Conference paper

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When diazo compounds meet with organoboron compounds

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Abstract: Transition-metal free reactions of diazo compounds with organoboron compounds provide some unique approaches for the formation of C–C, C–B and C–Si bonds. With *N*-tosylhydrazones as the precursors for non-stabilized diazo compound, this type of reaction becomes practically useful in organic synthesis. Transition-metal-free synthetic methodologies for borylation, *gem*-diborylation, *gem*-silylborylation arylation, 2,2,2-trifluoroethylation and *gem*-difluorovinylation have been successfully developed.

Keywords: C–B bond formation; diazo compounds; IMEBORON-16; organoboron compounds; transition-metal-free reaction.

Introduction

Diazo compounds are best known as metal carbene precursors in transition-metal-catalyzed reactions. The classic metal carbene transformations, such as cyclopropanations and C–H bond insertions, have been well-established as useful methods in organic synthesis [1–4]. More recently, transition-metal-catalyzed cross-coupling with carbene precursors have attarcted considerable attentions [5–11].

In addition to serve as metal carbene precursors, diazo compounds also function as nucleophiles because of the electron-rich character of the carbon bearing the diazo group [12]. An interesting reaction of diazo compounds as nucleophiles is the interaction with electron-defficient boron, generating a *tetra*-coordinated boron complex. Subsequently, one of the substituents (the X group) migrates from boron to carbon center, with simutanoues release of dinitrogen. The process can be considered as a formal carbene insertion into the B–X bond of the organoboron reagent (Scheme 1) [13].

Results and discussion

The reaction of α-diazocarbonyl compounds with organoborons was previously reported to form C–C bonds between alkyl or aryl and an α carbon of carbonyl group. Hooz and Linke [14] established the alkylation of diazonitrile, ethyldiazoacetate and diazoketones by means of trialkylboranes (Scheme 2a). The reactions reported by Hooz and Linke were limited by narrow scope and low efficiency. Further improvement was made by Brown, Hooz and coworkers by using dialkylchloroboranes, and alkyl- or aryldichloroboranes, which are more reactive boron reagents toward diazo compounds (Scheme 2b and c) [15, 16].

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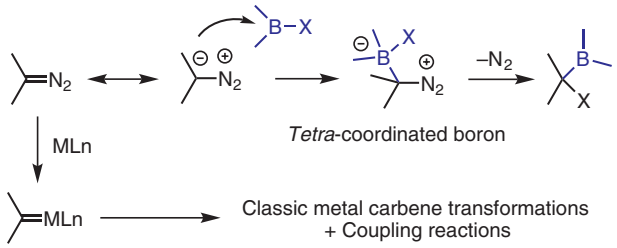
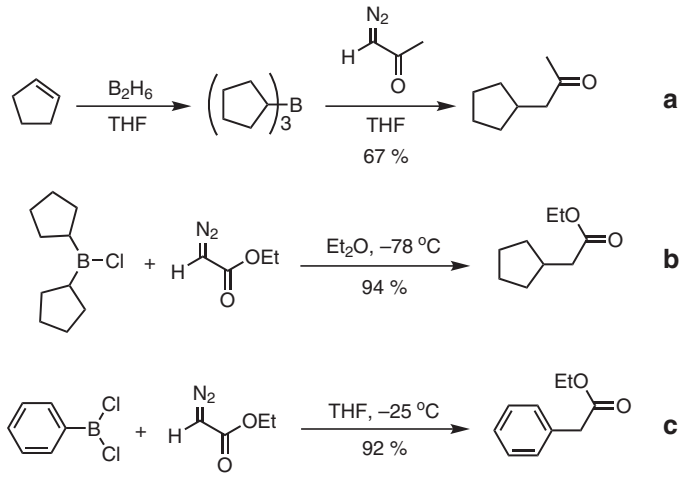


Scheme 1: Diazo compounds as nucleophiles vs. as carbene precusors.



