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Stereospecific Ni-Catalyzed Cross-Coupling of Potassium Alkenyltrifluoroborates with Alkyl Halides

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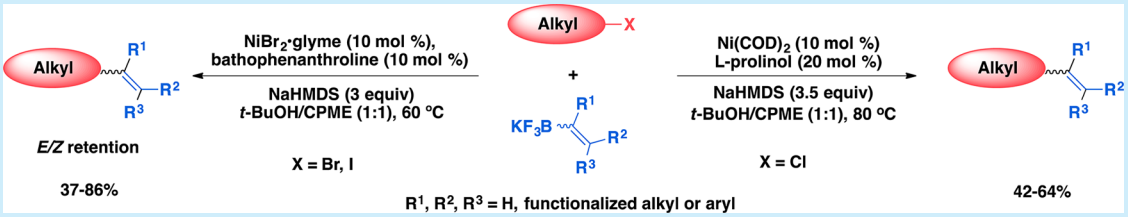
Supporting Information



ABSTRACT: A general method for the alkenylation of alkyl electrophiles using nearly stoichiometric amounts of the air- and moisture-stable potassium organotrifluoroborates has been developed. Various functional groups were tolerated on both the nucleophilic and electrophilic partner. Reactions of highly substituted *E*- and *Z*-alkenyltrifluoroborates, as well as vinyl- and propenyltrifluoroborates, were successful, and no loss of stereochemistry or regiochemistry was observed.

The stereoselective synthesis of olefins has long attracted the attention of the organic chemistry community.[1] Although since their discovery transition metal catalyzed cross-coupling reactions have focused mainly on $C(sp^2)-C(sp^2)$ bond formation, recent advances have also been made in the important field of $C(sp^2)-C(sp^3)$ coupling.[2,3] Among these, alkenylations of alkyl electrophiles have been of high interest because they allow rapid access to a broad array of highly substituted and sterically hindered olefins.[2b,3] With a wide variety of structurally diverse, functionalized, alkyl halides being commercially available or readily accessible, the challenge of the transformation remains the alkenyl nucleophile.[3] Previous studies have described the cross-coupling of alkenyl nucleophiles with primary iodides and bromides catalyzed by Pd, but most frequently Ni and Fe complexes are used because of their capacity to cross-couple secondary electrophiles without the undesired β-hydride elimination.[3] Despite remarkable advances in the field, the existing methods still present limitations. For example, the Kumada[4] or Negishi[5] stereospecific cross-couplings of alkenyl nucleophiles with secondary bromides and iodides were successfully achieved, but these transformations suffer from the instability of the organometallic nucleophile, along with a lack of functional group compatibility. The functional group tolerance and stability issues were solved by developing Stille alkenylations of alkyl iodides and bromides. However, the high toxicity of organostannanes makes the Stille cross-coupling a less desirable transformation.[6] Pd-[7] and Ni-catalyzed[8] Suzuki–Miyaura alkenylations were developed, and they present advantages over the aforementioned methods because of the stability, low toxicity, and functional group compatibility of organoborons. However, only isolated examples of Pd-[7] and Ni-catalyzed[8] cross-coupling of unhindered *E*-alkenylboronic acids with alkyl electrophiles have been reported. Additionally, similar to most heteroaryl- and alkylboronic acids, alkenylboronic acids are prone to rapid protodeboronation when stored on the benchtop,[9] and a large excess is required to achieve good yields.[10] More recently, the Fe-catalyzed Suzuki–Miyaura cross-coupling of alkenyl pinacol boronate esters with alkyl halides was reported.[11] Although these organoborons are more stable than their boronic acid equivalents, the substrate scope of the nucleophile remains limited (a silyl protected alcohol was the only functional group tolerated on the nucleophile), in addition to the inconvenience associated with the lack of atom economy of pinacol boronates. A major drawback in the reported Fe-catalyzed Suzuki–Miyaura alkenylation is the requirement to use super-stoichiometric amounts of *t*-BuLi.

