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Copper activation of boronic acids: factors affecting reactivity

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The generation of nucleophiles from the combination of aryl boronic acids and catalytic amounts of copper salt allows a reactivity distinct from other organometallic species, such as organolithiums or Grignard reagents. Here we examine how the electronic and steric properties of the boronic acid affect the formation of active nucleophiles and their subsequent reactivity with iminium-type compounds, showing that electron-rich substrates display reduced reactivity. Copyright © 2014 John Wiley & Sons, Ltd.

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Introduction

The generation of nucleophilic species via the activation of boronic acids and related compounds with copper salts is becoming a valuable strategy in synthesis.^[1-8] The advantages of such a system are clear: boronic acids are stable, readily available, easy to prepare, have a low toxicity and tolerate a wide range of functionalities in reaction partners, while copper salts are again very inexpensive (especially when compared with the more commonly employed noble metals) and relatively air and moisture stable. In addition, the low reactivity of unactivated boronic acids makes it possible to use functional groups incompatible with stronger nucleophiles such as organolithiums or Grignard reagents. Finally, the use of a catalytic amount of copper opens up the possibility of enantio-enriched products by appropriately chosen chiral ligands.^[9-13] These factors make copper/boronic acid nucleophiles some of the most attractive options available for carbon-carbon bond formation, and one certain to receive increasing attention in the future. In this work we examine the factors affecting the formation of these species and apply them in a copper-catalysed reaction.

Results and Discussion

While a great deal of work has been carried out on new methodologies utilizing copper catalysts, factors affecting the reactivity have not been intensively studied. Our group^[14] and the group of Shibasaki^[9] have observed activation of the aryl boronic acids and vinyl boronic esters, respectively, through the analysis of ¹¹B NMR spectra.

In our previous work^[14] we observed that more electron-poor boronic acids gave yields as good as, or better than, those obtained with electron-rich boronic acids (see Scheme 1). At the time we could offer no convincing explanation for this observation, despite the fact that such information could be useful for future advances in related processes.

Since a simplistic analysis would have suggested that electronrich copper nucleophiles should be more reactive, we postulated that the discrepancy could be caused by different rates for transmetallation, and hence different concentrations of active nucleophiles in solution.

To test this, we monitored the rate of transmetallation of electronically distinct boronic acids (as measured by varying $\sigma_{\rm p}$ values).^[15] The relevant boronic acid and a copper/bipyridyl complex were heated together in DMF, and the reaction was monitored by ¹¹B NMR. First we examined the rate of consumption of starting material (see Fig. 1). There was a clear trend where the electron-poor boronic acid was consumed rapidly, while the methoxy-substituted analogue was consumed at a much slower rate. After 300 min all of compound 1 had been consumed, compared with approximately 50% of 3. The unsubstituted phenyl boronic acid 2 fell neatly between these two extremes, at least at longer reaction times. This observation is perhaps not surprising: electron-withdrawing substituents would be expected to increase the electrophilicity of the boronic acid and hence accelerate nucleophilic attack to generate the boronate intermediate (indeed if formation of the boronate is irreversible, or essentially irreversible, under these conditions, then the consumption of starting material is simply a measure of the rate of nucleophilic attack).

This raised the question as to whether the increased reactivity was simply due to the increased electrophilicity of the boron species, or if other factors were involved. To answer this we analysed the percentage formation of the final product (see Fig. 2). These results were even more dramatic. Fluorine-substituted boronic acid (1) quickly reached complete conversion, whereas 4-methoxyphenyl boronic acid (3) had conversion of approximately 30% even after 6 h at 70 °C. Once again, phenyl boronic acid was between these two extremes.

Because of this very significant difference, it was clear that formation of active nucleophile was not faster simply due to

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Scheme 1. Copper-catalysed Petasis reaction. Yields obtained with electronically distinct boronic acids.



Figure 1. Consumption of boronic acid starting material.

increased concentrations of boronate, but rather both the formation of boronate and the transmetallation step were significantly slower for electron-rich compounds. This has significant implications for the use of such compounds in copper-activated procedures.

It is worth noting, however, that the difference in observed yields is not as dramatic as the difference in concentrations of



Figure 2. Formation of active nucleophile.

active nucleophiles. One plausible explanation for this is that, while the electron-rich nucleophiles are formed in lower amounts, their reactivity with electrophiles once formed is significantly higher than the reactivity of electron-poor nucleophiles.

To test the generality of our observations, we tried the same boronic acid/copper nucleophiles in a new reaction. We examined the possibility of developing a copper-catalysed addition of boronic acids to *N*-acyl quinolinium ions. This is an attractive route for the synthesis of substituted dihydroquinolines, a commonly encountered bioactive core.^[15–17] A metal-catalysed process has been developed for this reaction,^[15] and in that study it was found that a Ni(0) catalyst turned electron-deficient aryl boronic acids – normally unreactive in Petasis-type reactions – into viable nucleophiles (although yields were still lower than those observed for electron-neutral or electron-rich aryl boronic acids).

