ORGANIC LETTERS

2001
Vol. 3, No. 3
393−396

Cross-Coupling Reactions of Potassium Alkyltrifluoroborates with Aryl and 1-Alkenyl Trifluoromethanesulfonates

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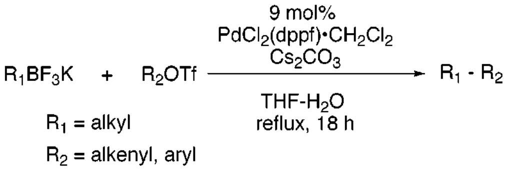
Received November 20, 2000

ABSTRACT



$$R_1BF_3K + R_2OTf \xrightarrow[\text{THF-}H_2O\text{, reflux, 18 h}]{9\text{ mol\% }PdCl_2(dppf)\cdot CH_2Cl_2\text{, }Cs_2CO_3} R_1 - R_2$$

R_1 = alkyl
R_2 = alkenyl, aryl

The palladium-catalyzed coupling reaction of potassium alkyltrifluoroborates with aryl- or alkenyltriflates proceeds to afford the corresponding arenes or alkenes in high yield. The borates are all solids, stable in air, and thus can be stored on the shelf indefinitely. The cross coupling can be effected using $PdCl_2(dppf)\cdot CH_2Cl_2$ as the catalyst in THF–H_2O in the presence of Cs_2CO_3. A variety of functional groups can be tolerated within the borate and/or the triflate coupling partner.

The palladium-catalyzed cross-coupling reaction of electrophiles with organometallic reagents has emerged as a versatile method for carbon−carbon bond formation.[1] Among all possible organometallics, tin (Stille coupling)[2] and boron derivatives (Suzuki coupling)[3] are most frequently used for these cross-coupling reactions because of their tolerance for a broad range of functional groups. The use of organoboron compounds is especially valued for several reasons: they are more easily accessed by a variety of routes, nontransferable groups can be readily incorporated into the organometallic, and the inorganic byproducts of the reaction are nontoxic and can be readily removed by simple workup procedures.

The palladium-catalyzed reaction of various 1-alkenyl- and arylboronic acids with electrophiles such as organic halides and triflates proceeds readily.[1,3,4] Trialkylboranes[1,3,5] and alkylborinate esters[6] are also generally efficient coupling partners. The scope of coupling reactions employing these latter organoboron derivatives, however, is limited by various selectivity characteristics exhibited by 9-BBN and related hydroborating reagents.

Except for the recent example of cyclopropylboronic acids or esters that possess significant sp^2-carbon character,[7] more highly oxygenated derivatives such as alkylboronic acids or esters have presented difficulties in Suzuki coupling reactions. For example, an early study utilizing alkylboronic acids

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10.1021/ol006896u CCC: $20.00

provided yields in the 20−30% range,[8] while coupling of methyl boronic acid required the addition of 40 mol % of triphenylarsine.[9] More recent studies show promise of improving this situation, although the scope of this particular protocol has not been fully investigated.[4b] A similar situation exists for various alkylboronic esters, wherein very low yields in the cross-coupling reaction were achieved[5b] unless highly toxic[10] thallium compounds such as TlOH or Tl_2CO_3 were utilized as bases for the reaction.[11] It has been assumed that this is because of the difficulty in transmetalation between the boronic ester and the intermediate Pd species.[11] Thus, although Suzuki coupling reactions incorporating aryl- and alkenylboron reagents are reasonably well in hand, new and effective methods for the successful coupling of simple primary alkylboron species are still subject to significant improvement.

Perhaps quite naturally, much of the recent development effort on the Suzuki coupling reaction has focused on metal ligand systems that facilitate the cross coupling and expand its scope.[4,5c,d] Much less effort has been concentrated on expanding the range of the organoboron coupling partner, which should be an equally rewarding endeavor.

