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Palladium-Catalyzed Direct Arylation of 2,6-Disubstituted Imidazo[2,1-*b*][1,3,4]thiadiazoles

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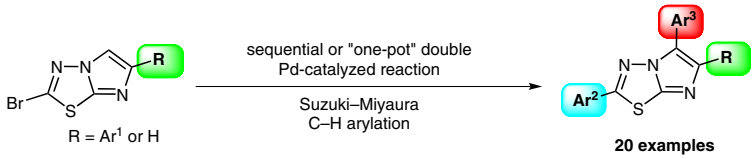

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Abstract This work reports the original synthesis of trisarylimidazo[2,1-*b*][1,3,4]thiadiazole derivatives using a C–H arylation process. The scope of the reaction demonstrated the critical importance of the electronic effects of each substituent on the efficiency of the reaction. In addition, a double efficient 'one-pot' functionalization at the C-2 and then at the C-5 positions of 2-bromo-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole derivatives was achieved using a sequential Suzuki–Miyaura–C–H arylation cascade procedure.

Key words imidazothiadiazole, Suzuki–Miyaura, palladium, C–H arylation, cross-coupling

Among the wide variety of synthetic methods used for heterocyclic functionalization, direct C–H and Suzuki palladium-catalyzed arylations are recognized as the most efficient strategies and have been well described over the past years.[1] The main advantage of these methodologies is that they avoid tedious reagent preparation, as compared to Stille or Negishi cross-couplings, that require the preparation of stannyl or organozinc derivatives.[2] Nevertheless, the latter methods remain crucial in C–C bond formation, for which other solutions have proved to be less efficient.

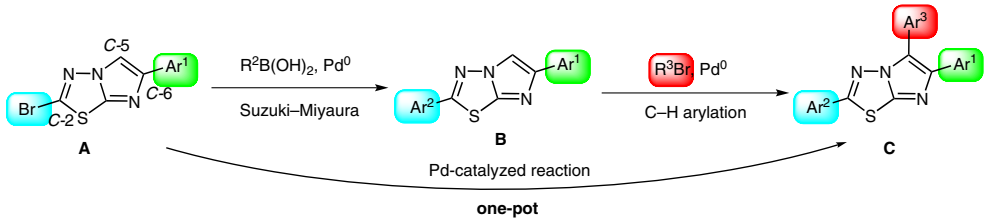
The direct C–H activation mode presents several advantages over Suzuki arylation. In view of the widespread interest in the synthesis of bioactive molecules and organic materials, the rapidity and easy access to reagents of this straightforward method heighten its usefulness. This cross-coupling has been efficiently carried out in many heterocyclic series leading to a versatile method compatible with thiophene, furan, imidazole, indole, pyrrole, pyrazole, imidazo[1,2-*a*]pyrimidine, indolizine, and oxazolo[4,5-*b*]pyridine skeletons.[3]

Our group is interested in the discovery and the functionalization of rare heterocyclic systems and was the first to develop C–H arylation at the C-2 indole position in order to build polycyclic indolocarbazole-like bioactive molecules.[4] More recently, we have built several fused bicyclic five-membered heterocycles and investigated their potency toward organometallic-mediated reactions as well as toward C–H arylations.[5]

The current focus of our research is on the imidazothiadiazole series due to the lack of versatile methods to obtain and functionalize them as well as the structure of the imidazo[2,1-*b*][1,3,4]thiadiazole core.[6] This series is of great interest in pharmaceutical chemistry and in the design of anticancer,[7] antitubercular,[8] and analgesic agents.[9] This prompted us to explore a palladium-catalyzed reaction toward C–H arylation in the 5,5-fused bicyclic series.[10]

There has been much interest in developing efficient synthetic methodologies to design poly- and regioselectively substituted imidazo[2,1-*b*][1,3,4]thiadiazoles.[11] Recently, we disclosed a method for the amidification and Suzuki–Miyaura cross-coupling of 2-bromo-imidazo[2,1-*b*][1,3,4]-thiadiazole derivatives **A**.[10] We report herein the use of direct arylation to functionalize 2,6-bisarylimidazo[2,1-*b*]-[1,3,4]thiadiazoles **B** at the C-5 position using aryl bromides. We also present an unprecedented synthesis of 2,5,6-trisaryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **C** using a 'one-pot' microwave-assisted Suzuki cross-coupling–C–H arylation process (Scheme 1).