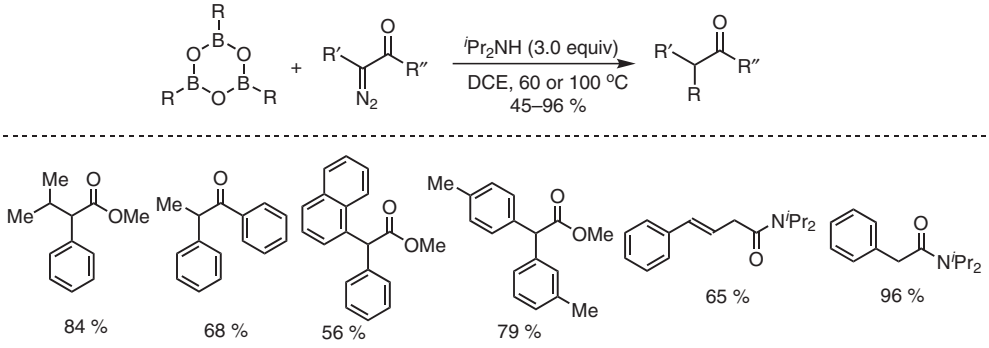
Scheme 2: The pioneering work on the reaction between diazo compounds and organoborons.

However, these otherwise very attractive transition-metal-free C–C bond forming reactions have received limited attention following therir publications, presumably because of the toxic and unstable boron compounds being used, and the reactions have to be carried out under stringent conditions. Besides, the scope of diazo substrates is very limited. Mechanistically, these reactions are initiated by the nucleophilic attack of diazo substrate to boron. Thus, increasing the electonpositivity in the boron center and/or increasing the nucleophilicity of diazo substrate should enhance the reaction. In view of the facts that organoboronic acids and their derivatives, which are usually stable, non-toxic and easily available, have gained tremendous popularity among synthetic organic community, it is thus worthwhile to investigate the reaction of diazo compounds with boronic acids and their derivatives.

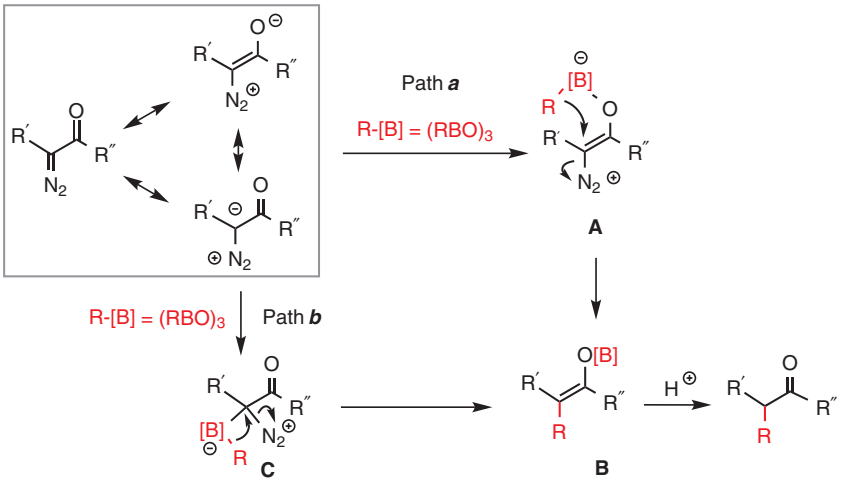
In the process of studying a Pd-catalyzed reaction of arylboronic acid with diazocarbonyl compounds [17], we have found that the C–C bond forming reaction occurred under transition-metal-free conditions. The reaction with phenylboron pinacolate gave no product, while the reaction with boroxine afforded moderate yield. The reaction is quite general in terms of the structure of diazocarbonyl compounds (Scheme 3) [18].

