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Efficient Methods for the Synthesis of 2-Hydroxyphenazine Based on the Pd-Catalyzed *N*-Arylation of Aryl Bromides

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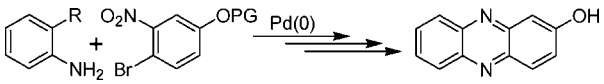
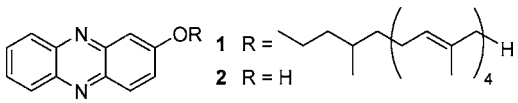
ABSTRACT



Substituted diphenylamines can be synthesized by Pd(0)-catalyzed *N*-arylation using *o*-nitroanilines and nitro-substituted aryl bromides for a substrate. Cyclization of the diphenylamines by various methods, including the intramolecular Pd(0)-catalyzed *N*-arylation, produces 2-methoxyphenazine which can easily be deprotected to give 2-hydroxyphenazine. This phenazine is required to synthesize methanophenazine, a novel redoxactive cofactor isolated from methanogenic archaea.

Many of the naturally occurring phenazines have biological activities rendering them attractive for medicinal chemistry. Today about 100 naturally occurring phenazines are known, the majority of which are produced by strains of *Pseudomonas* and *Streptomyces* species.[1] An exception is methanophenazine (**1**), the first and presently only phenazine from archaea. Methanophenazine (**1**) is a sesterterpene ether of 2-hydroxyphenazine (**2**), which has recently been isolated from the membranes of *Methanosarcina mazei* Gö1.[2] A number of experimental results indicate that the membrane integral compound plays a major role as an electron carrier in the energy metabolism of methane-producing archaea.[3] The total synthesis of this natural product[3b,4] faced, among other things, the problem of developing an efficient and reliable approach to 2-hydroxyphenazine (**2**).



Though this compound can be produced using the procedures developed by Kehrmann[5] and Ott,[6] both of which rely on the reaction of *o*-phenylenediamine with *p*-benzoquinones, the required phenazine **2** could only be obtained with varying and definitely unsatisfactory yields.[7] **2** May also be produced using benzofuroxan and hydroquinone via Beirut reaction.[8] The synthesis of asymmetrical phenazines, though, poses a general problem to the Beirut reaction.[9]

In general,[10] phenazines can be constructed via cyclization of suitably substituted diphenylamines. The literature reports, among others, both the reductive cyclization of *o*,*o*′-dinitro-

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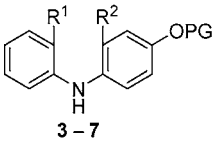
diphenylamines with Raney nickel,[11] of *o*-nitrodiphenylamines with $NaBH_4$/NaOMe or FeC_2O_4/Pb[12] and of *o*-nitro-*o*′-fluorodiphenylamines with $NaBH_4$/NaOEt[13] as well as the oxidative cyclization of *o*,*o*′-diaminodiphenylamines with $FeCl_3$/HCl.[14] In turn, the substituted diphenylamines required are traditionally accessible via nucleophilic aromatic substitution[15] and Ullmann−Goldberg condensation.[16] In general, these methods require harsh reaction conditions and cause problems ranging from restrictions with respect to the substitution pattern of the substrates obtained through to complex product mixtures and low yields.

These disadvantages should be avoidable if the diphenylamines were synthesized via the Buchwald−Hartwig reaction, i.e., Pd(0)-catalyzed *N*-arylation of aryl halides.[17] To produce 2-hydroxyphenazine (**2**) the synthesis and cyclization of the diphenylamines **3**−**7** was strongly considered.



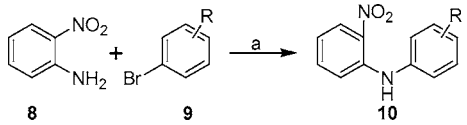
3 – 7

3 R^1= H, R^2= NO_2
4 R^1= NO_2, R^2= NO_2
5 R^1= Br, R^2= NO_2
6 R^1= Br, R^2= NH_2
7 R^1= NH_2, R^2= NH_2

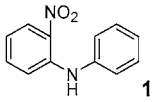
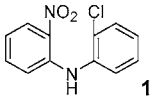
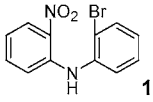
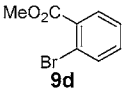
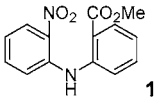
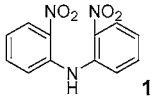
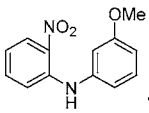
In this paper, a mild method for the efficient synthesis of substituted phenazines is presented, which is based on the Pd(0)- catalyzed transformation of *o*-nitroaniline with substituted aryl bromides and/or substituted anilines with substituted 1-bromo-2-nitroarenes and their subsequent cyclization. This pathway also serves to produce 2-hydroxyphenazine (**2**) in a few steps and with high yields from commercially available substrates.

