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2,3-Disubstituted Indoles via Palladium-Catalyzed Reaction of 2-Alkynyltrifluoroacetanilides with Arenediazonium Tetrafluoroborates

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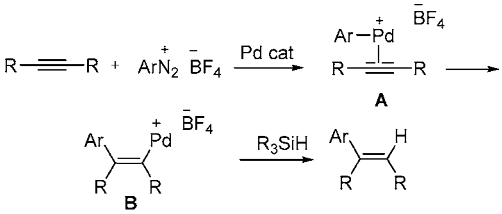
ABSTRACT

A novel palladium-catalyzed synthesis of free N−H 2,3-disubstituted indoles from arenediazonium tetrafluoroborates and 2-alkynyltrifluoroacetanilides is presented. The reaction tolerates a variety of useful substituents both in the starting alkyne and the arenediazonium salt, including bromo and chloro substituents, nitro, cyano, keto, ester, and ether groups, as well as ortho substituents such as methoxy and methyl groups.

We have recently found that the palladium-catalyzed reaction of arenediazonium salts with alkynes in the presence of R_3SiH gives hydroarylation products.[1] This reaction, the first application of alkyne-based palladium chemistry of arenediazonium salts,[2] proceeds via carbopalladation intermediates **B**, very likely preceded by π-alkyne-σ-arylpalladium complexes **A** (Scheme 1).

As π-alkyne-σ-arylpalladium complexes containing a proximate nitrogen nucleophile can undergo an intramolecular nucleophilic attack across the carbon−carbon triple bond activated by coordination to palladium,[3] we were attracted by the idea of using 2-alkynyltrifluoroacetanilides as the starting alkynes to involve arenediazonium salts in a new palladium-catalyzed synthesis of functionalized indoles **3**[4] via an aminopalladation/reductive elimination process (Scheme 2).[3] This approach might provide an exceedingly useful tool for appending indole rings to aniline fragments. We show here that such a transformation is possible and report the first utilization of arenediazonium salts in the construction of the functionalized pyrrole nucleus incorporated into indole systems.

Scheme 1



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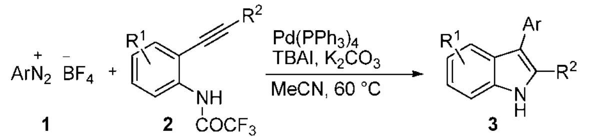
(1) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Persiani, D. *Org. Lett.* **2008**, *10*, 1597.

(2) For a review on the palladium-catalyzed chemistry of arenediazonium salts, see: Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622.

(3) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671.

10.1021/ol101321g

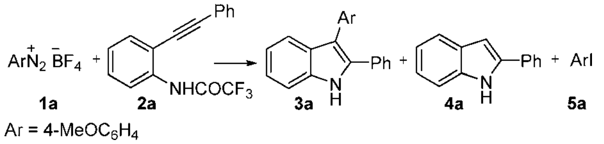
Scheme 2



We set out to use the reaction of **1a** with **2a** as a probe for evaluating the feasibility of the reaction. First attempts, however, met with failure. For example, complex mixtures (which we did not further investigate) were obtained under conditions commonly used with vinyl triflates,[5] aryl iodides,[5] bromides,[6] and triflates[6] [$Pd(PPh_3)_4$, K_2CO_3, MeCN], and no indole formation was observed. We envisaged that 2,3-disubstituted indoles might be accessible by reacting arenediazonium tetrafluoroborates with 2-alkynyltrifluoroacetanilides in the presence of TBAI provided that a iododediazoniation reaction[7] generating "ArPdI" species could be achieved under the reaction conditions.

To demonstrate this concept, we treated 2 equiv of **1a** with 1 equiv of **2a** in the presence of 5 mol % of $Pd(PPh_3)_4$ and 2 equiv of K_2CO_3 in MeCN at 60 °C for 2.5 h using a TBAI:**1a** ratio of 1.2:1. Pleasingly, **3a** was isolated in 40% yield along with a 50% yield of 4-iodoanisole, very likely formed via a iododiazoniation reaction (Table 1, entry 1).

Table 1. Optimization Studies[a]



entry	[Pd]	additive (equiv)	temp (°C)	time (h)	yield (%)[b] 3a	4a	5a[c]
1	$Pd(PPh_3)_4$	TBAI (2.4)	60	2.5	40		50
2	$Pd(PPh_3)_4$	TBAI (3)	60	2.75	52[d]		19
3	$Pd(PPh_3)_4$	TBAI (4)	60	1	69		
4	$Pd(PPh_3)_4$	TBAI (4)	40	12	*e*		
5	$Pd(PPh_3)_4$	TBAI (4)	50	3.45	52[f]		45
6	$Pd(PPh_3)_4$	NaI (2.2)/I_2 (0.2)	60	3.5	30	11	58
7	$Pd(PPh_3)_4$	KI (4)/ TBAI (0.2)	60	2.75	20	35	45
8	$Pd(PPh_3)_4$	KI (4)/ TBAI (1)	60	3.25	32	19	49
9	$Pd(OAc)_2$	TBAI (4)	60	5	13	42	27
10	$Pd_2(dba)_3$, PPh_3[d]	TBAI (4)	60	3	38[g]	13	42
11	$Pd_2(dba)_3$	TBAI (4)	60	4.25	48		30
12	$Pd(PPh_3)_4$	TBAI (4)	60	1	58[h]	tr	30
13	$Pd(PPh_3)_4$	TBAI (4)	60	5	50[i]	6	35

