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Site-selective Suzuki–Miyaura reactions of 2,3-dibromo-1*H*-inden-1-one

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ABSTRACT

The first transition metal-catalyzed cross-coupling reactions of 2,3-dibromo-1*H*-inden-1-one are reported. The Suzuki–Miyaura reaction of 2,3-dibromo-1*H*-inden-1-one with 2 equiv of arylboronic acid gave 2,3-diaryl-1*H*-inden-1-ones. The reaction with 1 equiv of arylboronic acid gave 2-bromo-3-aryl-1*H*-inden-1-ones with very good site-selectivity. The one-pot reaction of 2,3-dibromo-1*H*-inden-1-one with two different arylboronic acids afforded 2,3-diaryl-1*H*-inden-1-ones containing two different terminal aryl groups.

2,3-Diaryl-1*H*-inden-1-ones are of considerable pharmacological relevance.[1] Classic syntheses of these molecules rely on intramolecular Friedel–Crafts acylation reactions,[2] on the reaction of 3-(*p*-methoxybenzyl)phthalide with phenylmagnesium bromide and subsequent rearrangement,[3] and on the reaction of 2-phenyl-1*H*-inden-1,3(2*H*)-dione with phenylmagnesium bromide and subsequent extrusion of water.[4] 2,3-Diaryl-1*H*-inden-1-ones have also been prepared from dibenzoylmethane[5] and benzophenone derivatives.[6] Recent transition metal-catalyzed syntheses of 2,3-diaryl-1*H*-inden-1-ones include the reaction of 1-methoxy-4-(4′-methoxyphenylethynyl)-benzene with 2-bromobenzaldehyde[7] and the reaction of diphenyl acetylene with 2-bromobenzeneboronic acid.[8]

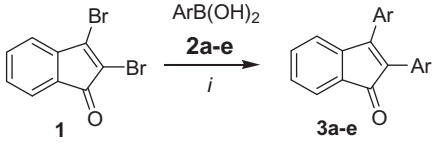
In recent years, a number of site-selective palladium(0)-catalyzed cross-coupling reactions of polyhalogenated heterocycles have been developed. The site-selectivity of these reactions is generally influenced by electronic and steric parameters.[9] We have reported site-selective Suzuki–Miyaura (S–M) reactions of tetrabrominated thiophene, *N*-methylpyrrole, selenophene, and of other polyhalogenated arenes and heteroarenes.[10]

Bellina and Sulikowski and their co-workers reported site-selective transition metal-catalyzed reactions of several dibromofuranones.[11] It occurred to us that 2,3-dibromo-1*H*-inden-1-one might be a suitable starting material for the synthesis of 2,3-diaryl-1*H*-inden-1-ones. The reactions of 2,3-dibromo-1*H*-inden-1-one with amines and C-nucleophiles, such as Grignard reagents, ethyl cyanoacetate, and ethyl acetoacetate, are known for a long time.[12] Surprisingly, transition metal-catalyzed cross-coupling reactions of 2,3-dibromo-1*H*-inden-1-one have, to the best of our knowledge, not been reported to date. Herein, we report the synthesis of 2,3-diaryl-1*H*-inden-1-ones by site-selective S–M reactions of 2,3-dibromo-1*H*-inden-1-one. The products are not readily available by other methods.

The S–M reaction of 2,3-dibromo-1*H*-inden-1-one (**1**)[13] with 2 equiv of arylboronic acids **2a–e** gave the 2,3-diaryl-1*H*-inden-1-ones 3a–**e** in excellent yields (Scheme 1, Table 1).

The best yields were obtained using 2.2 equiv of the arylboronic acid, $Pd(PPh_3)_4$ (5 mol %) as the catalyst, and K_2CO_3 (2 M aqueous solution) as the base (1,4-dioxane, 70 °C, 6 h).[14,15] The employment of $Pd(PPh_3)_2Cl_2$ proved to be less efficient in terms of yield. The reactions could be successfully carried out with both electron-rich and electron-poor arylboronic acids.

