Highly Efficient Synthesis of 2-Aryl-3-methoxyacrylates *via* Suzuki-Miyaura Coupling Reaction[†]

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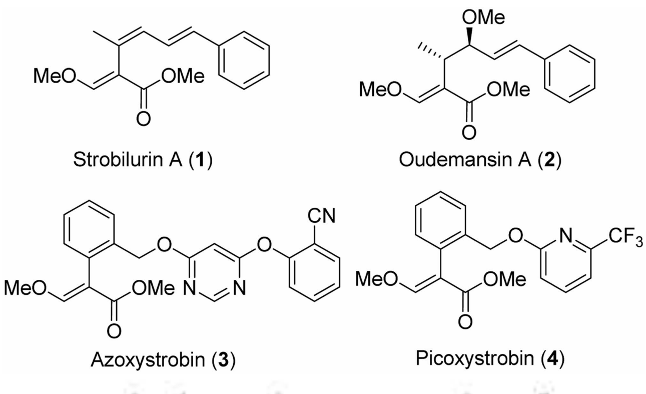
The Suzuki-Miyaura coupling reaction provides a convenient access to the carbon-carbon bond formation with high efficiency.[1] Recently, a number of 2-aryl-3-methoxyacrylates served as a key scaffold for the development of biologically active pharmaceuticals[2] and agrochemicals[3] (Figure 1). Especially, the discovery of the naturally-occurring fungicides, such as strobilurin A (**1**) and oudemansin A (**2**), possessing a β-methoxyacrylate moiety was immediately seized great attention by industrial research groups to open a new era of the strobilurin family including azoxystrobin (**3**)[4] and picoxystrobin (**4**).[5]

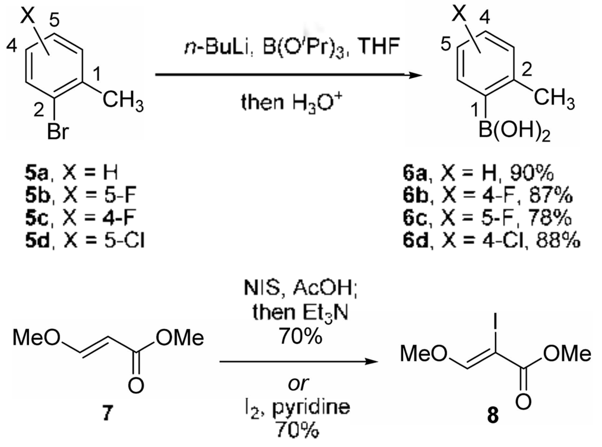
Although a plethora of methods has been established on the development of the Suzuki-Miyaura reaction of aryl (including heteroaryl) halides or triflates, the cross-coupling reaction of vinyl halides, in particular of α-halo-β-methoxyacrylate,[6] remains an attractive area for investigation. In the event, we envisioned a systematic study of this type of the reaction with various halo-substituted arylboronic acids.

The required arylboronic acids **6a-d** were easily prepared by following the literature method,[7] in which selective lithium-bromide exchange followed by in situ quenching with borate offered a high yielding procedure (Scheme 1). Next, α-iodo-β-methoxyacrylate **8** was conveniently synthesized via sequential iodonation and base-mediated elimination reactions of the corresponding β-methoxyacrylate 7.[8] Alternatively, **8** was also prepared *via* an in situ method using iodine in pyridine without loss of yields.[9]



Strobilurin A (**1**) Oudemansin A (**2**)
Azoxystrobin (**3**) Picoxystrobin (**4**)

Figure 1. Biologically active molecules having a β-methoxyacrylate moiety.



Scheme 1

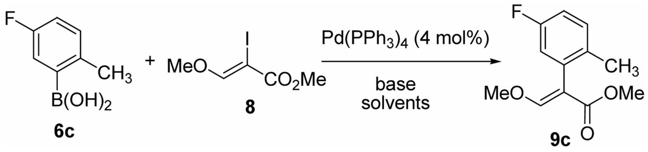
Subsequently, we examined the Suzuki-Miyaura reaction of α-iodo-β-methoxyacrylate **8** with 5-fluoro-2-methylphenylboronic acid **6c** in the presence of a suitable palladium catalyst. As illustrated in Table 1, our initial attempt was focused on the use of $Pd(PPh_3)_4$ (4 mol%) in combination with Na_2CO_3 (2.0 equiv) in DMF/H_2O at 70 °C for 20 h (entry 1). This reaction provided 2-(5-fluoro-2-methylphenyl)-3-methoxyacrylate **9c** in 22% yield. As a next step, we screened a range of co-solvent systems such as toluene/$EtOH/H_2O$, THF/H_2O and dioxane/H_2O to find out the solvent effects (entries 2-4).[10] The results obtained from reactions using the co-solvents system other than dioxane/H_2O turned out to be inferior. When a base was changed from Na_2CO_3 to K_2CO_3, the reaction yield was slightly increased (entry 3). Meanwhile, the use of K_3PO_4 in combination with a THF/H_2O system remarkably improved the reaction yield up to 86% in a shortened reaction period (entry 4). Finally, we were delighted to find the optimum conditions using K_3PO_4 in dioxane/H_2O to furnish **9c** in 96% yield (entry 5).

Using the optimized reaction conditions (Table 1, entry 5), we performed the Suzuki-Miyaura reaction of α-iodo-β-methoxyacrylate **8** with a variety of halo-substituted phenylboronic acids **6a-d**. As illustrated in Table 2, we obtained the coupling products **9a-d** in excellent yields.[11]

With the successful demonstration of Suzuki-Miyaura reaction for the synthesis of 2-aryl-3-methoxyacrylates **9**, we further explored the preparation of biologically interesting molecules. Therefore, we attempted transformation of **9d**

[†] Dedicated to Prof. Bong Young Chung on the occasion of his 61st birthday.

