DOI: 10.1002/ejoc.201500597

Oxidative Heck Reaction of Fluorinated Olefins with Arylboronic Acids by Palladium Catalysis

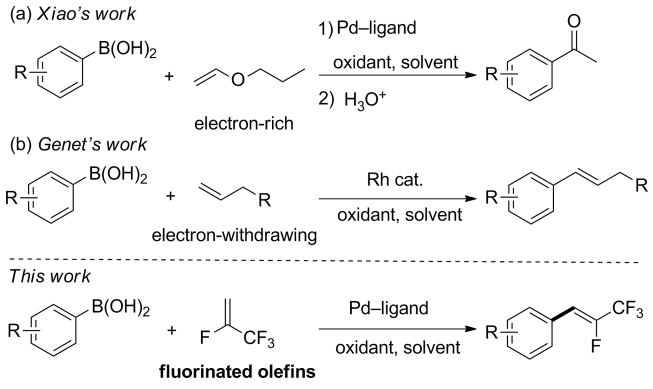
Yang Li,[a,b] Dong-Huai Tu,[a] Yu-Jie Gu,[a] Bo Wang,[a] Yao-Yu Wang,[b] Zhao-Tie Liu,*[c] Zhong-Wen Liu,[c] and Jian Lu*[a]

Keywords: Homogeneous catalysis / Oxidation / Stereoselectivity / Palladium / Alkenes

The palladium-catalyzed oxidative Heck reaction of 2,3,3,3-tetrafluoroprop-1-ene with various arylboronic acids was explored for the first time. This method provides a direct route to access (*Z*)-β-fluoro-β-(trifluoromethyl)styrenes with high stereoselectivity.

Introduction

Fluorinated compounds have played an important role in the fields of pharmaceutical science, agrochemistry, and materials science.[1,2] Significant efforts have been made to incorporate fluorinated groups into organic compounds. The Heck reaction between aryl halides and fluorinated olefins is a direct and atom-economic way to introduce fluoro groups. Progress has been made in this field, with several notable examples coming from some scientific research groups.[3,4] Arylboronic acid derivatives are an important class of compounds for coupling reactions, which are stable in air and to moisture, and they are compatible with a broad range of common functional groups.[5] The oxidative Heck reaction of arylboronic acids with common olefins has been disclosed by Xiao,[6] Genet (Scheme 1),[7] Larhed,[8] Jung,[9] and others.[10] However, to the best of our knowledge, the oxidative Heck reaction of arylboronic acids with fluorinated olefins has not been reported. On the basis of our previous oxidative Heck reaction,[11] herein, we present the first examples of the oxidative Heck reaction of various arylboronic acids with a fluorinated olefin under Pd catalysis.



Scheme 1. Palladium-catalyzed oxidative Heck reaction.

Conjugated aromatic systems with trifluoromethyl groups such as β-(trifluoromethyl)styrene derivatives have found wide use in organic light-emitting diodes and in other applications of materials chemistry,[12] such as in the organofluorine material of dipiperidinobenzene, which is a highly emissive fluorophore in solid states, such as in crystals and thin films (Figure 1). The synthesis of these compounds was difficult in the past.[13] For example, the synthesis of (*Z*)-β-fluoro-β-(trifluoromethyl)styrenes required two-step reactions.[14] Very recently, Nicholls[15] reported a method to prepare (*Z*)-β-fluoro-β-(trifluoromethyl)styrenes in (trifluoromethyl)acrylic acid by palladium-catalyzed vinyltrifluoromethylation of aryl halides through decarb-

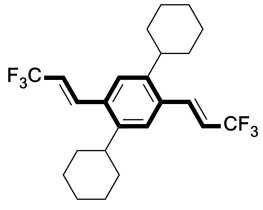


Figure 1. Structure of an organofluorine material.