Two reaction pathways are proposed to account for the reaction (Scheme 4). In path ***a***, the oxygen anion functions as a nucleophile to coordinate with the boron reagent to generate **A**, while in path ***b***, the carbon nucleophile interacts with the boron to generate **C**, both giving boron enolate **B** as the intermediate.

In the same year, Barluenga and co-workers reported the transition-metal-free couplings of hydrazones with arylboronic acids. Since *N*-tosylhydrazone is easily derived from the corresponding ketones or aldehydes, the reaction is highly attractive as a C–C bond forming method [19]. This reaction follows the same



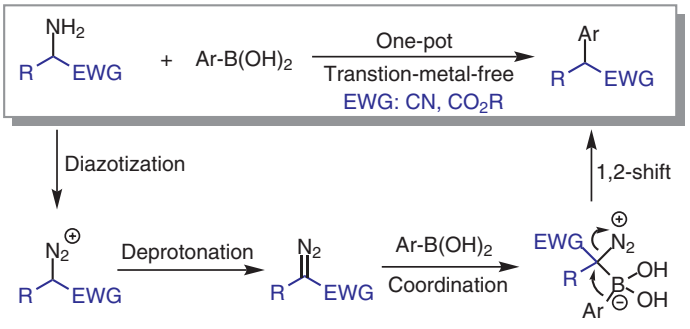
Scheme 3: Metal-free arylation and vinylation of α-diazocarbonyl compounds with boroxines.



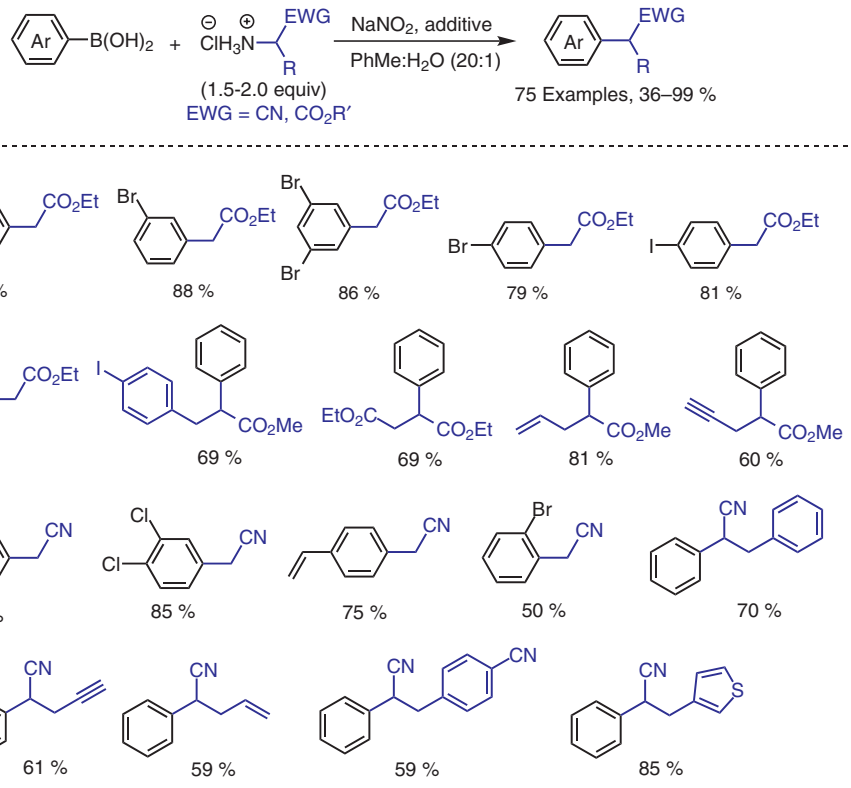
Scheme 4: Proposed reaction mechanism.

mechanism as described in Scheme 4, except that in this case the non-stablized diazo intermediate is generated in situ through Bamford–Stevens reaction [20, 21].

