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Palladium-Catalyzed Synthesis of Selectively Substituted Phenanthridine Derivatives

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Abstract: Selectively substituted phenanthridine derivatives are obtained by a facile reaction of *o*-alkylated aryl iodides, *o*-bromoarenesulfonylanilines and activated olefins in the presence of palladium and norbornene as catalysts. The reaction takes place under mild conditions to give the products in satisfactory yields using readily available starting materials.

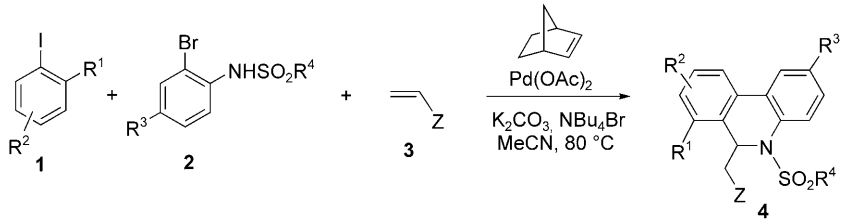
Keywords: catalysis; C–H activation; norbornene; palladium; phenanthridines; sequential reactions

Phenanthridine derivatives are a class of natural compounds with interesting biological and pharmaceutical activities, and much effort has been devoted to the development of direct and efficient methods for the synthesis of these systems.[1]

Palladium-catalyzed sequential reactions, which combine high selectivity with easy accessibility and use of starting reagents, mild reaction conditions and tolerance to a variety of functional groups, have attracted the attention of several researchers.[2] Here we report a facile and efficient catalytic synthesis of selectively substituted 5-arenesulfonyl-5,6-dihydrophenanthridines, taking advantage of our methodology for multi-component palladium- and norbornene-catalyzed syntheses.[3] It consists of sequential coupling of an *o*-substituted aryl iodide with a sulfonylated *o*-bromoaniline, insertion of an activated olefin, and aza-Michael cyclization. The procedure parallels the one we previously utilized for the synthesis of selectively substituted 6*H*-dibenzopyran derivatives by reaction of an *o*-substituted aryl iodide with an *o*-bromophenol and an electron-deficient olefin.[4] Replacing an *o*-bromophenol derivative with an *o*-bromoaniline one, required quite different conditions, however, to allow the timely involvement of each reagent in the sequence of bond formation. We have found that reacting an *o*-alkyl-substituted aryl iodide with an aryl bromide, containing a sulfonylated amino group in the *ortho* position, and an activated terminal olefin, in the presence of $Pd(OAc)_2$, norbornene, K_2CO_3 and NBu_4Br in MeCN at 80 °C under nitrogen leads to the formation of the desired product in satisfactory yields as shown in Table 1, which reports representative results.

As shown in Table 1 iodoarenes, containing *o*-alkyl substituents and 1-iodonaphthalene, readily reacted with *o*-bromo-*N*-arenesulfonylanilines and methyl acrylate to give the corresponding 5-arenesulfonyl-5,6-dihydrophenanthridines in satisfactory yields. The presence of either a methyl or a chloro group (entries 6 and 7) in the aniline ring did not appear to influence the outcome of the reaction, the corresponding cyclic compounds **4f** and **4g** being isolated with the same yield (84%) and comparable selectivity (96 and 91%, respectively). The more electron-withdrawing substituent NO_2 group (entry 8) gave **4h** in lower yield (75%). Substituents in the aromatic ring of the sulfonyl moiety somehow affected the reaction course, the best results being obtained with *o*-bromo-*N*-(*p*-chlorobenzenesulfonyl)aniline[6] (entries 10 and 12; $R^4 = C_6H_4$-4-Cl) followed by *o*-bromo-*N*-(benzenesulfonyl)aniline (entries 9 and 11; $R^4 = C_6H_5$) and *o*-bromo-*N*-(*p*-methylbenzenesulfonyl)aniline (entries 1 and 2; $R^4 = C_6H_4$-4-Me). Analogously, *o*-isopropyliodobenzene gave phenanthridines **4m** and **4d** in 78 and 70% yields, respectively (entries 13 and 4). An electron-withdrawing group in the arenesulfonyl ring exerted a significant positive effect in the reaction of 1-iodonaphthalene: dihydrophenanthridine derivative **4n** (entry 14) was isolated in an acceptable 62% yield using *o*-bromo-*N*-(*p*-chlorobenzenesulfonyl)aniline, while compound **4e** (entry 5) was obtained only in 31% yield using the *N*-tosylated *o*-bromoaniline,

