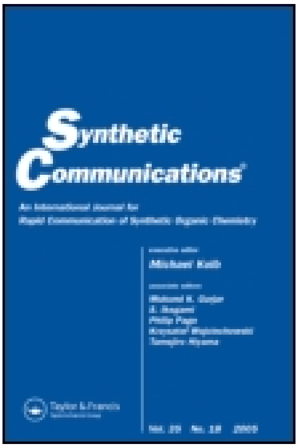

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Microwave-Assisted Ullmann-Type Coupling Reactions in Alkaline Water

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MICROWAVE-ASSISTED ULLMANN-TYPE COUPLING REACTIONS IN ALKALINE WATER

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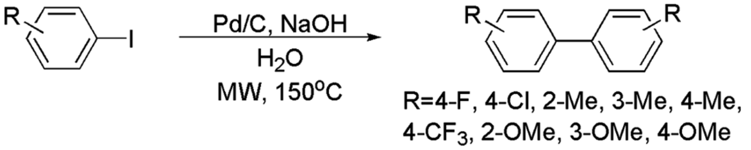
GRAPHICAL ABSTRACT



Abstract *Upon microwave irradiation, homocoupling reaction of aryliodides catalyzed by Pd/C in alkaline water media can be readily accelerated to form biaryls with excellent conversions and selectivities.*

Keywords Aqueous media; microwave; Pd/C; Ullmann-type coupling

INTRODUCTION

Coupling of aromatic compounds is of great importance in many applications, ranging from materials science to medicinal chemistry. Ullmann discovered the Cu-mediated homocoupling of aromatic compounds in the beginning of the past century.[1] The drawback of this method is the requirement for extensive use of copper under vigorous conditions. Although some Cu catalysts have been reported to promote Ullmann-type coupling reactions at room temperature,[2] scientists have studied and found many improvements for aromatic homo- and cross couplings.[3–5]

Most of recent work on Ullmann-type couplings have focused on the use of catalytic amounts of Pd-catalysts. $Pd(OAc)_2$ has been reported to catalyze biaryl formation in the presence of a quaternary ammonium salt, base, and a hydrogen source for *in situ* regeneration of Pd(0) species.[6] Similar conditions give unsymmetrical coupling products with appropriate choice of starting materials.[7] Related Pd-catalyzed, fluoride-mediated couplings have also been reported.[8] Further improvements on reactions in organic solvent have focused mostly on the development of different systems that reduce formed Pd(II) species to Pd(0).[9–13]

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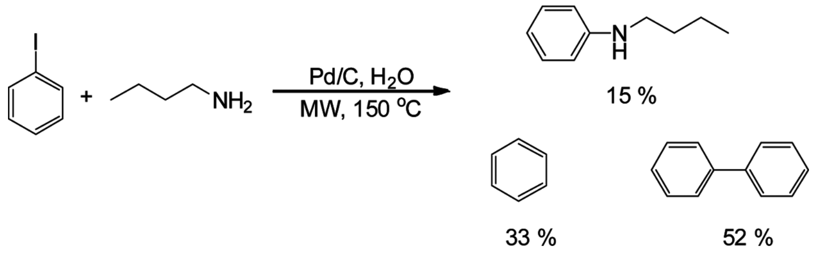


Scheme 1. Biphenyl formation during arylation of *n*-butylamine.

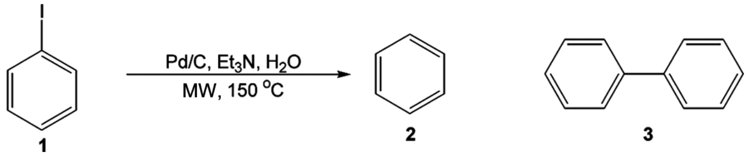
As a part of the search for environmentally sustainable solvents, homocoupling of halo-benzenes in supercritical CO_2 has been reported.[14] In addition, the use of water as a reaction media has attracted considerable interest.[15–20] The use of various reductants, such as molecular hydrogen,[15] zinc,[16] zinc with additives or CO_2,[17,18] and sodium formate with additives, have been studied in detail.[19,20] While in many cases good conversions and biphenyl selectivities may be achieved, long reaction times are still a frequent disadvantage.