A review of the literature showed that Pd(0)-catalyzed reactions of nitro-substituted anilines with aryl bromides have hardly been investigated. For example, not one Pd(0)-catalyzed amination of *o*-nitroaniline (**8**) is known, and only a few examples have been published of the transformation of meta- and para-substituted nitroanilines.[18] This might be due to the fact that nitro groups are very sensitive to basic reaction conditions.

Table 1. Pd-Catalyzed *N*-Arylation of *o*-Nitroaniline (**8**) with Aryl Bromides **9**[a]



8 **9** **10**

Entry	Ar–Br	Product	Yield [%]
1	 **9a**	 **10a**	30
2	 **9b**	 **10b**	65
3	 **9c**	 **10c**	68
4	 **9d**	 **10d**	91[b]
5	 **9e**	 **10e**	95
6	 **9f**	 **10f**	60

[a] Reagents and conditions: (a) 5 mol % of $Pd_2(dba)_3$, 7.5 mol % of *rac*-BINAP, 2 equiv of Cs_2CO_3, toluene 110 °C, 15−36 h. [b] 5 mol % of $Pd(OAc)_2$ was used as catalyst.

For this reason, the Pd(0)-catalyzed reaction of *o*-nitroaniline (**8**) with various substituted aryl bromides **9** to give diphenylamines **10** was studied first. After some preliminary experiments with different Pd(0) sources, phosphines, bases, and solvents, we found that these transformations could best be conducted with a combination of $Pd_2(dba)_3$ and *rac*-BINAP with Cs_2CO_3 as a base and toluene as a solvent. Further studies revealed that all reactions presented here can be catalyzed with 5 mol % $Pd_2(dba)_3$ and 7.5 mol % *rac*-BINAP. Under these conditions, **8** could be reacted with bromobenzenes **9a**−**f** to yield the diphenylamines **10a**−**f**. Reaction times varied between 15 and 36 h with yields ranging from 30 to 95% (Table 1). To obtain suitable precursors for the synthesis of **2** further studies focused on the Pd(0)-catalyzed transformation of substituted anilines **8**

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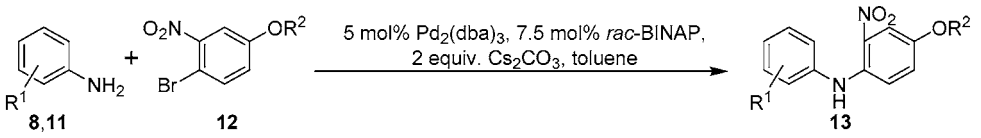
Table 2. Reaction of Anilines **8** and **11** with 4-Bromo-3-nitrophenol Derivatives **12**



8,11 12 13

Entry	Ar-NH_2	Ar-Br	T[°C]/t[h]	Diphenylamine	Yield [%]
1	**11a**	**12a**	110/24	**13a**	97[a]
2	**8**	**12a**	110/30	**13b**	98[b]
3	**8**	**12b**	80/17	**13c**	65[c]
4	**11b**	**12a**	100/50	**13d**	59[d]
5	**11c**	**12a**	110/24	**13e**	93

[a] 3.0 equiv of **11a** was used. [b] Microwave: 150 °C, 60 W, 8 h, 79%. [c] Microwave: 160 °C, 45 W, 30 min, 70%. [d] Microwave: 150 °C, 90 W, 2 h, 70%.

and **11** with 4-bromo-3-nitrophenol derivatives **12** to give the diphenylamines **13** (Table 2).

