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Synthesis and Characterization of Novel Quinone Methides: Reference Electrophiles for the Construction of Nucleophilicity Scales

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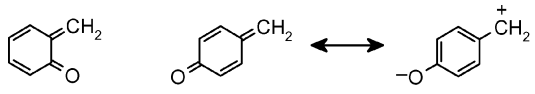
Dedicated to Professor Armin de Meijere on the occasion of his 70th birthday

Keywords: Electrophilicity / Nucleophilicity / Kinetics / Linear free-energy relationships / Quinone methides

Novel synthetic routes to the aryl-substituted quinone methides **3a**–**f** have been developed, and a previously reported Mannich approach has been used for the syntheses of the acceptor substituted quinone methides **2e**–**g**. The second-order rate constants for the reactions of **3c**–**f** and **2e**–**g** with the carbanions **9a**–**h** were determined photometrically in DMSO. With Equation (1), $\log k_2 = s(N + E)$, and the known nucleophilicity parameters N and s for the carbanions **9a**–**h**, it was possible to calculate the electrophilicity parameters E for these quinone methides. With E parameters between –12 and –17, these readily accessible quinone methides are recommended as reference electrophiles for the construction of nucleophilicity scales.

Introduction

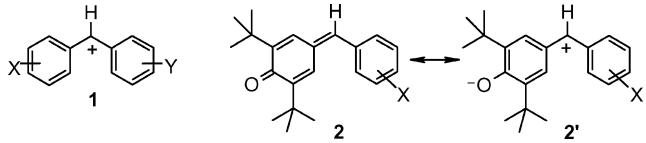
Quinone methides (QM) are formally obtained when one oxygen atom of a quinone is replaced by a methylene group. They are reactive intermediates in organic synthesis[1] and biosynthesis.[2] Recently they were reported to be efficient cross-linking and target-promoted alkylation reagents for DNA.[3] As QMs are capable of forming covalent bonds to amino acids and peptides, they serve as mechanism-based inhibitors of enzymes and as both promotors of tumor growth and anticancer drugs. Hence, the reactions of simple *ortho*- and *para*-QMs have been subject of a variety of kinetic studies by the groups of Wan,[4] Kresge,[5] and Richard.[6] Freccero used laser flash photolytic techniques for the generation of the parent quinone methides **o-QM** and **p-QM** and systematically quantified the reactivities of these highly reactive electrophiles towards O-, N-, and S-nucleophiles in aqueous solutions.[3,7]



o-QM **p-QM**

As the second-order rate constants for the hydration of simple QM model compounds were found to be 10^4–10^5 times smaller than those of their reactions with amines and thiols, the kinetic data provided important information about the efficiencies of QMs as alkylation agents under physiological conditions.[8] Variation of substituents in *ortho*-quinone methides revealed further insights into the reversibility of the QM adduct formation with deoxynucleotides.[9]

In recent years, we have established benzhydrylium ions **1** and structually related, aryl-substituted *para*-quinone methides **2** as reference electrophiles for the construction of the most comprehensive nucleophilicity scale presently available.[10,11]



1 **2** **2'**

From the second-order rate constants of their reactions with various classes of nucleophiles it was possible to calculate their electrophilicity parameters E as well as the N and s parameters of π-, σ-, and n-nucleophiles (e.g., carbanions,[11,12] alkenes,[10a,10b] amines and amino acids[13] or hydride donors[10a,14]) as defined by Equation (1).[15]

$$\log k_2(20\ ^\circ\mathrm{C}) = s(N + E) \quad (1)$$

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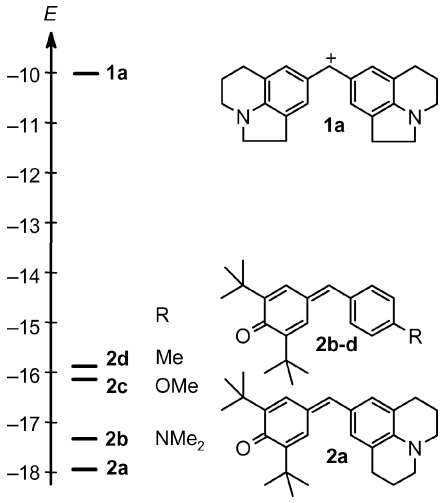
k_2: second-order rate constant (in $L\,mol^{-1}\,s^{-1}$)
E: electrophilicity parameter
N: nucleophilicity parameter
s: nucleophile-specific slope parameter

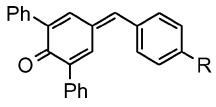
By employing different substituents X and Y in *p*- and *m*-position, the electrophilicities of **1** and **2** have been varied by almost 30 orders of magnitude while the steric situation around the center of electrophilicity was kept almost constant.

