Synthetic Methods

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Practical Metal-Free C(sp^3)–H Functionalization: Construction of Structurally Diverse α-Substituted *N*-Benzyl and *N*-Allyl Carbamates**

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Abstract: *Described is a practical and universal C–H functionalization of readily removable N-benzyl and N-allyl carbamates, with a wide range of nucleophiles at ambient temperature promoted by Ph_3CClO_4. The metal-free reaction has an excellent functional-group tolerance, and displays a broad scope with respect to both N-carbamates and nucleophile partners (a variety of organoboranes and C–H compounds). The synthetic utility in target- as well as diversity-oriented syntheses is demonstrated.*

α-Substituted nitrogen-containing heterocycles (N-heterocycles), like tetrahydroisoquinolines (THIQs), tetrahydroquinolines (THQs), and piperidines, represent ubiquitous structural motifs in numerous alkaloids exhibiting a wide range of pharmacological activities.[1] Among them, 1-benzyl THIQs are the most widely distributed[1a] and serve as key intermediates in the synthesis and biosynthesis[1c] of other types of alkaloids. For instance, tetrahydropalmatine (THP), isolated from *Corydalis*, has been demonstrated to possess significant analgesic effects and have therapeutic potential for heart disease and liver damage (Figure 1).[2a] Noscapine, mediated by the sigma receptor agonist activity, is well known for its antitussive effects, and reported to have promising effects in the treatment of several cancers and hypoxic ischemia in stroke patients.[2b] Besides the benzyl substructure, aryl and arylethyl substituents are often incorporated at C1. Solifenacin (trade name Vesicare), a competitive antagonist preventing acetylcholine from binding to the human muscarinic acetylcholine receptor, is used in the treatment for overactive bladder.[2c] Methylphenidate, a piperidine analogue, is known to be a psychostimulant drug for the treatment of attention deficit hyperactivity disorder (ADHD).[2d]

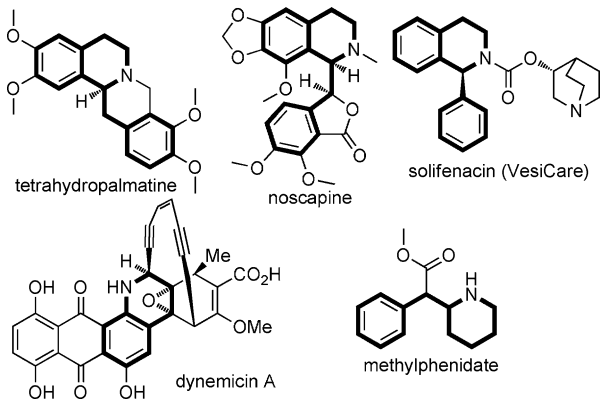

Figure 1. Bioactive C1-substituted THIQs, THQs, and piperidines.

Inspired by the importance of these compounds in modern pharmacology, significant efforts have been devoted to their construction, and current syntheses mainly rely on three strategies.[3] The two most frequently employed approaches for the synthesis of C1-substituted N-heterocycles are stereoselective cyclizations such as the Pictet–Spengler condensation, and hydrogenation of the C1-substituted imines as in the Bischler–Napieralski cyclization/reduction sequence. Recently, introduction of a carbon unit to the α-position of the N-heterocycles has been investigated as an alternative to the first two traditional methods. In particular, direct C–H functionalization of N-heterocycles with a variety of carbon nucleophiles presents an atom-economic protocol without prior installation of activating groups, and is therefore attractive.[4] A number of different approaches have been established for electron-rich amines, especially *N*-arylated THIQs and dimethylanilines, since the pioneering studies of the groups of Murahashi and Li.[5,6] However, the difficulty in removing the *N*-aryl group results in poor functional-group tolerance, and therefore limits the synthetic utility.[7] In sharp contrast, the functionalization of the C(sp^3)–H bond adjacent to readily removable amide or carbamate moieties proved to be much more challenging, probably owing to the reduced reactivity, and only a few examples have been disclosed so far.[8] The scope with respect to the nucleophile reported for each method is notably limited, and often focuses on only one

