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Brönsted acid catalyzed direct oxidative arylation of 1,4-naphthoquinone

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An inexpensive straightforward approach to direct oxidative twofold C-H arylation of 1,4-naphthoquinone catalyzed by readily available Brönsted acids was developed. Under the simple and easily achievable reaction conditions, electron-rich aromatics undergo Friedel-Crafts type functionalization to furnish 2-arylonaphthoquinones in good yields. The attempt to rationalize the scope and limitation of the approach based on desktop PC DFT calculation and reactivity indexes theory was taken up.

1. Introduction

Compounds based on naphthoquinone core are commonly present in a living nature. They exhibit important biologic as well as valuable pharmacologically properties e.g. antitumor,[1,2] antibiotic,[3,4] antiviral,[5,6] anti-malarial,[7,8] antifungal,[9,10] and antidiabetic[11]. Substituted naphthoquinones are also frequently applied as dyes for instance juglone, lawsone, plumbagin,[12] and were used as substrates in the syntheses of highly efficient phosphorus ligands[13,14] (**Fig. 1**).

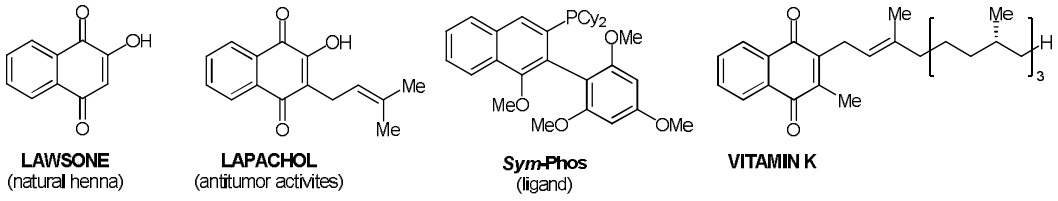

Fig. 1. Selected 1,4-naphthoquinone derivatives

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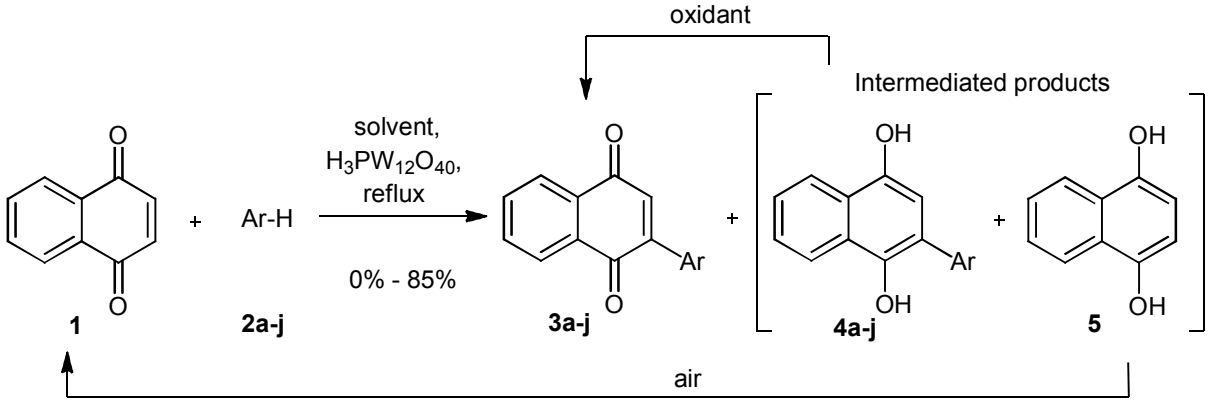
From the variety of known approaches to functionalization of quinones and naphthoquinones, the methods based on direct C-H arylation seem to be the most attractive. The most popular methods of arylation of quinones are based on its reaction with aryldiazonium salts.[1,15] However, such methods may be not efficient if an electron donating group (EDG) is present in a quinone core. Some other popular methods of preparation of aryl and heteroarylnaphthoquinones are based on transition metal catalyzed oxidative coupling of naphthoquinones with aromatic arenes or heterocycles in the presence of palladium acetate,[16] and arylation of naphthoquinones by *m*-(dialkylamino)phenols in the presence of copper acetate.[17] The methods based on Rh-catalyzed coupling of quinones with arylboronic acid derivatives,[18] and based on Suzuki-Miyaura coupling of 2-bromonaphthoquinone[15] had been also presented. Among the less popular methods of arylation are those employing palladium catalyzed reaction with aryl mercury chloride,[19] dehydrogenative coupling with aromatic carboxylates,[20] and oxidative C-H arylation in the reaction with boronic acids.[21]

The significant attention was attracted by the methods based on oxidative twofold C-H functionalization reactions, e.g. water mediated direct arylation of 1,4-benzoquinone by aromatic compounds catalyzed by $In(OTf)_3$,[22] or molecular iodine catalyzed and promoted by sonication heteroarylation of naphthoquinone in reaction with indoles.[23]

Due to increasing attention to this class of compound and a little development of rapid methods of their synthesis, we had focused on developing a new inexpensive approach to arylation of 1,4-naphthoquinone mediated by tiny amounts of simple Brönsted acids such as phosphotungstic acid ($H_3PW_{12}O_{40}$) and PTSA (*p*-toluenesulfonic acid), which is reported herein.

2. Results and Discussion

As a model target compound was selected 2-[4-(dimethylamino)phenyl]naphthalene-1,4-dione (**3a**) because of the structural simplicity and low yield reported in literature.[24] Since the used catalyst is acidic in character, we decided to use an acetic acid as additive in the reactions with substrates of basic character. After optimization of the reaction conditions (**Scheme 1**, **Table 1**) we have found that maximal 35% isolated yield of **3a** could be achieved in reaction of *N,N*-dimethylaniline (**2a**) with 2 folds excess of 1,4-naphthoquinone (**1**) run in DMSO and catalyzed by $H_3PW_{12}O_{40}$ on air, after 24 h of stirring (**Table 1**, entry 5). The optimal temperature for this reaction was 100 ^oC. The use of acetic acid was not helpful in term of yield but prevent naphthoquinone from decomposition observed in basic medium. We also found that the reactions not required an addition of oxidants, because formed (but not isolated) intermediates 2-[4-(dimethylamino)phenyl]naphthalene-1,4-diol (**4a**) and naphthalene-1,4-diol, (**5**) were spontaneously oxidized by air to furnish product **3a** and substrate **1** (**Scheme 1**).



