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Stereoselective Suzuki−Miyaura Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates with Alkenyl Bromides

Gary A. Molander* and Luciana A. Felix

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania,
Philadelphia, Pennsylvania 19104-6323

gmolandr@sas.upenn.edu

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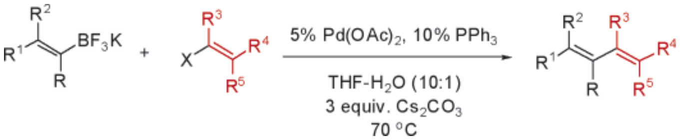

The stereoselective synthesis of conjugated dienes using air-stable potassium alkenyltrifluoroborates as coupling partners is described. The palladium-catalyzed cross-coupling reaction of potassium (*E*)- and (*Z*)-alkenyltrifluoroborates with either (*E*)- or (*Z*)-alkenyl bromides proceeds readily with moderate to excellent yields to give the corresponding (*E,E*)-, (*E,Z*)-, (*Z,E*)-, or (*Z,Z*)-conjugated dienes stereospecifically. The cross-coupling can generally be effected using 5 mol % of Pd(OAc)$_2$, 10 mol % of PPh$_3$, and 3 equiv of Cs$_2$CO$_3$ in THF−H$_2$O (10:1). A variety of functional groups are tolerated in both coupling partners.

Introduction

Stereo- and regiodefined conjugated dienes and polyenes are of great importance in organic chemistry owing to their presence in biologically active compounds, as well as for their application in reactions such as the Diels−Alder reaction. A number of methods for the preparation of conjugated dienes and polyenes have been developed utilizing various organometallic reagents. Among these procedures, the most efficient and widely employed are those based on the direct cross-coupling reaction of alkenylmetals with haloalkenes in the presence of a catalytic amount of a transition-metal complex.[1] Although several 1-alkenylmetal reagents undergo coupling reactions with haloalkenes, many of these have significant limitations when compared to an ideal synthetic procedure.

Alkenylmagnesium derivatives (Kumada coupling) have been associated with various undesirable characteristics including low chemoselectivity and low product yields.[2] The use of alkenylzincs as organometallic partners in Pd-catalyzed alkenyl−alkenyl coupling has proven to be extremely efficient. The organozinc cross-couplings (Negishi coupling) proceed with high catalytic reactivity, high yields, high stereoselectivity, and reasonable chemoselectivity.[3] However, in certain situations, operational difficulties make them unfavorable. Organozinc reagents must be prepared and utilized in situ and do not lend themselves to storage for long periods of time. This limitation renders them less than ideal for combinatorial procedures wherein scores of diverse air-stable organometallic precursors might be desired.

Among the most common storable organometallics, much attention has been focused on the use of tin (Stille coupling)[4] and boron derivatives (Suzuki−Miyaura coupling).[1b,5] Tin and boron reagents are most frequently used for diene synthesis because they are reasonably easily synthesized, they are tolerant of a variety of functional groups, and they afford high fidelity in the conversion of stereodefined substrates to products. Organoboron reagents in particular offer significant advantages. For example, alkenylboron compounds are more easily accessed by a variety of routes (e.g., transmetalation of alkenylmetals and hydroboration of alkynes by catalyzed and uncatalyzed procedures). Furthermore, the inorganic byproducts of the reaction with boron derivatives are nontoxic and can be readily removed by simple workup

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procedures. By contrast, tin presents several operational complications. The hydrostannation of alkynes is often capricious, and the regioselectivity of this reaction is sometimes difficult to predict.[6] Many tin compounds are toxic, and complete removal of tin-containing byproducts is a well-recognized problem. The presence of even traces of organotin compounds in organic products must be avoided, if possible.

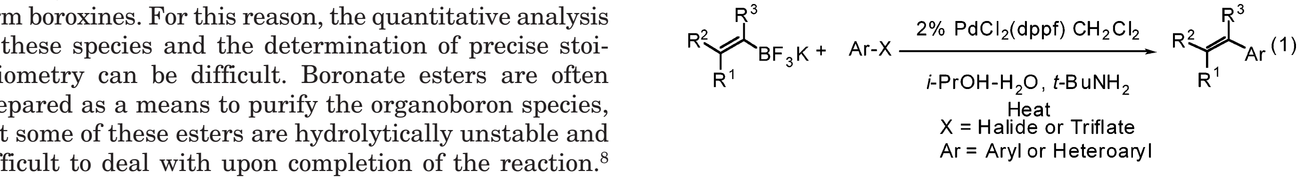
Although organoboron reagents have been extensively used in alkenyl−alkenyl cross-coupling reactions, there are some notorious problems with the reagents in current use. 1-Alkenyldialkylboranes, especially (*Z*)-1-alkenylboron derivatives, give relatively poor yields of the coupling products and low stereoselectivity.[7] In addition, these compounds possess a relatively high molecular weight, and thus, a large amount of waste material is produced that must be separated from the cross-coupled products. In general, *B*-alkenyl-9-BBN's are very reactive reagents, giving the cross-coupled products in high yields. Nevertheless, the scope of coupling reactions is limited by various characteristics exhibited by the organoborane including air sensitivity, reactivity toward some sensitive functional groups, and a lack of atom economy. Furthermore, disposal of cyclooctyl byproducts can present difficulties in coupling reactions of *B*-organo-9-BBN derivatives.

