Allylation Reactions in Aqueous Media: Development, Applications and Future Works

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Abstract: The use of allyltin, allylzinc and allylindium in the allylation of carbonyl compounds are facile methods for the syntheses of homoallylic alcohols. These water-stable complexes frequently allow for reaction conditions that are not only mild, but also permit the dispensing of organic solvents as reaction media. These synthesis methodologies are progressively being developed for stereoselective carbon-carbon bond formations for the purpose of assembling complex natural products.

1. Introduction

The traditional paradigm of carbon-carbon bond formation under harsh conditions with strict protocols is now being challenged through the discovery of alternative chemistries that offer synthetic chemists mild and process-tolerant procedures. In particular, allyltin, allylzinc and allylindium¹ chemistries are poised to replace traditional Grignard procedures.² The use of these peculiar organometallic compounds for the allylation of carbonyl compounds^{3,4} to form homoallylic alcohols are important reactions in the synthesis of biologically active molecules such as polyketides⁵, macrolides⁶, polyhydroxylated natural products⁷ and polyether antibiotics.⁸ In general, the allylmatal complex is formed *in situ* from the corresponding allylic halide and metal powder followed by the reaction with the carbonyl compounds, with or without the presence of acid catalysts (Figure 1). Varying proportions of water are tolerated, and frequently, even promoting the reaction. However, substrate sensitivity to water and other factors sometimes make aqueous-based reactions not fruitful or feasible, despite the inherent capabilities of such systems.

Figure 1. General procedure for the allylation of carbonyl compounds.

In this account of our group's research in this field, we would take the reader from the early developments to present chemistries, and our recent foray into enantioselective allylation reactions. We would also be discussing applications of these allylation reactions to the synthesis of natural products, with an overview of our strategies and a brief description of the problems we encountered and the interesting results obtained.

2. Development of Methodologies

Our early set of work focused on the stereoselective implementation of the allylation in aqueous media. A diastereoselective allylation of a chiral sugar derivative⁹ was first studied and Yb(OTf)₃¹⁰ was found to effectively catalyse

the allylation in DMF/H₂O mixture with excellent anti-diastereofacial selectivity and yield (Figure 2). Note that use of water alone can promote this reaction, albeit with lower diastereoselectivity. Interestingly, the isomer ratio was reversed with the use of allylsilane and SnCl₄ in place of the allylbromide-In system. The stereochemical result of the aqueous system was explained through Felkin-Anh's¹¹ or Cram's model¹², whereas that for the allylsilane system was attributed to a chelation-controlled reaction trajectory¹³.

Figure 2. Indium-mediated allylation of a sugar derivative.

The above work was further extended to the allylation of α -aminoaldehyde, foremost as a study on the effect of the nitrogen moiety on the diastereoselectivity. More importantly though, this could be a facile entry to enantiomerically pure β -amino alcohols that are present in many pharmacologically active compounds. Both indium- and zinc-mediated reactions were studied, with the results drawing a close parallel to the previously described glucose-derived aldehyde substrate (Figure 3).¹⁴ Note that zinc is unable to mediate the reaction in water alone, and this had prompted us to focus our attention on indium-mediated systems as part of our efforts to eliminate the use of organic solvents.

In our study on the stereochemistry of allylation for the purpose of natural product synthesis, we had found a stereoselective route to chiral tertiary alcohol through the allylation of a glucose-derived ketone (Figure 4).¹⁵ Excellent yields were obtained for this reaction and high diastereoselectivities were observed. Note that the use of La(OTf)₃ or Yb(OTf)₃ does not improve and even seems to reduce the diastereoselectivity in this reaction.

A chelation transition state was postulated to be responsible for the stereochemical outcome of the reaction (Figure 5). This is most likely the explanation for the reduced diastereoselectivities observed in the presence of an added Lewis acid.

Figure 3. In- or Zn-mediated allylation of protected α -aminoaldehyde.

Figure 4. Indium-mediated allylation of sugar-derived ketone.

Figure 5. Proposed chelation transition state.

The competition of added Lewis acids for the chelation sites favoured by the indium center would have reduced the yield of the chelation product and instead, increased the proportion of the non-chelation product.

