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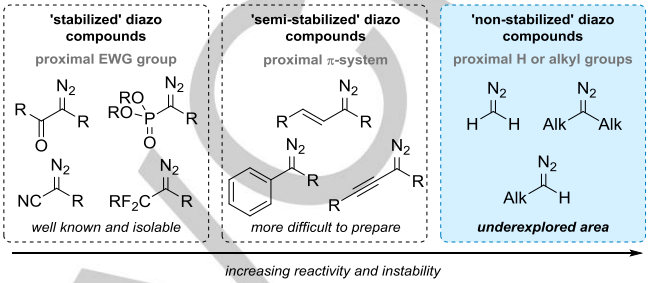
A New Versatile Route to Unstable Diazo Compounds via Oxadiazolines and Use In Aryl-Alkyl Cross-Coupling Reactions

Andreas Greb[a,†], Jian-Siang Poh[a,†], Stephanie Greed[a], Claudio Battilocchio[a], Patrick Pasau[b], David C. Blakemore[c] and Steven V. Ley[a,*]

Abstract: Coupling of readily available boronic acids and diazo compounds has emerged recently as a powerful metal-free carbon-carbon bond forming method. However, the difficulty in forming the unstable diazo compound partner in a mild fashion has hitherto limited their general use and scope of the transformation. Here, we report the application of oxadiazolines as precursors for the generation of an unstable family of diazo compounds using flow UV photolysis and their first use in divergent protodeboronative and oxidative C(sp^2)-C(sp^3) cross-coupling processes, with excellent functional group tolerance.

Diazo compounds represent a highly useful class of compounds in organic synthesis,[1] for example in cyclopropanation,[2] heteroatom-H[3] and C-H insertion[4] reactions. In particular, the reaction of diazo compounds with organoboron species has attracted considerable interest over the past few years, for example, in C(sp^2)-C(sp^3) cross coupling reactions.[5]

Our previous studies on the flow oxidation of hydrazones,[6] showed the effectiveness of utilizing *mild conditions* to generate and react diazo compounds with boronic acid. In particular, this allowed us to intercept the putative unstable boronic species and thereby enable access to alcohols[6] and powerful iterative bond forming processes.[7] Nevertheless, these studies were limited to the generation of 'semi-stabilized diazo compounds', compounds bearing either an adjacent aryl or vinyl group to the diazo moiety. To truly generalize this concept would require expansion into the elusive realm of 'non-stabilized diazo compounds', a class of compounds notorious for their intrinsic instability, toxic/hazardous nature and difficulty of preparation (Scheme 1).[1b] Within this class of reactive intermediates, dialkyl substituted diazo compounds pose a major challenge to both access and safely utilize these reactive species. If a mild method to generate these non-stabilized diazo compounds could therefore be realized, a more general method to enable aryl-alkyl cross-couplings may become possible, along with potential interception of the intermediate boron species to afford new chemistries.



Scheme 1. Families of diazo compounds.

While a multitude of methods have been developed to access diazo compounds, few allow the generation of the *non-stabilized* members of the family with sufficient generality. An interesting report by Warkentin *et al*. in 1989 showed that UV photolysis of 1,3,4-oxadiazolines at *ca*. 300 nm formed diazoalkanes.[8] Surprisingly, this approach has been largely overlooked by chemists as a potential route to forming unstable diazo compounds, and has never before been engaged in the development of new synthetic method. Oxadiazolines are available by a two-step, one-pot procedure from readily available ketones *via* condensation of acetic hydrazide and subsequent $PhI(OAc)_2$ mediated oxidation. In contrast to alternative diazo precursors such as hydrazones and nitrosoamides, oxadiazolines were found to be bench-stable over many months (also see SI for differential scanning calorimetry data).

At the outset of our investigation, we decided to exploit enabling flow technologies, to achieve more efficient irradiation compared with a batch reactor,[9] and to avoid the build-up of hazardous quantities of any unstable diazo compounds.[10-12] Initial studies began with the generation of oxadiazoline **1**, a potential precursor for the cyclic, non-stabilized diazo compound, 4-diazotetrahydropyran (**2**) (Scheme 2). Passage of an ethereal solution of **1** through a 10 mL reactor coil held at 10 °C and irradiated at 310 nm by a 9 W UV lamp, at a 0.125 mL min^{-1} flow rate (residence time = 80 min) led to the generation of a distinctively red solution. In-line IR spectroscopic analysis revealed two important features: a peak at 2040 cm^{-1} corresponding to the stretch of a diazo group confirmed the presence of diazo compound **2**; in addition, a peak at 1746 cm^{-1} corresponding to the C=O stretch of methyl acetate was observed, a useful gauge of assessing photolytic conversion of the oxadiazolines. Consequently, with this result we could now efficiently access non-stabilized diazo compounds using a flow protocol and then study their use in C(sp^2)-C(sp^3) cross-coupling (see SI for optimization results). This procedure is divergent depending upon the 'workup' conditions of the intermediate boron species.

