

Regioselective Cycloaddition of Potassium Alkynyltrifluoroborates with 3-Azetidinones and 3-Oxetanone by Nickel-Catalysed C–C Bond Activation

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Abstract: In the presence of a nickel catalyst, the intermolecular (4+2) cycloaddition of potassium alkynyltrifluoroborates with 3-azetidinones and 3-oxetanone leads to the formation of borylated dihydropyridinones and dihydropyranones without unwanted carbon-boron bond cleavage. The regioselectivity is influenced only by the trifluoroborate group, and only one regioisomer is obtained, whether the other alkyne substituent is an alkyl, vinyl, or (hetero)aryl group.

The cycloaddition of alkynylboron derivatives presents both a fantastic opportunity and a considerable challenge. The opportunity consists in the rapid synthesis of functionalised carbo- and heterocycles by an approach that complements the scope of carbon-hydrogen¹ and carbon-halogen² borylation of preformed substrates. The main challenge presented by the cycloaddition of alkynylboron derivatives is mostly that of regioselectivity.

Whereas, the regioselectivity of these reactions can be controlled by tethering or chelation,³ it often remains moderate as well as dependent on the substrate in cases involving the purely intermolecular addition of the alkynylboron reagent. In this context, the intermolecular metal-catalysed cycloadditions of alkynylboron reagents⁴ offer an access to motifs that are not easily accessible by solely heat-promoted cycloadditions.⁵ However, metal-catalysed intermolecular cycloadditions of alkynylboron reagents are very scarce.⁴ Importantly, the nickel-catalysed cycloaddition of cyclobutenones with alkynylboronic esters (Bpin) leads to the formation of a mixture of isomeric phenols in various ratios depending on the triple bond substituent (Fig. 1a).^{4c} Moreover, the elegant synthesis of heterocycles by rhodium-catalysed C–H functionalisation using *N*-methyliminodiacetic acid-protected alkynylboronates (BMIDA) also presents issues of regioselectivity when the alkyne is not terminal (Fig. 1b).⁶ Furthermore, the cobalt-catalysed cycloaddition of alkynylboronic esters with 1,3-dienes^{4a} and the copper-catalysed cycloadditions of alkynylboron reagents with azides^{4e,g,h} are very regioselective (Fig 1c), but this trait is not specific to the alkynylboron substrates, as evident when compared to the results obtained with other alkynes.⁷

Recently, others⁸ and we⁹ have developed the nickel-catalysed (4+2) cycloaddition of 3-azetidinones and 3-oxetanones with alkynes.¹⁰ However, attempts to extend this transformation to either alkynylboronic acids or the corresponding esters led to partial or complete decomposition of those alkynes without formation of the desired product.¹¹ With these challenging precedents in mind, we are delighted to report herein that potassium alkynyltrifluoroborates undergo a smooth cycloaddition with 3-azetidinones and 3-oxetanone without cleavage of the carbon-boron bond and with complete control of the regioselectivity, independently of the other substituent present on the triple bond (Fig. 1d).

Preliminary studies with alkynylboronic esters suggested that their nickel-catalysed (4+2) cycloaddition with *N*-Boc-3-azetidinone **1** (Boc = *tert*-butoxycarbonyl) could proceed, but the cycloadduct thus recovered had also undergone cleavage of the carbon-boron bond. Against these disappointing results, we turned our attention to the more robust potassium alkynyltrifluoroborates in the hope to prevent this pathway of decomposition.¹² This approach revealed itself fruitful, and we found that **1**, *N*-Ts-3-azetidinone **2** (Ts = *para*-tolylsulfonyl) and 3-oxetanone **3** underwent

smooth cycloaddition with alkynes **4–13** (Figure 2).¹³ Importantly, functionalised heterocycles **14–26** were obtained in good to excellent yields as single regioisomer, independently of the nature of the alkyne substituent R, whether it is an alkyl group (**14–16** and **25**), an olefin (**17** and **24**), an aryl group (**18–20**, **22**, **23** and **26**), or a heteroaryl group (**21**). The reactions of a terminal alkyne (R = H) led to complex mixtures of unidentified products, plausibly due to the uncontrolled oligomerisation of the alkyne.¹⁴

