JOC Article

Direct Vinylation and Difluorovinylation of Arylboronic Acids Using Vinyl- and 2,2-Difluorovinyl Tosylates via the Suzuki−Miyaura Cross Coupling

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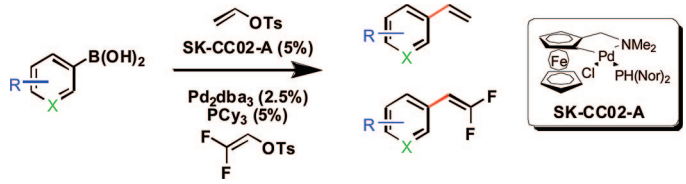

General reaction conditions were developed for the Pd(0)-catalyzed Suzuki−Miyaura coupling reaction of aryl boronic acids with a simple electrophilic vinylation reagent, vinyl tosylate, providing access to styrene derivatives in good yields. The easily accessible vinyl tosylate represents a stable and less toxic alternative to the vinyl halides and the triflate/nonaflate derivatives. Furthermore, this methodology was expanded to provide a facile and straightforward approach for the introduction of a *gem*-difluorovinyl substituent onto an aromatic ring using the similar and also readily available 2,2-difluorovinyl tosylate as the electrophilic complement.

Introduction

Styrene derivatives are valuable compounds both as advanced intermediates in the synthesis of fine chemicals and as precursors to functionalized polymers. Alkenes also act as a platform for the introduction of numerous functionalities, as well as being substrates for the Mizoroki−Heck[1] and metathesis reactions.[2] Metal-catalyzed cross-coupling strategies represent mild alternatives for the introduction of vinyl substituents onto an aromatic core, in particular due to the compatibility with a wide range of functional groups.[3] Several vinylation methods have been developed based on different organometallic reagents including vinylmagnesium (Kumada−Corriu),[4] vinyltin (Migita−Kosugi−Stille),[5] vinylsilicon (Hiyama),[6] vinylboron (Suzuki−Miyaura), [7] and others.[8] Although the vinyltin reagents are the most widely exploited in the cross-coupling approach, this strategy suffers from drawbacks such as high cost of the tin reagent, toxicity, and tedious chromatographic separation of the undesired tin waste products. On the other hand, vinylboron reagents such as boronic acids, esters, or trifluoroborate salts are less problematic and therefore represent viable alternatives to the tin-based reagents.[9]

Nevertheless, the majority of published work regarding metal-catalyzed vinylations exploits the olefinic moiety as the nucleophilic species. A complementary approach for introducing a vinyl group would be desirable, where an organometallic reagent couples with a vinylic electrophile. However, the use

(1) (a) Beletskaya, I. P.; Ceprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

(2) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (c) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: New York, 2003.

(3) (a) de Meijere, A.; Diederich, F. *Metal-catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (b) Tsuji, J. *Palladium Reagents and Catalysts, New Perspectives For the 21st Century*; Wiley: West Sussex, 2004. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis* Negishi E., Ed.; Wiley-Interscience: New York, 2002.

(4) Bumagin, N. A.; Andryukhova, N. P.; Beletskaya, I. P. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1987**, *36*, 1561.

(5) (a) Badone, D.; Cecchi, R.; Guzzi, U. *J. Org. Chem.* **1992**, *57*, 6321. (b) Grasa, G.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119. (c) Bumagin, N. A.; Andryukhova, N. P.; Beletskaya, I. P. *Dokl. Chem.* **1989**, *307*, 211. (d) Chrétien, J.-M.; Mallinger, A.; Zammattio, F.; Le Grognec, E.; Paris, M.; Montavon, G.; Quintard., J.-P. *Tetrahedron Lett.* **2007**, *48*, 1781.

(6) (a) Tuet, J. *Tetrahedron Lett.* **1999**, *40*, 1673. (b) Denmark, S. E.; Wang, Z. *J. Organomet. Chem.* **2001**, *624*, 372. (c) Denmark, S. E.; Butler, C. R. *Org. Lett.* **2006**, *8*, 63. (d) Denmark, S. E.; Butler, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 3690.

