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Ritter-type amidation of alkylboron derivatives with nitriles

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ABSTRACT

A mild and facile synthesis of amides from alkylboron compounds and nitriles promoted by copper acetate and $BF_3{\cdot}OEt_2$ at room temperature is disclosed.

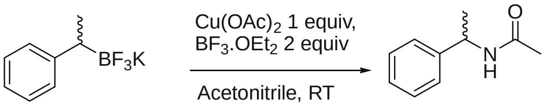
The search for new, simple and selective methods for the C–N bond formation remains a challenge for chemists. Among the classical approaches towards the amide functionality, the Ritter reaction appears as a general method for the amidation of alcohols or alkenes.[1] However, Ritter amidifications are usually performed using Lewis[2] ($SnCl_4$, $BF_3{\cdot}OEt_2$, $AlCl_3$, etc.) or Brønsted acids[3] (concentrated H_2SO_4 or AcOH) and high temperature. During the past decade, alternative milder methods were developed. Thus, Barret proposed a bismuth triflate-catalyzed amidation[4] and more recently, an iron-catalyzed Ritter reaction provided amides from benzylic alcohols in moderate to high yields.[5] However, these methods require high temperatures (100 °C and 150 °C, respectively), hence limiting the scope of the reaction. In addition, Ritter-type reactions were used for epoxide ring openings with nitriles to afford amides.[6]

Boronic acids and trifluoroborate salts are generally used as efficient cross-coupling partners in Suzuki reactions[7] or for 1,4-rhodium-catalyzed addition reactions.[8] Genet and Darses reported that the trifluoroborate functionality constitutes an excellent moiety for Suzuki–Miyaura type cross-couplings giving access to a large range of elaborated molecules.[9] Recently, different groups have shown that organotrifluoroborate salts could be used for the elaboration of highly functionalized molecules.[9,10] Thus, Molander and Ham reported that the relative stability of trifluoroborate salts tolerates significant chemical transformations such as the reductive amination[11] or S_N2 halide substitution of potassium bromoethyltrifluoroborate.[12] Recently, we have used boron compounds as nucleophilic partners in electrophilic fluorination reactions.[13]

During the course of our studies dealing with the peculiar reactivity of organotrifluoroborates, we became interested in studying the reactivity of the organoboron moiety towards nitriles under mild conditions. To the best of our knowledge, such specific reactivity for boronic derivatives has never been described to date. We discovered that the C–N bond formation could be promoted by a stoichiometric amount of copper acetate in the presence of two equivalents of boron trifluoride diethyl etherate at room temperature (Scheme 1).

In order to determine the role of each reagent, different experiments were carried out. Using the same experimental conditions but in the absence of copper acetate, the expected compound was not detected. Similarly, no reaction occurred in the absence of $BF_3{\cdot}OEt_2$. In consequence, each of these reagents is necessary for the amide bond formation.

The optimized conditions for the coupling involved the treatment of an organotrifluoroborate potassium salt (0.5 M in MeCN) with a stoichiometric amount of anhydrous $Cu(OAc)_2$ and two equivalents of $BF_3{\cdot}OEt_2$ at room temperature. Using these conditions, 1-phenyltrifluoroborate potassium salt afforded the corresponding acetamide in 75% isolated yield in 10 min (Table 1, entry 1). Similarly, diversely substituted benzyltrifluoraborates



Scheme 1. Copper-promoted addition of acetonitrile on alkytrifluoroborates.

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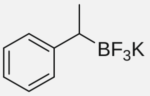
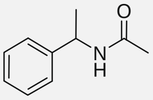
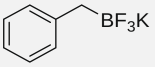
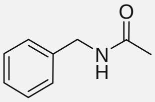
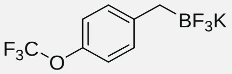
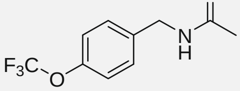
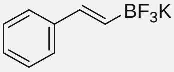
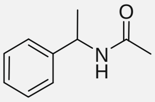
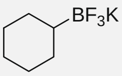
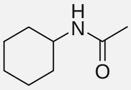
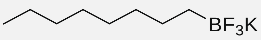
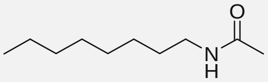
Table 1
Amidification of various boron compounds and acetonitrile

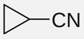
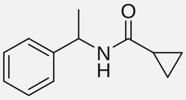
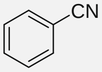
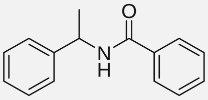
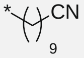
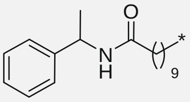
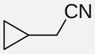
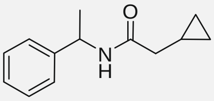
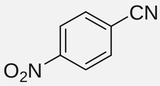
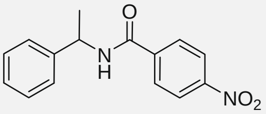
Entry	Substrates	Products	Yield[a] (%)
1			75
2			61
3			66
4			80
5			70
6			0

[a] Isolated yield.

