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One-Pot, Pd-Catalyzed Synthesis of *trans*-Dihydrobenzofurans from *o*-Aminophenols

Ericsson D. Coy B.,[†] Ljubisa Jovanovic,[‡] and Michael Sefkow*,[‡]

Universität Potsdam, Institut für Chemie, Karl-Liebknecht Strasse 24-25,
14476 Golm, Germany, and Universidad Nacional de Colombia, Facultad de Ciencias,
Departamento de Química, Laboratorio de Investigación en Productos Naturales
Vegetales, AA 14490, Cra 30 45-03, Bogotá, D.C., Colombia

sefkow@uni-potsdam.de

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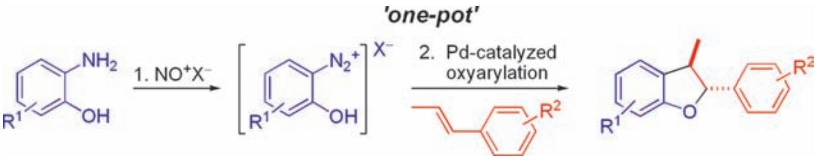
ABSTRACT



An efficient and facile synthesis of *trans*-dihydrobenzofurans has been accomplished from *o*-aminophenols and phenylpropenes via a novel (one-pot) diastereoselective Pd-catalyzed oxyarylation reaction. The development and optimization of this method is described.

The *trans*-2,3-disubstituted dihydrobenzofurans (DHBs) belong to an important class of heterocycles because many biologically active, naturally occurring 8,5′-neolignans and several synthetic derivatives possess this structural motif. The biological properties have attracted chemists in developing efficient syntheses for these *trans*-DHBs.[1] Several approaches have been described in the literature, in particular, oxidative coupling reactions, Lewis acid catalyzed and Schmid rearrangements, acid-catalyzed cycloadditions, radical-based cyclizations, Pummerer reactions, directed α-metalations, and transition-metal-mediated reactions, among others.[1] However, most of these methods suffer from low yields, undesired side products, low chemo- and/or diastereoselectivities, difficulties in product purification, and strong and/or precious reaction conditions.

Transition-metal-catalyzed C−C coupling reactions have become a very powerful tool in the arsenal of organic chemists, and palladium is the most widely used metal in such cross-coupling reactions. The Heck reaction represents a simple and efficient way to obtain variously substituted alkenes and other unsaturated compounds.[2,3]

A variation of the Heck reaction is the Pd-catalyzed oxyarylation[4] that seemed to be a promising methodology for an easy and efficient synthesis of DHBs (Figure 1). This reaction has been used in the past to obtain pterocarpans from substituted *o*-iodo- or *o*-chloromercuriophenols[5] and

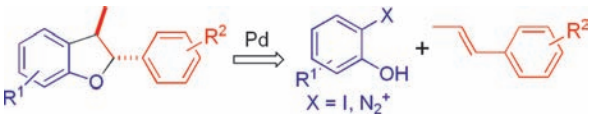


Figure 1. Synthetic approach to *trans*-DHBs via oxyarylation.

[†] Universidad Nacional de Colombia.
[‡] Universität Potsdam.
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2-propenyl-2,3-DHBs from vinylcycloalkanes and *o*-iodophenols.[6] To our knowledge, the synthesis of *trans*-2-aryl-3-methyl-DHBs by oxyarylation has never been reported.

The oxyarylation, an intermolecular $C(sp^2)-C(sp^2)$ coupling reaction,[7] can be regarded as a pseudo [3 + 2] cycloaddition involving a 2-hydroxyarylpalladium species as C_3 and an alkene as C_2 unit. In most studies reported thus far, *o*-iodophenols were employed as the C_3 precursor.[8] However, we found that oxyarylations using *o*-halophenols provided the *trans*-2-aryl-3-methyl-DHBs only in 10−30% beside substantial amounts of several unidentified side products. Under optimized conditions, the reaction of *o*-iodovanillin with anethole (**1**) gave the corresponding DHB (Figure 1, X = I) in less than 50% yield.[9] Consequently, oxyarylations using *o*-halophenols are not suitable for the synthesis of this type of DHBs.

