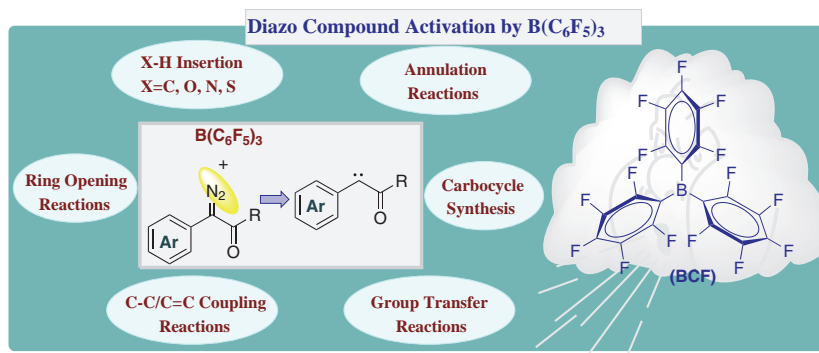


Activation of Diazo Compounds by Fluorinated Triarylborane Catalysts

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Abstract The diverse applicability of diazo compounds as versatile reagents has enlarged the chemical toolbox in organic synthesis. Over the past few decades, transition-metal-catalyzed diazo compound activation has ignited the classical synthetic methodology via utilizing highly reactive metal carbenoid species. Many reviews have also appeared in the literature that show the advantages and disadvantages of metal-catalyzed activation of diazo compounds. Recently, tris(pentafluorophenyl)borane-mediated diazo activation reactions has remodeled this research area due to the potential for mild, environmentally friendly, metal-free, nontoxic reaction conditions, and the diverse reactivity patterns of boranes towards diazo compounds. In this review, we discuss the reactivity of the boron–diazo precursor adducts with compounds using catalytic and stoichiometric halogenated triarylboranes and, the mechanism of N_2 release from the diazo reagent. This generates the reactive carbene species as a key intermediate which can further be exploited for O–H, N–H, S–H, and C–H insertions, azide insertion, carbonate transfer, C–C and C=C bond forming reactions, [2+2] or [2+4] cascade cyclization reactions, annulation reactions, etc.

- 1 Introduction
- 2 Diazo Activation Using Stoichiometric Boranes
- 3 Diazo Activation Using Catalytic $B(C_6F_5)_3$
- 4 $B(C_6F_5)_3$ -Catalyzed Diazo Activation Reactions
- 5 Conclusions

Key words diazo activation, α -diazo ester, carbene formation, borane, catalysis

1 Introduction

Diazo compounds are useful synthons that have served as a carbene source for a variety of functionalization reactions via the carbene transfer strategy.^{1–4} In general, transi-



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tion-metal-catalyzed carbenoid species have attained enormous success due to the high reactivity of metal carbenoids. Many reviews have also covered metal-catalyzed diazo activation reactions for the construction of nitrogen and non-nitrogen-based organic motifs. But the major disadvantages associated with these classical metal-catalyzed diazo activation reactions are the post-reaction contamina-

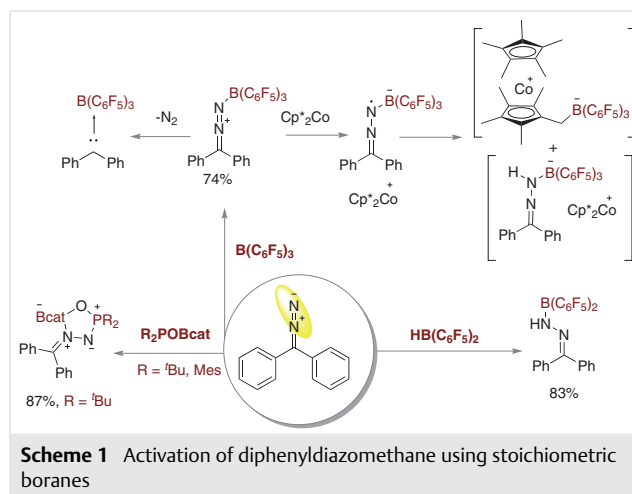
tion due to the use of precious and toxic metals and selectivity issues due to the high reactivity of metal carbenoid species that often affect the design and construction of drug molecules.^{5,6} To address these issues, in recent investigations, borane catalysis has been employed as a transition-metal-free and environmentally friendly approach.^{7,8} In particular, the continued effort to develop metal-free diazo activation reactions using tris(pentafluorophenyl)borane [B(C₆F₅)₃] as a catalyst has partially resolved the selectivity and toxicity issues.⁸ Comparative studies between metal carbenoid and metal-free carbene generation disclosed that synergic and metal-carbon (M-C) back-bonding interactions control the high reactivity of a metal carbenoid, whereas the high Lewis acidity of B(C₆F₅)₃ and the vacant p-orbital in the boron center promotes boron coordination with the diazo compounds and thus activates the diazo compounds.⁹

In this review, we have mainly emphasized the reactivity of diazo compounds in the presence of catalytic and stoichiometric tris(pentafluorophenyl)borane as well as related halogenated triarylboranes [B(Ar^X)₃]. The binding sites of the borane with the diazo compound and the mode of N₂ release are also discussed. We have catalogued the reactions by reaction type including O-H,¹⁰ N-H,^{11,12} S-H,¹³ and C-H insertions,^{14,15} azide insertion,¹⁶ carbonate transfer,¹⁷ C-C and C=C bond-forming reactions,^{18,19} cascade reactions,^{20,21} and annulation reactions,^{22,23} by utilizing diazo compounds as a carbene synthon in the presence of the borane B(C₆F₅)₃ as a metal-free catalyst.

2 Diazo Activation Using Stoichiometric Boranes

Although metal-catalyzed diazo activation has been well studied, the mechanism of activation of diazo compounds using Lewis acidic boranes has been less well explored. In this regard, the use of stoichiometric and catalytic reactions using boranes has shown a significant breakthrough in understanding their mode of activation. Although the reaction of diazo compounds with BF₃·OEt₂ has been previously studied,^{24,25} many new contributions to the field have emerged using triarylboranes, which is the focus of this review. In 2017, Stephan and co-workers reported that the Lewis acid-base adduct of Lewis acidic HB(C₆F₅)₂ and B(C₆F₅)₃ with the diazo compound diphenyldiazomethane (Ph₂CN₂) was important in its activation. However, the stoichiometric addition of B(C₆F₅)₃ and Ph₂CN₂ at -78 °C led to the N_{diazomethane}→B adduct [Ph₂CN₂B(C₆F₅)₃] in 74% yield (Scheme 1).²⁶ The N→B adduct was confirmed through ¹¹B and ¹⁹F NMR spectroscopic analysis. Evolution of N₂ from the Ph₂CN₂B(C₆F₅)₃ adduct at elevated temperature was also observed to furnish the proposed carbene C_{carbene}→B adduct Ph₂CB(C₆F₅)₃. DFT analysis supported the formation of the C_{carbene}→B adduct; evolution

of N₂ from Ph₂CN₂B(C₆F₅)₃ was found to be exergonic by 53 kcal/mol. The calculated bond length for C_{carbene}→B was found to be 1.66 Å, which resembles the C-B bond length found in B(C₆F₅)₃, and the calculated bond order was 0.64 for the C_{carbene}-B single bond. It was hypothesized that the steric bulk of the arene rings on Ph₂CN₂ prohibited the carbene insertion into B-C bonds. On the other hand, HB(C₆F₅)₂ in the presence of diphenyldiazomethane showed an unusual 1,1-hydroboration reaction to produce the corresponding compound having an N-N bond in 83% yield (Scheme 1).

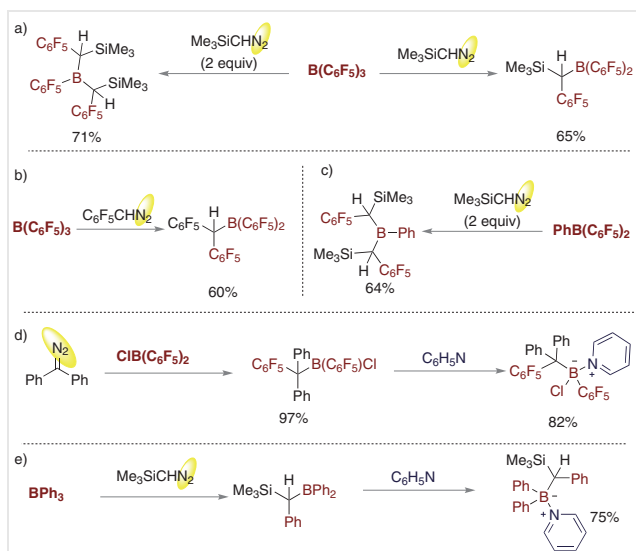


Stephan and co-workers also extended their study of diphenyldiazomethane and B(C₆F₅)₃ in the presence of Cp*₂Co. It was noted that diphenyldiazomethane, B(C₆F₅)₃ and Cp*₂Co produced a mixture of [Cp*₂Co][Ph₂CNNHB(C₆F₅)₃] and [Cp*₂Co(C₅Me₄CH₂B(C₆F₅)₃)]. However, a single electron transfer (SET) process was assumed to be operative from Cp*₂Co to Ph₂CN₂B(C₆F₅)₃ for the formation of [Cp*₂Co(C₅Me₄CH₂B(C₆F₅)₃)] (Scheme 1).²⁷

In 2020, Stephan also found that frustrated Lewis pairs (FLPs) R₂POBcat (R = ^tBu, mesityl, cat = catechol) derived from phosphine oxides and ClBcat reacted with Ph₂CN₂ to form the compound Ph₂C(N₂)BcatOPR₂ (R = ^tBu) in 87% yield (Scheme 1).²⁸ Unfortunately, a problem with isolation prevented the purification of the compound Ph₂C(N₂)BcatOPR₂ (R = mesityl), nevertheless single crystal X-ray analysis helped to assign the structure of the compound.

