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Identification of a Surprising Boronic Acid Homocoupling Process in Suzuki–Miyaura Cross-Coupling Reactions Utilizing a Hindered Fluorinated Arene

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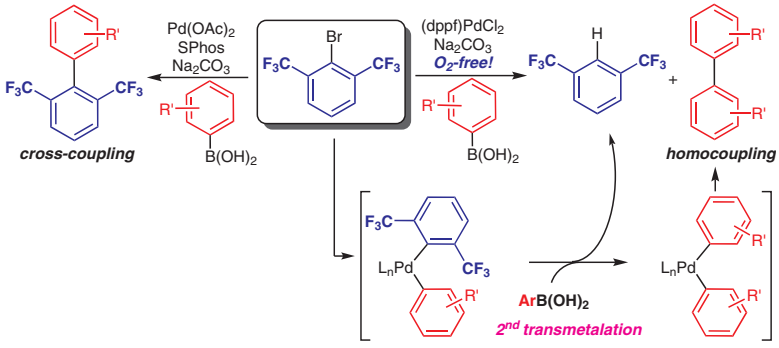
Dedicated to Professor Barry Trost in honor of his 80th birthday.

Published as part of the Cluster *The Power of Transition Metals: An Unending Well-Spring of New Reactivity*



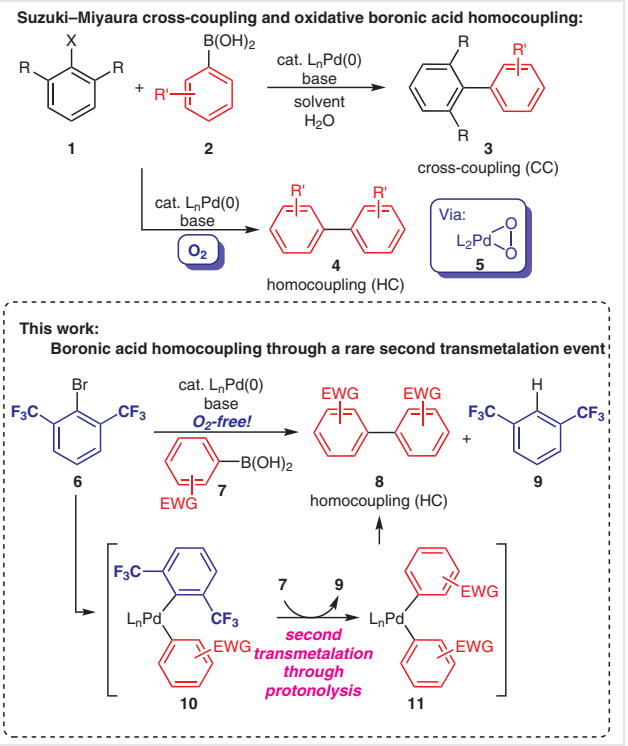
Received: 16.07.2020
Accepted after revision: 03.08.2020
Published online: 27.08.2020
DOI: 10.1055/s-0040-1707266; Art ID: st-2020-k0400-c

Abstract The Suzuki–Miyaura cross-coupling reaction of 2-bromo-1,3-bis(trifluoromethyl)benzene with arylboronic acids was evaluated and determined to suffer from the formation of large amounts of boronic acid homocoupling products in conjunction with dehalogenation. Homocoupling product formation in this process likely occurs through a rare protonolysis/second transmetalation event rather than by the well-established mechanism requiring the involvement of O_2. The scope of this boronic acid homocoupling reaction was investigated and shown to predominate with electron-deficient arylboronic acids. Finally, a good yield of cross-coupling products could be obtained by employing dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine (SPhos) as the ligand.