Boronic acids and boronate esters are the most commonly utilized derivatives in Suzuki cross-coupling reactions. By using 1-alkenylboronic acids and esters, high yields and excellent stereoselectivity can be achieved in the synthesis of dienes. Despite their efficiency and widespread use in alkenyl−alkenyl coupling, they present considerable problems. In particular, the boronic acids are subject to cyclic trimerization with loss of water to form boroxines. For this reason, the quantitative analysis of these species and the determination of precise stoichiometry can be difficult. Boronate esters are often prepared as a means to purify the organoboron species, but some of these esters are hydrolytically unstable and difficult to deal with upon completion of the reaction.[8] Moreover, the diols utilized to create the boronic esters (e.g., catechol or pinacol) add considerable expense to the overall process and, additionally, must be separated from the desired product after the coupling process. Usually the use of toxic thallium bases such as TlOH, TlOEt, or Tl_2CO_3 are required in the coupling reactions of boronic acids and esters to increase their reactivity.[9] As demonstrated by Kishi during the course of his palytoxin synthesis, a significant rate enhancement in cross-coupling was achieved by using an aqueous solution of TlOH.[10] Several other research groups have noted similar requirements within the context of complex molecule synthesis.[11]

In an attempt to resolve some of these shortcomings, we sought to introduce potassium alkenyltrifluoroborates as key reagents in the alkenyl−alkenyl coupling. It has previously been revealed that potassium organotrifluoroborates provide solutions to the problems inherent in other organoboron partners.[12] These organotrifluoroborates are readily prepared by the addition of inexpensive KHF_2 to a variety of organoboron intermediates.[13] They are monomeric, crystalline solids that are readily isolated and indefinitely stable in the air.

Previously, our research group has investigated the Suzuki−Miyaura cross-coupling reaction of alkenyltrifluoroborates with aryl halides and triflates. In the first of these studies, attention was focused on the use of potassium vinyltrifluoroborate as a uniquely practical vinylating agent.[14] Vinyldialkylboranes are reasonably difficult to synthesize and are inflammable. Vinylboronic acid and even vinylboronate esters are unstable to polymerization.[15] By contrast, the analogous vinyltrifluoroborate is readily synthesized and completely stable. It has been prepared in 200 g quantities and stored for long periods of time. It couples readily with a wide range of aryl triflates and halides, thus providing distinct advantages over its vinylmetallic counterparts.

Subsequently, a full study of the scope of cross-coupling of a variety of alkenyltrifluoroborates with functionalized aryl halides and triflates and with heteroaryl halides was undertaken.[16] In that study, the coupling of alkenyltrifluoroborates was determined to take place efficiently using $PdCl_2(dppf){\cdot}CH_2Cl_2$ as a catalyst in *i*-PrOH/H_2O, using *t*-$BuNH_2$ or Et_3N as a base (eq 1).



The alkenyltrifluoroborate cross-coupling reactions work well with both electron-rich and electron-poor aryl halides. Importantly, the reactions were determined to be stereospecific with regard to the organoboron partner.

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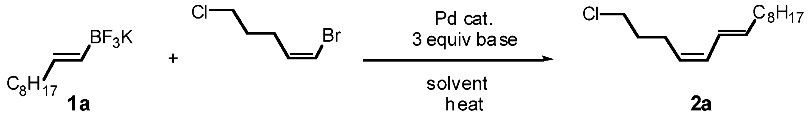
TABLE 1. Study of the Optimal Conditions for the Cross-Coupling Reaction of Potassium Alkenyltrifluoroborates with Alkenyl Bromides



