

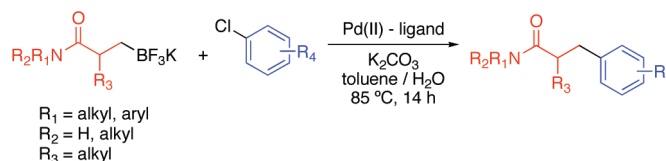
Use of Potassium β -Trifluoroborato Amides in Suzuki–Miyaura Cross-Coupling Reactions

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Potassium β -trifluoroborato amides were prepared and used as successful partners in Suzuki–Miyaura reactions with various aryl chlorides, including electron-rich and electron-poor derivatives, as well as several heteroaryl chloride partners.

Introduction

Organoborons are valuable synthetic intermediates for the preparation of a wide variety of organic molecules owing to their functional group tolerance and low toxicity.¹ β -Boryl carbonyl compounds,² which possess an anion equivalent β to a carbonyl group, constitute an important subclass of organoboron reagents. These synthons exhibit a charge-inverted reactivity compared to more traditional synthons, thus allowing potentially valuable, strategic C–C bond connections (Scheme 1). This is illustrated in Scheme 1, wherein the well-known Michael addition of nucleophiles to α,β -unsaturated carbonyl compounds³ takes advantage of the electrophilic character of the β carbon in α,β -unsaturated carbonyl substrates. In contrast, the corresponding carbon in β -boryl carbonyl derivatives bears a partial negative charge, acting as a nucleophile during the C–C bond-forming event.

Many studies have been devoted to the preparation of β -boryl carbonyl substrates, and the most important route is

certainly the transition-metal-catalyzed addition of diboron reagents to α,β -unsaturated carbonyl compounds. This procedure employs platinum,⁴ rhodium,⁵ nickel,⁶ or copper catalysts⁷ and permits the boration of a variety of α,β -unsaturated esters, nitriles, ketones, and amides. However, the engagement of the organoboron reagents thus formed has not been studied as extensively as their zinc⁸ or titanium⁹ counterparts.

Even though the metal-catalyzed cross-coupling reaction is by far the most important and widely used application of organoborons,^{1,10} surprisingly, the first use of β -borato esters in Suzuki–Miyaura reactions was reported only in 2006 by Snieckus et al.¹¹ Our group recently described the preparation of β -trifluoroborato esters and ketones and their

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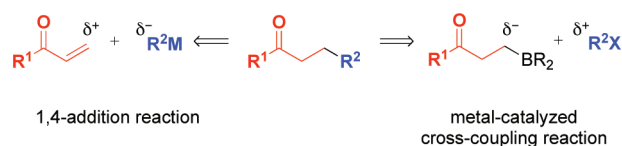
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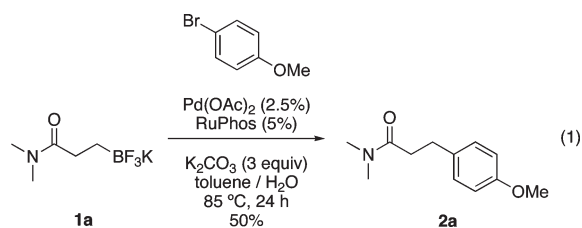
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SCHEME 1



successful use in Suzuki–Miyaura reactions.¹² The development of these methods permitted the cross-coupling of a wide variety of β -trifluoroborato ketones with aryl chlorides in good to excellent yields.¹³ Of special note, in contrast to the use of other β -metallo-substituted carbonyl reagents,¹⁴ no β -hydride elimination was observed during the reaction.

The preparation of β -borato amides has also been studied recently,⁶ but their use as coupling partners is even more scarce and challenging than the ester or ketone counterparts. To the best of our knowledge, our group published the only example of their application in the Suzuki–Miyaura reaction, which involved the use of a potassium β -trifluoroborato amide.¹² The desired cross-coupled product was isolated in only a moderate yield (eq 1).



Potassium organotrifluoroborates are counterparts of boronic acids/boronate esters that possess valuable physical and chemical properties,¹⁵ including indefinite stability to moisture and air and a low tendency to protodeboronate.¹⁶ Owing to these interesting characteristics, they have been subjected to extensive study over the past 10 years.¹⁵

Because of the usefulness of amide groups in organic synthesis, we envisioned that an extension of our previous work on potassium β -trifluoroborato ketones^{12,13} to the amide counterparts would be potentially useful. In addition to their significance in peptide chemistry, amide groups are also present in a number of chiral auxiliaries¹⁷ and are therefore important in asymmetric synthesis.

Herein, we report the preparation of various β -trifluoroborato amides and the first efficient Suzuki–Miyaura cross-coupling of these agents with various aryl and heteroaryl chlorides.

