

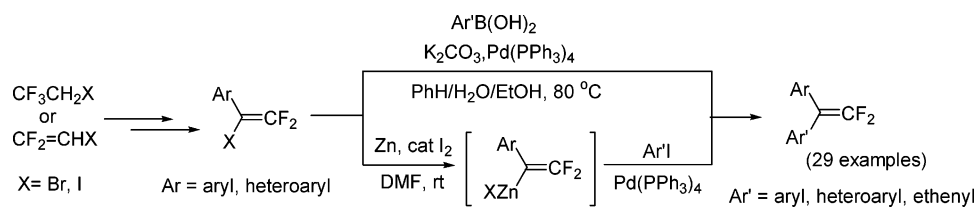
New Efficient Approach to 2,2-Diaryl-1,1-difluoro-1-alkenes and 1,1-Difluoro-2-aryl-1,3-dienes via Suzuki Coupling of α -Halo- β,β -difluorostyrenes

Anilkumar Raghavanpillai[†] and Donald J. Burton*

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242

donald-burton@uiowa.edu

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α -Halo- β,β -difluorostyrenes [$\text{ArCX} = \text{CF}_2$; $\text{X} = \text{Br, I}$; $\text{Ar} = \text{aryl, heteroaryl}$]; synthesized by the Pd(0)-catalyzed coupling reaction of the corresponding α -halo- β,β -difluoroethenylzinc reagents ($\text{CF}_2 = \text{CXZnCl}$, $\text{X} = \text{Br, I}$) with aryl iodides] were functionalized at the halogen site with arylboronic acids under Pd(0)-catalyzed Suzuki–Miyaura coupling reaction conditions to obtain 2,2-diaryl-1,1-difluoro-1-alkenes ($\text{ArAr}'\text{C} = \text{CF}_2$, $\text{Ar}' = \text{aryl, heteroaryl}$) in 51–91% isolated yield. The corresponding reaction with alkenylboronic acids produced 1,1-difluoro-2-aryl-1,3-dienes in 53–80% isolated yield. Alternatively, 2,2-disubstituted-1,1-difluoro-1-alkenes were synthesized in moderate yield by a zinc-insertion reaction at the halogen site of the α -halo- β,β -difluorostyrenes, followed by Pd(0)-catalyzed cross-coupling of the zinc reagent with aryl or alkenyl iodides.

Introduction

1,1-Difluoro-1-alkenes, in general, constitute a class of fluoro-organic compounds with interesting chemical,¹ material,² and biological properties.³ They exhibit unique chemical reactivities toward addition reactions,⁴ can be reduced to monofluoroalkenes, and are, therefore, considered an important intermediate en route to other classes of fluorinated organic molecules.⁵ 1,1-Difluoroalkenes are also potential mechanism-based inhibitors⁶ and are known to behave as a bioisosteric replacement of a

carbonyl group.^{1,7} The synthesis of 1,1-difluoroalkenes can be achieved by various methods that can be generalized into two broad strategies, Wittig-type chemistry and other methods.⁸

In Wittig and related syntheses, a difluoromethylene unit is introduced to aldehydes or ketones via a difluoromethylene ylide.⁹ The first synthetically useful preparation of a difluoromethylene ylide involved the reaction of triphenylphosphine

[†] Current address: DuPont Central Research & Development, Experimental Station, Wilmington, DE 19880, U.S.A.

(1) (a) *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Hudlicky, M., Ed.; Ellis Horwood: Chichester, U.K., 1976; Chapter 5. (b) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Tatlow, J. C., Smart, B. E., Eds.; Plenum Press: New York, 1994.

(2) (a) Reynolds, D. W.; Cassidy, P. E.; Johnson, C. G.; Cameron, M. L. *J. Org. Chem.* **1990**, *55*, 4448–4454. (b) Emsley, J. *New Sci.* **1989**, *122* (April 22), 46. (c) Mukai, H.; Ikukawa, S.; Nakayama, S.; Ito, A. Japanese Patent. JP 7138204, 1995.

(3) (a) *Selective Fluorination in Organic and Bioorganic Chemistry*; ACS Symposium Series No. 456; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991. (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Biological Chemistry*; Wiley: New York, 1991. (c) *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series No. 639; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996.

(4) (a) Ichikawa, J.; Wada, W.; Okauchi, T.; Minami, T. *J. Chem. Soc., Chem. Commun.* **1997**, 1537–1538. (b) Kendrick, D. A.; Kolb, M. *J. Fluorine Chem.* **1989**, *45*, 273–276. (c) Suda, M. *Tetrahedron Lett.* **1981**, *22*, 2395–2396. (d) Piettre, S. R. *Tetrahedron Lett.* **1996**, *37*, 2233–2236. (e) Herpin, T. F.; Motherwell, W. B.; Roberts, B. P.; Roland, S.; Weible, J. M. *Tetrahedron* **1997**, *53*, 15085–15100.

(5) (a) Hayashi, S.; Nakai, T.; Ichikawa, N.; Burton, D. J.; Naae, D. G.; Kesling, H. S. *Chem. Lett.* **1979**, 983–986. (b) Hayashi, S.; Nakai, T.; Ichikawa, N. *Chem. Lett.* **1980**, 651–654.

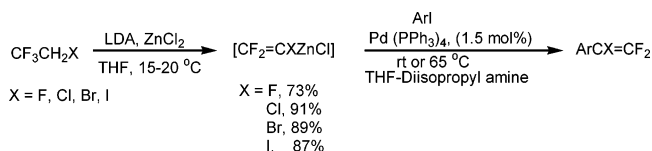
(6) (a) McDonald, I. A.; Lacoste, J. M.; Bey, P.; Palfreyman, M. G.; Ziena, M. *J. Med. Chem.* **1985**, *28*, 186–193. (b) McCarthy, J. R.; Matthews, D. P.; Semic, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439–7440. (c) Moore, W. R.; Schatzman, G. L.; Jarvi, E. T.; Gross, R. S.; McCarthy, J. R. *J. Am. Chem. Soc.* **1992**, *114*, 360–361. (d) Weintraub, P. M.; Holland, A. K.; Gates, C. A.; Moore, W. R.; Resvick, R. J.; Bey, P.; Peet, N. P. *Bioorg. Med. Chem.* **2003**, *11*, 427–431. (e) Madden, B. A.; Prestwich, D. G. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 309–314.