Aryl diazonium salts are efficient reagents in Heck reactions.[10] The influence of the substitution pattern of the alkenes on the outcome of the Heck reaction has been reported by Kikukawa et al.[11] Unfortunately, with phenylpropene's C_2 moiety, the C−C cross-coupling product was formed only in 6% yield. Based on this report we have developed a novel Heck-type oxyarylation (Figure 1, X = N_2^+) using anethole (**1**) and 2-hydroxybenzenediazonium tetrafluoroborate (**2**) as starting materials. When $Pd_2(dba)_3$ is employed as catalyst, $CaCO_3$[12] as base, and MeCN as solvent, the oxyarylation product, DHB **4**, is isolated in up to 85% yield and with up to 94:6 diastereoselectivity (Scheme 1, route A). Major drawbacks of this reaction are that the required diazonium salt is not commercially available and the yield for its preparation[13] from 2-aminophenol (**3**) does not exceed 33%.

For this reason, we considered carrying out both reactions successively in one pot by in situ generation of the diazonium salt from 2-aminophenol (**3**) using $NOBF_4$ and subsequent oxyarylation with anethole (**1**) to obtain *trans*-**4** (Scheme 1, route B). An initial experiment carried out in the presence of 1.2 equiv of $CaCO_3$ and 5 mol % of $Pd_2(dba)_3$ in MeCN at room temperature provided *trans*-**4**[14] in 41% yield (Table 1, entry 1).

According to the observation with isolated diazonium salts, this reaction proceed highly diastereoselective to afford the *trans*-**4**. The *cis* isomer was formed in less than 5% yield, as judged by the ^1H NMR spectrum of the crude product mixture. In addition to **4**, two side products were often isolated. These compounds were identified as *p*-anisaldehyde **5**, apparently derived from the reaction of alkene **1** with $NOBF_4$, and 4-nitroso-DHB **6**, formed by exposure of either the starting material **3** or the product **4** to an excess of $NOBF_4$. Several parameters (base, catalyst, solvent, diazotization reagent, times and temperatures) were optimized for the novel "one-pot" oxyarylation protocol. In addition, the

Scheme 1. Oxyarylation with Arenediazonium Salts

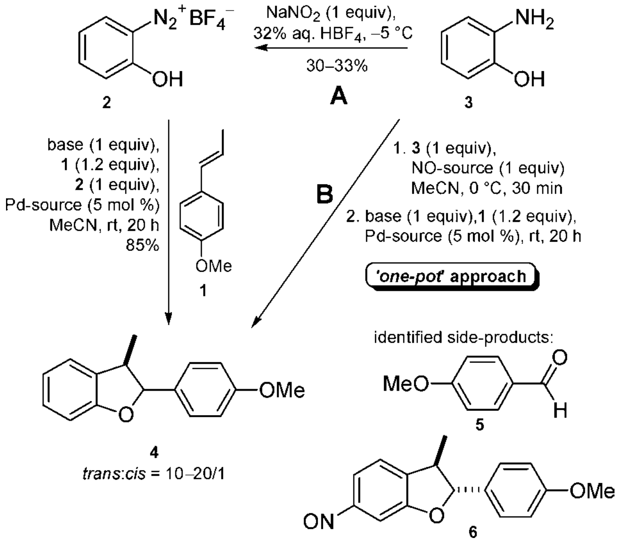
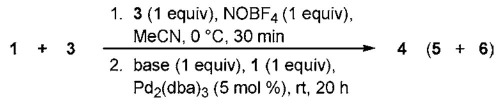


Table 1. Base and Counterion Effect on the Oxyarylation



entry	base	yield (%) of **4**[a]	ratio of products[b] *trans*-**4**/*cis*-**4**/**5**/**6**
1	$CaCO_3$	41	>10/1/<1/1.3
2	$BaCO_3$	53	>10/1/<1/1
3	$MgCO_3$	43	7/1/<1/0
4	$MnCO_3$	57	>10/1/<1/1.3
5	$ZnCO_3$	**64 (59)**	>10/1/<1/1.5
6	$CoCO_3$	38	6/1/<1/0
7	$Bi_2(CO_3)_3$	49	6/1/<1/1.8
8	M_2CO_3[c]	0	
9	Ca-Gly-PO_4	**62 (58)**	>10/1/<1/1.2
10	$CaSO_4$	43	6/1/0.7/1.3
11	$CaHPO_4$	44	7/1/1/1.1
12	$Ca_3(PO_4)_2$	49	7/1/<1/0
13	$CaSiO_3$	56	7/1/<1/1.1
14	CaO	42	>10/1/<1/<1
15	$Ca(OH)_2$	46	>10/1/<1/1.6

[a] Calculated by ^1H NMR using tetradecane as internal standard; yields of isolated product in parentheses. [b] Ratio determined by selected, differentiable ^1H NMR signals. [c] M corresponds to single valent metals such as Li^+, Na^+, Cs^+, and Ag^+.

