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Palladium/Norbornene-Catalyzed Synthesis of Heteroatom-Containing *o*-Teraryls from Aryl Iodides and Heteroarenes through Double C–H Activation in Sequence

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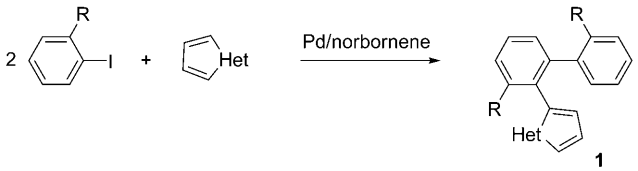
Arylated heterocycles are structures present in many compounds of great importance ranging from biologically and pharmaceutically active products to electronic organic materials.[1] During recent years several novel catalytic processes for the direct arylation of heterocycles have been reported.[2] Due to their wide applications, however, the development of new methods for the efficient and selective arylation of heterocycles still remains a challenging goal.

Herein we report a new catalytic procedure that allows the synthesis of heteroatom-containing *o*-teraryls through a sequence of steps occurring under the control of palladium and norbornene, both acting as catalysts.[3] The reaction involves intermolecular aryl–aryl and aryl–heteroaryl bond formation in sequence through direct C–H functionalization (Scheme 1). Direct C–H arylation of arene compounds overcomes the need for a functional group in one of the aryl moieties undergoing C–C coupling.



Scheme 1. One-pot reaction of an *o*-substituted aryl iodide with a heterocycle.

Product **1** combines the ubiquitous biphenyl structure with heterocyclic nuclei of wide biological and pharmaceutical interest.[2] The reaction depicted in Scheme 1 occurs under mild conditions (105–120 °C) using palladium acetate as precursor of the palladium(0) catalyst, norbornene, the *o*-substituted aryl iodide, a large excess of a heterocycle, and potassium carbonate as a base in DMF. 3,4-Ethylenedioxythiophene leads to satisfactory results even in a 25% excess with respect to the aryl iodide.

Good results were obtained with 1-naphthyl iodide and 2-isopropylphenyl iodide (see Table 1). An electron-withdrawing substituent such as the methoxycarbonyl group also gave

Table 1. Reaction of *o*-substituted aryl iodides with heterocycles.[a]

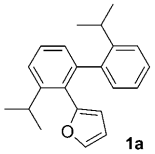
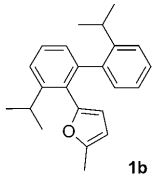
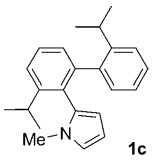
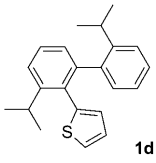
Entry	Aryl iodide	Heterocycle	*T* [°C]	Product **1**	Yield [%]
1[b]			105	 **1a**	68
2[b]			105	 **1b**	71
3[c]			120	 **1c**	66
4			120	 **1d**	70

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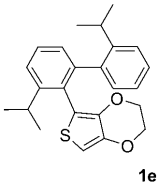
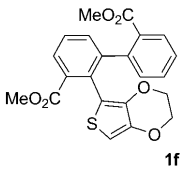
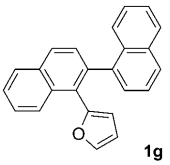
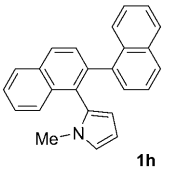
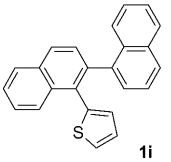
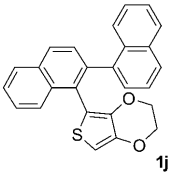
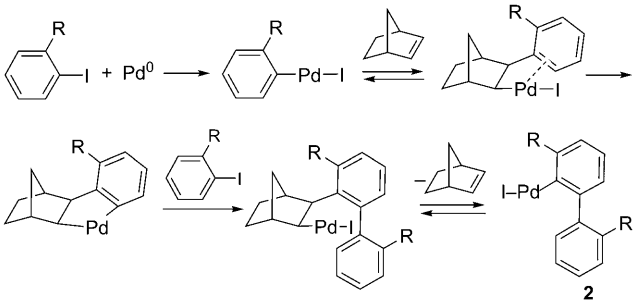
Table 1. (Continued)

