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Catalytic Synthesis of Potassium Acyltrifluoroborates (KATs) from Boronic Acids and the Thioimidate KAT Transfer Reagent

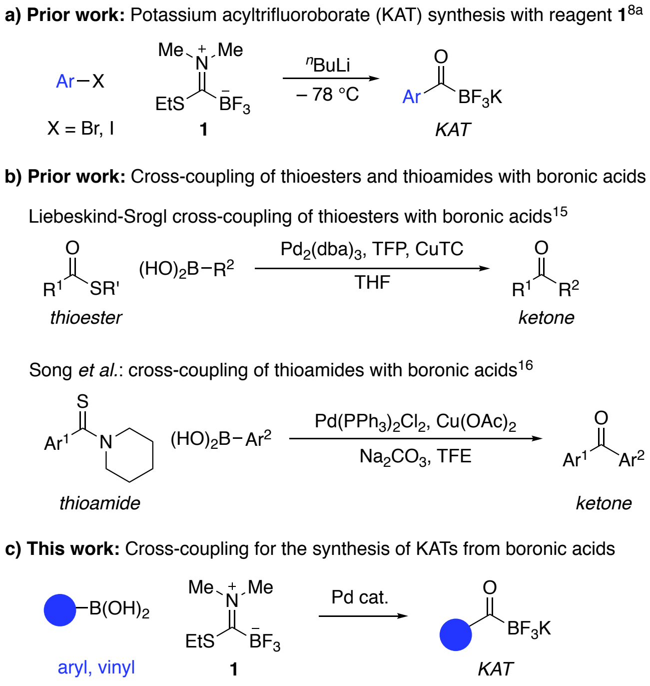
Anne Schuhmacher,[a] Sarah J. Ryan,[b] and Jeffrey W. Bode*[a]

Dedication ((optional))

Abstract: We report the synthesis of potassium acyltrifluoroborates (KATs) by a palladium-catalyzed cross-coupling of boronic acids and the thioimidate KAT transfer reagent. The combination of widely available aryl- and vinylboronic acids with commercially available thioimidate **1** using catalytic Pd^{II} and a Cu^{II} additive enables the preparation of KATs in high yields and with good functional group tolerance. This formal insertion of CO into organoboronic acids can also be applied to boronic acid pinacol esters and potassium organotrifluoroborates using a slightly modified procedure. The cross-coupling can be telescoped into the one-pot synthesis of amides and α-aminotrifluoroborates by exploiting the unique chemistry of KATs and their trifluoroborate iminium (TIM) derivatives.

Potassium acyltrifluoroborates (KATs) are robust, remarkable functional groups of increasing interest since their first report by Molander and co-workers.[1] Their unique chemistry includes rapid amide-forming ligations with hydroxylamines[2] or *N*-chloroamines[3] and condensations with amines to give stable zwitterionic trifluoroborate iminiums (TIMs).[4] KATs have been applied for protein conjugation,[5] the modification of peptides and proteins[2b,6] and for polymer and materials chemistry.[7] These advances have inspired a plethora of new methods to access KATs starting from aryl halides,[8] alkyl halides,[9] Grignard reagents,[10] aldehydes,[11] vinyl boronic acids,[12] alkynes,[13] and acid chlorides.[14] Although such methods allow for the preparation of many different KATs, they either require several synthetic steps or suffer from low functional group tolerance. Methods that deliver KATs by one-step reactions of commercial and widely available starting materials are still in high demand.

In this report we document the preparation of KATs by the coupling of commercial thioimidate KAT transfer reagent **1** with boronic acids (Figure 1c). This approach was inspired by the Liebeskind-Srogl cross-coupling between electrophilic organosulfur compounds, e.g. thioesters, and boronic acids, mediated by a Pd^0 catalyst and a copper additive.[15] Of particular relevance to this work was the recent report by Song and co-workers on the palladium-catalyzed cross-coupling of boronic acids with thioamides with Cu^{II} as an additive (Figure 1b).[16]



a) Prior work: Potassium acyltrifluoroborate (KAT) synthesis with reagent **1**[8a]

b) Prior work: Cross-coupling of thioesters and thioamides with boronic acids

Liebeskind-Srogl cross-coupling of thioesters with boronic acids[15]

Song *et al.*: cross-coupling of thioamides with boronic acids[16]

c) This work: Cross-coupling for the synthesis of KATs from boronic acids

Figure 1. Synthesis of potassium acyltrifluoroborates (KATs) from KAT transfer reagent **1**. a) Previous synthetic method for the preparation of KATs from arylhalides using ^{n}BuLi; b) cross-coupling of thioesters and thioamides with boronic acids for the preparation of ketones; dba = dibenzylideneacetone, TFP = tri(2-furyl)phosphine, CuTC = copper(I) thiophene-2-carboxylate; c) Palladium-catalyzed cross-coupling of reagent **1** with boronic acids.

