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Facile Access to Fluoromethylated Arenes by Nickel-Catalyzed Cross-Coupling between Arylboronic Acids and Fluoromethyl Bromide**

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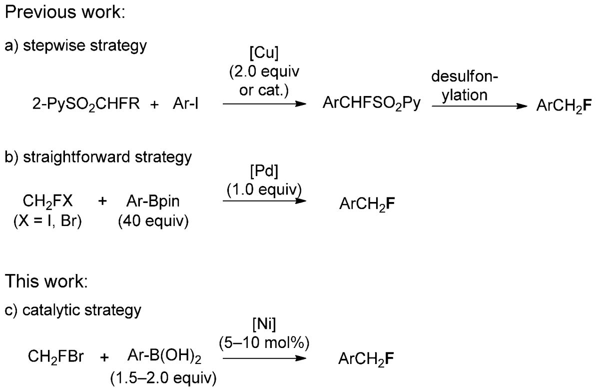
Abstract: *The nickel-catalyzed fluoromethylation of arylboronic acids was achieved with the industrial raw material fluoromethyl bromide (CH_2FBr) as the coupling partner. The reaction proceeded under mild reaction conditions with high efficiency; it features the use of a low-cost nickel catalyst, synthetic simplicity, and excellent functional-group compatibility, and provides facile access to fluoromethylated biologically relevant molecules. Preliminary mechanistic studies showed that a single-electron-transfer (SET) pathway is involved in the catalytic cycle.*

Fluoroalkylated arenes are present in many biologically active molecules and advanced functional materials owing to the unique properties caused by the fluorine atom(s).[1] Over the past few years, substantial efforts have been made in the preparation of such fluorinated compounds, and impressive progress has been achieved.[2] To date, palladium[2,3] and copper[2,4] catalysts have been mainly used to form Ar$-R_f$ bonds(R_f = fluoroalkyl) and thus to access fluoroalkylated arenes. Despite the importance of these synthetic methods, the catalysis of the cross-coupling/fluoroalkylation of arenes continues to attract great interest, especially the development of more sustainable catalysts based on first-row transition metals. Yet, except for copper, the use of other abundant first-row transition metals as catalysts has been scarcely explored.[5] Recently, we reported the nickel-catalyzed difluoroalkylation of arylboronic acids with functionalized difluoromethyl halides,[6] which represents a cost-efficient protocol for the preparation of functionalized difluoromethylated arenes. Inspired by this preliminary study, we envisioned the feasibility of a nickel-catalyzed fluoromethylation of arylboronic acids with a low-cost catalyst and industrial raw material fluoromethyl halides (Scheme 1 c). To the best of our knowledge, the nickel-catalyzed direct fluoromethylation of aromatics has not been reported thus far.[7] The reported nickel-catalyzed methylations of aromatics are limited by the use of methyl metal reagents (e.g. MeMgX, Me_3Al, and Me_2Zn) as coupling partners.[8] This is probably because the most accessible methyl electrophiles (e.g. MeI) are prone to dimerization and hydrodehalogenation.[9]



Scheme 1. Strategies for the fluoromethylation of aromatics.

In 2009, a palladium-mediated fluoromethylation of aryl boronates with fluoromethyl halides (CH_2FX, X = I, Br) has been reported (Scheme 1 b).[10] Although the method is straightforward, the requirement of a stoichiometric amount of palladium and an excess of the aryl boronate (40 equiv) restricts its widespread synthetic application. In this context, a stepwise strategy for the fluoromethylation of arenes through a copper-mediated monofluoroalkylation of aryl iodides, followed by desulfonylation, has been developed by Hu et al. (Scheme 1 a).[11] In this method, (2-pyridyl)sulfonyl-containing monofluoroalkylated reagents were used for the preparation of fluoromethylated arenes. Herein, we describe the nickel-catalyzed fluoromethylation of arylboronic acids with the industrial raw material fluoromethyl bromide (CH_2FBr; Scheme 1 c). The advantages of this reaction are the use of a low-cost nickel catalyst, mild reaction conditions, synthetic simplicity, and excellent functional-group compatibility. To demonstrate the utility of the protocol, fluoromethylated bioactive molecules have been synthesized using a late-stage fluoromethylation.