Scheme 1. Proposed pathway of arylation of 1,4-naphthoquinone (**1**)

Table 1. Synthesis of **3a**: optimization of the reaction conditions.

Entry	Oxidant	CH_3COOH	T, °C	Yield, %
1	$NaIO_3 \cdot H_2O$ (solid, 100 mol%)	200 mol%	70	18
2	$NaIO_3 \cdot H_2O$ (0,99% in H_2O,100 mol%)	200 mol%	70	19
3	none	200 mol%	70	23
4	none	none	70	28
5	none	none	100	35

$H_3PW_{12}O_{40}$ (1 mol%), DMSO, t= 24 h, reactions were carried out on air

The reaction of 1,4-naphthoquinone (**1**) with *N,N*-dimethylaniline (**2a**) in DMSO and stoichiometric amount of CH_3COOH catalyzed by p-toluenesulfonic acid furnished product **3a** in only 6% yield. Several by-products were also formed in the reaction. Although, the yields of by-products **6b, 6c, 6d** (**Fig. 2**) have not been measured, they were separated chromatographically, and their structures were confirmed by HR-MS and ^{1}H NMR analysis. This observation suggested that usual strong Brönsted acids, such as PTSA, could act as a catalyst in this arylation reaction, nevertheless their efficiency is limited due to low selectivity.

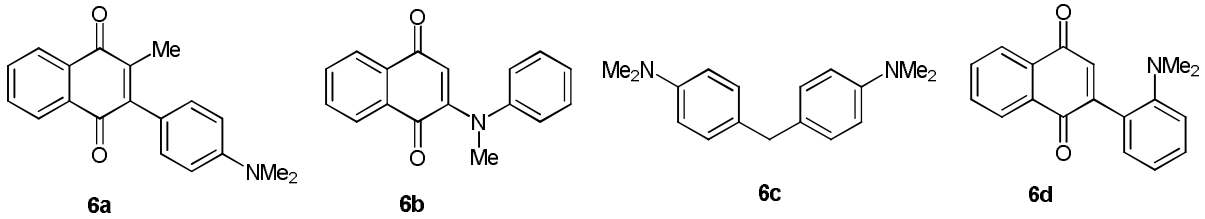
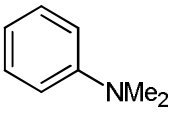
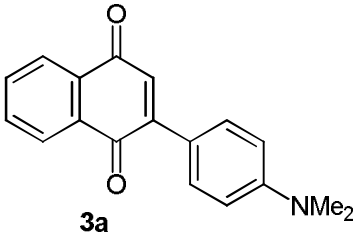
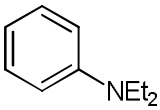
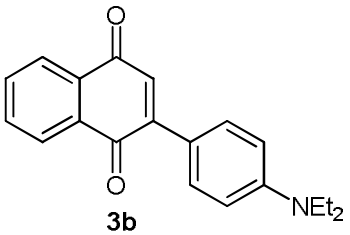
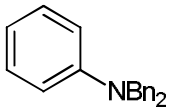
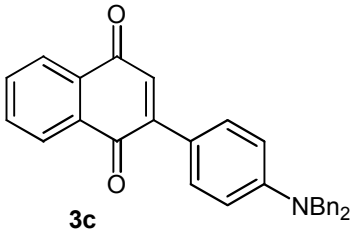
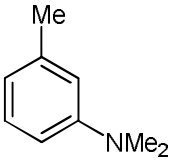
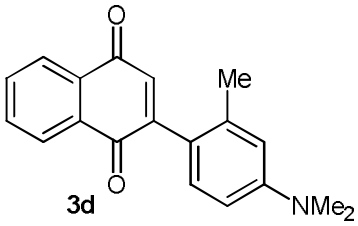
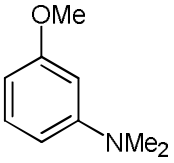
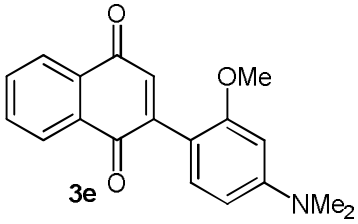
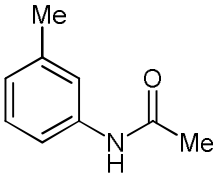
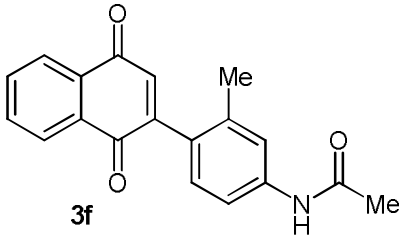
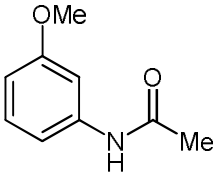
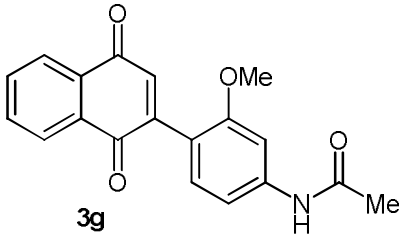


Fig. 2. By-products of reaction of **1** with **2,** catalyzed by *p*-toluenesulfonic acid.

Utilization of *N,N*- diethylaniline (**3b**) in the arylation reaction required an addition of stoichiometric amount of acetic acid. In such reaction, run at 100 °C and catalyzed by $H_3PW_{12}O_{40}$, product **3b** (2-[4-(diethylamino)phenyl]naphthalene-1,4-dione) was obtained in 31% yield. Similarly, products **3c-g** were obtained in low to moderate yields (**Table 2**) in reactions of 1,4-naphthoqunones with **2b-g**, run in CH_3COOH or DMSO in the presence of $H_3PW_{12}O_{40}$, used as catalyst, after stirring the reaction mixture on air, at 100 °C for 24 h. Furthermore, substrate **2e** is unstable on air and its decomposition has decreased the yield of the product **3e** down to 18% (**Table 2**, entry 6).