Initial attempts to couple phenylboronic acids with KAT transfer reagent **1** under standard conditions for Liebeskind-Srogl couplings did not afford the desired product (Table 1, Entry 1). In contrast, the conditions reported by Song for the coupling of thioamides and boronic acids provided some of the desired product (Table 1, Entry 2), although a complex reaction mixture was observed.

The Liebeskind-Srogl cross-coupling and Song's cross-coupling proceed via distinct mechanisms, offering an explanation for the difference in reactivity. While the Liebeskind-Srogl cross-coupling occurs via oxidative addition followed by transmetallation and reductive elimination, Songs' approach is reported to involve a Pd^{II} intermediate that is formed after desulfurization without an oxidative addition step. The product is delivered after transmetallation and reductive elimination; an oxidant is necessary to regenerate the catalyst.[16,17]

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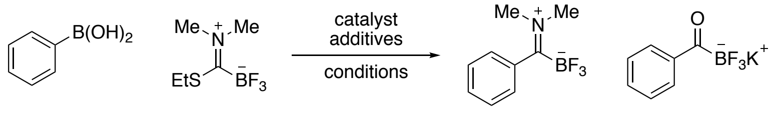
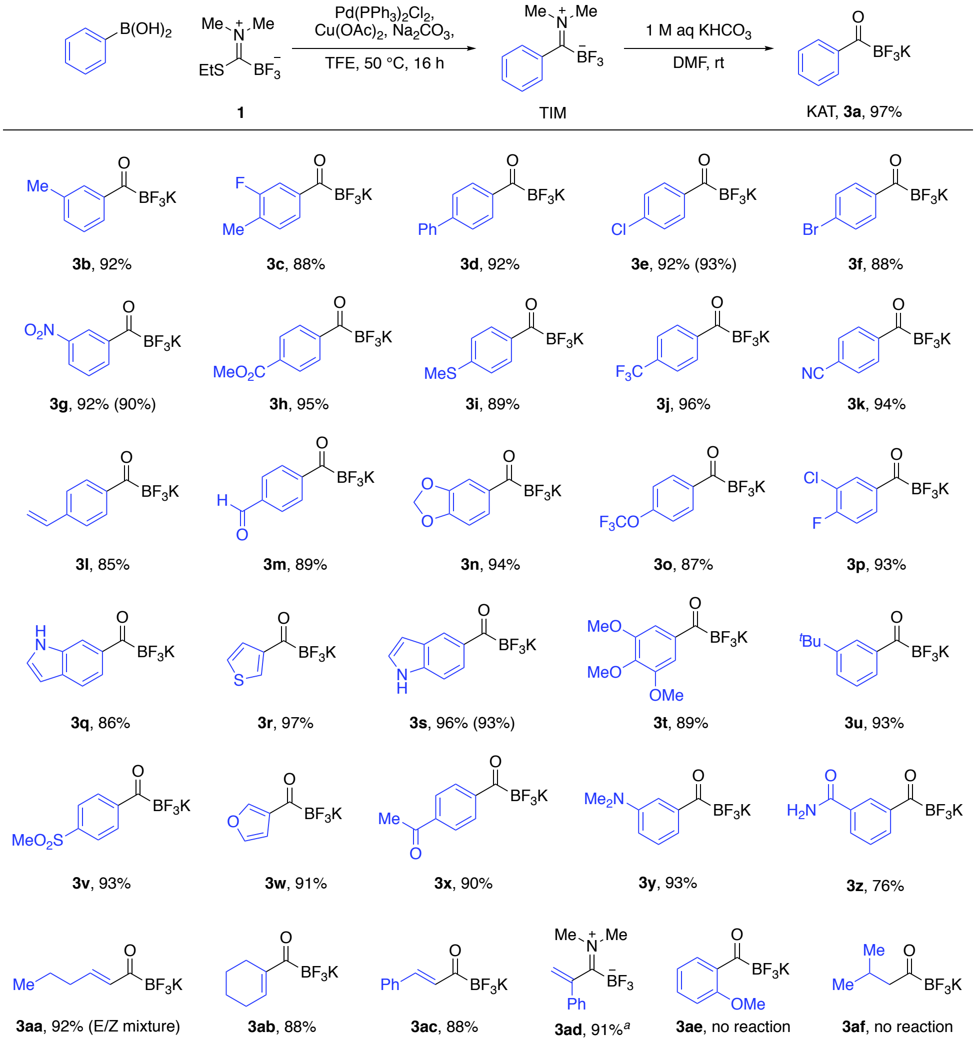
Table 1. Selected screening results for the cross-coupling between phenylboronic acid and thioimidate KAT transfer reagent **1.**