(7) Motherwell, W. B.; Tozer, M. J.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1437–1439.

and sodium chlorodifluoroacetate with carbonyl compounds.¹⁰ However, this route was useful only for aldehydes and polyfluorinated ketones to obtain the corresponding 1,1-difluoroalkenes and was unsuccessful for nonactivated ketones. The reaction between nonstabilized alkylidene triphenylphosphorane and halodifluoromethanes has been found to be a useful alternative to the above reaction but was not practical for nonfluorinated ketones. Reagents such as tris(dimethylamino)phosphine were required in the Wittig reaction with dibromodifluoromethane to effect this conversion.¹¹ Recently, 1,1-difluoroalkenes were synthesized using the Wittig method in moderate yield from in situ generated 1,1-difluoromethylene-phosphorus ylides [generated from (CF₃)₂Hg/NaI and a suitable phosphine] with aldehydes and ketones.¹² The synthesis of 1,1-difluoroalkenes by Wittig–Horner–Emmons chemistry is also known, where the reaction of diethyl 2-oxo-1,1-difluoropropylphosphonate with Grignard reagents produced 1,1-difluoroalkenes.¹³ A more general entry to 1,1-difluoroalkenes by Wittig-type chemistry was by the reaction of (diethylphosphonyl)difluoromethyl lithium¹⁴ or lithium difluoromethyldiphenylphosphine oxide with ketones and aldehydes.^{6d,e,15}

The alternative methods for the synthesis of 1,1-difluoroalkenes are generally based on metalation or related chemistry involving the addition of stabilized difluoroethenyl anions¹⁶ to electrophiles or to aryl and alkenyl iodides by palladium catalysis.¹⁷ 1,1-Difluoroalkenes with a wide range of substituents were readily synthesized from commercially available 2,2,2-trifluoroethyl *p*-toluenesulfonate via boron-, copper-, zinc-, or zirconium-mediated intermediates.¹⁸ In a recent report, various

SCHEME 1



1,1-difluoroalkenes were synthesized in two steps from 1-trifluoromethylethenylsilane, which involved an S_N2' reaction of 1-trifluoromethylethenylsilane with nucleophiles to construct 2,2-difluoroethenylsilanes and the subsequent substitution of the ethenyl silyl group with electrophiles to produce the desired 1,1-difluoroalkene.¹⁹ The synthesis of 1,1-difluoroalkenes by electrophilic mono- or difluorination²⁰ of the corresponding precursor or by the thermal decomposition of α,α-difluoro-β-lactones has also been reported.²¹ A facile synthesis of 1,1-difluoroalkenes by a base-induced elimination of alkyl-substituted difluoromethyl sulfones [prepared by the reaction of alkyl halides with in situ generated (benzenesulfonyl)difluoromethide] has recently been reported.²²

We have recently developed an efficient room-temperature methodology for the synthesis of α,β,β-trifluorostyrene from the readily available environmentally friendly precursor HFC-134a (CF₃CH₂F).²³ Metalation of HFC-134a with LDA in the presence of a zinc halide, followed by the Pd(0)-catalyzed coupling of the in situ generated trifluoroethenylzinc reagent with aryl iodides, produced α,β,β-trifluorostyrenes in very good isolated yields (Scheme 1). This methodology was later applied to a convenient general synthesis of α-halo-β,β-difluorostyrenes (Cl, Br, I) via the corresponding α-halo-β,β-difluoroethenylzinc reagents using commercially available precursors (Scheme 1).²⁴ The α-halo-β,β-difluorostyrenes (Cl, Br, I) thus generated could potentially be used as important synthons in organofluorine chemistry because they can be functionalized at the halogen site as well as the terminal olefin site to produce other chemically or biologically important organofluorine compounds.

To functionalize the halogen site of the α-halo-β,β-difluorostyrenes, the most attractive and simple pathway was a palladium-catalyzed cross-coupling reaction with an aryl or alkenylboronic acid to produce the corresponding 2,2-diaryl-1,1-difluoroalkenes or 1,1-difluoro-2-aryl-1,3-dienes.²⁵ The general Wittig methodology discussed for the synthesis of 1,1-difluoroalkenes was not suitable for the synthesis of 2,2-diaryl-1,1-difluoroalkenes as a result of the poor reactivity of the diaryl ketones in the Wittig reaction; even with the modified chemistry, the only product thus synthesized was 2,2-diphenyl-1,1-difluoro-

(18) Ichikawa, J. *J. Fluorine Chem.* **2000**, *105*, 257–263 (and references cited therein).

(19) Ichikawa, J.; Fukui, H.; Ishibashi, Y. *J. Org. Chem.* **2003**, *68*, 7800–7805.

(20) (a) Mathews, D. P.; Miller, S. C.; Jarvi, E. T.; Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* **1993**, *34*, 3057–3060. (b) Kim, K., II; McCarthy, J. R. *Tetrahedron Lett.* **1996**, *37*, 3223–3226.

(21) (a) Ocampo, R.; Dolbier, W. R., Jr.; Paredes, R. *J. Fluorine Chem.* **1998**, *88*, 41–50. (b) Dolbier, W. R., Jr.; Ocampo, R. *J. Org. Chem.* **1995**, *60*, 5378–5379.

(22) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5203–5206.

(23) (a) Anilkumar, R.; Burton, D. J. *Tetrahedron Lett.* **2002**, *43*, 2731–2733. (b) Raghavanpillai, A.; Burton, D. J. *J. Org. Chem.* **2004**, *69*, 7083–7091.

(24) (a) Anilkumar, R.; Burton, D. J. *Tetrahedron Lett.* **2002**, *43*, 6979–6982. (b) Anilkumar, R.; Burton, D. J. *J. Fluorine Chem.* **2005**, *126*, 833–841. (c) Anilkumar, R.; Burton, D. J. *J. Fluorine Chem.* **2004**, *125*, 561–566. (d) Anilkumar, R.; Burton, D. J. *J. Fluorine Chem.* **2005**, *126*, 457–463.

(8) (a) St. Jean, D. J., Jr.; Molander, G. A. Functions incorporating two halogens or a halogen and chalcogen. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, J. K., Eds.; Elsevier: Oxford, 2005; Vol. 4, pp 695–733. (b) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619–8683. (c) Percy, J. M. *Contemp. Org. Synth.* **1995**, *2*, 251–268.

(9) (a) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641–1715. (b) Burton, D. J. *J. Fluorine Chem.* **1999**, *100*, 177–199. (c) Kennewell, P. D.; Westwood, R.; Westwood, N. J. Functions incorporating two halogens or halogen and a chalcogen. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, A., Ress, C. W., Eds.; Elsevier: Oxford, 1995; Vol. 4, pp 607–704.

(10) (a) Fugua, S. A.; Duncan, W. G.; Silverstein, R. M. *J. Org. Chem.* **1989**, *30*, 1027–1029. (b) Burton, D. J.; Herkes, F. E. *J. Org. Chem.* **1967**, *32*, 1311–1318.

(11) (a) Nae, D. G.; Burton, D. J. *J. Fluorine Chem.* **1971**, *1*, 123–125. (b) Burton, D. J.; Wheaton, G. A. *J. Org. Chem.* **1983**, *48*, 917–926. (c) Serafinowski, P. J.; Barnes, C. L. *Tetrahedron* **1996**, *52*, 7929–7938. (d) Serafinowski, P. J.; Brown, C. A. *Tetrahedron* **2000**, *56*, 333–339.

(12) Nowak, I.; Robins, J. M. *Org. Lett.* **2005**, *7*, 721–724.

(13) (a) Tsai, H. J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 2143. (b) Tsai, H. J. *Phosphorus, Sulphur Silicon Relat. Elem.* **1997**, *122*, 247–259.