As part of our aim in developing reaction systems that function without any organic solvents, we developed a Sn/InCl₃ allylation system that demonstrated high diastereofacial selectivity in water (Figure 6).¹⁶ This InCl₃ catalysed reaction is proposed to occur through a transmetalation followed by a cyclic transition state to account for the strong *anti* preference of product formation. In the same paper, the allylation of various unprotected carbohydrates were also reported to have good to excellent yields with excellent diastereoselectivities.

As our laboratory is developing the chemistry of the Sn/InCl₃ system, we also had, at the same time, an interest in

Figure 6. InCl₃ promoted Sn mediated allylation of aldehydes in water.

Figure 7. Proposed mechanism for the *anti* preference.

the synthesis of fluorinated compounds. We first looked at methods to synthesize analogous compounds with trifluoromethyl group in place of methyl. The CF₃ moiety, with its high C–F strength, electron-withdrawing properties, both hydro- and lipo-phobicities, often impart unique properties to the equivalent hydrocarbon counterpart.¹⁸ This is especially so for pharmacologically active compounds. Thus, the Sn/InCl₃ allylation methodology was extended to the synthesis of

β -trifluoromethylated homoallylic alcohols using a novel 1,1,1-trifluoro-4-bromobut-2-ene as the allylic halide (Figure 8).¹⁹ Unlike previous observations, the reaction does not proceed without the catalysis of InCl₃. Another result of note is the strong *anti* or *syn* preference that is substrate-dependent.

Figure 8. Synthesis of β -trifluoromethylated homoallylic alcohols.

The above reaction is proposed to proceed *via* the same six-membered transition state as depicted in Figure 7 to result in the *anti* preference. However, the intense *syn* selectivity observed for 2-pyridinecarboxaldehyde and glyoxylic acid is explained through the bulky group of the aldehyde adopting the axial instead of the equatorial position as a result of a stabilizing five-membered ring chelation with the indium center (Figure 9).

Figure 9. Proposed transition states to account for the preferential formation of *syn* products.

A purely indium-mediated counterpart to the above reaction was also studied and the results were excellent in terms of yields and diastereoselectivities.²⁰ In addition, the *anti* and *syn* selectivities closely paralleled that of the Sn/InCl₃ system, and a similar transition state to account for the product stereochemistry is still pertinent. This simpler In-mediated allylation methodology was then adopted in preference over Sn/InCl₃ in our future work.

The study on the synthesis of organofluorine compounds continued with the synthesis of α -trifluoromethylated alcohols through allylation of the corresponding fluorinated aldehyde. This seemingly straightforward reaction is hampered by the difficulty of handling trifluoroacetaldehyde, which is a volatile compound with a strong tendency to exist as its hydrated form. Hence, traditional organometallic addition to this aldehyde would be difficult, and a water-tolerant methodology would be highly sought after. The most convenient starting material is the commercially available trifluoroacetaldehyde ethyl hemiacetal. This, surprisingly, lends

itself directly to our indium-mediated allylation without further treatment (Figure 10).²¹ Interestingly, in contrast to our past results, the product yield was attenuated by the addition of lanthanide triflates. In the same paper, the attempted use of a chiral auxiliary was unsuccessful. The use of the Sn/InCl₃ system was also studied and the results matches those of the In-mediated procedure as previously observed.

Figure 10. Indium-mediated allylation of trifluoroacetaldehyde ethyl hemiacetal.

The unusual absence of the ethoxy product was explained through a cyclic transition state with the favored coordination of the “hard” hydroxyl group with the “hard” indium centre instead of the relatively “soft” ethoxy group (Figure 11).

Figure 11. Mechanism proposed for the absence of ethoxy product.

Our continual search for alternative reaction systems that function well in water led us to the use of CF₃SO₃H as a Brønsted acid in the addition of allyltributylstannanes to aldehydes (Figure 12).²² Yields were good to excellent. Note that other mineral acids studied were not able to catalyse this reaction.

Figure 12. Addition of allyltributylstannanes to aldehydes in water catalysed by CF₃SO₃H.