2 equiv **1**, 1 equiv **2** **3a**

Entry	Catalyst	Additives	Conditions	Result (1:2:3a, in %)[a]
1	2.0 mol% $Pd_2(dba)_3$,, 10 mol% TFP[b]	2 equiv CuTC[c]	THF, 50 °C, 18 h	0 : 0 : 0
2	7.5 mol% $Pd(PPh_3)_2Cl_2$	2 equiv $Cu(OAc)_2•H_2O$, 0.5 equiv Na_2CO_3	TFE, 90 °C, 4 h[d]	0 : 32 : 0
3	7.5 mol% $Pd(PPh_3)_2Cl_2$	2 equiv $Cu(OAc)_2$, 0.5 equiv Na_2CO_3	TFE, 90 °C, 4 h	0 : 64 : 0
4	7.5 mol% $Pd(PPh_3)_2Cl_2$	2 equiv $Cu(OAc)_2$, 0.5 equiv Na_2CO_3	TFE, 50 °C, 18 h	0 : 99 : 0
5	5.0 mol% $Pd(PPh_3)_2Cl_2$	2 equiv $Cu(OAc)_2$, 0.5 equiv Na_2CO_3	TFE, 50 °C, 18 h	30 : 54 : 18
6	7.5 mol% $Pd(PPh_3)_2Cl_2$	2 equiv $Cu(OAc)_2$, 0.5 equiv Na_2CO_3	^{t}BuOH, 50 °C, 18 h	11 : 79 : 0

Detailed screening results can be found in the Supplementary Information. [a] Ratio determined with respect to fluorobenzene as an internal standard by ^{19}F NMR; [b] dba = dibenzylideneacetone, TFP = tri(2-furyl)phosphine; [c] CuTC = copper(I) thiophene-2-carboxylate; [d] TFE = 2,2,2-trifluoroethanol.



3b, 92% **3c**, 88% **3d**, 92% **3e**, 92% (93%) **3f**, 88%

3g, 92% (90%) **3h**, 95% **3i**, 89% **3j**, 96% **3k**, 94%

3l, 85% **3m**, 89% **3n**, 94% **3o**, 87% **3p**, 93%

3q, 86% **3r**, 97% **3s**, 96% (93%) **3t**, 89% **3u**, 93%

3v, 93% **3w**, 91% **3x**, 90% **3y**, 93% **3z**, 76%

3aa, 92% (E/Z mixture) **3ab**, 88% **3ac**, 88% **3ad**, 91%^{a} **3ae**, no reaction **3af**, no reaction

Scheme 1. Substrate scope for the cross-coupling of reagent **1** with boronic acids. Conditions: 2 equiv boronic acid, 1 equiv **1**, 7.5 mol% $Pd(PPh_3)_2Cl_2$, 2 equiv $Cu(OAc)_2$, 0.5 equiv Na_2CO_3. The yields are isolated yields. Reactions were performed on 0.2 mmol scale. Yields in parentheses are reported for reactions performed on 2 mmol scale. TIM intermediate purified by flash column chromatography. KAT isolated by washing with acetone after hydrolysis. ^{a}Isolated as the TIM; 1,4-addition of *N,N*-dimethylamine was observed as a major side product during TIM hydrolysis.