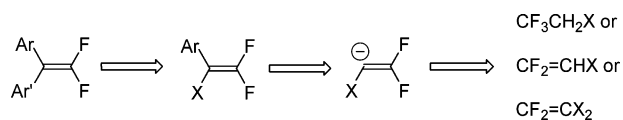
(14) (a) Obayashi, M.; Itoh, E.; Matsui, K.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323–2326. (b) Piettre, S. R.; Cabanas, L. *Tetrahedron Lett.* **1996**, *37*, 5881–5884.

(15) Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T.; Mathews, D. P.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 5571–5574.

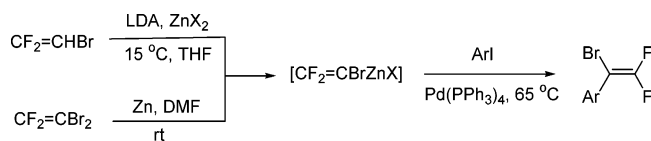
(16) (a) Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 1641–1644. (b) Percy, J. M. *Tetrahedron Lett.* **1990**, *31*, 3931–3932. (c) Patel, S. T.; Percy, J. M. *J. Chem. Soc., Chem. Commun.* **1992**, 1477–1478. (d) Bennet, A. J.; Percy, J. M.; Rock, M. H. *Synlett* **1992**, 483–484. (e) Lee, J.; Tsukasaki, M.; Snieckus, V. *Tetrahedron Lett.* **1993**, *34*, 415–418. (f) Kirihara, M.; Takuwa, T.; Takizawa, S.; Momose, T. *Tetrahedron Lett.* **1997**, *38*, 2853–2854.

(17) (a) Tellier, F.; Sauvetre, R.; Normant, J. F. *J. Organomet. Chem.* **1986**, *303*, 309–315. (b) Gillet, J. P.; Sauvetre, R.; Normant, J. F. *Synthesis* **1986**, 538–543. (c) Tellier, F.; Sauvetre, R.; Normant, J. F. *J. Organomet. Chem.* **1987**, *328*, 1–13. (d) Tellier, F.; Sauvetre, R.; Normant, J. F. *J. Organomet. Chem.* **1987**, *331*, 281–298. (e) Ichikawa, J.; Minami, T.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1992**, *33*, 3779–3782. (f) Ichikawa, J.; Ikeura, C.; Minami, T. *Synlett* **1992**, 739–740.

SCHEME 2



SCHEME 3



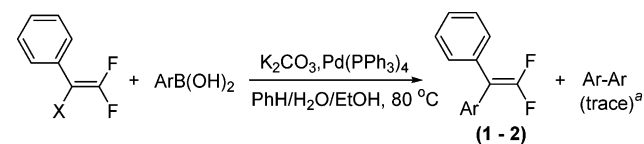
roethene.^{12,14,15} Unsymmetrically substituted 2,2-diaryl-1,1-difluoroethenes are generally not readily available, and their synthesis by the Wittig method requires suitable unsymmetrical diaryl ketones, which in turn need to be obtained either by arylation of suitable arylorganometallics or by Friedel–Crafts acylation.²⁶ The organometallic routes described for the successful synthesis of various 1,1-difluoroalkenes were also not useful for the synthesis of 2,2-diaryl-1,1-difluoroalkenes. Hence, we chose to functionalize the halogen site of the α -halo- β,β -difluorostyrenes by a palladium-catalyzed cross-coupling reaction and thus provide a novel convenient synthetic route for both symmetrical and unsymmetrical 2,2-diaryl-1,1-difluoroethenes, a useful addition in the 1,1-difluoroalkenes genus. The retrosynthetic pathway for the 2,2-diaryl-1,1-difluoroalkenes from commercially available fluorocarbons is outlined in Scheme 2.

Results and Discussion

Functionalization at the Halogen Site of α -Halo- β,β -difluorostyrenes Using Arylboronic Acids. The α -halo- β,β -difluorostyrene, in general, was prepared by the room-temperature metalation/coupling method described in our previous reports.²⁴ Metalation of 1 equiv of $\text{CF}_3\text{CH}_2\text{Cl}$ (HCFC-133a), $\text{CF}_3\text{CH}_2\text{Br}$, or $\text{CF}_3\text{CH}_2\text{I}$ with 2 equiv of LDA in the presence of ZnCl_2 at 15 °C generated the corresponding α -halo- β,β -difluoroethenylzinc reagents ($\text{CF}_2=\text{CXZnCl}$, X = Cl, Br, I). The Pd(0)-catalyzed coupling reaction of these zinc reagents with aryl iodides produced the corresponding α -halo- β,β -difluorostyrenes in excellent isolated yields (Scheme 1). α -Bromo- β,β -difluorostyrenes were alternatively prepared either by the metalation of $\text{CF}_2=\text{CHBr}$ with LDA in the presence of ZnCl_2 followed by the palladium-catalyzed coupling reaction of the zinc reagent with aryl iodides or by a zinc insertion into $\text{CF}_2=\text{CBr}_2$ followed by the Pd(0)-catalyzed coupling reaction of the zinc reagent with aryl iodides (Scheme 3).^{24c, 27}

Initially, we attempted the palladium-catalyzed cross-coupling reaction of the α -halo- β,β -difluorostyrenes with arylboronic acids to introduce an aromatic group at the halogen site. We

TABLE 1. Coupling Reactions of Various α -Halo- β,β -difluorostyrenes with 4-Fluorophenyl- or 1-Naphthylboronic Acids



entry	X	Ar	product	time (h)	yield (%)
1	Cl	4- FC_6H_4 -	1	24	NR
2	Br	4- FC_6H_4 -	1	8	81
3	Br	1-naphthyl	2	12	79
4	I	4- FC_6H_4 -	1	14	86
5	I	1-naphthyl	2	32	88

^a A total of 3–5% self-coupled product.

chose 4-fluorophenylboronic acid as our coupling partner because the course of the reaction could be monitored via ^{19}F NMR with respect to both coupling partners. Thus, α -chloro- β,β -difluorostyrene was heated with 4-fluorophenylboronic acid, aqueous K_2CO_3 (1 M), and 5 mol % $\text{Pd}(\text{PPh}_3)_4$ in a benzene–ethanol medium for 24 h, as per a typical reaction condition described for the palladium-catalyzed cross-coupling reaction of fluorinated vinyl bromides and arylboronic acids.^{25a,28} The ^{19}F NMR spectrum of the reaction mixture at various time intervals did not indicate any formation of 2-(4-fluorophenyl)-2-phenyl-1,1-difluoroethene (**1**; Table 1), and from the reaction mixture, α -chloro- β,β -difluorostyrene was recovered quantitatively. A small amount (3%) of a new product isolated from this reaction mixture was the self-coupled product of the boronic acid, 4,4'-difluorobiphenyl.²⁹ The lack of reactivity of the α -chloro- β,β -difluorostyrene in this reaction was presumably due to the poor reactivity of the internal chlorine to undergo oxidative addition.³⁰ Similar experiments were then performed with α -bromo- β,β -difluorostyrene and α -iodo- β,β -difluorostyrene, and the results are summarized in Table 1.