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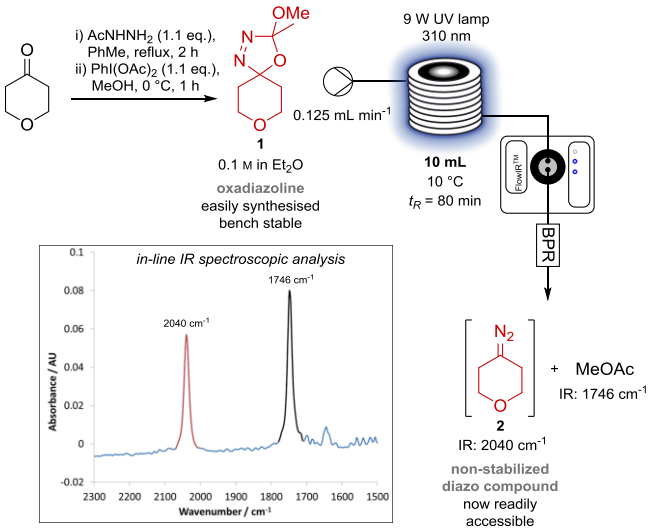
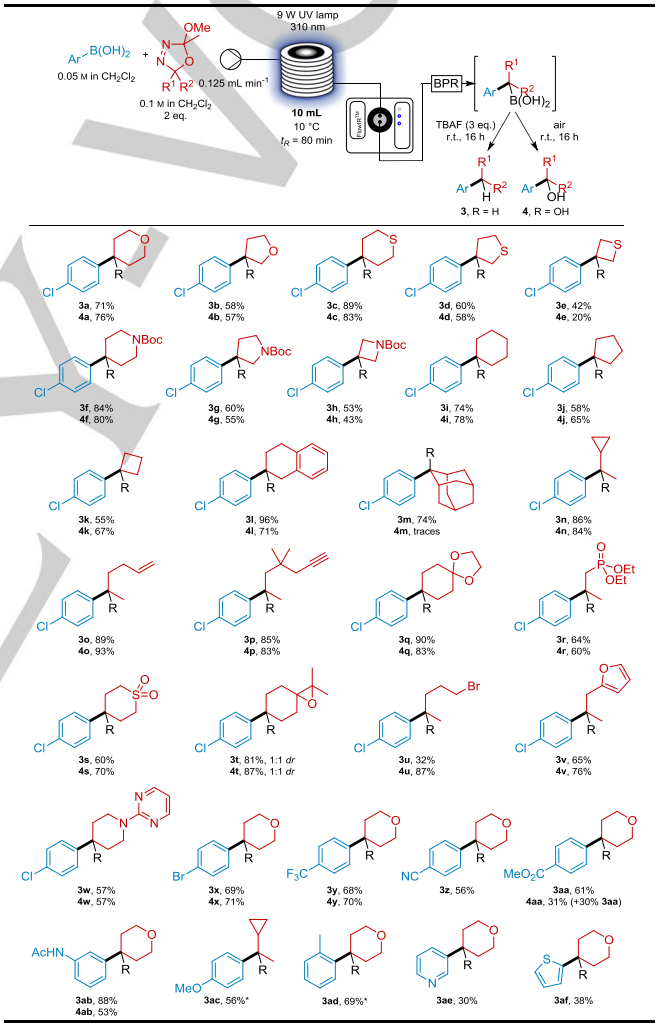


Scheme 2. Oxadiazolines as diazo precursors and access to non-stabilized diazo compound **2**.

