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Chemoselective oxidation of aryl organoboron systems enabled by boronic acid-selective phase transfer†

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We report the direct chemoselective Brown-type oxidation of aryl organoboron systems containing two oxidizable boron groups. Basic biphasic reaction conditions enable selective formation and phase transfer of a boronic acid trihydroxyboronate in the presence of boronic acid pinacol (BPin) esters, while avoiding speciation equilibria. Spectroscopic investigations validate a base-promoted phase-selective discrimination of organoboron species. This phenomenon is general across a broad range of organoboron compounds and can also be used to invert conventional protecting group strategies, enabling chemoselective oxidation of BMIDA species over normally more reactive BPin substrates. We also demonstrate the selective oxidation of diboronic acid systems with chemoselectivity predictable *a priori*. The utility of this method is exemplified through the development of a chemoselective oxidative nucleophile coupling.

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Introduction

The use of di- and multi-boron containing systems has become a powerful approach for the rapid synthesis of highly functionalized molecules from readily accessible starting materials.^{1,2} Chemoselectivity in these systems is currently achieved using only two approaches. Firstly, B-protecting groups render a specific boron unit unreactive under the prevailing reaction conditions. Widely used B-protecting groups include *N*-methyliminodiacetic acid (MIDA) esters,³ diamionaphthalene (DAN)-based aminoboranes,⁴ and potassium organotrifluoroborates (RBF₃K) (Scheme 1a).^{5–7} Secondly, self-activation/protection mechanisms allow discrimination of geminal and vicinal diboron compounds, enabling chemoselectivity within superficially equivalent systems (Scheme 1b).^{8–10}

B-protecting groups are the most widely adopted strategy and are compatible with sp, sp², and sp³ organoborons,^{1–7} while self-activation/protection is only applicable with sp³ organoborons.^{1,8,9} Accordingly, chemoselectivity within systems containing more than one aryl organoboron compound is currently only achievable by employing a suitable protecting group strategy. Based on

the broadly similar reactivity profiles of boronic acids and esters,¹¹ and the added complication of speciation equilibria,^{11–13} establishing chemoselective control within mixed organoboron systems represents a significant challenge. However, the identification of new chemoselective control mechanisms would be a fundamental advance, enabling the design and development of new synthetic methods for systems containing more than one reactive organoboron compound.

Here, we establish a new method for achieving chemoselectivity within systems containing two unprotected aryl

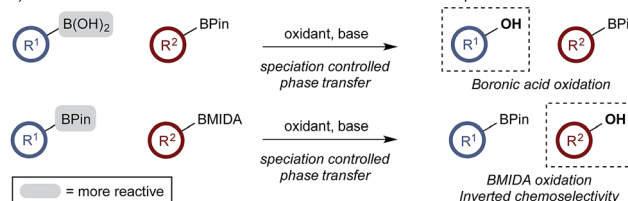
a) Previous work: chemoselectivity via protecting groups (Burke, Hall, Li, Molander, Sugimoto)



b) Previous work: chemoselectivity via self-activation/protection (Hall, Morken, Shibata)



c) This work: chemoselective oxidation via selective boronate formation/phase transfer



Scheme 1 Chemoselective reactions of diboron systems.

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organoboron compounds. Specifically, we show that chemoselective oxidation of aryl boronic acid/BPin systems can be achieved by selective boronate phase transfer while controlling potential solution speciation processes (Scheme 1c). In addition, we show that this approach can formally invert conventional chemoselectivity profiles using established MIDA protecting group chemistry. Spectroscopic investigations of the biphasic reactions provide insight into the mechanism by which chemoselectivity is achieved and how this may be predicted *a priori*.

Results and discussion

To probe chemoselectivity in systems containing two non-protected aryl organoboron compounds we selected a workhorse reaction. The Brown oxidation of an organoboron compound to the corresponding alcohol or phenol is a fundamental method within the synthetic organic chemistry toolbox.^{11,14} Boronic acids and esters are typically rapidly and indiscriminately oxidized and, consequently, chemoselective oxidation of a system containing two reactive organoboron compounds is unknown.

