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“On-Water,” Microwave-Assisted, Pd-Catalyzed Synthesis of Indoles from Imines and *o*-Difunctionalized Arenes

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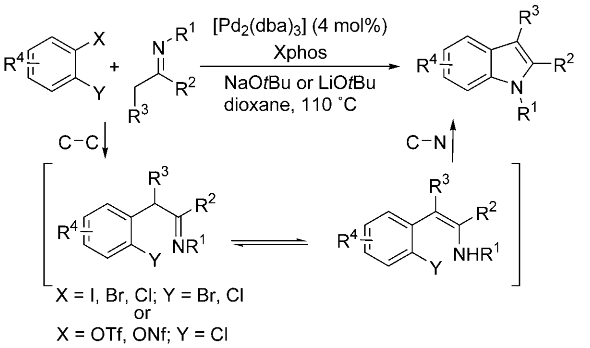
Abstract: Regioselectively substituted indoles are prepared by a Pd-catalyzed C–C/C–N bond-forming sequence from imines and *o*-dihaloarenes or *o*-haloarene sulfonates. The heterogeneous reaction as a suspension in water and under microwave heating offers important advantages in comparison with the conventional reaction in an organic solvent, among them, operational simplicity, the employment of KOH solutions instead of alkoxides, and a dramatic reduction of reaction times.

Keywords: heterogeneous catalysis · indoles · microwave chemistry · palladium · water chemistry

Introduction

The indole ring is one of the most important heterocyclic substructures in medicinal chemistry.[1] For this reason, although the repertoire of methodologies for the synthesis of indoles is enormous,[2] the discovery of new, efficient methods that allow the high-throughput synthesis of structurally diverse indoles is still a matter of great interest.[3]

In this context, we have recently reported a new Pd-catalyzed methodology for the synthesis of indoles from imines and *o*-dihaloarenes or *o*-haloarene sulfonates. The reaction consists in a cascade process that involves an imine α-arylation, followed by an intramolecular C–N-bond-forming reaction, promoted by the same Pd catalyst. We have shown that this methodology is very general and allows for the synthesis of a wide variety of indoles, which are regioselectively substituted on both rings (Scheme 1).[4]



Scheme 1. Synthesis of indoles through a Pd-catalyzed C–C/C–N cascade.

In recent years, the use of water as a solvent for organic reactions has gained increasing attention, mainly for economic, safety, and environmental reasons. In particular, the combination of water as the solvent and microwave heating as the energy source is becoming increasingly popular in sustainable chemistry.[5] Nevertheless, the attractiveness of water as a reaction medium is not only associated with the concept of Green Chemistry. In many cases, remarkable beneficial effects, in terms of reaction rates and selectivity, have been observed for reactions between reagents that are insoluble in aqueous media and therefore take place under suspension in water; the term “on water” was coined by Sharpless et al. to refer to this type of reaction.[6] As shown in a recent review,[7] the “on water” effect has been observed in different types of reactions, such as cycloadditions, pericyclic reactions, nucleophilic substitutions, and also in transition-metal-catalyzed, and in particular, Pd-catalyzed reactions.[8]

Taking into account the synthetic potential of the modular synthesis of indoles that we have developed, we wanted to investigate whether modification of the reaction conditions by the application of the “on water” concept, and the em-

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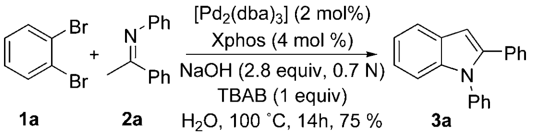
ployment of microwave heating, might exert any influence and lead to an improvement of the process. Our results have indeed shown remarkable and beneficial differences between the "on-water"/microwave-assisted reaction and the conventional process. Herein, we wish to report our conclusions.

Results and Discussion

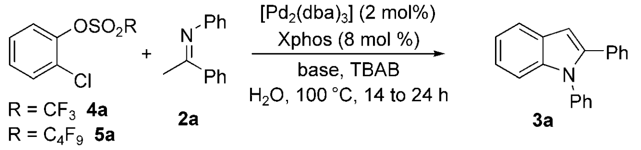
To test for conditions for the reaction as a suspension in water, we chose the synthesis, from *o*-dibromobenzene (**1a**) and imine **2a**, of indole **3a**. We employed the optimized catalytic system for the indolization in organic solvents, which consists of [$Pd_2(dba)_3$] (dba = dibenzylideneacetone) as the metal source and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) as the ligand. Notably, both coupling partners, as well as the ligand, are completely insoluble in aqueous media. Nevertheless, after some experimentation, we observed that the indolization reaction proceeds with good yield in an aqueous NaOH solution (0.7 N), in the presence of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst (Scheme 2). Remarkably, the reaction as a suspension in water takes place with NaOH employed as the base, whereas, in our previous studies in organic solvents, these reactions were very demanding in terms of the nature of the base and proceeded, successfully, only in the presence of NaO*t*Bu.



