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Metal-free Boronic Acids Addition to Silylnitronates.

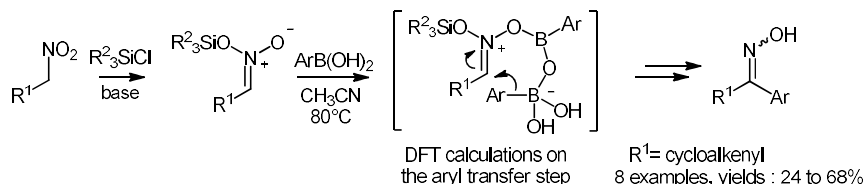
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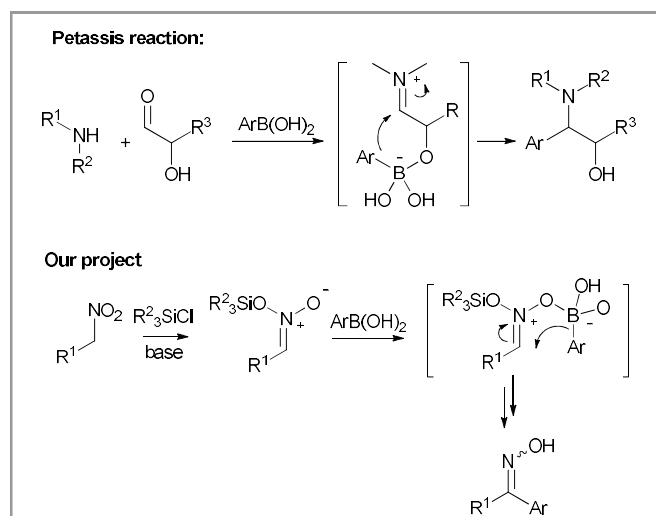
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Abstract We report for the first time a metal free addition of boronic acids to silylnitronates to afford oxime derivatives through aryl transfer on the carbon nitrogen double bond. A reaction mechanism has been proposed in relation with a DFT study on the key aryl transfer. This arylation process is effective for cycloalkenyl nitro derivatives leading to oximes that may be oxidatively converted into 3-arylisoxazole derivatives.

With the development of the Suzuki-Miyaura reaction, boronic acids have been recognized among the most useful arylation reagents.¹ Whereas such reaction requires an activation of the aryl group through a transmetalation process with various transition metals, in the absence of such metal, the boronic acids may still transfer its aryl moiety under prior conversion to a boronate intermediate. Highlighted with the discovery of the Petassis reaction,² this seminal Mannich type behaviour of boronic acids has given the impetus for the discovery of many other metal-free arylation and vinylation in the last ten years.³ However boronic acids remain moderately nucleophilic species which often require for efficient couplings, the installation of an intramolecular aryl transfer through ate complex formation.⁴ This is the case of the Petassis reaction where the lack of electrophilicity of simple imine derivatives may be overcome by neighbouring hydroxy groups (Scheme 1). Following our interest in nitro chemistry and considering known nucleophilic additions on nitronic acid derivatives (Nef type reactions),⁵ we surmised that nitronic derivatives might further interact with boronic acids to afford transient ate complexes prone to undergo an intramolecular aryl transfer onto the C-N unsaturated bond (Scheme 1).

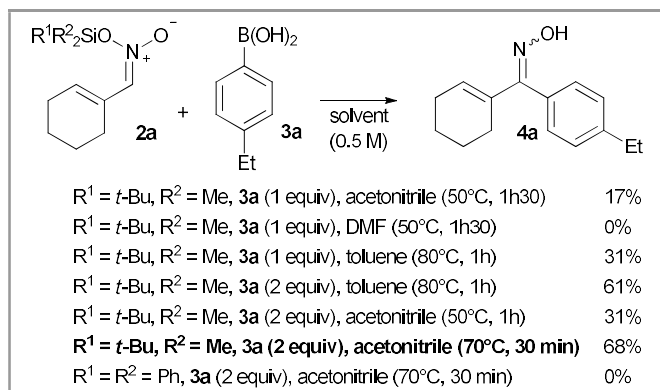


Scheme 1: Metal-free boronic acid addition to C-N double bonds

Due to the instability of nitronic esters (leading to oximes and aldehydes)⁶ or acylnitronates (leading to nitrile oxide at rt),⁷ we decided to focus our study on silylnitronic esters, a rather stable family of compounds easily prepared upon silylation of nitro derivative with trialkylsilyl chlorides and whose chemistry has been largely popularized by the studies of Seebach at the beginning of the 1980s.⁸

