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## Nickel-catalyzed Suzuki–Miyaura type cross-coupling reactions of (2,2-difluorovinyl)benzene derivatives with arylboronic acids

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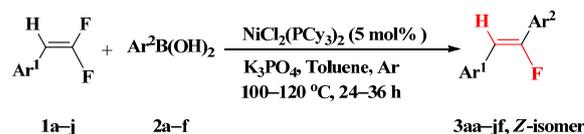
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An unprecedented highly stereoselective example of nickel-catalyzed Suzuki–Miyaura type cross-coupling reactions of (2,2-difluorovinyl)benzene derivatives with arylboronic acids was developed. The reaction proceeded efficiently in the presence of 5 mol%  $\text{NiCl}_2(\text{PCy}_3)_2$  and  $\text{K}_3\text{PO}_4$ , affording the Z-fluorostyrene derivatives in good to high yields with excellent regioselectivity.

The catalytic selective activation and functionalization of carbon–fluorine bonds are currently of great interest in organic synthesis.<sup>1</sup> They are still major challenges in synthetic chemistry due to great strength of the C–F bond. Transition metal-catalyzed cross-coupling reactions of organic fluorides with Grignard reagents,<sup>2</sup> organozinc reagents<sup>3</sup> and organoboron reagents<sup>4</sup> have been extensively investigated over the past few years and become an attractive alternative for the generation of carbon–carbon bonds. However, for those coupling reactions the electrophile coupling partners were mainly aryl fluorides,<sup>5</sup> the use of alkenyl fluorides as electrophilic substrates has been rarely reported.<sup>6</sup> In 2011, Nagai reported nickel- or palladium-catalyzed coupling reactions of tetrafluoroethylene or hexafluoropropylene with Grignard reagents with the assistance of a ligand ( $\text{PPh}_3$ ) leading to di-cross- and mono-cross-coupled products.<sup>7</sup> Ohashi and Ogoshi described the first example of Pd-catalyzed coupling reaction of tetrafluoroethylene (TFE) with arylzinc reagents in the presence of  $\text{LiI}$ , affording  $\alpha,\beta,\beta$ -trifluorostyrene derivatives in excellent yields.<sup>8</sup> The first and only example of Suzuki–Miyaura cross-coupling reaction of fluoroalkenes with aryl boronates was described by Ohashi and Ogoshi in 2013.<sup>9</sup> They found that perfluoroalkenes such as tetrafluoroethylene can be coupled with the aryl boronates in presence of 10 mol%  $\text{Pd}(\text{dba})_2$  and 20 mol%  $\text{P}i\text{Pr}_3$  under base-free conditions. As a continuation of our studies on the functionalization of C–F bonds in

*gem*-difluoroalkenes,<sup>10</sup> we herein report the nickel-catalyzed highly stereoselective Suzuki–Miyaura type coupling of (2,2-difluorovinyl)benzene derivatives with arylboronic acids (Scheme 1).

**Scheme 1** Ni-catalyzed coupling of (2,2-difluorovinyl)benzene derivatives with arylboronic acids



We began our investigation by examining the coupling reaction of 1-(2,2-difluorovinyl)-4-methoxybenzene **1a** with phenylboronic acid **2a** with catalytic amounts of various palladium and nickel catalysts (Table 1, entries 1–12). The results indicated that  $\text{NiCl}_2(\text{PCy}_3)_2$  was the most reactive nickel catalyst and afforded **3aa** in excellent yield and stereoselectivity (entry 12). In the absence of the catalyst, the reaction hardly proceeded and no desired product **3aa** was detected (entry 1). To our delight, 5 mol% of  $\text{NiCl}_2(\text{PCy}_3)_2$  was sufficient to carry out this reaction successfully (entry 13), however, when the amount of  $\text{NiCl}_2(\text{PCy}_3)_2$  was reduced to 1 mol%, the yield of **3aa** decreased obviously (entry 14). Further screening of bases revealed that  $\text{K}_3\text{PO}_4$  is the optimal base (entries 13 and 16–18). No expected product **3aa** was observed in absence of base (entry 15). It was found that 1.5 equivalents of phenylboronic acid **2a** were enough to make the coupling reaction proceed efficiently and decreasing the amount of the phenylboronic acid would result in low yield of **3aa** (entry 19). Furthermore, when the amount of phenylboronic acid increased to 2.0 equivalents, di-coupled product was formed (17%, GC-MS) (entry 20).