Using a number of oxadiazolines and readily available boronic acids or boroxines,[13] we were able to demonstrate a remarkably broad reaction scope and unusually high functional group compatibility (Table 1). With respect to the oxadiazoline component, a variety of pharmaceutically relevant 4-, 5- and 6-membered saturated heterocyclic examples were viable coupling partners, including pyran (**3a**), tetrahydrofuran (**3b**), tetrahydrothiopyran (**3c**), tetrahydrothiophene (**3d**), thietane (**3e**), *N*-Boc piperidine (**3f**), *N*-Boc pyrrolidine (**3g**) and *N*-Boc azetidine (**3h**) rings, providing moderate to excellent yields of the desired C(sp^2)-C(sp^3) cross-coupling products. It is particularly notable that the 4-membered rings were viable examples given the instability of 4-membered cyclic diazo compounds,[13] arising from the relief of ring strain when moving from a sp^2 to a sp^3 carbon center on reaction with electrophiles. Furthermore, tolerance of the tetrahydrothiophene and thietane moieties highlights examples where approaches using a tosylhydrazone route or carbon-centred radical approaches would fail, due to the tendency of these systems to undergo elimination/ring-opening. A number of carbocyclic examples spanning cycloalkyl groups (**3i-3l**) were also permissible substrates, along with the highly hindered adamantane substituent (**3m**). Tolerance of a cyclopropyl group (**3n**) is not only indicative of a non-radical based process for this C(sp^2)-C(sp^3) cross-coupling method, but also further exemplifies the advantages of this procedure over methods utilizing carbon-centered radicals (where cyclopropane ring-opened products would be obtained instead). In terms of functional group compatibility for the oxadiazoline component, olefins (**3o**), alkynes (**3p**), acetals (**3q**), phosphonates (**3r**), sulfones (**3s**), furans (**3v**) and pyrimidines (**3w**) were all viable substrates. Remarkably, both an epoxide (**3t**) and an alkyl bromide (**3u**) could participate in this coupling process, products that would be intractable to access using metal-catalyzed methods or harsh basic conditions. With respect to the boronic acid component, a variety of electron-deficient aromatic rings harboring various functional groups were possible substrates, including 4-bromo (**3x**), 4-trifluoromethyl (**3y**), 4-cyano (**3z**) and 4-methoxycarbonyl (**3aa**) substituents. Electron-rich examples were also tolerated, including 3-acetamide (**3ab**), 4-methoxy (**3ac**) and *o*-methyl (**3ad**) substituents, although for the two latter cases, a higher temperature was required to achieve protodeboronation. While lower yielding, heterocyclic boronic acids could also be employed in this protocol to provide useful amounts of desired cross-coupled product, for example, 3-pyridyl (**3ae**) and 2-thienyl (**3af**) substituents.

Table 1. Metal-free protodeboronative and oxidative C(sp^2)-C(sp^3) cross-coupling.



Yields stated are of isolated product. **Protodeboronation**: using 0.5 mmol of boronic acid, 1.0 mmol of oxadiazoline and 1.0 mmol of DIPEA, then workup using TBAF (3 eq.) and stirred further at r.t. for 16 h; * protodeboronation was conducted at 75 °C for 16 h. **Oxidation**: using 0.5 mmol of boronic acid, 1.0 mmol of oxadiazoline and 1.0 mmol of DIPEA, then workup by stirring further under air at r.t. for 16 h.

A simple switch in the workup procedure to stirring under air provided the oxidized C(sp^2)-C(sp^3) cross-coupled products, which exhibited a similar broad reaction scope and high functional

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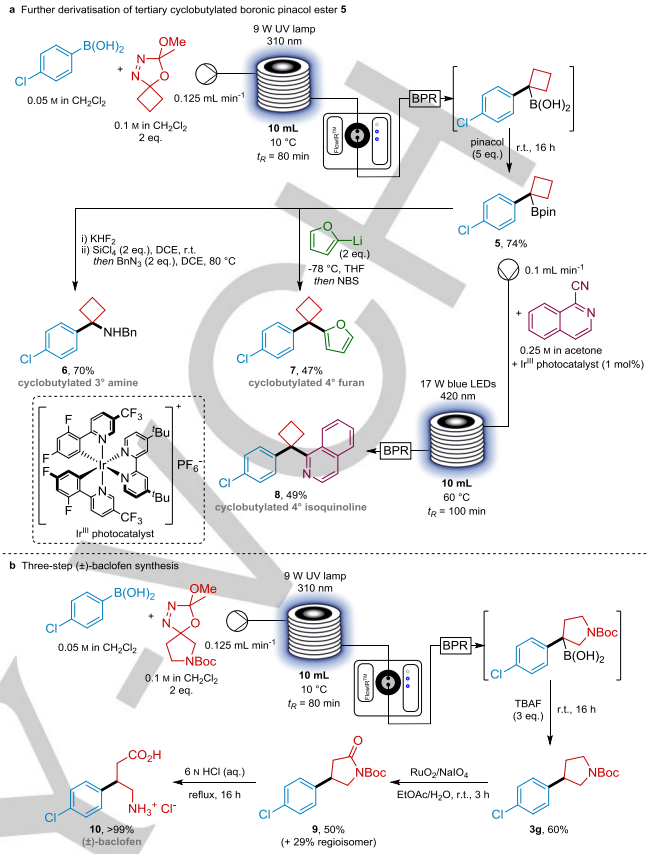
group compatibility (Table 1). Again, a variety of 4-, 5- and 6-membered saturated heterocyclic oxadiazolines could be coupled with 4-chlorophenylboronic acid to generate a variety of tertiary alcohols (**4a-4h**) in generally similar yields to the protodeboronative method. Similar yields were obtained for carbocyclic examples (**4i-4l, 4n**), with the exception of adamantane derivative **4m** where oxidation appeared to be extremely slow. For the functional group compatibility, olefins (**4o**), alkynes (**4p**), acetals (**4q**), phosphonates (**4r**), sulfones (**4s**), furans (**4v**) and pyrimidines (**4w**) all proceeded smoothly. A particular highlight was the tolerance of highly reactive functionalities such as an epoxide (**4t**) and alkyl bromide (**4u**). Electron-poor boronic acids (**4x**, **4y**) and electron-rich boronic acids (**4ab**) were also viable coupling partners, although in the case of **4aa**, protodeboronation appeared to be facile and 30% of the protodeboronative C(sp^2)-C(sp^3) cross-coupled product **3aa** was also obtained. This overall protocol is complementary to conventional Grignard addition but in many cases afforded products that are not compatible with organometallic species.

