New and Efficient Protocol for Arylation of Quinones

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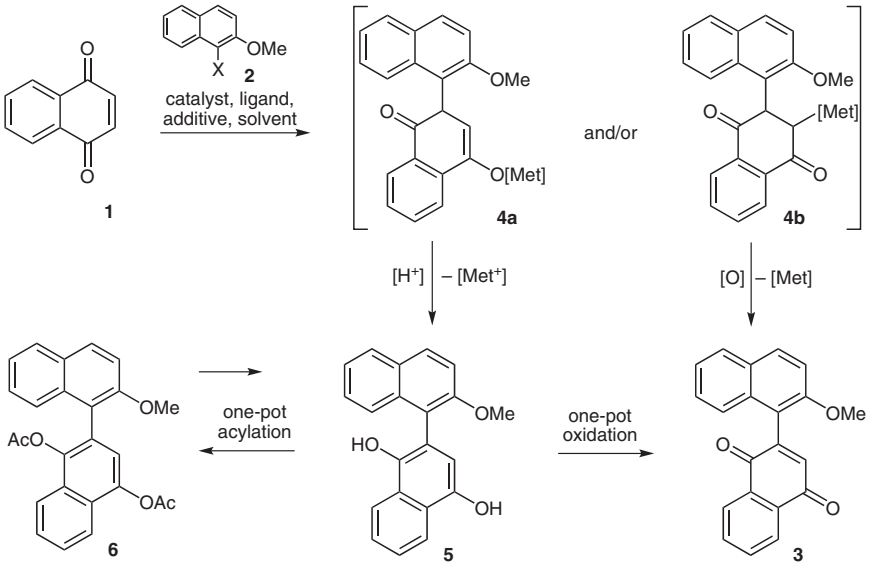
Abstract: A practical rhodium-mediated arylation of 1,4-quinones has been developed. The corresponding 2-aryl-1,4-quinones were obtained with excellent selectivity and high yields under convenient aerobic reaction conditions.

Key words: arylation, homogeneous catalysis, quinones, rhodium, cross-coupling

Substituted quinones and naphthoquinones constitute a common structural motif, important building blocks, and convenient precursors for numerous important natural products and pharmaceuticals.[1] Previously we pointed out that 2-arylnaphthoquinones are excellent precursors to highly active phosphorus ligands.[2] Depending on the substitution pattern 2-arylquinones can be obtained in good yields only by a few general methods such as oxidation of the corresponding aromatics,[3] cycloadditions yielding the quinone core,[4] transition-metal-mediated cross-couplings,[2,5] Meerwein reaction,[6] and in rare cases, by direct arylation protocols.[7] Thus, development of a general high-yield procedure leading to the substituted 2-arylquinones suitable for sterically demanded cases seems to be worthwhile. Herein we wish to describe a facile general synthesis of arylated quinones based on a direct Rh-catalysed coupling of quinones with arylboronic acid derivatives.

Sterically demanding and electron-rich 2-(2-methoxynaphth-2-yl)naphthoquinone (**3**) was selected as a model target compound to examine efficiency of the proposed coupling protocol. Incompatibility of naphthoquinone (**1**) with the strongly basic conditions does not allow us to use aryl halides and Mizoroki–Heck reaction. On the other hand, arylboronic acids are also readily available, and so we decide to utilise them in the oxidative Heck approach[2] to the quinones arylation. Although preliminary reactions provided the product in good yields the turnover number (ca. 3) of the used Pd catalyst turned out to be impractical [Scheme 1, additives: $Cu(OAc)_2$, $Na_2S_2O_8$, Me_3NO; solvents: AcOH, TFA, DMSO, DMF, MeOH, and their combinations]. The key difficulty we faced in this approach was low efficiency of reoxidation of Pd at moderate reaction temperature. We also found that both organic substrates can reduce Pd(II) species to form unreactive palladium black.

Although the transition-metal-catalysed additions to quinones[8] and to their mono ketals[9] leading to hydroquinones are known, they have never been accomplished in a way to provide the quinone products. Considering the



Scheme 1 Possible arylation pathways; X = leaving group: $B(OH)_2$ (**2a**), BF_3K (**2b**); cat. = [Rh], [Pd]

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known ability of hydroquinones to undergo efficient oxidation to quinones, we decided to perform tandem addition combined with a one-pot reoxidation of formed 2-arylhydroquinones to the 2-arylnaphthoquinones.

