2 mol %), Xantphos (2 mol %), Na₂CO₃ (3 equiv), and *N*,*O*-dimethylhydroxylamine hydrochloride (1.5 equiv) in toluene at 80 °C under

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TABLE 2. Synthesis of Weinreb Amides via Pd-Catalyzed Aminocarbonylation Using Xantphos[a]

Reaction scheme:

R—(aryl)—Br + HCl·HN(OMe)(Me) → [2–3 mol% Pd(OAc)₂, 2–6 mol% Xantphos, CO (1 atm), 3.0 equiv base, toluene, 80–120 °C, 5–22 h] → R—(aryl)—C(O)—N(OMe)(Me)

entry	ArBr	mol% Pd (L:Pd)	base	temp.	yield[b]	entry	ArBr	mol% Pd (L:Pd)	base	temp.	yield[b]
1	3-bromobenzonitrile (NC, Br)	2% (1:1)	Na₂CO₃	80°C	88%	12	2-bromo-1,4-dimethylbenzene (Me, Me)	2.5% (2:1)	K₃PO₄	100°C	87%
2	4-bromo-2-fluorobenzonitrile (F, NC, Br)	2% (1:1)	Na₂CO₃	80°C	90%	13	1-bromonaphthalene	2.5% (2:1)	K₃PO₄	100°C	97%
3	1-bromo-3-nitrobenzene (O₂N, Br)	2% (1:1)	Na₂CO₃	80°C	87%	14	2-bromobenzonitrile (Br, CN)	2.5% (2:1)	K₃PO₄	100°C	84%
4	3-bromothiophene (S, Br)	2% (1:1)	Na₂CO₃	80°C	91%	15	methyl 2-bromobenzoate (Br, OMe, O)	3% (2:1)	K₃PO₄	100°C	80%
5	1-bromo-4-chlorobenzene (Cl, Br)	2% (1:1)	Na₂CO₃	80°C	87%	16	2-bromoanisole (Br, OMe)	3% (2:1)	K₃PO₄	100°C	81%
6	tert-butyl (4-bromophenyl)(methyl)carbamate (t-BuO, N, Me, Br)	2% (1:1)	Na₂CO₃	80°C	95%	17	2-bromobenzotrifluoride (Br, CF₃)	3% (2:1)	K₃PO₄	110°C	94%[c]
7	4-bromoanisole (MeO, Br)	2% (1:1)	Na₂CO₃	80°C	89%	18	2-bromo-3-methylpyridine (Me, Br, N)	3% (2:1)	K₃PO₄	110°C	78%[c]
8	methyl 3-bromobenzoate (MeO₂C, Br)	2% (1:1)	Na₂CO₃	80°C	88%	19	1-bromo-2-cyclohexylbenzene (Br, Cy)	3% (2:1)	K₃PO₄	120°C	90%[c]
9	2-(3-bromophenyl)-1,3-dioxolane (Br)	2% (1:1)	Et₃N	80°C	93%	20	2-bromo-1,4-difluorobenzene (F, Br, F)	2.5% (2:1)	K₃PO₄	110°C	65%[c]
10	4-bromo-2-methoxyanisole (MeO, Br, OMe)	2% (1:1)	Et₃N	80°C	89%	21	4-chlorobenzonitrile (NC, Cl)	3% (2:1)	K₃PO₄	105°C	74%
11	4-bromobiphenyl (Br, Ph)	2% (1:1)	Et₃N	80°C	94%						

[a] Reaction conditions: 2–3 mol % of Pd(OAc)₂, 2–6 mol % of Xantphos, 1 mmol aryl bromide, 1.5 mmol N,O-dimethylhydroxylamine•HCl, 3 mmol base in toluene (2 mL) at 80–120 °C. [b] Yields are an average of two runs. [c] m-Xylene (2 mL) was used as the solvent.

1 atm of CO], a number of substituted aryl bromides were successfully transformed into the corresponding Weinreb amides (Table 2, entries 1–11).

One limitation of the method was in the use of *ortho*-substituted aryl bromides, which remained recalcitrant under the reaction conditions. However, reoptimization of the reaction parameters revealed that raising the reaction temperature and increasing the Xantphos to Pd ratio from 1:1 to 2:1 allowed for these more demanding substrates to be transformed into Weinreb amides in high yield (Table 2, entries 12–20). Additionally, K₃PO₄ proved more effective than Na₂CO₃ as base under these new conditions. It is evident that, at the higher reaction temperatures required for the *ortho*-substituted substrates, excess ligand increases the stability of the catalyst system.