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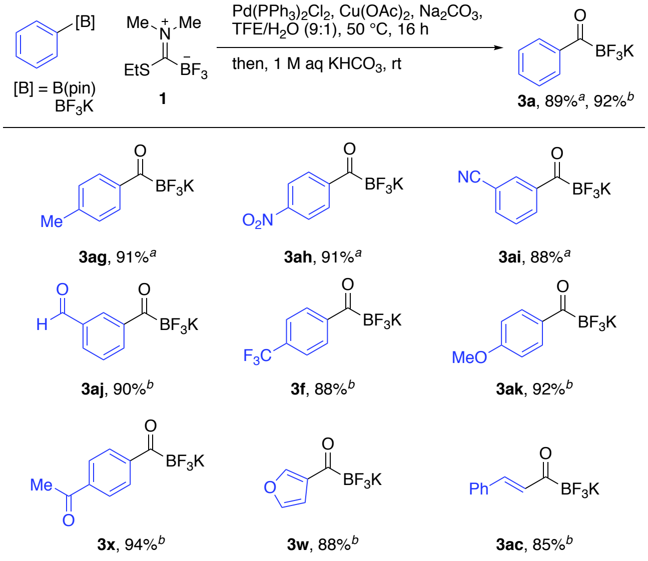
During the optimization of the cross-coupling conditions, we found that the reaction proceeded cleanly when conducted for longer times at lower temperatures. We chose cross-couplings with 7.5 mol% $Pd(PPh_3)_2Cl_2$, 2 equiv $Cu(OAc)_2$, and 0.5 equiv Na_2CO_3 in 2,2,2-trifluoroethanol (TFE) at 50 °C for 16 hours (Table 1, Entry 4) as the standard procedure for further experiments. The reaction was performed using 2 equiv of boronic acid to achieve good conversion even for more challenging substrates where protodeborylation was observed as a side product. We elected to use water-free conditions, as it allowed us to obtain the *N,N*-dimethyl TIMs, rather than the KATs, as the products. This facilitated purification, as the zwitterionic TIMs are amenable to isolation by column chromatography; the corresponding KATs were easily obtained after hydrolysis.

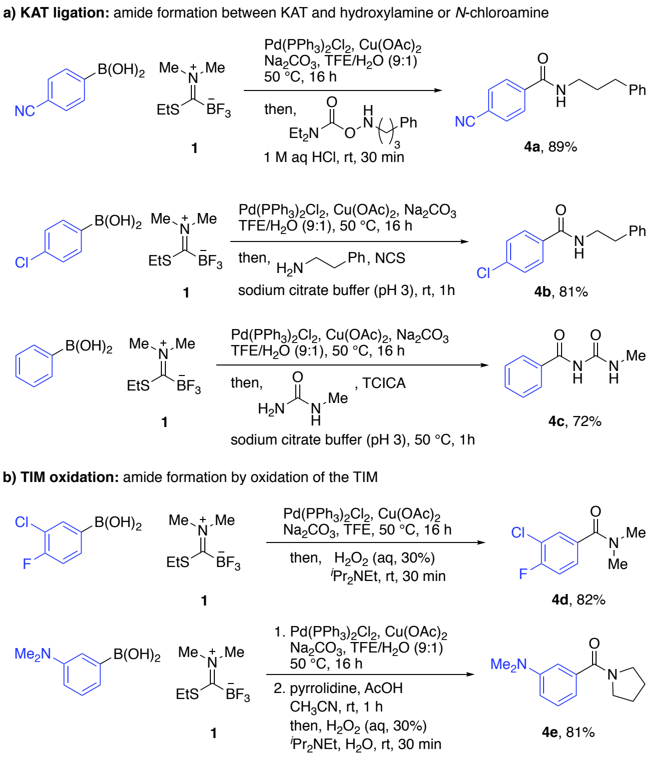
With these conditions in hand, we evaluated the cross-coupling of a variety of aryl- and vinylboronic acids bearing different substituents and functional groups (Scheme 1). The previous synthesis of KATs from transfer reagent **1** required ^{n}BuLi, which limited the functional group tolerance.[8a] KATs with sensitive functional groups can be prepared by less direct methods[8b,11b]. Since many boronic acids as well as transfer reagent **1** are commercially available, this new method offers a complementary one-step approach to both new and previously reported KATs, including examples with sensitive functional groups (e.g. **3l**, **3m**, **3q**, **3v**, **3z**) and olefinic KATs (**3aa** – **3ad**). We have additionally shown that the reaction is amenable to preparative scale without diminishing the yield (substrates **3e**, **3g**, and **3s**). While the coupling tolerated many sensitive functional groups, it is so far not successful for producing KATs from sterically-demanding ortho-substituted arylboronic acids, certain N-containing aromatic heterocycles, including pyridine- and quinolineboronic acids, alkynylboronic acids, or alkylboronic acids (details can be found in the Supporting Information).