Table 1. Synthesis of 5-arenesulfonyl-5,6-dihydrophenanthridines.[a]



Entry	R^1, R^2	R^3	R^4	Z	**4** Yield [%][b]
1	Me, H	H	C_6H_4-4-Me	CO_2Me	**4a**, 74 (83)[c]
2	Me, 4-Me	H	C_6H_4-4-Me	CO_2Me	**4b**, 81 (93)
3	Me, 4-OMe + 3-Me	H	C_6H_4-4-Me	CO_2Me	**4c**, 84 (94)
4	*i*-Pr, H	H	C_6H_4-4-Me	CO_2Me	**4d**, 70 (93)
5	-$(CH)_4$-	H	C_6H_4-4-Me	CO_2Me	**4e**, 31 (48)[d]
6	Me, 4-Me	Me	C_6H_4-4-Me	CO_2Me	**4f**, 84 (96)
7	Me, 4-Me	Cl	C_6H_4-4-Me	CO_2Me	**4g**, 84 (91)
8	Me, 4-Me	NO_2	C_6H_4-4-Me	CO_2Me	**4h**, 75 (96)
9	Me, H	H	C_6H_5	CO_2Me	**4i**, 76 (95)
10	Me, H	H	C_6H_4-4-Cl	CO_2Me	**4j**, 87 (97)
11	Me, 4-Me	H	C_6H_5	CO_2Me	**4k**, 85 (92)
12	Me, 4-Me	H	C_6H_4-4-Cl	CO_2Me	**4l**, 89 (94)
13	*i*-Pr, H	H	C_6H_4-4-Cl	CO_2Me	**4m**, 78 (95)
14	-$(CH)_4$-	H	C_6H_4-4-Cl	CO_2Me	**4n**, 62 (89)
15	Me, 4-Me	H	C_6H_4-4-Me	COMe	**4o**, 82 (96)
16	Me, 4-Me	H	C_6H_4-4-Me	CN	**4p**, 61 (90)

[a] *Reaction conditions:* aryl iodide (1.1 equiv.), aryl bromide (1.0 equiv.), activated terminal olefin (4 equiv.), norbornene (10 equiv.), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.2 equiv.), NBu_4Br (2.2. equiv.) in MeCN at 80 °C under N_2 for 48 h; $0.2 \cdot 10^{-2}$ mmol $Pd(OAc)_2$/mL MeCN.

[b] Isolated yield on the charged amount of aryl bromide. Conversion of aryl iodides is complete.

[c] In parentheses isolated yield based on converted aryl bromide.

[d] The corresponding carbazole 11-(4-methylbenzenesulfonyl)-11*H*-benzo[*a*]carbazole (Scheme 2) was also isolated in 31% yield.[5]