entry	catalyst/ligand (9 mol %)	solvent	base (3 equiv)	% yield (ds)[a]
1	$Pd(PPh_3)_4$	THF/H_2O (10:1)	Cs_2CO_3	81 (>99)
2	$Pd(OAc)_2/2PPh_3$	THF/H_2O (10:1)	Cs_2CO_3	87 (>99)
3	$Pd(OAc)_2/2PPh_3$	THF/H_2O (10:1)	K_2CO_3	67 (98)
4	$Pd(OAc)_2/2PPh_3$	THF/H_2O (10:1)	K_3PO_4	57 (92)
5	$Pd(OAc)_2/2PPh_3$	THF/H_2O (10:1)	Et_3N	46 (83)
6	$Pd(OAc)_2/2PPh_3$	THF/H_2O (10:1)	*t*-$BuNH_2$	80 (90)
7	$Pd(OAc)_2/2PPh_3$	THF/H_2O (10:1)	Na_2CO_3	57 (98)
8	$Pd(OAc)_2/2PPh_3$	*i*-$PrOH/H_2O$ (10:1)	*t*-$BuNH_2$	76 (95)
9	$Pd(OAc)_2/2PPh_3$	$MeOH/H_2O$ (10:1)	K_2CO_3	54 (88)
10	$Pd(OAc)_2/2PPh_3$	$EtOH/H_2O$ (10:1)	K_2CO_3	46 (86)
11	$Pd(OAc)_2/2PPh_3$	THF/EtOH (1:1)	Cs_2CO_3	73 (93.5)
12	$Pd(OAc)_2/2PPh_3$	*n*-$PrOH/H_2O$ (10:1)	K_2CO_3	65 (93)
13	$Pd(OAc)_2/2PPh_3$	DME/H_2O (10:1)	K_2CO_3	36 (80)
14	$Pd(OAc)_2/PPh_3$	THF/H_2O (10:1)	Cs_2CO_3	77 (>99)
15	$Pd(OAc)_2$/dppf	THF/H_2O (10:1)	Cs_2CO_3	56 (88)
16	$Pd(OAc)_2/2PCy_3$	THF/H_2O (10:1)	Cs_2CO_3	33 (95)
17	$PdCl_2(dppf)\cdot CH_2Cl_2$	*i*-$PrOH/H_2O$ (3:1)	*t*-$BuNH_2$	55 (95)
18	$PdCl_2(dppf)\cdot CH_2Cl_2$	*n*-$PrOH/H_2O$ (3:1)	Et_3N	53 (93)

[a] The ds is the predominance of the *Z,E* diastereomer over the *E,E* isomer in the crude reaction mixture.

Having established the efficiency and advantages of alkenyltrifluoroborates in coupling with aryl and heteroaryl electrophiles, we sought to extend their utility. Herein, we report the application of alkenyltrifluoroborates toward the stereospecific synthesis of conjugated dienes, highlighting the advantages in the utilization of this system for the construction of this synthetically important functionality.

Results and Discussion

We initially focused our attention on the determination of the optimal conditions for the Suzuki–Miyaura cross-coupling reaction of alkenyltrifluoroborates and alkenyl halides. Toward this end, we used a variety of catalysts, ligands, bases, and solvents. The reaction conditions were explored using stereodefined reagents to study the stereochemistry of the diene formed. Potassium *trans*-1-dec-1-enyltrifluoroborate and 6-chloro-*cis*-1-hex-1-enyl bromide were used as the coupling partners. The reactions were carried out in a reactor block, using 0.2 mmol of *cis*-6-chloro-1-hex-1-enyl bromide and 0.22 mmol of potassium *trans*-1-dec-1-enyltrifluoroborate in the presence of 9 mol % of catalyst/ligand, 3 equiv of base, and 2 mL of solvent heating at reflux overnight under a blanket of nitrogen (Table 1). The reactions were analyzed by quantitative gas chromatography using the internal standard method (undecane used as standard).

Surprisingly, the reactions carried out in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$ using alcohols as solvents and amines as bases (entries 16 and 17) led to only moderate yields and low stereoselectivity, even though these conditions had previously been used successfully for the coupling of potassium alkenyltrifluoroborates with aryl halides and triflates.