Scheme 2. Indolization reaction "on water": preliminary results.

These preliminary results prompted us to investigate this transformation in more detail and also to direct our attention to the reactions with *o*-chlorosulfonates. We have shown that these reactions are more versatile, from a synthetic point of view, since they represent a valuable strategy for the regioselective synthesis of indoles with substituents on the benzene ring. However, the reactions with sulfonates require very finely tuned experimental conditions, as a result of the lability of sulfonates in the presence of bases. As prototype reactions, we again chose the synthesis of **3a**, but employing *o*-chlorotriflate **4a** and *o*-chlorononaflate **5a**. In a series of experiments, we searched for a successful combination of reaction conditions for these transformations. We observed that the indolization of chlorosulfonates can, indeed, be performed as a suspension in water. The preliminary results showed that, akin to the conventional reactions, nonaflate **5a** gave better results than triflate **4a** (Table 1, entries 1 and 2).[9] Therefore, the optimization reactions were carried out with **5a**. The best results were obtained by employing a solution of KOH (1.5 M) in the presence of TBAB, as a phase-transfer catalyst.

Table 1. Preliminary results for the indolization reaction of *o*-chlorosulfonates reacting as a suspension in water.



	R	Base (equiv)/[N]	Conditions[a]	*t* [h]	*T* [°C]	Conversion [%][b,c]
1	CF_3	NaOH (2.8)/[0.7]	TBAB (0.5 equiv)	14	100	50
2	C_4F_9	NaOH (2.8)/[0.7]	TBAB (0.5 equiv)	20	100	80
3	C_4F_9	LiOH (2.8)/[0.7]	TBAB (0.5 equiv)	20	100	75
4	C_4F_9	KOH (2.8)/[0.7]	TBAB (0.5 equiv)	20	100	90 (65)
5	C_4F_9	KOH (6)/[1.5]	TBAB (0.5 equiv)	20	100	99 (75)
6	C_4F_9	KOH (6)/[1.5]	TBAB (1 equiv), toluene/H_2O, 1:2	20	reflux	66

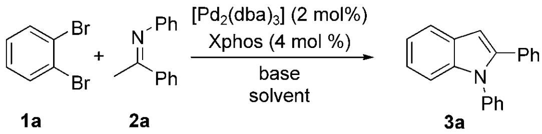
[a] Reaction conditions: [$Pd_2(dba)_3$] (2 mol %), Xphos (8 mol %), imine **2a** (0.5 mmol), $ArOSO_2R$ **4a** or **5a** (0.75 mmol). [b] Conversion based upon the disappearance of imine **2a** (GC/MS). [c] Isolated yield is indicated in brackets.

Some remarkable differences must be noted between the reaction "on water" and in organic solvent: 1) the reaction in an organic solvent is extremely demanding in terms of the base, we obtained the indole only if LiO*t*Bu or NaO*t*Bu was used as the base, whereas the "on water" reaction proceeds in either NaOH or KOH solutions; and 2) for the reaction in an organic solvent the sulfonate must be added slowly, over a period of 10 h, in order to achieve good conversion and to avoid decomposition to the alkoxide, whereas in the "on-water" process, the sulfonate is added in one portion at the beginning of the reaction and, in the heterogeneous mixture, is not hydrolyzed by the base.

Notably, if the reaction was carried out in a toluene/water biphasic mixture under otherwise identical reaction conditions (Table 1, entry 6), lower conversion was obtained than in the reaction in the absence of the organic solvent. These observations point to the important role of the "on-water" effect, which compares favorably, both with the homogenous reaction and with the reaction in a biphasic mixture. However, the reactions that occur as a suspension in water still require very long reaction times. For this reason, we decided to study the same transformations under microwave heating. To find suitable reaction conditions, we employed the reaction of **1a** with **2a** to form **3a** (depicted in Scheme 2) as a model reaction. In Table 2, representative data from the optimization process are presented.

Poor results were obtained under microwave irradiation for the reactions in dioxane. However, as a suspension in water, the microwave-promoted reactions proceeded with high conversions and in much shorter reaction times than the thermally heated equivalents, taking advantage of the high temperatures that can be achieved in the microwave heated experiments. Under the optimized reaction conditions (Table 2, entry 10), the reaction can be carried out in 45 min, providing the indole in excellent yield. Moreover,

Table 2. Optimization of the microwave-promoted, "on-water" reaction.



