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Metal-free C–C bond formation *via* coupling of nitrile imines and boronic acids†

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The challenges of developing sustainable methods of carbon–carbon bond formation remains a topic of considerable importance in synthetic chemistry. Capitalizing on the highly reactive nature of the nitrile imine 1,3-dipole, we have developed a novel metal-free coupling of this species with aryl boronic acids. Photochemical generation of a nitrile imine intermediate and trapping with a palette of boronic acids enabled rapid and facile access to a broad library of more than 25 hydrazone derivatives in up to 92% yield, forming a carbon–carbon bond in a metal free fashion. This represents the first reported example of direct reaction between boronic acids and a 1,3-dipole.

Introduction

The formation of carbon–carbon (C–C) bonds is one of the most fundamental transformations in organic synthesis.¹ Indeed, efforts to enable this transformation have occupied synthetic chemists for over a century. The vast majority of C–C bond-forming processes require the application of an organometallic species, or metal catalysis. Such reagents and catalysts are often associated with environmental concerns, in addition to their resources being finite in nature.² Consequently, more recent approaches towards C–C bond formation have emphasized the importance of sustainability in the development of new reaction manifolds.²

A member of the nitrilium betaine family of 1,3-dipoles, the nitrile imine (NI) functional group is a versatile intermediate that is generated *in situ* by the photolysis of a 2,5-substituted tetrazole moiety.^{3–5} NIs have recently been employed extensively within materials chemistry in polymer cross-linking and surface functionalization, and in biorthogonal chemistry as ligation handles and photo-affinity labels.^{6–10} Their widespread application is attributable to the traceless, light-activated nature of the formation of the dipole. While NIs are predominantly known for their role in 1,3-dipolar cycloadditions,^{5a,5c,5d,11} more recent reports have documented the pleiotropic reactivity profile of NIs with a range of nucleophiles, including carboxylic acids and thiols.^{10,12,13}

As part of our studies aimed at further understanding the reactivity of NIs, we were eager to harness the potential of this

versatile dipole in the context of light-activated, metal-free C–C bond formation. This study was developed using a mechanistic hypothesis elucidated from consideration of the Petasis–Mannich reaction, a multicomponent transformation which furnishes highly substituted amine derivatives (Scheme 1a).^{14–16} Following initial formation of an iminium intermediate from a primary or secondary amine and the corresponding aldehyde, coordination of a vinyl or aryl boronic acid to an α -hydroxy moiety of the iminium species generates the “ate” complex of the Petasis–Mannich.^{15,17} The principal feature of this complex is the increased nucleophilicity of the boronate moiety relative to the initial boronic acid.¹⁸ This pre-activation facilitates migration of the pendant R group into the electrophilic iminium center, forming the reaction product. We reasoned that NIs possessed similar properties to the analogous α -hydroxy iminium intermediate formed during the Petasis–Mannich reaction. The C-terminus of the NI may be considered a pseudo-iminium center, while the anionic N-terminus could readily facilitate boronate formation, in an analogous manner to the α -hydroxy moiety of a Petasis–Mannich substrate (Scheme 1b). If successful, this hypothesis would enable the migration of the aryl group of the boronic acid towards the NI dipole, allowing metal-free access to a range of aryl hydrazones, forging a new C–C bond using photochemical promotion.