Key words palladium catalysis, Suzuki–Miyaura reaction, cross-coupling, arylboronic acids, bromobistrifluoromethylbenzene

The Suzuki–Miyaura (SM) cross-coupling (CC) reaction (Scheme 1) represents one of the most powerful and widely used methods for the construction of biaryl compounds in both academic and industrial settings.[1] Research developments in this area over the last 50 years have led to a detailed understanding of the reaction mechanism that has permitted the identification of highly robust and efficient Pd catalysts[2] capable of operating at low catalyst loadings, making the reaction amenable to large-scale syntheses.[3] However, in addition to the desired CC product **3**, side-reactions prevalent in the SM CC reaction include dehalogenation of the aryl halide **1**, protodeboronation of the boronic acid **2**,[4,5] and homocoupling (HC).[5] These undesirable pathways must be suppressed to achieve high yields of the desired CC product. With regard to oxidative HC of boronic acid **2**, detailed mechanistic investigations[6] have implicated the formation of **4** through a Pd–peroxo species **5** generated by the presence of O_2 in the reaction mixture. As a result, rigorous exclusion of O_2 is required to avoid this unwanted reaction pathway.

Organofluorine compounds are used extensively in the pharmaceutical industry and in medicinal chemistry due to the unique properties of the C–F bond, which can increase lipophilicity and provide high metabolic stability.[7] There-



Scheme 1 Suzuki–Miyaura cross-coupling and competitive boronic acid homocoupling

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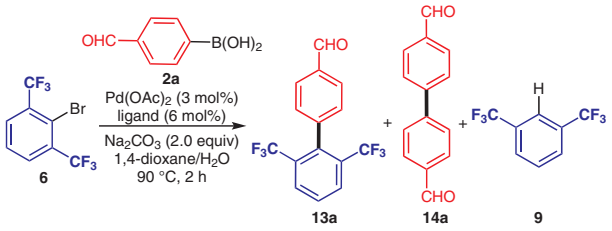
fore, the synthesis of fluorinated biaryls by using the SM CC reaction is a practical way to access new potentially useful therapeutics. As a result, we recently became interested in employing the fluorinated arene **6** in SM CC reactions (Scheme 1). Surprisingly, large amounts of the boronic acid HC product **8**, along with the dehalogenation product **9**, were obtained when employing electron-deficient arylboronic acids **7** although rigorous exclusion of O_2 was carried out. This result appears to have occurred through a rare second transmetalation (TM) event[8] facilitated by protonolysis of the 2,6-bis(trifluoromethyl)phenyl moiety of complex **10**. Here, we report our findings in support of this proposed pathway that, to the best of our knowledge, represent the first evidence of a second TM process in SM CC.

Initial investigation into the SM CC reaction of **6** was carried out by using the arylboronic acid **2a** while varying the phosphine ligand (Table 1). Surprisingly, the use of the commonly employed catalyst (dppf)$PdCl_2$ led to substantial amounts of the HC product **14a** (Table 1, entry 1). Rigorous exclusion of oxygen by setting up the reaction in an argon-filled glovebox with degassed solvent led to no improvement. Upon completion of the ligand survey shown in Table 1, we determined that Buchwald's 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) ligand[9] afforded high yields of the CC product **13a** (entry 14). However, an interesting trend was observed: regardless of the phosphine employed, the amount of HC product **14a** formed was similar to the amount of dehalogenated product **9** (entries 1–14). This observation implied that the formation of the boronic acid HC product **14a** and the dehalogenation product **9** were mechanistically related and not a result of O_2 in the system. Additionally, a control experiment employing (dppf)$PdCl_2$ as catalyst in the absence of **6** afforded only trace amounts of **14a**, further excluding the role of O_2.

The reaction scope in relation to the effect of the structure of the boronic acid on the efficiency of HC versus CC in this unique HC reaction was next investigated by employing electronically and sterically differentiated boronic acids **2** with (dppf)$PdCl_2$ as the catalyst (Scheme 2).[10] In general, electron-deficient boronic acids **2a–g** afforded HC products in preference to CC products. When (4-fluorophenyl)boronic acid (**2h**) was employed, equal amounts of HC and CC products were obtained; however, when the 3-fluorophenyl derivative **2i** was used, the amount of the HC product increased. This result highlights an important electronic effect whereby the electron-donating ability of the 4-fluoro substituent, by resonance, decreases the amount of HC formed, whereas a 3-fluoro substituent is purely electron-withdrawing, as the resonance effect is removed at this position. Additionally, when an electron-donating substituent (**2j–k**) or a simple phenyl group (**2n**) was used, the CC product predominated. Finally, *ortho*-substitution was either not tolerated (**2c**) or afforded the HC product (**2l**), and protection of the formyl group in **2a** as a 1,3-dioxolane (**2m**) led to a reduction in the amount of HC product.