	Base (equiv)/[N]	Conditions[a]	t [min]	T [°C]	Conversion [%][b,c]
1	NaO*t*Bu (2.8)	dioxane	20	110	14
2	NaO*t*Bu (2.8)	dioxane	20	150	30
3	NaO*t*Bu (2.8)	dioxane	20	160	52
4	KOH (3)/[0.75]	H_2O, TBAB (1 equiv)	60	140	77
5	KOH (3)/[1.5]	H_2O, TBAB (1 equiv)	20	140	80
6	KOH (3)/[1.5]	H_2O, TBAB (1 equiv)	20	150	80
7	KOH (3)/[1.5N]	H_2O, TBAB (0.5 equiv)	30	140	72
8	KOH (7.5)/[3N]	H_2O, TBAB (1 equiv)	30	150	99 (75)
9	KOH (7.5)/[3N]	H_2O	45	140	60
10	KOH (7.5)/[3N]	H_2O, TBAB (0.12 equiv)	45	140	99 (89)

[a] Reaction conditions: $[Pd_2(dba)_3]$ (2 mol%); Xphos (4 mol%); imine **2a** (0.5 mmol), 1,2-dibromobenzene (**1a**, 0.5 mmol). [b] Conversion based upon the disappearance of imine **1a** (GC/MS). [c] Isolated yield is indicated in brackets.

the quantity of the phase-transfer catalyst can be reduced to only 12 mol%. In the absence of TBAB, the indolization also takes place, but in lower conversion (Table 2, entry 9).

These conditions were applied to the synthesis of indoles from a set of imines and *o*-dihalobenzene derivatives, as well as *o*-chlorosulfonates. Representative examples are presented in Table 3.

The results obtained show that the "on-water"/microwave-promoted reaction provides comparable results, in terms of generality and yield, to the thermal process in an organic solvent that has previously been described, but shows significant advantages, such as a dramatic reduction in reaction times and the replacement of the *tert*-butoxide bases by a simple KOH solution. Moreover, from a practical point of view, in the reactions that occur as a suspension in water, the slow addition of the sensitive sulfonate is not required. Nevertheless, an excess of the sulfonate is still necessary to achieve complete conversion. As expected, the reactions with nonaflates provided better results than those with triflates (Table 3, entries 12 vs. 16, and 15 vs. 19). Importantly, under these conditions, the regioselectivity is also retained if *o*-bromochloro or *o*-chloroiodobenzene derivatives are employed (Table 3, entries 6–8); the C–C-bond formation occurs at the position of the more reactive halogen. The reactions with *o*-chlorosulfonates also proceed with total regioselectivity (Table 3, entries 11–20), with the C–C-bond formation taking place at the position of the sulfonate. This is an important feature as it allows the regioselective synthesis of indoles with substituents on the six-membered ring by employing *o*-chlorophenols as starting materials.

Conclusion

We have reported the beneficial effect of the "on-water"–microwave combination on the Pd-catalyzed cascade synthesis of indoles. The reactions take place under heterogeneous conditions: the coupling partners (imines and arenes), as well as the ligand for Pd, are insoluble in water. The main

Table 3. Generality of the microwave, "on-water" synthesis of indoles **3**.

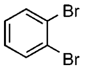
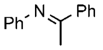
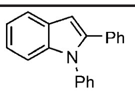
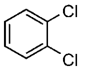
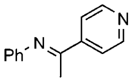
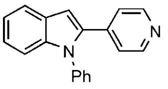
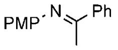
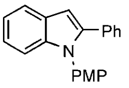
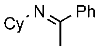
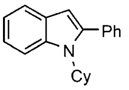
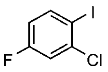
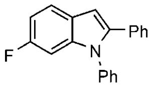
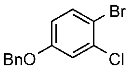
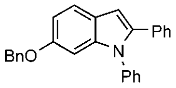
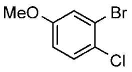
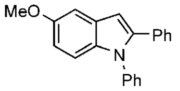
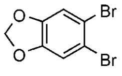
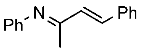
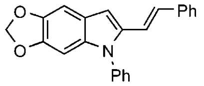
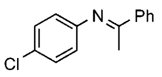
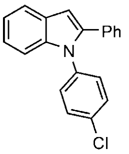
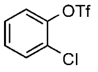
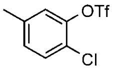
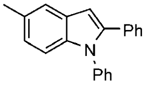
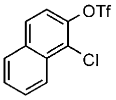
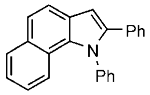
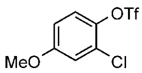
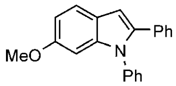
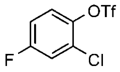
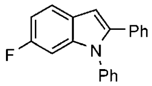
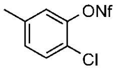
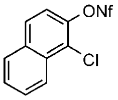
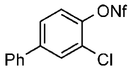
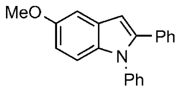
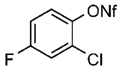
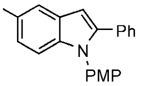
	Arene		Imine		Conditions[a,b]	Indole **3**		Yield [%][c]
1		**1a**		**2a**	45 min 140 °C		**3a**	89
2		**1b**		**2a**	45 min 140 °C		**3a**	72
3		**1a**		**2b**	45 min 160 °C		**3b**	67
4		**1a**		**2c**	60 min 160 °C		**3c**	60
5		**1a**		**2d**	40 min 140 °C		**3d**	77
6		**1c**		**2a**	45 min 160 °C		**3e**	62
7		**1d**		**2a**	30 min 150 °C		**3f**	61
8		**1e**		**2a**	45 min 160 °C		**3g**	68
9		**1f**		**2e**	30 min 150 °C		**3h**	60
10		**1a**		**2f**	45 min 160 °C		**3i**	64
11		**4a**		**2a**	45 min 160 °C		**3a**	75