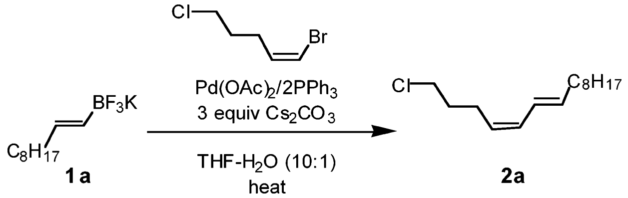
Through an empirical search for optimal reaction conditions, we determined that $THF-H_2O$ (10:1), $Pd(PPh_3)_4$, and Cs_2CO_3 (entry 1) provided the coupling product in high yield and stereoselectivity. We studied the reaction of $Pd(OAc)_2$ with different ligands. The use of a simple ligand such as PPh_3 in a 1:2 ratio with respect to the catalyst (entry 2) proved to be very efficient, generating the product in even higher yield than that observed when $Pd(PPh_3)_4$ was used as catalyst. Retention of stereochemistry was also observed, as the reaction transpired with >99% stereochemical fidelity. When we used PPh_3 in a 1:1 ratio we observed an inferior yield compared to that achieved when PPh_3 was used in a 1:2 ratio. The use of dppf and PCy_3 as ligands (entries 15 and 16) afforded the product in low yield and with isomerization.

To reduce the cost of the reaction, we turned our attention to the study of bases other than Cs_2CO_3. Reactions were carried out in the presence of $Pd(OAc)_2/2PPh_3$ and THF/H_2O (10:1), the most efficient catalyst and solvent, while varying the base. The use of NEt_3 (entry 5) afforded a low yield of product with isomerization, while *t*-$BuNH_2$ (entry 6) led to a high yield of the cross-coupling product, but unfortunately, the product was obtained with low isomeric purity (90%). Inorganic bases such as K_3PO_4 (entry 4) and Na_2CO_3 (entry 7) led to similar yields (55–57%) with isomerization, and K_2CO_3 afforded the product in moderate yield (67%) and high isomeric purity (98%). Subsequently, we attempted to improve the yield of this reaction by performing experiments with different solvents such as MeOH, EtOH, *n*-PrOH, or DME (entries 9, 10, 12, and 13). In the end, these solvents were largely ineffective.

The best conditions [$Pd(OAc)_2/2PPh_3$, Cs_2CO_3 in $THF-H_2O$ (10:1)] were subsequently employed to study the catalyst loading (Table 2) and the base loading (Table 3).

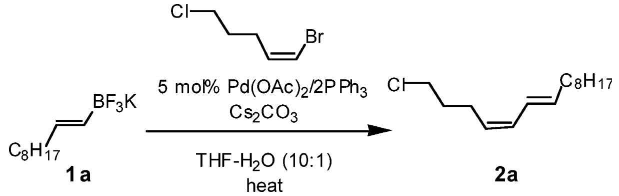
The results of these studies indicated that the use of 9 and 5 mol % of $Pd(OAc)_2/2PPh_3$ proved to be comparably effective (Table 2, entries 1 and 2). However, when the

TABLE 2. Study of the Catalyst Loading



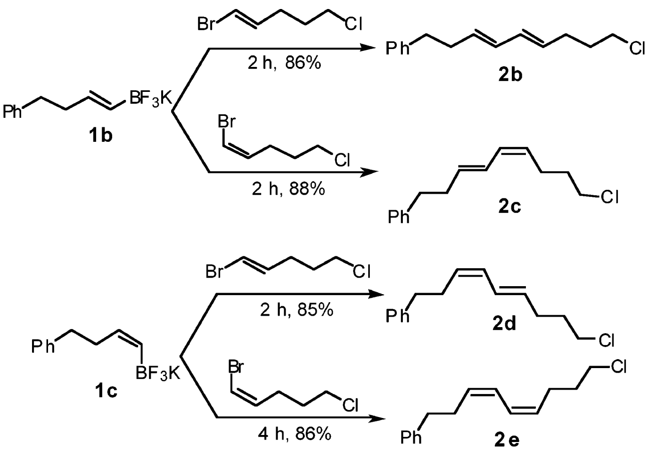
entry	mol % cat.	time (h)	% yield (GC)
1	9	12	87
2	5	12	85
3	2	18	55

TABLE 3. Study of the Base Loading



entry	base equiv	time (h)	% yield (GC)
1	3	12	87
2	2	15	70
3	1	15	40

SCHEME 1[a]



[a] Conditions: 5 mol % of $Pd(OAc)_2$/2PPh_3, 3 equiv of Cs_2CO_3, THF–H_2O (10:1).

loading was dropped to 2 mol % the yield noticeably decreased, thus revealing the minimum amount of catalyst needed for the reaction carried out on small scale.

A reduction in the amount of base to 2 equiv decreased the yield, and when only 1 equiv of base was used the yield was lowered substantially. These results demonstrated that 3 equiv of base was optimal (Table 3).

After verifying that the reactions needed to be performed under an inert atmosphere, the optimized conditions were subsequently applied to the synthesis of several conjugated dienes.