Scheme 2. Substrate scope for the cross-coupling with boronic acid pinacol esters and potassium organotrifluoroborates. Conditions: 2 equiv boronic acid pinacol ester or potassium organotrifluoroborate, 1 equiv **1**, 7.5 mol% $Pd(PPh_3)_2Cl_2$, 2 equiv $Cu(OAc)_2$, 0.5 equiv Na_2CO_3. The yields are isolated yields. Reactions were performed on 0.2 mmol scale. KAT was isolated by washing with acetone after cross-coupling and hydrolysis. ^{a}Prepared from the boronic acid pinacol ester; ^{b}Prepared from the potassium organotrifluoroborate.

We further established a protocol for the cross-coupling of boronic acid pinacol esters and potassium organotrifluoroborates (Scheme 2). The addition of water was required to achieve efficient *in-situ* hydrolysis to the boronic acid and the amount of critical for obtaining the KATs in good yields. Successful cross-coupling was performed using 9:1 TFE/H_2O. The *in-situ* hydrolysis did not proceed efficiently with only stoichiometric amounts of water, however the yield dropped if a larger ratio of water or only water was used as reaction solvent. Under the aqueous, basic cross-coupling conditions, the TIM was largely hydrolyzed to the KAT already. For some substrates minor amounts of the TIM were observed after the cross-coupling and aqueous $KHCO_3$ was added to hydrolyze any remaining TIMs. The KATs were purified by washing with Et_2O and CH_2Cl_2 or precipitation from acetone.

The clean formation of KATs and TIMs under these conditions facilitates their *in-situ* conversion into a variety of different products (Scheme 3 and 4). The choice of solvent dictated the formation of either the TIM or KAT during the cross-coupling reaction. While the TIM was formed in the absence of water, the KAT was obtained if water was added as a co-solvent. We established direct amide formation of secondary amides from the cross-coupling products by KAT ligation with a hydroxylamine or an *in-situ* formed *N*-chloroamine. In contrast to established carbonylation reactions, this approach serves as an entry to more exotic products, such as imide **4c** (Scheme 3a). For the preparation of tertiary amides, TIMs could be converted to the amide by treatment of the reaction mixture with hydrogen peroxide. The *N,N*-dimethylamine TIM formed during the cross-coupling with **1** could be exchanged with a different amine for the formation of other tertiary amides (Scheme 3b).[2,19]


a) KAT ligation: amide formation between KAT and hydroxylamine or *N*-chloroamine

b) TIM oxidation: amide formation by oxidation of the TIM

Scheme 3. Direct amide bond formation after cross-coupling with a hydroxylamine, an *N*-chloroamine or by TIM oxidation. The yields are isolated yields. Reactions performed on 0.2 mmol scale. NCS = *N*-chlorosuccinimide, TCICA = trichloroisocyanuric acid.

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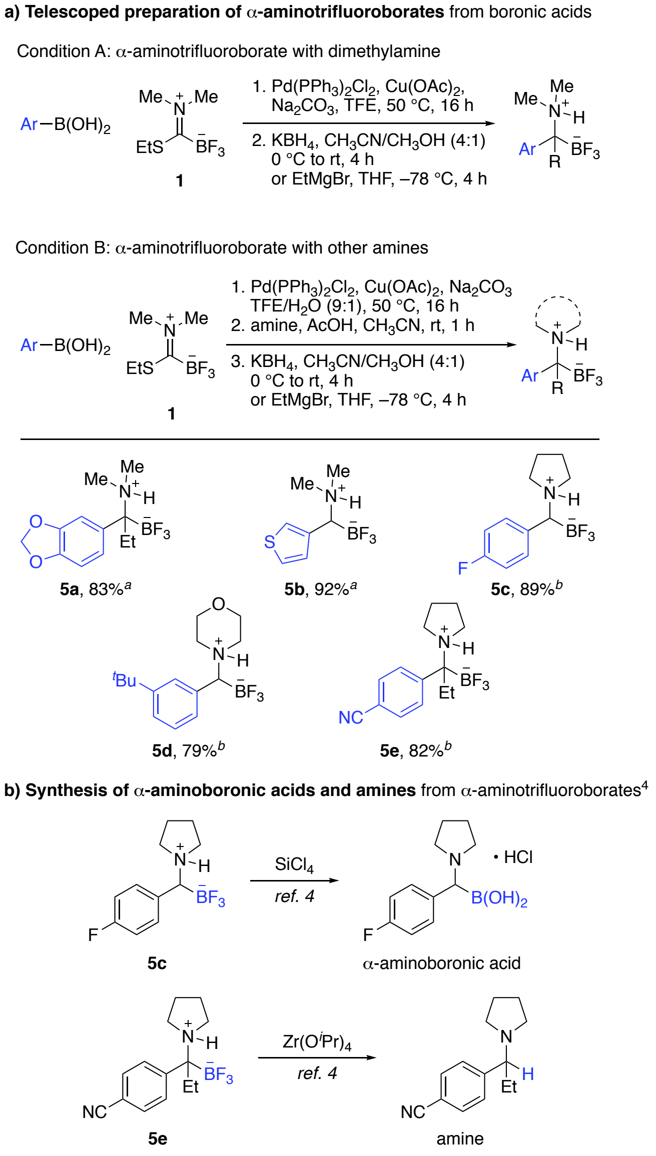
As amines and organoboronic acids are widely available, stable starting materials, this approach offers an operationally simple approach for the direct preparation of amides from organoboronic acids and amines. It complements oxidative aminocarbonylations of boronic acids, including the work of Wu on aminocarbonylation of organoboronic acids with *N*-chloroamines under high CO pressure.[20] Alternatively, Jiao and co-workers reported the aminocarbonylation of organoboronic acids with simple amines using O_2 as an oxidant.[21] Zhang and Ma reported the aminocarbonylation of boronic acids in a CO atmosphere with CuO as the oxidant.[22] Iranpoor and co-workers reported the Nickel-catalyzed aminocarbonylation of boronic acids using $Cr(CO)_6$ as the carbonyl source.[23]