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applicability of our methodology is demonstrated by using a variety of different alkenes and *o*-aminophenols as substrates.

From the results achieved with isolated diazonium salts we learned that the base has a strong influence on the outcome of the oxyarylation. Therefore, the base was systematically screened with respect to both cation (Table 1, entries 2−8) and anion (entries 9−15), while all other parameters remained unchanged. Carbonates from double or triple valent cations gave *trans*-**4** in 38−64% yield, with $MgCO_3$ and $CoCO_3$ being less effective and $ZnCO_3$ most effective. In addition, with Mg^{2+}, Co^{2+}, and Bi^{3+} as cations, significantly more *cis*-product was formed (∼15%). The best diastereoselectivities have been achieved with Mn^{2+} and Zn^{2+}. It is notable that the carbonates from monovalent cations, such as Li^+, Na^+, Cs^+, and Ag^+, completely failed to give any desired product. This result is unexpected since these bases are widely used in common Heck reactions.[4a]

The structure of the anion does not influence the outcome of the oxyarylation to that extent (Table 1, entries 9−15). Several nonbasic anions (sulfate, silicate and some phosphates) as well as the basic oxide and hydroxide have been examined using Ca^{2+} as counterion. In all cases, the yields of **4** were in the range between 42−62%. The stereoselectivity of the oxyarylation correlated with the basicity of the counterion. Whereas the basic oxide and hydroxide gave good stereoselectivities albeit low yields, the nonbasic anions provided ca. 7:1 mixtures of *trans*- and *cis*-**4**. As an exception, the nonbasic calcium glycero phosphate gave not only the best yield (62%) but also the best diastereoselectivity (>95:5) (Table 1, entry 9).[15]

Several solvents have been employed in Heck reactions[16] such as NMP, DMF, DMA, THF, or CH_2Cl_2, but in neither of these solvents did oxyarylation occur. Even PhCN[17] gave less satisfactory results compared to MeCN. Nitriles were the only solvent suitable to initiate the oxyarylation from diazonium salts, confirming the work by Eberlin et al.[18] They showed that arenediazonium salts and $Pd(dba)_2$ in MeCN undergo a time-dependent process involving ligand exchange. As a result of this phenomenon, a stable cationic intermediate having one MeCN molecule coordinated as ligand was formed slowly. This intermediate is likely to be the key intermediate in the Heck reaction using diazonium salts.[11]

Besides $NOBF_4$, nitrosyl hexafluorophosphate is the only other commercially available nitrosonium salt. $NOPF_6$ was thus examined as diazotizating agent (Table 2). The yield was significantly improved with $NOPF_6$ in comparison with $NOBF_4$, probably because of the hygroscopic nature of the latter one. Again, best results were achieved with $ZnCO_3$ and Ca-glycerophosphate as base (85 and 77%), though $ZnCO_3$ provided **4** with better *trans*-diastereoselectivity. A diazotization time of 30 min is sufficient since shorter periods of activation decreased the yields and longer diazotization times (24 h) gave only marginal better yields (Table 2, entries 4 and 5).

Table 2. $NOPF_6$ as Diazotizating Agent and Additives Effect

$$\mathbf{1} + \mathbf{3} \xrightarrow[\text{2. base (1 equiv), }\mathbf{1}\text{ (1 equiv), }Pd_2(dba)_3\text{ (5 mol \%), rt, 20 h}]{\text{1. }\mathbf{3}\text{ (1 equiv), }NOPF_6\text{ (1 equiv), MeCN, 0 °C, 30 min}} \mathbf{4}\ (\mathbf{5} + \mathbf{6})$$