(7) (a) Darses, S.; Michaud, G.; Genét, J.-P. *Tetrahedron Lett.* **1998**, *39*, 5045. (b) Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968. (c) Coleman, C. M.; O'Shea, D. F. *J. Am. Chem. Soc.* **2003**, *125*, 4054. (d) Peyroux, E.; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2004**, 1075. (e) Molander, G. A.; Brown, A. R. *J. Org. Chem.* **2006**, *71*, 9681.

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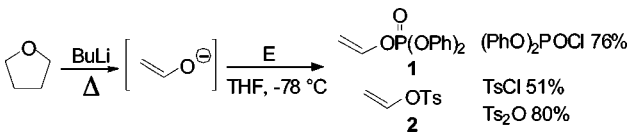
SCHEME 1. Synthesis of Vinyl Electrophiles



of vinyl halides is hampered by the low stability and boiling points of these coupling partners.[10] Vinyl iodide is actually the only candidate representing a manageable liquid at atmospheric pressure (bp 56 °C), but this particular substrate then suffers from severe instability hampering isolation and hence the reproducibility of its application in chemical transformations.[11]

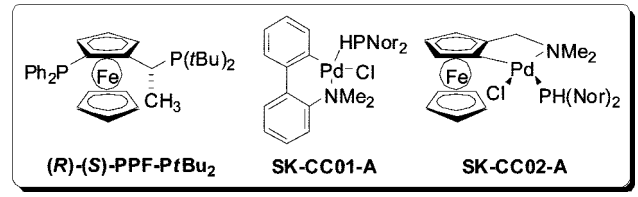
In this paper, we report on general reaction conditions for the use of a simple electrophilic vinylation reagent, represented by vinyl tosylate, in the Pd(0)-catalyzed Suzuki−Miyaura coupling reaction with arylboronic acids. This reagent represents a more stable and practical alternative to the vinyl halides and the triflate/nonaflate derivatives. Furthermore, we reveal an adaptation of this approach for the direct introduction of a *gem*-difluorovinyl substituent onto an aromatic ring starting from the easily accessible 2,2-difluorovinyl tosylate. As there is a keen interest in the use of difluoroalkenes as either bioisosteres of bioactive carbonyl compounds or as precursors for the preparation of other fluorinated compounds, our novel synthetic approach to these fluorinated styrene derivatives from a simple fluorine containing starting material could have high impact.

Results and Discussion

Synthesis of Vinyl Styrenes. Previously, we and others have demonstrated the viability of nonactivated alkenyl phosphates and tosylates, which are readily available from the corresponding ketones, to undergo a variety of Pd- or Ni-catalyzed coupling reactions.[12] Considering the high number of commercially available arylboronic acid derivatives, we examined the possibility of performing Suzuki−Miyaura couplings with either a vinyl phosphate or tosylate as a viable approach for introducing a vinyl group onto an aromatic ring.

The vinylic electrophiles were obtained in a straightforward manner by fragmentation of tetrahydrofuran upon treatment with butyllithium and trapping the formed enolate with either diphenylphosphoryl chloride/anhydride or tosyl chloride (Scheme 1).[13] These reagents displayed good stability as they showed no sign of degradation when stored in a freezer for several months.

Initial experiments on the suitability of these reagents for the introduction of vinyl groups are shown in Table 1. Utilizing the Ni(0)-catalyzed Suzuki−Miyaura conditions as previously published afforded the desired styryl derivatives in good yields with *O*-vinyl-*O,O*-diphenyl phosphate **1**, but significant deboronation of the boronic acids was detected (entries 1 and 2).[12c] At this point, it should be mentioned that deboronation severely complicates the chromatographic purification of the desired coupling products, and that this side reaction had to be eliminated in order to obtain an efficient protocol for the formation of styrene derivatives. Attention was then directed toward the more reactive vinyl tosylate **2** as the electrophile. Unfortunately, this change did not eliminate the problematic deboronation side reaction using the Ni(0)-catalyzed conditions (entry 3). Changes in ligand, solvent, base, or reaction temperature did not affect the yield nor the amount of deboronation in a positive direction (results not shown), and hence, we set forth to investigate alternative catalyst systems based on palladium(0) complexes.