Table 1 Catalyst Evaluation for the CC of **6** and **2a**[a]

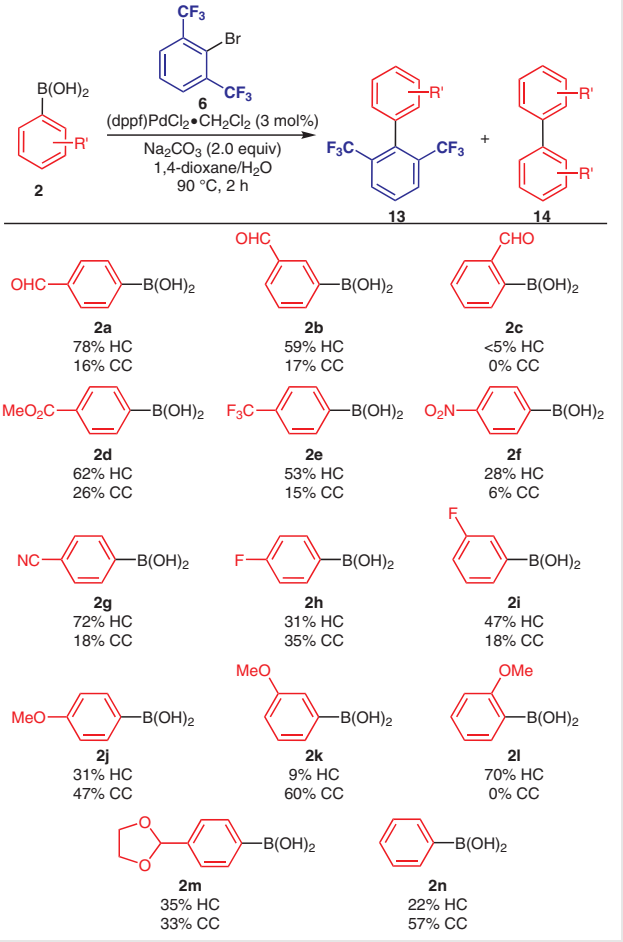


Entry	Ligand	Yield (%)		
		13a[b]	**14**[a]	**9**[b]
1	dppf[d]	17	78	65
2	PPh_3	56	15	10
3	P(*o*-Tol)$_3$	5	60	71
4	$P(C_6F_5)_3$	<5	14	12
5	PCy_3	<5	61	64
6	P(*t*-Bu)$_3$	44	9	7
7	PBu_3	<5	67	60
8	dppm[e]	8	42	38
9	dppe[f]	<5	9	5
10	dppp[g]	2	6	2
11	dppb[h]	6	6	2
12	Xantphos[i]	82	7	7
13	XPhos[j]	20	68	62
14	SPhos	93	10	6

[a] Reaction conditions: arene **6** (0.325 mmol), **2a** (0.650 mmol), Na_2CO_3 (0.650 mmol), $Pd(OAc)_2$ (3 mol%), ligand (6 mol%), 1,4-dioxane (0.7 mL), H_2O (0.25 mL).
[b] Determined by ^{19}F NMR spectroscopic analysis of the unpurified reaction mixture with $PhCF_3$ as standard.
[c] Determined by ^1H NMR spectroscopic analysis of the unpurified reaction mixture with dimethyl fumarate as standard.
[d] (dppf)$PdCl_2$·CH_2Cl_2 (3 mol%).
[e] $CH_2(PPh_2)_2$ (3 mol%).
[f] $Ph_2P(CH_2)_2PPh_2$ (3 mol%).
[g] $Ph_2P(CH_2)_3PPh_2$ (3 mol%).
[h] $Ph_2P(CH_2)_4PPh_2$ (3 mol%).
[i] 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (3 mol%).
[j] 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