A number of functional groups were tolerated under either set of conditions, including a nitrile, nitro, aryl fluoride, aryl chloride, *tert*-butyl carbamate, methyl ester, ethylene glycol-protected aldehyde, and trifluoromethyl group. Heteroaryl bromides, such as 2-bromo-3-methylpyridine and 3-bromothiophene, were also transformed to the corresponding Weinreb amides (Table 2, entries 4 and 18). Additionally, although unactivated aryl chlorides were unreactive, an activated aryl chloride, 4-chlorobenzonitrile, was also converted to product under these reaction conditions (Table 2, entry 21).

In addition to the formation of Weinreb amides, the conditions described proved extremely general for the atmospheric pressure aminocarbonylation of aryl bromides to produce other amides. Indeed, numerous 1°, cyclic and acyclic 2° amines, and anilines

TABLE 3. Synthesis of Benzamides via Pd-Catalyzed Aminocarbonylation Using Xantphos[a]

entry	ArBr	amine	product	yield[b]	entry	ArBr	amine	product	yield[b]
1				84%[c,d]	11				86%[f]
2				95%	12				91%[f]
3				91%	13				94%[f]
4				93%[e]	14				94%
5				87%	15				85%
6				91%[d]	16				84%
7				83%	17				80%
8				98%	18				84%
9				97%[d]	19				78%[d]
10				87%	20				89%[d]

[a] Reaction conditions: 2 mol % of Pd(OAc)$_2$, 2 mol % of Xantphos, 1 mmol aryl bromide, 1.5 mmol amine, 3 mmol Na$_2$CO$_3$ in toluene (2 mL) at 80 °C. [b] Yields are an average of two runs. [c] Reaction temperature was 60 °C. [d] Et$_3$N (3 mmol) was used as the base. [e] 0.5 mol % Pd(OAc)$_2$ and 0.5 mol % Xantphos. [f] Reaction temperature 100 °C.

could be employed under these conditions (Table 3). As in the synthesis of Weinreb amides, a number of functional groups were tolerated including nitriles, aryl chlorides, aryl fluorides, and methyl esters. Interestingly, if the methyl ester moiety in the substrate is *ortho* to the aryl bromide and a 1° amine was used, an *n*-alkyl phthalamide product was the exclusive product observed (Table 3, entries 15−17). Heteroaryl bromides, such as 3-bromopyridine and 3-bromoquinoline, were also converted into benzamides without complication (Table 3, entries 19 and 20).

The success of this method for the aminocarbonylation of aryl bromides at atmospheric pressure of CO suggested that this method could be expanded to include other nucleophiles, such as alcohols for the synthesis of esters. There have been some recent reports detailing very effective methods for the synthesis of methyl esters from aryl bromides,[5b] heteroaryl chlorides,[5b]

activated aryl sulfonates,[16] and unactivated aryl mesylates and tosylates.[5c] However, all but two of these methods, which were recently developed in our labrotory,[5c,17] require pressures above 1 atm of CO and thus require the use of specialized equipment. This pressure limitation is also due, in part, to the use of methanol since its boiling point of 65 °C limits reaction temperatures at atmospheric pressure.