This decade has seen a tremendous increase in the number of microwave-assisted organic syntheses that possibly accelerate reactions and occasionally enhance selectivity. This has become of great interest as a part of the search for environmentally sustainable chemical transformations.[21–24] Thus we have been interested in microwave-accelerated transformations that use water as a solvent and reactant.[25,26] During our efforts to develop environmentally friendly alkylations of amines,[26,27] we observed the formation of a biaryl side product (Scheme 1). This prompted us to study further the possible benefits of this reaction. Herein, we report the results of this initial study, which represents a new green way to couple iodo functional aromatic compounds.

RESULTS AND DISCUSSION

The studies to improve selectivity and conversion of the desired biphenyl product were started by screening the amount of amine added to the reaction mixture. *n*-Butylamine used in the experiments carried out previously reacts with itself to give di-*n*-butylamine and butylidene-*n*-butylamine.[27] Thus, a stable tertiary amine, triethylamine (Et_3N), was used instead. It was found that an increasing amount of amine significantly improved the conversion (Table 1, entries 2–6). Similarly, an increased amount of amine clearly improved the selectivity of the reaction as dehalogenation of the starting material became less favorable (entries 1–6). On the other hand, excessive addition of amine resulted in clearly reduced conversion (entry 1). Thus, the best selectivity was obtained using a sixfold molar excess of amine (entry 1), while the greatest conversion of the starting material was observed with the use of a fourfold molar excess to iodobenzene (entry 2). The reason for the decreased conversion with excessive use of amine is not fully understood. A plausible reason for this may be that the Et_3N and the starting material form a strongly separated phase where the reaction no longer proceeds in a rate similar to experiments utilizing lesser Et_3N amounts. The absence of Et_3N resulted in poor selectivity and conversion

Table 1. Effect of the amount of triethylamine



			Selectivity (%)	
Entry	Et_3N:PhI [mol:mol]	Conversion [%]	**2**	**3**
1	6:1	71	30	70
2	4:1	100	46	54
3	2:1	67	42	58
4	1:1	47	50	50
5	0.4:1	38	63	27
6	0:1	5	74	25
7[a]	1:1	0	0	0
8[b]	1:1	37	72	28
9[c]	1:1	41	85	15
10[d]	1:1	3	100	0

Conditions: Pd/C (50 mg, 4.8 mol%), Et_3N, H_20 (2 mL), MW irradiation (150 °C, 30 min).
[a] No Pd/C was used.
[b] Bromobenzene (0.49 mmol).
[c] Chlorobenzene (0.49 mmol).
[d] Biphenyl (38 mg, 0.25 mmol).

(entry 6). The starting material was recovered when Pd/C was left out of the reaction mixture (entry 7). Reductive coupling of bromobenzene and chlorobenzene could also be achieved, albeit with low conversion (entries 8 and 9). The possibility of degradation of the product during reaction was evaluated by treating biphenyl under identical conditions (entry 10). Only 3% or less of the starting biphenyl was converted to benzene, suggesting that formed biphenyls are quite stable under the reaction conditions.

The effects of some common inorganic bases were also evaluated. Inorganic bases may be of greater interest because of lower cost, simplified reaction mixtures, and possibly decreased leaching of Pd to water when compared to amines. Results in Table 2 demonstrate that the inorganic bases display lower conversions compared to equal amounts of Et_3N (compare entries 2 and 3, Table 1). On the other hand, the use of inorganic bases significantly improves the selectivity of the reaction. While an increased amount of Et_3N improved the conversion and selectivity of the reaction, an increase in inorganic base did not have an equally beneficial effect. A fourfold excess of base slightly increased the conversion while the selectivity remained virtually unaffected. The basicity of the solution may play a minor role. The calculated pH range for the Et_3N solutions used is 11.9–12.5 and that of the NaOH solution is 13.1–14. Hence, an increased basicity may have a beneficial influence. However, it is believed that the Et_3N alters the catalyst activity, leading to the observed differences between the inorganic bases and Et_3N. Of the inorganic bases examined, NaOH displayed the greatest conversion and was therefore chosen for further experiments.