The stereochemistry associated with alkenyl–alkenyl coupling is distinctly more complicated than, for example, alkenyl–aryl coupling, because four possible stereoisomers, that is, *E,E*-, *E,Z*-, *Z,E*-, and *Z,Z*-conjugated dienes, are possible for any given alkenyl–alkenyl coupling, and all due attention must be paid to this potentially complex stereochemical aspect. Cognizant of this, we examined the stereochemistry of this new Suzuki protocol. Thus, we reacted potassium (*E*)- and (*Z*)-4-phenyl-1-but-1-enyl trifluoroborate with (*E*)- and (*Z*)-1-bromo-5-chloropent-1-ene to conduct a comprehensive study of the stereoselectivity of this method for diene synthesis. The usefulness of the present method was demonstrated by the stereospecific synthesis (>99%) of the four geometrical isomers of 9-chloronona-3,5-dienylbenzene (Scheme 1).

9-Chloronona-(3*E*,5*E*)-dienylbenzene and 9-chloronona-(3*Z*,5*E*)-dienylbenzene were synthesized by reacting potassium (*E*)-4-phenyl-1-but-1-enyl trifluoroborate with (*E*)- and (*Z*)-1-bromo-5-chloropent-1-ene. The products were generated in yields of 86 and 88%, respectively, both with high isomeric purities (>99%). Potassium (*Z*)-4-phenyl-1-but-1-enyltrifluoroborate was reacted with (*E*)- and (*Z*)-1-bromo-5-chloropent-1-ene to give the (3*E*,5*Z*)- and (3*Z*,5*Z*)-isomers in 85 and 86% yields, respectively, both also with high isomeric purities (>99%). These results demonstrate that this method is stereospecific with regard to both coupling partners.

To test the scope of this procedure, we examined the cross-coupling reaction of **1b** with a variety of alkenyl bromides bearing different functionalities and with different substitution patterns (Table 4). In general, all of the reactions proceeded smoothly with moderate to excellent yields. Most importantly, the coupling turned out to be general with respect to a diverse array of functionality. The reaction showed compatibility with alcohol, ketone, aldehyde, ester, cyano, and amine groups despite the aqueous basic conditions.

Tri- and tetrasubstituted alkenyl halide substrates (entries 1 and 2) reacted with **1b** to provide the coupling products in good yields, showing that the method is not susceptible to steric hindrance. An alkenyl bromide bearing a free hydroxyl group (entry 3) led to the desired product in satisfactory yield (79%). Methods of introducing an *E*- or *Z*-alkenyl group α to aldehydes and ketones with strict control of regiochemistry are highly desirable. We have shown that α-bromo α,*β*-unsaturated carbonyl derivatives react with alkenyltrifluoroborates under palladium catalysis to afford the α-alkenyl-substituted product stereoselectively in excellent yield (entries 4 and 5). Despite the long reaction time (8 h), the reaction with α-bromoenone (entry 4) turned out to be among the highest yielding compared with the other substrates. The sluggishness of this reaction might have been anticipated on the basis of the low intrinsic reactivity of α-haloenones in Pd-catalyzed cross-coupling, but the high yield was a pleasant surprise in view of the general instability of such electrophiles. In an earlier study, the low reactivity was also observed when organozinc and organotin compounds were used.[17] Because of that low reactivity, the acetal-protected α-bromoenones were employed as key intermediates to improve the cross-coupling results.[18]

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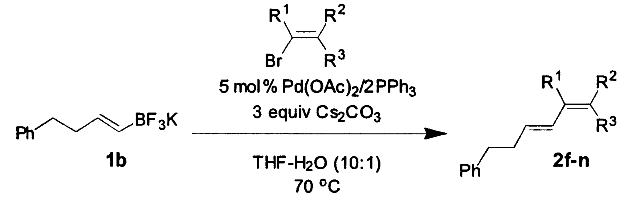
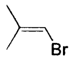
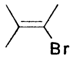
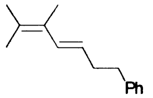
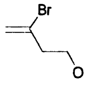
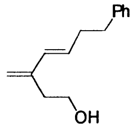
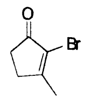
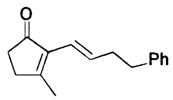
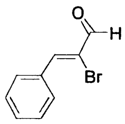
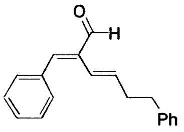
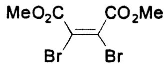
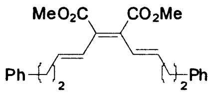
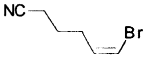
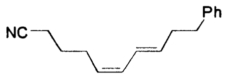
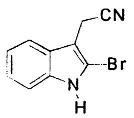
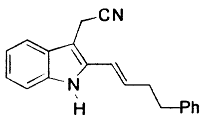
TABLE 4. Cross-Coupling of Potassium (*E*)-4-Phenyl-1-buten-1-enyltrifluoroborate 1b with Alkenyl Bromides