Table 2. Arylation of 1,4-naphthoquinone by substituted anilines

Entry	Substrate 2a-g	Solvent	Product 3a-f	Yield, %
1	 **2a**	DMSO	 **3a**	35
2		CH_3COOH		31[a]
3	**2b**	DMSO/CH_3COOH= 15/0.45	 **3b**	20[b]

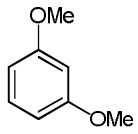
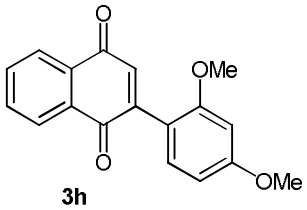
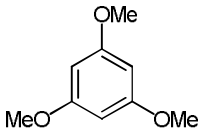
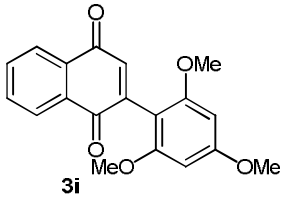
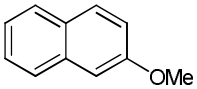
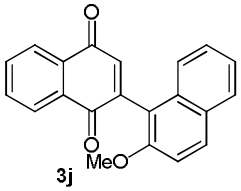
4	 **2c**	CH_3COOH	 **3c**	25[a]
5	 **2d**	CH_3COOH	 **3d**	37[a]
6	 **2e**	CH_3COOH	 **3e**	18[a]
7	 **2f**	CH_3COOH	 **3f**	Trace[a]
8		DMSO		Trace[a]
9	 **2g**	CH_3COOH	 **3g**	15[a]
10		DMSO		Trace[a]

$H_3PW_{12}O_{40}$ (1 mol%), t= 24 h, reactions were carried out on air at 100 ^oC, [a] 4 mmol of amine in 15 ml of solvent, [b] 8 mmol of amine in mixture of solvents in ratio 15/0.45.

To elucidate the scope of the reaction, several other aromatic substrates were utilized. The neutral substrates underwent arylation reaction without the addition of acetic acid. In reaction of 1,3,5-trimethoxybenzene (**2i**) with 1,4-naphthoquinone (**1**) product **3i** was formed in very good yield (85%) when acetone was used as solvent and $H_3PW_{12}O_{40}$ as Brönsted acid catalyst. Because of short (1.5 h) reaction time, the formed intermediate product **4i** (2-(2,4,6-trimethoxyphenyl)naphthalene-1,4-diol) was not completely oxidized by air, so it was oxidized into the product **3i** (2-(2,4,6-trimethoxyphenyl)naphthalene-1,4-dione) by adding a water solution of $NaIO_3$. Good yield (77%) of 2-(2,6-dimethoxyphenyl)naphthalene-1,4-diol (**11b**) was obtained in reaction of 1,4-naphthoquinone (**1**) and 1,3-dimethoxybenzene (**2h**) run in the similar conditions. 2-(2,4,6-Trimethoxyphenyl)naphthalene-1,4-dione **3i** could be also obtained in 88% yield in direct Friedel-Crafts arylation of 1,4-naphthoquinone catalyzed by strong Lewis acid ($Bi(OTf)_3$).[25] In contrast to

substrates **2h** and **2i**, less electron reach arenes, such as 2-MeO-naphthalene and 1,4-diMeO-benzene, were less active and products were obtained in trace amounts.

Table 3 Arylation of 1,4-naphthoquinone by methoxysubstituted arenes.

Entry	Substrate 9a-c	Product 10a-c	Yield, %
1	 **2h**	 **3h**	77
2	 **2i**	 **3i**	85[a]
3	 **2j**	 **3j**	Trace[b]

$H_3PW_{12}O_{40}$ (1 mol%), t= 24 h, reactions were carried out in acetone, on air, under gentle reflux.; [a] t= 1.5 h, product was oxidized by adding water solution of $NaIO_3$, [b]Reactions was carried out in CH_3COOH and DMSO as well as in the mixture of these solvents.

The observed above dependences may be rationalised by means of reactivity indices theory based on approachable computer simulation.[26,27,28,29,30] The global (N) and local (N_k) nucleophilic reactivity indices were calculated according to the equations recommended by *Parr*[31] and *Domingo*[32]. This model was also adopted for many other reaction systems.[33,34] In our case, the quantum chemical calculations were performed using DFT B3LYP/6-311++ G** and HF STO3G theoretical levels. According to the concept, the global nucleophilicities (N, eV) of arenes were calculated as the difference:

$$N=E_{HOMO}-E_{HOMO(tetracyanoethene)}$$

Thus local nucleophilicities (N_k), condensed to atom *k,* were calculated using global nucleophilicities N and *Fukui* functions f_k^- according to the equation:

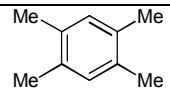
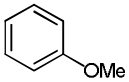
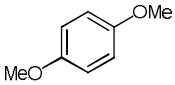
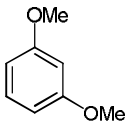
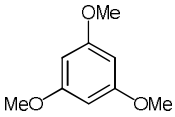
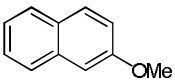
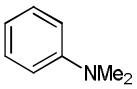
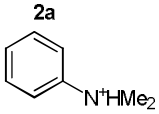
$$N_k=f_k^-N,$$