Initially, we focused our efforts on the nickel-catalyzed cross-coupling reaction of (1,1′-biphenyl)-4-ylboronic acid (**1a**) with fluoromethyl bromide (**2**) in the presence of a variety of diamine ligands (Table 1, entries 1–6). We observed that 1,10-phenathroline (phen, **L5**) showed higher activity than bipyridine (bpy) and bpy-based ligands **L1**–**L4**, providing fluoromethylated arene **3a** in 41 % yield (entry 6). Other diamine ligands, such as *N*,*N*′-dimethylethane-1,2-diamine and its derivatives, also afforded product **3a**, but in lower yields (for details, see the Supporting Information).

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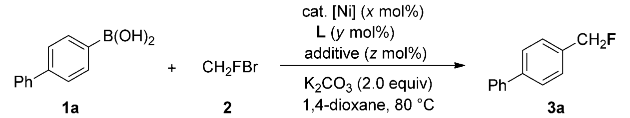
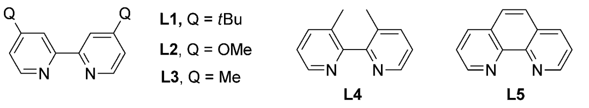
Table 1: Representative results for the optimization of the Ni-catalyzed fluoromethylation of **1a** with **2**.[a]



Entry	[Ni] (*x*)	**L** (*y*)	Additive (*z*)	Yield of **3a** [%][b]
1	$NiCl_2$·DME (10)	bpy (10)	–	29
2	$NiCl_2$·DME (10)	**L1** (10)	–	28
3	$NiCl_2$·DME (10)	**L2** (10)	–	34
4	$NiCl_2$·DME (10)	**L3** (10)	–	33
5	$NiCl_2$·DME (10)	**L4** (10)	–	35
6	$NiCl_2$·DME (10)	**L5** (10)	–	41
7[c]	$NiCl_2$·DME (10)	**L5** (10)	–	49
8[d]	$NiCl_2$·DME (10)	**L5** (10)	–	56
9[d]	$NiCl_2$·DME (10)	**L5** (10)	Py (10)	60
10[d]	$NiCl_2$·DME (10)	**L5** (10)	4-CF_3-Py (10)	62
11[d]	$NiCl_2$·DME (10)	**L5** (10)	4-MeO-Py (10)	71
12[d]	$NiCl_2$·DME (10)	**L5** (10)	4-MeO-Py (20)	75
13[d]	$NiCl_2$·DME (10)	**L5** (10)	DMAP (20)	91 (90)
14[e]	$NiCl_2$·DME (5)	**L5** (5)	DMAP (10)	90 (90)
15[e]	–	**L5** (5)	DMAP (10)	NR
16[e]	$NiCl_2$·DME (5)	–	DMAP (10)	NR
17[e]	$NiCl_2$·DME (5)	**L5** (5)	–	51

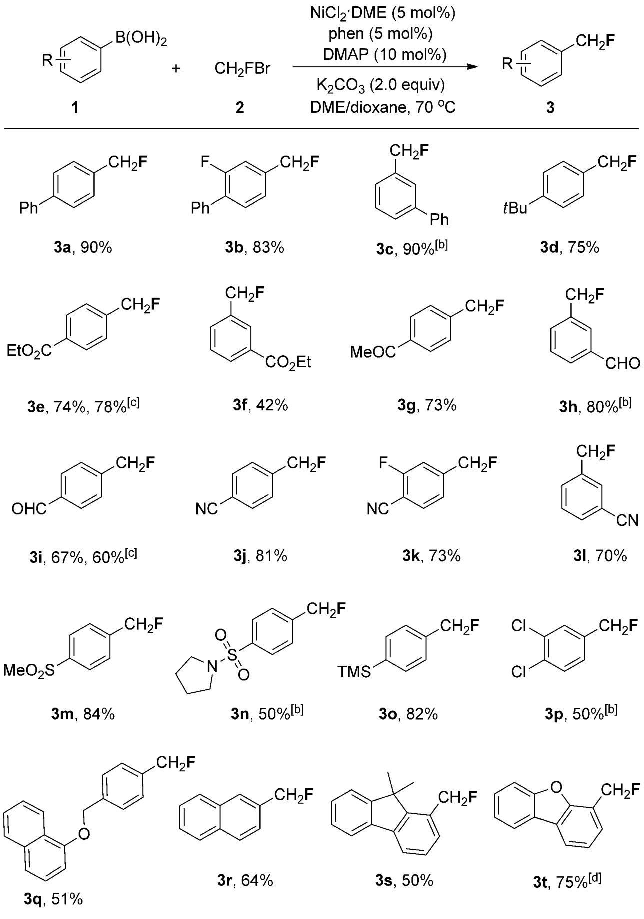
[a] Reaction conditions (unless otherwise specified): **1a** (1.5 equiv), **2** (2 mol L^{-1} in 1,4-dioxane, 0.3 mmol, 1.0 equiv), solvent (2 mL) for 12 h. [b] Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard; numbers in parentheses are yields of isolated products. [c] Reaction at 70 °C. [d] DME used as the solvent, 70 °C, 24 h. [e] DME/1,4-dioxane (v/v = 1:1) were used as solvent mixture.