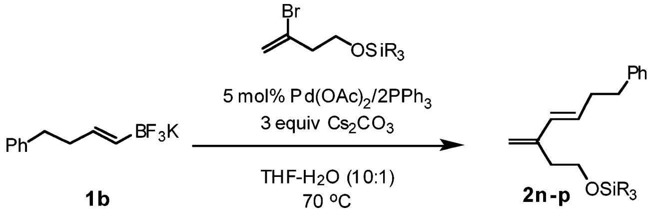


entry	substrate	product	% isoltd yield (time, h)
1		 **2f**	70, (4)
2		 **2g**	95, (6)
3		 **2h**	79, (2)
4		 **2i**	95, (8)
5		 **2j**	88, (2)
6		 **2k**	70, (5)[a]
7		 **2l**	78, (2)
8		 **2m**	90, (3)

[a] $PdCl_2dppf{\cdot}CH_2Cl_2$ was used as the catalyst.

One of the difficulties typically encountered during cross-coupling reactions under basic conditions is the saponification of esters. This difficulty can be overcome by the use of heterogeneous bases in the cross-coupling reactions.[19] Thus, we observed that ester groups remain intact using our optimal conditions (entry 6). The reaction of methyl dibromo maleic ester with 2 equiv of **1b** in the presence of 10 mol % of $Pd(OAc)_2/2PPh_3$ and 6 equiv of Cs_2CO_3 led to a mixture of monosubstituted product with protodehalogenation of the second bromide, along with the disubstituted product. When $PdCl_2dppf{\cdot}CH_2Cl_2$ was used as catalyst, the disubstituted product was observed as the only product (entry 6).

TABLE 5. Cross-Coupling of Potassium (*E*)-4-Phenyl-1-buten-1-enyltrifluoroborate 1b with Alkenyl Bromides Containing Different Silyl Ethers



entry	SiR3	product	% isolated yield
1	TIPS	**2n**	85
2	TBDMS	**2o**	80
3	TES	**2p**	80

The diene moiety is present in numerous naturally occurring compounds that exhibit biological activity. Thus, alkenyl–alkenyl cross-coupling reactions are widely used in the synthesis of natural products that contain the conjugated diene moiety. Most of these compounds incorporate alcohol functionalities within their skeleta that need to be protected during the course of the synthesis. Based on this reality, we examined the cross-coupling reactions of alkenyl halides bearing silyl ether protected alcohols to verify their compatibility with our method. An examination of this topic was particulary important because the trifluoroborates present an obvious source of fluoride, often used to deprotect silylated alcohols. In this particular study, we explored the cross-coupling reactions of alkenyl bromides bearing the most commonly used silyl ethers: TES, TBDMS, and TIPS (Table 5).

As observed in previous studies of organotrifluoroborate cross-coupling reactions,[11d,20] the silyl ether groups survived the reaction conditions, even though a fluoride counterion and base is present during the course of the reaction. In all cases, the silyl groups were retained and the products were acquired in excellent yields (80–85%). As discussed previously, the stability of the silyl ether groups for these reactions might be ascribed to the use of a heterogeneous system.

Continuing with our investigation, we applied the palladium-catalyzed cross-coupling reaction under the conditions established for the alkenyl bromides to different potassium alkenyltrifluoroborate partners as outlined in Table 6.

We used more highly substituted alkenyltrifluoroborates and also alkenyltrifluoroborates incorporating functionality to establish the generality of this method. Alkenyltrifluoroborates were easily synthesized by the addition of KHF_2 to the corresponding boronic acid or boronate ester. The organotrifluoroborates **1a**, **1e**, and