The coupling reaction between α -bromo- β,β -difluorostyrene and 4-fluorophenylboronic acid proceeded smoothly in 8 h with the complete disappearance of the styrene and boronic acid. ^{19}F NMR analysis of the reaction mixture revealed that the cross-coupled product **1** was formed in 93% yield along with a small amount of the self-coupled product (4,4'-difluorobiphenyl; 4%). The workup and purification of the reaction mixture produced an 81% isolated yield of **1**. When 1-naphthylboronic acid was used as a coupling partner with the α -bromo- β,β -difluorostyrene, the reaction was complete in 12 h and produced the cross-coupled product **2** in 79% isolated yield. The coupling reaction was then performed with α -iodo- β,β -difluorostyrene with the anticipation of a faster reaction, but with 4-fluorophenylboronic acid under similar reaction conditions a relatively slower reaction resulted. The reaction was complete in 14 h to produce a clean reaction mixture from which the cross-coupled product **1** was isolated in 86% yield. The coupling reaction was much slower in the case of 1-naphthylboronic acid with α -iodo- β,β -difluorostyrene, where the reaction was complete only after 32 h under similar conditions as those used for the coupling reaction of

(25) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Hassan, J.; Sevington, M.; Gozzi, C.; Schultz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469. (c) Suzuki, A. In *Metal Catalyzed Cross-Coupling reactions*; Diederich, F., Stang, P. J., Eds.; VCH: Weinheim, Germany, 1998; pp 49–97. (d) Suzuki, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 249–263.

(26) (a) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557–1565. (b) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7595–7598. (c) Devasagayaram, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 8411–8414. (d) Taber, D. F.; Sethuraman, M. R. *J. Org. Chem.* **2000**, *65*, 254–255.

(27) Nguyen, B. V.; Burton, D. J. *J. Org. Chem.* **1998**, *63*, 1714–1715.

(28) Chen, C.; Wilkoxen, K.; Huang, C. Q.; Strack, N.; McCarthy, J. R. *J. Fluorine Chem.* **2000**, *101*, 285–290.

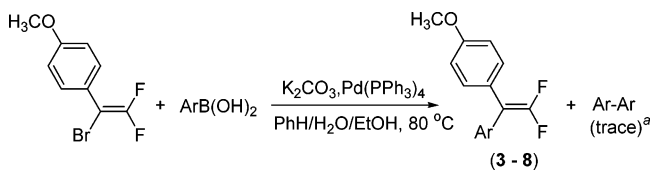
(29) Courtois, V.; Barhdadi, R.; Troupel, M.; Perichon, J. *Tetrahedron* **1997**, *53*, 11569–11576.

(30) (a) Grudhim, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062. (b) Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287–291.

α -bromo- β,β -difluorostyrene and 1-naphthylboronic acid. From this reaction mixture, the cross-coupled product was isolated in 88% yield. This observation suggests that the bulky halogen, the boronic acid, or both sterically influence the coupling reaction of the α -halo- β,β -difluorostyrenes with arylboronic acids.

The lack of reactivity of the α -chloro- β,β -difluorostyrene and the relatively longer reaction time in the coupling reaction of the α -iodo- β,β -difluorostyrene prompted us to consider the α -bromo- β,β -difluorostyrene as our major coupling partner for the further reactions. We then attempted this synthesis in a one-pot reaction, where the α -bromo- β,β -difluoroethenylzinc reagent (prepared by the metalation of $\text{CF}_3\text{CH}_2\text{Br}$ in a THF medium) was coupled with iodobenzene to obtain α -bromo- β,β -difluorostyrene. The crude reaction mixture was then heated with 4-fluorophenylboronic acid and additional Pd(0) catalyst (5 mol %) for 24 h. The ^{19}F NMR analysis of the reaction mixture did not show any cross-coupled product formation. In another experiment, the crude mixture of α -bromo- β,β -difluorostyrene obtained by the Pd(0)-catalyzed coupling of the α -bromo- β,β -difluoroethenylzinc reagent and iodobenzene was heated with additional Pd(0) catalyst (5 mol %), aqueous K_2CO_3 , and 4-fluorophenylboronic acid for 24 h, but no cross-coupled product was observed. We then performed a solvent exchange, where THF/hexane from the crude solution of α -bromo- β,β -difluorostyrene was substituted with benzene/ethanol (5:1), and the coupling reaction was performed with 4-fluorophenylboronic acid, aqueous K_2CO_3 , and additional Pd(0) catalyst (5 mol %); unfortunately, even in this reaction, we did not observe any cross-coupled product formation. Thus, our attempts to perform the successive coupling reactions in one pot failed to give a fruitful result, and it was desirable to isolate the α -bromo- β,β -difluorostyrenes before performing the second coupling reaction. A side reaction was noted during the palladium-catalyzed cross-coupling reaction of α -bromo- β,β -difluorostyrene with arylboronic acids, namely, the formation of a small amount of the self-coupled product of the arylboronic acids. Self-coupling of aryl groups of the arylboronic acids is well-documented in the literature;^{25b,31} the self-coupling process usually occurs when the cross-coupling process is slow. Suzuki–Miyaura reactions involving electron-donating aromatic halides and the presence of oxygen are known to produce more self-coupled product. Recent developments in this field demonstrated that the self-coupling of arylboronic acids can be used as an effective methodology for the quantitative preparation of biaryls by the modification of the reaction conditions in the boronic acid coupling reactions.³² Our cross-coupling partner, α -bromo- β,β -difluorostyrene, being an internal halide, is expected to have a longer reaction time in this coupling process and thus accounts for the formation of a small amount (typically 3–5%) of the self-coupled product. The separation of the self-coupled product

TABLE 2. Coupling Reactions of 2-Bromo-2-(4-methoxyphenyl)-1,1-difluoroethene with Various Arylboronic Acids



entry	Ar	product (3–8)	time (h)	yield (%)
1	C_6H_5-	3	5	79
2	1-naphthyl	4	8	85
3	4- FC_6H_4-	5	12	85
4	3- $\text{O}_2\text{NC}_6\text{H}_4-$	6	12	72
5	3,5-dimethylphenyl	7	12	78
6 ^b	3-thienyl	8	10	51

^a A total of 3–6% self-coupled product. ^b A total of 2.2 equiv of boronic acid was used; 8% of 3,3'-bithiophenyl was formed.

from the cross-coupled product in some cases was difficult due to their close R_f values and, therefore, requires careful chromatography. To reduce or eliminate the self-coupling reaction, several alternative coupling conditions, such as using a stronger base (NaOH), increasing the amount of base (5 equiv), using different solvents (THF, acetone), and increasing the amount of catalyst (10 mol %), were also attempted but failed to improve the reaction or resulted in a more complex reaction mixture. In one of those noteworthy trials, 1-bromo-2,2-difluorostyrene was heated with 4-fluorophenylboronic acid, aqueous NaOH, and 5 mol % $\text{Pd}(\text{PPh}_3)_4$ in a THF medium for 12 h. A ^{19}F NMR analysis of the reaction mixture revealed that the cross-coupled product **1** was formed in 65% yield along with the self-coupled product (4%) and unreacted 1-bromo-2,2-difluorostyrene (20%).