Results and discussion

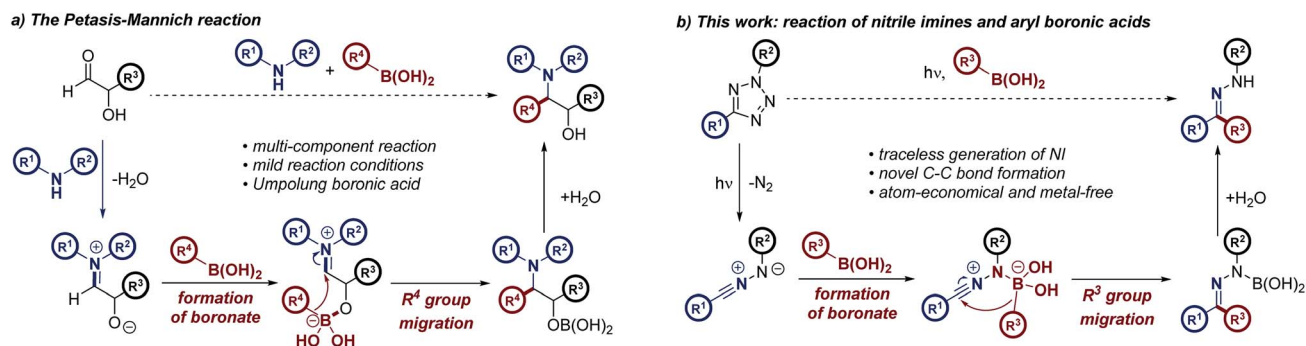
Preliminary studies into the development of the reaction utilized diaryl tetrazole **1a** and fluorinated boronic acid **2a** (see ESI for full details†). The quantum yields of the photolysis of 2,5-tetrazoles to furnish nitrile imines has previously been reported by several groups.^{19,20} These values are found to generally be very high (0.5–0.9), and a wide variety of tetrazoles have been shown to undergo photochemical degradation using a simple UV lamp designed for visualising TLC silica plates, therefore

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Scheme 1 (a) The key steps comprising the mechanism of the Petasis–Mannich multicomponent reaction. (b) Proposed formation of aryl hydrazones *via* the metal-free coupling of NIs and aryl boronic acids.

indicating the generality of the process. Initial conversions were shown to be highly dependent on the stoichiometry of boronic acid employed, however this effect was considerably less pronounced when exceeding three equivalents of **2a** (Table 1, entries 1–3). An additional challenge encountered was the undesired formation of hydrazide **4**, the formal hydration product of the intermediate NI. It was thought that the condensation of excess **2a**, forming the corresponding boroxine analogue, was responsible for the generation of water within the reaction mixture, leading to hydrazide formation.²¹ Efforts to prevent the generation of **4** focused on the introduction of drying agents, culminating in the generation of target hydrazone **3a** in 61% yield with minimal by-product formation (Table 1, entries 4–6).

Following on from the identification of these reaction conditions, we sought to exemplify the process by investigating a palette of aryl boronic acids in the reaction (Scheme 2a). The procedure was shown to furnish a broad range of aryl hydrazones in moderate to excellent yields, with a noted correlation on the electronic properties of the boronic acid (*cf.* **3b** and **3h**).

We propose that aryl groups with greater electron density have a greater migratory aptitude during the key step of the process (Scheme 1b), leading to improved conversions. This electronic activation of the substrate may be either conjugative or inductive in nature (*cf.* **3d** and **3g**). The transformation was also shown to be compatible with both *meta*- and *ortho*-substituted aryl boronic acids, with increased steric bulk having a relatively minor impact on reaction yield (*cf.* **3i**, **3j**, and **3k**). The lower conversion of **3a** relative to the isolated yield of **3k** is reasoned to be a consequence of the smaller scale used during reaction optimisation, promoting more rapid photolysis of **1a**, and subsequent rapid decomposition of the NI. A number of heterocyclic analogues were also synthesized in good to excellent yield (*e.g.* **3l** to **3o**). Alkyl boronic acids such as cyclopropyl and cyclohexyl systems were also examined, however none of the corresponding hydrazone was obtained, indicating the requirement for an aryl boronic acid derivative for successful reaction.

Having established the scope of the aryl boronic acid partner, the scope of the 2,5-diaryl tetrazole component was then assessed (Scheme 2b). Boronic acid **2b** was selected as a model substrate for this study as the moderate conversion of hydrazone **3e** during the previous phase of the study would highlight the impact of the tetrazole species on reaction yield. In most cases, modification of either aryl ring of the NI precursor was found to have a negligible impact on conversion (*e.g.* **3p** to **3t**). Both electron-rich and electron-donating substituents were compatible, with a small reduction in yield when employing electron-rich substituents (*cf.* **3r** and **3s**). The reaction was also found to be tolerant of *meta*- and *ortho*-substitution of the C-aryl ring of the tetrazole (*cf.* **3v** and **3x**), despite its proximity to the site of bond migration during the key step of the reaction.