To illustrate the utility of our newly developed protocol, we first turned to the trapping of the tertiary boronic acid derived from the coupling of 4-chlorophenylboronic acid and the cyclobutane oxadiazoline precursor, using excess pinacol as the final workup quench, which provided the valuable Bpin product **5** in 74% yield (Scheme 3a). General methods to access and assess the reactivity of these tertiary alkylboron pinacol esters are vastly underdeveloped, so this process serves as testament to enabling a versatile cross-coupling route to these highly valued organoboron intermediates. Utilization of **5** for the generation of valuable and pharmaceutically relevant tertiary cyclobutylamines was successfully demonstrated, providing the benzyl protected derivative **6** in 70% yield over two steps.[15] Furthermore, we were also able to construct quaternary carbon centres using two recently developed methodologies for C(sp^2)-C(sp^3) cross-coupling of boronic esters: reaction of **5** with 2-lithiofuran and a subsequent quench with *N*-bromosuccinimide (NBS) led to cyclobutylated furan derivative **7** in 47% yield;[16] whereas an iridium-catalyzed photoredox flow process[17] allowed us to couple 1-isoquinolinecarbonitrile to **5**, leading to cyclobutylated isoquinoline derivative **8** in 49% yield. Finally, we were further able to apply this process to the short three-step synthesis of the GABA receptor agonist drug, baclofen (**10**) (Scheme 3b).[18]



Scheme 3. Applications of the divergent C(sp^2)-C(sp^3) cross-coupling process.

In summary, this work clearly demonstrates how oxadiazolines may be used as efficient, bench-stable precursors for non-stabilized diazo compounds. Indeed, with these improvements in metal-free C(sp^2)-C(sp^3) cross-coupling, this process complements the well-established organometallic and organohalide cross-coupling procedures. In combination with readily available arylboronic acids, this newly developed flow method allows a myriad of potent, divergent, metal-free C(sp^2)-C(sp^3) cross-coupling processes exhibiting a very general reaction scope and unparalleled functional group tolerance, as well as access to new tertiary alkyl boronic pinacol ester derivatives. Further applications of these unstable diazo compounds are currently ongoing in our laboratories.

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Keywords: • boronic acids • cross-coupling • diazo compounds • flow chemistry • photochemistry

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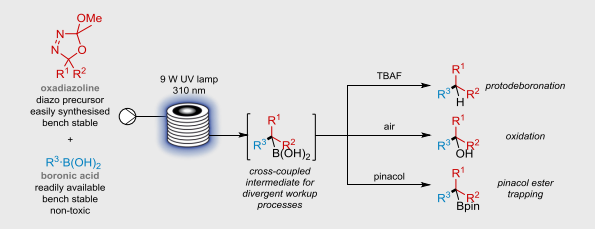

Photo-finish: A mild versatile method for the generation of highly unstable diazo compounds via photolysis of oxadiazolines and subsequent coupling with boronic acids is described. Simple changes in workup conditions allows the divergent generation of protodeboronated and oxidised products, along with boronic pinacol esters, with excellent functional group tolerance.

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