The S–M reaction of **1** with arylboronic acids **2a–c,f,g** (1.0 equiv) afforded the 3-aryl-2-bromo-1*H*-inden-1-ones **4a–e** in excellent yields and with very good site-selectivity (Scheme 2, Tables 2 and 3).[14,16] The first attack occurred at position 3 of **1**. During the optimization (Table 3), carried out for derivatives **4b**



Scheme 1. Synthesis of **3a–e**. Reagents and conditions: (i) **3a–e** (2.2 equiv), $Pd(PPh_3)_4$ (5 mol %), 2 M K_2CO_3 (aq), dioxane, 70 °C, 6 h.

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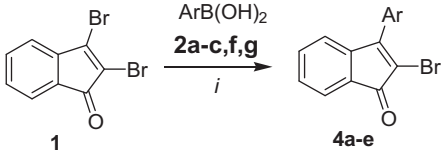
Table 1
Synthesis of **3a–e**

2,3	Ar	% (**3**)[a]
a	4-MeC_6H_4	100
b	4-FC_6H_4	95
c	3-$(MeO)C_6H_4$	98
d	C_6H_5	97
e	4-ClC_6H_4	93

[a] Yield of isolated products.



Scheme 2. Synthesis of **4a–e**. Reagents and conditions: (i) **2a–c**,**f**,**g** (1.0 equiv), $Pd(PPh_3)_4$ (3 mol %), 2 M K_2CO_3 (aq), dioxane, 45 °C, 4 h.

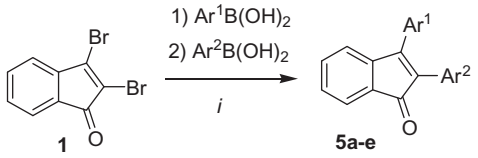
Table 2
Synthesis of 3-aryl-2-bromoinden-1-ones **4a–e**

2	4	Ar	% (**4**)[a]
a	**a**	4-MeC_6H_4	98
b	**b**	4-FC_6H_4	83
f	**c**	2,6-$(MeO)_2C_6H_3$	83[b]
g	**d**	3,5-$Me_2C_6H_3$	88
c	**e**	3-$(MeO)C_6H_4$	95[b]

[a] Yields of isolated products.
[b] Reaction temperature: 40 °C, the other reactions were carried out at 45 °C.

and **4e**, it proved to be very important to use exactly 1.0 equiv of the arylboronic acid and $Pd(PPh_3)_4$ (3 mol %) as the catalyst. The employment of $Pd(PPh_3)_2Cl_2$ resulted in a significant decrease of the yield and of the site-selectivity. The temperature played an important role. A good selectivity was achieved only when the reaction was carried out at 45 °C for **4b** (derived from the less reactive, electron poor arylboronic acid **2b**) or at 40 °C for **4e** (derived from the electron rich arylboronic acid **2c**) because the second cross-coupling was slow at this temperature. The formation of a mixture of starting material, mono- and di-substituted products was generally observed when the reaction was carried out at temperatures between 45 and 70 °C. In the case of highly reactive methoxy-substituted arylboronic acids (**2f,c**), the temperature had to be further decreased to 40 °C to achieve a good site-selectivity. The reactions were successful for both electron-rich and electron-poor arylboronic acids.

The one-pot reaction of **1** with two different arylboronic acids, which were sequentially added, afforded the unsymmetrical 2,3-diaryl-1*H*-inden-1-ones **5a–e** containing two different terminal aryl groups (Scheme 3, Table 4).[17,18] During the optimization, it



Scheme 3. Synthesis of **5a–e**. Reagents and conditions: (i) (1) $Ar^1B(OH)_2$ **2a**,**f**,**j** (1.0 equiv), $Pd(PPh_3)_4$ (3 mol %), 2 M K_2CO_3 (aq), dioxane, 45 °C, 4 h; (2) $Ar^2B(OH)_2$ **2b**,**f**,**h**,**i** (1.1 equiv), $Pd(PPh_3)_4$ (3 mol %), 70 °C, 6 h.