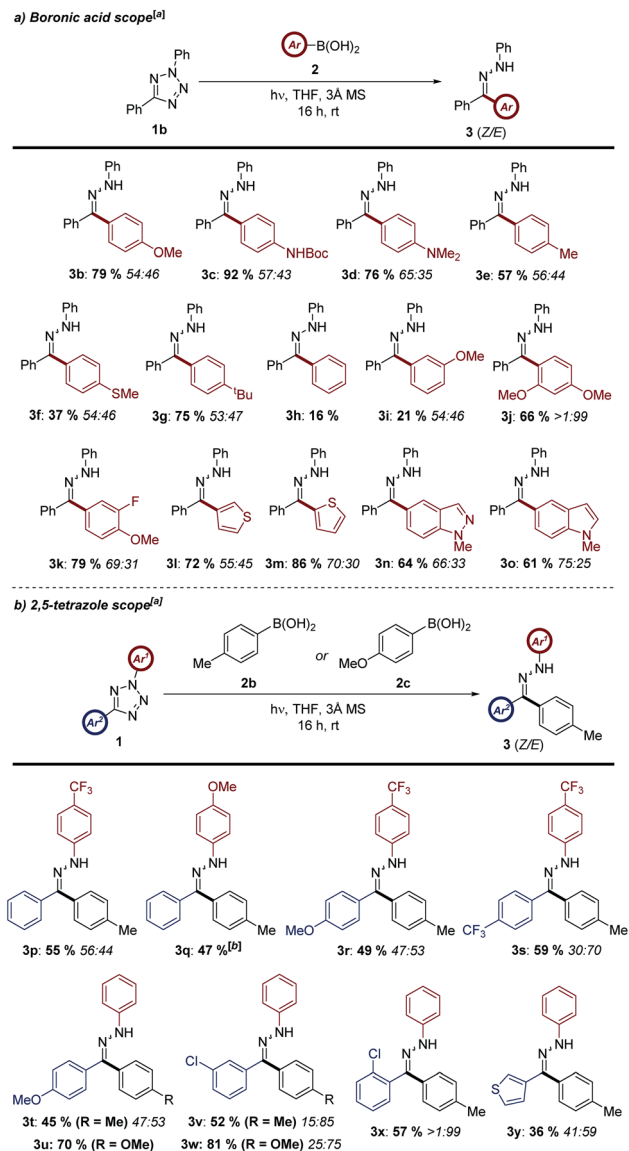
Representative yields of two tetrazole substrates from this study applied in conjunction with a more electron-rich boronic acid (**2c**) are shown in examples **3u** and **3w**. Based on this, it can be inferred that similar enhancements in yield would be observed in all of the above examples when employing a more reactive boronic acid. The majority of substrates were isolated as stereochemical mixtures of both the *Z* and *E* hydrazone derivatives. This was reasoned to be a consequence of the

Table 1 Optimization of reaction conditions^a

Entry	Eq iv. 2a	Additive	3a Conv. ^b [%]	4 Conv. ^b [%]
1	1	—	33	23
2	3	—	53	19
3	5	—	55	11
4	3	CH(OMe) ₃ ^c	38	21
5	3	3 Å mol. sieves ^d	46	8
6	3	3 Å mol. sieves ^{d,e}	61	2

^a Reaction conditions unless otherwise specified: **1a** (1 equiv.), **2a** (*x* equiv.), THF (0.1 M), 270–330 nm light, under N₂ at room temperature in a 50 mL quartz flask. ^b Determined by ¹⁹F NMR spectroscopy. ^c 10 equiv. ^d 400 mg mmol⁻¹. ^e Crushed.