The preceding work was applied to the diastereoselective synthesis of oxysterols in a water/ethanol solvent system. High yields and diastereoselectivities were obtained (Figure 13).²³

In the course of our study to find the optimum reaction media in indium-mediated allylations, we observed at the same time that the reaction media had a strong influence on

Figure 13. Diastereoselective synthesis of oxysterols.

regioselectivities (Figure 14).²⁴ Apparently, the γ -adduct is predominantly formed in organic and aqueous media, whereas the α -adduct is preferentially formed in water. Water must also be present in a substantial amount at 10 M, with the result from a 0.5 M experiment giving us mainly γ isomers. However, most importantly, this straightforward methodology allows for the formation of α -adducts in In-mediated systems, in which such regiochemistry can only be coaxed through steric interactions²⁵, di-indium complexes²⁶ or rearrangements²⁷.

Figure 14. Highly regioselective indium mediated allylation through media selection.

The results suggest the possibility of an interesting mechanistic origin and this enticed our further investigation.²⁸ We started with following the course of the reaction between cyclohexane carboxaldehyde with crotyl bromide mediated by indium in 10 M water (Figure 14). The reaction was complete with almost entirely the kinetically formed γ -adduct after 2h. After 4h, the α -adduct appeared and all γ -adduct was converted to the thermodynamically formed α -adduct after 24h. The reaction pathway of the thermodynamically controlled process was ascertained through a “cross-over experiment” (Figure 15). Results suggest the transient formation of the aldehyde and an allyl fragment.

Figure 15. Cross-over experiment.

Another set of data that assisted us in determining the mechanism is the allylation of a steroidal aldehyde (Figure 16). The conclusive stereochemistry from the X-ray diffraction analysis of the products points to an inversion of the chiral centre at C22 following the proposed reattachment of the allyl fragment to form the α -adduct. This anti-Cram product excluded the possibility of a “free” allyl fragment involved in the re-addition to the aldehyde.

The collated data converged to suggest a new mechanism for this indium-mediated allylation in water. This new proposed mechanism is not in line with the allyl anion transfer mechanism²⁹ or the mechanism arising from steric effects³⁰. A bond cleavage generating the parent aldehyde followed by a concerted rearrangement, perhaps by a retro-ene³¹, with subsequent 2-oxonia [3,3]-sigmatropic rearrangement³² is the most probable mechanism that fits all data (Figure 17). The entire investigation was completed with the study of the allylation using Sn and Zn,³³ with the results being similar to that of the In-mediated reaction.

With the mechanism elucidated, our group pro-

Figure 16. Stereochemical inversion at C22.

Figure 17. Proposed mechanism for rearrangement.

ceeded to exploit the applications of this novel reaction pathway in synthesis. Recent work had shown that the use of $\text{In}(\text{OTf})_3$ as a catalyst with CH_2Cl_2 as solvent is a highly versatile implement for the further manipulation of homoallylic alcohols. Our group had reported the formation of tetrahydrofuran moieties through further oxyindiation reaction³⁴, the synthesis of 22 α -sterols³⁵ and an enantioselective allyl transfer reaction³⁶. In some cases, yields and stereoselectivities were enhanced through the use of Brønsted acids³⁷. However, the discussions of such chemistries are beyond the scope of this account. Efforts are being directed to adopt these procedures in aqueous systems, in line with our laboratory's direction in developing "green" chemical processes.

3. Development of Enantioselective Allylation

Our group's initial investigations into the enantioselective allylation through the use of chiral promoters made use of the In /organic solvent system, with (–)-cinchonidine or (+)-cinchonidine as chiral promoters (Figure 18).³⁸ However, the enantiomeric excess was mostly moderate to good and achievable only through the use of excess chiral promoter (2 eq.). Most importantly, the protocol requires the use of dry organic solvents.

Figure 18. Enantioselective allylation using cinchonidine.

Following an earlier work by Nishiyama *et al.*³⁹, we proceeded to screen a series of potential C_2 -symmetric chiral bis(oxazoline) ligands⁴⁰ that might function well in aqueous systems. Initial results in $\text{EtOH}/\text{H}_2\text{O}$ pointed to the superiority of the iPrPYBOX ligand, and further work with screening of Lewis acids resulted in an excellent yield of 90% and an enantiomeric excess of 92% with $\text{Ce}(\text{OTf})_4$ hydrate as Lewis acid (Figure 19).⁴¹ However, this procedure required the use of excess ligand and catalyst, and alternative systems that are more economical were sought.

Figure 19. Enantioselective allylation reaction in aqueous medium.

