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2-Substituted 3-arylindoles through palladium-catalyzed arylative cyclization of 2-alkynyltrifluoroacetanilides with arylboronic acids under oxidative conditions†

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Free NH 2-substituted 3-arylindoles have been prepared usually in good to high yields through the palladium-catalyzed reaction of readily available 2-alkynyltrifluoroacetanilides with arylboronic acids under oxidative conditions. The reaction tolerates a variety of useful functional groups both in the arylboronic acid and in the alkyne, including chloro, formyl, and ester groups.

Enormous interest has been devoted to the synthesis of indole scaffolds. Because of their unique biological and physical properties, which make these target motifs useful for the preparation of pharmaceutical ingredients and innovative materials, this research area is continuously active.[1] In recent years, the focus was on transition metal-catalyzed transformations and particularly on the use of palladium catalysis.[2]

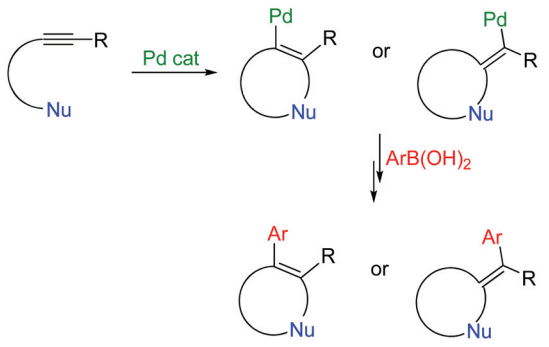
Among them, the palladium-catalyzed reaction of organic electrophiles with 2-alkynyltrifluoroacetanilides has been shown to constitute a versatile tool for the synthesis of 3- and 2,3-disubstituted indoles.[2c,3] A variety of organic electrophiles such as aryl/heteroaryl,[4] alkyl,[5] and alkynyl halides,[6] α-iodoenones,[7] aryl[4d] and vinyl triflates,[4c,e,g] arenediazonium tetrafluoroborates,[8] and allyl esters[9] have been successfully employed.

Organoboron reagents are widely used in carbon–carbon bond forming reactions.[10] Their availability, stability, good functional group tolerance, nontoxicity, and ease of handling make them very attractive aryl and vinyl donors. Nowadays, classical Suzuki cross-coupling reactions of organoboron compounds with aryl or vinyl halides or triflates represent a well established methodology in organic synthesis. In recent years, the palladium-based chemistry of organoboron compounds has been extended to include the oxidative carbonylation to form esters[11] and the reaction with carbon–carbon multiple bonds as coupling partners. In the latter context, the arylation of olefins *via* oxidative Heck reactions has attracted considerable interest.[12] Less attention has been paid to the palladium-catalyzed reaction of organoboron compounds with alkynes. Relatively few papers have shown its potential in the synthesis of polysubstituted olefins *via* hydroarylation[13] and diarylation[14] reactions.

We hypothesized that the palladium-catalyzed reaction of alkynes bearing proximate nucleophiles with boronic acids could provide a new access to functionalized heterocycles *via* a heteroarylation process (Scheme 1).

2-Alkynyltrifluoroacetanilides appeared to us to be particularly attractive substrates to probe the feasibility of this chemistry as in the case of success a new tool for the construction of the functionalized free NH pyrrole nucleus incorporated into the indole system would be available.

We started our study by examining the reaction of 2-phenylethynyltrifluoroacetanile **1a**[9] with 4-methoxyphenylboronic acid **2a** (2 equiv.) in the presence of $Pd(OAc)_2$ (0.05 equiv.), dppp (0.05 equiv.), and K_2CO_3 (2 equiv.) at 80 °C under a balloon of oxygen. The effect of solvents, other phosphine



Scheme 1 Our working hypothesis.