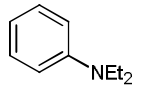
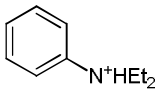
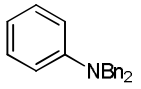
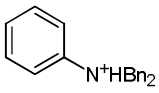
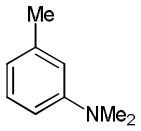
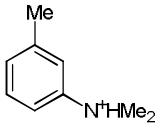
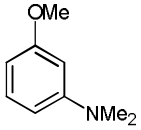
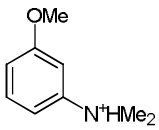
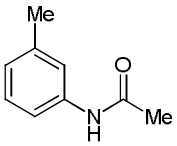
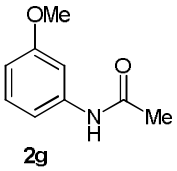
whereas f_k^- calculated as a square of the suitable HOMO coefficient of electronic population:

$$f_k^-=C_{HOMO}^2.$$

Moreover, the normalization condition of the Fukui function should be assured, namely $\int f(r)dr = 1$ or in its condensed at *k* atom version $\sum_k f_k^- = 1$. The maximum nucleophilic reactivity in the molecula will be situated at the site where the nucleophilic Fukui function f_k^- approaches its maximum value. A satisfied precision of global nucleophilicity calculation could be achieved in calculation on moderate DFT B3LYP/6-31G* theoretical level with consideration of only speculator orbitals acting in aromatic S_E2 reaction – the $2p^z$ component of HOMO.[35] Nevertheless, for a better precision, we have performed calculation on advanced B3LYP/6-311++G** theoretical level. The *Fukui* indexes f_k^- were calculated as sums of squares of coefficients of all 2p atomic orbitals constituted HOMO. To eliminate a phantom distribution of electronic population on irrelevant 3p and 4p orbital's and assure better matching of $\sum_k f_k^- = 1$ criteria, for the calculations of f_k^- we used HF STO3G method which consider only two first electronic shells. Also we did not take into the consideration the components of HOMO developed on other atoms then that constituted the aromatic rings. It should be noted, that despite high value of nucleophilicity of aromatic carbon atoms bonded with EDG, they do not undergo electrophilic substitution in usual conditions and so on cannot be compared with carbons bonding hydrogens. The results of the calculation are collected in **Table 4.**

Table 4. The nucleophilicity of selected arenes.

Nucleophile*	**E_{HOMO}, eV 6311+G****	**N, eV**	**f_k^- (N_k, eV)**					
			1-	2-	3-	4-	5-	6-
 **7**	-6.140	3.249	0.201 (0.673)	0.201 (0.673)	**2.33E-07 (7.6E-07)**	0.201 (0.673)	0.201 (0.673)	**2.33E-07 (7.6E-07)**
 **8**	-6.229	3.260	0.167 (0.544)	0.098 (0.319)	0.051 (0.166)	**0.233 (0.760)**	0.023 (0.075)	0.118 (0.385)
 **9**	-5.646	3.843	0.170 (0.653)	0.057 (0.219)	**0.087 (0.334)**	0.170 (0.653)	0.057 (0.219)	**0.087 (0.334)**
 **2h**	-6.117	3.372	0.100 (0.337)	0.244 (0.823)	0.000 (0.000)	**0.244 (0.823)**	0.100 (0.337)	0.000 (0.000)
 **2i**	-5.987	3.502	0.017 (0.060)	**0.327 (1.14)**	0.049 (0.172)	0.071 (0.249)	0.012 (0.042)	0.093 (0.326)
 **2j**	-5.770	3.719	**0.202 (0.751)**	0.114 (0.424)	0.002 (0.007)	0.107 (0.398)	0.034 (0.126)	0.011 (0.041)
 **2a**	-5.375	4.114	0.115 (0.473)	0.116 (0.477)	0.022 (0.090)	**0.199 (0.819)**	0.022 (0.090)	0.116 (0.477)
 **10**	-11.259	-1.77	0.000 (-0.000)	0.235 (-0.416)	0.189 (-0.334)	2E-05 (-3E-05)	0.192 (-0.340)	0.202 (-0.358)

	-5.364	4.125	0.115 (0.474)	0.112 (0.462)	0.018 (0.074)	**0.188 (0.776)**	0.026 (0.107)	0.109 (0.450)
2b 	-11.118	-1.63	1E-04 (-2E-04)	0.230 (-0.375)	0.193 (-0.314)	2E-05 (-3E-05)	0.189 (-0.308)	0.235 (-0.383)
11 	-5.563	3.926	0.118 (0.463)	0.103 (0.404)	0.017 (0.067)	**0.176 (0.691)**	0.027 (0.106)	0.100 (0.393)
2c 	-10.292[a]	-0.80	0.003[a] (-0.002)[a] 0.006[b] (-0.005)[b]	0.002[a] (-0.002)[a] 0.184[b] (-0.148)[b]	0.007[a] (-0.006)[a] 0.228[b] (-0.183)[b]	0.001[a] (-0.001)[a] 0.005[b] (-0.006)[b]	0.002[a] (-0.002)[a] 0.163[b] (-0.131)[b]	0.007[a] (-0.006)[a] 0.241[b] (-0.193)[b]
12 	-5.291	4.198	0.027 (0.113)	0.100 (0.420)	0.114 (0.479)	0.129 (0.542)	0.019 (0.080)	**0.208 (0.873)**
2d 	-10.806	-1.32	0.261 (-0.344)	0.141 (-0.186)	0.045 (-0.059)	0.251 (-0.330)	0.048 (-0.063)	0.069 (-0.091)
13 	-5.268	4.221	0.049 (0.207)	0.030 (0.127)	0.099 (0.418)	0.198 (0.836)	0.005 (0.021)	**0.234 (0.988)**
2e 	-10.106	-0.62	0.127 (-0.078)	0.141 (-0.087)	0.044 (-0.027)	0.200 (-0.123)	0.006 (-0.004)	0.120 (-0.074)
14 	-6.265	3.224	0.037 (0.119)	0.083 (0.268)	0.143 (0.461)	0.114 (0.368)	0.022 (0.071)	**0.209 (0.674)**
2f 	-6.028	3.461	0.080 (0.277)	0.002 (0.007)	0.104 (0.360)	0.216 (0.748)	0.001 (0.003)	**0.230 (0.796)**
2g								

*The HOMO energy of tetracyanoethylene is -9.489 eV at the same level of theory, [a] nucleophilicity at $\mathbf{C_6H_5}NR_2$, [b] nucleophilicity at $\mathbf{C_6H_5}CH_2$- substituents.