Table 4
Synthesis of **5a–e**

2	5	Ar^1	Ar^2	% (**5**)[a]
a,**h**	**a**	4-MeC_6H_4	4-$(MeO)C_6H_4$	93
a,**i**	**b**	4-MeC_6H_4	3-ClC_6H_4	89
f,**b**	**c**	2,6-$(MeO)_2C_6H_3$	4-FC_6H_4	86[b]
j,**h**	**d**	2-$(MeO)C_6H_4$	4-$(MeO)C_6H_4$	87[b]
a,**f**	**e**	4-MeC_6H_4	2,6-$(MeO)_2C_6H_3$	90

[a] Yields of isolated products.
[b] Reaction temperature: 40 °C.

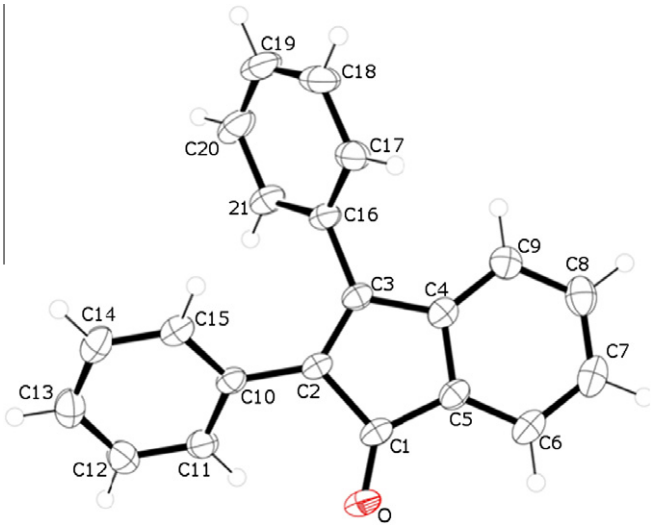


Figure 1. Crystal structure of **3d**.

proved to be important that the first step was carried out at 45 °C (or at 40 °C in case of **2f**,**j**) to achieve a good site-selectivity in favor of position 3 of the substrate. The second step had to be carried out at 70 °C to guarantee a complete reaction of position 2. All reactions proceeded in excellent yields. It was important to add the catalyst again when the second boronic acid was added. Otherwise, the yields decreased, more products are formed, and the products could not be isolated in pure form.

Table 3
Optimization of the synthesis of **4b** and **4e**

Entry	Conditions	*T* (°C)	%[a] (**4b**+**3b**)	%[a] (**4e**+**3c**)
1	$Pd(PPh_3)_2Cl_2$ (3 mol %), 2 M K_2CO_3 (aq.)	45	55+0	36+9
2	$Pd(PPh_3)_2Cl_2$ (3 mol %), K_3PO_4	45	47+0	51+10
3	$Pd(PPh_3)_4$ (3 mol %), 2 M K_2CO_3 (aq.)	20	Traces+0[b]	13+0[b]
4	$Pd(PPh_3)_4$ (3 mol %), 2 M K_2CO_3 (aq)	40	67+0[b]	95+0
5	$Pd(PPh_3)_4$ (3 mol %), 2 M K_2CO_3 (aq)	45	83+0	22+29[b]
6	$Pd(PPh_3)_4$ (3 mol %), 2 M K_2CO_3 (aq)	60	28+25[b]	19+39[b]

[a] Yields of isolated products.
[b] no complete conversion.

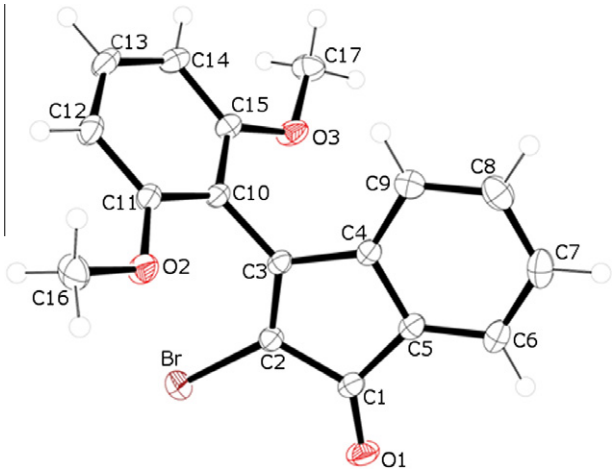
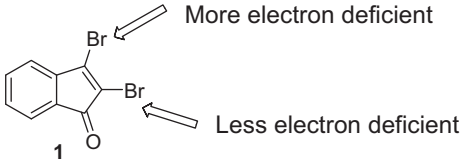


Figure 2. Crystal structure of **4c**.



