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Synthesis of Trifluorostyrene Derivatives by Palladium-Catalyzed Cross-Coupling of Lithium Trimethoxy(trifluorovinyl)borate with Aryl Bromides

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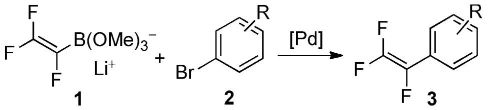
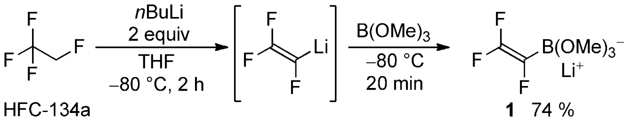
Trifluorostyrene (TFS) derivatives have been widely used as monomers for the preparation of polymers with fluorinated backbones.[1] However, they have seen little use in other research fields, such as medicinal chemistry, probably due to the lack of a convenient preparative method.[2] Most previous syntheses of TFS derivatives have involved multistep reaction sequences, often involving unstable reagents or intermediates and suffering from low overall yields.[1f,g,3] As a more direct synthetic route, the palladium-catalyzed cross-coupling of trifluorovinyl zinc reagents or trifluorovinyl tin reagents with aryl iodides has been described.[1e,4] Recently, a palladium-catalyzed reaction of tetrafluoroethylene (TFE) with arylzinc compounds has been reported to give TFS derivatives in moderate yields.[5] Although these catalytic methods are more efficient than other multistep approaches, their broad applicability suffers from the use of toxic and unstable reagents, such as organostannanes, organozinc reagents, or gaseous and explosive tetrafluoroethylene. Organoboron compounds have found widespread use in palladium-catalyzed Suzuki–Miyaura coupling reactions because they are easy to prepare, stable, and have relatively low toxicity.[6] In the context of TFS derivatives only two examples for the coupling of potassium (trifluorovinyl)trifluoroborate have been described so far.[7] Very recently, the copper-mediated coupling of potassium (trifluoromethyl)trimethoxyborate with aryl iodides has been reported.[8]

Herein, we report an efficient and convenient method for the introduction of a trifluorovinyl group based on the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction. This procedure employs stable borate **1** as the source of the trifluorovinylgroup and, thus, circumvents the inconvenient use of highly unstable TFE, toxic stannanes, or sensitive zinc reagents (Scheme 1).



Scheme 1. Synthesis of trifluorovinylarenes by cross-coupling.

Lithium trimethoxy(1,2,2-trifluorovinyl)borate **1** can be easily prepared in multigram quantities (25 g) by starting from 1,1,1,2-tetrafluorethane (HFC-134a), which is a cheap non-toxic bulk chemical commonly used as a refrigerant in air conditioners. In a one-pot synthesis HFC-134a was treated with two equivalents of *n*-butyl lithium to give the corresponding trifluorovinyl lithium in situ. Subsequent reaction with trimethoxyborane gave **1** in good yield (Scheme 2).[9] The product is an easy to handle white solid that is stable under anhydrous conditions.



Scheme 2. Preparation of lithium trimethoxy(trifluorovinyl)borate **1** from HFC-134a.

Crystals suitable for X-ray structure determination were obtained by cooling a saturated solution of **1** in THF to 4 °C. After one week, large colorless octahedral crystals of the THF adduct were isolated under a cold stream of nitrogen.[10] As expected, a distorted tetrahedral arrangement of the substituents around the boron atom is observed (Figure 1 a).[8] The bond lengths within the trifluorovinyl group closely resemble those in trifluoroethene.[11] Even the C–F bond to the α-fluorine atom (1.378 Å) is only marginally elongated compared with the C–F bonds in fluorinated ethenes. The lithium atom is coordinated in a distorted trigonal-bipyramidal geometry to four oxygen atoms and the α-fluorine atom of the trifluorovinyl group (Figure 1 b). The short Li–F contact of 2.253 Å is similar to the Li–F separations found in comparable structures.[12] Together the lithium