The analysis of **Table 4** clearly indicated the most reactive sites of the arenes. Therefore, it should be the preferred position for electrophilic attack of activated by acidic catalysts naphthoquinone. Those positions in the all cases were consistent with common sense consideration and actual regiochemistry of the reaction. The calculated value of local nucleophilicity, located at the active site, prove to be a crucial criteria conditioned possibility of the reaction to proceed. In the case of direct Friedel-Crafts

arylation of naphthoquinone, the minimal necessary local nucleophilicity was define on a level of about 0.7 eV. The reactivity seems to be also slightly differentiated by sterical hindrance of *ortho* substituents and amount of protonated, by an acidic solvent, substrates. In the reactions, leading in acidic medium, anilines form ammonium salts which have electrophilic character. For such salts, calculated values of local nucleophilicity were negative, also orbital HOMO could be situated on other then aniline core carbon atoms e.g. benzylic (**Table 4**). Thus only a free amine, presented in equilibrium with its salt, can act as nucleophile in the studied reaction. This explains lower yields of arylation reactions observed when substrates **2a-e** were utilized.

3. Conclusions

In summary, we have demonstrated effective, low-cost arylation of naphthoquinone by substituted electron rich arenes in the presence of catalytic amount of eco-friendly phosphotungstic acid and various solvents, which allowed obtaining 2-arylonaphthoquinones in moderate to excellent yields reaching 88%. The reactivity of the substrates and regiochemistry of substitution reactions were explained by the achievable desktop PC calculation. The extrapolation of the obtained results to other substrates should allow easy prediction of reaction outcome, which is depended on substitution pattern and reaction conditions.

Acknowledgements

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4. Experimental

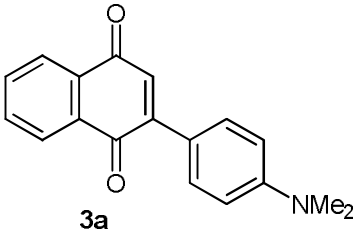
Computational procedure

The quantum-chemical calculations were performed on a regular desktop PC (4 core, 8GB RAM). Hybrid B3LYP, HF functionals and STO3G, 6-311++G** basis sets included within Spartan'10 software were applied.[29,30] Calculations of all critical structures were performed for the temperature T=298K and pressure p=1atm. Global nucleophilicity was calculated on B3LYP 6-311++G** theoretical level. The Fukui indexes were calculated as $f_{k^-(Cn)} = 2p_x^2+2p_y^2+2p_z^2$ of HOMO on a HF STO3G theoretical level.

Chemical studies

General. All reactions were carried out in open flask and were monitored on TLC. All oxidation reactions were controlled by two-dimensional TLC. The products were purified by column chromatography (f40 mm x 90 mm) using 50 grams of silica gel (Merck silica gel 60 (230–400 mesh)). ^{1}HNMR: spectra were recorded on Bruker AVANCE 500 in $CDCl_3$; chemical shifts are given in ppm relative to TMS, coupling constants (*J*) given in Hz. All melting points were measured using the BUCHI Melting Point M-560 apparatus and are not corrected. The HRMS (ESI) measurements were performed on Shimadzu LCMS-IT-TOF instrument. HPLC study was performed on a Merck reversed phase column: 250x4 mm, 5 μm, eluted by methanol/water. All commercially available substrates were used as received, and all known compounds were examined by comparison with authentic commercial samples.

2-[4-(Dimethylamino)phenyl]naphthalene-1,4-dione (3a)



3a

Variant 1. A 50 ml flask equipped with a magnetic stirrer was charged with naphthoquinone (**1**) (4 mmol; 632 mg), *N,N*-dimethylaniline (**2a**) (2 mmol; 242 mg; 253 µl), dimethylsulfide oxide (5 mL) and $H_3PW_{12}O_{40}$ (95 mg; 1 mol%). The flask was heated at 100 ^oC for 24 hour. After that time the flask was cooled down to room temperature and 15 ml of chloroform was added. Solution was washed with 20 ml of brine. The organic phase was separated and dried by MgSO4. Solvent was evaporated off under reduced pressure and the residue was purified by column chromatography on silica gel, using hexane/ethyl acetate (9/1) as an eluent. Yield 194 mg (35%). Mp= 140.5-141.5 ^oC.

Variant 2. A 50 mL flask equipped with a magnetic stirrer was charged with naphthoquinone (**1**) (8 mmol; 1.26 g), *N,N*-dimethylaniline (**2a**) (16 mmol; 482 mg; 504 µl), dimethylsulfide oxide (10 mL), CH_3COOH (225 µL), and p-toluenesulfonic acid (6.8 mg; 1 mol%). The flask was heated at 100 ^oC for 24 hour. After that time the reaction mixture was cooled down to room temperature and 15 mL of chloroform was added. Solution was washed with 20 ml of brine. The organic phase was separated and dried by MgSO4. Solvent was evaporated off under reduced pressure and the residue was purified by column chromatography on silica gel, using hexane/ethyl acetate (9 / 1) as an eluent. Yield 53 mg (6%) **3a**. HRMS (ESI): m/z= 278.1180 $[C_{18}H_{15}NO_2+H]^+$, m/z (theor.)= 278.1176, diff.= 1.44 ppm. From this reaction mixture was obtained by-product 2-[4-(dimethylamino)phenyl]-3-methylnaphthalene-1,4-dione (**6a**) in 7% yield (60 mg), other by-products **6b-6d** were isolated in trace amounts and characterized by NMR and HPLC-MS.

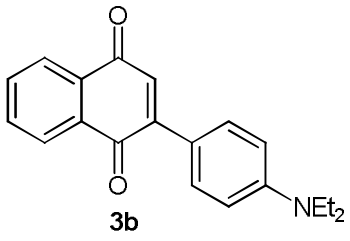
3a ^1H NMR (500.13 MHz. $CDCl_3$): δ= 3.05 (s, 6H, CH_3) 6.74-6.77 (m, 2H, CH) 7.02 (s, 1H, CH) 7.59- 7.62 (m, 2H, CH) 7.72-7.75 (m, 2H, CH) 8.08-8.11 (m, 1H, CH) 8.15-8.17 (m, 1H, CH) ^{13}C NMR (DEPT 135. 125.75 MHz. $CDCl_3$): δ= 40.07 (CH_3), 111.65 (CH), 125.61 (CH), 126.84 (CH), 130.92 (CH), 131.05 (CH), 133.29 (CH), 133.45 (CH).

