

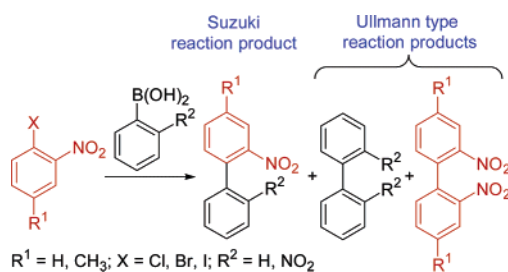
Synthesis of 2-Nitro- and 2,2'-Dinitrobiphenyls by Means of the Suzuki Cross-Coupling Reaction

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Mechanistic investigations and protocols for the synthesis of 2-nitrobiphenyls and 2,2'-dinitrobiphenyls are disclosed. It is revealed that obstacles appear during the transmetalation step when the phenylboronic acid is substituted with a nitro group in the 2-position, whereas when substituted in the 3- or 4-positions, the reaction follows similar patterns as found in the electrophilic substitution of nitrobenzenes, an observation that may be attributed to the elimination step of the catalytic cycle.

Projects in progress in our laboratory envisaged access to unsymmetrical substituted 2,2'-dinitrobiphenyls **3** ($R' \neq R''$) and 2-nitrobiphenyls **4** ($R' \neq R''$). The first mentioned class of compounds was required for the synthesis of various substituted benzo[c]cinnolines **7** and other compounds containing similar frameworks. 2-Nitrobiphenyls **4** were required for the synthesis of various substituted 9*H*-carbazoles **8** in general and carbazomycines (A-H)¹ in particular. Symmetrically substituted 2,2'-dinitrobiphenyls could easily be prepared according to an Ullmann-type protocol,² after which the biphenyl could be submitted to our recently disclosed process for the preparation of the benzo[c]cinnoline framework.³ The desired 9*H*-carbazole skeleton **8** might be arrived at by

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means of various previously reported methods⁴ utilizing 2-nitrobiphenyls **4** as substrates.

Initially we believed that the unsymmetrical substituted 2,2'-dinitrobiphenyls **3** ($R' \neq R''$) would be easily accessible by means of the palladium-catalyzed Suzuki cross-coupling reaction,⁵ since that protocol is one of the most efficient methods for the construction of C(sp²)–C(sp²) bonds: reaction of 2-nitrohalobenzenes **1** with 2-nitrophenylboronic acids **2** in the presence of a palladium catalyst. A literature screening revealed a vast amount of material concerning the Suzuki cross-coupling reaction,⁶ but surprisingly, very few reports touched on the preparation of nitro-substituted biphenyls, and to the best of our knowledge, any prior reports concern the preparation of unsymmetrically substituted 2,2'-dinitrobiphenyls **3**. Some recent reports, however, disclosed findings concerning the Suzuki cross-coupling of 2-nitrohalobenzenes with 2-substituted phenylboronic acid^{7–13} that possibly could be utilized for our synthetic pathway to the carbazole **8** framework.

Pd Catalysts. Suzuki cross-coupling reactions using a series of various ligands for the palladium catalyst has been reported,^{14,15} a feature that was included in our initial screening for suitable reaction conditions to our targets. Some of the most frequently used catalysts in this context are Pd(PPh₃)₄, Pd(OAc)₂, and PdCl₂ when the halobenzene is bromide or iodide. Preparation of 4-methyl-2,2'-dinitrobiphenyl **3b** was attempted according to the protocols by Buchwald and co-workers¹⁴ and by Tao and Boykin.¹⁵ However, under these conditions, the trials provided only low yields.