As shown in Scheme 2, several electrophilic boranes have been reacted with electronically varied diazomethanes to provide sterically demanding borane derivatives in high yields.²⁹ The new borane (Me₃SiCH(C₆F₅))B(C₆F₅)₂ was produced in 65% yield when a 2 M hexane solution of Me₃SiCH(N₂) interacted rapidly with stoichiometric amounts of B(C₆F₅)₃ in CH₂Cl₂ at -78 °C via insertion of Me₃SiCH(N₂) into a C-B bond. The product was purified by recrystallization. Again, the addition of 2 equivalents of Me₃SiCH(N₂) with B(C₆F₅)₃ at -78 °C provided the double in-

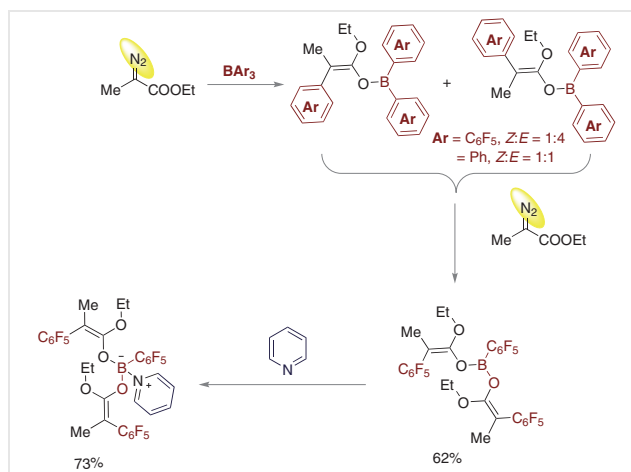
sersion product $(\text{Me}_3\text{SiCH}(\text{C}_6\text{F}_5))_2\text{B}(\text{C}_6\text{F}_5)$ in 71% yield (Scheme 2a). Likewise, $(\text{C}_6\text{F}_5)\text{CHN}_2$ reacted with $\text{B}(\text{C}_6\text{F}_5)_3$ affording the compound $(\text{C}_6\text{F}_5)_2\text{CHB}(\text{C}_6\text{F}_5)_2$ in 60% yield (Scheme 2b). Furthermore, the stoichiometric addition of $\text{PhB}(\text{C}_6\text{F}_5)_2$ with $\text{Me}_3\text{SiCH}(\text{N}_2)$ resulted in the double insertions of the carbene derived from $\text{Me}_3\text{SiCH}(\text{N}_2)$ into the B– C_6F_5 bonds which led to the formation of $(\text{Me}_3\text{SiCH}(\text{C}_6\text{F}_5))_2\text{BPh}$ in 64% yield (Scheme 2c). It was also found that mixing $\text{Me}_3\text{SiCH}(\text{N}_2)$ and $\text{ClB}(\text{C}_6\text{F}_5)_2$ showed a complex reaction mixture, but when $\text{ClB}(\text{C}_6\text{F}_5)_2$ was reacted with Ph_2CN_2 the compound $(\text{C}_6\text{F}_5)\text{ClB}(\text{C}_6\text{F}_5)_2$ was afforded in 97% yield (Scheme 2d). This product coordinated with the Lewis base pyridine (Py) to produce a salt $(\text{C}_6\text{F}_5)\text{ClB}(\text{Py})(\text{C}_6\text{F}_5)_2$ in 82% yield. In addition, the stepwise reaction of the weaker Lewis acid BPh_3 with $\text{Me}_3\text{SiCH}(\text{N}_2)$ and pyridine yielded compounds $\text{Me}_3\text{SiCH}(\text{Ph})\text{BPh}_2$ and $\text{Me}_3\text{SiCH}(\text{Ph})\text{B}(\text{Py})\text{Ph}_2$ in 75% yield (Scheme 2e).³⁰



Scheme 2 Stoichiometric reactions of boranes and diazo esters

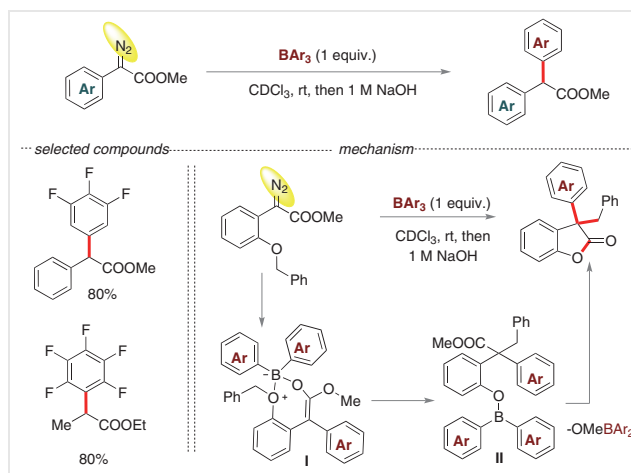
Stephan and co-workers showed that the stoichiometric addition of $\text{B}(\text{C}_6\text{F}_5)_3$ in ethyl α -diazopropanoate produced an *E* and *Z* mixture of boron enolates, which were subsequently converted into the double insertion product in 62% yield in the presence of another equivalent of ethyl α -diazopropanoate (Scheme 3).³⁰ The resulting enolate product reacted with pyridine leading to the corresponding adduct in 73% yield. Thus, this strategy illustrates the diverse reactivity of substituted boranes via the formation of multiple bonds, including B–C, B–H, and B–Cl, through the reactions of boranes with diazo compounds.

We have also investigated the stoichiometric addition of Lewis acidic boranes BAR_3 with α -diazo carbonyl compounds (1:1 ratio) in the aryl transfer reaction (Scheme 4).³¹ It was found by X-ray diffraction analysis that the triarylborane coordinated to the diazo compound through ester



Scheme 3 Stephan's work on the stoichiometric reaction of BAR_3 and ethyl α -diazopropanoate

O→B adduct formation rather than N→B formation as observed by Stephan and co-workers for Ph_2CN_2 .²⁶ Subsequently, at room temperature or higher, N_2 release rapidly occurred and the aryl group migrated from BAR_3 to the carbene carbon center yielding a similar borane enolate to that observed by Stephan and co-workers (Scheme 3).³⁰ The aryl migration efficiency was found to be improved by increasing the Lewis acid strength in the order of $\text{BPh}_3 < \text{B}(4\text{-FC}_6\text{H}_4)_3 < \text{B}(2,6\text{-F}_2\text{C}_6\text{H}_3)_3 < \text{B}(\text{C}_6\text{F}_5)_3 < \text{B}(3,4,5\text{-F}_3\text{C}_6\text{H}_2)_3$. We also found that the borane enolate generated from an α -diazo ester and borane could participate in addition reactions to carbonyls, anhydrides, nitriles, esters, isocyanates to offer a wide range of α -aryl functionalized β -hydroxy and β -keto esters.³² Using the new borane $\text{B}(3,4\text{-Cl}_2\text{C}_6\text{H}_3)_3$ with $(4\text{-MeOC}_6\text{H}_4)\text{C}(\text{N}_2)\text{CO}_2\text{Me}$, the aryl transfer $(4\text{-MeOC}_6\text{H}_4)\text{C}(3,4\text{-Cl}_2\text{C}_6\text{H}_3)\text{CO}_2\text{Me}$ product was isolated in 92% yield following work up. This product is a potential intermediate in the



Scheme 4 Stoichiometric reactions of BAR_3 and α -aryl- α -diazo esters

synthesis of diclofensine, an antidepressant developed by Hoffmann-LaRoche, and has been previously synthesized by a rhodium-catalyzed process.³³ Alternatively, when 2-benzyloxy-substituted diazo ester derivatives were employed in the standard reaction conditions, unexpected reactivity was observed through the formation of 3,3-disubstituted benzofuran-2(3*H*)-ones (Scheme 4). It was proposed, by detailed NMR studies and crossover experiments, that an unpredicted intramolecular attack of boron enolate **I** on the benzyl group followed by an aryl group transfer led to the desired product via intermediate **II**. Interestingly, this report disclosed the metal-free approach for the formation of sterically hindered C3 disubstituted lactones in a single-step process.