We envisioned that the aforementioned limitations (stability of the nucleophiles and of other reagents such as *t*-BuLi, large excess of organoborons, and pinacol waste) could be overcome by the use of potassium alkenyltrifluoroborates in a Ni-catalyzed Suzuki–Miyaura cross-coupling with various alkyl electrophiles. Alkenyltrifluoroborates are indefinitely air- and moisture-stable, and various stereochemically pure, highly substituted and functionalized structures (containing alkyl halides, esters, nitriles, ketones, etc.) can be easily accessed.[12] Encouragingly, the use of alkenyltrifluoroborates as an alternative to other organoborons in $C(sp^2)-C(sp^2)$ cross-couplings has been successfully demonstrated,[12] as well as the Ni-catalyzed cross-coupling of a wide array of potassium aryl- and heteroaryltrifluoroborates with alkyl halides.[13]

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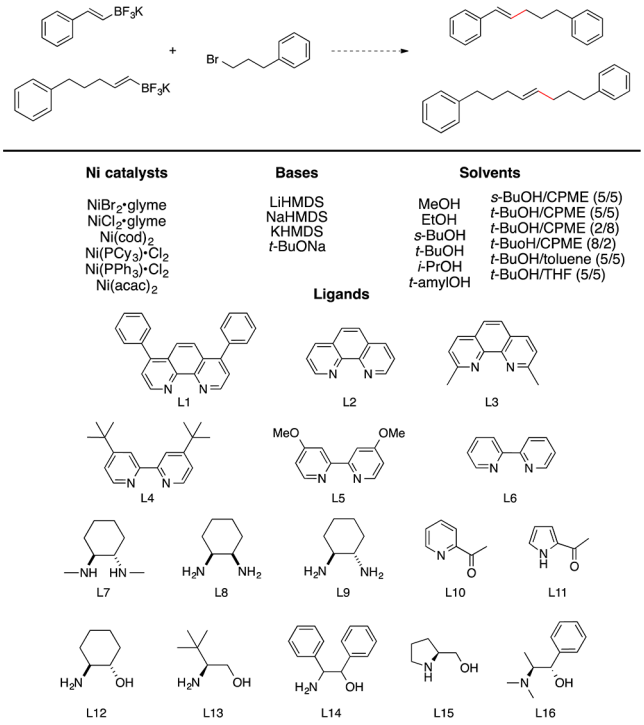
The success of our group in using parallel microscale high-throughput experimentation (HTE) for rapid reaction optimization[13,14] prompted us to apply it to the Ni-catalyzed cross-coupling of alkyl halides with potassium alkenyltrifluoroborates. Using 1-bromo-3-phenylpropane as the model electrophile and stoichiometric amounts of either (*E*)-2-styryltrifluoroborate or (*E*)-5-phenyl-pent-1-en-1-yltrifluoroborate as nucleophiles, a wide variety of catalyst/ligand combinations, solvents, and bases were screened at 60 and 80 °C (Scheme 1).

Scheme 1. Model Substrates and Catalytic Systems Tested *via* Parallel Microscale High-Throughput Experimentation (HTE)