To explore the reactivity of 2,6-bis-substituted imidazo[2,1-*b*][1,3,4]thiadiazole **B** under C–H activation conditions, a set of reactions involving **1** with bromobenzene as coupling partner was examined. $Pd_2(dba)_3$ or $Pd(ddpf)Cl_2$ were first used as palladium sources, Cs_2CO_3 as inorganic base, and dioxane at 150 °C under microwave irradiation; but only starting materials were recovered (Table 1, entries 1 and 2). A switch to $Pd(OAc)_2$ with an aliphatic phosphine



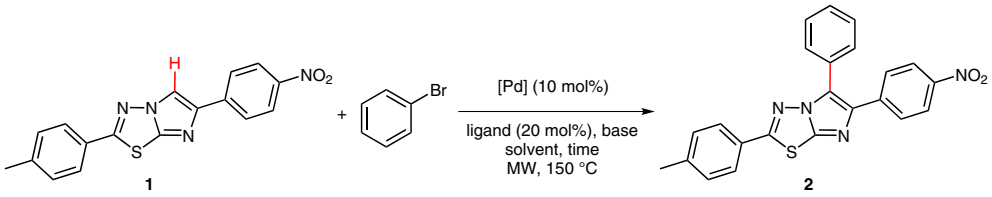
Scheme 1 Synthesis of tris-substituted imidazo[2,1-*b*][1,3,4]thiadiazoles

as ligand led to a very low but encouraging amount of product **2** (^{1}H NMR analysis of crude material showed the presence of **2** in approximately 10% yield, Table 1, entry 3). Using an aromatic phosphine, the desired compound **2** was formed in higher yield, but contaminated by residual starting material **1** (Table 1, entries 4 and 5) after each attempt at purification. To circumvent this problem we decided to find conditions leading to a complete conversion of **1**. With a bidentate palladium complex formed *in situ* using $Pd(OAc)_2$ (10 mol%) and Xantphos (20 mol%), the reaction was complete in one hour. Easier purification and the absence of byproducts led to the desired product **2** being isolated in a very good yield of 91% (Table 1, entry 6). Toluene (Table 1, entry 7) could be used instead of dioxane but, with DMF, byproducts appeared and yields of isolated product dramatically decreased. Other parameters, such as the amount of base and reaction time, were screened without any real benefit in conversion or yield.

With these optimized conditions in hand, we next investigated the scope of the reaction using a variety of 2,6-bis-substituted imidazo[2,1-*b*][1,3,4]thiadiazoles with only bromoaryl derivatives, as iodobenzene coupling partners produced no additional benefit (Table 2). DMF or toluene were used as solvents, depending on the solubility of the starting material. We initiated the construction of the tris-aryl library using derivatives of type **B** possessing a tolyl group in the Ar^2 position to prevent any alteration of the results induced by an additional reactive function. Whatever the bromobenzene used, replacing the R moiety nitro group by a strong electron-donating group, such as methoxy, greatly decreased conversion (Table 2, entries 2–4). It also appeared that the electronic depletion induced by R substitution was required to ensure C–H activation. This behavior was demonstrated using 4-nitrobromobenzene as coupling agent, when **8** was isolated in a very good 80% yield (Table 2, entry 6).

The direct arylation of 2,6-bis-substituted imidazo[2,1-*b*][1,3,4]thiadiazole appeared to be more efficient with electron-deficient aryl bromides, and the best results were obtained with a nitro group on R. With this further substitution, the nature of the aryl halide did not influence the conversion rate, and yields of isolated products **8**–**15** always

Table 1 Pd-Catalyzed C-5 Arylation of Imidazo[2,1-*b*][1,3,4]thiadiazoles[a]



Entry	[Pd]	Ligand	Base (equiv)	Solvent	Time (h)	Yield of **2** (%)
1	$Pd_2(dba)_3$	–	Cs_2CO_3 (3.0)	dioxane	1	–
2	$Pd(dppf)Cl_2$	–	Cs_2CO_3 (3.0)	dioxane	1	–
3	$Pd(OAc)_2$	PCy_3	Cs_2CO_3 (3.0)	dioxane	1	10[b]
4	$Pd(OAc)_2$	PPh_3	Cs_2CO_3 (3.0)	dioxane	1	51[b]
5	$Pd(OAc)_2$	P(*o*-tolyl)	Cs_2CO_3 (3.0)	dioxane	1	62[b]
6	$Pd(OAc)_2$	Xantphos	Cs_2CO_3 (3.0)	dioxane	1	100[b] (91[c])
7	$Pd(OAc)_2$	Xantphos	Cs_2CO_3 (3.0)	toluene	1	100[b] (80[c])
8	$Pd(OAc)_2$	Xantphos	Cs_2CO_3 (3.0)	DMF	1	89[b] (31[c])

[a] Reaction conditions: **1** (0.24 mmol), bromobenzene (1.5 equiv), [Pd] (10 mol%), ligand (20 mol%), base (3.0 equiv), and solvent (3 mL) at 150 °C under argon.
[b] Amount of **2** was estimated by ^{1}H NMR spectroscopy.
[c] Yields are given for isolated products.