[a] Unless otherwise stated, reactions were carried out at 60 °C on a 0.35 mmol scale using 2 equiv of **1a**, 1 equiv of **2a**, 2 equiv of K_2CO_3, and 5 mol % of [Pd] in 3 mL of anhydrous MeCN in the presence of a iodide source. [b] Yields are given for isolated products. [c] Calculated on **1a**. [d] 1.5 equiv of **1a** was used. [e] At 40 °C. [f] At 50 °C. [g] 4 equiv of PPh_3. [h] In the presence of 2 equiv of Cs_2CO_3. [i] In the presence of 2 equiv of K_3PO_4.

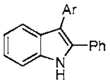
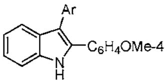
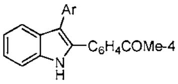
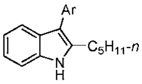
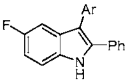
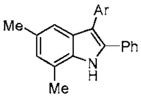
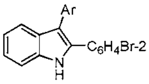
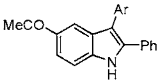
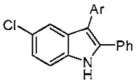
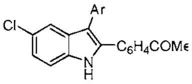
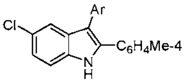
We then started an optimization study to explore the influence of bases, temperature, the source of Pd(0) species, and iodide anions on the reaction outcome (Table 1). The best result was obtained by increasing the TBAI:**1a** ratio to 2:1 (entry 3). Unsatisfactory results were obtained using $Pd(OAc)_2$ (entry 9) or $Pd_2(dba)_3$, with or without PPh_3 (entries 10 and 11), as well as decreasing the reaction temperature (entries 4 and 5). K_2CO_3 proved superior to Cs_2CO_3 or K_3PO_4 (entry 3 vs entries 12 and 13, respectively). However, we subsequently found that using Cs_2CO_3 affords slightly higher or similar yields in some cases (Table 2, entries 2 and 4 vs entries 3 and 5, respectively). Therefore, it seems advisible that the effectiveness of the bases be evaluated each time. Substituting NaI for TBAI produced **3a** in low yield (entry 6), and the use of KI in the presence of catalytic amounts (entry 7) or 1 equiv (entry 8) of TBAI proved unsuccessful as well.

The optimal reaction conditions were then employed when the reaction was extended to other arenediazonium salts and 2-alkynyltrifluoroacetanilides (Table 2). The corresponding indole derivatives were isolated in good to excellent yields with a variety of neutral and electron-rich arenediazonium salts. With electron-poor arenediazonium salts similar or better results could be obtained when a TBAI:**1** 1.5:1 ratio was used (entries 4 and 5 vs entry 6). The reaction tolerates a variety of useful substituents both in the starting alkyne and the arenediazonium salt component, including bromo and chloro substituents, nitro, cyano, keto, ester, and ether groups. The ability to incorporate bromo and chloro substituents makes this reaction particularly attractive for increasing the molecular complexity, for example, via transition metal-catalyzed coupling reactions. Arenediazonium salts containing ortho substituents such as methoxy and methyl groups also give the corresponding indole products in good to high yields (entries 10, 12, and 30). Formation of 3-unsubstituted indoles **4** was in some cases observed.

As to the mechanism, we believe that the reaction proceeds through a domino process that starts with a iododediazoniation step (Scheme 3, path a).[8,9] The oxidative addition of the resultant aryl iodide to Pd(0) affords a σ-arylpalladium iodide that coordinates to the C−C triple bond to give a π-alkyne-σ-arylpalladium complex **C**. A subsequent intramolecular aminopalladation step generates a σ-indolylpalladium intermediate **D** from which the desired free N−H indole is formed via reductive elimination and hydrolysis (not necessarily in this order).[3]

The intervention of an alternative mechanism involving the formation of σ-arylpalladium iodides through the reaction of σ-arylpalladium cations **E** with iodide anions (Scheme 3, path b) appears less likely. This view is supported by the observation that no indole formation was observed when **1a** and **2a** were subjected to the best conditions found substituting TBACl for TBAI, even prolonging the reaction time to 6 h (**2a** was recovered in 76% yield). If σ-arylpalladium chlorides were generated via trapping of **E**[10] with chloride anions, the known reluctance of aryl chlorides to undergo oxidative addition reactions with palladium catalysts coordinated to triphenylphosphine[11] should be circumvented and indoles should form to some extent.