Scheme 4. Possible explanation for the site-selectivity of cross-coupling reactions of **1**.

The structures of the products were established by 2D NMR experiments (NOESY, HMBC). The structures of **3d** and **4c** were independently confirmed by X-ray crystal structure analyses (Figs. 1 and 2).[19]

The site-selective formation of **4a–e** and **5a–e** can be explained by electronic reasons (Scheme 4). The first attack of palladium(0) catalyzed cross-coupling reactions generally occurs at the more electron deficient and sterically less hindered position.[9,20] Position 3 of 2,3-dibromo-1*H*-inden-1-one (**1**) is considerably more electron-deficient than position 2. Handy and Zhang reported a simple guide for the prediction of the site-selectivity of palladium(0) catalyzed cross-coupling reactions of polyhalogenated substrates based on the ^{1}H NMR chemical shift values of the non-halogenated analogs.[20] In fact, the ^{1}H NMR signal of proton H-3 of inden-1-one is shifted downfield compared to proton H-2.

In conclusion, we have reported site-selective Suzuki–Miyaura reactions of 2,3-dibromo-1*H*-inden-1-one which provide a convenient and site-selective approach to 2,3-diaryl-1*H*-inden-1-ones and 3-aryl-2-bromo-1*H*-inden-1-ones. The scope and applications of the methodology outlined herein is currently under investigation in our laboratories.