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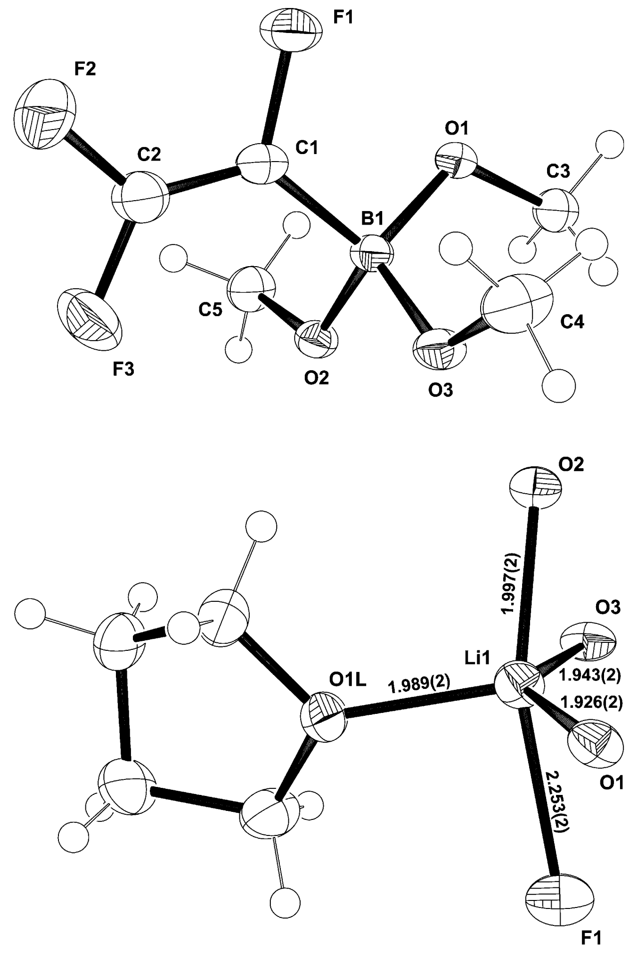
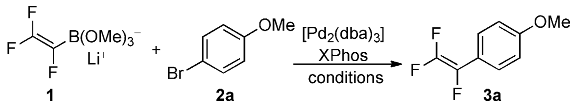


Figure 1. ORTEP[14] diagrams containing ellipsoids drawn at the 50% probability level. a) The molecular structure of the trimethoxy(1,2,2-trifluorovinyl)borate ion. b) The distorted trigonal-bipyramidal coordination sphere of the lithium ion. A part of the coordination polymer is depicted in the Supporting Information.

and borate ions form a one-dimensional coordination polymer.[13]

Table 1. Optimization of the conditions for the cross-coupling reaction.[a]

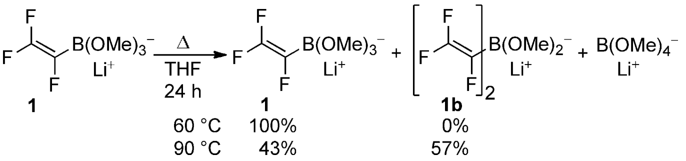


Entry	Solvent	Base	T [°C]	Conversion [%][b]
1	THF	none	60	19
2[c]	THF	none	60	4
3	THF	none	80	38
4	THF	none	90	44
5	2-MeTHF	none	60	15
6	2-MeTHF	none	80	20
7	glyme	none	60	20
8	glyme	none	80	12
9	toluene	none	60	0
10	DMF	none	60	0
11	dioxane	none	80	27
12	ethyl acetate	none	80	18
13	THF	K_3PO_4	60	100
14	THF	K_3PO_4	90	70
15	THF	KF	60	85
16	THF	KF	90	78
17	THF	CsF	60	93
18	THF	K_2CO_3	60	51
19	THF	Cs_2CO_3	60	93
20	THF	NaOMe	60	76
21	THF	Et_3N	60	27

[a] Reaction conditions: **2a** (0.5 mmol), **1** (1.0 mmol), $[Pd_2(dba)_3]$ (0.5 mol%), XPhos (1.0 mol%), base (0.5 mmol), solvent (2 mL), 60–90 °C, 15 h. [b] Based on the ratio of **3a** to **2a**, as determined by ^{1}H NMR spectroscopy. [c] LiCl (1.0 mmol) or tetra-*n*-butylammonium chloride (TBACl) (1.0 mmol) as the additive.