With regard to the use of alternative organoboron derivatives, it has been revealed that several potassium aryl- and 1-alkenyltrifluoroborates, easily prepared from organoboronic acids or esters, undergo the palladium-catalyzed coupling reaction with arenediazonium tetrafluoroborates[12] or diaryliodonium salts[13] as the coupling partners. In addition to their air stability, the greater nucleophilicity[14] of the potassium trifluoroborates over the corresponding organoboranes and organoboronic acid derivatives makes the fluoroborates potentially valuable starting materials for palladium-catalyzed cross coupling with sp^2-hybridized carbon centers. One caveat is that potassium aryltrifluoroborates appear reluctant to couple to aryl halides.[4b]

We believed that the enhanced nucleophilicity of alkyltrifluoroborates relative to their boronic acid and boronic ester analogues might be brought to bear on this problem. Herein, we outline the scope of the coupling reaction of potassium alkyltrifluoroborates with organic triflates as the coupling partner (eq 1).

$$\underset{\mathbf{1}}{R_1BF_3K} \quad + \quad \underset{\mathbf{2}}{R_2OTf} \xrightarrow[\text{THF-H}_2\text{O} \atop \text{reflux, 18 h}]{\text{9 mol\%} \atop {\text{PdCl}_2\text{(dppf)}\cdot\text{CH}_2\text{Cl}_2 \atop \text{Cs}_2\text{CO}_3}} \underset{\mathbf{3}}{R_1 - R_2} \qquad (1)$$

R_1 = alkyl

R_2 = alkenyl, aryl

Vedejs et al.[15] reported the reaction of arylboronic acids with potassium hydrogen fluoride, leading to potassium aryltrifluoroborates. Several groups have utilized a slight modification of this original procedure for the synthesis of various potassium organotrifluoroborates.[14,16] By adapting these methods, the formation of potassium alkyltrifluoroborates was achieved via the corresponding boronic acids and esters. The requisite alkylboronic acids and esters were readily synthesized using established literature protocols involving the addition of Grignard reagent to trimethylborate,[17] the hydroboration of alkenes with dibromoborane−dimethyl sulfide complex followed by hydrolysis,[18] and the catalytic hydroboration[19] of alkenes with catecholborane or pinacolborane. Treatment of the alkylated boronic acids or esters with KHF_2 afforded the corresponding potassium alkyltrifluoroborates as powders or crystalline solids in good yields. The products were indefinitely stable in the air.

The conditions for carrying out the coupling reaction were optimized by using phenyltriflate and potassium benzyltrifluoroborate in the presence of $PdCl_2$(dppf) (9 mol %). Briefly, utilizing a variety of different solvents (THF, DME, DMA, toluene, dioxane, EtOH) under both anhydrous and aqueous conditions, with an ensemble of diverse bases (e.g., Cs_2CO_3, K_2CO_3, K_3PO_4, CsOH, NaOAc, and KOH), we determined that the use of 9−10 mol % of $PdCl_2$(dppf) with 3 equiv of Cs_2CO_3 as a base in THF−H_2O heated at reflux were optimal, and these conditions were applied to the remainder of the substrates in the study.[20]

As outlined in the Table, the cross-coupling reaction of potassium alkyltrifluoroborates with various triflates proceeded readily with satisfactory yields in most cases. The reaction was tolerant of a variety of functional groups including ketones, esters, nitriles, and nitro groups despite the aqueous basic conditions. Of significance was the observation that although the reaction of nitrophenyltriflate

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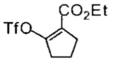
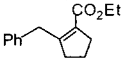
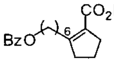
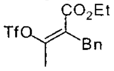
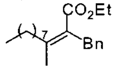
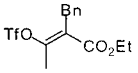
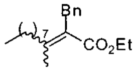
(20) **Representative Procedure for the Cross-Coupling Reaction of Triflates with Potassium Alkyltrifluoroborates. 1-(4-Acetylphenyl)-1-phenylmethane (3b).** To a suspension of potassium benzyltrifluoroborate (**1a**) (106 mg, 0.5 mmol), Cs_2CO_3 (489 mg, 1.5 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (36 mg, 0.045 mmol), and 4−acetylphenyltriflate (134 mg, 0.5 mmol) in THF (5 mL) was added water (0.5 mL) under an argon atmosphere, followed by heating at reflux. The reaction mixture was stirred at reflux temperature for 18 h, then cooled to room temperature, and diluted with water (10 mL) followed by extraction with ether (50 mL × 3). The ethereal solution was washed with 1 N HCl (10 mL) and brine (20 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography (eluting with hexane/ether 20:1) to yield **3b** (108 mg, 0.48 mmol, 96%).