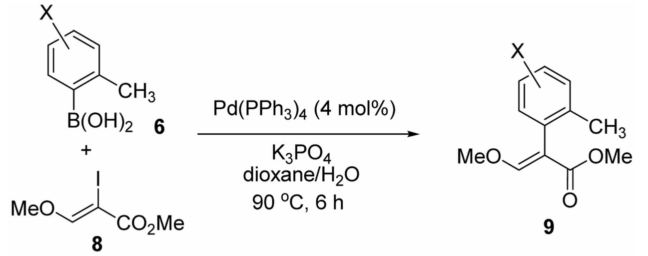
Table 1. Suzuki-Miyaura reaction of α-iodo-β-methoxyacrylate **8** with 5-fluoro-2-methylphenylboronic acid **6c**^{a}



entry	base	solvents	temp.	time	yield (%)^b
1	Na_2CO_3 (5 equiv)	DMF/H_2O	70 °C	20 h	22
2	Na_2CO_3 (2 equiv)	toluene/EtOH/H_2O	80 °C	5 h	41
3	K_2CO_3 (3 equiv)	toluene/EtOH/H_2O	80 °C	18 h	58
4	K_3PO_4 (3 equiv)	THF/H_2O	80 °C	8 h	86
5	K_3PO_4 (3 equiv)	dioxane/H_2O	90 °C	6 h	96

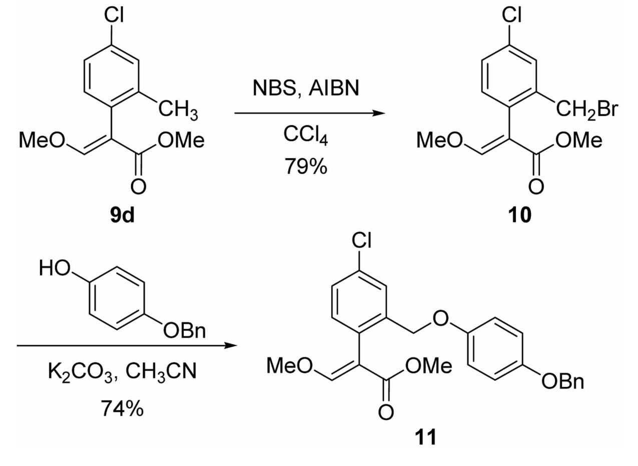
^{a}Reaction conditions: **8** (1 mmol), boronic acid **6c** (1.2 mmol), $Pd(PPh_3)_4$ (4 mol%), base, co-solvents (toluene/EtOH/H_2O = 4 mL/1 mL/2 mL; DMF/H_2O = THF/H_2O = dioxane/H_2O = 5 mL/1 mL). ^{b}Isolated yield.

Table 2. Suzuki-Miyaura reaction of α-iodo-β-methoxyacrylate **8** with arylboronic acids **6**^{a}



entry	boronic acid	product	yield (%)^b
1	X = H, **6a**	**9a**	85
2	X = 4-F, **6b**	**9b**	81
3	X = 5-F, **6c**	**9c**	96
4	X = 4-Cl, **6d**	**9d**	91

^{a}Reaction conditions: **8** (1 mmol), **6** (1.2 mmol), $Pd(PPh_3)_4$ (4 mol%), K_3PO_4 (3.0 mmol), dioxane/H_2O (5 mL/1 mL), 90 °C, 6 h. ^{b}Isolated yield.



Scheme 2

with N-bromosuccinimide (NBS) to obtain benzyl bromide **10** in 79% yield (Scheme 2).[5] Then, **10** was coupled with 4-benzyloxyphenol in the presence of K_2CO_3 to furnish aryl benzyl ether **11** in good yield.

In conclusion, we have developed a highly efficient and convergent synthesis of 2-aryl-3-methoxyacrylates via the Suzuki-Miyaura coupling reaction of α-iodo-β-methoxyacrylate **8** with arylboronic acids **6**. The biological activities of 2-aryl-3-methoxyacrylate derivatives will be reported in due course.

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11. ***General procedure***. To a flask was added α-iodo-β-methoxyacrylate **8** (1 mmol), $Pd(PPh_3)_4$ (4 mol%), arylboronic acid **6** (1.2 mmol), and K_3PO_4 (3.0 mmol) sequentially. The mixture was dissolved in dioxane/H_2O (5 mL/1 mL) and degassed with argon over 5 min. Then, the reaction mixture was stirred at 90 °C for 6 h. After cooled to rt, the mixture was diluted with EtOAc and washed with H_2O and brine solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* and the residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes). Data for **9d**: mp 65-72 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.21 (d, 1H, J = 5.1 Hz, 3.6 Hz), 7.15 (dd, 1H, J = 4.9 Hz, 1.3 Hz), 7.03 (d, 1H, J – 4.9 Hz), 3.83 (s, 3H), 3.70 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 160.1, 139.5, 133.5, 132.1, 130.9, 130.0, 125.8, 110.4, 62.2, 51.9, 19.8; MS (EI) m/z M^+ for $C_{12}H_{13}ClO_3$ calc. 240.055, found 241.95 (14), 239.95 (M^+, 42), 207.94 (41), 148.95 (41), 129.01 (45), 115.01 (38), 103.01 (43), 75.01 (100).