Entry	Aryl iodide	Heterocycle	T [°C]	Product **1**	Yield [%]
5			105	 **1e**	72
6			105	 **1f**	82
7[b]			105	 **1g**	62
8[c]			120	 **1h**	69
9			120	 **1i**	70
10			105	 **1j**	77

[a] Reactions were carried out for 24 h at 105–120 °C with $Pd(OAc)_2$ (0.018 mmol), K_2CO_3 (1.61 mmol), norbornene (0.36 mmol), the aryl iodide (1.43 mmol), and the heterocycle (furan, 2-methylfuran, *N*-methylpyrrole, and thiophene = 7.20 mmol) (3,4-ethylenedioxythiophene = 1.8 mmol) in DMF (16 mL) under nitrogen. Complete conversion of the aryl iodide. [b] Reaction run for 48 h. [c] Unprotected pyrrole does not allow formation of the desired product.

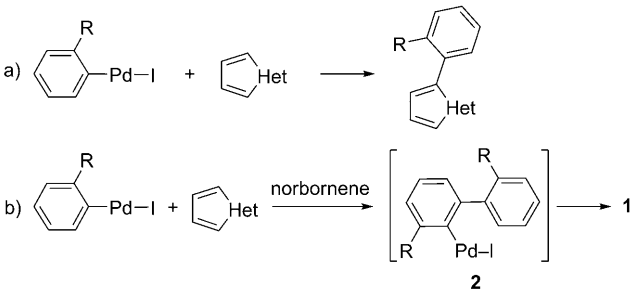
good results. Lower yields were obtained with other linear alkyl substituents (not reported in Table 1).

The reaction proceeds according to our protocol for the synthesis of biaryl derivatives[3] until a biarylpalladium iodide complex **2** is formed. An *ortho*-substituted iodobenzene reacts with palladium(0) to give the oxidative addition product,[4] which in turn inserts norbornene into the C_{aryl}–Pd bond.[5] This is followed by palladacycle formation[6] through arene C–H activation.[7] A second molecule of aryl iodide then attacks this species leading to the formation of a C–C bond between the two aryl groups, while palladium remains bonded to the norbornyl moiety. At this point steric hindrance causes norbornene deinsertion with formation of **2**.[3] The *ortho*-substituent in the aryl halide (or a condensed ring, as in 1-iodonaphthalene, not shown in Scheme 1) is necessary to cause the reaction sequence to evolve towards biaryl formation[3] rather than towards other products resulting from ArI attack on the norbornyl site of the palladacycle shown in Scheme 2.



Scheme 2. Simplified course of the reaction leading to a palladium-bonded biaryl **2**.

Complex **2** now effects a second C–H activation reacting with a heteroarene belonging to the class of furan, thiophene, and pyrrole. Since the heterocycle was present in the reaction mixture from the beginning it is amazing, however, that it reacts mainly at the end of the sequence (Scheme 3,



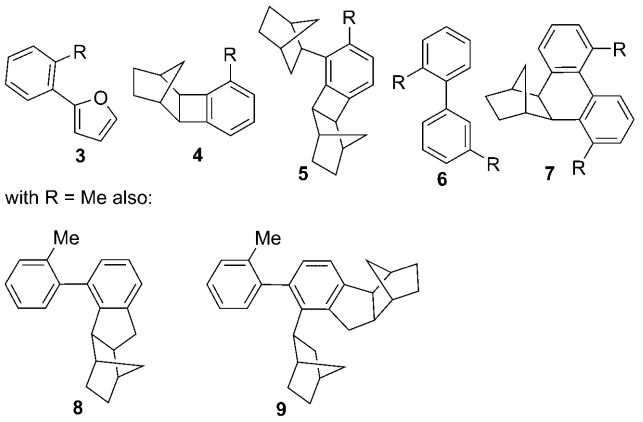
Scheme 3. Different reactivity of arylpalladium bonds in the absence or presence of norbornene.

route b) and not with the original aryl halide (Scheme 3, route a). This is due to the high reactivity of norbornene, which traps the palladium-bonded aryl, forming a palladacycle. Only after the attack of a second molecule of the aryl halide with expulsion of norbornene is the newly formed biarylpalladium bond of **2** able to react with the heterocycle.