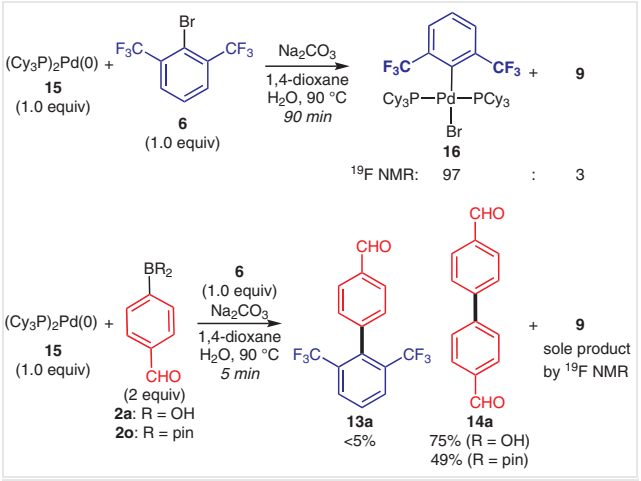
To further elucidate a possible anaerobic mechanism to account for the formation of the dehalogenation product **9** and boronic acid HC in this system, stoichiometric studies using ($Cy_3P)_2Pd(0)$ (**15**), as outlined in Scheme 3, were performed, because use of PCy_3 as a ligand afforded a high HC selectivity (Table 1, entry 5). The reaction of aryl bromide **6** with **15** under the typical CC reaction conditions, but in the absence of a boronic acid, led to the oxidative addition complex **16**, with the formation of only traces of the dehalogenated product **9**, as determined by ^{19}F NMR spectroscopy

(97:3 ratio of **16** to **9**). However, when the reaction was repeated in the presence of arylboronic acid **2a**, full conversion of the aryl bromide **6** into the dehalogenated product **9** was observed by ^{19}F NMR spectroscopy in only five minutes, affording a 75% NMR yield of **14a**, with only traces of the CC product **13a**. No other fluorine-containing compounds were detected by ^{19}F NMR spectroscopy. Repeating the reaction with the aryl pinacol boronate ester **2o** also resulted in complete conversion of the aryl bromide **6** into **9** within five minutes, with trace amounts of the CC product, but gave a reduced NMR yield of the HC product (49%), and unreacted **2o** was also detected by ^{1}H NMR spectroscopy of the crude mixture.



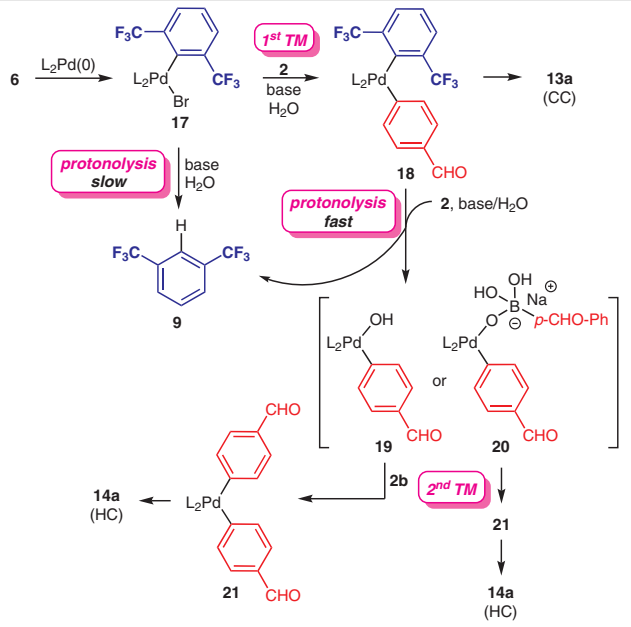
Scheme 2 Boronic acid homocoupling reaction scope employing **6**[10]