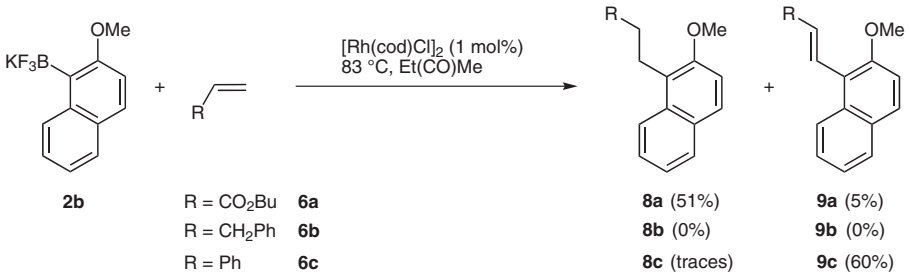
Series of different ligands and transition-metal-catalyst precursors were tested. It was found that Pd and Ru catalysts, $RhCl_3$, Wilkinson catalysts, and $[Rh(nbd)Cl]_2$ produce only trace amounts of the desired reaction products, such as **3**, or their reduced forms, such as **5**. Attempts to enhance catalysts effectiveness by addition of typical phosphorus ligands [Ph_3P, dppe, dppb, BINAP, S-Phos, Nap-Phos]; oxygen ligands [Ph_3PO, BINAP-O_2]; nitrogen ligands [neocuproine, PhCN, 2-(2-methoxyphenyl)-4,4-dimethyl-2-oxazoline, 2-(4-methylpyridyl)-4,4-dimethyl-2-oxazoline], or carbene ligand IMES, had practically no effect. We have also found that popular ligating solvents (MeCN, PyH, DME, diglyme, and diethylene glycol) did not increase the yields of the studied reactions either.

Eventually, we recognised that base-free rhodium-catalysed Heck-type reaction protocol recently developed for aryl-aryl coupling[10] allows to obtain more significant amounts (above 30%) of the desired product **3** when $[Rh(cod)Cl]_2$ and potassium 2-methoxynaphthyl trifluoroborate (**2b**) are utilised. Initially, the experiments were carried out in a Schlenk tube closed with a glass stopper under oxygen-free and moisture-free conditions in dry, freshly distilled acetone at 80–85 °C. The 1:1 to 1:4 mixtures of acetone–dioxane were also tested in order to decrease pressure developing in the reactor. Although we were able to run experiments safely even at 120 °C, the best yields were obtained in the 85–90 °C temperature range. The experiments run in *i*-Pr(CO)Me and Et(CO)Me gave identical results to those when run in pure acetone. Addition of small amounts of water did not affect the yields of **3** whereas addition of 25 vol% of water resulted in a 50% yield decrease. Therefore for convenience all subsequent experiments were performed in commercial 2-butanone without any additional purification under reflux (83 °C) or, in the reference Schlenk tube experiments, at 85 °C bath temperature. The addition of common phosphorus or nitrogen ligands did not result in any significant change in yields (Table 1, entries 1–6).

Interestingly, in addition to the quinone product **3** implied by the proposed mechanism of the reactions of this type catalysed by $[Rh(C_2H_4)_2Cl]_2 \cdot nPh_3P$,[10] in all our experiments we have observed significant amounts (up to 30%) of not oxidised product **5** which could be easily detected by means of 2D TLC when the TLC plate was left in the air for a while between two sequential developments in perpendicular directions. It seemed thus, that two independent reaction pathways leading to products **5** and **3** were involved (Scheme 1). That has been also confirmed by the experiments in which naphthoquinone was replaced with butyl acrylate (Scheme 2) where two possible products **8a** and **9a** were formed in 51% and 5% yields, respectively, with nearly equimolar ratio of *E*/*Z* isomers of **9a**. In the case of styrene (**6c**) there was observed an opposite selectivity – the unsaturated product **9b** was almost exclusively formed in 60% overall yield (*E*/*Z* = 4). Surprisingly, allylbenzene (**6b**) did not undergo the arylation reaction.