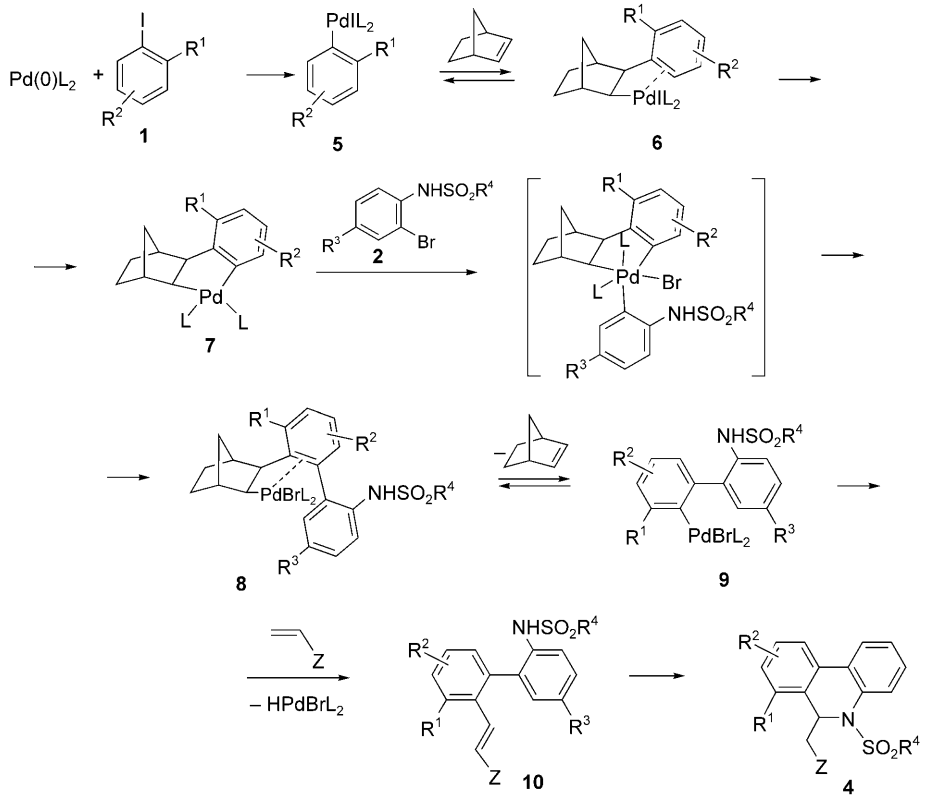
owing to the competitive formation of the corresponding carbazole (see below).

Besides acrylates only electron-poor olefins such as methyl vinyl ketone and acrylonitrile gave acceptable results (entries 15 and 16).

The proposed reaction pathway is depicted in Scheme 1. Oxidative addition of the aryl iodide to palladium(0) occurs faster than that of the aryl bromide (contained in the same mixture) to form the arylpalladium(II) iodide intermediate **5**.[7] In the presence of two types of olefins, a strained one such as norbornene and one activated by an electron-withdrawing substituent such as the alkoxycarbonyl group, complex **5** preferentially inserts the former (norbornene) to give the *cis,exo*-arylnorbornylpalladium species **6**.[8] Aromatic C–H activation[9] by electrophilic substitution leads to the palladium(II) metallacycle **7**.[10] At this point, unlike what was observed with palladium(0), the aryl bromide **2** reacts faster with **7** than the aryl iodide **1**, likely as a consequence of the *o*-bromoarenesulfonylaniline chelating effect. Selective arylation at the aromatic site of intermediate **7** to form species **8** is then promoted by the directing effect of the *o*-substituent in the aryl ring of palladacycle **7**.[3c] Aryl–aryl coupling could possibly involve the intermediacy of the palladium(IV) species reported in brackets.[11] The steric hindrance, exerted by the two *ortho* substituents in complex **8**, favors C–C bond cleavage with deinsertion of norbornene (which thus acts as a catalyst), to afford the biphenylylpalladium species **9**, able to insert the terminal olefin in a Heck-type reaction.[3a,c] The resulting vinylbiphenyl derivative **10** undergoes an intramolecular Michael-type reaction by attack of the amido group ($NHSO_2R^4$) on the vinyl group to generate the dihydrophenanthridine derivative **4**. The cyclization step, which should be catalyzed by the basicity of the medium, must take place quite easily since the open-chain precursor **10** has never been detected.

The use of *N*-sulfonylated *o*-bromoaniline derivatives is essential for the success of the reaction, which leads to very poor results, if any, with *N*-unsubstituted, monoalkylated, acetylated or trifluoroacetylated *o*-bromoaniline.