Phase Transfer Catalysts. Tetrabutylammonium bromide (TBAB) is known to stabilize colloidal palladium nanoparticles that act as catalysts in the Suzuki coupling of aryl bromides.¹⁶ Bedford and co-workers¹⁷ have shown that palladium acetate with TBAB in water could be used as an effective catalyst for the Suzuki cross-coupling

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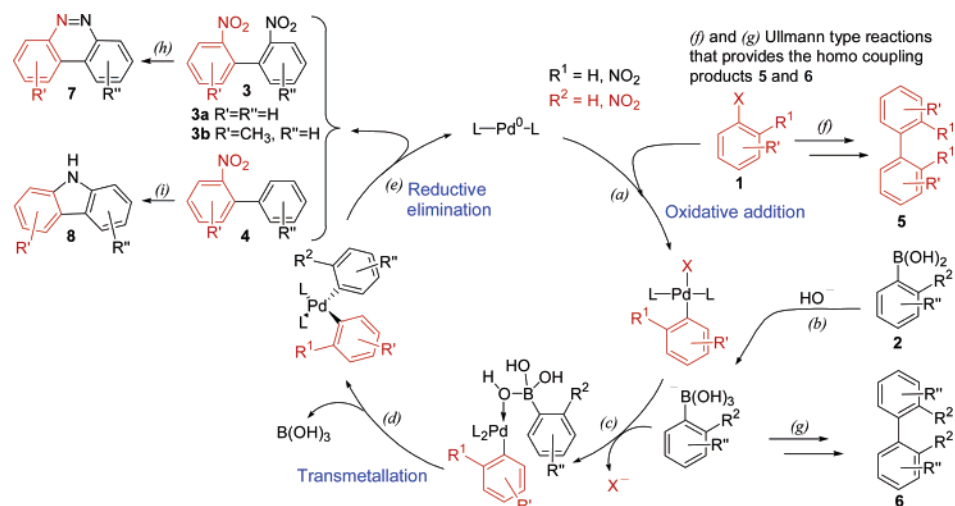
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SCHEME 1



reaction. Arcadi and co-workers¹¹ used Pd/C in a mixture of cetyl trimethylammonium bromide (CTAB) and water for the preparation of 2-nitrophenyl **4a** in high yields. Our attempts to synthesize 4-methyl-2,2'-dinitrophenyl **3b** by reacting 1-iodo-4-methyl-2-nitrobenzene with 2-nitrophenylboronic acid with either $(\text{Ph}_3\text{P})_4\text{Pd}$ or Pd/C as catalysts provided, however, only the Ullmann product 4,4'-dimethyl-2,2'-dinitrophenyl via homocoupling of the halo-aryl compound.¹⁸

Solvents. The use of a wide selection of solvents has been reported for the Suzuki cross-coupling reaction.^{8,10–13,19–25} During our introductory screening for suitable reaction conditions, a series of solvents was therefore included in our assessment. Our list of solvent investigated included acetone,¹³ dimethyl formamide (DMF)^{19–21} water,^{11,12,22,23} toluene,^{8,10,24,25} 1,4-dioxane,¹⁵ and dimethyl sulfoxide (DMSO).²⁶ The results of those experiments, however, failed to provide high yields comparable to those reported for other substituted biphenyls. Biphasic solvent systems, such as DMF and water in the presence of a phase transfer catalyst, for example, TBAB, has been used for Pd(OAc)₂-catalyzed Suzuki coupling reactions.^{20,22,23} Our attempt to utilize such conditions for the synthesis of 2,2'-dinitrophenyl **3a** revealed nevertheless a dramatic decrease in the yield (10–20%) compared to the reported examples lacking the nitro group in the 2,2'-positions.

Bases. Various base–solvent combinations have been reported to give improved Suzuki cross-coupling reaction,