In the general sense, small differences in reactivity of boronic acids and esters have been observed, albeit in non-competitive systems.¹⁵ Accordingly, to initiate this study, we examined the oxidation of naphthyl boronic acid **1a** and BPin ester **1b** under a variety of reaction conditions.[‡] Common oxidants such as H₂O₂, NaBO₃, *m*-CPBA provided an uncontrollable oxidation from which no useful rate discrimination was observed (a range of oxidants and reaction conditions were surveyed, see ESI[†]). However, milder oxidants were useful and, in particular, a small rate difference favoring a more rapid oxidation of **1a** was found using Oxone[®] under biphasic reaction conditions (Scheme 2 and Chart 1).[§] Specifically, the oxidation of **1a** appeared to show a significant conversion in the burst phase while the oxidation of **1b** exhibited a more linear profile.

Based on the observed reactivity profiles in the non-optimized, non-competitive system, we considered it might be possible to leverage chemoselectivity in the corresponding mixed system (*i.e.*, containing both a boronic acid and BPin ester). However, translating these reaction conditions to a model system consisting of **1a** and BPin **2b** provided high conversion but with only trace levels of chemoselectivity (Table 1, entry 1).

In a purely organic medium (THF), no conversion was observed either in the absence or presence of base (entries 2 and 3 – a range of bases was evaluated, see ESI[†]), likely due to the poor solubility of Oxone[®].¹⁶ However, upon addition of K₃PO₄ to the original biphasic system (*i.e.*, entry 1), we immediately noted moderate conversion, now with significant levels of



Chart 1 Oxidation of **1a** and **1b** using Oxone[®] under biphasic reaction conditions (THF/H₂O) over 30 min at 350 rpm (*vide infra*). Determined by HPLC using an internal standard, see ESI[†]§

Table 1 Chemoselective oxidation of B(OH)₂ **1a** vs. BPin **2b**: reaction optimization

Entry	Base	Temp. (°C)	Solvent	Conv. (1c : 2c) ^a
1	—	20	THF/H ₂ O (1 : 1)	95% (1.1 : 1)
2	—	20	THF	0%
3	K ₃ PO ₄	20	THF	0%
4	K ₃ PO ₄	20	THF/H ₂ O (1 : 1)	54% (13.5 : 1)
5	K ₃ PO ₄	60	THF/H ₂ O (1 : 1.5)	81% (18 : 1)
6	K ₃ PO ₄	70	CPME/H ₂ O (1 : 1.5)	100% (>99 : 1)

^a Determined by HPLC analysis using an internal standard. See ESI[†].

chemoselectivity for the desired oxidation of **1a** (entry 4). A systematic evaluation of the reaction medium composition and temperature (see ESI[†]) revealed that conversion and chemoselectivity could both be improved using additional H₂O at 60 °C (entry 5). A solvent survey revealed CPME as the optimum organic phase that allowed quantitative oxidation of the boronic acid and with very high levels of chemoselectivity at 70 °C under basic biphasic reaction conditions (entry 6 – a range of solvents was evaluated, see ESI[†]).¹⁶

Determination of the origin of chemoselectivity

Basic biphasic reaction conditions allow chemoselective oxidation of boronic acid **1a** over BPin **2b**. While a small difference in rate using **1a** and **1b** was observed in the non-competitive system (Chart 1), oxidation was non-selective in the equivalent mixed organoboron system (Table 1, entry 1), suggesting that kinetic discrimination based on reactivities of the organoboron reagents with the oxidant was not the origin of the observed selectivity.

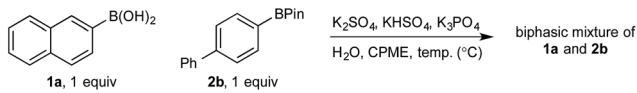
Several other data were notable: (i) Oxone[®] is poorly soluble in organic solvents¹⁷ and in the absence of H₂O, no reaction was



Scheme 2 Oxidation of **1a** and **1b** using Oxone[®].