Scheme 4. Telescoped formation of α-aminotrifluoroborates after cross-coupling. The α-aminotrifluoroborates can be converted into α-aminoboronic acids or amines. The yields are isolated yields. Reactions performed on 0.2 mmol scale. [a]α-aminotrifluoroborate with *N,N*-dimethylamine prepared with conditions A; [b]α-aminotrifluoroborate with other amines prepared with conditions B.

TIMs can be converted into α-aminotrifluoroborates by treatment with a Grignard reagent or potassium borohydride following a solvent exchange. This procedure could be applied to TIMs obtained after cross-coupling directly or to KATs, by treating them with a different amine to provide the corresponding TIM, and subsequently converting them to the α-aminotrifluoroborate. This allowed for the preparation of α-aminotrifluoroborates (Scheme 4a) without isolation of any intermediates. We have shown previously that α-aminotrifluoroborates can be hydrolyzed into α-aminoboronic acids using $SiCl_4$ or converted into amines by deborylation with $Zr(O^iPr)_4$ (Scheme 4b).[4]

In summary, we have developed a new method for the synthesis of aromatic and alkenyl KATs. The formal carbonylation of widely-available boronic acids and their derivatives, boronic acid pinacol esters or potassium organotrifluoroborates allows for the preparation of KATs that were not accessible previously and facilitates access to many common structures. The KATs or TIMs obtained after the cross-coupling reaction could be directly converted into amides, α-aminotrifluoroborates, α-aminoboronic acids, or amines.

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Keywords: acylboron compounds • cross-coupling • boronic acids • synthetic methods • zwitterions

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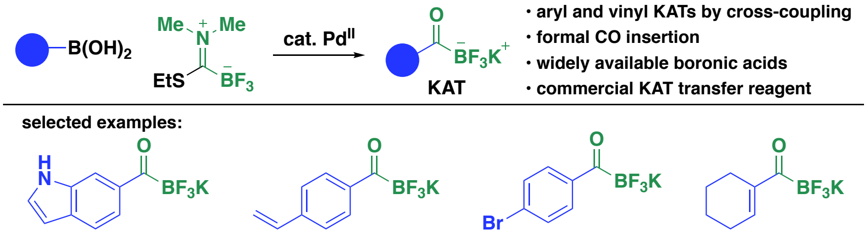

Formal COllaBoration. The palladium-catalyzed preparation of potassium acyltrifluoroborates (KATs) proceeds by a formal CO insertion into the C–B bond of widely available boronic acids, boronic acid pinacol esters, or potassium organotrifluoroborates with the thioimidate KAT transfer reagent. A variety of KATs can be prepared with good functional group tolerance in high yields. The direct modification of KATs allows for the telescoped preparation of amides, α-aminotrifluoroborates, and other aryl products – many of which are not directly accessible by established cross-coupling methods.

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