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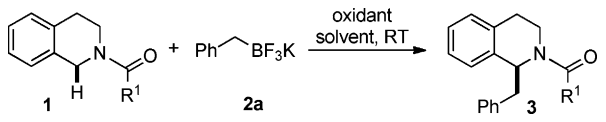
particular class. Moreover, the procedures usually require harsh reaction conditions (high temperature, strong acid, neat condition, etc.), the use of metals, and long reaction times, all of which are generally disadvantageous for achieving asymmetric variants because of the high probability of racemization at the benzyl position.[6k] Therefore, the development of a universal, mild, and efficient method for direct C–H functionalization of *N*-carbamate hetreocycles with a wide range of nucleophiles will not only provide a new strategy for natural product synthesis but also facilitate the quick construction of N-heterocycle libraries having structural variation at the C1-position for the discovery of novel, biologically interesting small molecules. Herein, we present a metal-free C(sp^3)–H functionalization of *N*-benzyl and *N*-allyl carbamates with diverse nucleophiles by triphenylcarbenium perchlorate (Ph_3CClO_4) oxidation.

The widespread availability and unique nucleophilicity of organoboranes have attracted growing interest in exploring new chemistry beyond the Suzuki–Miyaura coupling, including α-vinylation of aldehydes,[9a] transition metal catalyzed additions of boronic acids or boroxines to epoxides,[9b] oxocarbenium and *N*-acyliminium ions,[9c–d] Lewis acid mediated dialkyl ether synthesis from organotrifluoroborates and acetals,[9e–f] and C–H arylation of quinones and electron-deficient hererocycles such as pyridine and pyrimidine.[9h–j] Therefore, initially we examined the benzylation of the *N*-acyl THIQ **1** with potassium benzyltrifluoroborate (**2a**) at room temperature for reaction optimization (Table 1). A variety of commonly used oxidants for *N*-aryl THIQs, such as DDQ, $PhI(OAc)_2$, $Na_2S_2O_8$, CAN, O_2, and TBHP resulted in no reaction (entry 1). TEMPO oxoammonium salt[8b] ($T^+BF_4^-$; TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl) gave the desired product in 23% yield after 24 hours (entry 2). We then explored the carbocation oxidants, such as tropylium[10a,b] and trityl ions.[10c–g] While the tropylium cation ($C_7H_7BF_4$) did not facilitate the reaction, Ph_3CSbCl_6 afforded the product in 51% yield (entries 3 and 4). The counterion of the trityl cation proved to be crucial for the reaction efficiency, and Ph_3CClO_4[11] gave an 87% yield after 2 hours at room temperature (entries 4–8). Reaction optimization experiments identified CH_2Cl_2 as the best solvent, and CBz as the ideal amine protecting group (entries 8–11).

Table 1: Model reaction optimization.[a]