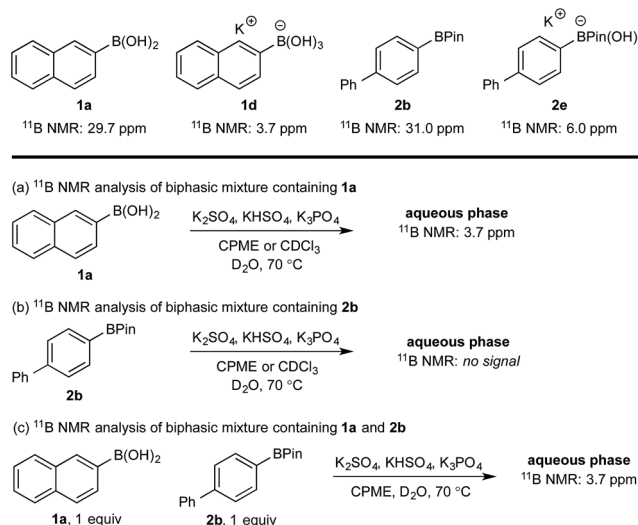


Table 2 Phase distribution of **1a** and **2b** in the presence of relevant inorganics and with temperature variation

				
Entry	Inorganics	Temp. (°C)	Organic : aqueous ^a (%)	
			1a	2b
1	—	20, 50, 70	>99 : 1	>99 : 1
2	K ₃ PO ₄	20	54 : 46	>99 : 1
3	K ₃ PO ₄	50	46 : 54	96 : 4
4	K ₃ PO ₄	70	29 : 71	98 : 2
5	KHSO ₄ , K ₂ SO ₄	20	>99 : 1	>99 : 1
6	KHSO ₄ , K ₂ SO ₄	50	>99 : 1	>99 : 1
7	KHSO ₄ , K ₂ SO ₄	70	98 : 2	>99 : 1
8	K ₃ PO ₄ , KHSO ₄ , K ₂ SO ₄	20	67 : 33	>99 : 1
9	K ₃ PO ₄ , KHSO ₄ , K ₂ SO ₄	50	59 : 41	>99 : 1
10	K ₃ PO ₄ , KHSO ₄ , K ₂ SO ₄	70	54 : 46	>99 : 1

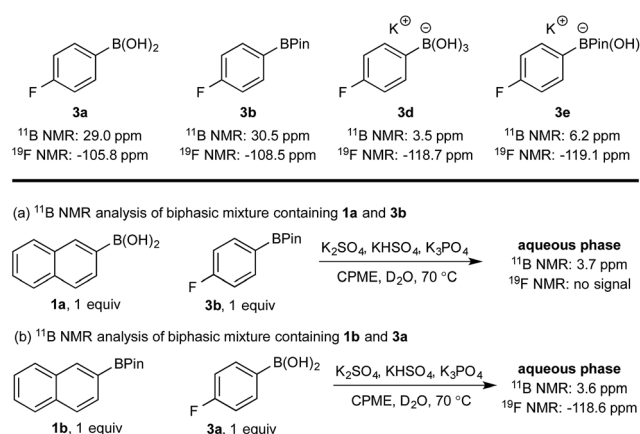
^a Determined by HPLC analysis using an internal standard. See ESI†

¹¹B NMR analysis of the aqueous phase of the biphasic monoboron system containing **1a** and relevant inorganics (again without KHSO₅) showed the presence of a single boron species with a resonance at 3.7 ppm, consistent with trihydroxyboronate **1d** (Scheme 4a) while no signal was detected in the aqueous phase for the equivalent experiment using only **2b** (Scheme 4b). Analysis of the corresponding model system containing both **1a** and **2b** revealed a single signal in the aqueous phase at 3.7 ppm, consistent with **1d** (Scheme 4c). This analysis agreed with the HPLC data (Table 2) and also supported selective phase transport of **1a** to the aqueous phase as its trihydroxyboronate derivative, **1d**.²⁷ No charged species (**1d** or **2e**) or anhydride formation were observed in a complementary analysis of the organic phase – only the neutral species (**1a** and **2b**) were observed.

Scheme 4 ¹¹B NMR analysis of mono- and diboron systems of **1a** and **2b** under representative biphasic conditions.