6a ^1H NMR (500.13 MHz. $CDCl_3$): δ= 2.18 (s, 3H, CH_3) 3.03 (s, 6H, $N(CH_3)_2$) 6.78-6.80 (m, 2H, CH) 7.16-7.18 (m, 2H, CH) 7.69- 7.73 (m, 2H, CH) 8.10-8.14 (m, 2H, CH). ^{13}C NMR (DEPT 135, 125.75 MHz. $CDCl_3$): δ= 14.88 (CH_3), 40.21 (CH_3), 111.32 (CH), 125.91 (CH), 126.47 (CH), 131.05 (CH),133.22 (CH), 133.26 (CH).

6b ^1H NMR (500.13 MHz. $CDCl_3$): δ= 3.43 (s, 3H, CH_3) 6.14 (s, 1H, CH) 7.12-7.14 (m, 2H, CH) 7.28-7.30 (m, 1H, CH) 7.38-7.42 (m, 2H, CH) 7.60-7.63 (m, 1H, CH) 7.69-7.72 (m, 1H, CH) 7.88-7.90 (m, 1H, CH) 8.07-8.09 (m, 1H, CH). ^{13}C NMR (DEPT 135, 125.75 MHz. $CDCl_3$): δ= 43.21 (CH_3), 72.43 (CH), 111.90 (CH), 125.24 (CH), 125.62 (CH), 126.38 (CH), 126.72 (CH), 129.62 (CH), 132.49 (CH), 133.92(CH).

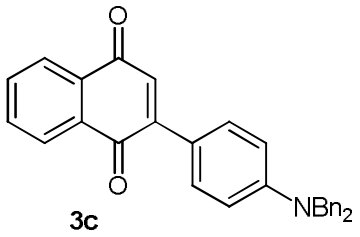
6c ^1H NMR (500.13 MHz. $CDCl_3$): δ= 2.92 (s, 12H, $N(CH_3)_2$) 3.83 (s, 2H, CH_2) 6.70-6.71 (m, 4H, CH) 7.07-7.08 (m, 4H, CH). ^{13}C NMR (DEPT 135, 125.75 MHz. $CDCl_3$): δ= 39.89 (CH_2), 40.95 (CH_3), 113.05 (CH), 129.42 (CH).

6d ^1H NMR (500.13 MHz. $CDCl_3$): δ= 2.06 (s, 3H, CH_3) 2.21 (s, 3H, CH_3) 3.31 (s, 3H, CH_3) 6.74-6.76 (m, 2H, CH) 6.85-6.88 (m, 2H, CH).



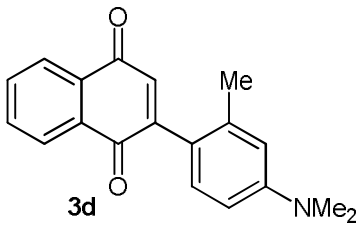
3b

2-[4-(diethylamino)phenyl]naphthalene-1,4-dione (**3b**) was prepared in a similar way as compound **3a**, using 1,4-naphthoquinone (**1**) (16 mmol; 2.53 g), *N,N*-diethylaniline (**2b**) (8 mmol; 1.286 ml), 15 mL of CH_3COOH (8 mmol, 450 µl) and $H_3PW_{12}O_{40}$ (230.4 mg; 1 mol%). Yield 757 mg (31 %). Mp= 99.6-102.2 °C. ^{1}H NMR (500.13 MHz. $CDCl_3$): δ= 1.21-1.24 (t, *J*= 7.1. 6H, $CH_2C\underline{H}_3$) 3.41-3.46 (q, *J*= 6.9, 4H, $C\underline{H}_2CH_3$) 6.72-6.75 (m, 2H, C<u>H</u>) 7.03 (s, 1H, C<u>H</u>) 7.59-7.62 (m, 2H, C<u>H</u>) 7.72-7.76 (m, 2H, C<u>H</u>) 8.09-8.18 (m, 2H, C<u>H</u>) ^{13}C NMR (DEPT 135, 125.75 MHz. $CDCl_3$): δ= 12.63 (<u>C</u>H$_2$), 44.46 (<u>C</u>H$_3$), 111.16 (<u>C</u>H), 125.66 (<u>C</u>H), 126.89 (<u>C</u>H), 130.52 (<u>C</u>H), 131.31 (<u>C</u>H), 133.29 (<u>C</u>H), 133.49 (<u>C</u>H). HRMS (ESI): m/z= 306.1507 $[C_{20}H_{19}NO_2+H]^+$, m/z (theor.)= 306.1489, diff.= 5.88 ppm



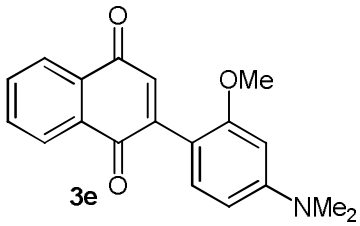
3c

2-[4-(dibenzylamino)phenyl]naphthalene-1,4-dione (**3c**) was prepared in a similar way as compound **3a**, using 1,4-naphthoquinone (**1**) (16 mmol; 2.53 g), *N,N*-dibenzylaniline (**2c**) (8 mmol; 1.984 g), 15 mL of CH_3COOH and $H_3PW_{12}O_{40}$ (230.4 mg; 1 mol%). Yield 821 mg (25 %). Mp= 145.3-146.7 °C. ^{1}H NMR (500.13 MHz. $CDCl_3$): δ= 4.74 (s, 4H, $C\underline{H}_2$) 6.81-6.84 (m, 2H, C<u>H</u>) 7.01 (s, 1H, C<u>H</u>) 7.26-7.31 (m, 6H, C<u>H</u>) 7.35-7.38 (m, 4H, C<u>H</u>) 7.53-7.56 (m, 2H, C<u>H</u>) 7.73-7.76 (m, 2H, C<u>H</u>) 8.09-8.18 (m, 2H, C<u>H</u>). ^{13}C NMR (DEPT 135, 125.75 MHz. $CDCl_3$): δ= 54.05 (<u>C</u>H$_2$), 112.11 (<u>C</u>H), 125.73 (<u>C</u>H), 126.52 (<u>C</u>H), 127.23 (<u>C</u>H), 128.84 (<u>C</u>H), 131.18 (<u>C</u>H), 131.45 (<u>C</u>H), 133.42 (<u>C</u>H), 133.58 (<u>C</u>H), HRMS (ESI): m/z= 430.1804 $[C_{30}H_{23}NO_2+H]^+$, m/z (theor.)= 430.1802, diff.= 0.43 ppm