Results and Discussion

Initially, several potassium β -trifluoroborato amides were prepared using the strategy developed by Yun and co-work-

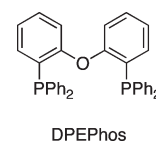


FIGURE 1. DPEPhos ligand.

TABLE 1. Preparation of Potassium β -Trifluoroborato Amides

1. B_2Pin_2 (1.1 equiv), $CuCl$ (3%), DPEPhos (3%), $NaOt-Bu$ (9%), THF / MeOH, 3 h 2. KHF_2 , MeCN, 0 °C, 3 h			
entry	reactant	RBF_3K	% isolated yield
1			60
2			57
3			68
4			98
5			95 ^a
6			55

^aSee ref 18 for the preparation of the α,β -unsaturated Weinreb amide (entry 5).

ers.^{7c} The starting commercially available α,β -unsaturated amides¹⁸ were treated with bis(pinacolato)diboron using a combination of a copper catalyst and a phosphine ligand (Figure 1).

The organoborons thus formed were converted to the corresponding trifluoroborate salts, in moderate to excellent yields, by quenching with a saturated aqueous solution of KHF_2 (Table 1).

With these trifluoroborates in hand, we then explored their application in Suzuki–Miyaura cross-coupling reactions using the inexpensive and easily available aryl chlorides. As mentioned above, our group reported the cross-coupling of potassium β -trifluoroborato amide **1a** with

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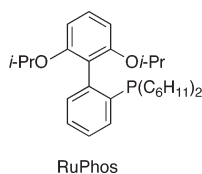
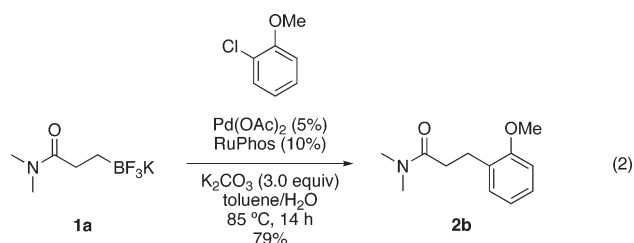


FIGURE 2. RuPhos ligand.

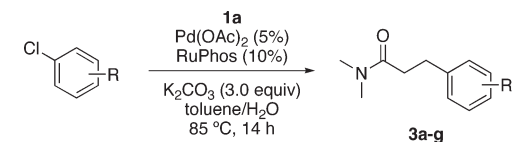
4-bromoanisole in an unoptimized 50% yield (eq 1). When these conditions were used for the cross-coupling of β -borato amide **1a** with 2-chloroanisole as the electrophile, the desired product was obtained in a yield lower than 50%. We determined that simply increasing the catalyst/ligand loading to 5 mol % of $\text{Pd}(\text{OAc})_2$ and 10 mol % of RuPhos (Figure 2), respectively, was suitable to carry out this reaction. Under these conditions, a 79% yield of the cross-coupled product **2b** was obtained (eq 2).



Encouraged by this result, we thus investigated the cross-coupling of β -trifluoroborato amide **1a** with various electron-poor aryl chlorides (Table 2). Pleasingly, all the electrophiles gave the desired cross-coupled products in very good yields. As expected, the reaction conditions were tolerant of many functional groups including nitriles, aldehydes, ketones, and esters. In particular, the conditions of the reaction were amenable to nitro groups, which are often reduced in the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction using alkylborane nucleophiles.¹⁹ In addition, ortho-, meta-, and para-substituted derivatives were all effective coupling partners. Of special note, all the reactions were run using only a small excess (1–2%) of the trifluoroborate. This is made possible by the resistance of these reagents to protodeboronation under conditions of the cross-coupling, making the organotrifluoroborates unique among organoboron coupling partners.

The study was then expanded to electron-rich aryl chlorides (Table 3), which are known to be more challenging electrophilic coupling partners than the electron-deficient counterparts.²⁰ The conditions developed worked equally well for these systems. The ortho-, meta-, and para-substituted derivatives, along with the more hindered substrate, 2-chloro-1,3-dimethylbenzene (Table 3, entry 3), were tolerant of the reaction conditions.