3 Diazo Activation Using Catalytic B(C₆F₅)₃

Most of the reactions involving Lewis acidic B(C₆F₅)₃ and diazo compounds have employed donor/acceptor-substituted diazo compounds, such as α -aryl- α -diazo esters, due to their higher stability. It is not surprising therefore that most studies involving diazo activation using B(C₆F₅)₃ have focused on α -aryl- α -diazo ester compounds. In general two binding modes of α -aryl- α -diazo esters with catalytic B(C₆F₅)₃ have been suggested in the literature including N_{diazo}→B or O_{carbonyl}→B adduct formation. However, the boranes were found to preferentially bind to the more Lewis basic oxygen of the carbonyl group to form the O→B adduct. This was found both experimentally and computationally (Figure 1).^{31,34,35} By DFT studies the C–N bond in the boron-coordinated diazo ester is longer and weaker (1.334 Å) than in the free uncoordinated diazo ester (1.318 Å).¹⁴ In addition, a shortening of the C–C bond length from 1.470 Å to 1.436 Å was also observed for the O→B adduct. As a result, release of nitrogen becomes easier. A subsequent study using DFT calculations with various donor/acceptor diazo compounds implied that the ease of N₂ release from the O→B adduct depended upon the electronic effect on the aryl ring (Ar) or the carbonyl group (e.g., ester, aldehyde, ketone, etc.) of the diazo ester (Figure 1b).³⁵ The calculations showed that there is a strong correlation between the reaction free energy of carbene formation and the activation barrier to N₂ release. Thus, generally there was a lower activation barrier to the process when a more stable carbene is generated. In the absence of a borane catalyst, it was demonstrated that the release of N₂ depends on only the substituents on the aryl ring rather than the R group in the donor/acceptor diazo compound. But, in the presence of B(C₆F₅)₃, the influence of aryl substituent and R group becomes significant for the generation of stable carbene→borane species. Indeed, aryl rings having a strong π -donor effect and the R groups with a weaker π -donor influence gave stronger binding ability of the carbene with the borane, thus improving the catalyst's efficiency in the diazo activa-

tion step. It is concluded that the formation of a stable carbene is expected to be thermodynamically favorable in the case of a stronger adduct by lowering the activation energy of N₂ release.

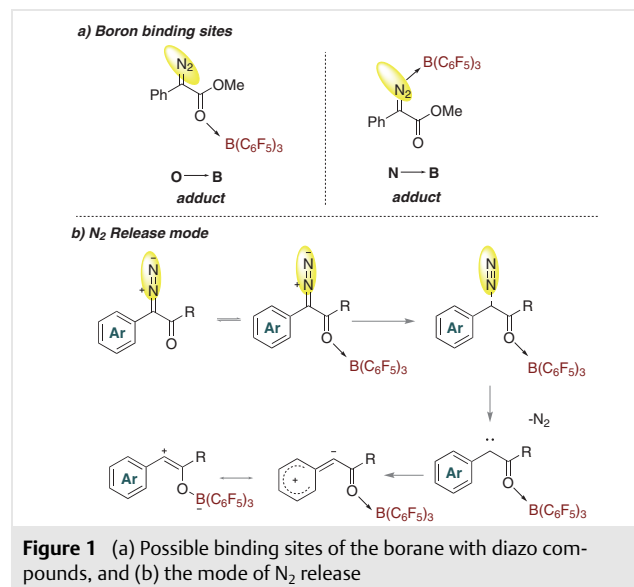


Figure 1 (a) Possible binding sites of the borane with diazo compounds, and (b) the mode of N₂ release

The stability of the carbene in the presence of a Lewis acidic borane is increased due to additional resonance stabilization as shown in Figure 1.

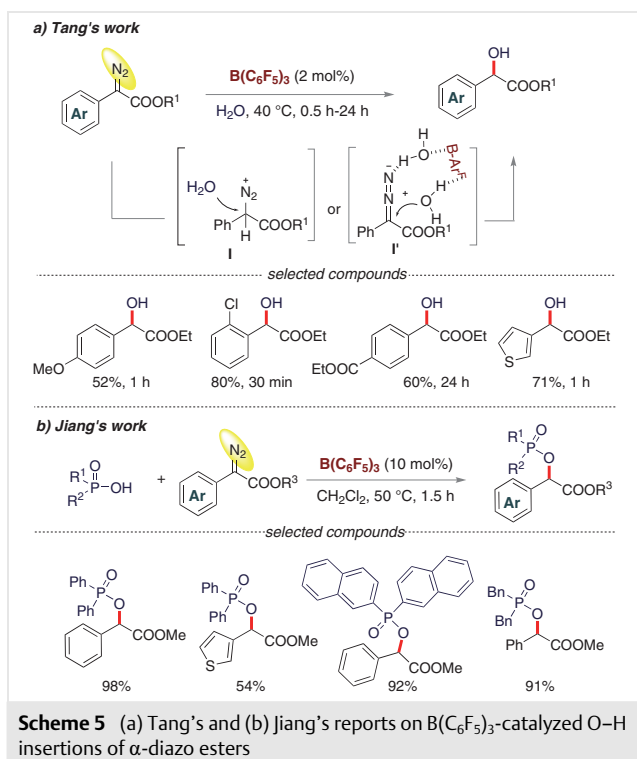
4 B(C₆F₅)₃-Catalyzed Diazo Activation Reactions

As discussed in Sections 2 and 3, reactive carbene species generated from the diazo precursor are electron deficient and are readily involved in various elegant transformations such as insertion reactions, cyclopropanation, annulation, and cascade reactions.

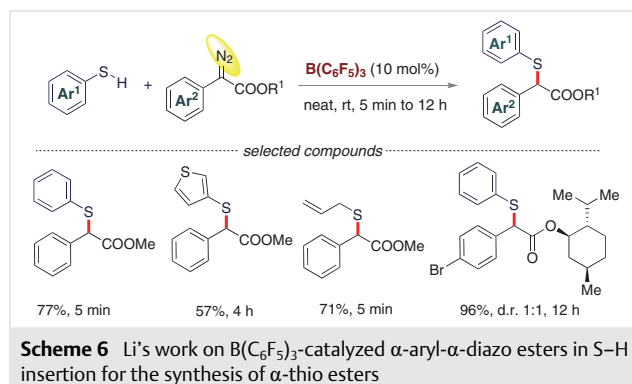
4.1 X–H (X = O, N, C, and S) Insertion Reactions

In 2018, Tang and co-workers introduced the B(C₆F₅)₃-catalyzed O–H bond insertion reactions of α -diazo esters in the presence of water as a hydroxy source to yield a series of α -hydroxy esters (Scheme 5a).¹⁰ Various α -diazo esters bearing OMe, Cl, and COOMe substituents at the aryl group and a thiophene-based α -diazo ester effectively participated in the O–H insertion reaction producing the corresponding products in reasonable yields. It should be noted that the Lewis acidic borane B(C₆F₅)₃ in the presence of water acts as Brønsted acid. As depicted in Scheme 5a, two different possible mechanisms are proposed. Either B(C₆F₅)₃·nH₂O assists in the protonation of the diazo ester to produce intermediate **I**, which is then attacked by water, or conversely, as demonstrated in intermediate **II**, the borane

serves as a bifunctional catalyst that could help both protonation and nucleophilic attack by water to produce the desired hydroxylated product. It was assumed that noncovalent interactions including N...H, F...H hydrogen bonding interactions, and O...B interactions associated with the water molecules could promote the nucleophilic attack. In 2021, α -phosphoryloxy carbonyl compounds were also reported by Jiang and co-workers (Scheme 5b).³⁶ They showed that various phosphinic acids including di(naphthalen-2-yl)phosphinic acid, and dibenzylphosphinic acid could be used as O–H insertion precursors in the presence of 10 mol% $B(C_6F_5)_3$ as a catalyst to afford C–O bonded products (α -phosphoryloxy carbonyls) in good to excellent yields.