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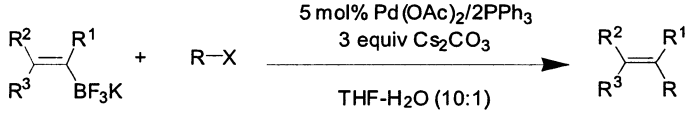
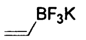
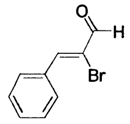
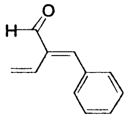
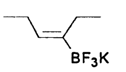
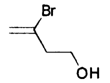
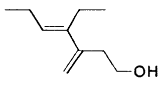
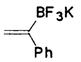
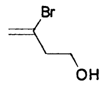
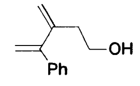
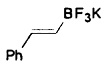
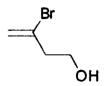
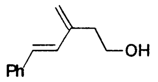
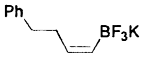
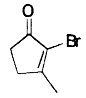
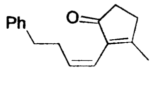
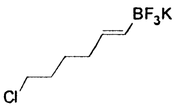
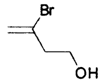
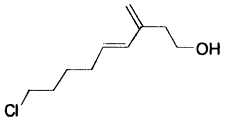
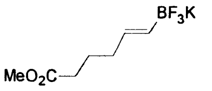
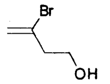
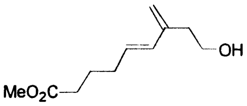
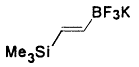
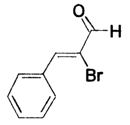
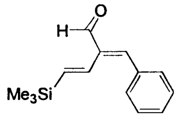
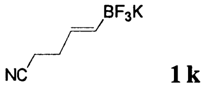
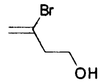
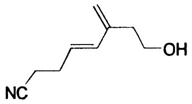
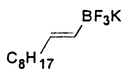
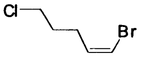
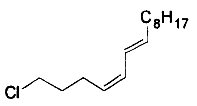
(19) Kawanaka, Y.; Ono, N.; Yoshida, Y.; Okamoto, S.; Sato, F. *J. Chem. Soc., Perkin Trans. 1* **1996**, 715–718.

(20) Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313–10318.

TABLE 6. Cross-Coupling of Alkenyl Bromides with Different Potassium Alkenyltrifluoroborates



1d-l 3a-i

entry	potassium alkenyltrifluoroborate	alkenyl bromide R-X	product	time (h)	% isolated yield
1	 **1d**		 **3a**	2.5	73
2	 **1e**		 **3b**	2	66
3	 **1f**		 **3c**	12	60
4	 **1g**		 **3d**	2	70
5	 **1c**		 **3e**	12	94
6	 **1h**		 **3f**	4	72
7	 **1i**		 **3g**	2	70
8	 **1j**		 **3h**	2	82
9	 **1k**		 **3i**	2	80
10	 **1a**		 **2a**	2	85

1h were obtained by hydroboration of the corresponding alkyne with dibromoborane,[21] followed by reaction with KHF_2 in Et_2O/H_2O. Vinyl trifluoroborate **1d** was prepared by transmetalation of commercially available vinylmagnesium bromide with trimethylborate followed by in situ addition of aqueous KHF_2. α- and β-styryl trifluoroborates (**1f** and **1g**) were synthesized from the commercially available boronic acids by direct treatment with KHF_2 in Et_2O/H_2O. (*Z*)-4-Phenyl-1-but-1-enyltrifluoroborate (**1c**) was prepared by rhodium-catalyzed *trans*-hydroboration of the corresponding alkyne with catecholborane to afford the (*Z*)-1-alkenylboronate ester.[22] Subsequent addition of

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(21) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311–1316.

(22) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990–4991.

KHF_2 to an $MeCN/H_2O$ solution of the boronate ester afforded the alkenyltrifluoroborate. Regioselective hydroboration of the corresponding alkynes with pinacolborane catalyzed by $HZrCp_2Cl$ afforded the alkenylboronate esters that were reacted with KHF_2 in $MeCN/H_2O$ to generate the organotrifluoroborates **1j** and **1k**.[23]

With the alkenyltrifluoroborates in hand, we began the study of the cross-coupling reactions. In most cases, the coupling reactions were carried out using 3-bromo-3-buten-1-ol, α-bromocinnamaldehyde, or 2-bromo-3-methyl-2-cyclopenten-1-one. These processes all proceeded with good yields. Once again, the reaction was tolerant of a variety of functional groups, establishing that both partners can contain functionality. Vinyltrifluoroborate reacted with α-bromocinnamaldehyde to give the product in good yield (entry 1). The influence of an α-substituent on the organoboron partner was investigated (entries 3 and 4). Potassium α- and β-styryltrifluoroborates were converted to the product in satisfactory yield. However, the reaction of an α-substituted organoboron partner was slower and the yield was lower than that of the β-substituted organoboron partner. Alkenyltrifluoroborates with halide and cyano substituents within the organic moiety were evaluated (entries 6 and 9). The cross-coupling proceeded with good yields (72 and 80%, respectively).