Decreasing the reaction temperature from 80 °C to 70 °C resulted in a slightly higher yield (49 %; entry 7). Encouraged by these results, we investigated a variety of nickel catalysts, bases, and solvents. The combination $NiCl_2$·DME, K_2CO_3, and DME gave the best result (entry 8; for details, see the Supporting Information); however, even under these optimized reaction conditions, **3a** was obtained in only 56 % yield along with unreacted substrate **2** in 38 % yield. Furthermore, the reaction conditions also resulted in the homocoupling and deboronylation of **1a**. This observation clearly suggested that the production of **3a** is slower than these competitive reactions. In order to address this issue, we envisaged the modulation of the steric and electronic properties of the nickel complex by the use of another ligand, thus accelerating the nickel-mediated catalytic cycle and improve the yield of **3a** further.

Accordingly, we examined pyridine derivatives with substituents of a different electronic nature in *para* position (entries 9–13). These derivatives had a beneficial effect on the reaction, with the electron-rich 4-methoxy pyridine leading to a higher yield than the electron-deficient 4-trifluoromethyl pyridine (entries 10 and 11). To our delight, when we used *N*,*N*-dimethylpyridine-4-amine (DMAP, 20 mol %), we obtained **3a** in 90 % yield upon isolation (entry 13). Furthermore, a decrease of the loading of $NiCl_2$·DME from 10 mol % to 5 mol % and the use of **L5** (5 mol %), DMAP (10 mol %), and K_2CO_3 (2.0 equiv) in a solvent mixture of DME/1,4-dioxane[12] at 70 °C provided **3a** in a comparable yield (entry 14). No product formation was observed in the absence of the nickel catalyst or the ligand **L5**, but **3a** could be obtained in 51 % yield without DMAP, thus demonstrating the essential roles of both the nickel catalyst and the ligand **L5** for the catalytic cycle (entries 15–17).

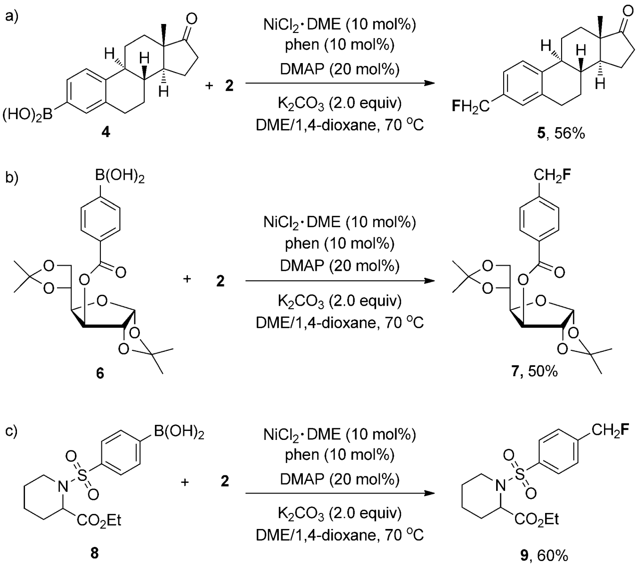
Upon the establishment of viable reaction conditions, a variety of arylboronic acids were employed as starting materials in this transformation (Scheme 2). Overall, substrates bearing electron-withdrawing substituents furnished the corresponding fluoromethylated arenes **3** in high yields. Electron-rich arylboronic acids also underwent the reaction smoothly, but the resulting products **3** were unstable upon purification by flash chromatography on silica gel (for details, see the Supporting Information). Many versatile functional groups, including base- and nucleophile-sensitive moieties, such as alkoxycarbonyl, enolizable ketone, formyl, cyano, methylsulfonyl, and sulfonamide groups, showed good toler-