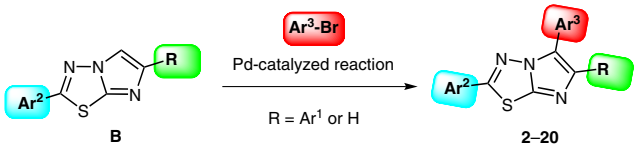
reached or exceeded 78% (Table 2, entries 6–14). Additionally the three *o*-, *m*-, or *p*-benzaldehyde substrates underwent a similar arylation reaction, indicating the negligible effect of steric hindrance (Table 2, entries 8–10).

To check the influence of the aryl group at the C-2 position, we prepared derivatives of type **B** possessing a nitro or a methoxy substituent on Ar^2. When electron-donating groups were positioned both on R and Ar^2, the reaction carried out with deactivated 4-nitrobromobenzene exhibited full C–H arylation efficiency (Table 2, entries 15 and 16). Surprisingly, the introduction of a nitro group on Ar^2 decreased the yields of **18** and **19** (Table 2, entries 17 and 18). This behavior appears mainly to be due to the high insolubility of the corresponding starting material of type **B** in toluene or dioxane. Additionally, further increase in microwave irradiation time led to several unidentified byproducts.

To complete this study, we suppressed the substituent at C-6 (R = H). The reaction was totally regioselective, and the nitrophenyl group was totally introduced at C-5. This C-5 versus C-6 C–H discrimination led to product **20** with an impressive 92% yield (Table 2, entry 20). This high level of selectivity opens novel perspectives that will be validated in due course.

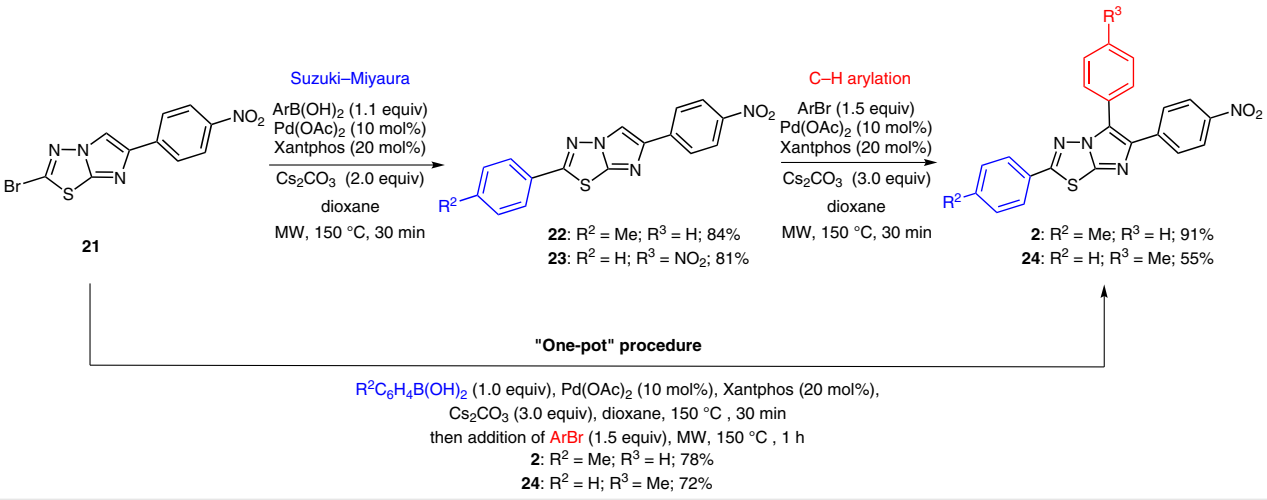
Next, we decided to explore the formation of 2,5,6-trisubstituted arylated imidazo[2,1-*b*][1,3,4]thiadiazoles in a 'one-pot' sequential Suzuki–Miyaura–C–H arylation procedure using synthesized 2-bromo-6-(het)arylimidazo[2,1-*b*][1,3,4]thiadiazoles (Scheme 2). Recently, we reported the synthesis of **22** and **23** via a Suzuki–Miyaura reaction under conditions very similar to those required for the above C-5 heteroarylation,[9] albeit with two differences: first, the activation mode (microwave only for C–H arylation), and second, the nature of the coupling agent, namely a boron derivative for the Suzuki reaction instead of an aryl bromide in the case of C–H arylation.