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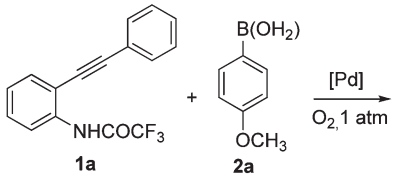
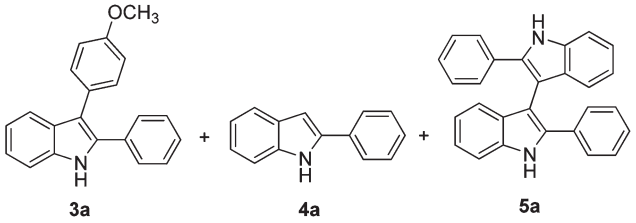
Table 1 Optimization studies[a]

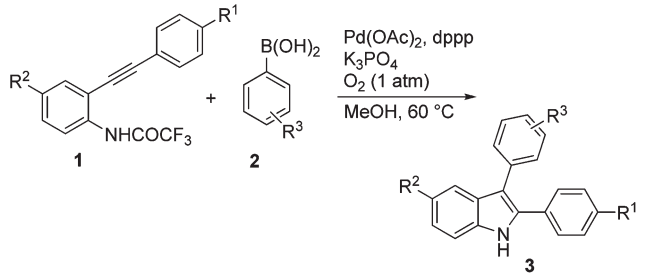




Entry	Ligand	Base	Solvent	T (°C)/t (h)	Yield[b] (%) 3a	4a	5a
1	dppp	K_2CO_3	MeCN	80/24	5	—	—
2	dppp	K_2CO_3	Dioxane	80/24	—	—	—
3	dppp	K_2CO_3	MeOH	80/2	68	3	—
4	dppp	Cs_2CO_3	MeOH	80/2	60	—	—
5	dppp	K_3CO_4	MeOH	80/1.1	40	—	—
6	dppp	NaOAc	MeOH	80/21	19	71	—
7	dppp	K_2CO_3	MeOH	60/2	68	—	—
8	**dppp**	**K_3PO_4**	**MeOH**	**60/1.5**	**76**	**—**	**—**
9[c]	dppp	K_3PO_4	MeOH	60/1.5	51	—	—
10[d]	dppp	K_3PO_4	MeOH	60/2.5	69	—	—
11	dpppO	K_3PO_4	MeOH	60/1.5	23	15	—
12	dppe	K_3PO_4	MeOH	60/1.5	69	—	—
13	Xantphos	K_2CO_3	MeOH	80/5	38	7	41
14	dppb	K_2CO_3	MeOH	80/3	17	53	—
15	dppm	K_2CO_3	MeOH	80/3	25	41	—
16	dppf	K_2CO_3	MeOH	80/6	11	46	14
17	PPh_3	K_2CO_3	MeOH	80/2	—	52	—
18	P(*o*-tol)$_3$	K_2CO_3	MeOH	80/2	10	66	—
19	Xphos	K_2CO_3	MeOH	80/5	32	40	—
20	—	K_3PO_4	MeOH	60/8	12	25	—
21	—	K_3PO_4	MeOH	60/7	4	90	—

[a] Unless otherwise stated, reactions were carried out on a 0.345 mmol scale in 2 mL of solvent under a balloon of oxygen using 1 equiv. of **3a**, 0.05 equiv. of $Pd(OAc)_2$, 0.05 equiv. of ligand, 2 equiv. of **2a**, and 2 equiv. of base. [b] Yields are given for isolated products. [c] With 1.2 equiv. of **2a**. [d] Under an atmosphere of air.

Table 2 Synthesis of 2,3-diarylindoles **3**[a]



Entry	R^1	R^2	R^3	Equiv. of **2**	Time (h)	Yield[b] % of **3**
1	H	H	4-OMe	2	1.5	76 **3a**
2	H	H	H	2	2	65 **3b**
3	H	H	4-CO_2Me	2	9	43 **3c**
4	H	H	4-CO_2Me	3	3	83 **3c**
5	H	H	4-Me	2	1	73 **3d**
6	H	H	2-Me	2	1.5	65 **3e**
7	H	H	1-Naph	2	2	58 **3f**
8	H	H	4-Cl	3	4	75 **3g**
9	H	H	4-Br	3	24	31 **3h**
10	H	H	3-CHO	3	2	66 **3i**
11	Cl	H	4-OMe	2	3	54 **3j**
12	4-COMe	H	H	2	4	55 **3k**
13	4-OMe	H	H	2	2	59 **3l**
14	4-OMe	H	4-Me	2	2	59 **3m**
15	4-OMe	H	4-CO_2Me	3	3	47 **3n**
16	H	4-CO_2Me	H	2	3	—
17	H	4,6-Me_2	H	2	24	34[c] **3o**
18	3-CO_2Me	H	4-SMe	2	4	71 **3p**