Initial screenings were conducted testing commercially available bidentate ligands such as DPPF, D-*t*-BPF and the Josiphos type ligands (Table 1, entries 4–6). The reactions were performed using Pd_2dba_3 as the palladium source, aromatic boronic acid (1.5 equiv), and **2** (1 equiv) in combination with anhydrous potassium phosphate as the base in THF. Although the Josiphos-type ligand did provide full conversion, only a 57% yield of the desired styrene could be secured upon column chromatography. Better results were obtained with the biphenylphosphine ligand X-Phos,[14] where full conversion was obtained with a 74% isolated yield (entry 7). Unfortunately, deboronation still remained an issue and couplings with boronic acids carrying either electron-withdrawing or electron-donating groups proved, that this side reaction was not influenced by electronic factors (entries 8 and 9).[15] The addition of water to the reaction mixture provided a partial solution to this side reaction, where lower yields of the deboronated byproduct was observed. Addition of water to the reaction medium is believed to increase the solubility of the preactivated organoboron−base complex providing a faster transmetalation, and most importantly, organoboron compounds are often less prone to undergo deboronation in the presence of water.[15b]

Changing the catalyst precursor to the commercially available palladacycle SK-CCO1-A in combination with potassium phosphate in a dioxane/H_2O solution at 100 °C also provided a good yield of the desired product (74%), but more importantly *deboronation was not detected* (Table 1, entry 10).[16] Although the complex SK-CCO2-A afforded a slightly lower yield in

(8) (a) For examples of more exotic vinyl cross-coupling reagents, see: Mikami, S.; Yorimitsu, H.; Oshima, K. *Synlett* **2002**, 1137. (b) Schumann, H.; Kaufmann, J.; Schmalz, H. G.; Böttcher, A.; Gotov, B. *Synlett* **2003**, 1783. (c) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997.

(9) (a) Darses, S.; Genét, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393. (b) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950. (c) Molander, G. A.; Fumagalli, T. *J. Org. Chem.* **2006**, *71*, 5743. (d) Molander, G. A.; Ham, J.; Seapy, D. G. *Tetrahedron* **2007**, *63*, 768.

(10) Boiling points at 1 atm: vinyl chloride = –13.4 °C, vinyl bromide = 16 °C, vinyl iodide = 56 °C.

(11) Synthesis of vinylarenes was achieved from $ArB(OH)_2$ and 1,2-dibromoethane where vinyl bromide was generated in situ by base-promoted elimination. Lando, V. R.; Monteiro, A. C. *Org. Lett.* **2003**, *5*, 2891.

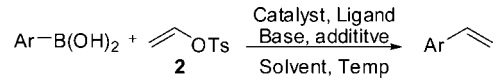
(12) (a) For some recent examples, see: Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349. (b) Ebran, J.-P.; Hansen, A. L.; Gøgsig, T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931. (c) Hansen, A. L.; Ebran, J.-P.; Gøgsig, T.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464. (d) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364. (e) Larsen, U. S.; Martiny, L.; Begtrup, M. *Tetrahedron Lett.* **2005**, *46*, 4261. (f) Klapars, A.; Campos, K. R.; Chen, C.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185.