Due to poor hydrolytic stability of trimethylsilyl nitronate, a bulkier *t*-butyl-dimethylsilyl group was selected for this study. The *t*-butyl-dimethylsilylnitronate **2a** was thus prepared in quantitative yield under treatment of nitromethylcyclohexene **1a** with 1.1 equiv of *t*-butyl-dimethylsilylchloride in the presence triethylamine (1.1 equiv) in dry acetonitrile. **2a** could be filtered fast on a small silica gel column without significant degradation. When **2a** was heated in acetonitrile together with 4-

ethylphenylboronic acid **3a** under argon, we were delighted to observe the formation of oxime **4a** resulting from the expected aryl transfer (Scheme 2). The low 17% isolated yield could be slightly increased selecting toluene at 80°C. Finally best conditions were obtained using a two-fold excess of boronic acid **3a** in acetonitrile at 70°C (Scheme 2).

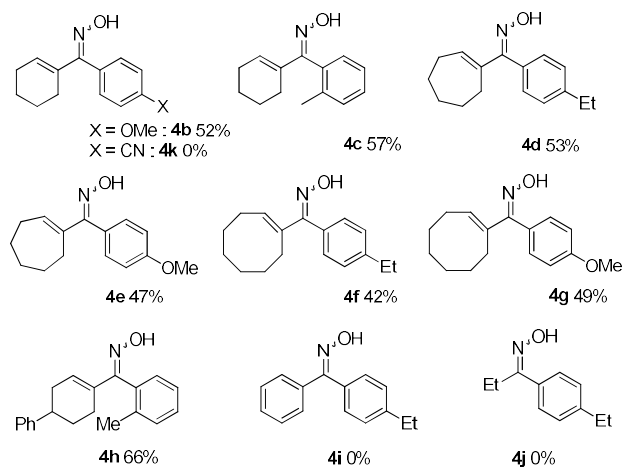
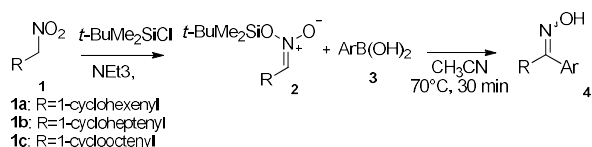


Scheme 2: Optimized conditions for the formation of **4a**

Changing the *t*-butyldimethyl silyl group by a triphenylsilyl group (Scheme 2) didn't lead to any formation of **4a** under the same conditions.

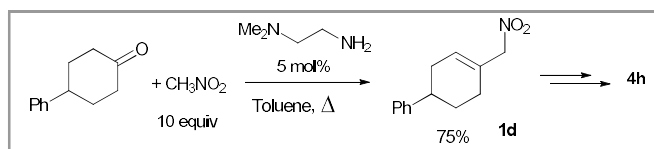
To evaluate the scope of this reaction, a set of *t*-butyldimethylsilyl nitronate **2** were prepared in quantitative yields from the corresponding nitro derivatives using the same procedure followed by fast filtration. The results of their reaction with different arylboronic acids are displayed in Table 1.

Table 1 Scope of the boronic acid addition to silylnitronate



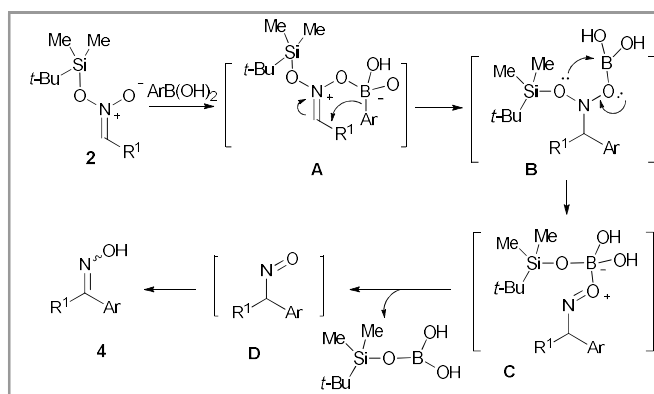
The coupling is only efficient for 1-nitromethylcycloalkenyl derivatives as shown by the various cyclohexenyl, cycloheptenyl and cyclooctenyl oximes **4** formed in moderate isolated yields from the corresponding silylnitronates. Electron-poor aryl boronic acids didn't seem to be effective as shown by the non