Table 1. Cross-Coupling of Organic Halides and Triflates with Potassium Alkyltrifluoroborates[a]

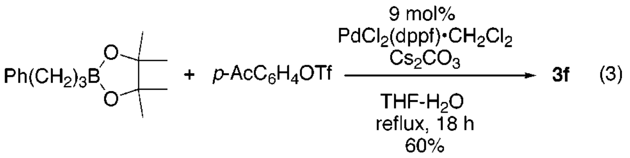
entry	substrate	triflate	product	% yield[b]
1	$PhCH_2BF_3K$ (**1a**)[c]	PhOTf (**2a**)	$PhCH_2Ph$ (**3a**)	(91)
2	**1a**[c]	*p*-AcC_6H_4OTf (**2b**)	*p*-$AcC_6H_4CH_2Ph$ (**3b**)	96
3	**1a**[c]	*p*-$NO_2C_6H_4OTf$ (**2c**)	*p*-$NO_2C_6H_4CH_2Ph$ (**3c**)	89
4	**1a**[c]	 (**2d**)	 (**3d**)	89
5	$PhCH_2CH_2BF_3K$ (**1b**)[c]	**2b**	*p*-$AcC_6H_4CH_2CH_2Ph$ (**3e**)	96
6	$Ph(CH_2)_3BF_3K$ (**1c**)[d]	**2b**	*p*-$AcC_6H_4(CH_2)_3Ph$ (**3f**)	84 (91)
7	$NC(CH_2)_5BF_3K$ (**1d**)[d]	**2c**	*p*-$NO_2C_6H_4(CH_2)_5CN$ (**3g**)	73
8	$BzO(CH_2)_6BF_3K$ (**1e**)[d]	**2d**	 (**3h**)	68
9	$Me(CO)(CH_2)_4BF_3K$ (**1f**)[d]	**2b**	*p*-$AcC_6H_4(CH_2)_4(CO)Me$ (**3i**)	79
10	$CH_3(CH_2)_7BF_3K$ (**1g**)[d]	*m*-CNC_6H_4OTf (**2e**)	*m*-$CNC_6H_4(CH_2)_7CH_3$ (**3j**)	65
11	**1g**[d]	*m*-$CF_3C_6H_4OTf$ (**2f**)	*m*-$CF_3C_6H_4(CH_2)_7CH_3$ (**3k**)	59
12	**1g**[d]	 (**2g**)	 (**3l**)	75
13	**1g**[d]	 (**2h**)	 (**3m**)	50[e]
14	**1a**[c]	*p*-IC_6H_4OTf (**2i**)	*p*-$TfOC_6H_4CH_2Ph$ (**3n**)	16
15	**1a**[c]	*p*-BrC_6H_4OTf (**2j**)	**3n**	70
16	**1a**[c]	*p*-ClC_6H_4OTf (**2k**)	*p*-$ClC_6H_4CH_2Ph$(**3o**)	57
17	$PhCH(Me)BF_3K$ (**1h**)[c]	**2b**	*p*-$AcC_6H_4CH(Me)Ph$ (**3p**)	4
18	$Br(CH_2)_6BF_3K$ (**1i**)[d]	**2b**	*p*-$AcC_6H_4(CH_2)_6Br$ (**3q**)	61

[a] The reactions were conducted using potassium alkyltrifluoroborates (0.5 mmol) and triflates (0.5−0.55 mmol) in the presence of $PdCl_2(dppf){\cdot}CH_2Cl_2$ (9 mol %) and Cs_2CO_3 (3 equiv) in THF−H_2O heated at reflux for 18 h. [b] Isolated yields. GC yields based on *n*-undecane or bibenzyl as an internal standard are in parentheses. [c] Borates were prepared via the Grignard method. [d] Borates were prepared via the catalytic hydroboration method. [e] As a 1:1 mixture of diastereomers.