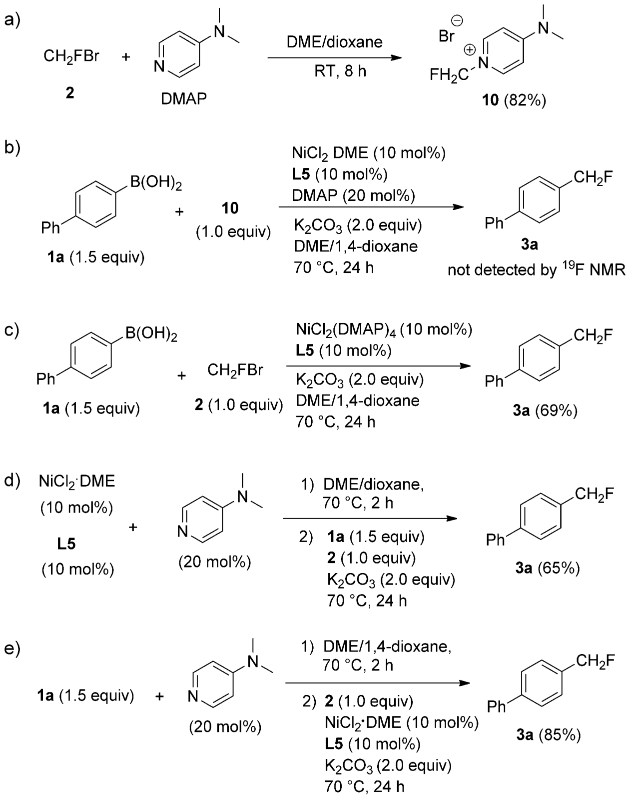
Scheme 2. Ni-catalyzed fluoromethylation of arylboronic acids **1** with **2**.[a] [a] Reaction conditions (unless otherwise specified): **1** (1.5 equiv), **2** (2 mol L^{-1} in 1,4-dioxane, 0.6 mmol, 1.0 equiv), DME/1,4-dioxane (1:1, v/v, 4 mL) for 24 h. [b] $NiCl_2$·DME (10 mol %), **L5** (10 mol %), DMAP (20 mol %). [c] Reaction on a gram scale. [d] **1** (2.0 equiv), reaction on a 0.3 mmol scale. DME = 1,2-dimethoxyethane.

ance toward the reaction conditions (**3e**–**n**). Additionally, the arylboronic acid bearing trimethylsilyl and chloride groups were competent partners, providing **3o** and **3p**, respectively, in moderate to good yields. Furthermore, the reactions of boronic acids derived from 2-naphthalene, 9,9-dimethyl-9*H*-fluorene, and dibenzo[*b*,*d*]furan also proceeded smoothly (**3r**–**t**). Finally, the syntheses of **3e** and **3i** on a gram scale were performed with high efficiency, and **3e** was even obtained in a higher yield (78 %) compared to its synthesis on a small scale, thus offering a reliable and practical access to highly functionalized fluoromethylated arenes.

We next demonstrated the usefulness of this protocol by the late-stage fluoromethylation in the synthesis of biologically active molecules. The treatment of estrone-derived arylboronic acid **4** with **2** afforded fluoromethylated compound **5** in good yield (Scheme 3a). The glucose-based substrate **6** also reacted smoothly, thus offering a facile access to fluorinated carbohydrates (e.g. **7**), which are of great interest in life sciences (Scheme 3b). Importantly, compound **9**, an inhibitor of N-type calcium channels,[13] could be rapidly prepared from **8** through the nickel-catalyzed process (Scheme 3c). Thus, this transformation is highly relevant for drug discovery and development.



Scheme 3. Late-stage fluoromethylation in the synthesis of biologically active molecules.