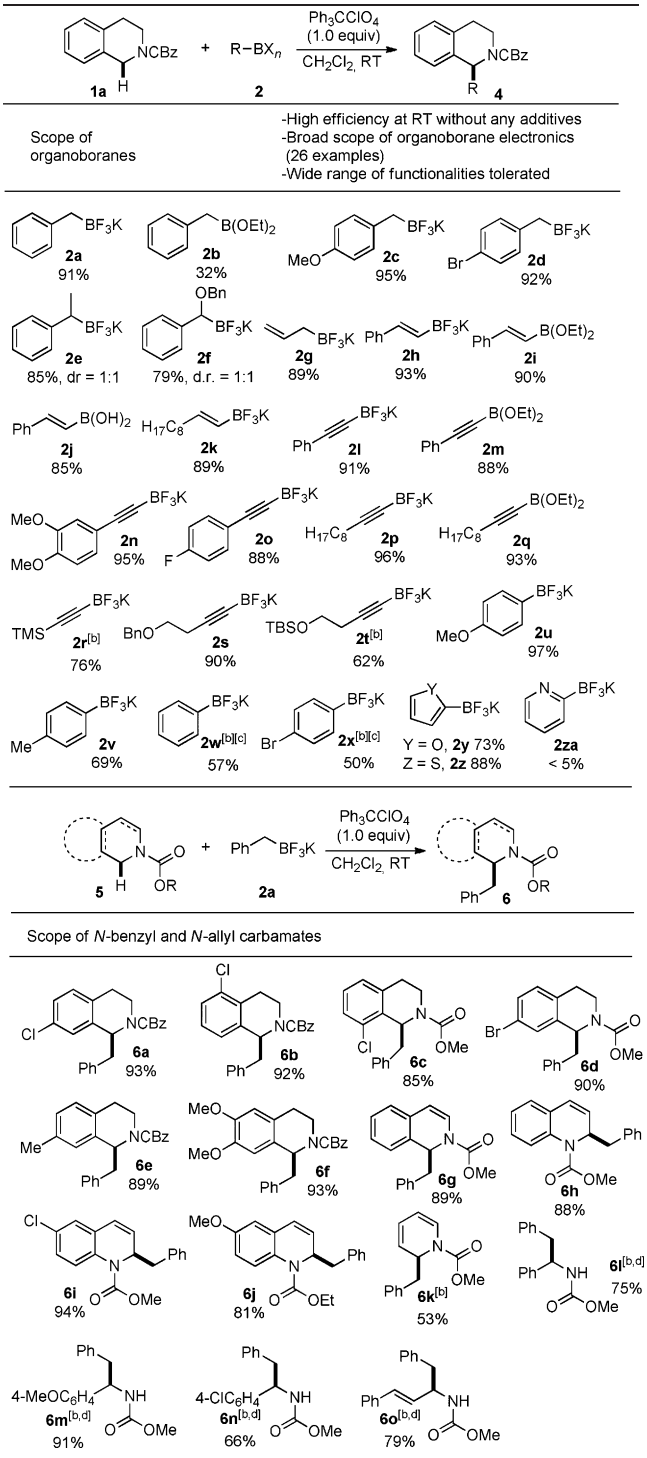
Entry	Oxidant	R^1	Solvent	*t* [h]	Yield [%][b]
1	oxidants[c]	OMe	CH_2Cl_2	24	< 5
2	$T^+BF_4^-$	OMe	CH_2Cl_2	24	23
3	$C_7H_7BF_4$	OMe	solvent[d]	24	< 5
4	Ph_3CSbCl_6	OMe	CH_2Cl_2	2	51
5	Ph_3CBF_4	OMe	CH_2Cl_2	2	45
6	Ph_3COTf	OMe	CH_2Cl_2	2	33
7	Ph_3CPF_6	OMe	CH_2Cl_2	2	48
8	Ph_3CClO_4	OMe	CH_2Cl_2	2	87
9	Ph_3CClO_4	CH_3	CH_2Cl_2	24	< 5
10	Ph_3CClO_4	OBn	CH_2Cl_2	2	91
11	Ph_3CClO_4	O*t*Bu	CH_2Cl_2	2	0

[a] The reaction was carried out with **1** (0.2 mmol), **2a** (0.4 mmol), and oxidant (0.2 mmol) in solvent (2.0 mL) at room temperature for the indicated periods. [b] Yield of isolated product. [c] DDQ, $PhI(OAc)_2$, $Na_2S_2O_8$, CAN, $O_2/CuCl_2$, and TBHP/$CuBr_2$. [d] CH_2Cl_2 or CH_3CN. CAN = ceric ammonium nitrate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBHP = *tert*-butyl hydrogen peroxide, Tf = trifluoromethanesulfonyl.

Examination of the scope with respect to organoborane partners has revealed that a broad range of nucleophiles are amenable to the reaction (Table 2). Electronically varied benzyl, allyl, alkenyl, alkynyl, and aryl trifluoroborate salts are compatible with the oxidation system and deliver the desired THIQ **4** in good to excellent yields. The use of corresponding boronate esters (**2i**, **2m**, and **2q**) and boronic acids (**2j**) provides comparable results to those of the potassium trifluoroborates, except for the benzyl boronate ester **2b**, and this is probably due to an oxidative decomposition under the reaction conditions.[9g] The secondary potassium benzyltrifluoroborates **2e** and **2f** also efficiently provide the branched benzyl THIQs, another important core unit within a multitude of biologically active natural products such as noscapine (Figure 1). Classically, the arylation of *N*-acyliminium ions requires strong nucleophiles, such as organometallic reagents and π-rich arenes.[12] As shown in Table 2, the reaction is efficient not only for the π-rich aryl (**2u**,**v**) and heteroaryl trifluoroborates (**2y**,**z**), but also for π-neutral (**2w**) and π-deficient (**2x**) arylboranes, though the latter two require slightly elevated temperatures. The N-heteroaryltrifluoroborate **2za** does not afford the desired product. Several commonly seen functionalities were tolerated, including halogens (**2d**, **2o**, and **2x**), benzyl ethers (**2s**), and silyl ethers (**2t**), and such moieties can serve as additional functional handles.