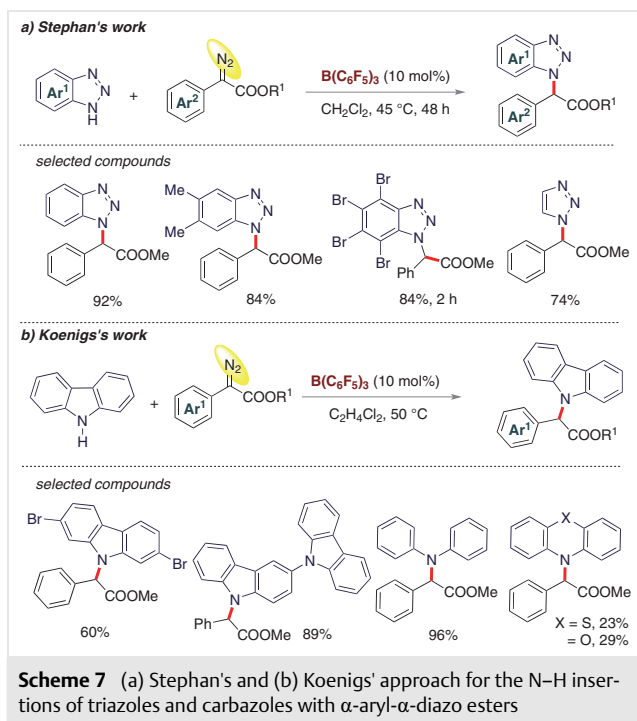
The borane-catalyzed S–H insertion reaction of thiols with α -aryl- α -diazo esters has also been demonstrated to form a new C–S bond. Li and co-workers have shown that the neat mixing of thiols with α -aryl- α -diazo esters produced the α -thio ester as a product (Scheme 6).¹³ Various thiols including thiophenol, thiophene-3-thiol, and propene-1-thiol effectively participated in the S–H insertion reaction to yield the desired α -thio ester derivatives as shown in Scheme 6. It is predicted that the formation of the reactive carbene intermediate is expected to be involved to promote the addition reaction with thiols followed by proton transfer to afford the final product.



Selective N-alkylation of benzotriazoles is challenging due to selectivity issues generating a mixture of N1 and N2-alkylated benzotriazoles.³⁷ In 2021, Stephan and co-workers successfully resolved this selectivity issue with the help of a borane catalyst. They found that N–H insertion of benzotriazoles was assisted by a borane enolate (O→B adduct) from $B(C_6F_5)_3$ and α -aryl- α -diazo esters which offered the site-selective N1-alkylation of various substituted benzotriazoles and triazoles (Scheme 7a).¹²

At the same time, Koenigs and co-workers developed a similar strategy for N–H insertion of carbazoles with α -aryl- α -diazo esters using the same borane as a metal-free catalyst (Scheme 7b).¹¹ Phenothiazines and phenoxazines also took part in the N–H insertion reaction to give the corresponding products in good to excellent yields. As proposed by the authors, the coordination of the carbonyl oxygen atom in the α -diazo ester substrate with the borane made the carbene a hard electrophile, which was consequently attacked by the hard nucleophilic nitrogen atom of the carbazole, according to the HSAB (Hard Soft Acid Base) principle.³⁸ These strategies demonstrate the development of a novel and metal-free borane-catalyzed C–N bond-forming reaction that could potentially substitute the more toxic and expensive transition-metal-catalyzed C–N coupling reactions in the area of N-heterocycle synthesis.

Activation of C–H bonds over the cross-coupling of C–X bonds has become attractive in synthetic transformations as it can be performed directly without using any prefunctionalized starting materials. However, while metal-catalyzed C–H activations are well-documented in the literature, the metal-free C–H bond functionalization using Lewis acids is not as extensively explored in the modern organic synthetic community. In this regard, C–H functionalization using the concept of O→B adduct formation between a diazo compound and a borane has been recently implemented. Indeed, Zhang and co-workers demonstrated that the borane-catalyzed *ortho* C–H functionalization of unprotected phenols could be accomplished with α -aryl- α -diazoacetates (Scheme 8a).¹⁵ They proposed that an intermolecular hydrogen bonding interaction between a fluorine atom of

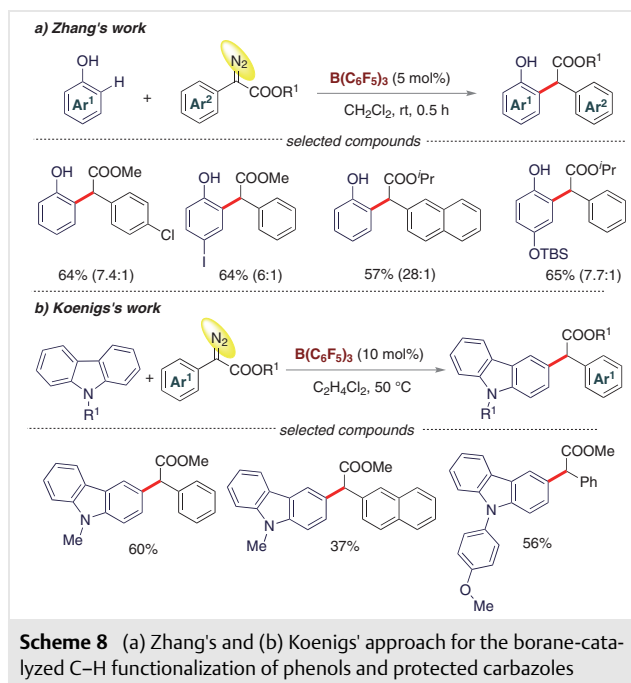


the $B(C_6F_5)_3$ catalyst and the phenolic O–H group is operative in attaining high chemoselectivity. In turn, control experiments including deuterium labeling on phenol (C_6H_5OD) confirmed that the phenolic O–H was the proton source in this reaction as a deuterium labeled product was found. The reaction with anisole instead of phenol gave the *ortho* and *para* C–H functionalized product in poor yields (13% and 9% yields, respectively), indicating the importance of a hydrogen-bonded assisted mechanism.

On the other hand, Koenigs and co-workers observed that *N*-protected carbazoles could exhibit C3–H functionalization with α -aryl- α -diazo esters to produce various C–C coupled products (Scheme 8b).¹¹ As demonstrated in Scheme 8, various *N*-protected carbazoles provided the corresponding C–H functionalized products in reasonable yields. Thus, these studies showed that the implementation of metal-free borane catalysts could potentially widen the synthetic scope of chemoselective reactions.

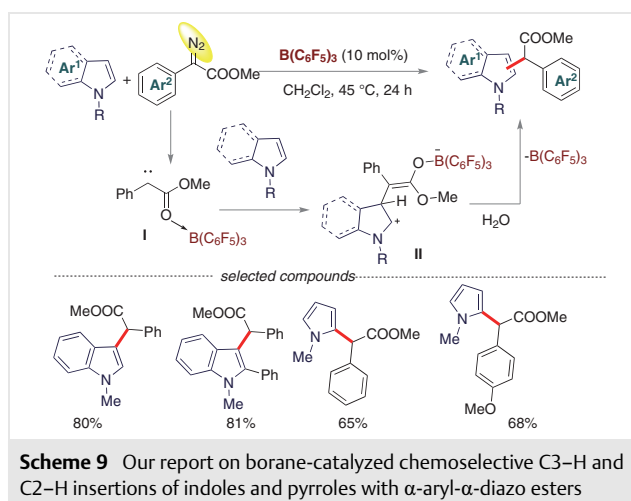
In 2020, we reported the chemoselective C3–H or C2–H insertions of indoles and pyrroles, respectively, with α -aryl- α -diazo esters achieved using $B(C_6F_5)_3$ as a metal-free catalyst (Scheme 9).¹⁴ Interestingly, protected and unprotected indoles smoothly reacted with the α -diazo esters to furnish C–C coupled products in excellent yields. No other N–H insertion product was observed for unprotected indoles.

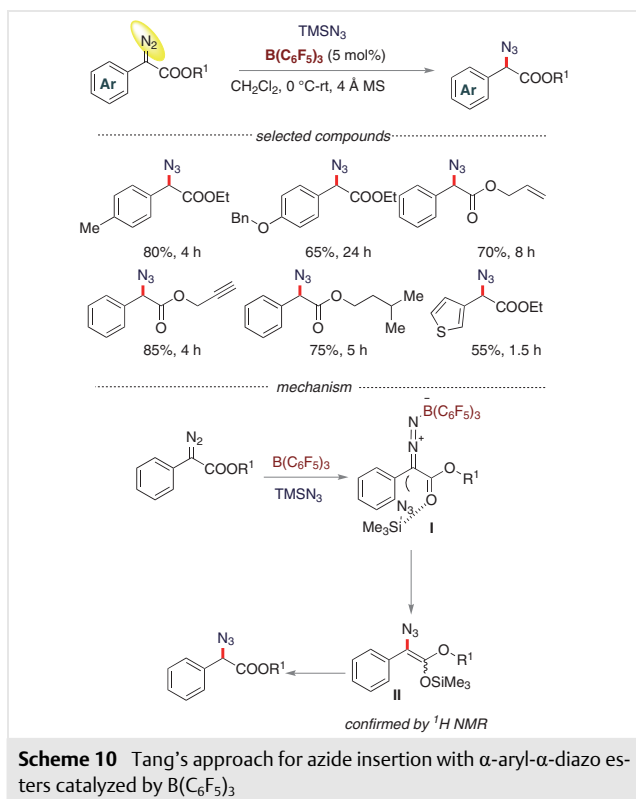
We have mechanistically investigated the reaction between the reactive carbene–borane intermediate **I** and indoles that initially leads to the formation of the kinetically



controlled C2 and C3 cyclopropanation species, which then furnishes a cationic intermediate **II** via cyclopropane ring opening. Finally, the desired C3-alkylated product is obtained by aromatization and proton transfer. In contrast, pyrrole governed electrophilic substitution at the C2 position yields the C2-alkylated product.