We examined the possibility of extending our copper catalysis conditions to reactions of this type (Table 1). To our delight we obtained the product, albeit in moderate yield (Table 1, entry 1). Use of *tert*-butoxide additives gave a small, but reproducible, improvement (Table 1, entry 3). This effect had been observed in cross-coupling reaction by Liu and co-workers, who proposed that the positive effect was due to the *tert*-butoxide coordinating to the boron to help transmetallation in addition to the lithium ion stabilizing the organocuprate intermediate.^[5] More interestingly, we once again observed the same trend, with electron-withdrawing groups improving the yield and electron-donating groups decreasing it (relative to unsubstituted phenyl boronic acid derivatives: Table 1 entries 3, 4 and 5). As such, it correlated well with our previous results and the rate of activation of the boron species, as shown by ¹¹B NMR.

We had previously observed that *ortho* substituents on the aryl boronic acid resulted in low or negligible yields. We re-examined their use in the current reaction, looking at 2-chlorophenyl boronic acid. We first monitored the reaction of 2-chlorophenyl boronic acid with copper bromide by ¹¹B NMR. The fact that this was rapidly consumed – similar to the results obtained above with 4-flurophenyl boronic acid – lends support to our hypothesis

Table 1. A copper-catalysed addition of aryl boronic acids to <i>N</i> -acyl quinolinium precursors				
CuBr (10 mol%), bipy (10 mol%) ArB(OH) ₂ , base OEt DMF, 4Å mol Sieves, OEt 24h, 70 °C 4 5a-d				
Entry	Ar	Base	Product	Yield (%)
1	Ph	none	5a	28
2	Ph	KO ^t Bu	5a	30
3	Ph	LiO ^t Bu	5a	34
4	4-MeOC ₆ H ₄	LiO ^t Bu	5b	28
5	$4-F-C_6H_4$	LiO ^t Bu	5c	49
6	2-CIC ₆ H ₄	LiO ^t Bu	5d	<5

for a high dependency on electronic factors. We next used this boronic acid for the addition to **4**. We observed only trace amounts of product formed (Table 1, entry 6). This led us to believe that in these cases it is the carbon–carbon bond-forming step (i.e. nucleophilic addition to the iminium) that is prevented by sterics, whereas the salt formation and transmetallation proceed as normal.

Furthermore, this highlights the complementarity between organocatalytic and metal-catalysed boronic acid activations – organocatalytic methods employing diols and related compounds work best with electron-rich boronic acids, particularly vinyl boronic acids, ^[18–20] whereas metal-catalysed processes make electron-poor aryl boronic acids at least viable reaction partners,



Figure 3. Proposed mechanism for the copper-catalysed process.

and at times they can even outperform electron-rich analogues.^[7,14,15] To date, however, organocatalytic methods have proven more successful at enantioselective variants, though recent advances are highlighting the opportunities for metal catalysed processes.^[16]

By analogy with the initially reported Ni-catalysed process,^[15-17] we tentatively propose the mechanism shown in Fig. 3. The transmetallation process leads to an aryl copper species,^[6] and this interacts with the iminium (**6**) to give a Cu(III) intermediate (**7**). This oxidative step is consistent with the proposed intermediary of Cu(III) species for reactions involving Cu(I) nucleophiles.^[21] Intermediate **7** undergoes reductive elimination to give the aryl substituted product **5** and regenerated Cu(I) salt. We examined the possibility of rendering the process asymmetric. Unfortunately we obtained **5a** in racemic form each time (see supporting information for ligands screened).

In conclusion, we have examined the factors influencing reactivity for copper-activated boronic acids, and provided insight that may help to explain the good performance of electron-poor variants. In addition, we employed copper/boronic acid nucleophiles in a separate C—C bond-forming process and observed a similar trend in reactivity. It is hoped that this will lead to further study and use of this highly attractive reagent system.

Experimental

General Procedure for the Copper-Catalysed Arylation of 4

Dry, degassed DMF (12 ml) was added to a mixture of copper bromide (0.142 mmol) and 2,2'-bipyridine (26.4 mg, 0.17 mmol) under N₂. The solution was stirred at 60 °C for 1 h. After this time, starting material **4** (351.2 mg, 1.42 mmol) and aryl boronic acid (2.84 mmol) were charged to the flask, along with powdered 3 Å molecular sieves. The solution was stirred at 70 °C under N₂ for 24 h and subsequently filtered on a short silica pad. The residue was then purified by column chromatography on silica gel.

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Supporting Information

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