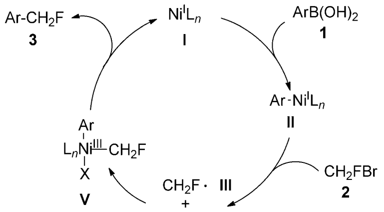
Scheme 4. The role of DMAP in the fluoromethylation. All yields were determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard.

To understand the role of DMAP in the reaction, several experiments were conducted (Scheme 4). First, the reaction of DMAP with **2** was attempted in order to rule out the possibility that this reaction occurs to give an active electrophilic species that later on serves as a coupling partner to produce the fluoromethylated arenes **3** (Scheme 4a). A fluoromethyl pyridinium salt **10** was indeed generated, but product **3a** was not formed when **10** was treated with arylboronic acid **1a** under the standard reaction conditions. Thus the role of DMAP in activating **2** could be excluded (Scheme 4b). Second, the following experiments were conducted to establish whether DMAP can function as a coligand to coordinate to the nickel complex and thus accelerate the catalytic cycle and improve the yields of products **3**. Product **3a** was obtained in a decreased yield of 69 % when substrate **1a** was treated with **2** in the presence of $NiCl_2(DMAP)_4$ **11**[14] and **L5** (Scheme 4c). A similar result was obtained in the reaction of **1a** with **2** in the presence of a nickel catalyst that was generated by the pretreatment of $NiCl_2$·DME with **L5** and DMAP (Scheme 4d). However, no reaction occurred in the absence of **L5** (Table 1, entry 16). On the contrary, **3a** was obtained in a comparable yield of 85 % when **1a** was pretreated with DMAP for 2 h, followed by the reaction of the resulting mixture with **2** in the presence of $NiCl_2$·DME and **L5** (Scheme 4e). Thus, these observations suggest that one of the roles of DMAP in the current process is the activation of the arylboronic acids to facilitate the transmetalation.[15] However, the possibility that DMAP coordinates with the active nickel complex to facilitate the catalytic cycle still cannot be ruled out.

In order to obtain some insight into the mechanism of the current reaction, several radical-inhibition experiments were conducted (for details, see the Supporting Information). Product **3a** was obtained in dramatically decreased yields, when the radical initiator AIBN (0.1 equiv) or the radical inhibitor hydroquinone (0.2 equiv) were added to the reaction of **1a** with **2** under otherwise standard reaction conditions. On the other hand, no reaction occurred when the electron scavenger 1,4-dinitrobenzene[5e] (0.2 equiv) was added. These results clearly indicate that a pathway featuring a single-electron transfer (SET) via a fluoromethyl radical is involved in the catalytic cycle.

In order to further probe the reaction mechanism, the dependence of the initial reaction rate on the concentrations of arylboronic acid **1a**, $NiCl_2$·DME, and **2** was examined (for details, see Figure S2 in the Supporting Information). A zero-order relationship of the initial rate with the concentration of **2** (Figure S2c) was observed; however both arylboronic acid **1a** and $NiCl_2$·DME showed first-order relationships (Figure S2a and b). These observations suggest that the arylboronic acid and the reactive nickel species are involved in the turnover-limiting step. Furthermore, a high concentration of $NiCl_2$·DME decreased the yield of **3a** as a result of the formation of some dimerized Ar−Ar product and unidentified defluorinated by-products (for details, see Table S8 in the Supporting Information). An increased concentration of $NiCl_2$·DME probably benefits the formation of Ar−Ar species from arylboronic acids and thus results in a Ni^0 species that can react with fluorinated substrates to generate some unidentified defluorinated products.[16] A similar defluorination side reaction occurred when **1a** was reacted with **2** under standard conditions with $Ni(cod)_2$ (10 mol%; cod = 1,4-cyclooctadiene) as the catalyst, leading to **3a** in only 32% yield (determined by ^{19}F NMR spectroscopy; for details, see Scheme S2 in the Supporting Information).

On the basis of these results and previous reports,[17] a plausible reaction mechanism involving a Ni^I/Ni^{III} catalytic cycle is proposed (Scheme 5). The reaction begins with the transmetalation between arylboronic acids and $[Ni^IL_n]$ (**I**), which may be generated through the comproportionation of in situ generated Ni^0 and the remaining Ni^{II} species.[17c,18] Subsequently, the resulting arylnickel complex $[Ar\text{-}Ni^IL_n]$ (**II**) reacts with **2** through a SET pathway to produce a fluoromethyl radical (**III**) and $[Ar\text{-}Ni^{II}(L_n)Br]$ (**IV**). This is not the turnover-limiting step in the overall catalytic cycle. Then, the recombination of **IV** with the newly formed radical **III** provides the key intermediate Ni^{III} species **V**, which undergoes a reductive elimination to afford **3** and regenerate **I** simultaneously.