The structure of **17** was unambiguously confirmed by X-Ray crystallography. In the crystal, the sp²-hybridised oxygen atom of the carbamoyl protective group establishes the shortest contact (2.635 Å) with the potassium ion (Figure 3a), whereas each potassium ion is in contact with six fluorine atoms of three other molecules of **17** at distances ranging from 2.756 Å to 3.001 Å (Figure 3b).[‡]

Three reaction paths could be considered to account for the formation of a single regioisomer in this nickel-catalysed (4+2) cycloaddition, and we will consider only the cases that lead to this specific regioisomer (Figure 4). The oxidative cyclisation of η^2, η^2 -alkyne-ketone-nickel complex **A** into metallacycle **B** (path *a*) would be in agreement with isolated complexes similar to **A**¹⁵ and with theoretical studies of the nickel-catalysed reductive coupling of alkynes with aldehydes.¹⁶ These studies suggest that electronic interactions have little effect on the regioselectivity and that steric effects are more prominent. However, other theoretical studies conducted with alkynes bearing alkyl, silyl and stannyl substituents suggest that the β -carbon elimination from **B** to **C** could be prohibited by high-energy barriers.¹⁷ Instead, the strained azetidinone and oxetanone would undergo oxidative addition to give intermediate **D**, followed by migratory insertion of the alkyne in either the C(sp²)-Ni bond (path *b*) or the C(sp³)-Ni bond (path *c*). The former would lead to **C** whereas the latter would lead to **E**. Given that we observed the formation of the same regioisomer for alkyne substituents R that are sterically very different, we assume that electronic effects are more significant than steric differentiation. Along these lines, it is relevant to consider that the trifluoroborate group is an inductive donor ($\sigma_I = -0.32$) whilst the π orbitals of the triple bond should not be affected by this group ($\sigma_R = -0.07$).¹⁸ This donation should make the alkyne act as nucleophile, and it would make path *b* more likely.¹⁷ Moreover, the contact observed between the potassium ion and the sp²-hybridised oxygen atom of the ketone (2.700 Å) in the crystal structure of **17** (Figure 3b) suggests the possibility of a directing effect by coordination that may favour the formation of **C** via path *b*.¹⁹ However, a coordination of the metal by one of the fluorine atoms of the trifluoroborate group in **E** might favour path *c*.²⁰ Overall, both paths *b* and *c* may contribute more than path *a* to the formation of the sole regioisomer observed in this reaction.

Other four-membered ring ketones could in principle exhibit the same reactivity.^{4c,10a,10b,10e} However, the reaction of alkynyltrifluoroborates remained limited to the (4+2) cycloaddition of **1–3** during our investigations. Specifically, the reaction of 3-methyl-3-phenylcyclobutan-1-one failed, and no reaction was observed at temperature ranging from 60 °C to 90 °C, whereas increasing the temperature to 110 °C led to decomposition. A similar behaviour was observed when a benzyl substituent was present next to the carbonyl of **2**.

As an example of synthetic application, we converted **14** into **27** in two steps. Indeed, the treatment of **14** with tetrabutylammonium tribromide²¹ afforded the corresponding vinyl bromide that was then engaged in Suzuki-Miyaura cross-coupling with para-methoxyphenylboronic acid to give **27** in 69% yield over the two steps (Scheme 1).²²