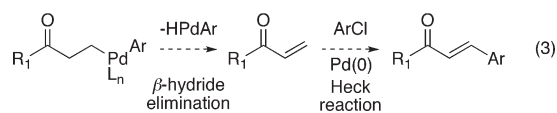
It is noteworthy that, as expected from our previous reported results,^{12,13} we did not observe the formation of the Heck product resulting from the β -hydride elimination of the palladium intermediate using this catalytic system (eq 3). When $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ was used in one of our

TABLE 2. Cross-Coupling of Potassium β -Trifluoroborato Amide **1a** with Various Electron-Poor Aryl Chlorides^a

entry	reactant	RBF ₃ K	% isolated yield
1			81
2			87
3			94
4			76
5			85
6			83
7			81

^aAll reactions were carried out using 0.25 mmol of aryl chloride and 0.253 mmol of potassium organotrifluoroborate **1a**.

previous studies,¹² a mixture of the desired compound with varying amounts (3–10%) of the corresponding unsaturated product was obtained. The use of the sterically hindered, electron-rich RuPhos as the ligand, which provides monoligated organopalladium intermediates, permits the exclusive formation of the desired cross-coupled product, presumably by increasing the relative rate of reductive elimination as compared to β -hydride elimination.²¹



To investigate the method further, attention was turned to heteroaryl chlorides (Table 4). Nitrogen-, oxygen-, and sulfur-containing heteroaryl chlorides of various ring sizes were studied. Under the developed conditions using RuPhos,

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TABLE 3. Cross-Coupling of Potassium β -Trifluoroborato Amide **1a** with Various Electron-Neutral and Electron-Rich Aryl Chlorides^a

entry	reactant	RBF ₃ K	% isolated yield
1			75
2			75
3			76
4			78
5			71
6			86

^aAll reactions were carried out using 0.25 mmol of aryl chloride and 0.253 mmol of potassium organotrifluoroborate **1a**.

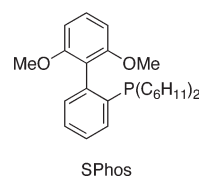
the desired cross-coupled compounds were isolated in low yields (entry 6, Table 4). These results prompted us to investigate another catalytic system, and we determined that 2.5 mol % of Pd(OAc)₂ in conjunction with 5 mol % of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, Figure 3) was more suitable for these cross-coupling reactions. These conditions permitted the formation of the desired cross-coupled products in moderate to very good yields, except for 2-chloropyridine, which proved to be an unsuitable coupling partner because only a trace amount of the expected cross-coupled product was obtained. Previous studies had shown that 2-bromopyridine was also a problematic substrate for these reactions, providing virtually none of the desired cross-coupling product but rather complex reaction mixtures.¹³

To demonstrate the scope of the method further, different potassium β -trifluoroboratoamides were cross-coupled with the unactivated 2-chloroanisole (Table 5). All the reactions were performed using the catalytic system composed of 5 mol % of Pd(OAc)₂ and 10 mol % of RuPhos, and the desired products were obtained in good to very good yields. Among the organotrifluoroborates studied, two proved to be particularly challenging substrates to cross-couple. The Weinreb amide derivative **1e** failed to

TABLE 4. Cross-Coupling of Potassium β -Trifluoroborato Amide **1a** with Various Heteroaryl Chlorides^a

entry	reactant	RBF ₃ K	% isolated yield
1			50
2			-
3			60
4			87
5			73
6			79(44) ^b
7			66
8			72

^aAll reactions were carried out using 0.25 mmol of heteroaryl chloride and 0.253 mmol of potassium organotrifluoroborate **1a**. ^bYield with Pd(OAc)₂ (5 mol %) and RuPhos (10 mol %).

**FIGURE 3.** SPhos ligand.

provide the desired cross-coupled product in useful and reproducible yields, and the acrylamide derivative **1f** did not afford any trace of the expected product. Disappointingly, preliminary screening of various ligands that had previously been shown to be useful (e.g., SPhos, XPhos, and CataCXium A) did not provide any improvement in these cases.

TABLE 5. Cross-Coupling of Various Potassium β -Trifluoroborato-amides with 2-Chloroanisole^a

entry	reactant	RBF ₃ K	% isolated yield
1			79
2			65
3			60
4			84
5			^b
5			^c

^aAll reactions were carried out using 0.25 mmol of 2-chloroanisole and 0.253 mmol of potassium organotrifluoroborates. ^bThe reaction of the Weinreb amide **1e** with 2-chloroanisole under the shown conditions did not permit the isolation of the desired cross-coupled product in a reproducible and useful yield. ^cNo trace of the desired cross-coupled product was obtained.

Conclusion

In conclusion, an efficient procedure for both the preparation of β -trifluoroborato amides and their engagement in Suzuki–Miyaura cross-coupling reactions using inexpensive aryl chlorides has been reported. These unprecedented results will allow the use of this chemistry for the synthesis of more complex molecules. α -Amino- β -borato amides could, for example, be prepared by this strategy and subsequently used as coupling partners to prepare functionalized dipeptides. We are currently investigating the use of chiral amides to access chiral β -borato amides.