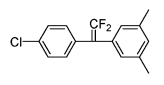
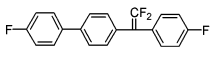
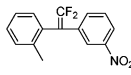



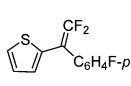


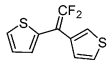
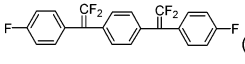
To check the generality of this reaction with various aryl or heteroarylboronic acids, we chose 2-bromo-2-(4-methoxyphenyl)-1,1-difluoroethene as our coupling partner. The cross-coupled product in this case is expected to be significantly different in R_f value than that of the self-coupled product, which facilitates the easy isolation of the cross-coupled product. Even though aryl halides, having electron-donating groups, are relatively less efficient coupling partners in the Pd(0)-catalyzed cross-coupling reaction with boronic acids,^{25b,33} the coupling reaction of 2-bromo-2-(4-methoxyphenyl)-1,1-difluoroethene with various boronic acids proceeded well under the typical reaction conditions described earlier to give the corresponding cross-coupled products (**3–8**) in good isolated yield along with traces of the self-coupled product (3–6%) and some unidentified byproducts (Table 2). 2-Bromo-2-(4-methoxyphenyl)-1,1-difluoroethene coupled with phenylboronic acid in 5 h under the standard reaction conditions to produce the cross-coupled product **3** in 79% isolated yield. Under similar conditions, 1-naphthylboronic acid yielded the cross-coupled product **4** in 85% isolated yield. Boronic acids, having an electron-withdrawing group in the aromatic ring, underwent the coupling reaction in 12 h to produce the corresponding cross-coupled product in good isolated yield. With 4-fluorophenylboronic acid as the coupling partner, the cross-coupled product **5** was isolated in 85% yield. Even though the nitro groups in the boronic acid and aryl halide are known to give an unwanted side reaction in some of the reported Suzuki–Miyaura coupling reactions, the reaction was quite successful in our case at producing the

(31) (a) Moreno-Manas, M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346–2351. (b) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33–41. (c) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395. (d) Gillmann, T.; Weeber, T.; Synlett **1994**, 649–650.

(32) (a) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541–1544. (b) Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525–2526. (c) Parrish, J. P.; Jung, Y. C.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett.* **2002**, *43*, 7899–7902. (d) Falck, J. R.; Mohapatra, S.; Bondlela, M.; Venkataraman, S. K. *Tetrahedron Lett.* **2002**, *43*, 8149–8151. (e) Kabalka, G. W.; Wang, L. *Tetrahedron Lett.* **2002**, *43*, 3067–3068. (f) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087–4089. (g) Cravotto, G.; Beggiato, M.; Penoni, A.; Palmisano, G.; Tollari, S.; Levaque, J.; Bonrath, W. *Tetrahedron Lett.* **2005**, *43*, 2267–2271.

(33) (a) Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993–2996. (b) Indolese, A. *Tetrahedron Lett.* **1997**, *38*, 3513–3516.

TABLE 3. Coupling Reactions of Various α -Bromo- β,β -difluorostyrenes with Selected Arylboronic Acids
$$\text{Ar} \begin{array}{c} \text{C}=\text{CF}_2 \\ | \\ \text{Br} \end{array} + \text{Ar}'\text{B}(\text{OH})_2 \xrightarrow[\text{PhH}/\text{H}_2\text{O}/\text{EtOH}, 80^\circ\text{C}]{\text{K}_2\text{CO}_3, \text{Pd}(\text{PPh}_3)_4} \text{Ar} \begin{array}{c} \text{C}=\text{CF}_2 \\ | \\ \text{Ar}' \end{array} + \text{Ar}'\text{-Ar}' \text{ (trace)}$$

Entry	Ar	Ar'	Ar(Ar')C=CF ₂	Time (h)	Yield (%)
1 ^a	4-FC ₆ H ₄ -	C ₆ H ₅ -	4-FC ₆ H ₄ (C ₆ H ₅)C=CF ₂ (1)	12	75
2	4-FC ₆ H ₄ -	C ₁₀ H ₇ -	4-FC ₆ H ₄ (C ₁₀ H ₇)C=CF ₂ (9)	15	83
3	3-NO ₂ C ₆ H ₄ -	4-FC ₆ H ₄ -	3-NO ₂ C ₆ H ₄ (4-FC ₆ H ₄)C=CF ₂ (10)	8	75
4	3-NO ₂ C ₆ H ₄ -	C ₆ H ₅ -	3-NO ₂ C ₆ H ₄ (C ₆ H ₅)C=CF ₂ (11)	6	78
5	4-ClC ₆ H ₄ -	4-FC ₆ H ₄ -	4-ClC ₆ H ₄ (4-FC ₆ H ₄)C=CF ₂ (12)	6	76
6	4-ClC ₆ H ₄ -	3,5-dimethylphenyl	 (13)	10	87
7 ^b	4-BrC ₆ H ₄ -	4-FC ₆ H ₄ -	 (14)	12	73
8 ^a	2-CH ₃ C ₆ H ₄ -	4-FC ₆ H ₄ -	2-CH ₃ C ₆ H ₄ (4-FC ₆ H ₄)C=CF ₂ (15)	24	91
9	2-CH ₃ C ₆ H ₄ -	3-O ₂ NC ₆ H ₄ -	 (16)	14	90
10 ^{b, c}	2-CF ₃ C ₆ H ₄ -	4-FC ₆ H ₄ -	2-CF ₃ C ₆ H ₄ (4-FC ₆ H ₄)C=CF ₂ (17)	240	41
11 ^{b, c}	2-CF ₃ C ₆ H ₄ -	C ₆ H ₅ -	2-CF ₃ C ₆ H ₄ (C ₆ H ₅)C=CF ₂ (18)	168	57
12 ^a		C ₆ H ₅ -	 (19)	24	78
13 ^a		4-FC ₆ H ₄ -	 (20)	19	79
14 ^b			 (21)	28	74
15 ^b	4-(CF ₂ =CBr) ₂ C ₆ H ₄ -	4-FC ₆ H ₄ -	 (22)	12	76

^a Isolated product was contaminated with 1–3% of the self-coupled product. ^b A total of 2.2 equiv of boronic acid was used. ^c The product was contaminated with ~10–12% of the self-coupled product.

coupled product **6** in 72% isolated yield.^{33b,34a} Boronic acids with an electron-releasing group also coupled well under standard reaction conditions to produce the corresponding cross-coupled product **7** in 78% isolated yield. The heterocyclic boronic acid, 3-thienylboronic acid, was also then used for this coupling reaction. Under the prolonged reaction conditions, a slight decomposition of the boronic acid was observed, and by using an excess (2.2 equiv) of the boronic acid, we obtained a 51% isolated yield of the cross-coupled product **8** and 8% of the 3,3'-bithiophenyl.³⁵