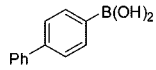
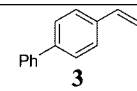
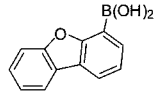
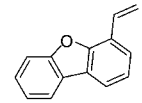
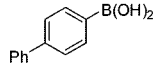
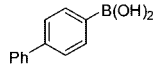
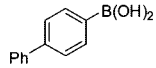
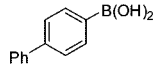
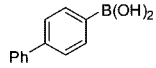
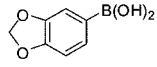
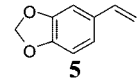
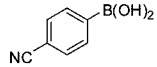
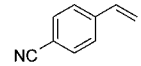
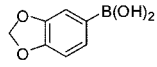
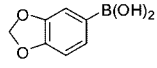
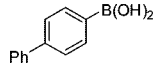
(13) (a) Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2001**, 4189 For earlier references, see: (b) Letsinger, R. L.; Pollart, D. F. *J. Am. Chem. Soc.* **1956**, *78*, 6079. (c) Rernbaum, A.; Siao, S. P.; Indictor, N. *J. Polym. Sci.* **1962**, *116*, 517.

(14) (a) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484. (b) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6173. (c) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523.

(15) (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am.Chem. Soc.* **2003**, *125*, 11818. (b) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881.

TABLE 1. Optimization of the Suzuki−Miyaura Coupling



Entry	Boronic acid	Reaction conditions	Product	Yield[a]
1		$Ni(COD)_2$ (5%), HBF_4PCy_3 (10%) K_3PO_4 (3 equiv.), THF, 70 °C	 **3**	81%[b]
2		$Ni(COD)_2$ (5%), HBF_4PCy_3 (10%) K_3PO_4 (3 equiv.)THF, 70 °C	 **4**	75%[b]
3		$Ni(COD)_2$ (5%), HBF_4PCy_3 (10%) K_3PO_4 (3 equiv.), THF, 70 °C	**3**	80%[b]
4		Pd_2dba_3 (2.5%), DPPF (5%), K_3PO_4 (3 equiv.), THF, 70 °C	**3**	15%[c]
5		Pd_2dba_3 (2.5%), D*t*BPF (5%), K_3PO_4 (3 equiv.), THF, 70 °C	**3**	63%[c]
6		Pd_2dba_3 (2.5%), (R)-(S)-PPF-P*t*Bu_2 (5%), K_3PO_4 (3 equiv.), THF, 70 °C	**3**	57%[b]
7		Pd_2dba_3 (2.5%), X-Phos (5%), K_3PO_4 (3 equiv.), THF, 70 °C	**3**	74%[b]
8		Pd_2dba_3 (2.5%), X-Phos (5%), K_3PO_4 (1.7 equiv.), Dioxane/H_2O, 100 °C	 **5**	68%[b]
9		Pd_2dba_3 (2.5%), X-Phos (5%), K_3PO_4 (1.7 equiv.), Dioxane/H_2O, 100 °C	 **6**	91%[b]
10		SK-CC01-A (5%), K_3PO_4 (1.7 equiv.), Dioxane/H_2O, 100 °C	**5**	74%
11		SK-CC02-A (5%), K_3PO_4 (1.7 equiv.), Dioxane/H_2O, 100 °C	**5**	72%
12		SK-CC02-A (5%), K_3PO_4 (2.7 equiv.), Dioxane/H_2O, 100 °C	**3**	88%[d]

[a] Isolated yield after chromatographic purification. [b] Substantial deboronation observed. [c] Conversion rates; compound not isolated. [d] Reaction run with 0.3 mmol of boronic acid and 0.45 mmol of vinyl tosylate.

comparison to SK-CCO1-A (entry 11), this palladium complex led to a much cleaner reaction as determined by ^1H NMR analysis of the crude reaction mixture. Finally, a more reliable system was obtained upon application of the aromatic boronic acid as the limiting reagent with 1.5 equiv of **2** (entry 12).

These optimized coupling conditions were tested against a variety of aromatic boronic acids, the results of which are depicted in Table 2. Boronic acids containing either electron-withdrawing or electron-donating groups underwent successful coupling with vinyl tosylate **2** in good to excellent isolated yields (entries 2–7 and 13). The neopentyl glycol ester of some of the boronic acids was also tested and provided comparable reactivity (entries 1, 4, and 9) and even improved the isolated yield of the 2-vinyl-6-methoxynaphthalene shown in entry 6.[17,18] This coupling protocol was tested against several heteroaromatic boronic esters and gratifyingly the styrene derivatives could be secured in good yields ranging from 79 to 88% (entries 9–11). A drop in reactivity was observed when the coupling was attempted with boronic acids carrying substituents in ortho position as exemplified in entry 12 upon comparison with entry 13. Finally, a double coupling was attempted with the diboronic acid depicted in entry 8 providing the 4,4′-divinylbiphenyl in a 59% isolated yield.