Initial attempts to apply the conditions utilized for the aminocarbonylation reactions previously described were plagued by formation of arene via unwanted reduction of the aryl bromide. During the optimization of the process, we discovered that this side reaction could be completely suppressed by replacing toluene solvent and the inorganic base with Et$_3$N. The Et$_3$N in this system not only acts as solvent and base but may also provide an efficient means for conversion of Pd(OAc)$_2$ to the active Pd(0) catalyst.[18]
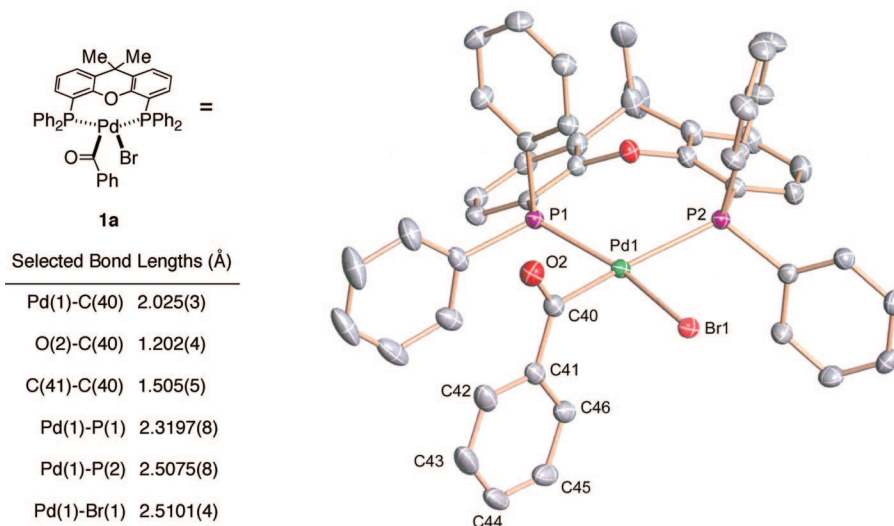
FIGURE 1. X-ray crystal structure and selected bond lengths of (Xantphos)Pd(Br)COPh. Thermal ellipsoids at 30% probability and two THF molecules removed for clarity.

TABLE 4. Synthesis of Methyl Esters via Pd-Catalyzed Alkoxycarbonylation Using Xantphos

entry:	1	2	3	4	5	6
	80%	89%	92%	89%	91%	90%

This Xantphos-based catalyst system is capable of converting aryl bromides to the corresponding methyl esters at 70 °C under an atmosphere of CO. Though a 10-fold excess of methanol was employed, the conditions are suitably mild to allow the presence of various functional groups, including an ethyl ester (with no observable transesterification), aryl fluoride, nitrile, and *tert*-butyl carbamate. A heteroaryl bromide, 4-bromoisoquinoline, was also transformed to the corresponding methyl ester (Table 4, entry 6). Unfortunately, due to the low reaction temperatures, more challenging substrates remained recalcitrant. For example, exposing 2-cyclohexylbromobenzene to these reaction conditions resulted in no detectable conversion of the starting aryl bromide or formation of the desired product. Despite this limitation, we believe this system represents the most general system to date for the atmospheric pressure amino- and alkoxycarbonylation of aryl bromides.

In an attempt to gain insight into the mechanism of these Pd-catalyzed transformations, we set out to prepare and isolate a Xantphos-coordinated Pd-acyl complex. Recrystallization of the material obtained from combining Pd$_2$(dba)$_3$, Xantphos, and benzoyl bromide provided the desired complex, which was demonstrated to be a chemically and kinetically competent

catalyst for the carbonylation reaction.[19] The structure of the complex was determined by single-crystal X-ray analysis (Figure 1). Interestingly, though the solution state structure for the complex was clearly the *trans*-coordinated isomer (as determined by the single resonance in the ^{31}P NMR spectrum), the solid state structure contained the phosphines bound in a *cis*-configuration. Although the coordinatively flexible nature of the Xantphos framework has been previously discussed,[20] the *cis*-configuration of the complex in the solid state is somewhat unusual. Most neutral Xantphos−Pd(II) complexes containing aryl ligands have been shown to be *trans*-configured in the solid state.[20−22]

Though the discrete mechanistic underpinning of this coordinative flexibility remains unclear, we believe that it may play a critical role in the efficiency of this catalytic system. As pointed out by the Merck group in their work on BINAP-Pd-catalyzed carbonylation of aryl bromides,[5b] previous mechanistic studies on carbonylation reactions of aryl halides have been performed on catalytic systems containing only monodentate

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(19) See Supporting Information.

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phosphines.[23] The mechanisms proposed in these studies often involve dissociative steps in which a monophosphine exits the coordination sphere of the metal to allow for binding of carbon monoxide or the nucleophile. As such, dissociative mechanisms are expected to be less favorable (though not impossible) in systems containing bidentate ligands, and it is not clear that systems involving bidentate ligands proceed in this way. It is possible that associative mechanisms may be involved, and the Merck group has suggested several possibilities. Unfortunately, no detailed mechanistic studies have yet been carried out on bidentate catalyst systems to make definitive arguments.