After the successful synthesis of several 2-aryl-2-(4-methoxyphenyl)-1,1-difluoroethenes, a variety of α -bromo- β,β -difluorostyrenes with electron-releasing and electron-withdrawing groups in the aromatic ring were coupled with selected boronic acids. The Pd(0)-catalyzed Suzuki–Miyaura coupling is known to be efficient for aryl halides with electron-withdrawing groups,^{25b} and there have been many examples

where Ni(0)-catalyzed coupling reactions of arylboronic acids proceeded well for the aryl halides with electron-donating groups, too.^{32,34,36} In our case, generally the reaction proceeded well for styrenes both having electron-releasing and electron-withdrawing groups in the aromatic ring under the typical reaction conditions to produce the corresponding 2,2-diaryl-1,1-difluoroethenes in excellent isolated yield (Table 3). 2-Bromo-2-(4-fluorophenyl)-1,1-difluoroethene coupled with phenyl as well as 1-naphthylboronic acid under typical reaction conditions to produce the corresponding 2,2-diaryl-1,1-difluoroalkenes **1** and **9** in 75 and 83% yields, respectively. 2-Bromo-2-(3-nitrophenyl)-1,1-difluoroethene coupled with 4-fluorophenylboronic acid as well as phenylboronic acid to produce the corresponding coupled products **10** and **11** in 75 and 78% respective isolated yields, demonstrating the tolerance of the nitro group during this coupling process. 2-Bromo-2-(4-chlorophenyl)-1,1-difluoroethene reacted with 4-fluorophenylboronic acid and 3,5-dimethylphenylboronic acid to give the corresponding cross-coupled products **12** and **13** with the chlorine

(34) (a) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024–8030. (b) Wallow, T. I.; Novak, M. B. *J. Org. Chem.* **1994**, *59*, 5034–5037.

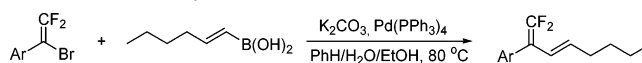
(35) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron* **1979**, *35*, 329–340.

(36) Lipshutz, B. H.; Sclafani, A. J.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139–2144.

intact in the aromatic ring in 76 and 87% isolated yields. The coupling reaction of 2-bromo-2-(4-bromophenyl)-1,1-difluoroethene with 1.1 equiv of 4-fluorophenylboronic acid produced mainly the product resulting from the coupling of the aromatic bromine site, leaving the vinyl bromine site intact [4-FC₆H₄-C₆H₄-C(Br)=CF₂]. When 2.2 equiv of 4-fluorophenylboronic acid was used, the coupling reaction was feasible for both of the bromine sites to produce the bis-coupled product **14** in 73% isolated yield. This preference for the aromatic bromine site over the alkenyl bromine site indicates the relatively difficult nature of this internal alkenyl bromide to undergo a coupling reaction with boronic acids. 2-Bromo-2-(2-methylphenyl)-1,1-difluoroethene reacted with 4-fluoro- and 3-nitrophenylboronic acids to produce the corresponding coupled products **15** and **16** in 91 and 90% yields, respectively. However, the coupling reaction of the corresponding trifluoromethyl analogue, 2-bromo-2-(2-trifluoromethylphenyl)-1,1-difluoroethene, was very sluggish, and only a partial reaction was noticed even after many days when the reaction was performed with 1.1 equiv of 4-fluorophenylboronic or phenylboronic acid. With additional boronic acid during the course of the reaction (1.1 equiv), complete conversion of the styrene to the coupled products was achieved. Isolation of the cross-coupled products **17** and **18** from these reaction mixtures by chromatography was tedious, and the isolated product was contaminated with ~10–12% of the self-coupled product in both cases (close *R_f* values). The coupling reaction of 2-bromo-2-(2-thienyl)-1,1-difluoroethene with three different boronic acids was attempted. Phenyl and 4-fluorophenylboronic acids reacted under normal coupling reaction conditions to produce the cross-coupled products **19** and **20** in 78 and 79% yields, respectively. The coupling reaction of 2-bromo-2-(2-thienyl)-1,1-difluoroethene with 3-thienylboronic acid required an excess (2.2 equiv) of the boronic acid for the completion of the reaction, and the cross-coupled product **21** was formed in 74% isolated yield. 1,4-Bis-(1-bromo-2,2-difluoroethenyl)benzene coupled with 4-fluorophenylboronic acid to produce the corresponding bis-coupled product **22** in 76% isolated yield. Thus, in general, the palladium-catalyzed cross-coupling reaction of the α -bromo- β,β -difluorostyrenes with arylboronic acids was feasible with styrenes having electron-donating and electron-withdrawing (including nitro) groups at different positions in the aromatic ring (including *ortho*-methyl) and with the heterocyclic 2-thienyl analogue.

Functionalization at the Bromine Site of α -Bromo- β,β -difluorostyrenes Using Alkenylboronic Acids. The successful completion of the coupling reaction of α -bromo- β,β -difluorostyrenes with an arylboronic acid prompted us to study similar coupling reactions with alkenylboronic acids, as the resulting 1,1-difluoro-2-aryl-1,3-dienes could be useful building blocks in organic synthesis. Initially, the coupling reaction of α -bromo- β,β -difluorostyrene with 1.1 equiv of *trans*-hex-1-enylboronic acid was attempted. ¹⁹F NMR analysis of the reaction mixture at various time intervals revealed that the reaction was sluggish, and after 48 h, a mixture of products consisting mainly of the cross-coupled product **23** (41%), the self-coupled product, and the reduced product difluorostyrene (PhCH=CF₂; 18%) were obtained.³⁷ At the early stage of the reaction, unreacted bromostyrene and the coupled products were the only constituents, but the formation of the reduced product was observed after heating the reaction mixture for a prolonged period. As the reaction progressed, a part of the boronic acid was converted

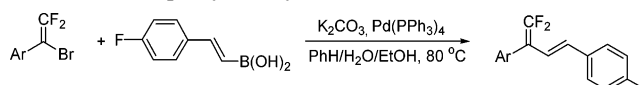
TABLE 4. Coupling Reactions of α -Bromo- β,β -difluorostyrenes with *trans*-Hex-1-enylboronic Acid



entry	ArCF=CF ₂	product	time (h)	yield ^a (%)
1 ^b	C ₆ H ₅ CBr=CF ₂	23	32	64
2 ^b	4-FC ₆ H ₄ CBr=CF ₂	24	85	74
3 ^b	4-MeOC ₆ H ₄ CBr=CF ₂	25	9	80

^a Isolated dienes are unstable when neat. ^b A total of 2.2 equiv of boronic acid was used

TABLE 5. Coupling Reactions of Various α -Bromo- β,β -difluorostyrenes with *trans*-2-(4-Fluorophenyl)ethenylboronic Acid



entry	ArCF=CF ₂	product	time (h)	yield (%) ^a
1 ^b	C ₆ H ₅ CBr=CF ₂	26	95	53
2 ^b	4-FC ₆ H ₄ CBr=CF ₂	27	168	69
3 ^b	4-MeOC ₆ H ₄ CBr=CF ₂	28	10	79

^a Isolated dienes are unstable when neat. ^b A total of 2.2 equiv of boronic acid was used.