Organic azides are very useful synthons that are utilized as valuable building blocks for the synthesis of N-heterocycles. The development of catalytic protocols employing triarylboranes as a metal-free and sustainable reaction catalyst for the synthesis of organic azides is highly desirable.



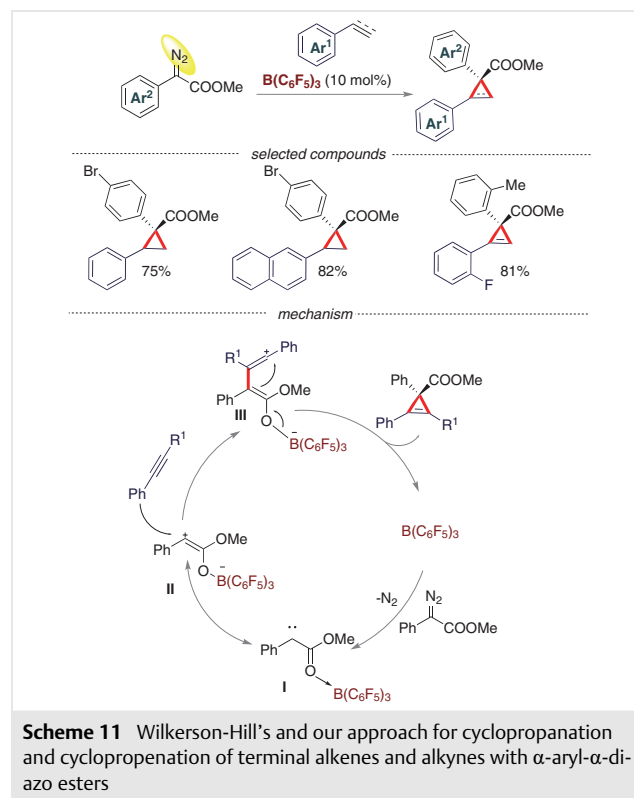


In this context, Tang and co-workers disclosed that azide insertion by α -aryl- α -diazo esters could be carried out using 5 mol% $B(C_6F_5)_3$ and azidotrimethylsilane ($TMSN_3$) as an azide source (Scheme 10).¹⁶ Alkene- and alkyne-substituted diazo esters were compatible under the reaction conditions without showing any cyclopropanation or cyclopropenation reaction products. Mechanistically it was proposed that the diazo group coordinated with the borane, and the TMS group assisted in the activation of the carbonyl group through coordination between Si and O as depicted in intermediate **I**. Nucleophilic attack by the azide onto the diazo compound led to the silyl enol ether as an intermediate **II**. The *E/Z*-isomeric mixture of silyl enol ether was confirmed through 1H NMR. Following acid-mediated hydrolysis during column chromatography, the desired product was afforded. Furthermore, the synthesis of 1,3,5-triazoles was also carried out using an azide in one pot using a copper-catalyzed click chemistry approach.

4.2 Synthesis of Carbocycles

Among the most common strained ring carbocycles, the smallest unit cyclopropane has gained enormous attention in organic synthesis as they are ubiquitous in natural products and frequently used in materials science.³⁹ Due to their unique reactivity, cyclopropanes are also widely used as starting materials in many transformations.³³ The typical synthesis of cyclopropanes using a [2+1] cycloaddition re-

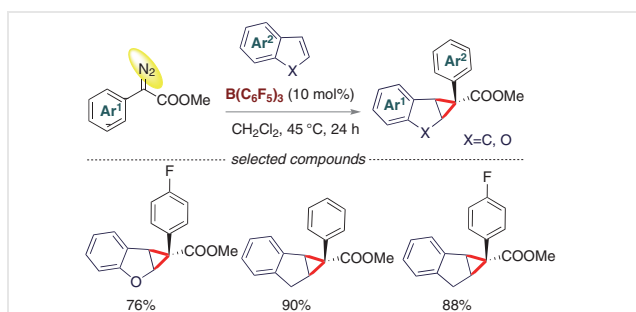
action has been well explored using metal catalysis via the formation of a metal carbene intermediate.⁴⁰ In 2020, Mancinelli and Wilkerson-Hill introduced a complementary $B(C_6F_5)_3$ -catalyzed approach for the cyclopropanation reaction of unactivated alkenes using diazo compounds as a reactive carbene synthon (Scheme 11).⁴¹



The substrates having halogen functionalities were tolerated nicely to produce corresponding cyclopropanes with excellent yields using 10 mol% catalyst in 1,2-dichloroethane at 50 °C for 14–16 h. However, the diazo compounds dimethyl diazomalonate, ethyl diazocynoacetate, and ethyl diazoacetate were unsuccessful in producing the desired cyclopropanated product. At the same time, we also reported the cyclopropanation of alkenes using 10 mol% catalyst in CH_2Cl_2 at 45 °C for one day.¹⁴ Subsequently we examined the cyclopropenation of alkynes (Scheme 11). A wide range of cyclopropene products could be afforded using 10 mol% of freshly prepared $B(C_6F_5)_3$ in 1,2-dichloroethane solvent at 50–65 °C temperature.⁴² The mechanism was proposed to proceed in a similar manner to that described earlier through $O \rightarrow B$ adduct formation and subsequent loss of N_2 to form a borane-coordinated reactive carbene species **I** which can be better described by the resonance stabilized intermediate **II**. Subsequently, nucleophilic attack from the acetylene onto **II** leads to another carbocation intermediate **III** having a new C–C bond. Finally, intramolecular attack from the boron enolate onto the car-

bocationic center in **III** delivers the cyclopropene with the regeneration of the boron catalyst. It was found that internal alkynes gave low yields compared to terminal alkynes. Interestingly, a competitive experiment using a substrate with both terminal alkene and alkyne functionalities revealed that only the alkene functionality participated in the cyclopropanation reaction without touching the alkyne.

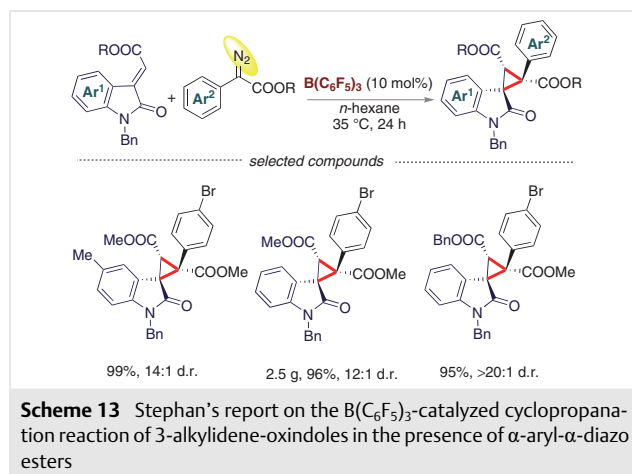
In our continued effort towards developing Lewis acid catalysts for organic synthesis, we also examined the reactivity of benzo-fused furans and indenes using the same borane catalyst (Scheme 12).¹⁴ In all cases, the C=C bond in the 5-membered ring took part in a [2+1] cycloaddition reaction with the α -aryl- α -diazo esters to yield a range of substituted cyclopropanes.



Scheme 12 Our work on $B(C_6F_5)_3$ -catalyzed cyclopropanation of benzofurans and indenes using α -aryl- α -diazo esters

As illustrated in Scheme 12, various benzofurans and indenes reacted smoothly with α -aryl- α -diazo esters in the presence of 10 mol% $B(C_6F_5)_3$ under mild conditions to produce the functionalized cyclopropane derivatives in good to excellent yields and as a single diastereoisomer. A DFT study revealed that the cyclopropanation took place with a significantly lower energy barrier than C–H insertions for all the heterocycles, however this was found to be the kinetic product. For indoles and pyrroles, C–H insertion became thermodynamically feasible because the cyclopropanated product was less unstable and the energy barrier to the C–H insertion was low enough to be possible under the reaction conditions. It was calculated that a highly diastereoselective cyclopropanated product is preferred for benzofurans and indenes as the energy barrier (32.6 kcal/mol) is too high for the formation of the thermodynamic C–H insertion products rather than cyclopropanation.