Based on the work by Yamamoto and Yanagisawa *et al.*⁴², we explored the use of a (S)-BINAP·AgOTf complex to develop a catalytic system for enantioselective allylation. Following the reported procedure, but using a $\text{H}_2\text{O}/\text{EtOH}$ mixture instead of dry THF, we generated the complex by stirring (S)-BINAP and AgOTf at 25 °C for 30 min in the dark. Use of 5 mol% of this catalyst for the reaction between benzaldehyde and allyltributyltin afforded the (S)-enriched product in 61% yield and 54% ee after 14h of stirring in the absence of light. This encouraging result prompted us to screen a series of other chiral diphosphines and reaction conditions (Figure 20) and 66% ee was achieved with (S)-Tol-BINAP at a temperature of –40 °C.

To further improve the above results, we surveyed the use of other transition metal complexing agents in place of AgOTf. Apparently, from the metals screened, only Ag(I) salts are active, and little effect was observed from the counterion. With the final choice of $\text{Ag}(\text{NO}_3)$, we studied the reaction with different aldehydes (Figure 21). Yields were good to excellent, with good ee were observed for aromatic aldehydes. However, the results for aliphatic, olefinic and acetylenic aldehydes were only low to moderate.

Although the use of the above BINAP system had produced some positive results, it was an unsatisfactory system. The use of Ag(I) salts had made mandatory the conduct of the entire reaction process in the dark. In addition, although good ee was obtained for aromatic aldehydes, other aldehydes gave poor results. This precluded the universal application of this catalyst as part of our synthetic tool. Our laboratory thus continued to search for new chiral complexes to address these shortfalls.

Most recently, our laboratory had found a con-

Figure 20. Catalytic enantioselective allylation.

Figure 21. Catalytic enantioselective allylation using (S)-Tol-BINAP·AgNO₃.

venient method to form chiral indium complexes from In(III), the first reported case of such catalysts. Our first successful attempt was through the use of (S)-BINOL. The chiral complex was prepared simply by stirring (S)-BINOL with InCl₃ in the presence of molecular sieves and CH₂Cl₂ as solvent. The formed (S)-BINOL-In(III) complex was used catalytically for the enantioselective allylation of aldehydes by allyltributyltin in dichloromethane (Figure 22).⁴³ Moderate to good yields with consistently high enantioselectivities were obtained. Similar protocol and results were obtained with a chiral bis(oxazoline) ligand ("PYBOX").⁴⁴ Further investigations reveal the importance of the organotin reagent for the formation of the chiral indium complex. Our laboratory is currently focusing on adapting this system to the allylation in aqueous media.

4. Applications of Allylation in Synthesis

4.1 Antillatoxin

In order for methodologies to mature into useful routine synthetic tools, it is necessary to apply the developed concepts and procedures to the synthesis of complex molecules, in particular, the synthesis of natural products.

Antillatoxin, an ichthyotoxin isolated from a marine cyanobacterium (*Lyngbya majuscula*), was reported in 1995 by Orjala *et al.*⁴⁵ Its intriguing chemical structure and potent biological activity prompted several groups⁴⁶, including us, to embark on its total synthesis. Our focus, however, was to assemble the

molecule with carbon-carbon bond formations in aqueous medium. We envisioned that the assembly of the antillatoxin molecule could occur from two major fragments, 1 and 2 (Figure 23). The stereochemistry and structure of fragment 2 suggest that the C4-C5 bond may be formed from allylation of the conjugated aldehyde with an allylic bromide that possesses functional groups that could further be transformed to form the desired fragment.

The first work we embarked on was to carry out the allylation on the model aldehyde, cinnamaldehyde, using 2-bromocrotylbromide (R" = Br in Figure 23).⁴⁷ Contrary to our established protocols, no reaction occurred through the use of the basic In/H₂O system. Addition of lanthanide triflates increased the reaction rate but yield was still poor. Further work established the requirement to use, in addition to La(OTf)₃ catalyst, saturated ammonium chloride with sonication in order to bring the reaction to good yields. This final protocol was further applied to different aldehydes (Figure 24). The selectivities for *anti:syn* range from no selectivity to excellent selectivity. Unfortunately, the aldehyde substrate for our key step to the advanced intermediate of antillatoxin gave *anti:syn* ratio of 50:50.