although the generality of these protocols is not clear. In the present project, we have thus investigated the effect of the base, pathway (b), Scheme 1. Throughout our base screening, the following compounds were investigated: KH_2PO_4 , K_2HPO_4 , K_3PO_4 ,^{20,24,25} Na_2CO_3 ,^{8,10,22} K_2CO_3 ,^{11–13} $\text{Ba}(\text{OH})_2$,¹⁹ and Et_3N .²¹ Trial reaction of 2-nitrophenylboronic acid and 2-nitro-halobenzene with KH_2PO_4 as base in combination with the biphasic solvent system DMF–H₂O provided a yield of 30%²⁷ of 2,2'-dinitrophenyl **3a**. These promising results prompted us to perform a thorough investigation of that protocol by means of statistical experimental design²⁸ and multivariate regression,²⁹ although further improvements with respect to the yields were not accomplished. Nevertheless, the protocol found to provide the highest yield of 2,2'-dinitrophenyl **3a**²⁷ was subjected to further explorative investigation. An increased quantity of the catalyst Pd(OAc)₂, augmenting from 2 to 10 mol %, did not provide an improved yield of the desired product **3a**, but a significant quantity of **6** (pathway (g), Scheme 1) was found. A yield of 29% of **6** was achieved when 10 mol % of Pd(OAc)₂ was used compared to a yield of 13% when 2 mol % Pd(OAc)₂ was used. However, several attempts to use the most common catalyst, Pd(PPh₃)₄, for the Suzuki cross-coupling reaction for our target **3** provided only low yields. Changing the halogen atom (Br, I) of the 2-nitrohalobenzene did not appear to play any significant role for the course of the reaction. It is known that phenylboronic acid **2** may undergo homocoupling to provide the

(18) **Reaction Conditions.** K_2CO_3 (3.2 mmol), Pd(PPh₃)₄ or Pd/C (3%), CTAB (1 mmol), 1-iodo-4-methyl-2-nitrobenzene (1.6 mmol) and 2-nitrophenylboronic acid (1 mmol) were placed under N₂ in a sealed tube with H₂O (8 mL). The mixture was stirred and heated at 150 °C for 4 h, samples were analyzed by GC–MS, and % yields were calculated by means of a correction factor with 1-chloro-2,4-dinitrobenzene as internal standard. The homocoupling product 4,4'-dimethyl-2,2'-dinitrophenyl was obtained in 7% yield with $(\text{Ph}_3\text{P})_4\text{Pd}$ as catalyst and 36% yield with Pd/C as catalyst.

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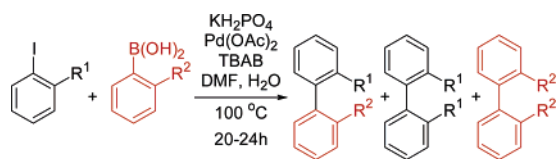
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(27) **Reaction Conditions.** KH_2PO_4 (2.0 mmol), Pd(OAc)₂ (0.02 mmol), TBAB (0.2 mmol), 1-bromo-2-nitrobenzene (1.0 mmol) **1**, and 2-nitrophenylboronic acid (1.5 mmol) **2** were placed under N₂ atmosphere into a sealed tube that contained DMF/H₂O (5 mL:0.25 mL). The resulting mixture was stirred and heated at 150 °C for 20 h, samples were analyzed by GC–MS, and % yields were calculated by means of a correction factor with 1-chloro-2,4-dinitrobenzene as internal standard. Title compound 2,2'-dinitrophenyl was determined in a yield of 30%.

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SCHEME 2. Suzuki Cross-Coupling Trials with KH_2PO_4 as Base in DMF and H_2O


	R ¹	R ²	Ullmann products		
1 ^a	NH ₂	NO ₂	6% 4b	35%	3%
2	OCH ₃	NO ₂	53% 4c	18%	nd
3	NO ₂ , 4-CH ₃	NO ₂	7% 3b	9%	13%
4	NO ₂	OCH ₃	52% 4c	nd	9%
5	NO ₂	CH ₃	49% 4d	nd	7%
6	NO ₂	CF ₃	4% 4e	6%	nd
7	NO ₂	Cl	58% 4f	nd	16%
8	NO ₂	NH ₂	48% 4b	nd	24%
9	NO ₂	H	41% 4a	nd	nd
10 ^b	H	NO ₂	41% 4a	58%	nd
11 ^c	NH ₂	H	3% 9	63%	9%
12 ^d	NO ₂	NO ₂	30% 3a	-	-