After demonstrating the generality of the organoboranes as nucleophiles, we next explored the scope of carbamate substrates **5** with **2a** (Table 2). Structurally and electronically varied cyclic *N*-benzyl carbamates worked efficiently to afford the desired benzylation products in excellent yields (**6a**–**f**). Dihydroisoquinoline (DHIQ; **6g**) was also a competent substrate for the transformation. Additionally, cyclic *N*-allyl carbamates proved to be suitable substrates. Electronically varied *N*-carbamate dihydroquinolines (DHQs; **6h**–**j**) and dihydropyridine (DHP; **6k**) were also tolerated. Given the variety of known protocols that utilize the enamine moiety in DHIQ (**6g**) and DHP (**6k**) as a reactive handle for further functionalization, such as cycloadditions, alkylations, oxidations, and reductions,[13a] the direct construction of C1-substituted *N*-carbamate DHIQs and DHPs could provide opportunities to develop a structurally and stereochemically diverse library of alkaloid-like compounds through diversity-oriented synthesis.[13] Besides the cyclic substrates, electronically varied acyclic *N*-benzyl carbamates (**6l**–**n**) and *N*-allyl carbamate (**6o**) also serve as precursors for the direct C–H benzylation. To the best of our knowledge, this is the first example of direct C–H functionalization of *N*-allyl carbamates such as cyclic DHQ and DHP, and acyclic (**5o**) substrates to date.

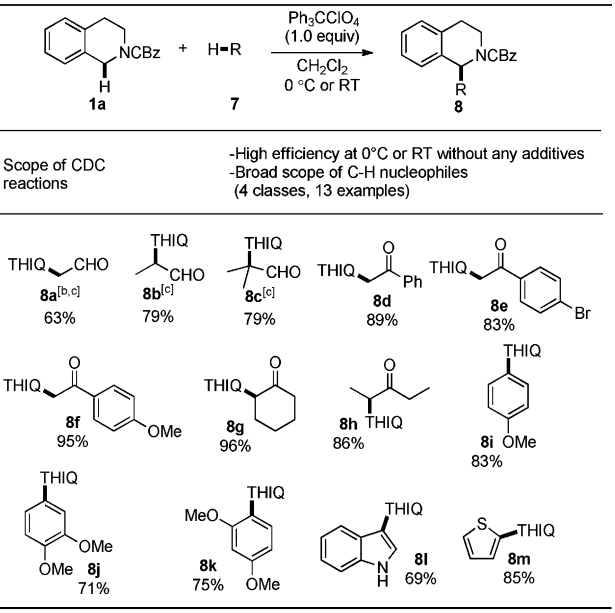
Table 2: The scope of organoboranes and N-heterocycles.[a]



[a] Unless otherwise specified, the reaction was carried out with **1a** or **5** (0.2 mmol), **2** (0.4 mmol), and Ph_3CClO_4 (0.2 mmol) in CH_2Cl_2 (2.0 mL) at RT for 2 h. [b] Nucleophiles were added once the oxidation process was complete. [c] Reaction was performed at 40 °C. [d] Reaction was performed at 60 °C. CBz = benzyloxycarbonyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl,

The successful C–H functionalization of *N*-benzyl and *N*-allyl carbamates with organoborane nucleophiles prompted us to explore the feasibility of cross-dehydrogenative coupling

Table 3: The scope of CDC reactions.[a]