[a] Reactions were carried out at 60 °C under a balloon of oxygen on a 0.345 mmol scale in 2 mL of MeOH using 1 equiv. of **3**, 0.05 equiv. of $Pd(OAc)_2$, 0.05 equiv. of dppp, 2 or 3 equiv. of **2**, and 2 equiv. of K_3PO_4. [b] Yields are given for isolated products. [c] Calculated by NMR analysis.

ligands, bases, and temperature on the yield of **3a** was explored and some of our results are shown in Table 1.

Under a variety of conditions, the competitive cyclization of **1a** to **4a** revealed to be a significant side reaction (entries 11, 13) or even the main reaction path (entries 6, 14–21). In a few cases the dimer **5a** was also isolated in significant yield (entries 13, 16). Formation of variable amounts of 4,4′-dimethoxybiphenyl, possibly derived from the palladium-catalyzed coupling of **2a**, was also observed.

Solvents were found to play a key role. MeOH was by far the most effective (entry 3) while MeCN and dioxane gave disappointing results (entries 1, 2). Among the bases that we tested, moderate to good yields were obtained with K_2CO_3, Cs_2CO_3, and K_3PO_4 (entries 3–5) whereas using NaOAc afforded **3a** in low yield, the main reaction product being **4a** (entry 6). Lowering temperature to 60 °C gave the same result with K_2CO_3 (entry 7) while K_3PO_4 afforded **3a** in higher yield (entry 8).

Interestingly, when 2-(phenylethynyl)aniline was treated with **2a** under the same conditions the starting material was recovered in 55% yield after 7 h and only traces of **3a** were detected showing that the protecting/activating trifluoroacetyl group plays a key role in the success of the reaction, possibly generating an anionic nucleophile.

Decreasing the excess of boronic acid to 1.2 equiv. (entry 9) or changing oxygen with air as the final oxidant (entry 10) led to lower yields. As to the ligands, poor yields were obtained omitting them (entries 20, 21) or in the presence of monophosphines (entries 17–19). Bidentate phosphines such as Xantphos, dppb, dppm, dppf, and dppO[15] were also ineffective (entries 11, 13–16).

Thus, the optimized conditions described in entry 8 of Table 1 were chosen for exploring the scope of this chemistry.

As shown in Table 2, electron-neutral and electron-rich arylboronic acids, even bearing a methyl substituent in the *ortho* position, work quite well when 2-(phenylethynyl)trifluoroacetanilide (R^1 = R^2 = H) is used as the alkyne (entries 1, 2, 5, 6).

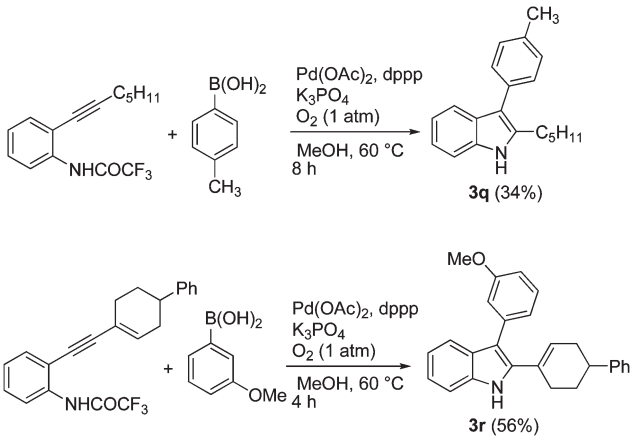
The lower yield obtained when 1-naphthylboronic acid was employed possibly arises from a less facile transmetalation due to steric effects (entry 7). The relatively electron-poor 4-chlorophenylboronic acid also gave the desired indole derivative in high yield (entry 8). It is interesting that the remaining halide functionality may serve as a valuable handle for increasing molecular complexity through transition metal-catalyzed cross-coupling reactions. However, only a 31% yield of the corresponding indole was obtained with 4-bromophenylboronic acid (entry 9). 2-(Phenylethynyl)aniline, derived from the hydrolysis of the trifluoroacetamido group, and **4a**, derived from the intramolecular cyclization of **1a**, were isolated in 20 and 34% yield, respectively. Very likely, competitive oxidative addition of the carbon–bromo bond to Pd(0) species generated under the reaction conditions may take place. This decreases the excess of the arylboronic acid, thus favoring the formation of by-products. Electron-poor arylboronic acids proved to be less effective, probably because of their lower nucleophilicity (entry 3), and an excess of 3 equiv. was required to afford the indole derivative in good to high yields (entries 4 and 10).