A possible mechanism to account for the results obtained is consistent with a second TM pathway[8] that presumably requires a Pd–C protonolysis[11] event to permit TM of the arylboronic acid (Scheme 4). For example, the HC of the organometallic coupling partner in Negishi[8a] or Kumada[8b] coupling reactions is well established to occur through this second TM by a direct aryl–aryl exchange that predominates when reductive elimination is slow. However, such a pathway is not possible in the SM reaction because transmetalation between Pd and arylboron derivatives is known[12] to require a Pd–O–B interaction. Therefore Pd does not undergo direct aryl–aryl exchange with boronic acids. As a result, a protonolysis of the more sterically hindered 2,6-bis(trifluoromethyl)phenyl group of **18** to generate **9** directly and to provide a possible competent intermediate (**19** or **20**)[12] for a second TM with **2** to lead to HC product **14a** via **21** seems to be required. This is surprising because Pd–C bonds are relatively inert to protonolysis.[11] This pathway appears to be unique to this system with its 2,6-bis(trifluoromethyl) substitution; moreover, it requires a boronate derivative because formation of **9** was minimal in the absence of a boronic acid, whereas it was rapidly generated in the presence of boron derivatives **2** (Scheme 3). Therefore, **18** might be subjected to direct protonolysis by the boronic acid to afford **20**,[12d] or protonolysis might simply be facilitated by the presence of the second aryl group of complex **18** introduced after the first TM. The latter seems more likely because both the boronic acid **2a** and the boronate ester **2o** induced rapid dehalogenation of **6** (Scheme 3). Additionally, it is well appreciated that the rate of transmetalation of aryl pinacol boronates is lower than that of the corresponding boronic acid in SM CC reactions.[12d] Therefore, the use of boronate **2o** instead of boronic acid **2a** should provide a reduced rate of HC formation in the stoichiometric reactions in Scheme 3 if a second TM occurs. The presence of unreacted boronate **2o** and the reduced yield of **14a** when boronate **2o** is used instead of boronic acid **2a** is fully consistent with this argument.[13]



Scheme 3 Stoichiometric studies employing $(Cy_3P)_2Pd$

According to the proposal outlined in Scheme 4, the ratio of CC to HC products should be dictated by the rate of reductive elimination of **18** relative to the outlined HC pathway. For cases where reductive elimination of **18** is slow, HC products should predominate.[8] The results obtained from an investigation of the reaction of **6** with various boronic

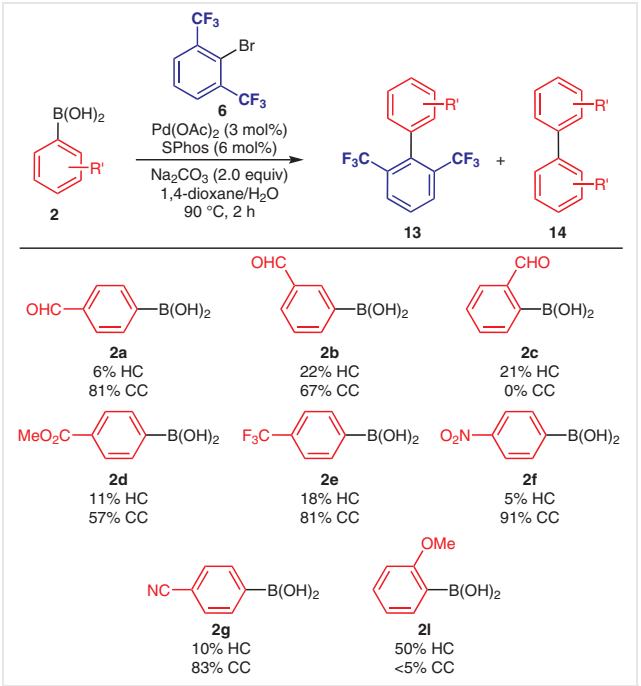


Scheme 4 Possible mechanism for HC formation in the absence of O_2 through a protonolysis/second transmetalation pathway