[a] Department of Catalyst, Xi'an Modern Chemistry Research Institute,
Xi'an 710065, P. R. China
E-mail: lujian204@263.net
http://www.mcri204.com.cn
[b] Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of the Ministry of Education, College of Chemistry and Materials Science, Northwest University,
Xi'an 710069, P. R. China
[c] Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University,
Xi'an 710119, P. R. China
E-mail: ztliu@snnu.edu.cn
http://www.snnu.edu.cn

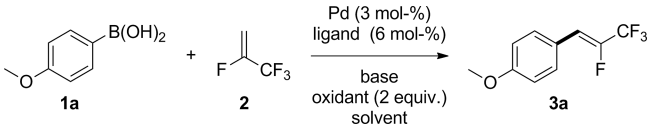
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500597.

oxylative cross-coupling. We envisioned that the reaction of arylboronic acids with 2,3,3,3-tetrafluoroprop-1-ene, which is a commercially available reagent, could be performed in a single step.

Results and Discussion

We initially chose (4-methoxyphenyl)boronic acid (**1a**) as a substrate for the screening of this coupling transformation. A solution of (4-methoxyphenyl)boronic acid (**1a**) and 2,3,3,3-tetrafluoroprop-1-ene (**2**) in DMF was stirred in the presence of $Pd(PPh_3)_2Cl_2$ (3 mol-%) as a catalyst, PCy_3 (6 mol-%, Cy = cyclohexyl) as an additive, and benzoyl peroxide (BPO, 2 mmol) as an oxidant. Only (*Z*)-β-fluoro-β-(trifluoromethyl)styrene (**3a**) was formed in a low yield of 18%, albeit with a high *Z*/*E* ratio (Table 1, entry 1).

Table 1. Optimization of the palladium-catalyzed coupling of arylboronic acids with 2,3,3,3-tetrafluoroprop-1-ene.[a]



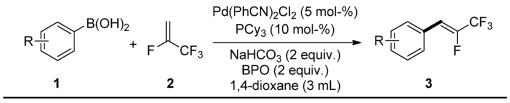
Entry	Catalyst	Ligand	Base	Yield [%][b]	*Z*/*E* ratio[c]
1	$Pd(PPh_3)_2Cl_2$	PCy_3	Na_2CO_3	18	99:1
2	–	PCy_3	Na_2CO_3	0	99:1
3	$Pd(PPh_3)_2Cl_2$	–	Na_2CO_3	0	–
4	$Pd(PPh_3)_4$	PCy_3	Na_2CO_3	7	–
5	$Pd(MeCN)_2Cl_2$	PCy_3	Na_2CO_3	5	99:1
6	$Pd(PhCN)_2Cl_2$	PCy_3	Na_2CO_3	28	99:1
7	$Pd(PhCN)_2Cl_2$	PPh_3	Na_2CO_3	2	99:1
8	$Pd(PhCN)_2Cl_2$	dppp	Na_2CO_3	2	99:1
9	$Pd(PhCN)_2Cl_2$	$tBu_3{\cdot}BF_4$	Na_2CO_3	19	99:1
10	$Pd(PhCN)_2Cl_2$	BINAP	Na_2CO_3	2	99:1
11	$Pd(PhCN)_2Cl_2$	PCy_3	$NaHCO_3$	46	99:1
12	$Pd(PhCN)_2Cl_2$	PCy_3	K_2CO_3	5	99:1
13	$Pd(PhCN)_2Cl_2$	PCy_3	Na_2HPO_4	27	99:1
14	$Pd(PhCN)_2Cl_2$	PCy_3	Et_3N	0	–
15[d]	$Pd(PhCN)_2Cl_2$	PCy_3	$NaHCO_3$	66	99:1
16[d,e]	$Pd(PhCN)_2Cl_2$	PCy_3	$NaHCO_3$	89	99:1
17[d,f]	$Pd(PhCN)_2Cl_2$	PCy_3	$NaHCO_3$	22	99:1