with *B*-alkyl-9-BBN provided a mixture of reduced aniline products,[21] good yields of coupled product were obtained under our conditions without difficulty (entries 3 and 7). A good yield of geometrically pure alkene[22] was obtained by the reaction with (*Z*)-alkene **2g** (entry 12), whereas the use of (*E*)-alkene **2h** afforded a mixture of diastereomeric products (entry 13). Highly selective coupling with the C−X bond in 4-bromo- and 4-iodophenyltriflate was observed. Unfortunately, the use of 4-iodophenyltriflate provided 4,4′-bis(trifluoromethylsulfonyloxy)biphenyl arising from homocoupling of the iodides in addition to the desired coupled product (entries 14 and 15). Thus, the reactivity of the electrophile in our reaction systems with the alkyltrifluoroborates decreases in the order Br > OTf ≫ Cl as reported for organotin[23] and *B*-alkyl-9-BBN[21] reagents. Finally, the yield of the reaction with secondary alkylborates such as potassium 1-phenethyltrifluoroborate was not satisfactory (entry 17). In this case, the generation of styrene by β-elimination and ethylbenzene by dehydroboronation were the predominant reaction pathways.

The mechanism of the reaction has not been studied in detail, but the question arises as to whether the alkyltrifluoroborates are hydrolyzed in situ to provide the corresponding alkylboronic acids, which subsequently undergo cross coupling. To address this issue, some preliminary experiments have been performed. For example, when potassium 3-phenylpropyltrifluoroborate was exposed to water for 4 days at room temperature, the ^{11}B NMR revealed that a new signal was observed at δ 33.5 ppm in addition to the resonance at δ 5.6 ppm for the original compound. This observation indicated that alkylboronic acids (for which the ^{11}B NMR signal typically appears at δ 31.9 ppm[24]) could be generated in situ. To explore further the nature of the reactive species under our conditions, we examined the coupling reaction using 3-phenylpropylboronic acid[24] and the corresponding pinacol ester using 4-acetylphenyltriflate as the coupling partner. Somewhat surprisingly, under our optimized reaction conditions these compounds afforded 77% (eq 2) and 60% (eq 3) isolated yields of cross-coupled products, which is

$$Ph(CH_2)_3B(OH)_2 + p\text{-}AcC_6H_4OTf \xrightarrow[\text{THF-}H_2O \text{ reflux, 18 h } 77\%]{\text{9 mol\% } PdCl_2(dppf){\cdot}CH_2Cl_2 \; Cs_2CO_3} \mathbf{3f} \quad (2)$$



(3)

nearly the same yields obtained in the reaction of the potassium 3-phenylpropyltrifluoroborate (entry 6). This observation is not only of possible mechanistic importance

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for the present study but of potential synthetic value in its own right because satisfactory cross-coupling reactions of alkylboronic acids have been achieved previously only with difficulty,[8,25] even when thallium bases have been used.

Thus although boronic acids generated in situ could very well be the reactive species under our reaction conditions, fluorinated boron species such as RBF_3^-, $RBF_2(OH)^-$, and/or $RBF(OH)_2^-$ might also be involved. Wright et al.[8] have argued that such intermediates could be the key species in the reaction of fluoride-mediated coupling of boronic acids, and these derivatives undoubtedly exist during the hydrolysis process of potassium alkyltrifluoroborates. It is also possible that the reaction is somehow accelerated by fluoride ions. Conclusions concerning these issues await further, more detailed kinetic and mechanistic investigations.

In summary, the first palladium-catalyzed cross-coupling reactions of potassium alkyltrifluoroborates with aryl- and alkenyltriflates have been achieved. The inclusion of water was found to be essential, and Cs_2CO_3 was determined to be the most effective base. Functionalized alkyltrifluoroborates are readily available utilizing a Grignard approach as well as by hydroboration of alkenes employing several different hydroborating protocols. The alkyltrifluoroborates are solids that are easily handled (i.e., indefinitely stable in the air). As a consequence, this could be prove to be a watershed discovery for combinatorial synthesis, because a variety of highly functionalized, structurally diverse alkyltrifluoroborates can be synthesized and stored in bulk, awaiting coupling. Additionally, we have discovered that alkylboronic acids and esters can be coupled under the same conditions, and this development awaits further investigation. The present method thus provides a new and effective approach to alkylated aromatic and alkenyl compounds. Further study on the scope and detailed mechanism of the reaction is in progress.

Acknowledgment. We thank Mr. Jason Burke for the preparation of potassium 6-bromohexyltrifluoroborate. We acknowledge the National Institutes of Health (GM-48580) and Merck & Co., Inc., for their generous support of our program.

Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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