Hydroxyboronates **1d** and **2e** are distinguishable by ¹¹B NMR (see ESI†) and the assignment of the observed ¹¹B NMR signal at 3.7 ppm was attributed to **1d**. However, it is conceivable that *in situ* hydrolysis of **2b** could occur to deliver **2a** and ultimately its trihydroxyboronate derivative (**2d**), which has a similar ¹¹B NMR resonance to **1d** (3.6 ppm, see ESI†). The **2d** signal may be obscured by **1d**, preventing detection at low concentration. To ensure a robust assignment, we analyzed two mono-fluorinated diboron systems by ¹¹B and ¹⁹F NMR analysis (Scheme 5).

¹¹B and ¹⁹F NMR analysis of the aqueous phase of the system containing **1a** and **3b** revealed a single ¹¹B NMR signal at 3.7 ppm, consistent with **1d**; no ¹⁹F NMR signals were detected (Scheme 5a). Conversely, analysis of the mixture of **1b** and **3a** showed one ¹¹B NMR signal at 3.6 ppm and one ¹⁹F NMR signal at −118.6 ppm, both of which were consistent with trihydroxyboronate **3d** (Scheme 5b). Thus, these experiments support the hypothesis of a selective boronic acid trihydroxyboronate formation and that diol transfer is inhibited.

Scheme 5 ¹¹B and ¹⁹F NMR analysis of mono-fluorinated diboron systems under representative biphasic conditions.

Temporal profiling of the aqueous phase *via* variable temperature NMR provided further data to assist in explaining the observed trends (Fig. 1 – for temperature/temporal profiling of all systems, see ESI†). Consistent with the HPLC analysis (Table 2), variable temperature ^{11}B NMR revealed that **[1d]** increased with temperature, with no detectable increase in **[1a]**, **[2b]** or **[2e]**.²⁸ **[1d]** also increased over time (see ESI†). This combined HPLC and NMR data set assists with the interpretation of the non-intuitive temperature-proportional increase in chemoselectivity.²⁹

The rate of oxidation was found to be rapid in the burst phase (see Chart 1 and ESI†). Therefore, the rate determining process for oxidation under the developed biphasic reaction conditions appears to be phase transfer of the organoboron species to the aqueous phase, which is assisted by trihydroxyboronate formation. Since oxidation occurs exclusively in the aqueous phase and BPin hydroxyboronate formation was not observed under the reaction conditions, chemoselective oxidation is achieved since boronic acid phase transfer is significantly more favorable than BPin transfer (Scheme 6).

Interestingly, in the absence of the active oxidant (KHSO_5), protodeboronation was observed to increase proportionally with both time and temperature giving the expected product $\text{B}(\text{OH})_4^-$.^{30,31} In the oxidative system this was not particularly problematic, since the rate of oxidation was rapid. However, this has clear implications for transition metal catalysis using organoboron species under basic biphasic reaction conditions (*e.g.*, Suzuki–Miyaura cross-coupling) in which transmetallation proceeds *via* the neutral organoboron species¹⁵ and must engage a presumably largely organic phase-bound catalyst.

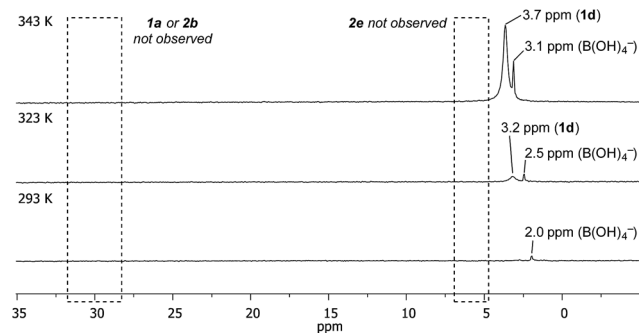


Fig. 1 Temperature- and time-proportional concentration of **1d** in the aqueous phase by ^{11}B NMR analysis.



Scheme 6 Spectroscopically observed organoboron species.

Lastly, formation of trihydroxyboronate from the boronic acid or hydroxyboronate from the BPin ester requires access to HO^- . Boronic acids have typically greater aqueous solubility than the corresponding BPin.¹¹ *clog P* calculations (see ESI†) indeed indicate greater aqueous solubility for boronic acids *vs.* BPins and this was also found for the corresponding boronate adducts. For example, boronic acid **1a** has *clog P* = 2.64 while BPin **1b** has *clog P* = 5.58. The corresponding boronates display the same trend with **1d** *clog P* = 0.50 and **1e** *clog P* = 3.44. Accordingly, since no charged species were observed in the organic phase, we believe that selective ionization of the boronic acid occurs either at the organic/aqueous interface or in the aqueous phase following transfer of the neutral species due to its comparatively greater solubility.