Scheme 5. Proposed reaction mechanism.

In conclusion, we have demonstrated an efficient and straightforward method for the preparation of fluoromethylated arenes. The reaction employs a low-cost nickel catalyst and DMAP as an additive, and can be used for the preparation of a wide range of arylboronic acids with high efficiency under mild reaction conditions. This protocol features synthetic simplicity and can be used for the late-stage fluoromethylation of biologically relevant molecules. Preliminary mechanistic studies showed that a SET pathway via a fluoromethyl radical is involved in the nickel-based catalytic cycle. Further studies to uncover the detailed reaction mechanism and to develop derivative reactions are under way in our laboratory and will be reported in due course.

Keywords: arylboronic acids · cross-coupling · fluoromethylation · fluoromethylbromide · nickel

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[1] For recent reviews, see: a) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3; b) P. Maienfisch, R. G. Hall, *Chimia* **2004**, *58*, 93; c) Special issue *Fluorine in the Life Sciences*, *ChemBioChem* **2004**, *5*, 557; d) F. Babudri, G. M. Farinola, F. Naso, R. Ragni, *Chem. Commun.* **2007**, 1003; e) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; f) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320.

[2] For selected reviews, see: a) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470; b) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475; c) C. Hollingworth, V. Gouverneur, *Chem. Commun.* **2012**, *48*, 2929; d) T. Besset, C. Schneider, D. Cahard, *Angew. Chem. Int. Ed.* **2012**, *51*, 5048; *Angew. Chem.* **2012**, *124*, 5134; e) F.-L. Qing, *Chin. J. Org. Chem.* **2012**, *32*, 815; f) X. Wang, Y. Zhang, J. Wang, *Sci. Sin. Chim.* **2012**, *42*, 1417.

[3] E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679.

[4] M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909.

[5] For pioneering studies on fluoroalkyl nickel complexes, see: a) G. G. Dubinina, W. W. Brennessel, J. L. Miller, D. A. Vicic, *Organometallics* **2008**, *27*, 3933; b) A. Klein, D. A. Vicic, C. Biewer, I. Kieltsch, K. Stirnat, C. Hamacher, *Organometallics* **2012**, *31*, 5334; c) C.-P. Zhang, H. Wang, A. Klein, C. Biewer, K. Stirnat, Y. Yamaguchi, L. Xu, V. Gomez-Benitez, D. A. Vicic, *J. Am. Chem. Soc.* **2013**, *135*, 8141; for Ni^0-catalyzed free-radical perfluoroalkylations of aromatics, see: d) Q.-L. Zhou, Y.-Z. Huang, *J. Fluorine Chem.* **1989**, *43*, 385; e) X.-T. Huang, Q.-Y. Chen, *J. Org. Chem.* **2001**, *66*, 4651; for Ni^0-catalyzed difluoroacetylation of vinylzirconium compounds, see: f) M. K. Schwaebe, J. R. McCarthy, J. P. Whitten, *Tetrahedron Lett.* **2000**, *41*, 791.

[6] Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 9909; *Angew. Chem.* **2014**, *126*, 10067.

[7] For transition-metal-catalyzed monofluoroalkylations, see: a) N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 541; b) Y. Guo, B. Twamley, J. M. Shreeve, *Org. Biomol. Chem.* **2009**, *7*, 1716; c) C. Guo, X. Yue, F.-L. Qing, *Synthesis* **2010**, 1837; d) C. Guo, R.-W. Wang, Y. Guo, F.-L. Qing, *J. Fluorine Chem.* **2012**, *133*, 86; e) Y. Liang, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 5520; f) X. Jiang, S. Sakthivel, K. Kulbitski, G. Nisevich, M. Gandelman, *J. Am. Chem. Soc.* **2014**, *136*, 9548; for a radical fluoromethylation of heteroarenes, see: g) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95; for the direct fluoromethylation of arenes with fluoromethanol, see: h) G. A. Olah, A. Pavlath, *Acta Chim. Acad. Sci. Hung.* **1953**, *3*, 425; i) G. A. Olah, A. Pavlath, *Acta Chim. Acad. Sci. Hung.* **1953**, *3*, 203.