Due to the propensity of **5** to be oxidised on air, the isolation of pure **5** proved difficult. Thus, **5**, isolated by column chromatography (about 30% yield) underwent rapid and quantitative oxidation into **3** in a short time. Nevertheless, product **5** was characterised in the presence of **3** by its MS and NMR spectra, and also as the corresponding bis(acylated) derivative after treatment of the reaction mixture with Ac_2O in PyH. This preliminary study indicated that the development of an efficient one-pot methodology for oxidation of hydroquinone to quinone would be desirable. The simplest oxidation of **5** to **3** by exposure to air worked well for small-scale experiments (up to 0.5 mmol) but it was not efficient in the case of preparative runs. From numerous available oxidants used for the oxidation of hydroquinones, we have selected inorganic metaperiodate salts due to their very gently oxidative character. Solid $NaIO_4$ used in twofold molar excess resulted in the complete conversion of **5** to **3** in 64 hours. The tetrabutyl ammonium metaperiodate used in the same excess allowed to achieve the complete oxidation during several minutes. However, application of tetrabutyl ammonium salts should be limited because of their cost. Eventually, we found that a mixture of Bu_4NBr (0.25 equiv), $NaIO_4$ (1 equiv), and Bu_4NIO_4 (0.25 equiv) added to the reaction mixture after three hours led to full and clean oxidation of **5** to **3** in 18 hours. However, attempts to perform similar oxidation in situ gave poor results. The reactions run in a Schlenk tube under argon gave more product **5** but only a slightly better yield of **3** was obtained after oxidation (Table 1, entries 6 and 7).

Easily available triolborates,[11] for example, compound **10** (Figure 1), have been also tested as substrates in the stud-



Scheme 2 Rhodium-catalysed arylation of alkenes

Table 1 Synthesis of **3**: Optimisation Experiments

Entry	Precatalyst (mol%)	Ligand (mol%)	Temp (°C)	Solvent	Atmosphere	Oxidant	Time (h)	Additive	Yield of **3** (%)[a]
1	$[Rh(cod)Cl]_2$ (0.4)	–	83	Et(CO)Me	air	air	24	–	15
2	$[Rh(cod)Cl]_2$ (0.8)	–	83	Et(CO)Me	argon	–	–	–	41; 32 (**5**)[b]
3	$[Rh(cod)Cl]_2$ (0.8)	–	85	dioxane	argon	air	24	–	19
4	$[Rh(cod)Cl]_2$ (3)	Neocuproine (9)	85	*i*-Pr(CO)Me	argon	air	24	–	32
5	$[Rh(cod)Cl]_2$ (3)	dppb (9)	80	*i*-Pr(CO)Me	argon	air	24	–	59
6	$[Rh(cod)Cl]_2$ (0.8)	–	85	Me(CO)Me	argon	air or IO_4^-	24	–	57
7	$[Rh(cod)Cl]_2$ (0.8)	–	83	Et(CO)Me	air	air or IO_4^-	24	–	55
8	$[Rh(cod)Cl]_2$ (0.8)	–	83	Et(CO)Me	air	IO_4^-	24	$B(OH)_3$	64
9	$[Rh(cod)_2]BF_4$ (1)	–	83	Et(CO)Me	air	IO_4^-	24	$B(OH)_3$	83
10	$[Rh(nbd)_2]BF_4$ (1)	–	83	Et(CO)Me	air	air	24	–	trace
11	$[Rh(cod)Cl]_2$ (1)	COD (20)	83	Et(CO)Me	air	IO_4^-	24	$KHSO_4$	87
12	$[Rh(cod)Cl]_2$ (1)	COD (20)	83	Et(CO)Me	air	IO_4^-	24	$B(OH)_3$	72
13	$[Rh(cod)Cl]_2$ (2)	COD (20)	83	Et(CO)Me	air	IO_4^-	24	$B(OH)_3$	78

[a] Isolated yield.
[b] Isolated as bis(acetate) **6** in separate experiments when excess of Ac_2O in PyH was added to the reaction mixture after it was cooled down to r.t.