We have conceived that this chemistry may be expanded by empoying other methods of in situ generation of diazo intermediates. As shown in Scheme 5, under almost neutral reaction conditions, the α-aminoesters, α-aminonitriles can be converted into the diazo intermediates through diazotization and deprotonation. The reaction of this diazo intermediate with arylboronic acid forms C–C bond. The entire



Scheme 5: Deaminative coupling of α-aminoesters and nitriles with arylboronic acids.



Scheme 6: Selected examples of the transition-metal-free deaminative coupling.

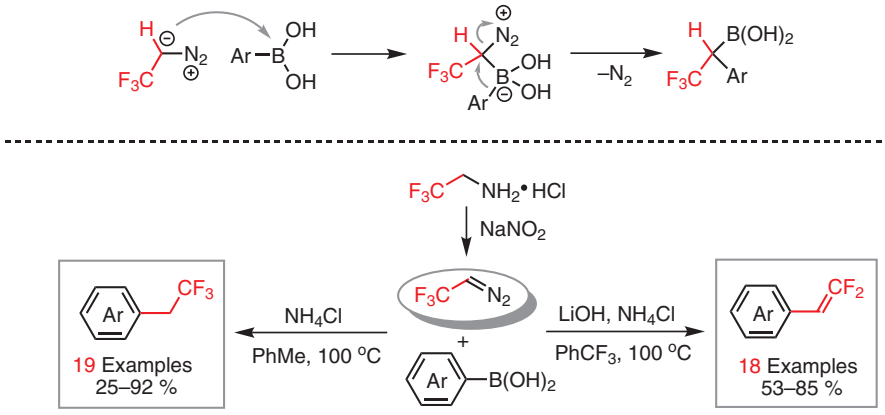
process is a transition-metal-free deaminative coupling of α-aminoesters, α-aminonitriles with arylboronic acids. The reaction conditions are very mild under almost neutral conditions [22].

The reaction shows excellent functional group tolerance. In the report 75 examples of the reaction have been demonstrated, and some reactions have been carried out in a gram-scale. Some selected examples have been summarized in Scheme 6. Since the reaction is under tranistion-metal-free conditions, various useful functional groups such as halogen substituents can be tolerated, which is beneficial for the further transformations. This is a highly reliable method for the synthesis of α-aminoesters and α-aminonitriles. These compounds have attracted attentions because of their importance, and much efforts have been devoted to the synthetic method development, mostly by employing transition-metal-catalyzed approaches.

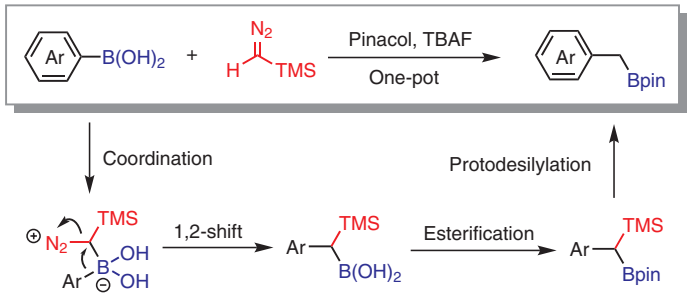
Similarly, we can use 2,2,2-trifluorodiazoethane, generated from the corresponding amine, to develop a method for trifluoroethylation and *gem*-difluorovinylation of organoboronic acids, depending on the reaction conditions (Scheme 7) [23]. The reactions follow similar mechanism, except the final terminating step. Under weak acidic conditions, the reaction was terminated by protonation to afford trifluoroethylation products. Under week basic conditions with LiOH as the additive, the reaction is terminated by elimination of fluoride rather than protonation, giving *gem*-difluorovinylation product. Both reactions shows wide substrate scope.

Furthermore, with trimethylsilyldiazomethane ($TMSCHN_2$), we could develop a method for homologating the arylboronic acids, by employing very similar method. The transformation is shown in Scheme 8. First, the coordination of the diazo substrate to boronic acid, followed by 1,2-shift, esterification with pinacol, and finally protodesilylation to afford the pinacol benzylboronates. The reaction gave the homologation products in moderately good yields [24].