[a] Reaction conditions: **1a** (1 mmol), **2** (18 mmol), catalyst (3 mol-%), ligand (6 mol-%), base (2 mmol), BPO (2 mmol), DMF (3 mL), 110 °C, 14 h. dppp = 1,3-bis(diphenylphosphino)propane, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [b] Determined by ^{19}F NMR spectroscopy by integrating the signal of the product relative to that of ethyl *p*-fluoroacetophenone as an internal standard. [c] Determined by ^{19}F NMR spectroscopy. [d] 1,4-Dioxane (3 mL) was used as the solvent. [e] $Pd(PhCN)_2Cl_2$ (5 mol-%), PCy_3 (10 mol-%). [f] Compound **2**: 5 mmol.

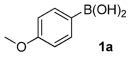
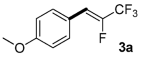
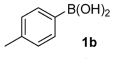
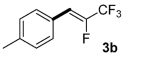
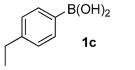
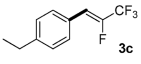
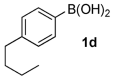
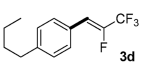
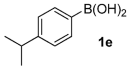
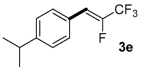
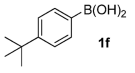
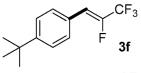
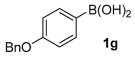
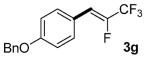
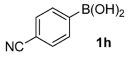
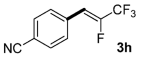
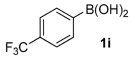
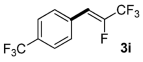
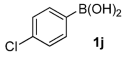
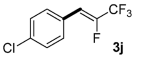
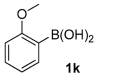
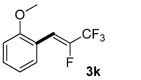
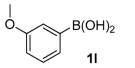
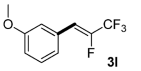
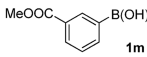
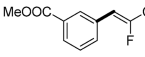
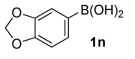
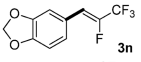
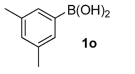
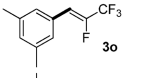
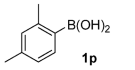
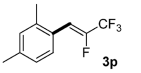
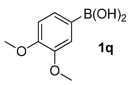
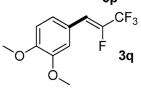
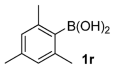
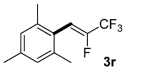
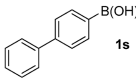
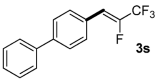
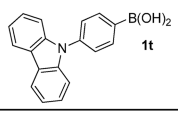
Control experiments revealed that the metal and ligand were both indispensable for the reaction (Table 1, entries 2 and 3). The influence of the palladium catalyst was then examined; $Pd(PhCN)_2Cl_2$ was found to be the best precatalyst for the reaction (Table 1, entries 4 and 5). Next, a variety of ligands with varied electronic and steric properties were explored, and tricyclohexylphosphine gave the best yields of the products (Table 1. entries 6–10). Further, we studied the influence of base on the coupling reaction and found that $NaHCO_3$ was the best choice for the reaction (Table 1, entries 11–14). Moreover, if 1,4-dioxane was selected as the reaction solvent, **3a** was obtained in 66% yield with a *Z*/*E* ratio >99:1, as determined by ^{19}F NMR spectroscopy, and the *Z* isomer was obtained as the major product (Table 1, entry 15). Finally, we also investigated the effect of varying the catalyst loading. Increasing the loading of $Pd(PhCN)_2Cl_2$ and PCy_3 to 5 and 10 mol-%, respectively, resulted in the formation of **3a** in an excellent yield of 89% (Table 1, entry 16). On the basis of this condition, we reduced the volume of **2** to 5 mmol with 5 mol-% catalyst. To our surprise, the yield decreased to 22% (Table 1, entry 17). Hence, the optimized reaction conditions involved the following: $Pd(PhCN)_2Cl_2$ (5 mol-%), PCy_3 (10 mol-%), BPO (2 equiv.), $NaHCO_3$ (2 equiv.), and 1,4-dioxane at 110 °C for 14 h. To explore the scope of the coupling reaction, various arylboronic acids were then examined with **2** by using $Pd(PhCN)_2Cl_2/PCy_3$ as the catalyst and $NaHCO_3$ as the base. The results are summarized in Table 2. *para*-Substituted phenylboronic acids reacted smoothly with **2** to afford the products in good to excellent yields (Table 2, entries 1–10). In general, the yields of the reactions of arylboronic acids with electron-donating groups were higher than those of arylboronic acids with electron-withdrawing groups. For instance, the yield of **3a** was significantly higher than that of **3h**. Substrates having *meta* or *ortho* substituents also afforded products in satisfactory yields (Table 2, entries 11–13). Trisubstituted arylboronic acids were also tested, and the corresponding products were formed in good yields (Table 2, entries 14–17). The substrate scope was extended to target compounds with tetrasubstituted substrates such as (2,4,6-trimethylphenyl)boronic acid, which afforded the desired product in 52% yield (Table 2, entry 18). 4-Biphenylboronic acid was also tested for the coupling reaction: it performed the same as other *para*-substituted groups and afforded the desired product in acceptable yield (Table 2, entry 19). Furthermore, a carbazole-derived boronic acid was also converted into the corresponding product in moderate yield (Table 2, entry 20). Notably, the yield was low due to the high volatility of the product.