[8] For selected reports, see: a) E. Wenkert, T. W. Ferreira, E. L. Michelotti, *J. Chem. Soc. Chem. Commun.* **1979**, 637; b) A.

Sygula, Z. Marcinow, F. R. Fronczek, I. Guzei, P. W. Rabideau, *Chem. Commun.* **2000**, 2439.

[9] Z. Liang, W. Xue, K. Lin, H. Gong, *Org. Lett.* **2014**, *16*, 5620.

[10] a) H. Doi, I. Ban, A. Nonoyama, K. Sumi, C. Kuang, T. Hosoya, H. Tsukada, M. Suzuki, *Chem. Eur. J.* **2009**, *15*, 4165; b) H. Doi, M. Coto, M. Suzuki, *Bull. Chem. Soc. Jpn.* **2012**, *85*, 1233.

[11] a) Y. Zhao, B. Gao, C. Ni, J. Hu, *Org. Lett.* **2012**, *14*, 6080; b) Y. Zhao, C. Ni, F. Jiang, B. Gao, X. Shen, J. Hu, *ACS Catal.* **2013**, *3*, 631. During the preparation of our manuscript, a nickel-catalyzed stepwise synthesis of fluoromethylated arenes was reported, see: c) Y.-M. Su, G.-S. Feng, Z.-Y. Wang, Q. Lan, X.-S. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 6003; *Angew. Chem.* **2015**, *127*, 6101. During the production of our manuscript, a palladium-catalyzed fluoromethylation of arylboronic esters with fluoromethyl iodide was reported; see: d) J. Hu, B. Gao, L. Li, C. Ni, J. Hu, *Org. Lett.* **2015**, DOI: 10.1021/acs.orglett.5b01361.

[12] A solvent mixture of DME/1,4-dioxane was used because of the repeatability of the reaction.

[13] F. Radford, R. Lynch, S. L. Mellor, C. J. Hobbs, J. C. Gilbert, S. Stokes, A. Glen, A. Fiumana, N. J. Smith, C. G. Earnshaw, L. J. S. Knusten, WO 2005068448.

[14] The structure of **11** was confirmed by X-ray crystallographic analysis (see the Supporting Information). CCDC 1400297 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[15] Pyridine can effectively dissociate boroxines and facilitate the transmetalation event. See: M. A. Beckett, G. C. Strickland, K. S. Varma, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik, *J. Organomet. Chem.* **1997**, *535*, 33.

[16] For Ni^0-catalyzed C−F bond activation, see: M. Tobisu, T. Xu, T. Shimasaki, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 19505.

[17] For mechanistic studies of Ni-catalyzed Suzuki reactions of unactivated alkyl electrophiles, see: a) A. Wilsily, F. Tramutola, N. A. Owston, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 5794; b) S. L. Zultanski, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 624; for mechanistic studies of Ni-catalyzed Negishi reactions of unactivated alkyl electrophiles, see: c) G. D. Jones, J. L. Martin, C. McFarland, O. R. Allen, R. E. Hall, A. D. Haley, R. J. Brandon, T. Konovalova, P. J. Desrochers, P. Pulay, D. A. Vicic, *J. Am. Chem. Soc.* **2006**, *128*, 13175; d) V. B. Phapale, E. Bunuel, M. Garcia-Iglesias, D. J. Cardenas, *Angew. Chem. Int. Ed.* **2007**, *46*, 8790; *Angew. Chem.* **2007**, *119*, 8946; e) X. Lin, D. L. Phillips, *J. Org. Chem.* **2008**, *73*, 3680; f) N. D. Schley, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 16588; for an overview of mechanistic issues regarding Ni-catalyzed cross-couplings of unactivated alkyl halides, see: g) X. Hu, *Chem. Sci.* **2011**, *2*, 1867.

[18] a) J. Cornella, E. Gomez-Bengoa, R. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 1997; b) G. Yin, I. Kalvet, U. Englert, F. Schoenebeck, *J. Am. Chem. Soc.* **2015**, *137*, 4164.

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