Table 2 Synthesis of Derivatives **2**–**19**[a]



Entry	R	Ar^2	Ar^3	Solvent	Product	Yield (%)[c]
1	4-$O_2NC_6H_4$	4-MeC_6H_4	Ph	dioxane	**2**	91
2	4-$MeOC_6H_4$	4-MeC_6H_4	Ph	dioxane	**3**	15[b]
3	4-$MeOC_6H_4$	4-MeC_6H_4	4-$MeOC_6H_4$	dioxane	**4**	10[b]
4	4-MeC_6H_4	4-MeC_6H_4	Ph	dioxane	**5**	45[b]
5	4-$O_2NC_6H_4$	4-MeC_6H_4	4-$MeOC_6H_4$	dioxane	**6**	16[b]
6	4-$MeOC_6H_4$	4-MeC_6H_4	4-$O_2NC_6H_4$	toluene	**7**	80
7	4-$O_2NC_6H_4$	4-MeC_6H_4	4-$O_2NC_6H_4$	toluene	**8**	90
8	4-$O_2NC_6H_4$	4-MeC_6H_4	4-$HOCC_6H_4$	toluene	**9**	81
9	4-$O_2NC_6H_4$	4-MeC_6H_4	3-$HOCC_6H_4$	toluene	**10**	79
10	4-$O_2NC_6H_4$	4-MeC_6H_4	2-$HOCC_6H_4$	toluene	**11**	78
11	4-$O_2NC_6H_4$	4-MeC_6H_4	4-FC_6H_4	toluene	**12**	84
12	4-$O_2NC_6H_4$	4-MeC_6H_4	4-NCC_6H_4	toluene	**13**	81
13	4-$O_2NC_6H_4$	4-MeC_6H_4	4-$F_3CC_6H_4$	toluene	**14**	80
14	4-$O_2NC_6H_4$	4-MeC_6H_4	4-$MeOCC_6H_4$	toluene	**15**	78
15	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	toluene	**16**	81
16	4-MeC_6H_4	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	toluene	**17**	81
17	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	toluene	**18**	38
18	4-MeC_6H_4	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	toluene	**19**	38
19	H	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	toluene	**20**	92

[a] Reaction conditions: 2,6-bisarylimidazo[2,1-*b*][1,3,4]thiadiazole **B** (1.0 equiv), bromobenzene (1.5 equiv), $Pd(OAc)_2$ (10 mol%), Xantphos (20 mol%), Cs_2CO_3 (3.0 equiv) in dioxane or toluene (3 mL for 0.24 mmol) at 150 °C for 1 h under argon.
[b] Conversion estimated by ^1H NMR spectroscopy.
[c] Isolated yield.



Scheme 2 Synthesis of of trisarylimidazo[2,1-*b*][1,3,4]thiadiazole by a 'one-pot' procedure

Taking advantage of this similarity, we first synthesized **2** and **24** in 76% and 45% overall yields. Next we tried a one-pot sequential synthesis using Cs_2CO_3 and 10 mol% of $Pd(PPh_3)_4$ and 20 mol% of Xantphos in dioxane at 150 °C. After 30 minutes, reaction was complete (as monitored by TLC) and the bromo-aryl derivative was added. The reaction was stirred at 150 °C for an additional hour. This new strategy gave a slight increase in yield, and **2** was obtained in 78% yield. Concerning compound **24**, this 'one-pot' sequential reaction gave a real benefit as the yield from **24** rose to 72% instead of 45% by the stepwise synthesis. The high potential of the method proved its efficiency and is currently being used in our laboratory in other programs aimed at designing biologically active compounds.

The results achieved in this study enable us to put forward a mechanism for the observed palladium-catalyzed C–H arylation. In the literature, four main pathways involving S_EAr, CMD (concerted metalation–deprotonation), nCMD, and the Heck mechanism, are currently proposed.[10] In order to choose or discard certain possibilities, we first tried to identify the role of the C-5–H bond acidity with a deuterium incorporation experiment.[12] However, the treatment of disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles with KOH in a mixture of dioxane and D_2O did not reveal any exchange in C-5 position. This result was not sufficient to determine the mechanism involved in this direct C–H arylation and therefore to justify the presence of an electron-donating group in C-2 position and the use of an electrophilic palladium complex containing an electron-withdrawing aryl group. On this basis, a plausible mechanism is proposed in Scheme 3; DFT calculations will be needed to draw firm conclusions.