Scheme 2 (a) Boronic acid substrate scope. (b) Nitrile imine substrate scope using (2b) as the reaction partner, and examples of elevated yields when employing 4-methoxyphenylboronic acid (2c) as the reaction partner. ^aReaction conditions: tetrazole (0.25 mmol), boronic acid (0.75 mmol), and 3 Å mol. sieves (100 mg) under N₂ in THF (2.5 mL), stirred under 270–330 nm light for 16 h in a 50 mL quartz flask. ^bIsolated as the ketone.

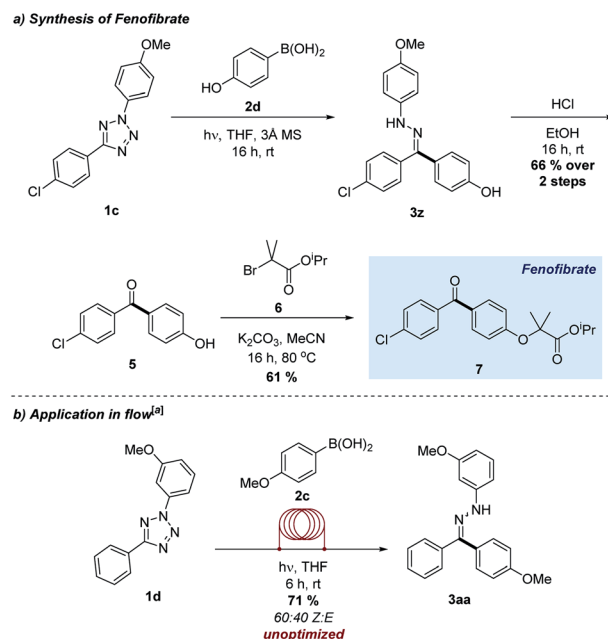
application of UV light *via* the photoisomerization of hydrazone products upon exposure to the reaction conditions (*vide infra*). The major isomer has been assigned as the aryl group of the boronic acid in an antiperiplanar arrangement with the lone pair of the sp² hybridised nitrogen. This is based both on our mechanistic rationale for the reaction, and previous literature precedent for nitrilium-based 1,3-dipoles.²² Interestingly, *ortho*-substitution of either the boronic acid and tetrazole substrates resulted in improvements in stereoselectivity in selected examples (*e.g.* 3j and 3x).

One of the most attractive aspects of this novel transformation is the absence of any exogenous reagents other than

the input tetrazole and boronic acid. As a means of further demonstrating the applicability of this emerging process, we applied the method to the transition-metal free synthesis of fenofibrate, a marketed hypolipidemic agent (Scheme 3a).²³ The combination of 4-hydroxyphenylboronic acid and tetrazole 1c using the optimized conditions formed the intermediate hydrazone 3z, which was hydrolysed and combined with alkyl bromide 6 to generate the target molecule in excellent overall yield. This approach represents a viable alternative to existing synthetic routes towards this compound, which often require additional steps or excessive quantities of harmful reagents.²⁴

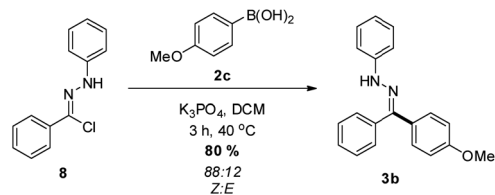
Given the practical difficulties often associated with performing light-driven reactions on a large scale, we were interested in the application of the transformation using a flow chemistry reactor. Flow methods are particularly powerful when combined with photochemistry, as it may afford more efficient exposure to the light source when compared to a traditional reaction vessel.²⁵ Pleasingly, photolysis of tetrazole 1d in the presence of boronic acid 2c using a flow reaction manifold successfully furnished the desired hydrazone 3aa in good yields (Scheme 3b). Furthermore, this transformation was accomplished on a larger scale and in shorter time compared to the batch process.

While the photolysis of 2,5-tetrazoles is often viewed as an attractive method of NI generation, we also sought to demonstrate an alternative approach. The treatment of hydrazonyl chloride 8 with potassium phosphate²⁶ in the presence of boronic acid 2c was found to yield the desired hydrazone 3b in excellent yield (Scheme 4), with an enriched Z : E ratio, which again suggests isomerization when using UV light. Indeed, subjecting this sample to the photochemical conditions



Scheme 3 (a) Synthesis of a marketed pharmaceutical agent. (b) Application in a flow reactor. ^[a]0.75 mmol scale.