Experimental Section

Preparation of Potassium β -Trifluoroborato-*N,N*-dimethylpropanamide (1a).¹² CuCl (90.0 mg, 0.9 mmol), sodium *tert*-butoxide (259.5 mg, 2.7 mmol), and DPEPhos (484.7 mg, 0.9 mmol) were combined in a flask that was evacuated and filled with nitrogen. THF (28 mL) was added, and the mixture

was stirred for 30 min at room temperature. A solution of bis(pinacolato)diboron (8.45 g, 33.0 mmol) in THF (28 mL) was added dropwise. Additional THF (28 mL) was used to rinse the flask containing the bis(pinacolato)diboron. The mixture was stirred for 30 min before cooling to 0 °C. At this point, *N,N*-dimethylacrylamide (3.0 g, 30.0 mmol) and methanol (2.4 mL, 60.0 mmol) were successively added, and the mixture was stirred for 30 min at 0 °C followed by 5 h at room temperature. The resulting suspension was filtered through Celite, rinsing with EtOAc (3 \times 15 mL). The filtrate was concentrated under reduced pressure, and the resulting oil was dissolved in MeCN (90 mL) and cooled to 0 °C. Saturated aq KHF₂ (4.5 M, 20 mL, 90.0 mmol) was added dropwise. The resulting suspension was stirred for 3 h, concentrated under reduced pressure, and then placed under high vacuum overnight. The crude product was then extracted with hot acetone (3 \times 40 mL). The insoluble salts were filtered off, and the filtrate was concentrated in vacuo. To the crude solid obtained after drying overnight under vacuum was added Et₂O (50 mL), and the suspension was sonicated for 30 min and then filtered to provide the desired potassium β -trifluoroborato amide **1a** as a white solid in 60% yield (3.7 g, 18 mmol): mp = 125–128 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.92 (s, 3H), 2.75 (s, 3H), 2.05–2.00 (m, 2H), 0.17 (br s, 2H); ¹³C NMR (125.8 MHz, DMSO-*d*₆) δ 176.2, 40.0, 34.7, 30.2; ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ –138.7 (m); ¹¹B NMR (128 MHz, DMSO-*d*₆) δ 4.53 (br s); IR (KBr) 2922, 1631 cm^{–1}; HRMS (ES[–]) *m/z* calcd. for C₅H₁₀BF₃NO (M – K⁺) 168.0813, found 168.0802.

Representative Procedure for the Suzuki–Miyaura Cross-Coupling Reaction of Potassium β -Trifluoroboratoamides and Aryl Electrophiles: Preparation of 3-(2-Methoxyphenyl)-*N,N*-dimethylpropanamide (2b). **Method A.** To a mixture of potassium β -trifluoroborato-*N,N*-dimethylpropanamide (**1a**) (418.2 mg, 2.02 mmol), 2-chloroanisole (285.2 mg, 2.0 mmol), K₂CO₃ (829.3 mg, 6.0 mmol), Pd(OAc)₂ (22.5 mg, 0.1 mmol), and RuPhos (93.3 mg, 0.2 mmol) under nitrogen was added toluene/H₂O (5:1, 10.0 mL). The reaction was heated at 85 °C with stirring under a nitrogen atmosphere for 14 h and then cooled to rt. A solution of pH 7 buffer (10.0 mL) was added, and the resulting mixture was extracted with EtOAc (3 \times 6 mL). The organic layer was dried (MgSO₄) and then filtered. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography to afford the product as a colorless oil in 79% yield (331.3 mg, 1.6 mmol): ¹H NMR (500 MHz, CDCl₃) δ 7.22–7.16 (m, 2H), 6.91–6.82 (m, 2H), 3.82 (s, 3H), 2.96–2.93 (m, 2H), 2.95 (s, 3H), 2.94 (s, 3H), 2.59 (m, 2H); ¹³C NMR (125.8 MHz, CDCl₃) δ 172.9, 157.6, 130.3, 129.8, 127.5, 120.6, 110.3, 55.3, 37.2, 35.4, 33.8, 26.7; IR (neat) 2935, 1633, 1243 cm^{–1}; HRMS (CI⁺) *m/z* calcd for C₁₂H₁₈NO₂ (M + H⁺) 208.1338, found 208.1336.

Acknowledgment. This work was generously supported by the National Institutes of Health (General Medical Sciences) and Merck Research Laboratories. BASF is thanked for their donation of bis(pinacolato)diboron. We also acknowledge Frontier Scientific and Johnson Matthey for a donation of palladium catalysts and Professor Stephen L. Buchwald (MIT) for a sample of phosphine ligands.

Supporting Information Available: Experimental procedures, spectral characterization, and copies of ¹H, ¹³C, ¹¹B, and ¹⁹F spectra for all compounds prepared by the method described. This material is available free of charge via the Internet at <http://pubs.acs.org>.