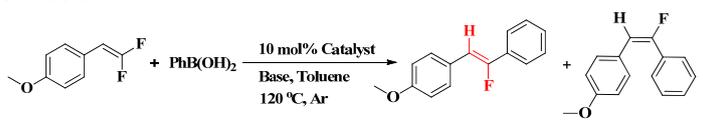
With the optimized reaction conditions in hand (Table 1, entry 13), we further explored the scope of the novel nickel-catalyzed Suzuki–Miyaura type cross-coupling reactions of different *gem*-difluoroalkenes with arylboronic acids (Table 2). It was found that *gem*-difluoroalkenes bearing electron-donating groups such as  $\text{CH}_3\text{O}$  and  $\text{OCH}_2\text{O}$  on the benzene ring were somewhat more reactive and provided the coupled Z-isomers in good to high yields. The *ortho* substituent on the benzene ring has no significant influence on the reactivity of *gem*-difluoroalkene substrates (**1g** vs. **1h**).

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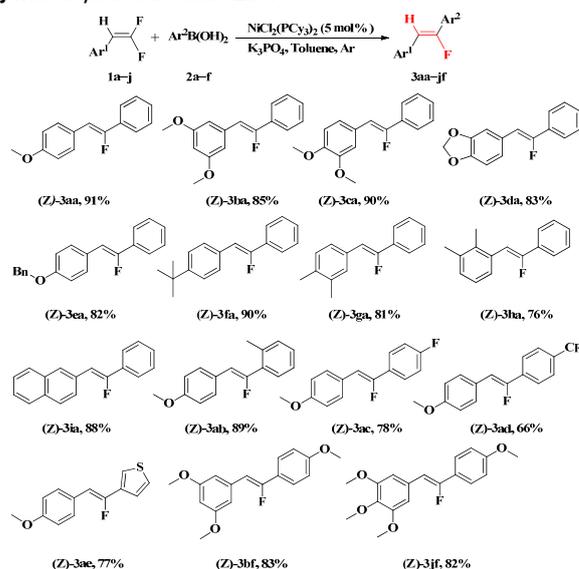
**Table 1** Optimization of reaction conditions<sup>a</sup>


| Entry | Catalyst (10 mol%)   | 2a (equiv.) | Base (2.0 equiv)                | Yield of 3aa (%) (Z/E) <sup>b</sup> |
|-------|--|-------------|---------------------------------|-------------------------------------|
| 1     | none   | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 0                                   |
| 2     | PdCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>           | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 0                                   |
| 3     | Pd(PPh <sub>3</sub> ) <sub>4</sub>                           | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 3(100/0)                            |
| 4     | PdCl <sub>2</sub> (dppf)                                     | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 25(100/0)                           |
| 5     | NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>           | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 0                                   |
| 6     | NiCl <sub>2</sub>  | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 5(100/0)                            |
| 7     | NiCl <sub>2</sub> (dppe)                                     | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 22 (100/0)                          |
| 8     | NiCl <sub>2</sub> (dppf)                                     | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 25 (100/0)                          |
| 10    | NiCl <sub>2</sub> (dppp)                                     | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 31(100/0)                           |
| 11    | NiBr <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>           | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 34 (96/4)                           |
| 12    | NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>           | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 98 (100/0)                          |
| 13    | NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (5 mol%)  | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 100 (99/1)                          |
| 14    | NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (1 mol%)  | 1.5         | K <sub>3</sub> PO <sub>4</sub>  | 65 (100/0)                          |
| 15    | NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (5 mol %) | 1.5         | none                            | 0                                   |
| 16    | NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (5 mol %) | 1.5         | Na <sub>2</sub> CO <sub>3</sub> | trace                               |
| 17    | NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (5 mol %) | 1.5         | Cs <sub>2</sub> CO <sub>3</sub> | 22                                  |
| 18    | NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (5 mol %) | 1.5         | <i>t</i> -BuOK                  | 27(100/0)                           |
| 19    | NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (5 mol %) | 1.0         | K <sub>3</sub> PO <sub>4</sub>  | 76(100/0)                           |
| 20    | NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (5 mol %) | 2.0         | K <sub>3</sub> PO <sub>4</sub>  | 82(100/0)                           |