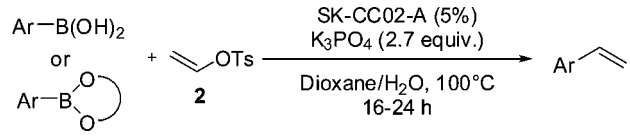
In order to test the utility of the vinylation methodology, the coupling conditions were performed on a scale ten times greater

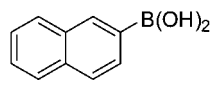
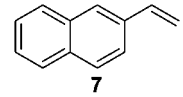
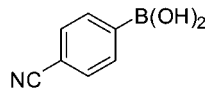
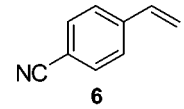
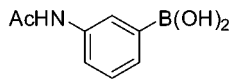
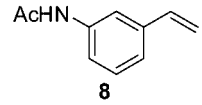
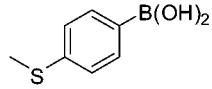
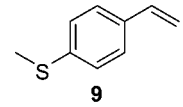
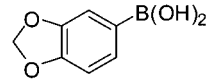
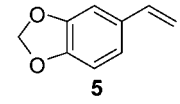
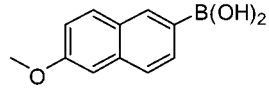
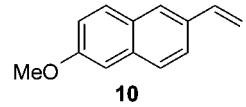
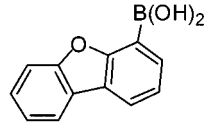
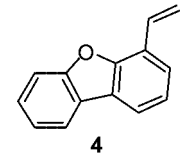
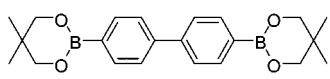
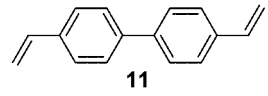
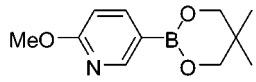
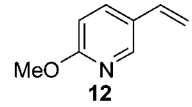
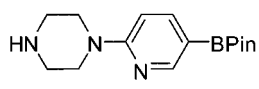
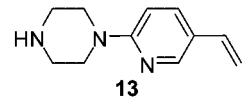
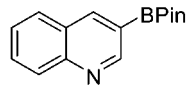
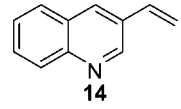
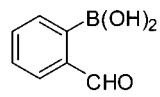
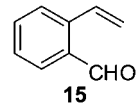
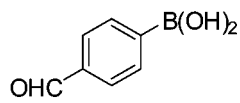
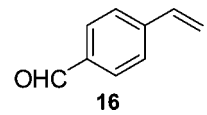
(16) The SK-CC01-A and SK-CC02-A complexes are air-stable, commercially available Pd complexes from Solvias.

(17) 2-Vinyl-6-methoxynaphthalene is a key intermediate in the Albermale synthesis of naproxen; see: de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086.

(18) Despite the presence of water in the reaction mixture, the BF_3K salt of the naphthalen-2-yl boronic acid only afforded 55% isolated yield of the corresponding 2-vinylnaphthalene. See ref 9.