entry	base	additive	yield (%) of **4**[a]	ratio of products[b] *trans*-**4**/*cis*-**4**/**5**/**6**
1	$CaCO_3$		53	>10/1/<1/2
2	$ZnCO_3$		**85 (79)**	>10/1/<1/1.1
3	Ca-Gly-PO_4		**77 (73)**	7/1/1.1/0
4	$ZnCO_3$	*c*	24	>10/1/<1/13
5	$ZnCO_3$	*d*	**88 (82)**	>10/1/0/0
6	$ZnCO_3$	Bu_4NCl	33	>10/1/9.5/<1
7	$ZnCO_3$	MS 3 Å	44	>10/1/<1/<1
8	$ZnCO_3$	10 eq H_2O	43	>10/1/1.2/3.6
9	$ZnCO_3$	*e*	29	>10/1/4/3.5
10	$ZnCO_3$	$NOPF_6$[f,g]	27	3/1/3/1.5

[a] Calculated by ^1H NMR using tetradecane as internal standard; yields of isolated product in parentheses. [b] Ratio determined by selected, differentiable ^1H NMR signals. [c] Oxyarylation immediately after addition of $NOPF_6$. [d] Oxyarylation 24 h after addition of $NOPF_6$. [e] 2 equiv of $NOPF_6$ used for diazotization. [f] 1 equiv of $NOPF_6$ added after oxyarylation, and reaction proceeded for a further 20 h. [g] Formation of **6** (ca. 30%) occurred after treatment of purified **4** with 1 equiv of $NOPF_6$ for 20 h.

Several additives were often applied in Heck reactions to further increase the yields.[19] In our hands, additives, such as Bu_4NCl, 3 Å molecular sieves, or water, do not contribute to improve the yield of the oxyarylation (Table 2, entries 6−8). In contrast, all additives decreased the yield of compound **4**. Notably, Bu_4NCl increased the yield of aldehyde **5**, which can be also prepared in 52% yield by treatment of anethole (**1**) with 1 equiv of $NOPF_6$.

Although 1 equiv of water is present throughout the oxyarylation reaction due to the in situ diazotization, addition of extra water decreased the yield of **4** and promoted the formation of **6**. On the other hand, removal of water by addition of 3 Å molecular sieve also decreased the yield of **4** and provided many unidentified side products. As expected, a second equivalent of $NOPF_6$, either added at the beginning of diazotization or after oxyarylation decreased the yield of DHB and increased the formation of **5** and **6** (Table 2, entries 9 and 10).

The influence of the catalyst was examined with respect to catalyst load, transition metal used, and nature of the ligand. The catalyst load was studied using $Pd_2(dba)_3$ as reference. The yield of oxyarylation product was comparable at either 5 or 10 mol % catalyst load but significantly

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(15) It should be noted that the yields given in Tables 1−4 refer to calculated yields based on the integrals of selected product signals in the ^1H NMR spectra of the crude products (δ_H at 1.3 and 5.2) with those of tetradecane added as internal standard. However, in several experiments, we purified the products by chromatography and found marginal differences between calculated and isolated yields (ca. 5%).

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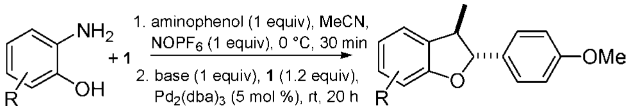
decreased when only 1 mol % of $Pd_2(dba)_3$ was applied. As a consequence, all further experiments were carried out with 5 mol % catalyst load.

Several other Pd catalysts, $Pd(OAc)_2$, $Pd(acac)_2$, and $[Pd(Ph_3P)]_4$, as well as the novel *N*-heterocyclic carbene palladium complexes ([(SIPr)Pd(cinnamyl)Cl],[20] $[Pd(IPr)Cl_2]_2$,[21] and PEPPSI-IPr[22]), commonly used in Heck reactions,[23] were compared with $Pd_2(dba)_3$ in their efficiency to catalyze the oxyarylation. Only with $Pd(OAc)_2$ was DHB **4** obtained in a similar yield (84%, $Pd_2(dba)_3$: 85%), although the diastereoselectivity was decreased significantly (88:12, $Pd_2(dba)_3$: >95:5), while $Pd(acac)_2$ provided **4** in 58% and $[Pd(Ph_3P)]_4$ in 49% yield. All Pd−NHC complexes failed to give the DHB. Any catalyst comprising a different transition metal, such as Ni(II), Cu(I), Ag(I), and Pt(0), also failed to catalyze the oxyarylation.