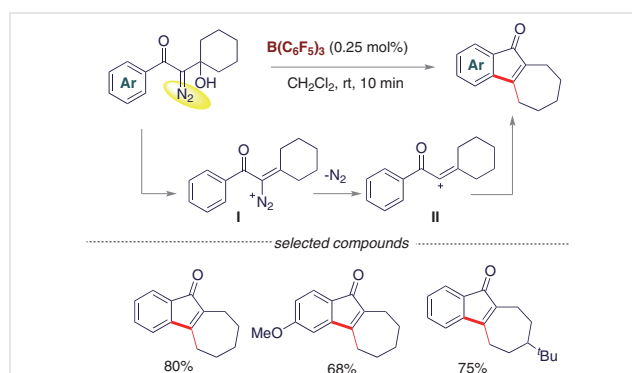
In 2023, Stephan and co-workers extended the cyclopropanation reaction to 3-alkylidene-oxindoles in the presence of diazo esters and catalytic $B(C_6F_5)_3$ (Scheme 13).⁴³ The spirocyclopropane-oxindole products were attained in excellent yields and high diastereoselectivities (up to d.r. 20:1). This newly developed protocol was also utilized for scale-up synthesis (up to 2.5 g, 96% yield).



Scheme 13 Stephan's report on the $B(C_6F_5)_3$ -catalyzed cyclopropanation reaction of 3-alkylidene-oxindoles in the presence of α -aryl- α -diazo esters

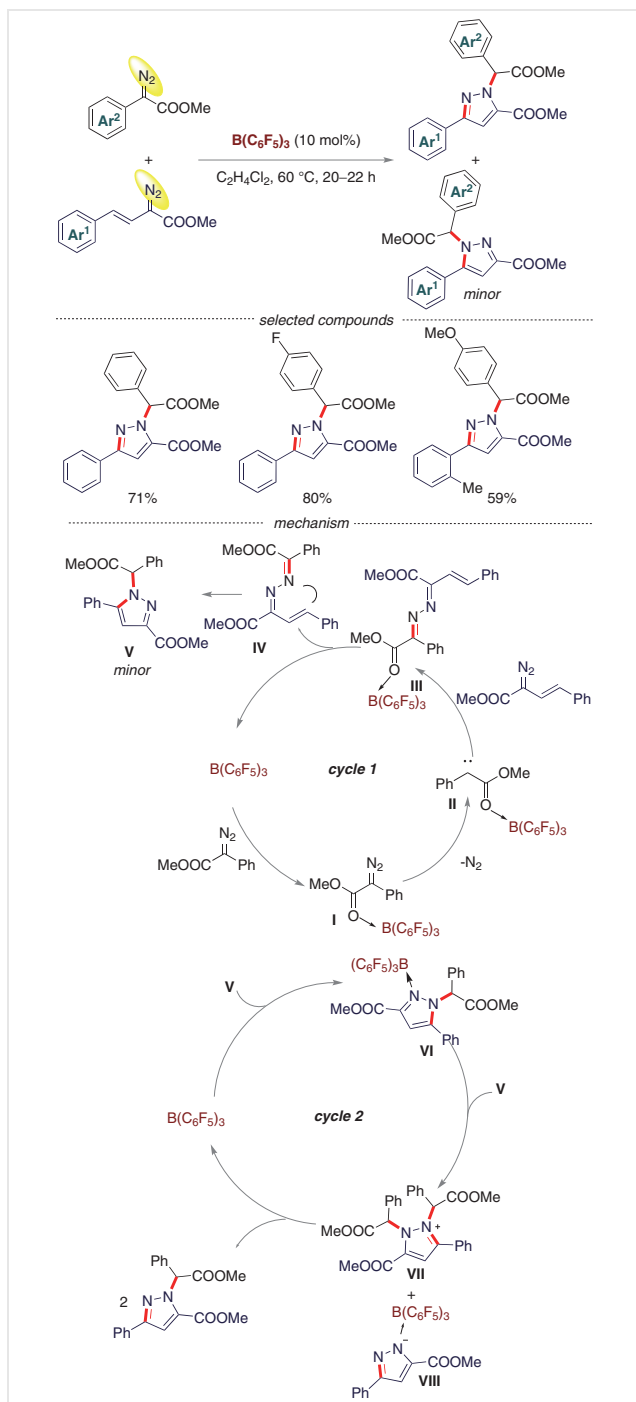
4.3 Annulation Reactions

The annulation reaction strategy is a useful strategy commonly employed to synthesize cyclic organic architectures.⁴⁴ The recent breakthroughs in annulation reactions have been spurred by using triphenylborane as a metal-free catalyst. In 2018, Brewer and Fang found that β -hydroxy- α -diazo ketones underwent intramolecular electrophilic vinylation in the presence of 0.25 mol% $B(C_6F_5)_3$ (Scheme 14).²² It was indicated that $B(C_6F_5)_3$ coordinates with N_2 of the diazo precursor assisting the formation of the vinyl diazonium ion **I** via a dihydroxylation process. Following the elimination of N_2 from intermediate **I**, the vinyl cation **II** is generated. Afterwards, the vinyl cation **II** (destabilized by the carbonyl group) exhibits ring expansion to give the tricyclic, seven-membered final products through loss of the proton. As shown in Scheme 14, OMe and ^tBu substituted β -hydroxy- α -diazo ketones gave the corresponding indenones in reasonable yields.



Scheme 14 Brewer's report on the borane-catalyzed synthesis of tricyclic inden-1-ones from β -hydroxy- α -diazo ketones

In 2022, we reported a Lewis acid catalyzed cyclization reaction using conjugated diene and dienophiles to form pyrazoles (Scheme 15).²⁰ By mixing two distinct diazo compounds (an α -aryl- α -diazo ester and an α -vinyl- α -diazo ester), *N*-substituted pyrazoles could be afforded as a major

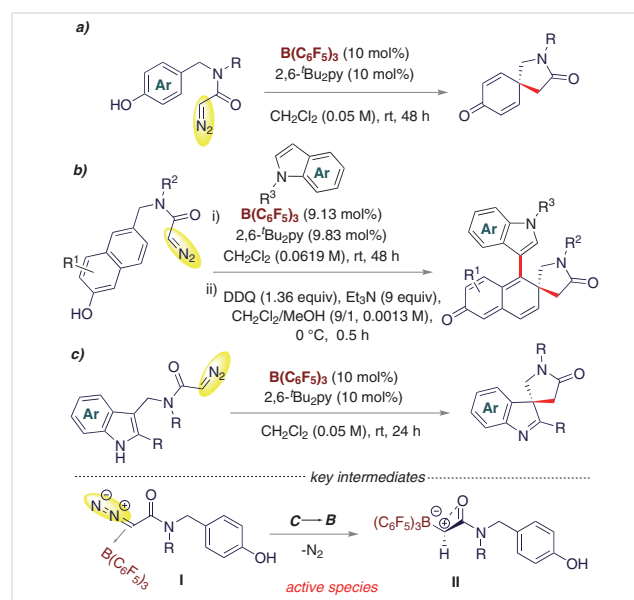


Scheme 15 Borane-catalyzed synthesis of *N*-substituted pyrazoles using two different diazo esters

and minor regioisomer. Various conjugated diene and dienophiles were screened under the standard reaction conditions to provide a wide range of *N*-substituted pyrazoles in near quantitative yields. Mechanistically it was proposed that the α -aryl- α -diazo ester was activated by $B(C_6F_5)_3$ through the O \rightarrow B adduct **I**. Reactive carbene species **II** was then generated by the release of N_2 from **I**. Next, reactive carbene species **II** reacted with the conjugated α -vinyl- α -diazo ester to form O \rightarrow B hydrazine adduct **III**, which subsequently cyclizes to give the *N*-substituted pyrazoles as the minor isomer **V** via intermediate **IV**, and the catalyst is regenerated. The minor isomer could then be interconverted to give the major isomer by a second $B(C_6F_5)_3$ -catalyzed cycle. The minor isomer **V** formed an N \rightarrow B adduct **VI** with $B(C_6F_5)_3$ which then reacts with another molecule of minor isomer **V** to provide the more thermodynamically stable isomer (major) via the formation of **VII** and **VIII**.

So far, we have discussed that diazo esters could bind with the borane through the formation of either the B \rightarrow O adduct or the B \rightarrow N adduct, but, recent findings by Nemoto and co-workers proposed a third activation mode (Scheme 16).²³ They suggested that the activation mode of the borane with the diazo compound could be switched to a B \rightarrow C adduct **I**. Subsequently, the B \rightarrow C adduct can lead to N_2 evolution to generate active species **II**. As outlined in Scheme 16, various terminal α -diazo amides in the presence of the borane catalyst led to dearomative spiro cyclizations. Not only with phenols and naphthols, but also indoles gave the spirocyclic product via dearomatization.

It was rationalized that cooperative noncovalent interactions including π - π stacking between the pentafluoro-



Scheme 16 Nemoto's report on the $B(C_6F_5)_3$ -catalyzed dearomatization reaction of phenols, naphthols and indoles with α -diazo amides. DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

benzene rings on the borane and the phenol, and F–C interactions between one of the fluorine atoms and the diazo carbon stabilized the B–C bond and facilitated neighboring group participation with the amide group to generate the active carbene species. The intermediate **II** could then go on to form various spirocyclic motifs, such as cyclohexadienones, tetraenones, and indolenines, through a dearomatization reaction under ambient conditions. It was observed that 2,6-di-*tert*-butylpyridine was acting here as a proton scavenger and thus enhanced the yield of the reaction.