In conclusion, we have developed an intermolecular (4+2) cycloaddition of potassium alkynyltrifluoroborates triggered by nickel-catalysed C–C bond activation of azetidinones and oxetanone. In contrast to previous attempts with alkynylboronic acids or their derivatives,¹¹ the

reactions proceed without the undesired cleavage of the carbon-boron bond. Moreover, the reactions lead to the formation of a single regioisomer of dihydropyridinones and dihydropyranones, independently of the nature of the other alkyne substituent. This remarkable feature is in stark contrast with most metal-catalysed intermolecular cycloadditions of alkynylboron derivatives reported to date.^{4a,c,d,f,i,6} This work expands the scope of metal-catalysed C–C bond activation²³ and of the chemistry of alkynylboron derivatives.²⁴ Finally, it offers new possibilities for the synthesis of organoboron compounds that are vital to modern organic synthesis.²⁵

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- 4** (R = *n*-Bu), **5** (R = *c*-C₆H₁₁), **6** (R = *c*-C₃H₅), **7** (R = 2-propenyl), **8** (R = Ph), **9** (R = *p*-MeOC₆H₄), **10** (R = *p*-CF₃C₆H₄), **11** (R = 3-thienyl), **12** (R = Me), **13** (R = 2-naphthyl).
- Terminal alkynes are very challenging substrates for Ni-catalysed (4+2) cycloaddition reactions with **FOUR-MEMBERED RING KETONES**.^{8A,10B,10E} **ACTUALLY, ONLY ONE SUCCESSFUL EXAMPLE HAS BEEN DESCRIBED WITH TERT-BUTYLACETYLENE AND 1**,^{10B} **A CYCLOADDITION LIKELY PERMITTED BY THE SLOW OLIGOMERISATION OF THIS STERICALLY HINDERED ALKYNE.**

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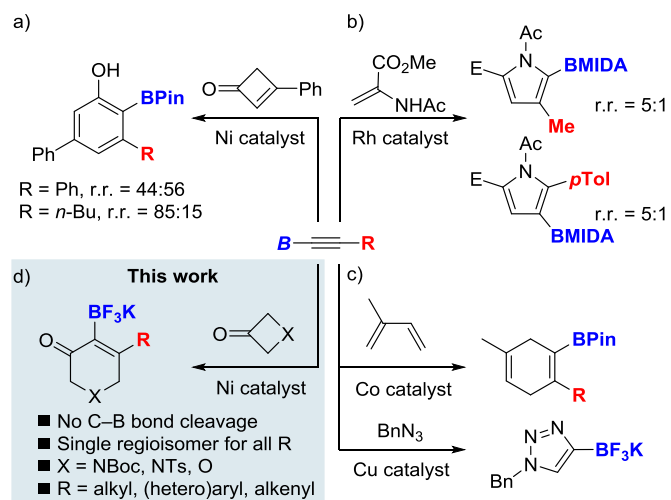


Fig. 1 Metal-catalysed cycloadditions of alkyneboron derivatives.

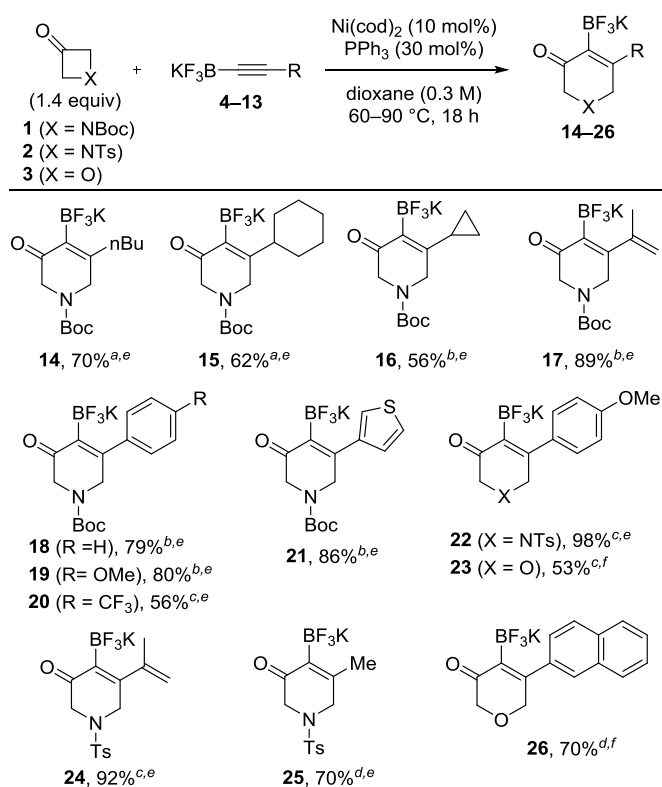
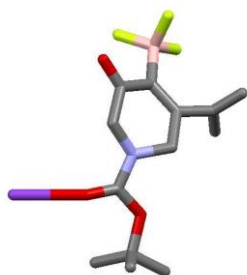