The reaction proceeded with high stereoselectivity to form predominantly the *Z* isomer of styrenes **3**. The mixture contained less than 7% of the minor *E* isomer. This result is in agreement with that observed in the Heck reaction in the conventional stereochemistry. The *Z* selectivity stems from both the stability of the olefin (thermodynamic) and a lower energy barrier in the transition state (kinetic), both of which lead to the *Z* isomer.[16] The trifluoromethyl and isopropyl groups are comparable in size[17] in coupling products **3**, and the *Z* selectivity of the reaction is governed by the stability of the alkene products in which the larger trifluoromethyl group and the aryl group are in the *trans* orientation. The configuration of the isomers was determined by comparison of the fluorine and the vinylic proton in the ^1H NMR spectra of fluoroalkenes **3**. Nenajdenko[14] reported that the $J_{F,H}$ vinylic hydrogen coupling constants

Table 2. Conversion of arylboronic acids into (*Z*)-β-fluoro-β-(trifluoromethyl)styrenes through the Pd-catalyzed oxidative Heck reaction.[a]



1 2 3

Entry	Boronic acid	Product	Yield [%][b]	*Z*/*E* ratio[c]
1	 **1a**	 **3a**	89 (79)	99:1
2	 **1b**	 **3b**	90 (78)	96:4
3	 **1c**	 **3c**	87 (75)	97:3
4	 **1d**	 **3d**	77 (69)	97:3
5	 **1e**	 **3e**	78 (62)	97:3
6	 **1f**	 **3f**	56 (42)	97:3
7	 **1g**	 **3g**	71 (69)	98:2
8	 **1h**	 **3h**	54 (48)	96:4
9	 **1i**	 **3i**	71 (60)	97:3
10	 **1j**	 **3j**	69 (58)	95:5
11	 **1k**	 **3k**	67 (61)	93:7
12	 **1l**	 **3l**	73 (68)	>99:1
13	 **1m**	 **3m**	71 (61)	98:2
14	 **1n**	 **3n**	68 (62)	96:4
15	 **1o**	 **3o**	67 (50)	96:4
16	 **1p**	 **3p**	82 (69)	96:4
17	 **1q**	 **3q**	77 (59)	97:3
18	 **1r**	 **3r**	64 (52)	97:3
19	 **1s**	 **3s**	65 (58)	99:1
20	 **1t**	**3t**	76 (71)	98:2