Further investigations of the substrate scope showed that substituents on the anilide ring have a strong influence on the reaction outcome, at least with the substituents that we tested. None of the indole product was observed with the 4-COOMe group (entry 16). Apparently, the presence of a strongly electron-withdrawing substituent decreases the nucleophilicity of the (anionic) trifluoroacetamide fragment favoring instead the hydrolysis of the amide bond. The corresponding alkynylaniline, derived from the hydrolysis of the amide bond, was isolated in 85% yield. Only a 34% yield of the corresponding indole was obtained when the 4,6-dimethyl derivative (entry 17) was employed, most probably because of the *ortho* effect of the 6-methyl group decreasing the acidity of the NH bond and, consequently, the concentration of the anionic nucleophile.

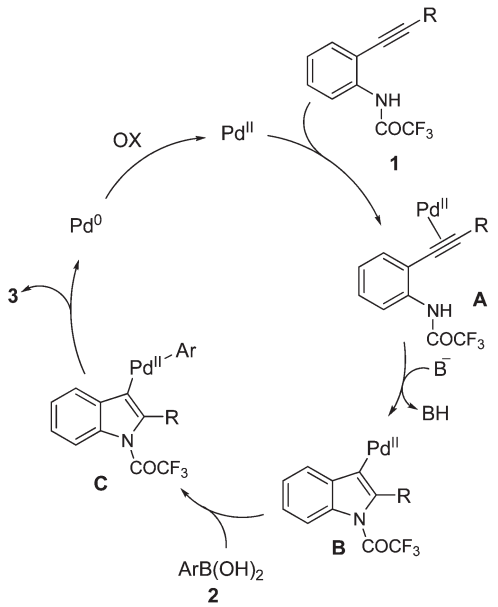
Both electron-donating and -withdrawing substituents are tolerated on the other aromatic ring (entries 11–15, 18), although yields are in some cases slightly lower than those observed with the parent phenyl ring.

Finally, the cyclization of 2-(heptyn-1-yl)- and 2-(4-phenylcyclohex1-en-1-yl)trifluoroacetanilide with 4-methyl- and 3-methoxyphenylboronic acid, respectively, afforded the corresponding indole derivatives **3q** and **3r** in moderate yields (Scheme 2).

As to the mechanism, we believe that the reaction proceeds through a process (Scheme 3) that starts with the formation of the π-alkynepalladium complex **A**. A subsequent intramolecular nucleophilic attack of the anionic nitrogen across the activated carbon–carbon triple bond gives the σ-indolylpalladium complex **B**. Its reaction with arylboronic acid affords the intermediate **C** from which the indole derivative **3** is obtained by reductive elimination. An oxidation step then regenerates the active palladium catalyst. However, the formation of **3**, at least in part, through the alternative aminopalladation/reductive elimination pathway that involves an arylpalladium complex



Scheme 2 The palladium-catalyzed synthesis of 2-alkyl- and 2-alkenyl-3-arylindoles.



Scheme 3 Proposed reaction mechanism.

arising from the reaction of palladium with the arylboronic acid[16] cannot be ruled out.

In conclusion, an efficient alternative approach to free N–H 2,3-disubstituted indoles from 2-alkynyltrifluoroacetanilides and arylboronic acids under oxidative conditions has been developed. The new method affords indole derivatives usually in good to high yields and tolerates a variety of useful functional groups both in the arylboronic acid and in the alkyne, including chloro, formyl, and ester groups, as well as *ortho* substituents in the arylboronic acid.

Acknowledgements

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