^a Reaction time = 48h. ^b Reaction time = 72 h. ^c Heated at 125 °C for 20 h. ^d Reaction conditions provided in ref 27. nd = not detected.

symmetrical substituted biphenyl **6**.³⁰ Dyker and Kellner³¹ have reported that the Ullmann products are produced under Suzuki conditions in high yield as a result of the electron-withdrawing group (NO₂). Pd(OAc)₂ in DMF (or DMA) contributed also to induction of the Pd-catalyzed Ullmann coupling reaction of aryl iodides or bromides. Crossover experiments that were performed revealed that our protocol²⁷ also provided the Ullmann-type coupling products **5** and **6**. Homocoupling of 1-halo-2-nitrobenzene **1** following pathway (f), Scheme 1, provides the symmetrically substituted product **5** (R' = 4-CH₃), whereas homocoupling of phenylboronic acid **2**, pathway (g), Scheme 1, will provide the symmetrical substituted compound **6**.

Various 2'-Substituted 2-Nitrobiphenyls. The protocol developed above²⁷ was also tried for the synthesis of a series of various 2'-substituted 2-nitrobiphenyls, see Scheme 2. Even though high conversions (60–100%) were achieved, the yield varied in the range 3–58%, which immediately suggests a subtle balance of steric and electronic influence in the various substituents. The obstacles with the NO₂ group in the 2-position may be related to findings disclosed in a recent report³² that states not only that the 2-nitro group of the reacting species operates as an electron-withdrawing group but also that the nitro group intervenes in the coordination of the incoming palladium atom.

Some recent reports on the synthesis of 2-nitrobiphenyl^{11–13} disclose the utilization of potassium carbonate as base in combination with various polar solvents, namely, water with TBAB, water with CTAB, or pure

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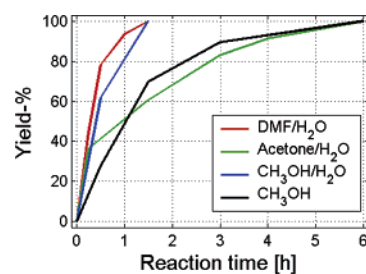
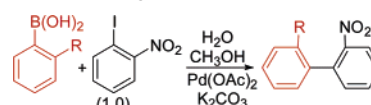


FIGURE 1. Synthesis of 2-nitrobiphenyl in various solvents. Conditions: K₂CO₃ (2 mmol, 0.276 g), Pd(OAc)₂ (0.02 mmol, 4.5 mg), 1-iodo-2-nitrobenzene (1 mmol, 0.249 g), and phenylboronic acid (1 mmol, 0.122 g) were placed under N₂ atmosphere in a round-bottom flask containing solvent/water (5 mL:1 mL) or solvent (5 mL). The reaction mixture was stirred at 20 °C for 1.5–6 h.

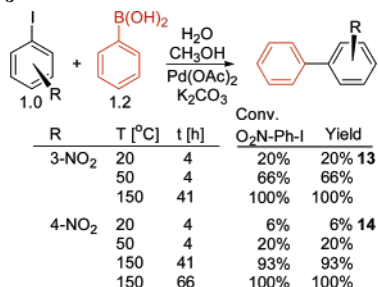
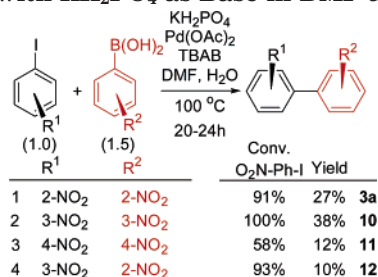
SCHEME 3. Suzuki Cross-Coupling Trials with K₂CO₃ as Base in CH₃OH and H₂O