[a] Reaction conditions: Arylboronic acid (1.0 mmol), **2** (18 mmol), $Pd(PhCN)_2Cl_2$ (5 mol-%), PCy_3 (10 mol-%), $NaHCO_3$ (2 mmol), BPO (2 mmol), 1,4-dioxane (3.0 mL), 110 °C, 14 h. [b] Determined by analysis of the product by ^{19}F NMR spectroscopy with *p*-fluoroacetophenone as an internal standard. The values in square brackets are the yields of the isolated products. [c] Determined by ^{19}F NMR spectroscopy.

range from 28.0 to 36.3 Hz for *Z* isomers and from 18.2 to 21.6 Hz for *E* isomers (Scheme 2).

Scheme 2. Assignment of configuration of isomeric alkenes **3**.

Conclusions

In summary, we developed a new strategy for the facile synthesis of (*Z*)-β-fluoro-β-(trifluoromethyl)styrene derivatives through the palladium-catalyzed oxidative Heck reaction of commercially available 2,3,3,3-tetrafluoroprop-1-ene as a fluorine source. The wide scope and particularly the tolerance to a large number of important arylboronic acids make this strategy remarkably practical for the streamlined synthesis of functional styrenes.

Experimental Section

General Procedure: The reaction was performed in an autoclave containing a 10 mL Teflon reaction tube. The catalyst (0.05 mmol), ligand (0.10 mmol), and a magnetic stir bar were placed in the tube, which was then capped with a stopper. Then, *p*-anisylboronic acid (1 mmol), base (2 mmol), oxidant (2 mmol), and the solvent (3 mL) were added to the tube. The autoclave was cooled down to –100 °C by using liquid nitrogen, and then a fixed amount of 2,3,3,3-tetrafluoropropylene was added. Finally, the autoclave was heated in an oil bath at 115 °C for 6 h. Upon completion of the reaction, the autoclave was cooled down to room temperature and vented carefully to discharge the excess amount of 2,3,3,3-tetrafluoropropylene. Water (60 mL) and *p*-fluoroacetophenone (80 mg) were added, and then the product was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under atmospheric pressure. The crude products were determined by ^{19}F NMR spectroscopy by using *p*-fluoroacetophenone as an internal standard.

***CAUTION*:** *Because of the high volatility of the products, the reaction must be performed carefully.*

Acknowledgments

The authors gratefully acknowledge financial support from the National Natural Science Foundation of China (NSFC) (grant number 21327011), the Program for Changjiang Scholars and Innovative Research Team in University (IRT_14R33), and the Post Doctoral Research Project of Shaanxi Province, and also thank Professor Chao Wang (SNNU) for helpful discussions.

[1] a) P. Krisch (Ed.), *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, Germany, **2004**; b) J.-P. Bégué, D. Bonnet-Delpon (Eds.), *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, NJ, **2008**; c) I. Ojima (Ed.), *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chich-

ester, UK, **2009**; d) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589; e) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; f) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. D. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; g) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; h) C. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 2895–2906; i) Y. Li, A. Studer, *Angew. Chem. Int. Ed.* **2012**, *51*, 8221–8224; *Angew. Chem.* **2012**, *124*, 8345–8348.

[2] a) M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231; *Angew. Chem.* **2005**, *117*, 218–234; b) M. Schlosser, *Angew. Chem. Int. Ed.* **2006**, *45*, 5432–5438; *Angew. Chem.* **2006**, *118*, 5558–5572; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; d) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; e) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1–PR43; f) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324–1327; g) E. Merino, C. Nevado, *Chem. Soc. Rev.* **2014**, *43*, 6598–6608; h) H. Egami, M. Sodeoka, *Angew. Chem. Int. Ed.* **2014**, *53*, 8294–8308; *Angew. Chem.* **2014**, *126*, 8434–8449.