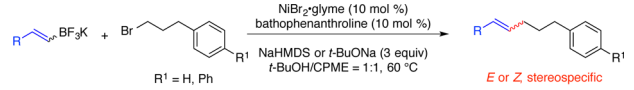


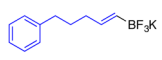
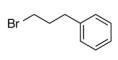
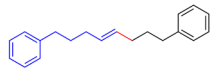
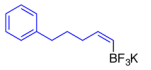
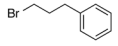
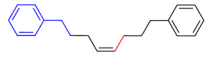
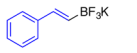
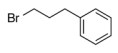
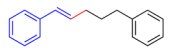
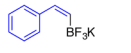
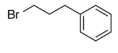
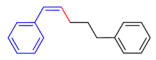
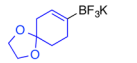
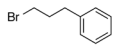
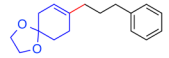
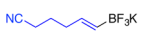
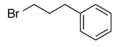
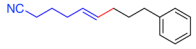
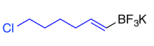
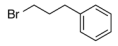
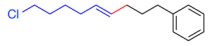
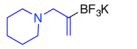
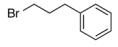
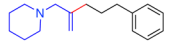
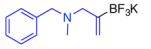
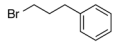
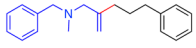
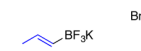
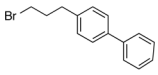
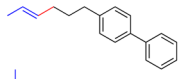
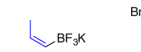
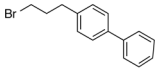
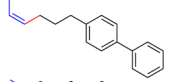
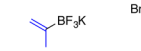
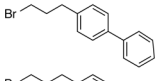
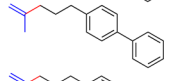
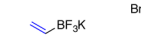
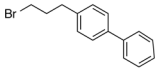
During the HTE, it was observed that the counterion on the base was significant for the outcome of the reaction. LiHMDS provided the desired compound in good yields; however, the yields using NaHMDS were superior. KHMDS, on the other hand, resulted in very low reactivity. NaHMDS in *t*-BuOH provided similar yields to those using *t*-BuONa, and the HMDS formed seems to have no role in the reaction. However, for the ease of the HTE screenings setup, LiHMDS, NaHMDS, or KHMDS was used in combination with various protic solvents to generate a wide range of alkoxides in situ. As expected,[15] the hydrolysis of the potassium organotrifluoroborates was dependent on the amount and the nature of the base, as well as the protic solvent. It was found that at least 3 equiv of base were necessary to achieve good yields, probably to achieve a fast enough rate of hydrolysis of the potassium organotrifluoroborate. Also, it was observed that methoxides and ethoxides provide very low yields, and mostly protodeboronation of the trifluoroborate was observed. Use of a nonprotic solvent (CPME, THF, toluene) in combination with a secondary or tertiary alcohol reduced the undesired protodeboronation and increased the yield of the desired cross-coupled product.

The increase in temperature did not lead to any significant difference in terms of yields, and unless otherwise noted, the reactions were run at 60 °C to ensure smoother conditions.

Although several ligands showed reactivity to a certain extent, we observed that bathophenthroline (**L1**) was the top ligand, especially when the reaction was scaled to 1 mmol and when the best conditions applied to other classes of halides and alkenyltrifluoroborates were used. Interestingly, bathophenanthroline, 2-acetyl pyridine (**L10**), and 2-acetyl pyrrole (**L11**) also provided the desired compound in good yields. $NiBr_2$·glyme and $Ni(COD)_2$ showed similar reactivity for the model substrates, but because $Ni(COD)_2$ is air-sensitive and needs to be stored in the freezer in the glovebox, the more stable $NiBr_2$·glyme was preferred. For proof of concept, some reactions were set up outside of the glovebox, and similar overall average yields were obtained (see Table 1, entries 2 and 4, and Table 2, entries 3, 4, and 11).

Table 1. Substrate Scope for the Ni-Catalyzed Cross-Coupling of Potassium Alkenyltrifluoroborates



entry	trifluoroborate	halide	product	yield %
1				86(81[a],78[b])
2				61[c,e,f]
3				78
4				52[c,e,f]
5				80
6				64
7				60
8				61
9				53
10				81[c]
11				73[c,d]
12				68[c]
13				72[c]

[a]Reaction using 2-acetylpyridine instead of bathophenanthroline. [b]Reaction using 2-acetylpyrrole instead of bathophenanthroline. [c]Reaction run at 80 °C. [d]Product ratio Z/E = 95/5 from starting material potassium propen-1-yltrifluoroborate Z/E = 95/5. [e]Product ratio Z/E > 98/2. [f]Reaction set up outside the glovebox, using *t*-BuONa instead of NaHMDS.