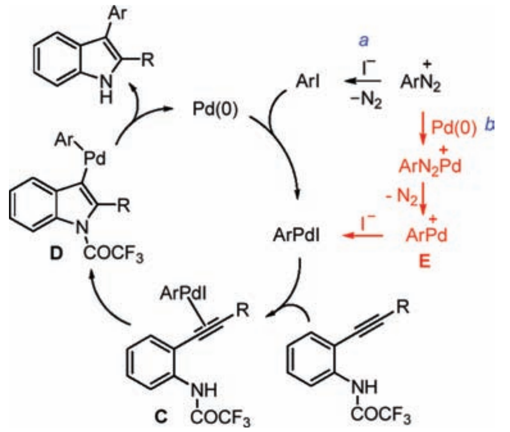
Table 2. Synthesis of Free N−H 2,3-Disubstituted Indoles **3** via Palladium-Catalyzed Reaction of Arenediazonium Tetrafluoroborates **1** with 2-Alkynyltrifluoroacetanilides **2**[a]

entry	product	Ar		yield%[b]	
1		4-$MeOC_6H_4$	A	69	**3a**
2		Ph	A	72	**3b**
3		Ph	A	76[c]	**3b**
4		4-$MeCOC_6H_4$	A	90	**3c**
5		4-$MeCOC_6H_4$	A	89[c]	**3c**
6		4-$MeCOC_6H_4$	B	96	**3c**
7		3-$CF_3C_6H_4$	B	85	**3d**
8		4-MeC_6H_4	A	84	**3e**
9		4-$NO_2C_6H_4$	B	93	**3f**
10		2-$MeOC_6H_4$	A	69	**3g**
11		4-ClC_6H_4	B	89	**3h**
12		2-Me,4-	A	49	**3i**
13		3-$MeOC_6H_4$	A	68	**3j**
14		Ph	A	82	**3k**
15		4-MeC_6H_4	A	86	**3l**
16		4-CNC_6H_4	B	86	**3m**
17		4-$MeOC_6H_4$	B	65	**3n**
18		Ph	A	63	**3o**
19		4-ClC_6H_4	B	89	**3p**
20		4-MeC_6H_4	A	81	**3q**
21		4-CNC_6H_4	B	71[d]	**3r**
22		4-MeC_6H_4	A	86	**3s**
23		4-$MeOC_6H_4$	A	50[e]	**3t**
24		4-FC_6H_4	A	70	**3u**
25		4-MeC_6H_4	A	66	**3v**
26		4-$NO_2C_6H_4$	B	91	**3w**
27		Ph	A	68	**3x**
28		4-$MeCOC_6H_4$	B	74	**3y**
29		4-$NO_2C_6H_4$	B	75[f]	**3z**
30		2-Me,4- $MeOC_6H_3$	A	66	**3za**

[a] Unless otherwise stated, reactions were carried out at 60 °C in 1−5.5 h on a 0.35 mmol scale using 2 equiv (Procedure A) or 1.5 equiv (Procedure B) of **1**, 1 equiv of **2**, 2 equiv of K_2CO_3, 5 mol % of $Pd(PPh_3)_4$, 4 equiv (Procedure A) or 3 equiv (Procedure B) of TBAI in 3 mL of anhydrous MeCN. [b] Yields are given for isolated products. [c] In the presence of Cs_2CO_3. [d] **4r** was isolated in 21% yield. [e] **4t** was isolated in 29% yield. [f] **4z** was isolated in 12% yield.

In conclusion, an efficient approach providing free N−H 2,3-disubstituted indoles in good to high yields from arenediazonium tetrafluoroborates and 2-alkynyltrifluoroacetanilides has been developed. The new method tolerates a variety of useful functional groups both in the alkyne and in the arenediazonium salt component, including bromo and chloro substituents, nitro, cyano, keto, ester, and ether groups, as well as ortho substituents.

Scheme 3



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Supporting Information Available: A complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For recent reviews on the palladium chemistry of indoles, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (e) Patil, S.; Buolamwini, J. K. *Curr. Org. Synth.* **2006**, *3*, 477. (f) Ackermann, L. *Synlett* **2007**, 507. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (h) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (i) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673.

(5) (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915. (b) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363.

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(7) (a) Barbero, M.; Degani, I.; Dughera, S.; Fochi, R. *J. Org. Chem.* **1999**, *64*, 3448. (b) Hubbard, A.; Okazaki, T.; Laali, K. K. *J. Org. Chem.* **2008**, *73*, 316.

(8) Fabrizi, G.; Goggiamani, A.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 4067.

(9) Control experiments revealed that arenediazonium salts are quickly converted into the corresponding aryl iodides in the presence of TBAI. For example, 4-methoxybenzene tetrafluoroborate is converted to 4-iodoanisole in 73% yield after 5 min at 60 °C.

(10) Yamashita, R.; Kikukawa, K.; Wada, F.; Matsuda, T. *J. Organomet. Chem.* **1980**, *201*, 463.

(11) Aryl chlorides did not give indole derivatives upon treatment with 2-alkynyltrifluoroacetanilides using $Pd(PPh_3)_4$ and Cs_2CO_3 or K_2CO_3 in MeCN even at temperatures as high as 120 °C. Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Adv. Synth. Catal.* **2006**, *348*, 1301.