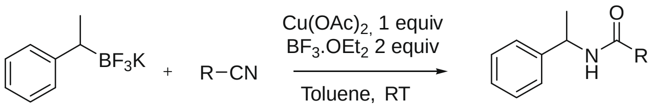
afforded the expected amides in 61–66% yield (Table 1, entries 2 and 3). However, it is worth noting that for primary benzyltrifluoroborates, the reaction generally requires longer reaction times (up to 48 h) in order to obtain a good conversion. Interestingly, trans-2-phenylvinylboronic acid (Table 1, entry 4) afforded the unexpected *N*-(1-phenylethyl)acetamide in 80% yield. Formation of the latter can be explained by considering that the attack of the nucleophile (acetonitrile) is favoured on the most reactive benzylic position. Secondary alkylboronic acids give also the expected product. Nevertheless their lower reactivity involves also a longer reaction time (up to 96 h), and hence oxidative degradation. Thus, cyclohexanol was identified as a major by-product when cyclohexylboronic acid was used as a substrate (Table 1, entry 5). The limitation of this reaction appeared for primary potassium alkyltrifluoroborate salts, as no conversion was observed. In this case, the reduced alkane (here octane) was the only newly formed compound (Table 1, entry 6).

The scope and limitations of this protocol were examined using a series of nitriles. However, as some nitrile parts of this study were solid, we had to check if the presence of a solvent would have an impact on the outcomes of the reaction. Accordingly we repeated the reaction between 1-phenyltrifluoroborate potassium salt and acetonitrile in toluene at a concentration of 0.5 M. The nitrile was introduced in 10-fold excess, copper acetate and $BF_3 \cdot OEt_2$ in onefold and twofold excesses, respectively (Scheme 2). Using these conditions, the expected acetamide was isolated in 75%. This result demonstrated that the presence of a solvent was not deleterious. According to the same experimental procedure, we tested a series of primary alkylnitriles, (Table 2, entries 1, 3 and 4). Each of these reactions afforded the corresponding amide in good isolated yield in 1 h at room temperature. Similarly, the amide obtained from benzonitrile was isolated in 70% yield (Table 2, entry 2). As expected, the presence of electron-withdrawing groups on the aromatic ring decreases the nucleophilicity of the nitrile and favours the dimerization of the boron compound. Thus, in the case of 4-nitrobenzonitrile (Table 2, entry 5) a GC analysis revealed the formation of amide and 2,3-diphenylbutane (dimer) in a 1:1 ratio. In the case of 4-bromoacetonitrile, the expected compound was not observed. On the other hand, the reduced bromide was detected as the major by-product.

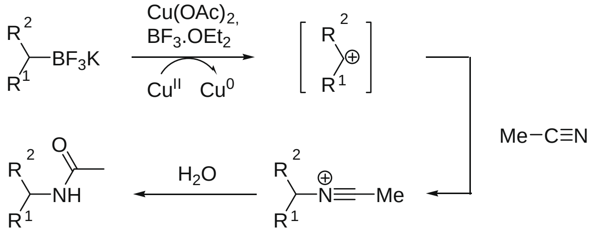
Table 2
Amidification of various nitriles with potassium 1-phenylethylboronate

Entry	Substrates	Products	Yield[a] (%)
1			85
2			70
3			93
4			70
5			51[b]

[a] Isolated yield.
[b] Determined by GC analysis.



Scheme 2. Amidification with potassium 1-phenylethylboronate and different nitriles.



Scheme 3. Proposed mechanism for the Ritter-type amidification.

Based on the afore-mentioned results and on the basis of the mechanism proposed for the Ritter amidification,[14] we believe that the combination of copper acetate and boron trifluoride generates an oxidative complex able to reverse the polarity of the C–B bond, hence creating a carbocation that is able to react subsequently with the nucleophilic nitrogen atom of the nitrile (Scheme 3).

Upon quenching, the latter intermediate is hydrolyzed affording the corresponding amide. Two major observations support this mechanism. Firstly, a precipitate of metallic copper was observed every time the coupling occurred. Secondly, we excluded the mechanism that involved direct oxidation of the boronate with the corresponding alcohol as no alcohol was detected by GC analyses for any of these tests with the exception of the reaction with octyltrifluoroborate (Table 1, entry 6). However, in this case, no amide was detected. This result demonstrates that in our conditions the ‘classical’ Ritter-type mechanism does not occur. Nevertheless, in some case, Table 1 entry 4 and Table 2 entry 5, the mechanism could be different. The product obtained (Table 1 entry 4) or the formation of 2,3-diphenylbutane (Table 2, entry 5) suggests a free radical intermediate. In these two cases, the active species could result from the reaction of $BF_3{\cdot}OEt_2$ with alkyltrifluoroborate affording the very reactive RBF_2 entity.[15]

In conclusion, we have developed a mild and efficient method for the preparation of amides from nitriles and trifluoroborate potassium salt derivatives promoted by copper acetate and boron trifluoride. This transformation was realized at room temperature without the need of ligand for the copper. We propose that the coupling involves an oxidative nucleophilic substitution mechanism followed by the subsequent attack of the nitrile as nucleophile. More detailed mechanistic investigations are currently under way in our laboratory, in order to understand the exact role of copper acetate and boron trifluoride diethyl etherate.

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