[3] a) K. Hirotaki, T. Hanamoto, *J. Org. Chem.* **2011**, *76*, 8564–8568; b) H. Zhang, C.-B. Zhou, Q.-Y. Chen, J.-C. Xiao, R. Hong, *Org. Lett.* **2011**, *13*, 560–563.

[4] a) G. K. S. Prakash, H. S. Krishnan, P. V. Jog, A. P. Iyer, G. A. Olah, *Org. Lett.* **2012**, *14*, 1146–1149; b) M. Ohashi, H. Saijo, M. Shibata, S. Ogoshi, *Eur. J. Org. Chem.* **2013**, 443–447.

[5] a) H. Serizawa, K. Aikawa, K. Mikami, *Org. Lett.* **2014**, *16*, 3456–3459; b) C.-P. Zhang, J. Cai, C.-B. Zhou, X.-P. Wang, X. Zheng, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 9516–9518; c) A. R. Mazzotti, M. G. Campbell, P. Tang, J. M. Murphy, T. Ritter, *J. Am. Chem. Soc.* **2013**, *135*, 14012–14015.

[6] a) J. Ruan, X. Li, O. Saidi, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 2424–2425; b) L. Zhang, C. Dong, C. Ding, J. Chen, W. Tang, H. Li, L. Xu, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 1570–1578.

[7] R. Martinez, F. Voica, J. Genet, S. Darses, *Org. Lett.* **2007**, *9*, 3213–3216.

[8] a) M. M. S. Andappan, P. Nilsson, H. Schenck, M. Larhed, *J. Org. Chem.* **2004**, *69*, 5212–5218; b) P.-A. Enquist, P. Nilsson, P. Sjöberg, M. Larhed, *J. Org. Chem.* **2006**, *71*, 8779–8786.

[9] K. S. Yoo, C. H. Yoon, K. W. Jung, *J. Am. Chem. Soc.* **2006**, *128*, 16384–16393.

[10] For a recent review, see: L. R. Odell, J. Sävmarker, J. Lindh, P. Nilsson, M. Larhed, *Addition Reactions with Formation of Carbon–Carbon Bonds: (v) The Oxidative Heck Reaction*, in: *Comprehensive Organic Synthesis II* (Eds.: G. A. Molander, P. Knochel), 2nd edition, Elsevier, **2014**, vol. 7, p. 492–537.

[11] Y. Li, D. Xue, W. Lu, X. Fan, C. Wang, J. Xiao, *RSC Adv.* **2013**, *3*, 11463–11466.

[12] M. Shimizu, Y. Takeda, M. Higashi, T. Hiyama, *Angew. Chem. Int. Ed.* **2009**, *48*, 3653–3656; *Angew. Chem.* **2009**, *121*, 3707–3710; *Angew. Chem.* **2009**, *121*, 3707.

[13] a) H. Yanai, T. Taguchi, *Eur. J. Org. Chem.* **2011**, 5939–3954; b) W. R. Dolbier Jr., T. A. Gray, K. Onnishi, *Synthesis* **1987**, *10*, 956–958.

[14] A. A. Goldberg, V. M. Muzalevskiy, A. V. Shastin, E. S. Balenkova, V. G. Nenajdenko, *J. Fluorine Chem.* **2010**, *131*, 384–388.

[15] S. Kathiravan, I. A. Nicholls, *Org. Lett.* **2015**, *17*, 1874–1877.

[16] V. G. Nenajdenko, V. N. Korotchenko, A. V. Shastin, E. S. Balenkova, *Russ. Chem. Bull.* **2004**, *53*, 1034–1064.

[17] D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320–1367; *Angew. Chem.* **1990**, *102*, 1363–1409; *Angew. Chem.* **1990**, *102*, 1363.

Received: May 11, 2015
Published Online: June 5, 2015