ied arylation reaction. Unfortunately, high basicity of **10** induced significant decomposition of naphthoquinone and **3** was formed only in trace amounts. Several acidic additives [$MeCO_2H$, $PrCO_2H$, $B(OH)_3$, KH_2PO_4, $KHSO_4$, Bu_4NHSO_4] were used to override the basicity of **10**, but with very little success. On the other hand, we have observed a strong effect of acidic additives in the reactions involving trifluoroborate as substrates. The organic acids, Bu_4NBF_4 and Bu_4NHSO_4, added in equimolar amounts, broke down the catalytic cycle completely, and the products were formed only in trace amounts. In contrast, the inorganic acidic salts and $B(OH)_3$ added equimolarly or in a few-fold excess increased the yields (Table 1, entries 7 and 8). This phenomenon could probably be explained by an increased ability of low-soluble inorganic compounds to scavenge nucleophilic chloride anion from the organic mixture. The hypothesis was partially supported by the observation that an addition of Bu_4NBr stopped the reaction completely while utilisation of ionic rhodium complex $[Rh(cod)_2]BF_4$ resulted in a significant increase of yield (Table 1, entries 8 and 9). Nevertheless, when used in large excess, an acid probably underwent reaction with trifluoroborate to a significant extent and resulted in some lowering of yield. Surprisingly, we did not achieve good reaction yields by using ionic $[Rh(nbd)_2]BF_4$. It looks then that COD ligand present in the precatalyst serves the purpose the best. Ability of the diene ligands to act as efficient ligands in 1,4-addition reactions catalysed by Rh has been known. It has been postulated that some diene ligands are maintained in the coordination sphere of rhodium during the entire catalytic cycle allowing excellent yields and selectivity to be achieved without addition of any other ligand.[9] Moreover, in our case addition of 20 mol% of free COD to the reaction mixture resulted in a significant increase of yield (Table 1, entries 8, 11–13).

In this way, the following optimal reaction conditions were established: ratio of potassium trifluoroborate to naphthoquinone as 1:1.5 (reverse of reagent ratio does not affect the reaction yield significantly); 0.2 M solution in Et(CO)Me, 1 mol% of $[Rh(cod)Cl]_2$, 20 mol% of COD; 1 equivalent of $B(OH)_3$ or $KHSO_4$; reflux in the open air for 18 hours followed by oxidation by Bu_4NBr (0.25 equiv), $NaIO_4$ (1 equiv) and Bu_4NIO_4 (0.25 equiv) at room temperature for the next 18 hours. This protocol was used without any additional optimisation for the determination of reaction scope and limitations. It is worth mentioning that an alternative approach to **3** via Suzuki reaction protocol by the utilisation of 2-bromonaphoquinone, corresponding boronic acid, and 10 mol% of $[(t\text{-}Bu_3P)_2Pd]$, run under argon in anhydrous DMF, brings only 50–60% yield (depending on the scale) of the desired product **3**.

As shown in Figure 1 different types of aromatic trifluoroborates either unsubstituted **11** and **13**, possessing electron-donating group (EDG) **2b**, **12**, and **17**; electron-withdrawing group (EWG) **14**, **15**, and **16**; sterically hindered by two *ortho* substituents **2b** and **12**; and several differently substituted commercially available quinones **1**, **18–21**, were tested together under the developed arylation conditions.

Similarly to the Suzuki-type couplings, electron-donating substituents in boronic acids facilitated the arylation. Boronic acids possessing EWG substituents were less reactive. We were unable to obtain any significant yields of