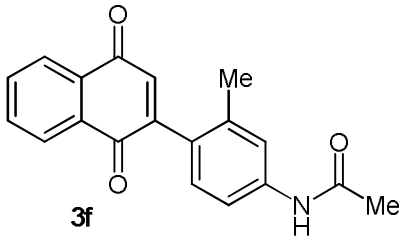
3d

2-[4-(Dimethylamino)-2-methylphenyl]naphthalene-1,4-dione (**3d**) was prepared in a similar way as compound **3a**, using 1,4-naphthoquinone (**1**) (6.64 mmol; 1.05 g), *N,N*,dimethyl-3-methylaniline (**2d**) (3.32 mmol; 448.6 mg), 15 mL of CH_3COOH and $H_3PW_{12}O_{40}$ (95.6 mg; 1 mol%). Yield 360 mg (37 %). Mp= 158.3-159.2 °C. ^{1}H NMR (500.13 MHz $CDCl_3$): δ= 2.25 (s, 3H, $C\underline{H}_3$) 3.02 (s, 6H, $N(C\underline{H}_3)_2$) 6.61-6.63 (m, 2H, C<u>H</u>) 6.91 (s, 1H, CH) 7.11-7.13 (m, 1H, C<u>H</u>) 7.76-7.78 (s, 2H, C<u>H</u>) 8.12-8.18 (m, 2H, CH). ^{13}C NMR (DEPT 135, 125.75 MHz. $CDCl_3$): δ= 21.39 (<u>C</u>H$_3$), 40.31 (<u>C</u>H$_3$), 109.51 (CH), 114.07 (CH), 125.93 (CH), 127.01 (CH), 131.04 (CH), 133.61 (CH), 135.77 (CH). HRMS (ESI): m/z= 292.1335 $[C_{19}H_{17}NO_2+H]^+$, m/z (theor.)= 292.1332, diff.= 1.03 ppm



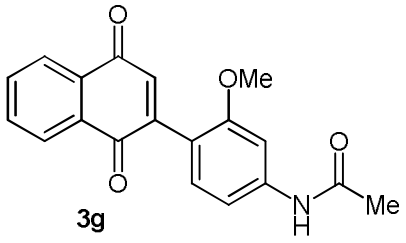
3e

2-[4-(Dimethylamino)-2-methoxyphenyl]naphthalene-1,4-dione (**3e**) was prepared in a similar way as compound **3a**, using 1,4-naphthoquinone (**1**) (6.64 mmol; 1.05 g), 3-methoxy-*N,N*-dimethylaniline (**2e**) (3.32 mmol; 501.7 mg), 15 mL of CH_3COOH and $H_3PW_{12}O_{40}$ (95.6 mg; 1 mol%). Yield 183 mg (18 %). Mp= 144.2-145.6 °C. ^{1}H NMR (500.13 MHz. $CDCl_3$): δ= 3.04 (s, 6H, $N(C\underline{H}_3)_2$) 3.82 (s, 3H, $OC\underline{H}_3$) 6.27 (s, 1H, C<u>H</u>) 6.37-6.39 (d, *J*= 8.83, 1H, C<u>H</u>) 7.09 (s, 1H, C<u>H</u>) 7.20-7.21 (d, *J*= 8.51, 1H, C<u>H</u>) 7.72- 7.74 (m, 2H, C<u>H</u>) 8.09- 8.15 (m, 2H, C<u>H</u>). ^{13}C NMR (DEPT 135, 125.75 MHz. $CDCl_3$): δ= 40.36 ($N(CH_3)_2$), 55.52 (CH_3), 95.52 (CH), 104.44 (CH), 125.73 (CH), 126.86 (CH), 132.13 (CH), 133.29 (CH), 133.32 (CH), 134.80 (CH). HRMS (ESI): m/z=308.1271 $[C_{19}H_{17}NO_3+H]^+$, m/z (theor.)= 308.1281, diff.= -3.25 ppm



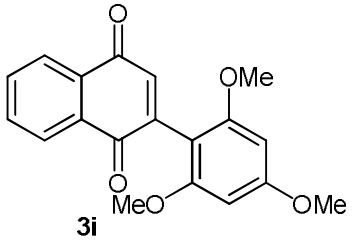
3f

***N*-[4-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3-methylphenyl]acetamide (3f)** was prepared in a similar way as compound **3a**, using 1,4-naphthoquinone (**1**) (10 mmol; 1.58 g), *N*-(3-methylphenyl)acetamide (**2f**) (5 mmol; 745 mg), 15 mL of DMSO or CH_3COOH and $H_3PW_{12}O_{40}$ (144 mg; 1 mol%). Trace amount of product was obtained.



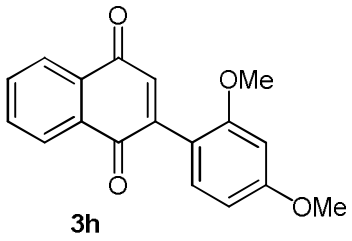
3g

***N*-[4-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3-methoxyphenyl]acetamide (3g)** was prepared in a similar way as compound **3a**, using 1,4-naphthoquinone (**1**) (20 mmol; 3.16 g), *N*-(3-methoxyphenyl)acetamide (**2g**) (10 mmol; 1.65 g), 15 mL of CH_3COOH and $H_3PW_{12}O_{40}$ (288 mg; 1 mol%). Yield 483 mg (15 %). Mp= 209-210 ^oC. ^1H NMR (500.13 MHz. $CDCl_3$): δ= 2.21 (s, 3H, $NHCOC\underline{H}_3$) 3.80 (s, 3H, $OC\underline{H}_3$) 6.89-6.91 (m, 1H, CH) 7.04 (s, 1H, CH) 7.18-7.20 (d, J=8.20, 1H, CH) 7.42 (s, 1H, CH) 7.59 (s, 1H, CH) 7.75-7.79 (m, 2H, CH) 8.11-8.17 (m, 2H, CH). ^{13}C NMR (125.75 MHz. $CDCl_3$): δ= 24.80, 25.36, 55.82, 103.22, 111.00, 125.99, 126.94, 130.95, 132.15, 133.60, 133.70, 136.61, 140.74, 140.74, 147.22, 157.98, 168.42, HRMS (ESI): m/z= 322.1070 $[C_{19}H_{15}NO_4+H]^+$, m/z (teor,)= 322.1074, diff.= -1.24 ppm