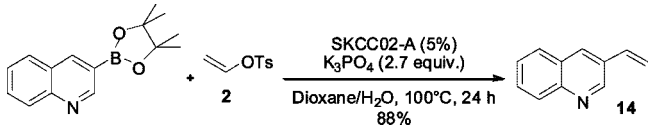
TABLE 2. Suzuki−Miyaura Couplings with Vinyl Tosylate 2



Entry	Aryl-BR_2	Product	Yield [%][a]
1		 **7**	99 (95)[b]
2		 **6**	89
3		 **8**	89[c]
4		 **9**	90 (88)[b]
5		 **5**	85
6		 **10**	60 (76)[b]
7		 **4**	89
8		 **11**	59
9		 **12**	88
10		 **13**	79
11		 **14**	81
12		 **15**	63[c]
13		 **16**	90

[a] Isolated yield after chromatographic purification. Conditions: boronic acid (0.3 mmol) and **2** (0.45 mmol). [b] The neopentyl glycol ester of the boronic acid was used instead. [c] Some deboronation of the boronic acid detected.

SCHEME 2. Large-Scale Coupling



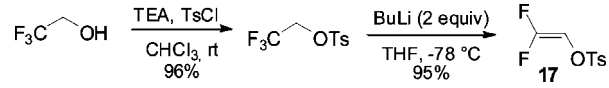
that those of Table 1. Coupling of the pinacol boronic ester of 2-quinoline on a 3 mmol scale (Scheme 2), furnished the desired styrene in an 88% isolated yield, which represents a slight increase compared to the same coupling as shown Table 2, entry 11.

Synthesis of 2,2-Difluorovinylstyrenes. We then turned our attention to the application of a fluorinated vinylic electrophile to obtain fluorinated styrene derivatives. Introduction of fluorine to biologically active compounds often provides a positive effect on their pharmacokinetic properties.[19] In particular, the *gem*-difluorovinyl group represents a viable bioisostere for aldehydes and ketones,[20] where the CF_2 group is isopolar to an oxygen atom.[21] Furthermore, *gem*-difluoroalkenes have been exploited as precursors for the synthesis of other fluorinated compounds and polymers.[22] Hence effective methods for their introduction are of high value.

There are only few methods for introducing 2,2-difluorovinyl groups on an aromatic core. The most common approach relies on the use of Wittig-type reactions with a difluoromethylene phosphorus ylide.[23] Thermal decomposition of *gem*-difluoro-β-lactams has also been reported.[24] Nenajdenko et al. recently disclosed the conversion of hydrazones of aryl aldehydes to *gem*-difluorovinyl styrenes via catalytic olefination with dibromodifluoromethane in the presence of CuCl.[25] However, the desired alkenes were furnished in yields of less than 40%. A Julia olefination was adapted by Prakash, Olah, and co-workers for the introduction of a difluorovinyl group using bromodifluoromethyl phenyl sulfone, but here three steps are required for this transformation starting from the aryl aldehyde.[26] Finally, a palladium-catalyzed cross coupling of aryl halides with 2,2-difluorovinylzinc was reported leading to the desired fluorinated styrenes.[27] The zinc reagent was prepared from either 2,2-difluorovinyl bromide (bp 6 °C at 1 atm) or the corresponding iodide which is not commercially available.

In this work, we explored the possibility of using 2,2-difluorovinyl tosylate as an electrophilic difluorovinylating agent in a Suzuki−Miyaura cross coupling strategy for accessing these fluorinated styrene derivatives. In a convenient manner, the difluorinated vinyl tosylate **17** was obtained as an oil by a two-step sequence in an overall 91% yield starting from commercially available trifluoroethanol (Scheme 3).[28]

SCHEME 3. Synthesis of 2,2-Difluorovinyl Tosylate



The optimized conditions applied for couplings with **2** only afforded the desired 2,2-difluorostyrenes in low yield. Instead, conditions reported by Fu et al. using Pd_2dba_3 (2.5%), HBF_4PCy_3 (10%) in combination with K_3PO_4 as the base in a H_2O/dioxane solvent mixture at 100 °C proved sufficiently reactive providing a 79% of the desired 4-(2,2-difluorovinyl) benzonitrile (results not shown).[29] Lowering the ligand loading to 5% increased the catalytic efficiency of the system affording a 90% yield of the desired fluorinated styrene (Table 3, entry 1).