Fig. 2 Scope of the nickel-catalysed (4+2) cycloaddition of potassium alkynyltrifluoroborates with 4-membered heterocyclic ketones **1-3**. Yields of isolated products. (a) 1.8 mmol of alkyne; (b) 1.2 mmol of alkyne; (c) 0.6 mmol of alkyne; (d) 0.36 mmol of alkyne; (e) at 60 °C; (f) at 90 °C.

a)



b)

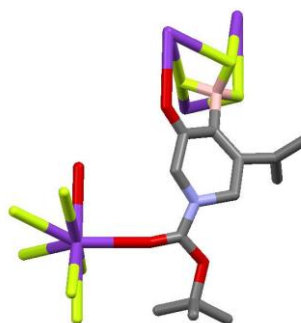


Fig. 3 Single crystal structure of **17** (hydrogen atoms are omitted for clarity); a) asymmetric unit showing the shortest contact with the potassium ion, b) structure showing all O-K and F-K contacts.

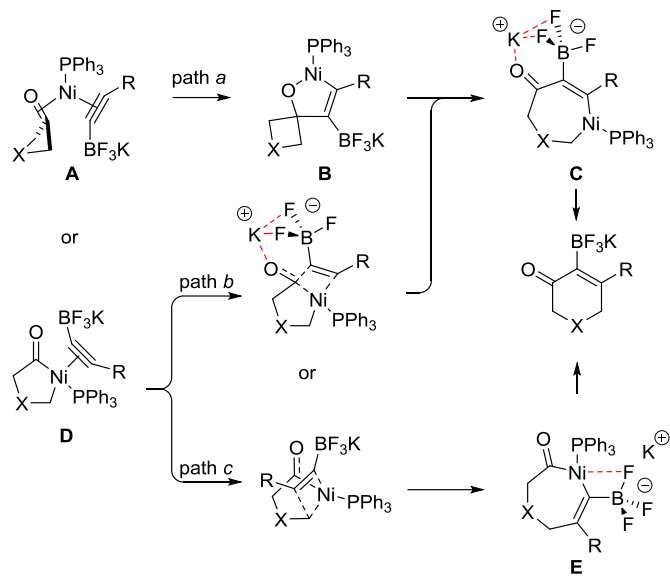
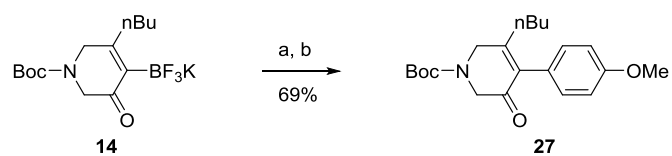


Fig. 4 Plausible origin of the regioselectivity.



SCHEME 1. TWO-STEP CONVERSION OF COMPOUND 14 INTO 27. (A) *N*-BU₄NBR₃ (1 EQUIV), THF/WATER (1:1), RT, 1 H; (B) *P*-MeOC₆H₄B(OH)₂ (3 EQUIV), K₃PO₄ (3 EQUIV), Pd₂(DBA)₃ (0.08 EQUIV), SPHOS (0.16 EQUIV), TOLUENE, 80 °C, 3 H.