It is worth noting that reaction b) of Scheme 3 occurs in the best way without the need for adding phosphine ligands. The reason for this behavior is unclear but is related to the effect of the environment of our reaction, including that of the *ortho* substituent. A certain degree of steric hindrance around the metal seems to be necessary. In agreement with this we observe that 1-naphthyl and 2-isopropylphenyl iodides are good substrates. In general we observe that secon-

dary products increase when the steric hindrance of an alkyl group R decreases. The electronic effect shown by an *ortho* CO_2Me group also turns out to be positive. Thus the nature of the effect caused by R groups deserves further study.

The secondary products derive from competing reactions and show a different distribution depending on the *ortho* substituent. Those found with *o*-substituted iodobenzene and furan are reported in Scheme 4. Analogous products are

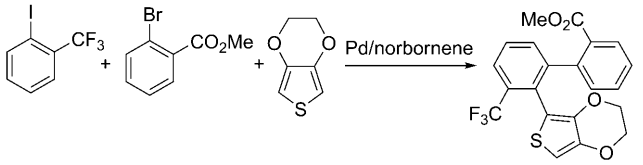


Scheme 4. Secondary products found in the reaction of *o*-substituted iodobenzene and furan.

present with the other heterocycles. Apart from product **3**, which results from the direct attack of the starting aryl iodide on the heterocycle and **6**, which results from hydrogenolytic aryl coupling, they incorporate norbornene in different ways as we already reported.[8] For example with R = *i*Pr, products **3**–**7** are all formed in 3–5% each. In addition an *ortho* methyl group readily forms condensed cyclopentane structures **8** (12%) and **9** (3%) by cyclization with norbornene,[9] and also **3** (R = Me) is present in a significant amount (12%), while the yield of **1** is 53%.

Notably the reaction can be extended to the more complex case of an *ortho*-substituted aryl iodide, an aryl bromide,[3c] instead of two molecules of aryl iodide,[3d] and a heterocycle. Yields and selectivities are lower, however, and further study is required to find out the best conditions. Thus, the following reaction gives the product in 49% yield (Scheme 5).

In summary, a simple one-step catalytic process for the synthesis of heteroatom-containing *o*-teraryl derivatives from readily accessible aryl iodides and heterocycles has



Scheme 5. One-pot reaction of an *o*-substituted aryl iodide and an aryl bromide with a heterocycle.

been developed taking advantage of the unique opportunities offered by the palladium/norbornene system. Further investigations are in progress to expand the scope of the reaction.

Experimental Section

The general procedure is illustrated for the case of 2-isopropyliodobenzene and furan: 2-Isopropyliodobenzene (0.35 g, 1.43 mmol), furan (0.49 g, 7.2 mmol), norbornene (34 mg, 0.36 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol), and K_2CO_3 (0.22 g, 1.61 mmol) in DMF (16 mL) were stirred with a magnetic bar in a closed Schlenk-type flask under nitrogen at 105 °C for 48 h. At the end of the reaction the mixture was allowed to cool to room temperature, diluted with EtOAc (30 mL), washed three times with brine (3×30 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was analyzed by GC and ^1H NMR spectroscopy. The product was isolated by flash column chromatography on silica gel using a 95:5 mixture of hexane–EtOAc as eluent to obtain compound **1a** as a white powder in 65% yield (0.141 g).

Acknowledgements

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Keywords: catalysis · C–C coupling reaction · C–H activation · heterocyclic compounds · palladium

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