3i

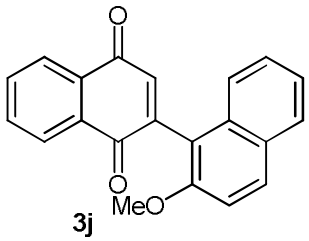
2-(2,4,6-trimethoxyphenyl)naphthalene-1,4-dione (3i). A 150 mL flask equipped with a magnetic stirrer was charged with naphthoquinone (**1**) (60 mmol; 9.5 g), 1,3,5-trimethoxybenzene (**2i**) (30 mmol; 5.0 g), acetone (75 mL), and $H_3PW_{12}O_{40}$ (98 mg; 1 mol%). The flask was heated under reflux for 1.5 hour. After that time product was oxidized by adding $NaIO_3$ (27 mmol, 5.94 g) in 25 mL of H_2O and heated under reflux for 24 hours to complete an oxidation of intermediate product. The oxidation of reactions are controlled by two-dimensional TLC (TLC with applicated reaction mixture develops in solvents system hexane/ acetone (3/1) and after 15 min of conditioning time it was developed again in a perpendicular to previous direction). Afterwards the solvent was removed under reduced pressure, a residue was separate from water by filtration and dissolved in 200 mL of chloroform. The solution was dried by $MgSO_4$. $MgSO_4$ was filtered off followed by solution was concentrated down to 25 mL and applicated on column with 50 g of silica gel. The crude product was eluted by about 500 ml of chloroform. After evaporating of solvent the crude product was heated in 70 mL *t*-buthylmethyl ether for 60 minutes. After cooling down flask to room temperature pure product was filtered off, washed by a little amount of *t*-buthylmethyl ether and dried under reduced pressure at 90 ^oC for 1 hour. Obtained in such way product contains about 1.6% of naphthoquinone, which could be complete removed by longer heating of the sample under high vacuum. Yield 8.3 g (85 %). Mp= 183 ^oC. ^1H NMR (500.13 MHz. $CDCl_3$): δ= 3.74 (s, 6 H, $OC\underline{H}_3$) 3.87 (s, 3 H, $OC\underline{H}_3$) 6.21 (s, 2 H, C<u>H</u>) 6.96 (s, 1 H, C<u>H</u>) 7.73- 7.75 (m, 2 H, C<u>H</u>) 8.11-8.14 (m, 2 H, C<u>H</u>). ^{13}C NMR (DEPT 135, 125.75 MHz. $CDCl_3$): δ= 55.41 (CO<u>C</u>H), 55.83 ($O\underline{C}H_3)_3$, 90.81 (<u>C</u>H), 125.90 (<u>C</u>H), 126.82 (<u>C</u>H), 133.24 (<u>C</u>H), 133.42 (<u>C</u>H), 138.67 (<u>C</u>H). HRMS (ESI): m/z= 325.1066 $[C_{19}H_{16}O_5+H]^+$, m/z (theor.)= 325.1071, diff.= -1.54 ppm.



3h

2-(2,6-dimethoxyphenyl)naphthalene-1,4-dione (3h) was prepared in a similar way as compound **3i**, using 1,4-naphthoquinone (60 mmol; 9.5 g), 1,3-dimethoxybenzene (**2h**) (30 mmol; 4.1 g, 3.9 ml), 75 mL of acetone and $H_3PW_{12}O_{40}$ (98 mg; 1 mol%). Yield 6.7 g (77%). ^1H NMR (500.13 MHz. $CDCl_3$): δ= 3.79 (s, 3H, $C\underline{H}_3$) 3.87 (s, 3H, $C\underline{H}_3$) 6.56-6.60 (m, 2H, C<u>H</u>) 7.04 (s, 1H, C<u>H</u>) 7.21-7.22 (d, *J*= 8.51, 1H, C<u>H</u>) 7.74-7.76 (m, 2H, C<u>H</u>) 8.10-8.17 (m, 2H, C<u>H</u>). ^{13}C NMR (DEPT

135, 125.75 MHz. $CDCl_3$): δ= 55.51 ($O\underline{C}H_3$), 55.74 ($O\underline{C}H_3$), 99.06 (<u>C</u>H), 104.71 (<u>C</u>H), 125.92 (<u>C</u>H), 126.95 (<u>C</u>H), 131.67 (<u>C</u>H), 133.49 (<u>C</u>H), 133.61 (<u>C</u>H), 136.26 (<u>C</u>H). HRMS (ESI): m/z= 317.0770 $[C_{18}H_{14}O_4+Na]^+$, m/z (theor.)= 317.0784, diff.= -4.42 ppm



3j

2-methoxy-1,2'-binaphthalene-1',4'-dione (3j) was prepared in a similar way as compound **3a**, using 1,4-naphthoquinone (10 mmol; 1.58 g), 2-methoxynaphthalene (**2j**) (5 mmol; 0.79 g), 15 mL of CH_3COOH or DMSO and $H_3PW_{12}O_{40}$ (144 mg; 1 mol%). Trace amount of product was obtained. Mp= 121–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ= 3.90 (s, 3 H) 7.09 (s, 1 H) 7.37–7.40 (m, 2 H) 7.44 (t, *J* = 7.2 Hz, 1 H) 7.62 (d, *J* = 8.4 Hz, 1 H) 7.81–7.83 (m, 2 H) 7.86 (d, *J* = 8.4 Hz, 1 H) 7.98 (d, *J* = 9.2 Hz, 1 H) 8.19–8.23 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ= 56.6, 113.1, 116.9, 123.8, 123.9, 126.2, 127.1,127.2, 128.4, 129.0, 131.1, 132.4, 132.5, 132.6, ^{133}.7, 133.8, 139.3, 147.1, 154.4, 183.8, 185.1. Anal. Calcd for $C_{21}H_{14}O_3$: C, 80.24; H, 4.49. Found: C, 79.75; H, 4.81.

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