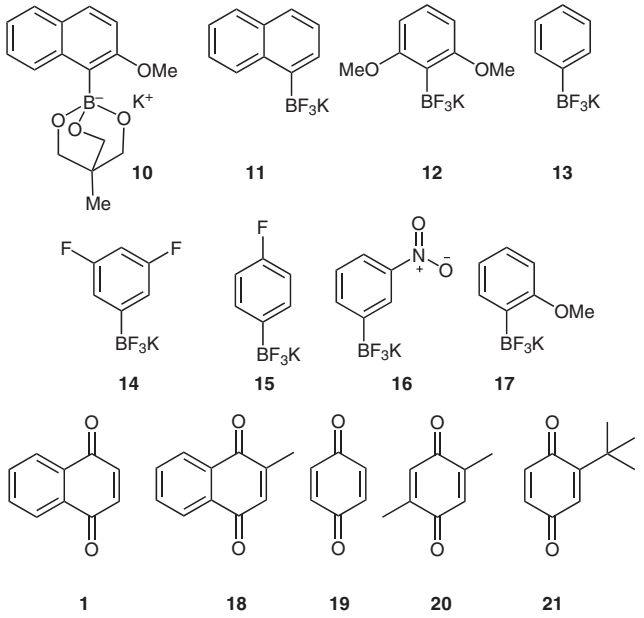
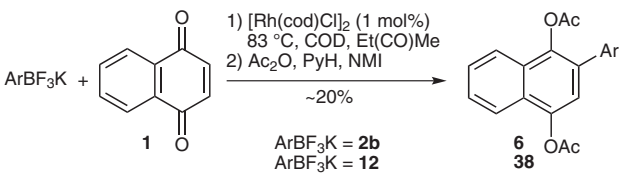


Figure 1 Tested aromatic boronic acid derivatives, quinines, and naphthoquinones

the quinone products using trifluoroborates having EWGs like 3-NO_2 or double 3-F, in those reactions the reduction of **1** was observed and the significant amounts of 1,4-dihydroxynaphtalene derivative were isolated. In addition, the hydroquinone products possessing EWG in the aromatic ring were not compatible with the oxidation protocol so the formed products had to be isolated with no oxidation applied. The yields of corresponding products are given in Table 2.

Some steric hindrance around the trifluoroborate site did not play any significant role and compounds having two *ortho* substituents were coupled very well (Table 1, entry 11; Table 2, entries 2, 10, 12, 16). The hindrance in the quinone core was, however, significant. Thus, compounds **18** and **20** (Table 2, entries 8, 13) underwent transformation with low conversion. Quinone **21** bearing only one, even though large, substituent reacted efficiently and gave two isomeric products **37a** and **37b** in 3:1 ratio in excellent yield (Table 2, entry 14). It is interesting that we did not observe the formation of bisarylated benzoquinones derived from **19**.

Unstable dihydroxynaphthalenes could be isolated as bis(acetates) **6** and **38** after treatment of the corresponding reaction mixture with Ac_2O in PyH and catalytic amount of *N*-methylimidazole (Scheme 3). The products obtained from benzoquinone were much more resistant to oxidation and could be isolated by flash column chromatography.



Scheme 3 One-pot synthesis of dihydroxynaphthalene bis(acetates)

Table 2 Arylation of Quinones and Naphthoquinones by Potassium Trifluorarylboronates under the Optimised Conditions[12]