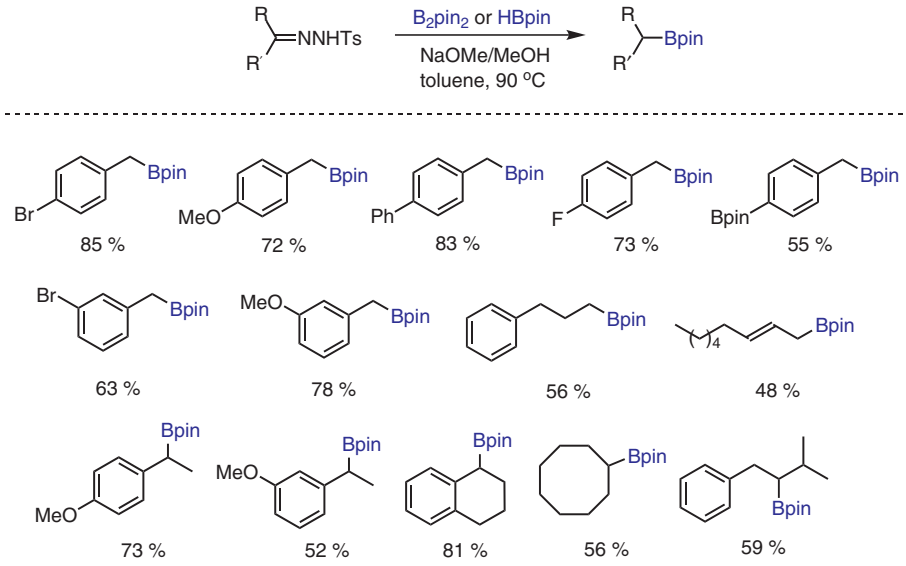
To further develop the chemistry, we can consider varying the migrating group X, as shown in Scheme 1. An interesting development along this line is the use of diboron or borane reagent, in which two C–B bonds can be formed. Thus, with *N*-tosylhydrazone as the precusor of diazo compounds, we have developed



Scheme 7: 2,2,2-Trifluoroethylation and *gem*-difluorovinylation of organoboronic acids with 2,2,2-trifluorodiazoethane.

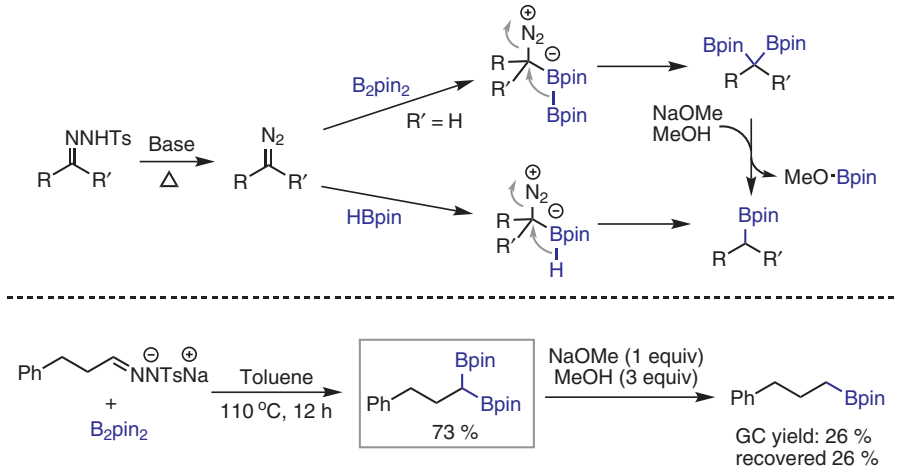


Scheme 8: Homologation of arylboronic acid.