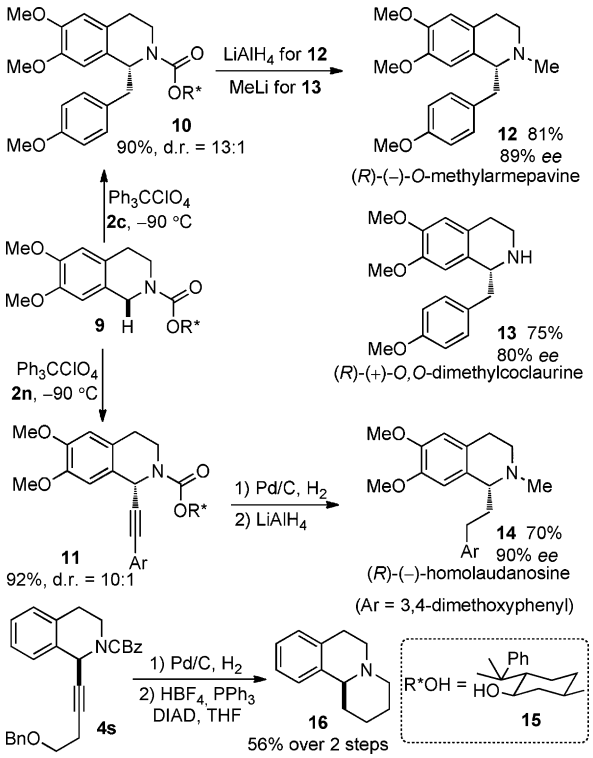


[a] The reaction was carried out with **1a** (0.2 mmol) and Ph_3CClO_4 (0.2 mmol) in CH_2Cl_2 (2.0 mL) followed by **7** (0.5 mmol) at 0 °C or RT for 0.5–8 h. [b] 1.0 mmol acetaldehyde was employed. [c] **7** was added after the oxidation with 2,6-dichloropyridine (0.4 mmol).

(CDC)[5] under the same reaction conditions (Table 3). Interestingly, the CDC reactions of **1a** with a number of carbon nucleophiles including aldehydes (**8a–c**), and aromatic and aliphatic ketones (**8d–h**), together with π-rich arenes (**8i–k**) and heteroarenes (**8l**,**m**), proceed smoothly at room temperature to deliver the products in good to excellent yields.

The universal and mild method for the C–H functionalization of readily removable carbamates led us to investigate its application to the enantioselective synthesis of bioactive natural products (Scheme 1). The carbamate **9**, prepared in one step from 6,7-dimethoxy-THIQ and 8-phenylmenthyl chloroformate,[14] was subjected to the standard reaction conditions with organoboranes **2c** and **2n** at −90 °C to give excellent yields of benzylated (**10**; d.r. = 13:1) and alkynylated (**11**; d.r. = 10:1) THIQs, respectively. Subsequently, the major diastereomers of **10** and **11** were separated, and further transformed into three molecules through a single- or two-step modification. The compound **10** reacted with $LiAlH_4$ and MeLi to furnish **12** and **13**, respectively, with efficient recovery of the chiral auxiliary **15** (86% and 80%).[15] Sequential reduction of **11** with the H_2 on Pd/C and $LiAlH_4$ afforded **14** in 64% yield from **9**.[15a] The alkyne **4s** was converted into the tricyclic **16** by hydrogenation and HBF_4-mediated Mitsunobu reaction in 56% yield.[16]

As discussed above, a small N-heterocycle library with structural variation at the C1-position was rapidly constructed using this universal C–H functionalization protocol with a wide range of nucleophiles (Tables 2 and 3; see the Supporting Information). The cytotoxicities of these compounds in human prostate cancer (PC3 and DU145), docetaxel-resistant prostate cancer (PC3R), and human liver



Scheme 1. Synthetic applications. DIAD = diisopropyl azodicarboxylate.