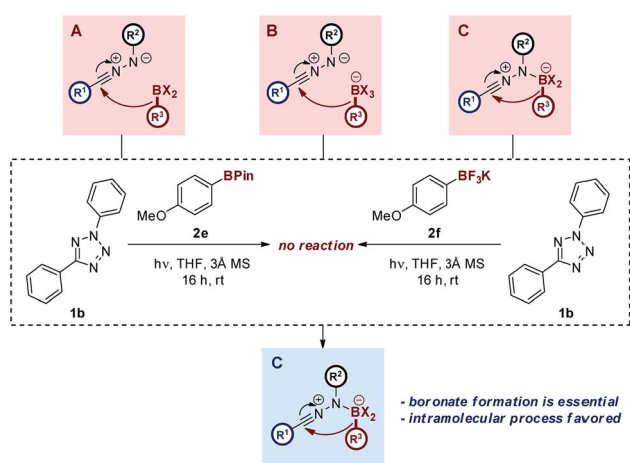




Scheme 4 The use of hydrazone chlorides as an NI precursor.

outlined above resulted in a 55 : 45 mix of geometric isomers. In addition to this, the base promoted reaction manifold was also employed on a 5 mmol scale to furnish **3b**, with a similar (72%) isolated yield obtained. A comprehensive investigation into the application of hydrazone chlorides within this reaction manifold is currently underway within our laboratory, and will be reported in due course.

The proposed reaction mechanism is believed to proceed in an analogous manner to the Petasis–Mannich reaction, as outlined above (Scheme 1). This hypothesis is supported by the increased reactivity of electron-rich boronic acid substrates within the reaction manifold, a feature that is shared by the Petasis–Mannich.^{17a,27} Control experiments involving either the pinacol ester or potassium trifluoroborate analogue of boronic acid **2c** have failed to yield the expected hydrazone (Scheme 5). Attempts to form the more electrophilic ArBF_2 species by treatment of the potassium trifluoroborate analogue with TMSCl^{29} led to multiple unidentifiable products. The incompatibility of the pinacol ester substrate provides evidence towards the formation of an anionic nucleophilic boron species during the reaction mechanism, owing to the established reluctance of boron-pinacol esters to form boronates (paths B and C, Scheme 5).²⁸ The migration of the aryl group from the boronate to the NI is also likely to favour an intramolecular process, as deduced from the lack of product formation when employing the highly nucleophilic trifluoroborate analogue (path C, Scheme 5).¹⁸ Additional spectroscopic and computational studies are on-going in order to further delineate the mechanism of reaction.



Scheme 5 Preliminary mechanistic investigations.

Conclusions

In conclusion, we have demonstrated the novel reaction of NIs with aryl boronic acids in a traceless, light-activated procedure. This transformation has been shown to be highly general, furnishing over 25 hydrazone analogues in moderate to excellent yields. The method can be utilized in the synthesis of pharmaceutically relevant compounds, and may also be employed at scale, either *via* the application of flow chemistry, or through the use of an alternative NI source such as the hydrazone chloride. The transformation serves as a powerful example of the utility of photochemistry and metal-free syntheses in the pursuit of robust and sustainable methods of C–C bond formation.

Experimental

General procedure for the synthesis of aryl hydrazones 3a–3z

To an oven-dried quartz round-bottom flask (50 mL) equipped with a stirrer bar was added 3 Å molecular sieves (400 mg mmol^{-1}), tetrazole (1 equiv.), and boronic acid (3 equiv.). The mixture was dissolved in THF (10 mL mmol^{-1}), purged with N_2 and irradiated under a UV lamp (270–330 nm) with stirring for 16 hours. The reaction mixture was diluted with ethyl acetate, filtered through Celite and rinsed with additional ethyl acetate. The crude solution was concentrated under vacuum and purified by column chromatography.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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