Table 2. Effect of inorganic bases

Entry	Base	Base:PhI [mol:mol]	Conversion [%]	Selectivity (%)	
				2	**3**
1	$NaHCO_3$	2:1	27	6	94
2	$NaHCO_3$	4:1	33	6	94
3[a]	$NaHCO_3$	4:1	4	12	88
4	Na_2CO_3	2:1	31	7	93
5	Na_2CO_3	4:1	33	7	93
6[a]	Na_2CO_3	4:1	7	7	93
7	K_2CO_3	2:1	27	7	93
8	K_2CO_3	4:1	30	8	92
9[a]	K_2CO_3	4:1	6	8	92
10	NaOH	0.5:1	14	4	96
11	NaOH	1:1	33	3	97
12	NaOH	2:1	37	6	94
13	NaOH	4:1	40	8	92
14[a]	NaOH	4:1	9	7	93

Conditions: Pd/C (50 mg, 4.8 mol-%), base, H_2O (2 mL), MW irradiation (150 °C, 30 min).
[a] Oilbath heating (150 °C, 30 min).

The effect of heating and some additives was evaluated by treating iodobenzene with Pd/C and a base under different conditions. These results are summarized in Table 3. Comparison of results obtained by oil bath heating (Table 2, entries 3, 6, 9, 12, and Table 3, entry 1) with other results demonstrates that microwave irradiation may significantly improve reaction rates. Recently it was discovered that the use of simultaneous air cooling during microwave heating of reaction mixtures leads to erroneous temperature measurements if an infrared (IR) temperature sensor is used to collect the temperature data.[28] Therefore, results obtained using our

Table 3. Effect of additives, heating and reaction time

Entry	Base	Base:PhI [mol:mol]	Heating method	Time [min]	Conversion [%]	Selectivity (%)	
						2	**3**
1	Et_3N	2:1	150 °C, OB	30	36	33	67
2	Et_3N	2:1	50 W, MW	10	36	33	67
3[a]	Et_3N	2:1	150 °C, OB	30	62	27	73
4	Et_3N	4:1	150 °C, MW	15	96	55	45
5	NaOH	4:1	150 °C, MW	120	68	8	92
6[b]	NaOH	4:1	150 °C, MW	30	72	14	86
7[c]	NaOH	4:1	150 °C, MW	60	90	34	66
8[d]	NaOH	4:1	150 °C, MW	60	96	53	47
9[e]	NaOH	4:1	150 °C, MW	60	58	19	81

Conditions: Pd/C (50 mg, 4.8 mol%), Et_3N, H_2O (2 mL).
[a] No water used.
[b] Pd/C (100 mg, 9.6 mol%).
[c] Zn (16 mg, 50 mol-%) added.
[d] Al (7 mg, 50 mol-%) added.
[e] Mg (6 mg, 50 mol-%) added.

microwave setup also may be affected by a higher temperature than that recorded by the instrument. However, while the heating method had little effect on selectivity in reactions with inorganic bases, reactions with Et_3N carried out in oil baths seemed to have improved selectivities. Oil bath heating (entry 1, Table 3) resulted in notably lower conversions but improved selectivity when compared to continuous microwave irradiation at the same temperature (entry 3, Table 1). Similarly, the use of continuous 50-W microwave irradiation without cooling (entry 2, Table 3) reduced the reaction time by one third. The optimum amount of Et_3N gave good conversions in extremely short times (entry 4, Table 3). As earlier noted, the amount of amine significantly affected the reaction rate, while the amount of inorganic bases did not display a similar effect. Fortunately, longer reaction times required to achieve improved conversion did not result either in decreased selectivity (entry 5, Table 3) or decomposition of biphenyls.