We then proceeded to switch the bromine moiety to the methyl ester (R" = CO₂Me in Figure 23) with the use of

Figure 22. Enantioselective allylation using catalytic (S)-BINOL-In(III) complex.

Figure 23. Retrosynthetic analysis of antillatoxin.

Figure 24. Modified optimum condition for allylation.

Figure 25. Diastereoselective allylation to obtain target product.

(*Z*)-2-(bromomethyl)-2-butenate and excellent *syn* preference was obtained, resulting in our desired target molecule in good yield (Figure 25).⁴⁸

We were interested at that time in generating fragment 2 with the *anti* configuration, in addition to the correct *syn* configuration, at C4–C5 for the purpose of structure–activity studies. Our proposed transition state for the predominance of *syn* products could be explained by our previously reported cyclic transition state (Zimmerman–Traxler⁴⁹). Hence, *E*-isomers are expected to give the *anti* product, whereas the *Z*-isomer is expected to give the *syn* product. Both *E*- and *Z*-isomers of 2-(bromomethyl)but-2-enyloxy(tert-butyl) diphenylsilane were then synthesized from methyl (*Z*)-2-(bromomethyl)-2-butenate. Study of the stereochemical outcome of the reaction was conducted using the above In/La(OTf)₃ system in THF/H₂O. Yields and diastereoselectivities were consistently high, and contrary to our expectation, strong *syn* preferences for both geometric isomers were observed. From the fact that the reaction does not occur in the absence of La(OTf)₃, and that the allylic bromide recovered after the reaction still retained the same configuration, an open-chain anti-periplanar transition state was proposed (Figure 26).⁵⁰ Application of the procedure to the synthesis of fragment 2 resulted in good yields and diastereoselectivities. Note that a variation of this procedure was also reported by us in which α -regioselectivity was obtained from a secondary allylic bromide, most likely through 1,3-allylic shift of the indium species which proceeded to react similarly to the preceding reaction.⁵¹

In the same paper, our group had also reported the use of (–)-cinchonidine (see Figure 18) in our attempts to realize the correct enantiomer at the same time. However, under the reaction conditions for the use of cinchonidine as a chiral promoter, no reaction occurred for the silyl protected allyl bromide. However, the reaction proceeded upon removal of the protecting group and facilitated the reaction to achieve good ee and excellent *syn:anti* ratio (Figure 27).

4.2 (±)-Methylenolactocin and (±)-Phaseolinic Acid

Methylenolactocin possesses interesting anti-tumor activity⁵². The high functionality and stereochemistry have made its synthesis a challenge for many research groups.⁵³ Phaseolinic acid is a metabolite isolated from the fungus *M. phaseolina*⁵⁴, and is also a subject for synthetic studies⁵⁵. Both natural products contain the α -methylene- β -butyrolactone building block, which could be derived from an allylation reaction (Figure 28).

The allylic bromide was obtained in the *Z* configuration from two steps starting with methyl acrylate. This was used in the In-mediated allylation of hexanal (Figure 29). With water alone, no products were obtained due to rapid formation of the undesired diester. Reducing the proportion of water with a THF/H₂O medium reduces diester formation and results in an equal proportion of *anti* and *syn* products. Interestingly, the *anti* product cyclizes to form the esterified target, the methylated form of (±)-methylenolactocin. The *syn* product could easily be cyclized and transformed to (±)-phaseolinic acid according to reported procedure.⁵⁵ Hence, both products are useful in this synthesis. The yield of the desired product pair was good when the reaction was conducted in the absence of solvents. This procedure thus generates two highly advanced intermediate that could be transformed in a short and efficient manner to the two interesting natural products.

4.3 Apoptolidin and FD-891

Apoptolidin is a potent apoptosis-inducing agent isolated from *Nocardopsis* sp.⁵⁶, with the first total synthesis of this structurally intriguing and challenging compound reported recently by Nicolaou *et al.*⁵⁷ FD891 was isolated from the fermentation broth of *Streptomyces graminofaciens* A-8890⁵⁸

Figure 26. Proposed mechanism for observed diastereoselectivities.

Figure 27. Enantioselective synthesis of fragment 2.

Figure 28. Retrosynthetic analysis of (±)-methylenolactocin and (±)-phaseolinic acid.

Figure 29. Optimizing the allylation of keto-ester.