Running the reaction with *o*-iodotoluene, *N*-tosyl-*o*-bromoaniline and methyl acrylate in the absence of

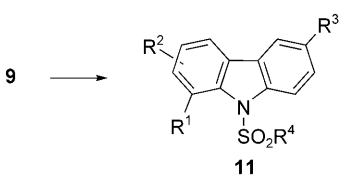


Scheme 1. Proposed reaction pathway to 5-arenesulfonyl-5,6-dihydrophenanthridines.

norbornene under the standard conditions of Table 1, led to the exclusive formation of methyl *o*-methylcinnamate in 98% yield; the *o*-bromotosylanilide was recovered unconverted. This result points to the key role played by norbornene in driving the reaction towards the formation of palladacycle precursor **6**, which is then followed by the steps depicted in Scheme 1, namely cyclopalladation, aryl–aryl coupling accompanied by norbornene deinsertion, aryl–vinyl coupling in sequence, and final intramolecular Michael reaction.[12]

The main problem we had to face stemmed from the tendency of complex **9** to form the carbazole ring (**11**, Scheme 2)[5] rather than allowing Heck coupling with an activated olefin to give **10** (Scheme 1), prior to the final Michael reaction leading to the phenanthridine ring **4**.

As previously reported,[5] a coordinating solvent, such as DMF, promotes carbazole ring formation, probably because it favours bromide dissociation from palladium complex **9**. We thus resorted to the less coordinating MeCN as solvent and added NBu_4Br[13] to retard cyclization of **9** to **11**. The result was quite satisfactory but the added salts also favoured oxidative addition of the starting aryl iodide to palladium(0) to form complex **5**[14] and its subsequent reaction with methyl acrylate to give the corresponding Heck product, methyl *o*-methylcinnamate.[15] To prevent an early reaction of the activated terminal olefin with aryl iodide **1**, norbornene was added in a large excess (10:1 molar ratio to the aryl halide). In this way the course of the initial step was shifted towards norbornene insertion and palladacycle formation according to Scheme 1. Noteworthy, the large amount of norbornene did not appear to counteract efficiently the deinsertion step from intermediate **8** to **9**, which is caused predominantly by the steric hindrance exerted by the bulky sulfonylated aniline.



Scheme 2. Carbazole ring formation from intermediate **9**.

In conclusion, we have been able to obtain phenanthridine derivatives starting from readily available reagents through an accurate balance of the competing processes, in particular the one leading to carbazoles in place of phenanthridines. The association of sulfonylated anilines with an ammonium salt and a large excess of norbornene in MeCN as solvent was found to be a prerequisite for the palladium-catalyzed

reaction with aryl halides and activated olefins to occur efficiently.

Experimental Section

General Procedure for the Synthesis of 5-Arenesulfonyl-5,6-dihydrophenanthridines

A Schlenk-type flask, equipped with a magnetic stirring bar, was charged with $Pd(OAc)_2$ (5 mg, 0.022 mmol), norbornene (413 mg, 4.4 mmol), the desired aryl iodide (0.48 mmol), the aryl bromide (0.44 mmol), and the activated olefin (1.76 mmol) in MeCN (10 mL). K_2CO_3 (138 mg, 1.0 mmol) and NBu_4Br (322 mg, 1.0 mmol) were then added as solid powder and the resulting reaction mixture was stirred in an oil bath at 80 °C for 48 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using an 80:17:3 mixture of hexane-AcOEt-CH_2Cl_2 as eluent.

Acknowledgements

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[12] This result also rules out the possibility that the reaction leading to **4** proceeds through an alternative pathway consisting of methyl *o*-methylcinnamate formation, Michael addition of the arenesulfonyl *o*-bromoaniline and final intramolecular arylation in sequence. This alternative pathway to **4** was further excluded on the ground that methyl *o*-methylcinnamate and *o*-bromo-*N*-tosylaniline did not react under the reaction conditions.

[13] NBu_4Cl completely inhibited the formation of compound **4** while only a 15% yield was obtained in the presence of NBu_4I.

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