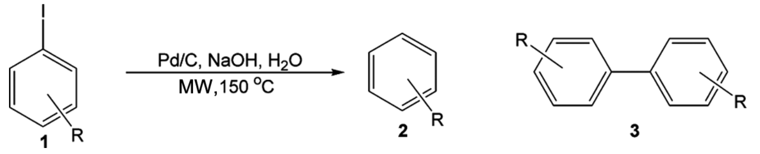
Reactions carried out in the absence of water using Et_3N as the base gave greater conversions (Table 3, entry 3) compared with results obtained with water (entry 1). In addition, the selectivity improved slightly when water was not used. Attempts to carry out the reaction under microwave irradiation without water resulted in either cracked test tubes or explosions. The use of inorganic bases required water as reaction media.

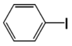
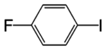
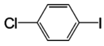
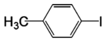
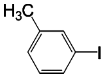
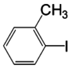
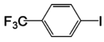
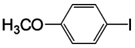
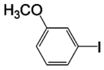
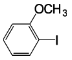
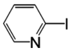
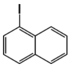
Recently, rhodium was found to catalyze homocoupling of halobenzenes.[29] This prompted us to test other carbon-supported catalysts. Contrary to previous observations, the use of Rh/C instead of Pd/C gave only trace amounts of products. Similarly, the use of Ru/C resulted in recovery of starting material. A Pt/C-catalyzed reaction, on the other hand, gave a 10% conversion with 69% selectivity. Thus, Pd/C was the best catalyst under our conditions.

Reports on reductive homocouplings of halobenzenes suggest that availability of vacant, catalytically active Pd(0) sites are essential for improving the selectivity and the conversion of the reaction.[20] Increased amount of Pd significantly improved both the conversion and the selectivity (Table 3, entry 6), thus confirming previous observations. Another way to increase vacant Pd(0) sites is to provide mechanisms for reduction of oxidized Pd species. This has been achieved by addition of reducing agents such as hydroquinone,[9] molecular H_2,[15] or Zn, sodium formates which in situ generate H_2.[16,19] We evaluated the effect on the reaction outcome of Zn and Al additives in aqueous media, knowing that these metals in water can generate in situ H_2 (being thus a substitute for molecular H_2). Observation of enhanced conversions suggest that the amount of catalytically active Pd(0) sites have increased (entries 7 and 8). However, increased H_2 pressure results in formation of Pd-hydride species, which concomitantly increase the undesired reduction of iodobenzene to benzene.[20] It has been suggested that this undesired reduction may be avoided by addition of polyethylene glycol (PEG) or phase-transfer catalysts to the reaction mixture. These apparently reduce the formation of Pd hydrides, which leads to dehalogenation, by essentially microencapsulating the catalyst from an excess of H_2 gas. In contrast to the addition of Zn and Al, 50 mol% magnesium granules added to the reaction mixture improved the conversion of the starting material slightly without affecting the selectivity too much.

Various substituted aromatic compounds were treated with Pd/C in alkaline water under microwave irradiation to evaluate the possibility of preparing functional biphenyls (Table 4). Literature does not provide a clear indication whether electron-withdrawing (EWG) or electron-donating groups (EDG) facilitate Pd-catalyzed homocoupling reactions. In fact, previous reports give mixed suggestions on the preference for either EWG or EDG in Pd-catalyzed reductive couplings.[8,9] Our results imply that both EWG and EDG substituents in the *para* position increased the reaction rate. However, aromatic compounds substituted with EDG displayed markedly greater conversions (entries 8–10) compared to iodobenzene and compounds bearing EWGs. Some substituted iodobenzenes were observed to display minor impurities ($\sim$2%) due to migration of coupling site (entries 6–10 and 12). These minor impurities displayed analogous mass spectra as the desired product. For instance, 3-iodoanisole displayed only one other impurity (3,4′-dimethoxybiphenyl) in addition to the expected anisole, which is a result of reductive

Table 4. Various substituted aromatics: steric and electronic effects



Entry	Compounds	Conversion (%)	Selectivity (%)	
			2	**3**
1		46	9	91
2		56	7	93
3		55	5	95
4		41	13	87
5		35	12	88
6		14	67	20 (3)
7		56	5	92 (3)
8		76	6	92 (2)
9		80	5	93 (2)
10		84	8	90 (2)
11		47	3	83 (14)
12		15	13	60 (27)