R	n [mmol]	T [°C]	t [h]	Yield
1 ^a H	1.0	20	5	96% 4a
	1.0	20	1.5	99% 4a
2 OCH ₃	1.0	20	28	95% 4c
3 CH ₃	1.2	50	24	99% 4d
4 CF ₃	1.2	50	24	~3% 4e
5 Cl	1.2	50	24	~2% 4f
6 NH ₂	1.2	75	5	nd 4b
7 ^b H	1.0	20	4	99% 4g

^a Reaction was carried out in methanol (5 mL). ^b The halo-aryl reagent for this experiment was 1-chloro-2,4-dinitrobenzene, a reaction that provided 2,4-dinitrobiphenyl as the only product. nd = not detected.

acetone as reaction medium. The reaction temperatures were in the range 60–110 °C with a reaction time of 1–24 h. During the present study, further investigations of analogous protocols with potassium carbonate as the base have been carried out. Figure 1 shows the course of the reaction of four discrete Suzuki cross-coupling experiments, namely, with DMF–water (5:1), acetone–water (5:1), methanol–water (5:1) or pure methanol as reaction medium, respectively.

As the reaction profiles illustrate, the two reactions conducted with DMF–water and methanol–water as reaction media both provided 2-nitrobiphenyl in quantitative yields after only 1.5 h of reaction time. The other two experiments approached quantitative yields as well, although after an additional 4.5 h of reaction time. In contrast to prior work, our protocol requires a lower reaction temperature, namely, within a temperature range of only 20–50 °C. Moreover, our protocol did not require the presence of any phase transfer catalyst or any supporting ligand for the palladium catalyst. Attempt to synthesis 2,2'-dinitrobiphenyl **3** with this protocol failed. This spurred us on to undertake investigations that could reveal information about which step in the catalytic cycle (Scheme 1) was being obstructed. Since the reaction between the 2-nitro-haloarene **1** (R¹ = NO₂, R' = H) and phenylboronic acid **2** (R² = R'' = H) proceeds smoothly in high yield (Scheme 3), a comparative experiment was to react a haloarene **1** (R¹ = R' = H) with 2-nitrophenyl boronic acid **2** (R² = NO₂, R'' = H), a reaction that failed.

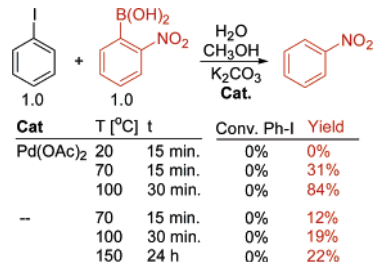
SCHEME 4. Suzuki Cross-Coupling Experiments with K_2CO_3 as Base in Methanol and Water

SCHEME 5. Attempt To Synthesize 3,3', 4,4', and 2,3'-Dinitrobiphenyl by Means of Suzuki Cross-Coupling with KH_2PO_4 as Base in DMF and H_2O


These experiments show that the reaction step (a), the oxidative addition, proceeds without any obstacle with the nitro group present, which was confirmed by the reaction between 2,4-dinitrochlorobenzene and phenylboronic acid, a reaction that provided nearly quantitative yield of the expected product 2,4-dinitrobiphenyl **4g**.

Widdowson and Wilhelm^{32a} have proposed that a nitro group in the 2-position may coordinate an incoming Pd atom. In view of that we initially assumed that this also was the major reason for the obstacles related to the formation of 2,2'-dinitrobenzene **3**. It was therefore surprising to observe that the corresponding reaction with 3-nitrophenylboronic acid proceeded much faster than with 4-nitrophenylboronic acid, Scheme 4.

These observations could not be attributed to the transmetalation step and to NO₂-Pd coordination only but rather to the elimination step, pathway (e) of Scheme 1. If the elimination step of the catalytic cycle is considered to be analogous with the behavior of S_EAr reactions in the presence of strongly deactivating substituents, Scheme 4 reveals somewhat expected proportions between the outcome of the experiments. With the NO₂ group in the 2- and 4-position, unstable resonance forms of the intermediate appear, while this is not the case with the NO₂ group in the 3-position. Moreover, similar results were achieved in trials to synthesize 3,3'-dinitrobiphenyl **10**, 4,4'-dinitrobiphenyl **11**, and 2,3'-dinitrobiphenyl **12**, Scheme 5.