Having developed a working oxyarylation protocol, various substituted 2-aminophenols were examined as substrates for diazotization/oxyarylation (Table 3). With electron-donating groups (e.g., chloro, Table 3, entry 1) or electron-withdrawing groups (e.g., carboxylic acids or esters, Table 3, entries 5 and 7) *para* to the hydroxy group, acceptable yields of the corresponding oxyarylation products (44−85%) have been achieved. Reasonable yields of DHBs (59−84%) were also obtained when substrates with electron-withdrawing groups *para* to the amino group (Table 3, entries 2, 4, and 6) were employed. Not surprisingly, 2-amino-3-hydroxypyridine did not give the desired product since pyridines act as donators for complexation of transition metals (Table 3, entry 3). It should be noted that free carboxyl groups are tolerated, although the yields are diminished by ∼20−25%.

Table 3. Substitution Effect of Different 2-Aminophenols

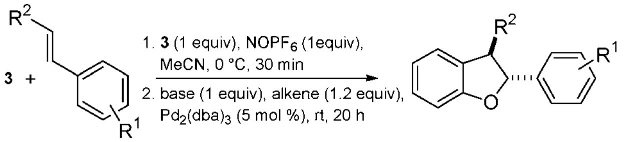


entry	2-aminophenol	yield[a] (%)
1	2-amino-4-chlorophenol	**85 (79)**
2	2-amino-5-nitrophenol	49
3	2-amino-pyridin-3-ol	0
4	4-amino-3-hydroxybenzoic acid	59
5	3-amino-4-hydroxybenzoic acid	44
6	methyl 4-amino-3-hydroxybenzoate	**84 (79)**
7	methyl 3-amino-4-hydroxybenzoate	64

[a] Calculated by ^1H NMR using tetradecane as internal standard by means of selected, differentiable ^1H NMR signals at around δ_H 5.1−5.4 from the obtained DHBs; yields of isolated products in parentheses.

Likewise, the suitablility of various phenylpropenes for their conversion to DHBs was examined (Table 4). Unsubstituted arylpropenes failed to yield any oxyarylation product (Table 4, entries 1 and 2). Good yields of DHBs (73−85%) have been achieved with 4-hydroxy- or alkoxy-substituted phenylpropenes unsubstituted at the *ortho* position of the aromatic ring (Table 4, entries 6−10). Phenols can be used unprotected. Any *ortho* substituent at the aromatic ring (Table 4, entries 3−5) dramatically reduces the reaction rate and decreases the yield of product (18−26%). Cinnamic alcohol and derivatives with a heteroatom at the propenyl moiety completely failed to afford the corresponding DHBs (Table 4, entries 11 and 12).

Table 4. Substitution Effect on Starting Material Alkene



entry	alkene	yield[a] (%)
1	*trans*-β-methylstyrene	0
2	*trans*-stilbene	0
3	(*E*)-1-methyl-2-(prop-1-enyl)benzene	26
4	(*E*)-1,3,5-trimethoxy-2-(prop-1-enyl)benzene	18
5	(*E*)-1,4-dimethoxy-2-(prop-1-enyl)benzene	26
6	(*E*)-1,2,3-trimethoxy-5-(prop-1-enyl)benzene	**73 (70)**
7	isoeugenol	**85 (81)**
8	isomyristicin	**77 (71)**
9	isosafrol	**80**
10	methyl isoeugenol	**81**
11	*cis*-cinnamyl alcohol	0
12	cinnamyl methyl ether	0

[a] Calculated by ^1H NMR using tetradecane as internal standard by means of selected, differentiable ^1H NMR signals at around δ_H 5.1−5.4 from the obtained DHBs; yields of isolated products in parentheses.

In conclusion, a novel, convergent, stereoselective synthesis of *trans*-DHBs from commercially available *o*-aminophenols and arylpropenes was developed via diazotization and Pd-catalyzed oxyarylation in a “one-pot” process. An important class of natural products, namely 8,5′-neolignans, which comprises a similar DHB core, is accessible with good yields and diastereoselectivities under mild conditions.

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Supporting Information Available: Experimental procedure, spectral data, ^1H and ^{13}C NMR spectra, and a sample calculation of the yields. This material is available free of charge via the Internet at http://pubs.acs.org.

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