For the cross-coupling of borate **1** with aryl halides, we chose *para*-bromoanisole **2a** as the model substrate. After initial qualitative experiments, we decided to use $[Pd_2(dba)_3]$ (DBA = dibenzylideneacetone) and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) as the catalyst system for the optimization of the reaction conditions.[15] A survey of aprotic solvents without added bases showed that a variety of ethers were suitable for the reaction, with THF being the most promising (Table 1, entries 1–8 and 11). In contrast, no conversion was observed in toluene or DMF (Table 1, entries 9 and 10). Different inorganic salts were tested as basic additives, and indeed increased the conversion of **2a**, the best results being obtained with K_3PO_4 (Table 1, entry 13). CsF and Cs_2CO_3 were slightly less effective, whereas the amine base Et_3N was essentially ineffective (Table 1, entries 17, 19, and 21). We also examined the influence of reaction temperature with and without added base. In the absence of base, increasing the reaction temperature increased the conversion (Table 1, entries 3 and 4), whereas, in the presence of K_3PO_4 or KF, a higher reaction temperature led to slightly lower conversion (Table 1, entries 13, 14, 15, and 16).

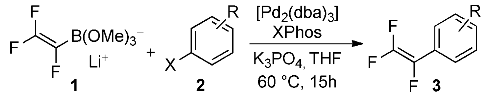
Control experiments showed that borate **1** in THF is stable at 60 °C, whereas heating to 90 °C causes disproportionation of **1** into lithium dimethoxybis(1,2,2-trifluorovinyl)borate **1b** and lithium tetramethoxyborate (Scheme 3).[16] The role of the base in the coupling reaction remains unclear at present. Conceivably, the additives remove halide ions or $B(OMe)_3$, which is formed as a by-product and which we found to inhibit the reaction.[17]



Scheme 3. Disproportionation of **1** at elevated temperature in THF.

We briefly investigated the influence of the halogen leaving group on the cross-coupling reaction. With aryl iodides the coupling product was formed, but consistently lower conversions were observed than with the corresponding aryl bromides (Table 2). Aryl chlorides, however, did not give any detectable conversion. Interestingly, the conditions for

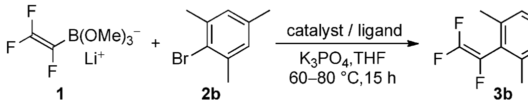
Table 2. Comparison of different aryl halides as electrophiles.[a]



Entry	R	Yield [%][b]		
		X=Cl	X=Br	X=I
1	4-OMe	0	100	55
2	3-OMe	–	76	61
3	4-Me	0	85	72
4	2-Me	–	79	36

[a] Reaction conditions: **2** (0.5 mmol), **1** (1.0 mmol), [Pd$_2$(dba)$_3$] (0.5 mol%), XPhos (1.0 mol%), K_3PO_4 (0.5 mmol), THF (2 mL), 60 °C, 15 h. [b] Based on the ratio of **3** to **2**, as determined by ^{1}H NMR spectroscopy.

Table 3. Comparison of different ligands.[a]