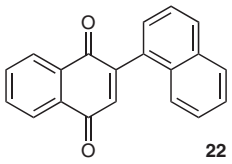
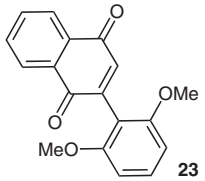
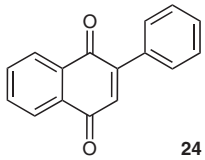
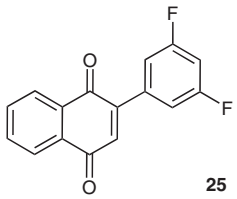
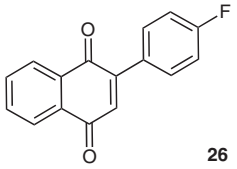
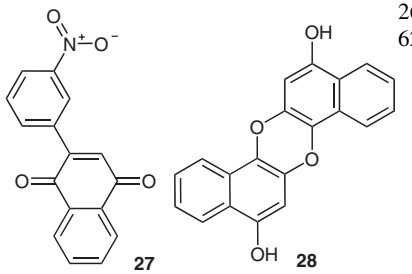
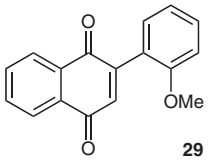
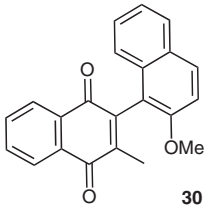
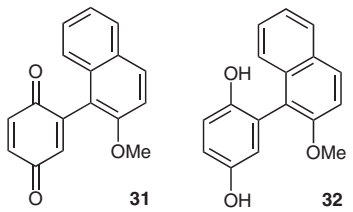
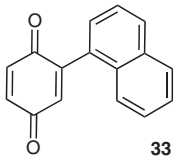
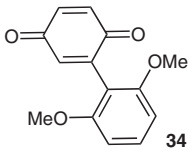
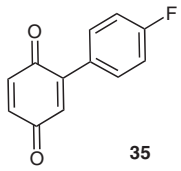
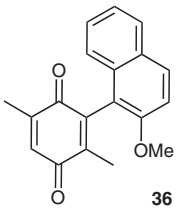
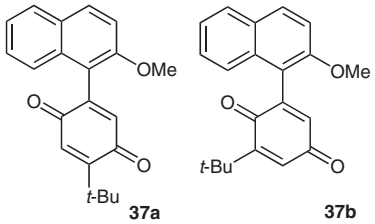
Entry	Substrates	Product	Yield (%)[a]
1	**1**, **11**	 **22**	72
2	**1**, **12**	 **23**	80
3	**1**, **13**	 **24**	72
4	**1**, **14**	 **25**	17[a]
5	**1**, **15**	 **26**	22[a,b]
6	**1**, **16**	 **27** **28**	26[a] (**27**) 62[a] (**28**)[c]
7	**1**,**17**	 **29**	79
8	**18**, **2b**	 **30**	10

Table 2 Arylation of Quinones and Naphthoquinones by Potassium Trifluorarylboronates under the Optimised Conditions[12] (continued)

Entry	Sub-strates	Product	Yield (%)[a]
9	**19**, **2b**	 **31** **32**	60 (**31**)[a] 37 (**32**)[a]
10	**19**, **11**	 **33**	50
11	**19**, **12**	 **34**	63
12	**19**, **15**	 **35**	15[a,b]
13	**20**, **2b**	 **36**	traces[b]
14	**21**, **2b**	 **37a** **37b**	67% (**37a**) 22% (**37b**)

[a] Isolated without oxidation step.
[b] Yield of the products in mixtures with starting material as calculated from NMR or GC-MS spectra.
[c] Tentative structure assignment.

Concluding, we have developed a practical approach to the synthesis of arylated quinones and naphthoquinones based on a straightforward Rh-catalysed direct arylation. The importance of this approach is that a variety of substituted quinones and naphthoquinones can be synthesised from readily available substrates usually in high yields and that the syntheses can be run under open air in technical-grade solvents and with low catalyst loading. We are currently exploring the application of this methodology to the synthesis of chiral atropoisomeric ligands useful in different types of asymmetric reactions.

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(11) Yamamoto, Y.; Takizawa, M.; Yu, X. Q.; Miyaura, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 928.
(12) **Typical Coupling Procedure**: A glass vial was loaded with $[Rh(cod)Cl]_2$ (5 mg, 0.01 mmol), Et(CO)Me (5 mL) and COD (35 μL, 0.2 mmol). Then, **1** (137 mg, 1.5 mmol), **2b** (264 mg, 1 mmol), and $KHSO_4$ (137mg, 1 mmol) were sequentially added with stirring. The vial was then equipped with a condenser capped with a PP-cap and was put into a (95 °C) hot oil bath to be stirred for 18 h. After that time, the reaction mixture was allowed to cool down to r.t. Products **3** and **5** could be isolated by MPLC on this stage or only **3** after oxidation.
Oxidation: $NaIO_4$ (213 mg, 1 mmol) and Bu_4NBr (80 mg, 0.25 mmol) were added to the coupling reaction mixture and stirred at r.t. for 3 h. Bu_4NIO_4 (110 mg, 0.25 mmol) was then added. After 21 h of stirring at r.t. solvent was evaporated off, and **3** was chromatographically isolated (SiO_2, 20–400 mesh; hexane–acetone, 6:1) to yield **3** (273 mg, 87%); mp 121–123 °C. ^1H NMR (400 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 (100 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.