2-Nitrophenylboronic acid degrades very rapidly under the influence of palladium, Scheme 6. When the corresponding experiment is conducted in the absence of palladium, even at elevated temperatures, only a small fraction of the 2-nitrophenylboronic acid is degraded into nitrobenzene. The iodobenzene is found untouched in both cases and suggests that Pd catalyses the degradation of 2-nitrophenylboronic acid into nitrobenzene. This degradation reaction of the boronic acid group appears to be much faster than the oxidative addition step, pathway (a) of Scheme 1.

SCHEME 6. 2-Nitro-phenylboronic Acid Degraded to Nitrobenzene under the Influence of Palladium


In conclusion, we have disclosed new protocols for the synthesis of unsymmetrical substituted 2-nitrobiphenyls **4** and unsymmetrical substituted 2,2'-dinitrobiphenyls **3**, although in only low yields in the case of the latter class of compounds. It is found that the nitro group of 2-nitrosubstituted phenylboronic acids intervenes during the reaction and represents an obstacle for the course of the Suzuki-type reaction. Moreover, when 2-nitrophenylboronic acid is reacted with a non-nitro-substituted haloarene, a significant homocoupling of the haloarene proceeds concomitant with the Suzuki cross-coupling reaction.

Experimental Section

Representative Procedure with KH_2PO_4 as Base in DMF and H_2O . A sealed tube or a round-bottom flask equipped with reflux condenser with N₂ atmosphere was charged with KH_2PO_4 (1.3 mmol, 0.177 g), 2-nitrophenylboronic acid (1.5 mmol, 0.228 g), TBAB (0.2 mmol, 0.065 g), 1-iodo-2-nitrobenzene (1 mmol, 0.249 g), and Pd(OAc)₂ (0.02 mmol, 4.48 mg), using a mixture of DMF (5 mL) in H₂O (0.75 mL). The reaction mixture was heated at 100 °C (oil bath) with stirring for 24 h. The resulting mixture was diluted with H₂O (30 mL) and extracted with ether (3 × 30 mL). The organic phase was analyzed by GC-MS with internal standard. Target product 2,2'-dinitrobiphenyl was obtained in a yield of 27–30%. Only small quantities of unconverted 1-iodo-2-nitrobenzene and small quantities of nitrobenzene formed via degradation of 2-nitrophenylboronic acid were determined in the final reaction mixture.

Representative Procedure with K_2CO_3 as Base in CH_3OH and H_2O . To a round-bottom flask under N₂ atmosphere was transferred a solution of methanol (5 mL) and water (1 mL). K_2CO_3 (2.0 mmol, 0.276 g), Pd(OAc)₂ (0.02 mmol, 4.5 mg), the nitrohalobenzene (1.0 mmol), and the phenylboronic acid (1.0–1.2 mmol) were then added. The resulting reaction mixture was heated at 20–75 °C under stirring. Samples were withdrawn (1.5–28 h) and analyzed by GC-MS. A correction factor with 1-chloro-2,4-dinitrobenzene as the standard was used for the purpose of quantification.

Workup and Purification. The crude product obtained after evaporation under reduced pressure was added to *n*-hexane and heated with a heating gun until reflux. The resulting yellow solution was filtered and allowed to cool, and white crystals (22 mg, ~100% purity measured by GC) of triphenyl boroxin were formed, which were removed by filtration. The hexane solution was evaporated under reduced pressure to afford yellow crystals (73 mg, ~100% purity measured with GC, 93% recovery from the total yield) of target product 2-nitrobiphenyl.

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Supporting Information Available: General experimental information and copies of ¹H NMR spectra for compounds **3a**, **4a–d**, **4f–g**, **10**, and **12–14**. This material is available free of charge via the Internet at <http://pubs.acs.org>. JO051589T