Entry	Pd source	[mol%]	Ligand[b]	[mol%]	T [°C]	Conversion [%][c]
1	[Pd$_2$(dba)$_3$]	0.5	none	–	60	0
2	[Pd$_2$(dba)$_3$]	0.5	XPhos	1.0	60	50
3	[Pd$_2$(dba)$_3$]	0.5	XPhos	2.0	60	47
4	[Pd$_2$(dba)$_3$]	2.5	XPhos	5.0	60	70
5	[Pd$_2$(dba)$_3$]	0.5	XPhos	1.0	80	60
6	[Pd$_2$(dba)$_3$]	2.5	XPhos	5.0	80	100
7	[Pd$_2$(dba)$_3$]	0.5	MePhos	1.0	60	29
8	[Pd$_2$(dba)$_3$]	0.5	SPhos	1.0	60	2
9	[Pd$_2$(dba)$_3$]	0.5	JohnPhos	1.0	60	4
10	[Pd$_2$(dba)$_3$]	0.5	DavePhos	1.0	60	4
11	[Pd$_2$(dba)$_3$]	0.5	BrettPhos	1.0	60	0
12	[Pd$_2$(dba)$_3$]	2.5	RuPhos	5.0	60	12
13	[Pd$_2$(dba)$_3$]	0.5	P*t*Bu$_3$	1.0	60	17
14	[Pd$_2$(dba)$_3$]	0.5	P*t*Bu$_2$Me	1.0	60	3
15	[Pd$_2$(dba)$_3$]	0.5	PPh$_3$	1.0	60	5
16	[Pd$_2$(dba)$_3$]	0.5	PCy$_3$	1.0	60	3
17	[Pd$_2$(dba)$_3$]	0.5	XantPhos	1.0	60	1
18	[Pd$_2$(dba)$_3$]	0.5	IPrNHC	2.0	60	0
19	[Pd(OAc)$_2$]	1.0	XPhos	1.0	60	16
20	[Pd(dppf)Cl$_2$]	1.0	none	–	60	0

[a] Reaction conditions: **2b** (0.5 mmol), **1** (1.0 mmol), catalyst, ligand, K_3PO_4 (0.5 mmol), THF (2 mL), 60–80 °C, 15 h. [b] MePhos = 2-dicyclohexylphosphino-2′-methylbiphenyl, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl, DavePhos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, BrettPhos = 2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl, RuPhos = 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl, Cy = cyclohexyl, XantPhos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, IPrNHC = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, DPPF = 1,1′-bis(diphenylphosphino)ferrocene. [c] Based on the ratio of **3b** to **2b**, as determined by ^{1}H NMR spectroscopy.

the recently reported copper-mediated coupling of (trifluoromethyl)trimethoxyborate with aryl iodides were ineffective for the coupling of trifluorovinylborate **1** with either bromo- or iodoarenes.[8]

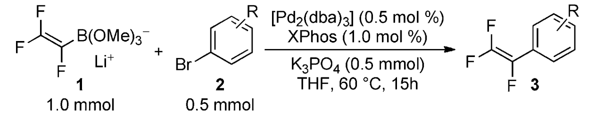
With bromomesitylene **2b**, a more challenging substrate, which gave only 50% conversion under our initially optimized conditions, we tested several different phosphine ligands (selected examples are presented in Table 3). Among these, only XPhos was found to be suitable, as even structurally related Buchwald ligands[15] gave significantly lower conversions. Eventually, we achieved complete conversion of **2b** by increasing the catalyst loading to 5 mol% palladium and raising the temperature to 80 °C (Table 3, entry 6).

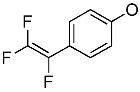
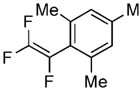
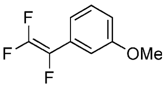
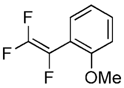
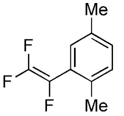
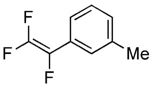
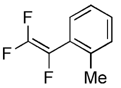
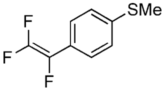
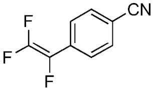
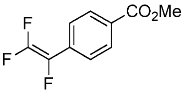
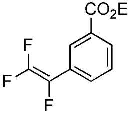
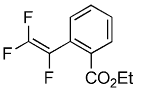
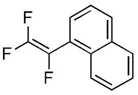
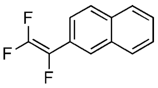
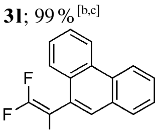
We successfully applied the reaction conditions to the synthesis of different substituted trifluorvinylarenes **3** (Table 4). By using catalyst loadings of 1 mol% Pd, different bromobenzenes with methyl or methoxy substituents could be coupled. Likewise, 1- and 2-bromonaphthalene, as well as 9-bromophenanthrene, proved to be good substrates for the reaction.