The least electrophilic benzhydrylium ion **1a** and the most reactive *tert*-butyl-substituted quinone methide so far characterized (**2d**) differ by almost six orders of magnitude in electrophilicity (Scheme 1).



Scheme 1. Reactivities of the quinone methides **2a**–**d** in comparison with the least reactive benzhydrylium ion **1a**.

This large gap has been bridged by the 2,6-diphenyl-substituted quinone methides **3a** and **3b** for which the electrophilicity parameters *E*(**3a**) = –12.18 and *E*(**3b**) = –13.39 had been determined.[11]



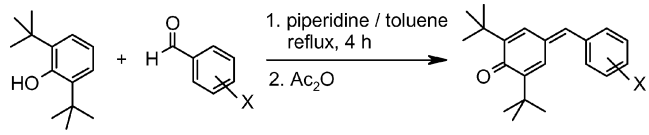
	R	*E*
3a	OMe	–12.18
3b	NMe_2	–13.39

The practical application of **3a** and **3b** was limited, however, by the very cumbersome syntheses of these compounds.[16] We now report on more efficient syntheses of **3a** and **3b** as well as on a straightforward access to other quinone methides of similar structure and the determination of their electrophilicities.

Results and Discussion

Syntheses

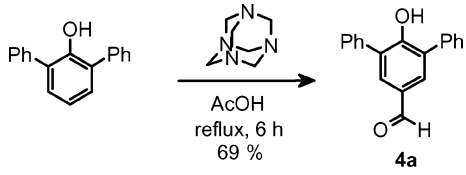
The method previously reported[17] for the syntheses of **2a**–**d** and **2g** was adjusted to the syntheses of the fluorine substituted quinone methides **2e**–**f** (Scheme 2).



	X	Yield /%
2e	3-F	59
2f	3,5-F_2	47
2g	4-NO_2	68

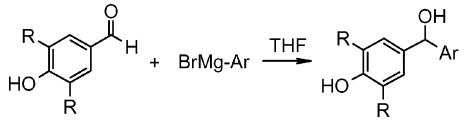
Scheme 2. Synthesis of the *tert*-butyl-substituted quinone methides **2e**–**g**.

The analogous Mannich synthesis did not work for other types of quinone methides. For their syntheses, the 4-hydroxy-substituted benzhydrols **5** were used as key-intermediates. According to Unangst et al., 4-hydroxy-3,5-diphenylbenzaldehyde **4a** is efficiently synthesized by treating the commercially available 2,6-diphenylphenol with urotropin in acetic acid (Duff reaction, Scheme 3).[18]



Scheme 3. Synthesis of 4-hydroxy-3,5-diphenylbenzaldehyde **4a** by Duff reaction.

Treatment of **4a** or of the commercially available hydroxybenzaldehydes **4b** and **4c** with 2.4 equiv. of arylmagnesium bromide in THF gave the hydroxybenzhydrols **5a**–**f** (Scheme 4).

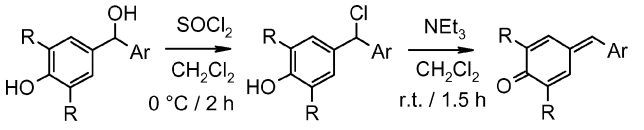


	R	Ar		Yield /%
4a	Ph	4-MeO-C_6H_4	**5a**	83
4a	Ph	4-Me_2N-C_6H_4	**5b**	79
4a	Ph	C_6H_5	**5c**	73
4b	OMe	4-MeO-C_6H_4	**5d**	83
4b	OMe	4-Me_2N-C_6H_4	**5e**	43
4c	Me	4-Me_2N-C_6H_4	**5f**	69

Scheme 4. Grignard reaction for the synthesis of the hydroxybenzhydrols **5a**–**f**.