productive addition of 4-cyanophenyl boronic acid. Under prolonged heating, the degradation of **2a** was only observed without any formation of **4k**. All oximes were obtained as single diastereomers, however, we failed to determine their *cis* or *trans* stereochemistry. Surprisingly, the silylnitronate of nitromethylbenzene didn't form the expected adduct **4i** with 4-ethylboronic acid. This lack of reactivity was also observed for 1-nitropropane showing the high sensibility of this reaction to electronic factors. Though these results limit the scope of this reaction, it should be noted that 1-nitromethylcycloalkenyl derivatives are easily prepared on large scale from their related cycloalkanone derivatives using a Knoevenagel type condensation with nitromethane^[9] Indeed, this strategy could be easily adapted to reach more complex substituted oximes choosing among the relatively wide range of commercially available cycloalkanones. Thus oxime **4h** (Table 1) was prepared starting from 4-phenylcyclohexanone which was efficiently converted to nitro **1d** under heating in a toluene/nitromethane mixture in the presence of catalytic amount of *N,N*-dimethylethylenediamine (Scheme 3).



Scheme 3: 4-phenylcyclohexanone conversion into **1d**

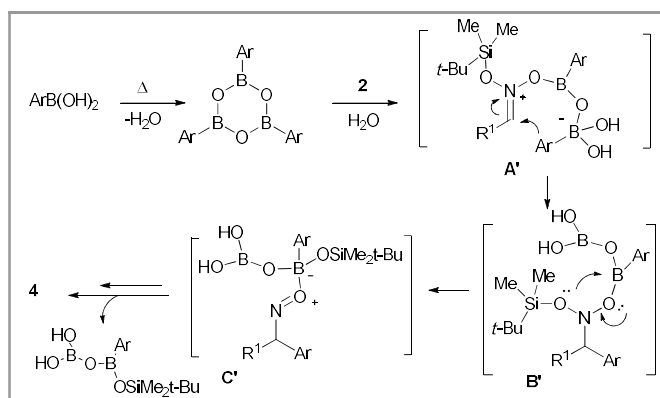
A possible reaction mechanism for the silylnitronates conversion into oximes is displayed in Scheme 4. After complexation of the silylnitronate with the boronic acid, aryl transfer affords an instable intermediate **B** whose fragmentation lead to chelated nitroso **C**. Further fragmentation and nitroso-oxime tautomerism give the final compound **4**. An alternative concerted migration/fragmentation of intermediate **B** directly to **D** could be also proposed. The formation of *O*-silyl oximes which might have been also expected was not observed.



Scheme 4 Possible mechanism for the conversion of **2** into **4**

To gain further insight into the mechanism of this reaction, we performed density functional theory (DFT) calculations to model the aryl transfer from the boric acid to the nitronate moiety. Despite all our efforts to model the aryl transfer from intermediate **A** to intermediate **B** (Scheme 4), we were not able to disclose a transition state with an energy barrier lower than

30 kcal/mol, which is probably associated with a mechanistic pathway unlikely to occur under our reaction conditions. In the Petassis reaction of α -hydroxy-aldehydes, the aryl transfer is usually explained via the formation of an intermediate boronate followed by an intramolecular 1,5-shift of the aryl moiety from the boron to the carbon of the imine function.² As shown by the results of our modelization (Figure 1, path A), a similar mechanism as disclosed in scheme 4 requires that the C,N,O atoms of the nitronate adopt an out-of-plan geometry which is highly energy demanding. In an attempt to reduce this out of plane deformation, we envisioned that a second boron atom might be involved through the intermediacy of boronic anhydrides formed during the reaction (Scheme 5).



Scheme 5 Alternative mechanism for the conversion of **2** into **4** with two Boron atoms