<sup>a</sup>Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), base (1.0 mmol), toluene (1 mL), 120 °C, 24–36 h, Ar. <sup>b</sup>The ratios of *E/Z* isomers in the crude reaction mixture were determined by <sup>19</sup>F NMR or GC. Yields determined by GC analysis and based on **1a**. The configuration of the *Z*-isomer **3aa** (after purification) was determined by its <sup>3</sup>J<sub>H-F</sub> coupling constant in the <sup>1</sup>H NMR spectrum.

2-(2,2-Difluorovinyl)naphthalene was also good substrate for this reaction, the corresponding product **3ia** being obtained in high yield. Unfortunately, when *gem*-difluoroalkenes bearing electron-withdrawing (-CN) groups on the benzene ring were used as substrates, no coupled products were obtained and moderate amounts of side products, fluorovinyl aryl ethers, along with the starting materials were observed<sup>10e</sup>. Both aliphatic difluoroalkene such as 1,1-difluoro-2-benzyl ethylene and heteroaryl difluoroalkene such as 3-(2,2-difluorovinyl)furan were poor substrates and only trace amounts of the expected products were furnished. The presence of halogen atom (Cl or Br) on the benzene ring would afford a mixture of the mono-coupled and di-coupled products because the C–Cl or C–Br bond also involved in the coupling reaction. For example, when 1-chloro-4-(2,2-difluorovinyl)benzene was used as substrate, a mixture of the mono-coupled product, 1-chloro-4-(2-fluoro-2-phenylvinyl)benzene (30%, GC-MS) and di-coupled product, 4-(2-fluoro-2-phenylvinyl)-1,1'-biphenyl (32%, GC-MS), was obtained.

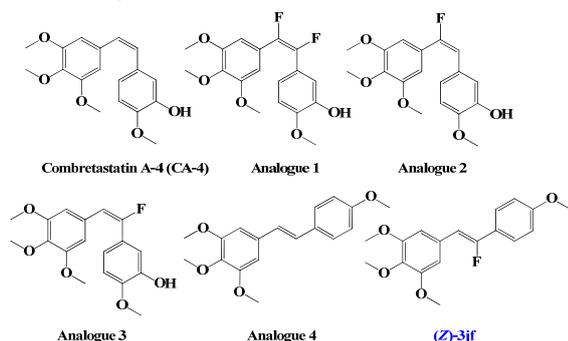
Arylboronic acids containing both electron-donating groups, such as Me and OMe (**2b** and **2f**), and electron-withdrawing groups, such as F and CF<sub>3</sub> (**2c** and **2d**), were well tolerated and the desired products were obtained in moderate to high yields. Arylboronic acid with substituent at *ortho* position in the benzene ring was also coupled smoothly to give the corresponding *Z*-fluorostyrene in high yields (**3ab**). Replacement of arylboronic acid with heteroarylboronic acid would lead to a decrease in yield (**3ae**).

**Table 2** Reactions of various (2,2-difluorovinyl)benzene derivatives **1a–j** with arylboronic acids **2a–f**

<sup>a</sup>Reaction conditions: **1a–j** (1.0 mmol), **2a–f** (1.5 mmol), K<sub>3</sub>PO<sub>4</sub> (2.0 mmol), toluene (2 mL), 100–120 °C, 24–36 h, Ar. <sup>b</sup>Isolated yields. The configuration of the *Z*-isomer **3aa–jf** was determined by its <sup>3</sup>J<sub>H-F</sub> coupling constant in the <sup>1</sup>H NMR spectra (ca. 40.0 Hz for *Z*-isomers and 21.0 Hz for *E*-isomers).