Table 3. (Continued)

	Arene	Imine	Conditions[a,b]	Indole **3**	Yield [%][c]
12	 **4b**	**2a**	45 min 160 °C	 **3j**	76
13	 **4c**	**2a**	45 min 160 °C	 **3k**	49
14	 **4d**	**2a**	45 min 160 °C	 **3l**	47
15	 **4e**	**2a**	45 min 160 °C	 **3m**	48
16	 **5b**	**2a**	45 min 160 °C		**3j** 92
17	 **5c**	**2a**	45 min 160 °C		**3k** 63
18	 **5d**	**2a**	45 min 160 °C	 **3n**	93
19	 **5e**	**2a**	45 min 160 °C		**3m** 70
20	**5b**	**2c**	45 min 160 °C	 **3o**	85

[a] Reactions with *o*-dihaloarenes: [$Pd_2(dba)_3$] (2 mol%), Xphos (4 mol%), imine **1** (0.5 mmol), 1,2-dihaloarene **2** (0.5 mmol). [b] Reactions with *o*-haloarene sulfonates **4** or **5**: [$Pd_2(dba)_3$] (2 mol%), Xphos (8 mol%), imine (0.5 mmol), sulfonate (0.75 mmol). [c] Isolated yield.

advantages to performing the reaction under heterogeneous conditions and microwave heating, over the homogenous reaction in organic solvent under conventional heating, are as follows: 1) the reaction times are dramatically reduced; 2) the use of an organic solvent is avoided; 3) an aqueous solution of KOH is employed, in place of alkaline *tert*-butoxide; 4) the slow addition of the sensitive *o*-haloarene sulfonates is no longer necessary; and 5) the catalyst loading can be reduced. As a consequence, the advantages and simplicity of this experimental protocol cause it to be, in many cases, the method of choice for the high-speed synthesis of substituted indoles.

Experimental Section

General information: The reactions under thermal conditions were carried out in a RR98030 12 place Carousel Reaction Station™ from Radleys Discovery Technologies, equipped with gas-tight threaded caps with a valve, cooling reflux head system, and digital temperature controller. The reactions under microwave irradiation were carried out in a Biotage Initiator™ apparatus, with power and pressure control, at constant temperature. Palladium salts and ligands were purchased from Aldrich and Strem and were used without further purification. The starting materials, imines and noncommercial 1,2-dihaloarenes, *o*-chlorotriflates and *o*-chlorononaflates, were prepared as previously reported in reference [4b].

General procedure for the synthesis of indoles 3 under suspension in water and microwave heating: A reaction tube was charged with Xphos (24.9 mg, 0.04 mmol, 8 mol%), tetrabutylammonium bromide (20 mg, 0.062 mmol, 0.125 equiv), [$Pd_2(dba)_3$] (9.62 mg, 0.01 mmol, 2 mol%), imine **2** (0.5 mmol), the corresponding 1,2-dihaloarene **1** (0.5 mmol) or *o*-halosulfonate **4** or **5** (0.75 mmol), and aqueous KOH (1.25 mL, 3 N, 7.5 equiv). The tube was sealed and irradiated at the appropriate temperature (140–160 °C) for a period of 30–45 min (see Table 3). The reaction mixture was allowed to cool to RT and treated with CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer extracted with additional CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product mixture was purified by column chromatography.

Most of the indoles **3** synthesized have previously been reported by us in reference [4b]. Characterization data for new compounds is included in the Supporting Information.

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