Generality of the chemoselective oxidation process

With effective reaction conditions for this model system, the generality of the chemoselective oxidation was explored (Scheme 7).

The biphasic reaction conditions were found to be general across a wide variety of aryl boronic acid and BPin ester reaction partners. Conversion to products over a 1 h reaction time were generally high and the chemoselectivity for boronic acid oxidation was typically >20 : 1 and exclusively selective (>99 : 1) in many cases, regardless of functionality or regiochemistry and whether boronic acid or BPin (*e.g.*, **3a–8a** *vs.* **3b–8b**). Alkenyl



Scheme 7 Chemoselective oxidation of aryl diboron system: $\text{B}(\text{OH})_2$ *vs.* BPin substrate scope. Ratio given for oxidation of **Xa** : **Xb**. Determined by HPLC, see ESI†

boronic acids were less effective substrates, giving mixtures of products.

With a framework for chemoselective oxidation of reactive diboron systems established, we sought to explore whether this biphasic protocol could challenge conventional reactivity profiles. BPin esters are typically readily oxidized in the presence of BMIDA esters.^{13d} However, we reasoned that it might be possible to reverse this profile and selectively oxidize the BMIDA component of a BMIDA/BPin aryl diboron system *via* speciation-controlled hydrolysis of the BMIDA³² and oxidation of the latent boronic acid (Scheme 8).

In the event, heating the reaction mixture to 80 °C for 15 min in the absence of Oxone® provided a smooth hydrolysis, which avoided any diol equilibration, and returning to 70 °C before addition of the oxidant allowed chemoselective oxidation of ArBMIDA in the presence of ArBPin (Scheme 9).

Once more, the efficiencies and selectivities of the process were typically excellent, with some diminished selectivity observed using specific heterocyclic derivatives (*e.g.*, **18b**, **24b**). Addition of Oxone® after the hydrolysis event was necessary to avoid buffering of the basic medium. This buffering effect impeded the rate of hydrolysis providing sufficient time for equilibration and ultimately diminishing the chemoselectivity of the process.

This BMIDA oxidation process provided the opportunity to further confirm the hypothesis of the requirement to physically separate the two boron residues in order to achieve chemoselectivity. Diboron compound **27** (where both boron residues were located on the same aryl unit) was a very poor substrate that, under optimized conditions, delivered a mixture of the desired phenol **22b** as well as **22a** (the product of BPin oxidation and BMIDA hydrolysis), **22c** (the product of global oxidation), but mainly **28** (the product of equilibration) (Scheme 10).³²

Chemoselective oxidation of diboronic acid systems

Chemoselectivity in this system has been driven by competing boronate formation between dissimilar organoboron compounds (B(OH)₂ vs. BPin). However, the formation of aryl boronates, and therefore aqueous solubility, is heavily influenced by the electronics of the aryl unit.¹⁹ Specifically, substitution on the aryl unit will influence the Lewis acidity of the boronic acid and can heavily influence the aqueous solubility. Based on this, we reasoned that chemoselective discrimination within a system containing two boronic acids might be



Scheme 9 Chemoselective oxidation of aryl diboron system: BMIDA vs. BPin substrate scope. Ratio given for oxidation of Xf : Xb. Determined by HPLC, see ESI.†



Scheme 10 Attempted chemoselective oxidation of diboron compound **27**. Determined by HPLC, see ESI.†

achievable by exploiting electronic effects to drive competitive boronate formation and subsequent selective phase transfer. The relative chemoselectivity might then be gauged *a priori* by assessing the phase separation by HPLC or NMR. This proved to be feasible and was initially evaluated using several electronically distinct phenylboronic acids vs. 2-naphthyl boronic acid **1a** (Scheme 11).