In cases for which the standard conditions resulted in incomplete conversion of the bromoarene, we adjusted the temperature or catalyst loading to achieve complete conversion. These adjustments were necessary to obtain pure products because mixtures of the starting bromoarene and the corresponding trifluorovinylarene product are effectively inseparable by chromatography. Thus, for *ortho*-substituted arenes a reaction temperature of 80 °C was necessary to reach complete conversion. Substrates with electron-withdrawing substituents proved to be significantly less reactive and required higher catalyst loadings of 5 mol% to completely convert the bromoarene. At first glance, this finding is surprising, since aryl halides with electron-withdrawing substituents are usually particularly good substrates for palladium-catalyzed cross-couplings, giving good yields and high catalyst turn-over numbers.[18] This high reactivity has been attributed to the fact that electron-poor aryl halides undergo oxidative addition to palladium(0) complexes faster than electron-rich aryl halides.[19] In a competition experiment between *para*-bromoanisole **2a** and *para*-bromobenzonitrile **2i**, we observed preferential reaction of the electron-poor compound **2i** in a 2.6:1 ratio, albeit in a low conversion of 36%, which is comparable to the reaction of **2i** alone under these conditions (see Table 4). This result indicates that, as expected, oxidative addition of bromobenzonitrile **2i** to the palladium catalyst is faster than oxidative addition of bromoanisole **2a**. However, one of the subsequent steps, transmetalation or reductive elimination of the product, is less efficient for the palladium aryl intermediate with an electron-deficient aryl group, and it is the efficiency of this step that determines the yield of the catalytic process. A similar correlation was recently observed for the palladium-catalyzed direct arylation of pyridine *N*-oxides, for which the coupling with electron-poor aryl halides was significantly less effective than with electron-rich aryl halides.[20] Currently, we are investigating the reactivity of isolated palladium aryl complexes to elucidate the influence of the aryl substituent on the transmetalation.

In conclusion, the preparation of TFS derivatives by palladium-catalyzed cross-coupling of trifluorovinylborate **1** and aryl bromides is a straightforward and convenient method that employs stable, easily handled starting materials and avoids the use of toxic, dangerous, and unstable reagents. Therefore, this method helps to make trifluorovinylarenes

Table 4. Synthesis of substituted trifluorostyrene derivatives **3**. Isolated yields based on **2**.



 **3a**; 97 %	 **3b**; *50 %*,[a] 99 %[b,c]	 **3c**; *76 %*,[a] 96 %[d]
 **3d**; *86 %*,[a] 99 %[c]	 **3e**; *67 %*,[a] 99 %[c]	 **3f**; *75 %*,[a] 86 %[d]
 **3g**; *79 %*,[a] 70 %[c]	 **3h**; *78 %*,[a] 99 %[b]	 **3i**; *41 %*,[a] 96 %[b]
 **3j**; 99 %[b]	 **3k**; 99 %[b]	 **3l**; 99 %[b,c]
 **3m**; 99 %	 **3n**; 97 %	 **3o**; 99 %

[a] Yields (in italics) based on the ratio of **3** to **2**, as determined by ^{1}H NMR spectroscopy. [b] [Pd$_2$(dba)$_3$] (2.5 mol %), XPhos (5.0 mol %). [c] Reaction temperature 80 °C instead of 60 °C. [d] By using (XPhos)–palladium(II)–phenethylamine chloride (1.0 mol %) as the precatalyst (see the Supporting Information for the structure of this compound).

more readily available for investigations of potential applications in other fields of chemistry, such as materials science or medicinal chemistry.

Experimental Section

General procedure for the palladium-catalyzed trifluorovinylation: In a closed vial, under argon, K$_3$PO$_4$ (106 mg, 0.5 mmol), **1** (192 mg, 1.0 mmol), [Pd$_2$(dba)$_3$] (2.3 mg, 0.0025 mmol), XPhos (2.4 mg, 0.005 mmol), and arylhalide **2** (0.5 mmol) in THF (2 mL) were stirred for 15 h at 60 °C. The reaction mixture was diluted with pentane and filtered through a short plug of silica gel. Evaporation of the solvent under reduced pressure gave the product.

Acknowledgements

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Keywords: borates · cross-coupling · fluorine · palladium · trifluorovinyl compounds

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