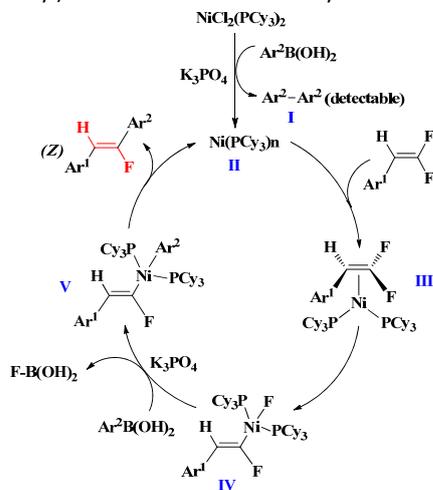
Combretastatin A-4 (CA-4) shows potent cytotoxicity against a wide variety of human cancer cell lines and thus is considered as a lead compound for development of anticancer drugs.<sup>11</sup> Up to now, numerous novel bioactive derivatives of CA-4 have been discovered such as analogues 1–4 (Scheme 2).<sup>12</sup> To demonstrate potential utility of this Ni-catalyzed coupling reaction, we designed and synthesized a fluorinated analogue of Combretastatin A-4, compound (Z)-3jf. The preliminary bioassay results indicated that among the tested target compounds (3aa–jf), only (Z)-3jf displayed potent cytotoxic activity ( $IC_{50}$ =736.2 ng/mL) against human cancer MCF-7 cells. Although the activity of compound (Z)-3jf is relatively weaker than that of Combretastatin A-4 ( $IC_{50}$ =74.8 ng/mL), this compound deserves further evaluation of cytotoxicity assay.

**Scheme 2** Analogues of Combretastatin A-4



According to literature reports,<sup>5b, 13</sup> a plausible reaction mechanism is depicted in Scheme 3. With the assistance of  $K_3PO_4$  and  $Ar^2B(OH)_2$ ,  $NiCl_2(PCy_3)_2$ , which is considered as an efficient catalyst precursor for the Suzuki reaction,<sup>14</sup> was reduced to the catalytic active species  $Ni(PCy_3)_n$  II. The Ni(0)-catalyzed coupling reaction involved in the following three steps: the oxidative addition of *gem*-difluoroalkenes to generate IV, transmetalation of  $Ar^2B(OH)_2$  and reductive elimination of the Ni complex V. This Z-selectivity in the formation of fluorostyrenes might be ascribed to the fact that the Ni complex IV seems to be generated predominantly because of steric repulsion between aryl group ( $Ar^1$ ) and phosphine ligand.

**Scheme 3.** The proposed mechanism for Ni-catalyzed reaction of (2,2-difluorovinyl)benzene derivative with arylboronic acid



In summary, we have developed an efficient synthesis of Z-fluorostyrene derivatives via a Suzuki-Miyaura type reaction of (2,2-difluorovinyl)benzene derivative with arylboronic acid in the presence of 5 mol%  $NiCl_2(PCy_3)_2$  and  $K_3PO_4$ . The use of nickel catalyst is essential for the activation of the carbon–fluorine bond and a selective C–F monofunctionalization reaction was achieved. This work significantly expands the substrate scopes of Suzuki-Miyaura cross-coupling reactions. Further study to apply this transformation is under way.

## Acknowledgements

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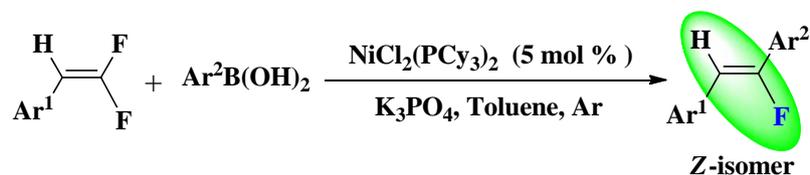
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### Graphical abstract:



An unprecedented highly stereoselective example of nickel-catalyzed Suzuki–Miyaura type cross-coupling reactions of (2,2-difluorovinyl)benzene derivatives with arylboronic acids was developed.