to the self-coupled product, and there was no boronic acid available for cross-coupling. At this stage, the reduced product began to be observed as the oxidatively added α -bromo- β,β -difluorostyrenepalladium(II) species {PhC[Pd(PPh₃)₂Br]=CF₂} was converted presumably to the reduced product as a result of the nonavailability of the boronic acid for the transmetalation process. We then attempted this coupling reaction with an excess (2.2 equiv) of *trans*-hex-1-enylboronic acid; the reaction was complete in 32 h, and from the reaction mixture, the cross-coupled product **23** was isolated in 64% yield. A similar reaction with 2-bromo-2-(4-fluorophenyl)-1,1-difluoroethene was sluggish; with an excess of boronic acid (2.2 equiv) and refluxing for 85 h, complete conversion occurred, and the cross-coupled product **24** was isolated in 74% yield. α -Bromo- β,β -difluorostyrene with an electron-donating group in the aromatic ring, 2-bromo-2-(4-methoxyphenyl)-1,1-difluoroethene, coupled with *trans*-hex-1-enylboronic acid in 9 h to produce the cross-coupled product **25** in 80% isolated yield. Table 4 summarizes the results of the coupling reactions of several α -bromo- β,β -difluorostyrenes with *trans*-hex-1-enylboronic acid.

Cross-coupling reactions of α -bromo- β,β -difluorostyrenes with *trans*-2-(4-fluorophenyl)ethenylboronic acid were also attempted, and a reaction trend similar to that observed in the coupling reaction of α -bromo- β,β -difluorostyrenes with *trans*-hex-1-enylboronic acid was observed (Table 5). The coupling reaction of α -bromo- β,β -difluorostyrene with 1.1 equiv of *trans*-2-(4-fluorophenyl)ethenylboronic acid was sluggish, and after 48 h, ¹⁹F NMR analysis of the reaction mixture revealed that the cross-coupled product **26** was formed in 44% yield, along with the self-coupled product (8%) and the reduced product (PhCH=CF₂; 18%). When the same reaction was performed with an excess (2.2 equiv) of boronic acid, the reaction was complete in 95 h to afford a 53% isolated yield of the cross-coupled product **26**. The reaction of 2-bromo-2-(4-fluorophenyl)-1,1-difluoroethene with an excess (2.2 equiv) of *trans*-2-(4-fluorophenyl)ethenylboronic acid was also attempted, and after 168 h at reflux, complete conversion was noted. From this reaction mixture the cross-coupled product **27** was isolated in

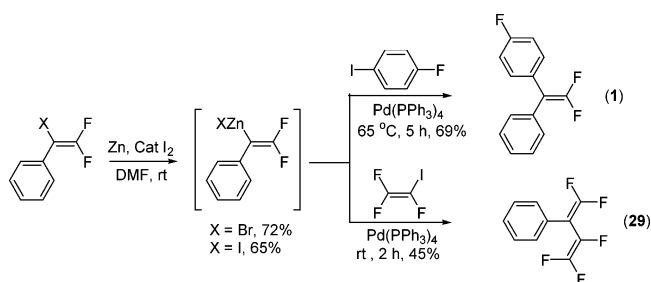
(37) Nguyen, B. V.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 7758–7764.

69% yield. The coupling reaction of 2-bromo-2-(4-methoxyphenyl)-1,1-difluoroethene with an excess (2.2 equiv) of *trans*-2-(4-fluorophenyl)ethenylboronic acid was complete in 10 h to obtain the cross-coupled product **28** in 79% isolated yield.

A clear electronic effect on the reactivity was observed during the coupling reactions of α -bromo- β,β -difluorostyrenes with alkenylboronic acids (Tables 4 and 5). In general, α -bromo- β,β -difluorostyrenes with an electron-releasing group coupled relatively faster with alkenylboronic acids than did those having an electron-withdrawing group or a phenyl group. However, such a trend was not noticed during the corresponding coupling reaction with arylboronic acids, where an electron-releasing or electron-withdrawing group did not show any significant difference in reactivity (Tables 2 and 3). Generally, aryl or alkenyl halides having electron-withdrawing groups undergo oxidative addition relatively faster than those having electron-releasing groups, thus, are expected to couple faster.^{30,38} It has also been established that the electron-withdrawing groups in the aryl or alkenyl halide do accelerate the reductive elimination process, whereas steric effects play a significant role in the transmetalation process.^{25a,b,38d,39,40} Because aryl and alkenylboronic acids expressed significant differences in reactivity during the coupling reaction with the α -bromo- β,β -difluorostyrenes (the oxidative addition process is the same in both reactions), the transmetalation or the reductive elimination process would be significant in determining the rate of this coupling reaction. The reactivity differences of the α -bromo- β,β -difluorostyrenes toward *trans*-hex-1-enylboronic acid or *trans*-2-(4-fluorophenyl)ethenylboronic acid remain unclear, and more mechanistic studies need to be performed to explain these results.

Functionalization at the Halogen Site of the α -Halo- β,β -difluorostyrene via the Corresponding Zinc Reagent [$C_6H_5C(ZnX)=CF_2$]. We have also explored another possible way to functionalize the α -bromine site of the α -halo- β,β -difluorostyrenes, namely, via the corresponding zinc reagent followed by a palladium-catalyzed coupling reaction with aryl or alkenyl iodides. Thus, a solution of α -bromo- β,β -difluorostyrene was treated with acid washed zinc powder in DMF at room temperature or 75 °C for 12 h; ¹⁹F NMR analysis of both of the reaction mixtures indicated that <15% of the zinc reagent [$C_6H_5C(ZnBr)=CF_2$] was formed. In another experiment, iodine was used as an activating agent, where acid-washed zinc powder was treated with 10 mol % iodine in DMF followed by the addition of the α -bromo- β,β -difluorostyrene at room temperature.⁴¹ ¹⁹F NMR analysis of this reaction mixture revealed the presence of the desired zinc reagent (72% vs PhCF₃ as an internal standard) along with a small amount of the reduced product (PhCH=CF₂; 19%). To improve the yield of the zinc reagent, the zinc-insertion reaction was also attempted under heating conditions as well as in other solvents such as diglyme and dimethylacetamide (DMA). The heating of the reaction mixture containing zinc (activated with iodine) and α -bromo- β,β -difluorostyrene in DMF at 75 °C for 12 h produced a 1:1