These slightly modified conditions were then tested against several different boronic acids. We were pleased to find that this catalytic system provided the fluorinated coupling products in yields ranging from 46 to 98%. Once again the boronic esters could be applied without loss in reactivity (entries 3, 8, and 10–12). Finally, heteroaromatic boronic esters were subjected to the conditions at hand and a 69% and 75% yield of the styrene derivatives could be secured upon column chromatography (entries 11 and 12).

Conclusion

In conclusion, two catalytic systems were developed for the introduction of either a vinyl or 2,2-difluorovinyl moiety onto an aromatic ring via Pd(0)-catalyzed Suzuki−Miyaura coupling with arylboronic acids. Both catalytic systems proved insensitive to the intrinsic nature of the boronic acid allowing the presence of both electron-withdrawing or electron-donating functionalities and heteroaromatic systems. Furthermore, the protocol appears to be scalable demonstrating the usefulness of this methodology. Further work is now in progress to obtain systems allowing for the introduction of both mono and fully fluorinated vinyl moieties as well as the implementation of these new styrene derivatives in the synthesis of biologically active compounds. This work will be reported in due course.

Experimental Section

3-Vinylquinoline[30] (14): General Procedure for the Suzuki−Miyaura Couplings of Vinyl Tosylate (2) with Boronic Acids. 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (765 mg, 3.00 mmol), and **2** (892 mg, 4.50 mmol), SK-CC02-A ((91 mg, 0.15 mmol) were dissolved in dioxane (20 mL). K_3PO_4 (2 M, 4.0 mL) was then added, and the reaction vessel was sealed using a Teflon screwcap and removed from the glovebox. The reaction mixture was heated for 19 h at 100 °C and monitored by TLC. After the reaction was complete, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel using pentane/ethyl acetate (10:1) as eluent. This afforded 408 mg of the title compound (88% yield) as an orange oil: H NMR (400 MHz, $CDCl_3$) δ (ppm)

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(26) Prakash, G. K. S.; Wang, Y.; Hu, J.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 1361.

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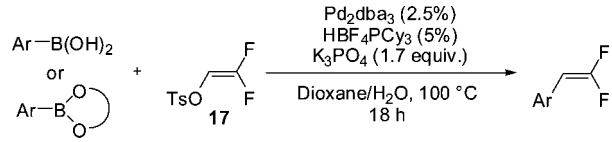
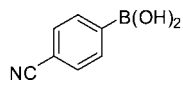
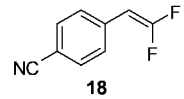
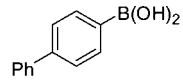
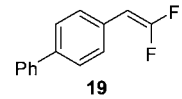
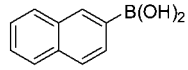
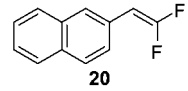
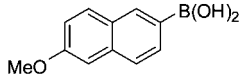
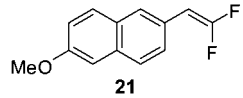
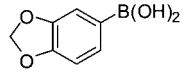
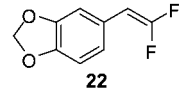
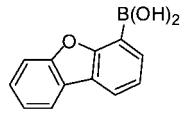
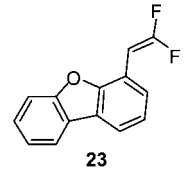
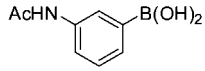
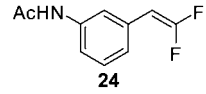
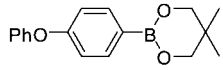
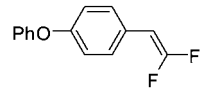
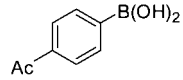
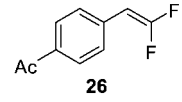
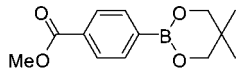
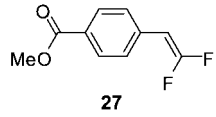
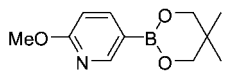
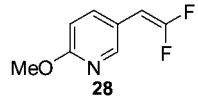
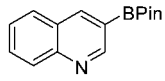
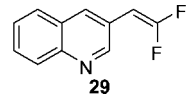
(29) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282.