acids and (dppf)$PdCl_2$ as catalyst (Scheme 2) further support this proposal. Because of the high electron-withdrawing ability of the CF_3 groups, reductive elimination from complex **18** to afford the CC product should be slow when electron-deficient boronic acids are employed (e.g., **2a–g** or **2i**), due to the polarity mismatch of forming a C–C bond between two electropositive carbon atoms. Additionally, the steric effect of the two *ortho* CF_3 groups in the 2,6-disubstituted compound inhibits CC. As a result, the protonolysis/second TM can compete, leading to preferential boronic acid HC. In contrast, electron-rich boronic acids (e.g., **2h**, **2j**, or **2k**) should show an increased rate of reductive elimination from the analogous unsymmetrical $L_nP(Ar)Ar'$ complex of **18** by minimizing this polarity mismatch, leading to increased amounts of CC products, as observed (Scheme 2). On the other hand, an electron-rich sterically hindered boronic acid (**2l**) presumably favors HC on steric grounds. Finally, the increase in selectivity for CC when Xantphos or SPhos was used as ligand (Table 1, entries 12 and 14) can be rationalized in terms of an increased rate of reductive elimination of **18** due to the large bite angle and the steric hinderance associated with these two ligands, respectively.[14]

Overall, the formation of HC byproducts in the SM CC reaction of fluorinated arene **6** appears to be due its unique properties resulting from the high electron-withdrawing ability of the two CF_3 groups and from the steric effect of their 2,6-disubstitution pattern, which together lead to surprisingly easy protonolysis, facilitating a second TM. This problem is exacerbated when electron-deficient arylboronic acids are employed as coupling partners in the reaction. The unique ability of intermediates such as **18** to undergo protonolysis of the 2,6-bis(trifluoromethyl)aryl group warrants further investigation and is probably not facilitated by retro-concerted metalation–deprotonation[10] enabled by the presence of HCO_3^-, as control experiments in which NaOH or KF was used as the base in the reactions shown in Scheme 2 afforded no improvements in CC selectivity.[15] High selectivities toward boronic acid HC with aryl bromide coupling partners other than **6** have not been identified. For example, preliminary studies with perfluorinated bromobenzene and boronic acid **2a**, 2-bromo-1,3-dimethoxybenzene and boronic acid **2l**, or 2-bromo-1,3,5-triisopropylbenzene and boronic acid **2l** all afforded the CC product as the major product.

Finally, successful CC with arene **6** was achieved by using a Pd catalyst derived from SPhos[9] (Table 1, entry 14). As a result, the substrate scope of the CC reaction of **6** with specifically electron-deficient arylboronic acids was further evaluated (Scheme 5).[16] In general, good yields of CC products were obtained except when employing arylboronic acids with *ortho*-substituents (**2c** and **2l**).



Scheme 5 CC reaction of aryl halide **6** with electron-deficient aryl boronic acids with SPhos as ligand[14]

In conclusion, a novel mechanism for boronic acid HC in SM CC reactions was discovered that occurs under anaerobic conditions. This HC pathway is unique to the 2,6-bis(trifluoromethyl)phenyl substitution pattern of aryl halide **6**, which presumably reduces the rate of reductive elimination leading to CC when employing an electron-deficient boronic acid; this permits a surprisingly facile protonolysis to compete, enabling a second TM. Because of the significance of the SM CC reaction and of organofluorine compounds,

the findings described here provide a valuable guide to future developments of SM CC reactions employing fluorinated arenes as coupling partners. Additionally, these results point to an alternative operable mechanism for boronic acid HC in SM CC reactions where the rate of reductive elimination might be slow (e.g., asymmetric CC of tri- or tetrasubstituted biaryls).[17]

Funding Information

Startup funding was provided by the Virginia Commonwealth University and the Bill and Melinda Gates Foundation (The Medicines for All Institute, grant number OPP1176590)

Acknowledgment

B.D. thanks the American Chemical Society for a summer research fellowship as a part of the ACS Project SEED Program. We thank Dr. Joseph Turner (VCU) for assistance in collecting HRMS data.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707266.

