

Carbon-carbon bond formation using flow chemistry

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(Phys.org)—Traditionally, C-C bond forming reactions require the use of a precious metal, such as palladium, to catalyze the reaction. Precious metals are expensive and because pharmaceutical ingredients require a very low metal content, these reactions are not practical for medicinal chemistry. This has prompted many scientists to seek alternative coupling reactions that do not use precious metals. Prior research with boronic acids has demonstrated that metal-free cross-coupling reactions are possible, but the reaction conditions are prohibitive for a generalizable synthesis.

In the current research Claudio Battilocchio, Florian Feist, Andreas Hafner, Meike Simon, Duc N. Tran, Daniel M. Allwood, David C. Blakemore, and Steve V. Ley of the University of Cambridge devised a synthetic strategy that makes use of a transient boronic [acid](#) intermediate which they had observed in their previous research. Their synthetic strategy uses a flow chemistry technique that allows them to safely work with diazo compounds. They have devised a general strategy in which they can add multiple, different diazo compounds to various boronic acid intermediates to form a variety of complex organic structures. Their work appears in *Nature Chemistry*.

Steven Ley's group has perfected a flow chemistry technique that allows them to safely work with diazo compounds, which are normally highly reactive and toxic. The technique ensures that only small amounts of the diazo compound are produced at one time and subsequently reacted. Furthermore, the toxic compounds are completely contained within the

apparatus. In previous studies, they observed that in their metal-free cross coupling reactions using their flow [chemistry technique](#), a transient boronic acid intermediate is produced. In this study they sought to use it as a precursor for synthetic reactions.

The first step was to isolate the boronic acid species in an effort to study its behavior and versatility. Boronic acids are highly reactive, but their corresponding esters are less so. Battilocchio, et al. isolated the boronic acids as a pinacol ester derivative to investigate the effects of adding various diazo compounds. Furthermore, they also optimized the reaction by changing the rate and amount of diazo compound that is added to the boronic acid.

The diazo compound and the boronic acid can house a variety of organic substituents, leading to the possibility of creating a variety of diverse organic compounds. Once the diazo compound reacts with the boronic acid, trapping the newly formed boronic acid with pinacol or protodeboronation of this intermediate provides the final product.

Their method allowed an iterative process whereby different diazo compounds were consecutively added to the initial boronic acid. They were able to successfully generate complex [organic compounds](#) with up to three newly formed C-C bonds. These compounds would be difficult to produce using traditional methods.

Finally, they demonstrated the versatility of their approach by intercepting the boronic acids with aldehydes. This rational was used to make a precursor to Bakuchiol, a naturally occurring product used in some pharmaceuticals.

Battilocchio, et al. demonstrated using flow generated diazo compounds that they are able to add one, two, or three different organic components to a transient boronic acid intermediate. Their technique allows for the

synthesis of a variety of complex organic [compounds](#) via a C-C addition reaction that does not involve the use of [precious metals](#).

More information: Claudio Battilocchio et al. Iterative reactions of transient boronic acids enable sequential C–C bond formation, *Nature Chemistry* (2016). [DOI: 10.1038/nchem.2439](https://doi.org/10.1038/nchem.2439)

Abstract

The ability to form multiple carbon–carbon bonds in a controlled sequence and thus rapidly build molecular complexity in an iterative fashion is an important goal in modern chemical synthesis. In recent times, transition-metal-catalysed coupling reactions have dominated in the development of C–C bond forming processes. A desire to reduce the reliance on precious metals and a need to obtain products with very low levels of metal impurities has brought a renewed focus on metal-free coupling processes. Here, we report the in situ preparation of reactive allylic and benzylic boronic acids, obtained by reacting flow-generated diazo compounds with boronic acids, and their application in controlled iterative C–C bond forming reactions is described. Thus far we have shown the formation of up to three C–C bonds in a sequence including the final trapping of a reactive boronic acid species with an aldehyde to generate a range of new chemical structures.

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