(30) Hsu, M. C.; Junia, A. J.; Haight, A. R.; Zhang, W. *J. Org. Chem.* **2004**, *69*, 3907.

(31) Koch, H. F.; Lodder, G.; Koch, G. J.; Bogdan, D. J.; Brown, G. H.; Carlson, C. A.; Dean, A. B.; Hage, R.; Han, P.; Hopman, J. C. P.; James, L. A.; Knape, P. M.; Roos, E. C.; Sardina, M. L.; Sawyer, R. A.; Scott, B. O.; Testa III, C. A.; Wickham, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 9965.

TABLE 3. Suzuki−Miyaura Couplings with 2,2-Difluorovinyl Tosylate 17



Entry	Aryl-BR_2	Product	Yield [%][a]
1		 **18**	90
2		 **19**	98 (98)[b,c]
3		 **20**	81 (89)[d]
4		 **21**	50
5		 **22**	46
6		 **23**	76
7		 **24**	75
8		 **25**	94[b]
9		 **26**	85
10		 **27**	70[e]
11		 **28**	75[b]
12		 **29**	69[b]

a Isolated yield after chromatographic purification. *b* Boronic acid (0.3 mmol) and **17** (0.45 mmol) was used. *c* THF at 70 °C for 22 h used instead. *d* The neopentyl glycol ester of the boronic acid was used instead. *e* Some deboronation of the boronic ester detected.

9.02 (s, 1H), 8.07 (d, 1H, J = 8.8 Hz), 8.06 (s, 1H), 7.78 (d, 1H, J = 8.4 Hz), 7.66 (t, 1H, J = 8.8 Hz), 7.51 (t, 1H, J = 8.4 Hz), 6.85 (dd, 1H, J = 17.6, 11.2 Hz), 5.97 (d, 1H, J = 17.6 Hz), 5.45 (d, 1H, J = 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.2, 147.8, 133.9, 132.6, 130.4, 129.38, 129.37, 128.1, 128.0, 127.0, 116.5; GCMS $C_{11}H_9N$ [M^+] calcd 155, found 155.

4-(2,2-Difluorovinyl)benzonitrile (18):[31,32] Generel Procedure for the Suzuki−Miyaura Couplings of Difluorovinyl Tosylate

(3) with Boronic Acids. Compound **17** (70.2 mg, 0.30 mmol), 4-cyanophenylboronic acid (66.2 mg, 0.45 mmol), HBF_4PCy_3 (5.5 mg, 0.015 mmol), and Pd_2dba_3 (6.9 mg, 0.0075 mmol) were dissolved in dioxane (2 mL). K_3PO_4 (1.27 M, 0.4 mL) was then added, and the reaction vessel was sealed using a Teflon screwcap and removed from the glovebox. The reaction mixture was heated for 18 h at 100 °C and monitored by TLC. After the reaction was complete, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel using pentane → pentane/CH_2Cl_2 (1:1) as eluent. This afforded 44.7 mg of the title compound (90% yield) as a yellow solid: mp 69 °C (lit.[32] mp 69–70 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, 2H, J = 8.0 Hz), 7.42 (d, 2H, J = 8.0 Hz), 5.33 (dd, 1H, J = 25.6, 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.1 (dd, J = 299.2, 290.1 Hz), 135.5 (t, J = 7.0 Hz), 132.6, 128.3 (dd, J = 6.8, 3.0 Hz), 118.8, 110.7, 81.9 (dd, J = 29.8, 12.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –84.3 (dd, J = 35.7, 26.3 Hz), –86.5 (dd, J = 35.7, 4.1 Hz); GCMS $C_9H_4F_2N$ [M^+] calcd 165, found 165.

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Supporting Information Available: Experimental details and copies of ^{1}H NMR, ^{13}C NMR, and ^{18}F NMR spectra for all new products. This material isavailable free of charge via the Internet at http://pubs.acs.org.

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