Figure 30. Retrosynthetic analysis of apoptolidin and FD-891 showing a common intermediate.

Figure 31. Allylation of sugar-derived aldehyde.

with cytotoxic activity against tumor cells *in vitro*. Its stereochemical structure was recently confirmed.⁵⁹ These two macrolactones possess the macrocyclic cores that may be constructed from a common homoallylic moiety (Figure 30).

Using a sugar-derived aldehyde as a chiral substrate, four isomers are possible from an allylation reaction. It was found, after optimization, that a Sn/NaI/TBAI aqueous system gave the best yield and selectivity for the desired product.⁶⁰ Other systems tested either resulted in cleavage of the acetal group or a lesser selective reaction giving a mixture of isomers. The stereochemical outcome was explained by a non- α -chelation control in the reaction pathway.

4.4 Dysiherbaine

Dysiherbaine is a neurotoxic amino acid isolated from *Dysidea herbacea*.⁶¹ Several groups had approached the total synthesis of this compound.⁶² However, our strategy is to obtain the advanced intermediate of dysiherbaine stereoselectively through an allylation of a keto-ester (Figure 32). This was based on our earlier work on the stereoselective synthesis of chiral amino alcohols via a Mukaiyama aldol reaction⁶³. The stereochemical control on such substrates was proposed to occur through

π -stacking interactions between the carbonyl and aromatic ring, hence imparting facial selectivity to the approach of the nucleophile (Figure 33).

Prior to the actual synthesis of our targeted advanced intermediate, the reaction was studied with a series of substrates.⁶⁴ Results show that the THF/H₂O and methanol reaction media are superior, in terms of yield and diastereoselectivities, to that of DMF (Figure 34). In applying this methodology to the synthesis of the advanced intermediate of dysiherbaine, only a single desired isomer was obtained.⁶⁵

Figure 32. Retrosynthetic analysis of Dysiherbaine.

Figure 33. Facial selectivity of proposed substrate for allylation.

Figure 34. Results of allylation of β -amino keto-ester.

Figure 35. Retrosynthetic analysis of AG7088.

Figure 36. Allylation of β -amino aldehyde.

Figure 37. Proposed mechanism for allylation.

4.5 AG7088

AG7088 is a HRV 3C^{pro} inhibitor that inhibits the proteinases of coronaviruses. This compound is thus a potential cure for the “common cold” and modifications of it may be a remedy for Severe Acute Respiratory Syndrome. This compound may be derived from two fragments, with one of the fragments obtained from a stereospecific allylation (Figure 35).

Using an indium-mediated allylation reaction in a medium of EtOH/H₂O, the desired *syn* product was obtained in good yield and unusually high selectivity (Figure 36).⁶⁶ This diastereoselectivity may be explained through a Felkin-Anh chelation model in which steric repulsion between the isopropyl group and the CO₂Me group may account for the disfavoured of one of the transition states (Figure 37).

However, from the report by Steurer and Podlech⁶⁷ and our experience, there may be an additional factor contributing to such high selectivity besides the proposed steric repulsion. By looking at the substrate structure, the isoxazole group on the α -amino group may most likely be participating in the transition state. A study with other amino protecting groups had borne out this fact (Figure 38).

The contribution to the increased diastereoselectivity by the isoxazole moiety may be the greater rigidity of the transition state imparted through its additional coordination with the indium centre by the isoxazole nitrogen (Figure 39). This would reduce the stability of the sterically disfavoured transition state even further by preventing the interacting groups from moving away from one another. An unusually high *syn* selectivity is therefore observed.

Figure 38. Substituent on α -amino group influencing stereoselectivity.

Figure 39. Mechanism to account for the participation of isoxazole group.

5. Conclusion

Adaptations of carbon-carbon bond forming reactions from strictly anhydrous to aqueous media have been intensely studied in recent years, in part driven by the “green chemistry” movement. Our group’s work on allylation in such reactions have demonstrated the feasibility of such systems to closely mimic or even surpass that of traditional Grignard and similar reactions. The challenge and general direction is to develop enantioselective systems that are effective in aqueous media. Routing such chemistries to the synthesis of natural products and other biologically active compounds would bring us to the ultimate “enzyme mimic”, and efforts are still being made to this end in our laboratory.

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