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(10) **Biphenyl-4,4′-dicarbaldehyde (14a); Typical HC Procedure**
A crimp-cap vial equipped with magnetic stirrer bar was charged with (dppf)$PdCl_2$·CH_2Cl_2 (8.2 mg, 0.010 mmol), (4-formylphenyl)boronic acid (**2a**; 97.9 mg, 0.653 mmol), Na_2CO_3 (69.2 mg, 0.653 mmol), and 2-bromo-1,3-bis(trifluoromethyl)benzene (**6**; 95.7 mg, 0.327 mmol). The vial was sealed with a crimp-cap septum and filled with Ar by using three vacuum–purge cycles. Degassed (Ar sparge) 1,4-dioxane (0.70 mL) and H_2O (0.25 mL) were added, and the vial was immersed in an oil bath at 90 °C for 2 h, then cooled to r.t. H_2O was added and the mixture was extracted with CH_2Cl_2 (2 × 4 mL). The combined organics were mixed with $PhCF_3$ (60.0 μL, 0.488 mmol) as an added standard, and an aliquot was diluted in $CDCl_3$ for quantitative ^{19}F NMR spectroscopy. The organics were then dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography [silica gel, hexanes–EtOAc (0–25%)] gave a white solid; yield: 53.2 mg (77%); mp 141–143 °C; R_f = 0.26 (25% EtOAc–hexanes).
^1H NMR (600 MHz, $CDCl_3$): δ = 10.09 (s, 2 H), 8.00 (d, *J* = 8.0 Hz, 4 H), 7.80 (d, *J* = 8.0 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 191.7, 145.5, 135.9, 130.4, 128.0. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}O_2$: 211.0759; found: 211.0788.

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(13) The results obtained are also consistent with the formation of HC product **14a** from **21** through a bimetallic-catalyst-exchange mechanism where aryl–aryl exchange between two molecules of **18** occurs to generate **21** along with a symmetrical Pd complex bearing two 2,6-bis(trifluoromethyl)phenyl fragments

that would need to undergo protonolysis to form **9** and reenter the catalytic cycle. For an example of bimetallic exchange, see: Wang D., Izawa Y., Stahl S. S.; *J. Am. Chem. Soc.*; **2014**, *136*: 9914

(14) Other strategies to facilitate reductive elimination using electron-deficient fluorinated styrenes as additives have been reported. It is possible that coordination of electron-deficient arene **9** to the Pd-intermediates involved in these processes might play a role in the observed reaction outcomes. For examples, see: (a) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186. (b) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544. (c) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387.

(15) See the Supporting Information.

(16) **2′,6′-Bis(trifluoromethyl)biphenyl-4-carbaldehyde (13a): Typical CC Procedure**

A crimp-cap vial equipped with magnetic stirrer bar was charged with $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), SPhos (8.3 mg, 0.020 mmol), (4-formylphenyl)boronic acid (**2a**; 97.9 mg, 0.653 mmol), Na_2CO_3 (69.2 mg, 0.653 mmol), and 2-bromo-1,3-bis(trifluoromethyl)benzene (**6**; 95.7 mg, 0.327 mmol). The vial was sealed with a crimp-cap septum and filled with Ar by using three vacuum–purge cycles. Degassed (Ar sparge) 1,4-dioxane (0.70 mL) and H_2O (0.25 mL) were added, and the vial was immersed in an oil bath at 90 °C for 2 h, then cooled to r.t. H_2O was added, and the mixture was extracted with CH_2Cl_2 (2 × 4 mL). The combined organics were mixed with $PhCF_3$ (60.0 µL, 0.488 mmol) as an added standard, and an aliquot was diluted in $CDCl_3$ for quantitative ^{19}F NMR spectroscopy. The organics were then dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography [silica gel, hexanes–EtOAc (0–25%)] gave a yellow oil; yield: 84.6 mg (85%); R_f = 0.59 (25% EtOAc–hexanes).

^1H NMR (600 MHz, $CDCl_3$): δ = 10.09 (s, 1 H), 7.99 (d, *J* = 8.0 Hz, 2 H), 7.91 (d, *J* = 8.0 Hz, 2 H), 7.68 (t, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.8, 140.3, 138.7, 136.1, 130.9 (q, *J* = 30.0 Hz), 130.8, 129.4 (q, *J* = 5.0 Hz), 128.5, 128.2, 123.1 (q, *J* = 275.0 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ = –57.5. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{15}H_9F_6O$: 319.0558; found: 319.0578.

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