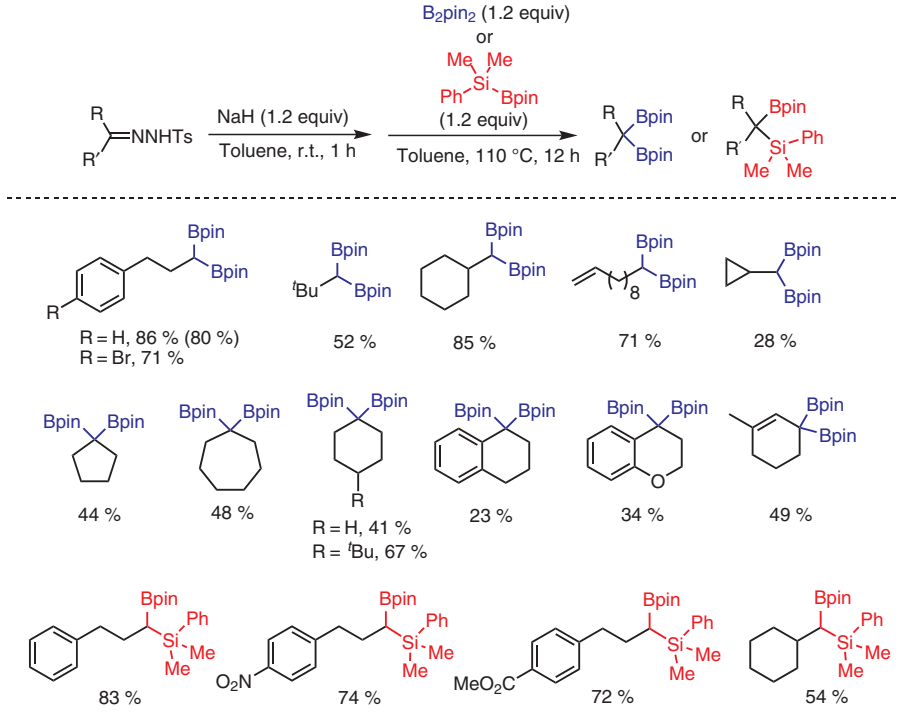


Scheme 9: Transition metal-free synthesis of pinacol alkylboronates from tosylhydrazones.

a transition-metal-free C–B bond forming transformations. The reaction represents an alternative access toward pinacol alkylboronates. The reaction works well over a wide range of *N*-tosylhydrazone substrates, with both diboron and also borane reagents (Scheme 9) [25].



Scheme 10: The mechanistic rationale and control experiments.



Scheme 11: *gem*-Diborylation and *gem*-silylborylation of *N*-tosylhydrazone.

The mechanistic rationale is shown in Scheme 10. The diazo intermediate is first generated in situ in the presence of base, reacting with borone, then 1,2-hydrogen shift occurs to give the product directly. While in the case of B_2pin_2, 1,2-Bpin shift occurs to afford *gem*-diboron intermediate, which is then followed by protodeborylation to give the product. In the absence of proton source, we could isolate the *gem*-diboron product in 73 % yield, which was a strong evidence to support the proposed reaction mechanism.

On the other hand, the mechanistic experiment demonstrates the potential of developing a method for the synthesis of *gem*-diboron compounds. Indeed, under the conditions that proton source is absent, the *gem*-diboron compounds could be obtained in moderately high yields. Very similarly, *gem*-silylborylation compounds could be obtained by using silylborane (pinBSiMe$_2$Ph). The reaction shows wide substrate scope for both cases (Scheme 11) [26].

Conlusions

From the reactions presented in this lecture, it can be concluded that the reaction between nucleophilic diazo carbon and electron-deficient boron center is a general process and can be utilized in various transformations. In particular, the 1,2-shift of the substituent from boron to the diazo carbon generates C–C, C–B and C–Si bonds. The interemdirates can be further applied to various transformations. By using tosylhydrazone as the non-stablized diazo compound precursors, this type of reaction becomes practically useful in organic synthesis [27–33].

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