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14. *General procedure for the synthesis of* **3a–e** *and* **4a–e**: The reaction was carried out in a pressure tube. To a suspension of **1** (144 mg, 0.5 mmol), $Pd(PPh_3)_4$ (2.5–3.0 mol % per cross-coupling), and boronic acid **2** (0.5–0.55 mmol per cross-coupling) in dioxane (5 mL) was added a 2 M solution of K_2CO_3 (aq) (1 mL). The mixture was heated at the indicated temperature (40–70 °C) under Argon atmosphere for 4–6 h. The reaction was diluted with water and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, EtOAc/heptanes).
15. *2,3-Diphenyl-1H-inden-1-one (***3d***).* Starting with **1** (144 mg, 0.5 mmol) and phenylboronic acid (135 mg, 1.1 mmol), **3d** was isolated as a colorless solid (137 mg, 97%). Reaction temperature: 70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04–7.07 (m, 1H, ArH), 7.16–7.22 (m, 6H, ArH), 7.30–7.34 (m, 6H, ArH), 7.45–7.51 (m, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 121.3, 123.0, 127.7, 128.1, 128.5, 128.8, 129.0, 129.3, 130.0 (CH), 130.8, 132.4, 132.7 (C), 133.4 (CH), 145.2, 155.3 (C), 196.0 (CO). IR (KBr): ν = 3380, 3070 (w), 1700, 1604, 1455, 1444, 1348, 1178, 1157, 1149, 1081, 1065 (m), 1027, 1010, 999, 929, 918, 858, 840, 807 (w), 780, 760, 751, 723, 699, 675 (s), 637, 612, 587, 549 (s), 1205, 1183, 1156, 1065, 1042 (m), 818, 742, 701 (s), 617, 610, 587, 562, 537 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 282 ([M]$^+$, 100), 265 (16), 252 (47), 239 (03), 176 (06), 126 (12). HRMS (EI, 70 eV): calcd for $C_{21}H_{14}O$ [M]$^+$: 282.10392; found: 282.10341.
16. *2-Bromo-3-(2,6-dimethoxyphenyl)-1H-inden-1-one (***4c***).* Starting with **1** (144 mg, 0.5 mmol), $Pd(PPh_3)_4$ (18 mg, 3 mol %) and 2,6-dimethoxyphenylboronic acid (91 mg, 0.5 mmol), **4c** was isolated as a colorless crystalline solid (143 mg, 83%). Reaction temperature: 40 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.71 (s, 6H, $2OCH_3$), 6.58–6.68 (m, 3H, ArH), 7.05–7.18 (m, 2H, ArH), 7.22–7.34 (m, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 54.8 (OCH_3), 103.0 (CH), 107.8 (C), 120.1 (CH), 120.6 (C), 121.8, 127.1 (CH), 128.3 (C), 129.8, 132.7 (CH), 144.3, 153.3, 156.7 (C), 189.1 (CO). IR (KBr): ν = 3009, 2965, 2934, 2836 (w), 1729, 1594, 1583, 1470, 1457, 1441, 1423 (s), 1358, 1300 (w), 1290 (m), 1249 (s), 1189, 1169, 1151 (w), 1101, 1078, 1028 (s), 952, 942, 918, 903, 873, 845 (w), 817, 800, 771, 756, 729, 721 (m), 703 (s), 667, 650, 633, 614, 595, 577, 544 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 344 ([M]$^+$, ^{79}Br, 43), 265 (13), 250 (100), 234 (16), 207 (14), 165 (14). HRMS (EI, 70 eV): calcd for $C_{17}H_{13}O_3{}^{79}Br$ [M]$^+$: 344.00481; found: 344.00480.
17. *General procedure for the one-pot synthesis of* **5a–e**: The reaction was carried out in a pressure tube. To a suspension of **1** (288 mg, 1.0 mmol), $Pd(PPh_3)_4$ (35 mg, 3 mol %), and $Ar^1B(OH)_2$ (1.0 mmol) in dioxane (5 mL) was added a 2 M solution of K_2CO_3 (aq) (1 mL). The mixture was heated at 40–45 °C under Argon atmosphere for 6 h. The reaction mixture was cooled to 20 °C and $Ar^2B(OH)_2$ (1.1 mmol) and an additional amount of $Pd(PPh_3)_4$ (35 mg, 3 mol %) was added. The reaction mixture was heated under Argon atmosphere for 6 h at 70 °C. After cooling to 20 °C, the mixture was diluted with water and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptanes).
18. *2-(4-Methoxyphenyl)-3-(p-tolyl)-1H-inden-1-one (***5a***).* Starting with **1** (288 mg, 1.0 mmol), *p*-tolylboronic acid (136 mg, 1.0 mmol), and 4-methoxyphenylboronic acid (167 mg, 1.1 mmol), **5a** was isolated as a colorless crystalline solid (303 mg, 93%). Reaction temperature: 45 °C (first step), 70 °C (second step). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.81 (d, *J* = 8.5 Hz, 2H, ArH), 7.12–7.21 (m, 1H), ArH), 7.14–7.28 (m, 8H, ArH), 7.52–57 (m, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.5 (CH_3),

55.2 (OCH_3), 113.6, 121.0, 127.7 (CH), 123.3 (C), 128.5, 128.6, 129.5 (CH), 130.0, 130.9 (C), 131.3 (CH), 131.6 (C) 133.3 (CH), 139.3, 145.6, 154.0, 159.1 (C), 197.0 (CO). IR (KBr): ν = 3031, 2997, 2917, 2832 (w), 1606, 1591, 1574, 1511, 1484 (m), 1451 (s), 1426, 1369, 1314, 1282 (m), 1246, 1234 (s), 1205, 1183, 1156, 1065, 1042 (m), 818, 742, 701 (s), 617, 610, 587, 562, 537 (w) cm^{-1}. GC–MS (EI, 70 eV): m/z (%) = 326 ($[M]^+$, 100), 311 (20), 268 (11), 239 (19), 163 (06). HRMS (EI, 70 eV): calcd for $C_{23}H_{18}O_2$ $[M]^+$: 326.13019; found: 326.13013.

19. CCDC 797044 (**3d**) and 797045 (**4c**) contain all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223 336 033; or deposit@ccdc.cam.ac.uk.
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