It is notable, however, that while the *cis*-chelating ligand BINAP is very effective for Pd-catalyzed carbonylation reactions, it requires CO pressures >1 atm. On the other hand, the Xantphos system reacts rapidly at 1 atm. We think that it is reasonable to suggest that greater efficiency of the Xantphos system might arise from the greater flexibility of the ligand system. We believe that Xantphos more readily dissociates one of its phosphine groups, making dissociative pathways more accessible than for BINAP. Alternatively, if the bidentate systems are proceeding exclusively via associative mechanisms, it is possible that the configuration with *trans*-phosphines provides a lower energy pathway than the *cis*-configuration, which is a pathway that is not possible using BINAP. While this discussion is speculative, at present we favor the former (dissociative) pathway.

Conclusion

In summary, we have described the development of a Pd-catalyzed carbonylation protocol employing Xantphos as the ligand. This method has been demonstrated to be effective for the direct synthesis of Weinreb amides, benzamides, and methyl esters from the corresponding aryl bromides at atmospheric pressure. In addition, a putative catalytic intermediate, (Xantphos)Pd(Br)benzoyl, was synthesized, and an X-ray crystal structure was obtained. This crystal structure revealed that this species possesses, in contrast to the majority of Pd-aryl complexes ligated by Xantphos, a *cis*-coordinated palladium center.

Experimental Section

The following is a representative example of the synthesis of a Weinreb amide from the corresponding aryl bromides via Pd-catalyzed carbonylation under atmospheric pressure CO. A complete description of all experimental details, including procedures for the preparation of benzamides and methyl esters, can be found in the Supporting Information. Note: carbon monoxide is a highly toxic gas and should only be used in a well-ventilated fume hood and with proper leak detection equipment.

4-Cyano-3-fluoro-*N*-methoxy-*N*-methylbenzamide (Table 2, entry 2). An oven-dried culture tube (18 × 150 mm) equipped with a Teflon coated magnetic stir bar was sealed with a 14/20 rubber septum (inverted), evacuated, backfilled with nitrogen, and cooled under nitrogen. Pd(OAc)$_2$ (2 mol %, 0.02 mmol, 0.02 equiv, 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv, 11.6 mg), *N,O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv, 146 mg), and Na$_2$CO$_3$ (3 mmol, 3 equiv, 318 mg) were added by briefly removing the rubber septum. The rubber septum then was secured with several wrappings of electrical tape. 4-Bromo-2-fluorobenzonitrile (1 mmol, 0.200 g) and toluene (2 mL) were added dropwise via syringe. The reaction then was purged for ∼30 s with CO$_{(g)}$; following the gas purge, a balloon was connected to the reaction using a short length of rubber tubing (∼1 in.), a needle adapter, and a 20 G needle. This balloon was then inflated with CO$_{(g)}$, and the reaction tube was submerged in an 80 °C preheated oil bath. The reaction mixture was heated at 80 °C with vigorous stirring until the aryl halide had been completely consumed as judged by GC analysis (18 h). The reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate (∼10 mL), filtered through a plug of Celite (eluting with ethyl acetate), and concentrated under reduced pressure. The crude product mixture was purified by flash column chromatography on silica gel (20−50% ethyl acetate in hexanes) to provide the title compound as a light yellow-orange solid (181 mg, 95%): mp 43−44 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.71−7.66 (m, 1H), 7.60−7.52 (m, 2H), 3.54 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.38, 164.23, 160.79, 140.84, 140.74, 133.36, 124.70, 124.65, 116.64, 116.35, 113.42, 103.26, 103.06, 61.59, 33.17 (observed complexity due to C−F splitting; definitive assignments have not yet been made); ^{19}F NMR (282 MHz, CDCl$_3$) δ −106.1; IR (neat, cm^{-1}) 3090, 2977, 2940, 2823, 2239, 1652, 1622, 1566, 1503, 1459, 1428, 1386, 1251, 1198, 1182, 1115, 990, 941, 887, 835, 750, 733, 714, 682, 668. Anal. Calcd for C$_{10}$H$_9$FN$_2$O$_2$: C, 57.69; H, 4.36. Found: C, 57.64; H, 4.37.

Supporting Information Available: Characterization data of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) One exception in the recently prepared (Xantphos) Pd(CF$_3$)Ph, which has been shown to be *cis*-configured in the solid state. See ref 21c.

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