The reaction of an alkenyltrifluoroborate bearing an ester group gave the coupled product in good yield (entry 7). This result differs from that obtained when the same alkenyltrifluoroborate **1i** was used for the alkenyl-aryl coupling under $PdCl_2(dppf)CH_2Cl_2$, *i*-PrOH−H_2O, and *t*-$BuNH_2$ conditions. In that case, the coupled product was obtained in low yield (33%) because of competitive ester hydrolysis. The prolonged reaction time and use of basic conditions in a homogeneous system contributed to the hydrolysis of the ester. In the present case, the shorter reaction time and the use of a heterogeneous system appears to prevent ester hydrolysis. Trimethylsilylethenyl trifluoroborate was used as coupling partner giving the product in 82% yield (entry 8). The TMS group survived during the coupling, even though again a fluoride source was present.

Conclusion

In summary, the palladium-catalyzed cross-coupling reaction of potassium alkenyltrifluoroborates with alkenyl bromides has been achieved chemo- and stereoselectively with moderate to excellent yields. This procedure possesses several advantages when compared with other methods. The alkenyltrifluoroborates can be prepared easily by different routes, including transmetalation and both catalyzed and noncatalyzed hydroboration. The ease of isolation, purification, storage, and handling makes them attractive intermediates for laboratory and industrial use and especially for combinatorial chemistry. A variety of functionalized alkenyltrifluoroborates can be synthesized and stored for long periods of time. The ready availability of stereodefined (*E*)- and (*Z*)-alkenyltrifluoroborates and the high stereoselectivity observed in the cross-coupling reactions make this method a very efficient route to synthesize virtually all classes of isomerically pure conjugated dienes. Moreover, a variety of sensitive functional groups are tolerated in both partners. Silyl protecting groups for alcohols can be used, even though a fluoride source is present. Another important advantage is that the use of toxic thallium bases is not required. As a consequence, this procedure can be used successfully in complex molecule synthesis.[19]

Experimental Section

General Procedure for Suzuki−Miyaura Cross-Coupling Reactions. Preparation of 1-Chloropentadeca-4,6-diene (2a). To a mixture of potassium (*E*)-1-dec-1-enyltrifluoroborate (**2a**) (370.4 mg, 1.1 mmol), (*Z*)-1-bromo-5-chloropent-1-ene (183.5 mg, 1 mmol), Cs_2CO_3 (977 mg, 3 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and PPh_3 (26 mg, 0.1 mmol) was added THF−H_2O (10:1, 4 mL). The reaction was heated at 70 °C with stirring under a nitrogen atmosphere for 2 h, cooled to rt, and diluted with water (3 mL). The resulting mixture was extracted with Et_2O. The organic layers were combined and washed with 1 N HCl and brine, dried over $MgSO_4$, and then filtered. The solvent was removed under vacuum, and the crude product was purified by silica gel chromatography (eluting with hexane) to afford a colorless oil (200 mg, 85%): ^1H NMR (500 MHz, $CDCl_3$) δ 6.30 (ddt, $J = 15, 10.9, 1.2$ Hz, 1H), 6.01 (dd, $J = 10.9, 10.7$ Hz, 1H), 5.69 (dt, $J = 15, 6.9$ Hz, 1H), 5.24 (dt, $J = 10.7, 7.7$ Hz, 1H), 3.54 (t, $J = 6.6$ Hz, 2H), 2.32 (q, $J = 7.7$ Hz, 2H), 2.10 (q, $J = 7.0$ Hz, 2H), 1.86 (dt, $J = 14.2, 6.7$ Hz, 2H), 1.39 (dt, $J = 14.2, 7.2$ Hz, 2H), 1.30−1.27 (m, 10H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 135.7, 130.2, 127.2, 125.2, 44.4, 32.9, 32.5, 31.9, 29.5, 29.3, 29.3, 29.2, 24.8, 22.7, 14.1; HRMS (CI) *m/z* calcd. for $C_{15}H_{27}Cl$ (M^+) 242.1800, found 242.1805; IR (neat) 2927, 2856, 1709 cm^{-1}.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM35249) for funding. Additionally, we thank Merck Research Laboratories, Amgen, Johnson & Johnson, and Johnson Matthey for additional support of this research. We also thank Dr. Rakesh Kohli for the HRMS data.

Supporting Information Available: Full experimental details and copies of all NMR spectra (^1H, ^{13}C, ^{19}F, and ^{11}B). This material is available free of charge via the Internet at http://pubs.acs.org.

JO050286W

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[23] Pereira, S.; Srebnick, M. *Organometallics* **1995**, *14*, 3127−3128.