In 2023, Stephan and co-workers reported [2+4] and [2+2] cascade cyclization reactions starting from *N*-protected imines and α -diazo ketones using $B(C_6F_5)_3$ as a catalyst (Scheme 17).²¹ Importantly, by altering the *N*-protecting group in the imine, different reactivity was observed. When *N*-*tert*-butoxycarbonyl imines were reacted with α -diazo ketones, a series of β -lactams were synthesized via a [2+2] cascade cyclization process. In contrast, the use of *N*-benzoyl imines as imine partners with α -diazo ketones led to oxazinone derivatives via a [2+4] cycloaddition process. The reactions proceeded through a reactive ketene intermediate which is formed by a Wolff rearrangement. Subsequently, the ketene reacts with the imines to offer either β -lactams or oxazinone derivatives with good yields.

4.4 C–C Bond Scission and C=C Bond Forming Reactions

Carbon–carbon (C–C) bond-forming reactions are considered the backbone of synthetic organic chemistry. In 2019, Prabhu and co-workers demonstrated that the reaction of allylic alcohols with α -aryl- α -diazo esters in the presence of $B(C_6F_5)_3$ as a catalyst resulted in the formation of a new C–C bond (Scheme 18).¹⁸

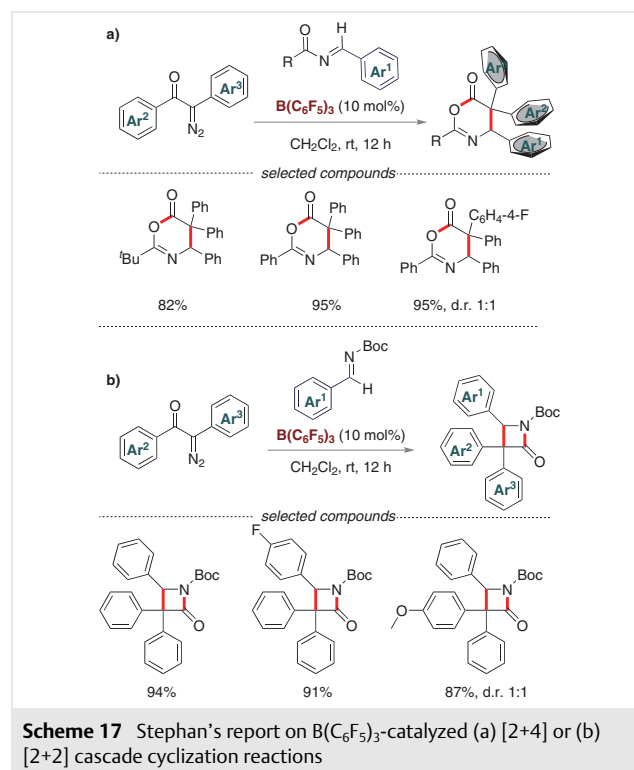
Several cinnamyl alcohols reacted with α -diazo esters to give the desired products in moderate yields. The mechanism was proposed to proceed through the B→N adduct **I**, which then gives borane-coordinated reactive carbene species **II** following N_2 release. The intermediate **II** is suggested to be stabilized by the extended conjugation with the adjacent aryl group as in **II'**. Following, nucleophilic attack by the allylic β - sp^2 -carbon onto intermediate **II**, the borane-coordinated cation species **III** is formed. Cationic intermediate **III** is then converted into a four-membered cyclic intermediate **IV**, eventually giving the desired C–C coupled product via intermediate **V** with the regeneration of the borane catalyst.

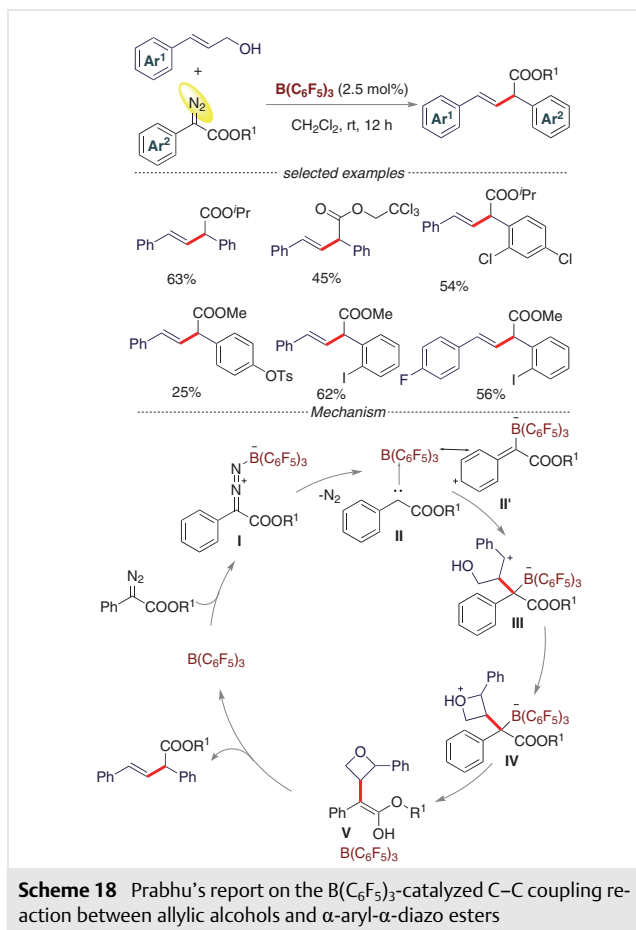
In our previous work, we have investigated the $B(C_6F_5)_3$ -catalyzed formation of C=C bonds from the reaction of benzyl aryl esters with α -diazo esters (Scheme 19).¹⁹ Not only did the benzyl diaryl esters show benzylic alkenylation, but also aryl-alkynyl and aryl-alkenyl esters were effectively used to afford the desired propargylic alkenylation product. Unfortunately, the *E/Z*-selectivity of the alkene product

when using asymmetric esters and α -diazo esters was poor. Optimization of the reaction conditions suggested that the reaction did not proceed without a catalyst and $B(C_6F_5)_3$ was proven to be the best catalyst for this transformation. It became clear from DFT experiments that borane preferred to coordinate with the carbonyl oxygen of the aryl ester rather than the nitrogen or carbonyl oxygen of the diazo ester. The $O_{\text{arylester}} \rightarrow B$ adduct (intermediate **I**) helped in the generation of a carbenium species **II** as indicated in Scheme 19. Following, nucleophilic attack by the diazo ester, and an E_2 -type elimination reaction with the help of intermediate **III**, the C=C coupled product is generated with loss of N_2 and benzoic acid from intermediate **IV**.

4.5 Group Transfer Reactions

In 2019, Prabhu and co-workers envisioned a borane-catalyzed carbene transfer reaction using di-*tert*-butyl dicarbonate as a carbonate donor and α -diazo esters as the carbene acceptor (Scheme 20).¹⁷ The authors proposed a similar mechanism to that proposed in their previous study (Scheme 18) in that the $B(C_6F_5)_3$ forms N→B adduct **I** with the diazo ester which subsequently is converted into resonance stabilized intermediate **II/II'**. The nucleophilic carbonate then interacts with intermediate **II** to give a $B(C_6F_5)_3$ stabilized oxonium ylide **III**. In the next step, **III** is converted



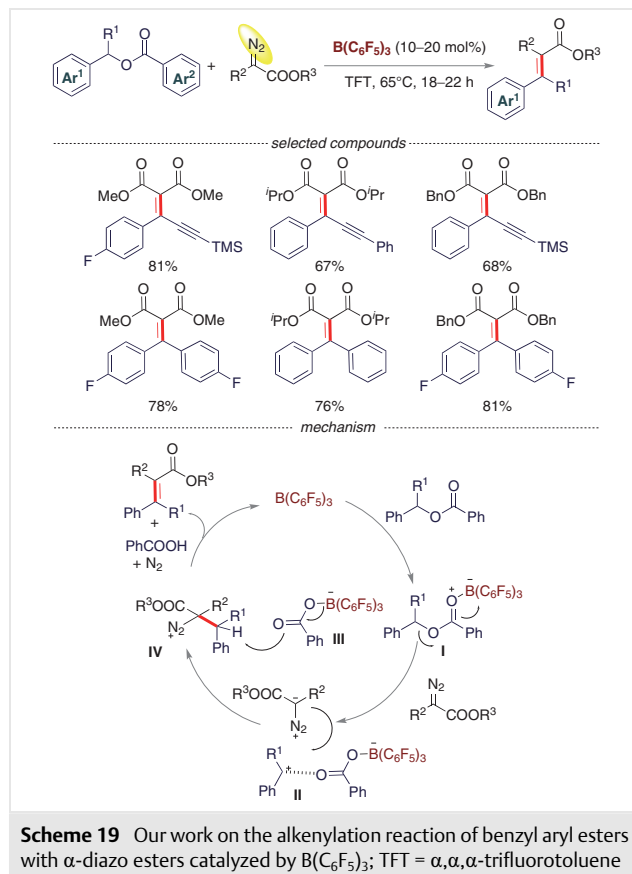


into intermediate **IV** containing the carbonate functionality, which reacts with another molecule of **II** to furnish intermediate **V**. The desired product is then realized by the elimination of a cation stabilizing R^1 group as depicted in Scheme 20.