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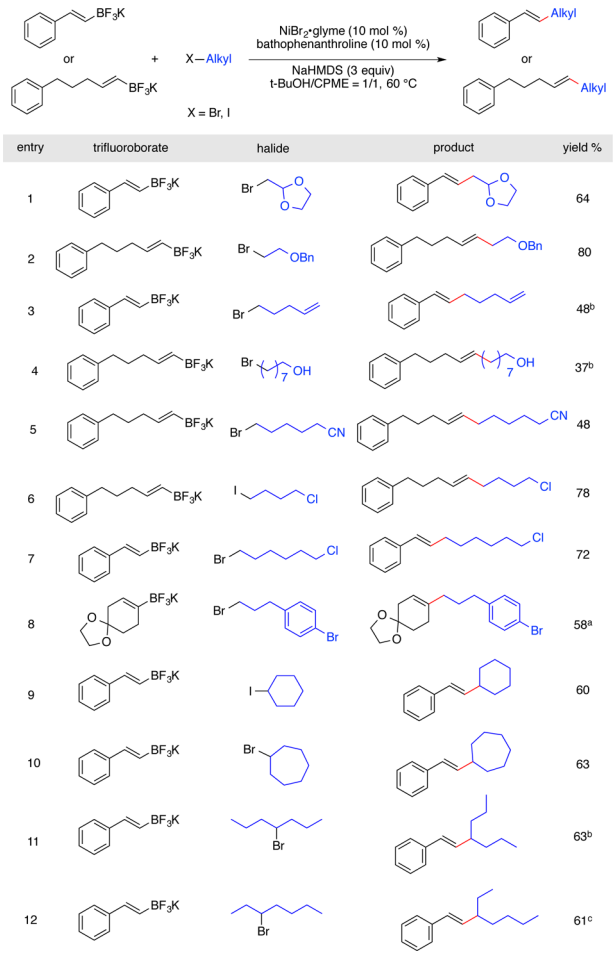
Table 2. Substrate Scope for the Ni-Catalyzed Alkenylation of Various Bromide and Iodide Electrophiles



[a]Potassium trifluoro(1,4-dioxaspiro[4,5]dec-7-en-8-yl)borate was used to facilitate the purification of the describe product. Similar crude ^{1}H NMR yields were obtained when using potassium (*E*)-2-styryltrifluoroborate and potassium (*E*)-(5-phenylpent-1-en-1-yl)trifluoroborate. [b]Reaction setup outside the glovebox, using *t*-BuONa instead of NaHMDS, ran at 80 °C. [c]Isomerization linear/branched observed by ^{1}H NMR in a ratio: (*E*)-(3-ethylhept-1-en-1-yl)benzene/(*E*)-(3-methyloct-1-en-1-yl)benzene (*E*)-non-1-en-1-ylbenzene = 85/10/5.

As a result of the HTE screenings, the best conditions were found to be 10 mol % $NiBr_2$·glyme, 10 mol % bathophenanthroline, and 3 equiv of NaHMDS as the base in a mixture of *t*-BuOH/CPME = 1:1. Some examples were performed using *t*-BuONa to establish the equivalency of NaHMDS in *t*-BuOH and *t*-BuONa (see Table 1, entries 2 and 4, and Table 2, entries 3, 4, and 11).

Because the published alkenylation methods are limited, especially in terms of substrate scope and functional group compatibility of the nucleophilic partner,[4,5,11] the conditions found were first applied to the cross-coupling of various stereochemically pure potassium alkenyltrifluoroborates (1.05 equiv) with 3-phenyl-1-bromopropane or 3-(4-biphenyl)-1-bromopropane (Table 1).