Note: Conditions: starting aryliodide (0.49 mmol), Pd/C (50 mg, 4.8 mol%), 1 M NaOH (2 mL, 4:1 mol/mol). MW 150 °C, 60 min; side product ratio in parentheses: e.g., 2,3′-dimethoxybiphenyl.

dehalogenation (entry 9). Electron-donating substituents appear to be more susceptible for dehalogenation, resulting in lower selectivities. However, a clear difference in selectivity between electron-releasing and electron-withdrawing groups could not be identified. Reported observation of intramolecular C-H activation of the methoxy group to give triaryls was not observed.[30] It is worth mentioning that the reaction of *p*-iodochlorobenzene under the condition gave only homo-coupling product 4,4′-dichlorobiphenyl without cross-coupling chlorophenyl-iodobenze or dehalogenated products such as biphenyl and monochlorobiphenyl (entry 2).

Some reports indicate that biaryl formation of *O*-substituted haloaromatics is not favored because of steric hinderance.[13] In fact, *o*-iodotoluene together with 1-iodonaphthalene displayed the lowest conversion of all functional aromatic compounds. These results suggest that steric effects are of importance in the reaction that takes place. While the conversion for iodotoluenes was observed to decrease in the order of $p > m > o$ substitution (entries 4–6), the contrary was observed for iodoanisoles. The opposite, contradicting trend with iodoanisoles compared to iodotoluenes, suggests that the oxygen lone pair in the ether linkage may alter the catalyst activity.

Selected reactions were run on a larger scale to isolate products, to confirm conversions calculated by gas chromatography (GC), and to evaluate possibilities for scaleup. The CEM Discovery microwave reactor was fitted with an 80-mL pressure-resistant glass reactor. A 10-fold amount of all reagents were fed in to the reactor, and an identical irradiation program with simultaneous cooling was used. In this way, 0.21 g (53% yield, 62% by GC) of biphenyl was obtained after 2.5 h reaction at 150 °C. Similarly, 43% yield (53% by GC) of 4,4′-dimethoxybiphenyl and 62% (67% yield by GC) of 2,2′-dimethoxybiphenyl was obtained after 2 h. The longer reaction times required are most likely due to difficulties associated with microwave penetration through the reaction media, thus again demonstrating the beneficial effect of microwave irradiation versus conventional thermal heating.

EXPERIMENTAL

Caution! Experiments carried out in the absence of water under microwave irradiation resulted in frequent explosions. The use of water was therefore necessary.

Experiments were carried out by placing a Teflon-covered magnetic stir bar, 0.49 mmol substrate, a predetermined amount of base, and water into a pressure-resistant glass tube. The volume of water added to the reaction mixture in all experiments was 2 mL, unless otherwise stated. The test tube was sealed with a Teflon-covered cap and placed into a cavity of microwave reactor (Discover, CEM Corp.) using continuous microwave irradiation to maintain 150 °C with simultaneous cooling. The microwave intensity was 60 ± 3 W at the end of the reaction. After the reaction, the reaction mixture was allowed to cool to room temperature and extracted once with 2.5 mL diethyl ether or CH_2Cl_2. The organic layer was analyzed by GC (Shimadzu GC2014 equipped with FID-detector) and GC-MS (Jeol SUN-200, electron impact ionization system).

The purity of all starting materials was determined to be >98% by GC. Products were identified from their mass spectra and retention times of the authentic compounds. The conversions and selectivities were calculated using calibration curves made by peak areas of each product and starting compounds in GC chromatograms.

CONCLUSION

A facile way to prepare biphenyls in water has been developed. The use of microwaves permits the Pd/C-catalyzed reaction to proceed with good yields and good selectivity in alkaline water. The reaction proceeds very slowly without the use of microwave irradiation. The choice between organic (amines) and common inorganic bases gives a convenient way to choose reaction conditions resulting in rapid conversion or good selectivity. The use of inorganic bases is particularly attractive as the only organic materials used are the starting material and products thereof. This may simplify the product isolation process considerably. Results also suggest that the reactions may be scaled up, although this requires somewhat longer reaction times.

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