4.6 Ring-Opening Reactions

Following on from the above discussion in Section 4.2, our studies on C–H insertion of pyrroles and indoles and our cyclopropanation/cyclopropanation studies with various multiple bonded species (alkynes, alkynes, benzofurans, and indenenes) led us to also investigate the reactivity of furans. To our surprise, the reactions of furans with α -aryl- α -diazo esters in the presence of catalytic borane led to a new reactivity pathway that resulted in the ring opening of the furan (Scheme 21).¹⁴

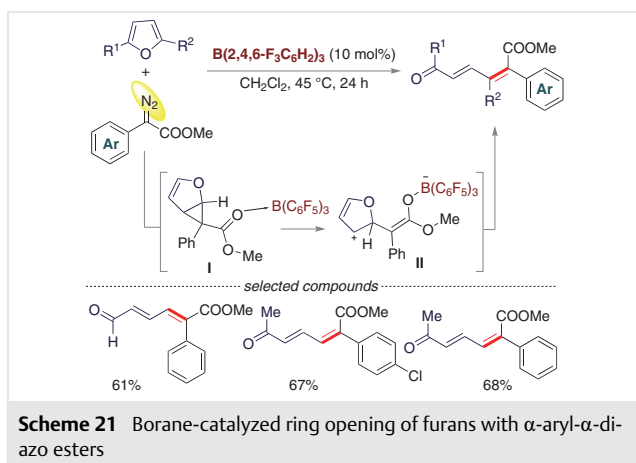
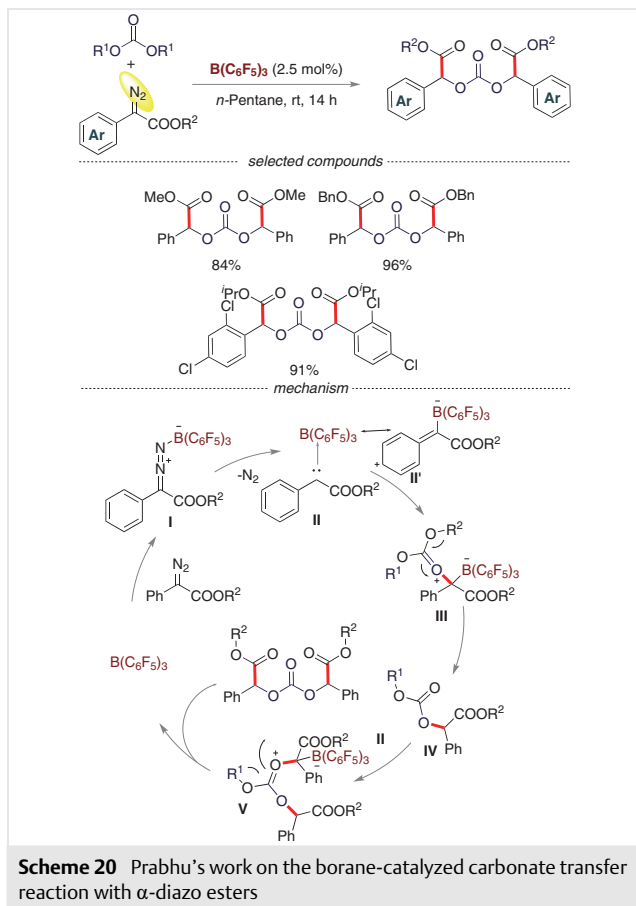
Although the ring-opening reaction worked well with $B(C_6F_5)_3$, we observed that the slightly less Lewis acidic borane tris(2,4,6-trifluorophenyl)borane [$B(2,4,6-F_3C_6H_2)_3$] was a better catalyst for this transformation. Our DFT studies helped us to understand the difference in reactivity. The



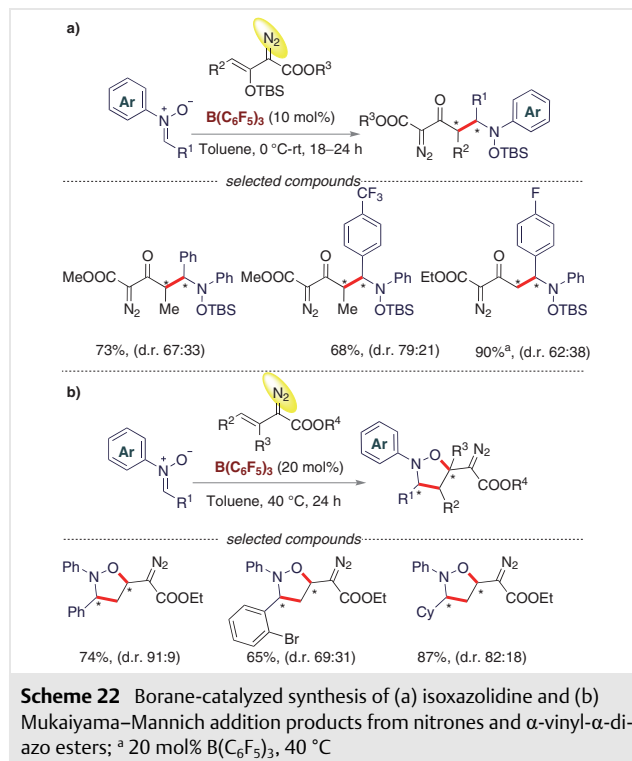
α -diazo ester O \rightarrow B adduct led to loss of N_2 as described earlier, and reaction with the furan leads to the kinetically controlled C2 and C3 cyclopropane intermediate **I**. The resulting product is then afforded via the electrocyclic ring opening of the cationic intermediate **II**. This happens due to the formation of strained cyclopropanated species **I** followed by the stability of carbocation **II**.

4.7 Miscellaneous Reactions of Diazo Compounds with $B(C_6F_5)_3$

In 2023, we showed that α -vinyl- α -diazo esters showed divergent reactivity with borane catalysts in the presence of nitrones (Scheme 22).⁴⁵ By switching the diazo precursor and the reaction conditions ($B(C_6F_5)_3$ loading and temperature), either isoxazolidines or Mukaiyama–Mannich addition products could be afforded in which the diazo functionality was untouched. A range of isoxazolidine and Mukaiyama–Mannich addition products were isolated in moderate to good yields and good diastereoselectivities. In these reactions the inability of the borane to activate the diazo functionality was proposed to be due to the preferential



binding of the borane to the nitron. The highly functionalized diazo-containing products could be utilized in further reactivity using rhodium-based catalysts.



5 Conclusions

In conclusion, we have discussed recent literature on Lewis acidic triarylborane-mediated diazo compound activation. Most of these studies have employed $B(C_6F_5)_3$ as an alternative to the previously reported precious transition-metal-catalyzed diazo activation. Various modes of diazo activation by $B(C_6F_5)_3$ have been proposed for diazo esters through $O \rightarrow B/N \rightarrow B/C \rightarrow B$ adduct formation. Mechanistic insights from DFT studies have helped to interpret the mode of activation in these compounds and suggest that the $O \rightarrow B$ adduct is the most likely in the case of α -diazo esters to generate the borane stabilized carbene intermediate. DFT studies have also aided in understanding the catalytic reaction mechanism in the presence of the substrate as well as to understand the different reaction scopes and selectivities.

Stoichiometric and catalytic addition of $B(C_6F_5)_3$ and other fluorinated triarylboranes to diazo compounds has led to various boron-based organic complex molecules involving B–N, B–C bonds and valuable organic transformations including O–H, N–H, S–H, and C–H insertions, azide insertion, carbonate transfer, C–C and C=C bond forming reactions, cycloadditions, and annulation reactions. Recent findings also revealed that the diazo group in vinyl diazo esters could remain intact in the presence of $B(C_6F_5)_3$ when reacted with nitrones. We foresee that the utilization of borane catalysis involving diazo compounds will advance

main group inorganic chemistry towards highly selective organic reactions, and it will pave a new direction in the area of borane-catalyzed synthetic methodology. Overall, this review offers an excellent guideline for the synthesis of high-value-added molecules, such as natural products and biologically active drug compounds, using Lewis acidic boranes as a metal-free catalyst.

Conflict of Interest

The authors declare no conflict of interest.

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