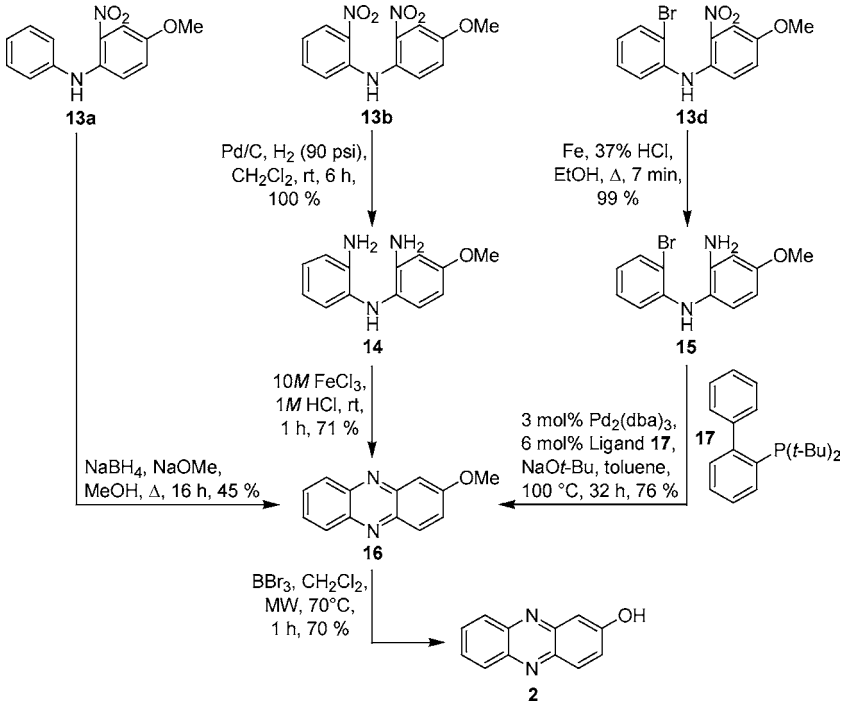
It was found that the combination of $Pd_2(dba)_3$, *rac*-BINAP, Cs_2CO_3, and toluene mentioned above provided an appropriate system for the synthesis of the diphenylamines **13**, too. For example, the reaction of **8** with **12a** and **12b** gave the *o*,*o*′-dinitrodiphenylamines **13b** and **13c** in a yield of 98 and 65%, respectively (Table 2, entries 2 and 3). The same method provided the *o*-nitrodiphenylamines **13a** and **13d** (Table 2, entries 1 and 4). Compounds **13a**−**d** are potential substrates for the synthesis of **2**. The reactions of diphenylamines **13b**−**d** demonstrated that the relatively long reaction times could be dramatically reduced when the reactions were performed under microwave irradiation (Table 2).[19] Thus, the application of microwaves accelerated the synthesis of **13c** from **8** and **12b** by more than 30 times. Once again, the benefit of microwave irradiation in transition metal catalyzed reactions has been demonstrated. The reaction of **8** and **12a** also proved that the successful formation of diphenylamines **13** absolutely required a Pd(0) complex. In the absence of $Pd_2(dba)_3$ under otherwise identical conditions **13b** could not be detected even after 36 h; at best, traces of **13b** could be observed after 72 h.

In all, **13a**, **13b**, and **13d** provided three substrates for the transformation into 2-hydroxyphenazine (**2**) (Scheme 1). Using Holliman's method,[12a] **13a** was reductively cyclized to give 2-methoxyphenazine (**16**) with an excess of $NaBH_4$/NaOMe in MeOH. However, the 45% yield of this method made it rather unattractive. The transformation of **13b** to **2** was much more successful. The reduction of *o*,*o*′-dinitrodiphenylamine **13b** with H_2, Pd/C gave the *o*,*o*′diaminodiphenylamine **14** in quantitative yield. Subsequently, the oxidative cyclization of **14** with $FeCl_3$/HCl provided **16** in a 71% yield. Deprotection of **16** with BBr_3 finally led to the isolation of 2-hydroxyphenazine (**2**). Again, the reaction time could be markedly reduced by applying microwave irradiation (here: from 16 to 1 h if performed at 70 °C in a sealed vial). The method presented allows for the synthesis of 2-hydroxyphenazine (**2**) in four steps with a total yield of 50%.

Finally we examined whether **2** could also be obtained via a combination of inter- and intramolecular Buchwald−Hartwig reactions (Scheme 1). *o*-Amino-*o*′-bromodiphenylamine **15** was chosen as a substrate for the intramolecular *N*-arylation, which could be generated via reduction of the Buchwald−Hartwig product *o*-bromo-*o*′-nitrodiphenylamine **13d** with Fe/HCl, in almost quantitative yield. For the intramolecular cyclization, the combination of $Pd_2(dba)_3$, *rac*-BINAP, and Cs_2CO_3 proved to be unsuitable. After some

(19) All microwave-assisted reactions were performed with a Discover single-mode cavity microwave synthesizer (CEM Corp.), producing continuous irradiation at 2450 MHz.

Scheme 1. Synthesis of 2-Hydroxyphenazine (**2**)



experimentation, it was established that the reaction proceeded smoothly by employing $Pd_2(dba)_3$, ligand **17**, and NaO-*t*-Bu as reagents. The intramolecular amination of **15** to give **16** was achieved with this combination of reagents in 76% yield.

In conclusion, it has been demonstrated that substituted diphenylamines can be synthesized by using *o*-nitroanilines and nitro-substituted aryl bromides as substrates via Pd(0) catalyzed *N*-arylation. The cyclization of the diphenylamines with different methods, including the intramolecular Pd(0) catalyzed *N*-arylation leads to phenazines. Future investigations will tackle the question of whether phenazines can also be obtained in a single synthetic step by combining inter- and intramolecular Pd(0)-catalyzed *N*-arylations.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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