In conclusion, we have reported here the direct arylation of 2,5-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles to obtain a novel class of trisubstituted imidazo[2,1-*b*]-[1,3,4]thiadiazole derivatives.[13,14] Moderate to excellent yields were achieved from readily available aryl bromides, particularly those with an electron-withdrawing substituent. A study to discriminate between the C-5 and C-6 positions was carried out and showed a high selectivity for the C-5 position. Finally, we developed a 'one-pot' Suzuki–Miyaura–C–H arylation procedure at the C-2 and C-5 positions, respectively. This synthetic pathway gave higher yields than a stepwise strategy.

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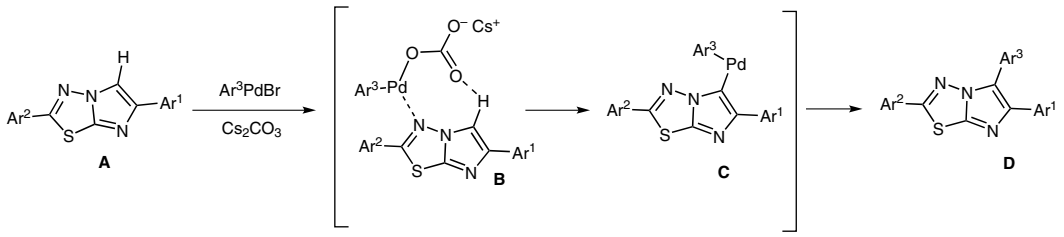

Scheme 3 Proposed mechanism of C–H arylation

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561317.

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(13) **General Procedure**
A solution of 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazole derivative (1.0 equiv), Cs_2CO_3 (3.0 equiv) and (het)aryl bromide (1.5 equiv) in dry 1,4-dioxane or toluene (3 mL for 80 mg) was degassed by argon bubbling for 15 min. Xantphos (0.2 equiv) and $Pd(OAc)_2$ (0.1 equiv) were then added, and the mixture was heated to 150 °C for 60 min under microwave irradiation. After removing the solvent *in vacuo*, the crude product was purified by flash chromatography on silica gel.

(14) **2-(4-Methylphenyl)-5-phenyl-6-(4-nitrophenyl)imidazo-[2,1-*b*][1,3,4]thiadiazole (2)**
The reaction was carried out as described in general procedure using **1** (80 mg, 0.24 mmol, 1.0 equiv) and bromobenzene (37 µL, 0.36 mmol, 1.5 equiv) in dioxane (3 mL). The crude product was purified by flash chromatography on silica gel (PE–CH_2Cl_2, 2:8 to 0:1) to afford **2** as a yellow solid (90 mg, 91%). R_f = 0.36 (PE–CH_2Cl_2, 2:8); mp >260 °C. IR (ATR diamond): ν = 1593, 1505, 1481, 1338, 1324, 1108, 1084, 971, 856, 816, 739, 708, 681 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.7 Hz, 2 H, 2 × H_{Ar}), 7.83 (d, *J* = 8.7 Hz, 2 H, 2 × H_{Ar}), 7.77 (d, *J* = 8.1 Hz, 2 H, 2 × H_{Ar}), 7.65 (dd, *J* = 7.6, 1.5 Hz, 2 H, 2 × H_{Ar}), 7.56–7.44 (m, 3 H, 3 × H_{Ar}), 7.30 (d, *J* = 8.1 Hz, 2 H, 2 × H_{Ar}), 2.46 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.6 (Cq), 146.8 (Cq), 145.3 (Cq), 142.8 (Cq), 141.4 (Cq), 140.0 (Cq), 130.1 (2 × CH_{Ar}), 129.6 (2 × CH_{Ar}), 129.3 (CH_{Ar}), 129.2 (2 × CH_{Ar}), 128.5 (Cq), 128.0 (2 × CH_{Ar}), 127.5 (Cq), 127.0 (2 × CH_{Ar}), 126.0 (Cq), 124.0 (2 × CH_{Ar}), 21.8 (CH_3) ppm. HRMS (EI-MS): *m/z* calcd for $C_{23}H_{16}N_4O_2S$: 413.10667 [M + H]$^+$; found: 413.10692.