Under representative reaction conditions in the absence of oxidant, phenylboronic acids **3a**, **4a**, **5a**, and **7a** were found to preferentially distribute to the aqueous phase while **1a** remained comparatively more organic phase-bound (**1a** org/aq average = 71/29). This translated to chemoselective oxidation of the phenyl boronic acid species over **1a** in all cases. In the case of the strongly electron-deficient boronic acid **29a**, protodeboronation occurred rapidly and phase distribution was less reliable as an indicator of selectivity. While the measured phase distribution allowed prediction of the favored oxidation, the exact ratio of oxidation products could not be extrapolated from this analysis. This phenomenon was also found to be transferable across a range of substrates (Table 3).

The efficiencies and chemoselectivities of the process were not as pronounced as more substantially differentiated diboron



Scheme 8 Inverting established chemoselectivity: oxidation of BMIDA in the presence of BPin.



Scheme 11 Phase distribution and chemoselective oxidation of electronically distinct aryl boronic acids vs. **1a**. Determined by HPLC, see ESI.†

Table 3 Chemoselective oxidation of aryl boronic acids

Entry	R ¹ B(OH) ₂	R ² B(OH) ₂	Conv. ^a	Oxidation (R ¹ : R ²) ^{a,b}
1			86%	4 : 1
2			62%	3 : 1
3			71%	3 : 1
4			85%	2 : 1
5			42%	2 : 1

^a Determined by HPLC analysis using an internal standard. See ESI.†

^b Ratio given for oxidation of R¹-B(OH)₂ : R²-B(OH)₂.

systems (e.g., B(OH)₂ vs. BPin in the studies above); however, this represents the first chemoselective oxidation of two ostensibly equivalent boronic acid species based on subtle differences in the substitution of the pendant aryl unit.^{33,34}

Chemoselective oxidative nucleophile coupling

The medium-controlled chemoselective reaction manifold can potentially be leveraged to provide a number of enabling synthetic methods. As a demonstration, we have developed a chemoselective oxidative nucleophile coupling (Scheme 12).

Following chemoselective oxidation, a Chan–Evans–Lam etherification^{35,36} of the generated phenol with the remaining BPin can be effected. This process proceeds with high efficiency for the desired cross-coupled product with minimal homo-coupling detected. Biaryl ethers are prominent scaffolds in natural products, pharmaceuticals, agrochemicals, and materials,³⁷ for example, the anticancer agents, including **36**.³⁸ Modern catalysis methods, such as Ir-catalyzed C–H activation,³⁹ have provided convenient methods for accessing



Scheme 12 Chemoselective oxidative nucleophile coupling.

borylated arenes with substitution patterns that are not readily accessible by other methods. As such, this chemoselective oxidative nucleophile coupling process provides a novel and step-efficient synthesis of valuable chemotypes from readily accessible precursors.

Conclusions

In conclusion, chemoselective oxidation of boronic acid/BPin systems can be readily achieved in a basic biphasic reaction medium. Conventional protecting group strategies can be overturned to allow oxidation of BMIDA compounds in the presence of a normally more reactive BPin species. Spectroscopic investigations revealed that chemoselectivity is derived from a selective boronate formation and phase transfer of boronic acids to the aqueous phase. We have also shown that it is possible to chemoselectively oxidize a mixture of two boronic acids and predict the outcome of the reaction *a priori* by HPLC analysis of the phase distribution of the reacting partners. Lastly, the concept of chemoselectivity *via* medium control enabled the development of a chemoselective oxidative nucleophile coupling. The data in this study has significant ramifications for enabling chemoselectivity in non-protected organoboron systems as well as for the understanding of catalytic reactions of organoboron compounds in biphasic media.

Abbreviations

CPME	Cyclopentyl methyl ether
DAN	Diaminonaphthalene
HPLC	High performance liquid chromatography
MIDA	<i>N</i> -Methyliminodiacetic acid/ <i>N</i> -methyliminodiacetate
NMR	Nuclear magnetic resonance
Pin	Pinacolato
rt	Room temperature

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Notes and references

‡ The following numbering key has been used throughout: $R(BOH)_2 = \mathbf{Xa}$; $RBPIn = \mathbf{Xb}$; $ROH = \mathbf{Xc}$; $RB(OH)_3^- = \mathbf{Xd}$; $RBPIn(OH)^- = \mathbf{Xe}$; $RBMIDA = \mathbf{Xf}$.

§ Line added as a visual aid – no function has been fitted.

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