SCHEME 4



mixture of the zinc reagent and the reduced product. The zinc-insertion reaction (zinc activated with iodine) of α -bromo- β,β -difluorostyrene in diglyme produced a poor yield of the zinc reagent (~25%), whereas in DMA, a 68% yield of the zinc reagent was observed. The formation of the zinc reagent was established by hydrolysis and iodolysis experiments; hydrolysis of the zinc reagent reaction mixture with acetic acid produced the reduced product PhCH=CF₂ in 84% yield,³⁷ whereas iodolysis produced 67% of the α -iodo- β,β -difluorostyrene.^{23d} The zinc reagent was also synthesized in 65% yield from α -iodo- β,β -difluorostyrene by treatment with activated zinc powder and catalytic iodine (5 mol %) in DMF at room temperature, as per the conditions described for α -bromo- β,β -difluorostyrene. After obtaining the zinc reagent in moderate yield, we have attempted the cross-coupling reaction of the zinc reagent with aryl or alkenyl iodides. Thus, the zinc reagent generated in DMF was treated with 4-fluoriodobenzene and catalytic Pd(PPh₃)₄ (1.5 mol %) at 65 °C for 5 h. ¹⁹F NMR analysis of the reaction mixture showed complete conversion of the zinc reagent to the cross-coupled product 2-(4-fluorophenyl)-2-phenyl-1,1-difluoroethene (**1**; Scheme 4). From this reaction mixture, pure **1** was isolated in 69% yield. The coupling reaction of the zinc reagent with iodotrifluoroethylene was also attempted at room temperature, and this reaction produced a 45% isolated yield of the cross-coupled product **29** (Scheme 4) thus establishing that α -halo- β,β -difluorostyrenes could be alternatively functionalized via the corresponding zinc reagents.⁴² We have also attempted to synthesize **29** by a Pd(0)-catalyzed coupling reaction of the trifluoroethenylzinc reagent (generated by the metalation of HFC-134a in THF) with α -iodo- β,β -difluorostyrene at 65 °C but failed to obtain any traces of **29**.²³ Though the relative yields of the coupled products are moderate in the zinc-insertion/coupling process in comparison to the boronic acid mediated coupling reaction, absence of the self-coupled product and the relatively easier separation of the cross-coupled product make this method attractive.

Conclusion

In conclusion, we have explored the possible functionalization at the halogen site of α -halo- β,β -difluorostyrenes; α -bromo- β,β -difluorostyrenes and α -iodo- β,β -difluorostyrenes underwent a coupling reaction with various aryl and alkenylboronic acids in the presence of catalytic Pd(PPh₃)₄ to produce the corresponding 2,2-diaryl-1,1-difluoro-1-alkenes and 1,1-difluoro-2-aryl-1,3-dienes in good isolated yield. The reactivity of various α -halo- β,β -difluorostyrenes was compared; the α -chloro- β,β -difluorostyrene was not reactive, whereas α -bromo- β,β -difluorostyrene reacted relatively faster compared to the α -iodo- β,β -

(38) (a) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434–442. (b) Amatore, C.; Jutanod, A. *J. Organomet. Chem.* **1999**, *576*, 254–278. (c) Ricci, A.; Angelucci, F.; Bassetti, M.; Sterzo, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 1060–1071. (d) Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981–4991.

(39) (a) Kim, M. Y.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696–1697. (b) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504–6511.

(40) Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 954–959.

(41) Huo, S. *Org. Lett.* **2003**, *5*, 423–425.

(42) Burton, D. J.; Inouye, Y.; Headley, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 3980–3982.

difluorostyrene. The coupling reaction of α -bromo- β,β -difluorostyrenes with electron-withdrawing vinylboronic acids was sluggish. 2,2-Disubstituted-1,1-difluoro-1-alkenes were alternatively synthesized in moderate yield by the coupling reaction of the zinc reagent generated from the α -halo- β,β -difluorostyrenes with aryl or alkenyl iodides. Overall, both of these approaches serve as a convenient first general synthetic route for 2,2-diaryl-1,1-difluoro-1-alkenes and 1,1-difluoro-2-aryl-1,3-dienes, virtually making it possible to introduce any aryl (alkenyl) group at the 2 position in a symmetrical or unsymmetrical fashion.

Experimental Section

General Procedure for the Coupling Reaction of α -Halo- β,β -difluorostyrenes with Aryl- or Ethenylboronic Acids: Synthesis of 2,2-Diaryl-1,1-difluoro-1-alkenes and 1,1-Difluoro-2-aryl-1,3-dienes (1–28). A 50-mL three-necked round-bottom flask fitted with a condenser attached to a nitrogen tee, a septum, and a stopper was assembled while hot and cooled with a steady stream of nitrogen. The flask was charged with benzene (15 mL), ethanol (3 mL), water (3 mL), and the α -halo- β,β -difluorostyrene (1.0 mmol). With the nitrogen flow on, the boronic acid (1.1 mmol), potassium carbonate (0.410 g, 3.0 mmol), and tetrakis(triphenyl)phosphine palladium (0.060 g, 5 mol %) were added through the side neck. The mixture was heated at reflux, and the reaction progress was monitored by ^{19}F NMR and TLC. After the reaction period, the crude reaction mixture was cooled to room temperature, diluted with ethyl acetate (30.0 mL), and washed with water (2 \times 25 mL). The organic layer was dried (anhyd Na_2SO_4), and the solvent was evaporated under vacuum. The residue was then subjected to careful column chromatography over silica gel using hexanes, hexane/ CH_2Cl_2 , or hexanes/ EtOAc as the eluent, depending on the product polarity, to afford various 2,2-diaryl-1,1-difluoroalkenes and 1,1-difluoro-2-aryl-1,3-dienes.

Synthesis of $[\text{C}_6\text{H}_5\text{C}(\text{ZnX})=\text{CF}_2]$ and Subsequent Coupling with Aryl or Alkenyl Iodides: Synthesis of 2,2-Disubstituted-1,1-difluoro-1-alkenes. A suspension of activated (acid-washed) zinc powder (obtained from a commercial supplier; 0.507 g, 7.8 mmol) in DMF (20 mL) was stirred with iodine (0.198 g, 0.78 mmol) at room temperature; after the iodine color disappeared, the zinc was treated with 2-bromo-2-phenyl-1,1-difluoroethene (0.850 g, 3.9 mmol), and the mixture was heated to 80 $^\circ\text{C}$ for 2 min and stirred at room temperature for 12 h. ^{19}F NMR analysis of the resulting brown solution showed a 72% yield of the zinc reagent $[\text{PhC}(\text{ZnBr})=\text{CF}_2]$ along with a 19% yield of the reduced product ($\text{PhCH}=\text{CF}_2$).³⁷

^{19}F NMR of $\text{PhC}(\text{ZnBr})=\text{CF}_2$ (AB pattern): δ -79.4 (d, J = 57.6 Hz, 1F), -79.9 (d, J = 58.7 Hz, 1F).

The zinc reagent $\text{PhC}(\text{ZnBr})=\text{CF}_2$ (2.8 mmol) generated by the above method was treated with 4-fluoriodobenzene (0.532 g, 2.4 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.048 g). The mixture was heated at 65 $^\circ\text{C}$ for 5 h, cooled to room temperature, and triturated with hexanes (4 \times 20 mL). The organic extracts were washed with water (3 \times 20 mL) and dried over anhyd Na_2SO_4 . The evaporation of the solvent followed by column chromatography over silica gel (eluent: hexane) afforded the cross-coupled product **1** as a colorless liquid in 69% (0.386 g, 1.66 mmol) yield.

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Supporting Information Available: Experimental and characterization data for 2,2-diaryl-1,1-difluoro-1-alkenes (**1–22**), 1,1-difluoro-2-aryl-1,3-dienes (**23–28**), and 2-phenyl-1,1,3,4,4-pentafluorobutadiene (**29**). This material is available free of charge via the Internet at <http://pubs.acs.org>

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