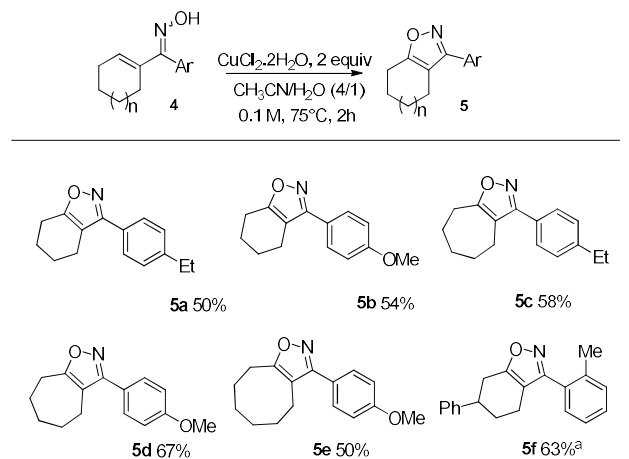
Figure 1 summarizes the DFT calculations performed on the crucial aryl transfer steps following the two proposed reaction mechanisms. In pathway A (Scheme 4), the silylnitronate molecule initially forms a non-covalent molecular complex with one single boric acid molecule (state RA in Fig. 1-A). Then the aryl group is transferred from the boric acid moiety to the nitronate moiety in a single step, passing through transition state TSA and leading to the adduct PA. As mentioned above, pathway A is associated with a very high free energy barrier of 34 kcal/mol. The alternative pathway B (Scheme 5), on the other hand, exhibits a much smaller barrier of 22 kcal/mol, thus corresponding to a reduction in activation free energy of more than 10 kcal/mol with respect to mechanism A. Most importantly, the transition state of pathway B, namely TSB, differs substantially from TSA. Though the formation of a 7-membered ring transition state TSB might be considered less favourable than the 5-membered ring TSA, TSB is stabilized by an internal H-bond between the terminal boric acid OH group and the oxygen atom that links the silyl to the nitronate moieties. Another key difference between the two transitions states lies in the local structure around the Nitrogen atom of the nitronate group, as shown in the insets of Fig. 1. Indeed, both transition states require a partial disruption of the planarity of the nitronate group but the geometry distortion is stronger in TSA than in TSB. The computed out-of-plane distance between the Nitrogen atom and the COO plane of the nitronate moiety are 0.38 °Å and 0.25 °Å for TSA and TSB, respectively. It should be stressed that even a small difference in planarity may affect the transition states energy substantially, because the out-of-plane distortion tends to

disrupt the local delocalisation of π electrons, which plays a key role in the stability of the chemical group.

In order to support this mechanistic proposition, we decided to examine the behaviour of silyl nitronate **2a** towards phenyl boroxine instead of phenyl boronic acid. Using the former anhydride directly, the key synthetic intermediate displaying two boron atoms complexed to the silyl nitronate should be formed more easily leading to a potential raises in yield. While heating **2a** with 2.5 equivalent of phenyl boronic acid led to phenyl-cyclohexenyl oxime **4l** in a poor 24% yield after 30 min heating, the same reaction performed with 1 equi of triphenylboroxine led to **4l** in 32% yield. Though not impressive, this raise in yields supports a potential effect of boronic anhydrides on the mechanism of this reaction.

With these unsaturated oximes in hand, we next envisioned their conversion into oxazole derivatives. Several conditions for oxidative transformation of α,β -unsaturated oximes into oxazoles have been reported in the literature.^[10] The reaction may be observed using various oxidants such as manganese oxide, copper salts used in stoichiometric amount or together with oxygen. Indeed, when oximes **4a** was heated in acetonitrile in the presence of copper chloride we observed the formation of isoxazole **5a** in a moderate 54% isolated yield (Table 2). Attempts to perform this reaction in other solvents such as DMF or THF resulted in lower yields. Further optimisation for this known transformation was not pursued and Table 2 displays the results of the cyclizations, under these conditions, of various oximes **4** formed after boronic acids addition. All oximes gave fused isoxazoles **5** in good to moderate yield.

Table 2 Isoxazoles **5** from oximes **4**



^aThe reaction was left for 12h for completion.

In conclusion, We have disclosed a new interaction of boronic acids with silyl nitronates.^[11] This aryl transfer from a boron atom onto the electrophilic C=N double bond of nitronates extends the previously disclosed oxime synthesis through aryl magnesium^[12] and aryl lithium^[13] additions onto silyl nitronates. When performed on nitromethylcycloalkenyl derivatives, the resulted oximes may be easily converted to fused isoxazoles under oxidative conditions.^[14] We are currently exploring the potential of various catalysts to trigger the addition of boronic acids onto less reactive alkyl silylnitronate species.