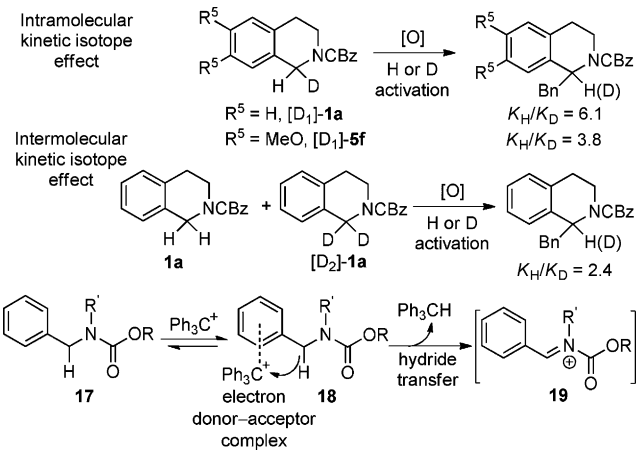


Figure 2. Mechanistic studies for carbamate oxidation by Ph_3CClO_4.

carcinoma (HepG2) cell lines were evaluated using the MTT assay. While most of them did not show any cytotoxicity towards DU145 and HepG2 cell lines ($IC_{50} > 50$ μM), some of them exhibit inhibitory activity towards PC3 and PC3R cells (see the Supporting Information). The C1-arylethynyl THIQs **4l**-NH[17] (9.8 ± 0.5 μM) and **4o**-NH (9.0 ± 1.6 μM) show comparable potency as cisplatin (8.0 ± 0.5 μM) towards PC3R cells, whereas our compounds are sevenfold less potent (18.8 ± 0.5 μM and 21.2 ± 2.7 μM) than cisplatin (2.79 ± 0.5 μM) against PC3 cells. These preliminary results not only suggest that C1-arylethynyl THIQs are promising anticancer hits worthy of further exploration, but also demonstrate the practicability of the facile method in chemical library construction and drug discovery.

In the Ph_3C^+-mediated C–H oxidations, a hydride abstraction mechanism to give carbenium ions was prevalent, but no mechanistic experiment was performed.[10c–i] Therefore, kinetic isotope studies were conducted and several aspects of the data merit further comment. Firstly, the substrates showed a kinetic isotope effect, thus suggesting that the C–H bond cleavage is involved in the rate-determining step (Figure 2). Secondly, the intermolecular KIE (2.4) for **1a** is lower than its intramolecular one (6.1), thus indicating that a reactive intermediate is formed prior to C–H cleavage, and its formation is not rapidly reversible.[18] Thirdly, the more reactive substrate, **5f**, shows a lower intramolecular KIE (3.8) than the less reactive **1a** (6.1). This implies that bond cleavage is easier for substrates which react more quickly, and is counter to the observation for DDQ-mediated C–H cleavage which proceeds through radical cation intermediates and initiated by a single-electron transfer.[18c] The phenomenon, however, can be well explained by a hydride transfer process.[18] Lastly, the coupling efficiency was not affected by 1 equivalent of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) or TEMPO, thus suggesting that a radical intermediate might not be involved in the reaction. In the tropylium-mediated amine oxidation, formation of an electron donor–acceptor (EDA) complex was proposed for the tropylium ion and aryl ring in the substrate before C–H cleavage.[10b,19] Therefore, we envision the formation of an EDA complex between Ph_3C^+ and the aryl ring (see **18**), followed by an irreversible[10c] one-step hydride abstraction to generate the *N*-acyliminium ion **19** for subsequent nucleophilic addition.

In summary, we have developed a practical and universal C–H functionalization of readily removable *N*-benzyl and *N*-allyl carbamates with a wide range of nucleophiles at ambient temperature promoted by Ph_3CClO_4. The metal-free reaction has an excellent functional-group tolerance, and displays a broad scope with respect to both *N*-carbamates and organoborane partners. CDC reactions with a variety of C–H nucleophiles were also achieved. The synthetic utility of the reactions in target-oriented synthesis was exemplified by the enantioselective synthesis of three bioactive molecules. The facile method is also practical for diversity-oriented synthesis and the discovery of biologically interesting small molecules, as demonstrated by the rapid access to a small N-heterocycle library with structural variation at C1, and the discovery of C1-arylethynyl THIQs as selective anticancer hits. We envision that the mild method outlined herein will provide a platform for future efforts in the development of catalytic asymmetric C–H functionalization of a variety of *N*-carbamates.

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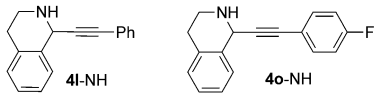

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