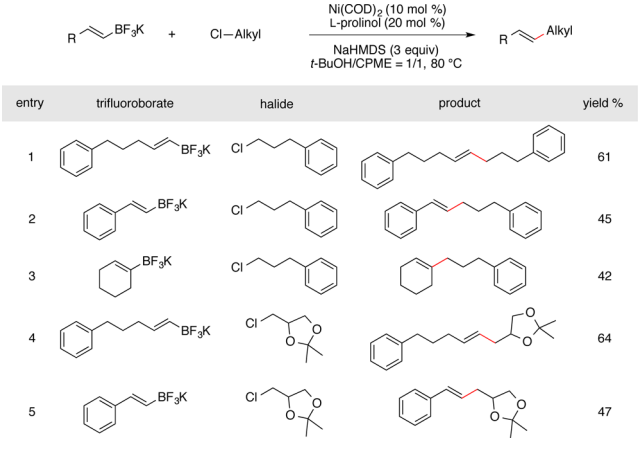
Reasonable functional group tolerance on the nucleophilic partner was observed, including substrates containing acetals (Table 1, entry 5), amines (Table 1, entries 8 and 9), alkyl nitriles (Table 1, entry 6), and notably alkyl chlorides (Table 1, entry 7), which could not be present on Grignard reagents and would not be compatible with the use of *t*-BuLi.[11] Transition metal catalyzed Suzuki–Miyaura cross-coupling of vinyl or propenylboronic acids or boronate esters has never been reported. Under the conditions developed, vinyltrifluoroborate and various propenyltrifluoroborates smoothly underwent the reaction in good yields (Table 1, entries 10–13), overcoming the limitations and disadvantages encountered with the boronic acid analogues.[11,12] It is important to notice the stereospecificity of the transformation, as both the (*E*)- and (*Z*)-isomers of the same trifluoroborates underwent the reaction with retention of stereochemistry about the olefin (Table 1, entries 1–4 and entries 10–11).

The scope of alkyl electrophiles was then extensively expanded (Table 2). In terms of functional group tolerance, acetals (Table 2, entry 1), benzyl ethers (Table 2, entry 2), a distal olefin (Table 2, entry 3), a nitrile (Table 1, entry 5), and in modest yields an alcohol (Table 2, entry 4) were tolerated. Alkyl bromides and iodides reacted chemoselectively, leaving the alkyl chlorides intact and available for further functionalization (Table 2, entries 6 and 7). Additionally, the chemoselectivity of the C(sp^3)–Br bond in the presence of the C(sp^2)–Br bond on the same electrophile was observed, another important observation in terms of bidirectional functionalization (Table 2, entry 8). Secondary cyclic iodides (Table 2, entry 9) and bromides (Table 2, entry 10) were successfully coupled. Although 4-bromoheptane cross-coupled without any branched/linear isomerization (Table 2, entry 11), 3-bromobutane provided the major desired product, along with ∼15% isomerization products (Table 2, entry 12).

Although we were pleased to observe the chemoselectivity of alkyl iodides and bromides over alkyl chlorides, it became clear that the initial reaction conditions developed could not be applied to the cross-coupling of alkyl chlorides. Various bromides and iodide salts (KI, LiI, LiBr, CuBr, CuI) were tested as additives in various ratios to initiate the cross-coupling of alkyl chlorides, but all turned out to be unsuccessful. Inspired by previously developed conditions for the Ni-catalyzed cross-coupling of alkyl electrophiles,[13] the catalytic system was switched to $Ni(COD)_2$ (10 mol %) and L-prolinol (20 mol %) at 80 °C. Under these conditions, increasing the amount of trifluoroborate (1.3 equiv) and base (3.5 equiv) provided the desired products in moderate to good yields (Table 3).

In conclusion, a method has been developed for the Ni-catalyzed alkenylation of alkyl bromides and iodides using

Table 3. Ni-Catalyzed Cross-Coupling of Alkyl Chlorides with Potassium Alkenyltrifluoroborates



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virtually stoichiometric amounts of the air and moisture stable nucleophile. An increase in temperature and a slight excess of nucleophile were required to achieve moderate to good yields for the cross-coupling of alkyl chlorides. The transformation showed reasonable functional group tolerance and a very broad structural diversity of both coupling partners. Crucially, the reaction was stereospecific, leading to highly substituted alkenes without loss of stereochemistry. Additionally, cross-coupling of branched secondary electrophiles was performed in good yields without any branched/linear isomerization.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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