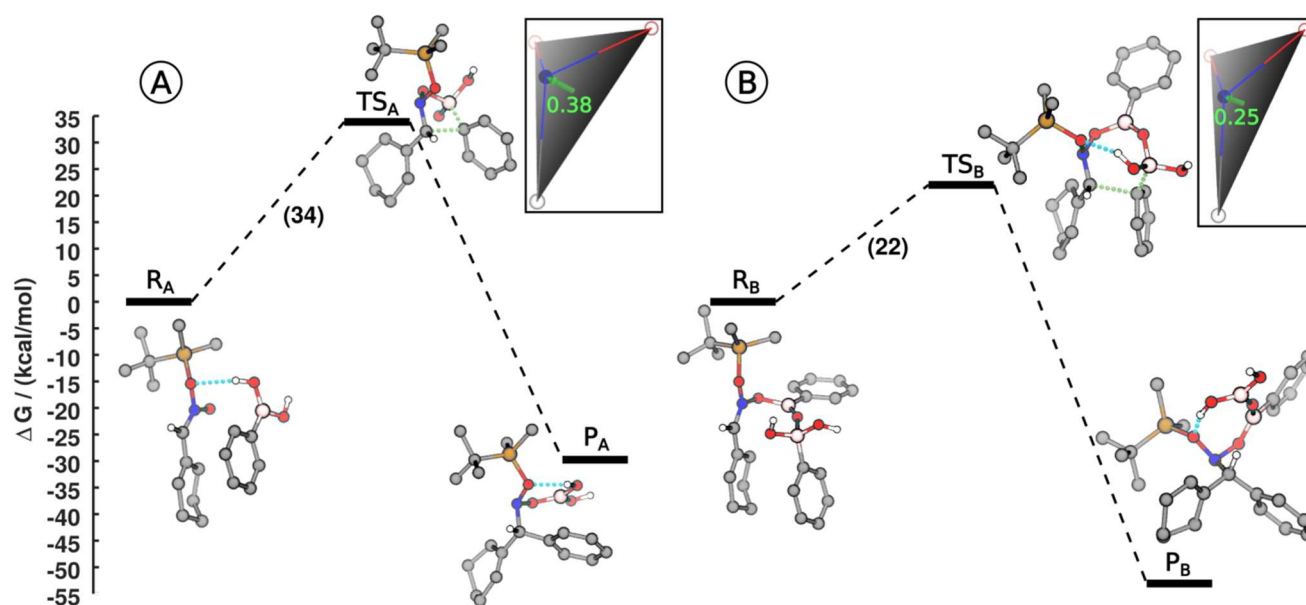


Figure 1: Computed free energy pathways of the aryl transfer reaction. Panels A and B correspond to pathways A (Scheme 4) and B (Scheme 5), respectively. Optimized molecular structures for each stationary state are represented for each energy level. Most H atoms are hidden for the sake of clarity. Only polar hydrogens and the CH group directly attached to the nitronate moiety are represented. Hydrogen bonds are represented with light blue dotted lines while forming/breaking bonds at the transition states are represented with green dotted lines. For each transition state, the out-of-plane deformation of the nitronate group is shown in an inset: the COO plane is shown in black and the distance in $^{\circ}\text{A}$ between this plane and the Nitrogen atom is shown in green.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References and Notes

- (1) For reviews on boronic acids, see: (a) "Boronic acids: Preparation and Applications in Organic Synthesis, Medicine and Materials", D. G. Hall Ed, Wiley-VCH, Weinheim, Germany, 2011. (b) "Boron reagents in Synthesis", *ACS Symposium Series*, Ed. A. Coca, 2016, vol. 1236.
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- (11) A typical procedure is given for the preparation of **4a** from **1a**: Et₃N (1.1 mmol, 0.15 ml) was added to a stirred solution of allylic nitro compound **1a** (1 mmol, 141 mg) and tert-butyldimethylsilyl chloride (1.1 mmol, 166 mg) in acetonitrile (2ml). The reaction mixture was stirred for 30 minutes at room temperature and quickly filtered through a small column of silica gel with 100 ml of dichloromethane to give after evaporation of the solvent nitronate **2a** as a yellow oil formed in quantitative yield (256 mg, 1 mmol). 4-Ethylphenyl boronic acid (2 equiv, 1mmol, 150 mg) was added to a solution of **2a** (1 equiv, 0.5 mmol, 128 mg) in acetonitrile (1 ml). After degassing with argon, the reaction mixture is heated at 70 ° C under argon for 30 minutes. Evaporation of the solvent under reduced pressure followed by purification by flash chromatography on silica gel (PE/Et₂O, 100:0 to 80:20) afforded oxime **4a** as an orange solid (78 mg, 0.34 mmol, 68%). **MP**: 161 °C.

Rf = 0.35 (PE /Et₂O 80:20). **¹H NMR** (400 MHz, CDCl₃) δ 8.97 (br, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 5.71 – 5.61 (m, 1H), 2.70 (q, *J* = 7.6 Hz, 2H), 2.39 – 2.29 (m, 2H), 2.10 – 2.04 (m, 2H), 1.71 – 1.54 (m, 4H), 1.28 (t, *J* = 7.6 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 160.3, 144.4, 135.3, 135.0, 130.1, 128.7, 127.7, 28.8, 26.2, 24.7, 22.5, 22.2, 15.4. **HRMS**: calculated for C₁₅H₁₉NO: 229.1467, found 229.1464. **I.R. (thin film)**: 3214, 3038, 2932, 2866, 1551, 1447, 1262, 997, 968, 823, 737, 722.

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