Alcohols **5a**,**c**,**d**, i.e., compounds with Ar = 4-MeO-C_6H_4 or C_6H_5 have been converted into the benzhydryl chlorides **6a**,**c**,**d** by treatment with thionyl chloride. The reactions of **6a**,**c**,**d** with triethylamine gave the quinone methides **3a**,**c**,**d** (Scheme 5), in analogy to the method reported by Pospisek.[19]

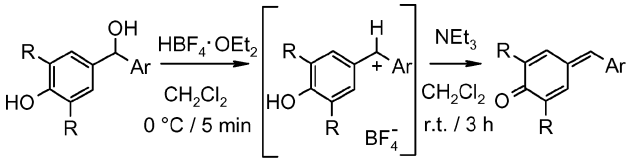
Addition of ethereal HBF_4 to a solution of the dimethylamino-substituted 4-hydroxybenzhydrols **5e**,**f** in dichloromethane at 0 °C led to the formation of the dark-violet



	R	Ar		Yield /%
5a	Ph	4-MeO-C_6H_4	**6a**	**3a** 70
5c	Ph	C_6H_5	**6c**	**3c** 71
5d	OMe	4-MeO-C_6H_4	**6d**	**3d** 62

Scheme 5. Synthesis of **3a**,**c**,**d** via the benzhydryl chlorides **6a**,**c**,**d**.

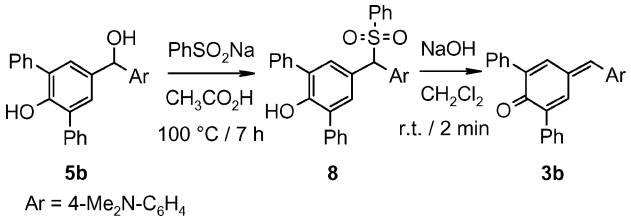
benzhydrylium tetrafluoroborates **7e**,**f** which yielded the quinone methides **3e**,**f** after treatment with triethylamine (Scheme 6).



	R	Ar		Yield /%
5e	OMe	4-Me_2N-C_6H_4	**7e**	**3e** 84
5f	Me	4-Me_2N-C_6H_4	**7f**	**3f** 80

Scheme 6. Synthesis of **3e**,**f** via the intermediate benzhydryl cations **7e**,**f**.

Both methods described in Schemes 5 and 6 failed for the synthesis of **3b**. Following a procedure described by Jerkeman and Koutek,[20] **5b** was converted into the sulfone **8** by refluxing with $PhSO_2Na$ in aqueous acetic acid. Agitation of a dichloromethane solution of **8** with concentrated aqueous sodium hydroxide gave rise to the formation of **3b** (Scheme 7). This method has previously been employed for the synthesis of other quinone methides by Koutek.[21]

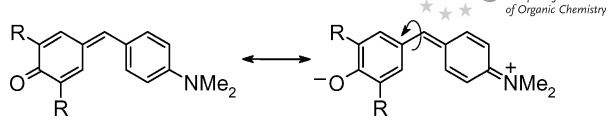


5b **8** **3b**

Ar = 4-Me_2N-C_6H_4

Scheme 7. Synthesis for **3b** via the sulfone **8**.

In the case of the dimethylamino-substituted quinone methides **2b**, **3b**, **3e**, and **3f** the zwitterionic resonance structure drawn in Scheme 8 is gaining importance. Rotation around the exocyclic double bond of the quinone methide >ring, therefore, occurs which results in a coalescence of the NMR signals of the substituents R. The coalescence phenomena were poorly reproducible, however, possibly because the rotation of the cyclohexadiene ring requires (acid) catalysis, and we have abstained from determining the corresponding rotational barriers.



Scheme 8.

The dimethylamino-substituted compounds **3b**,**e**,**f** are intensively red, while all the other quinone methides are yellow. Their UV/Vis absorption maxima between 350 and 533 nm are shown in Figure 1.

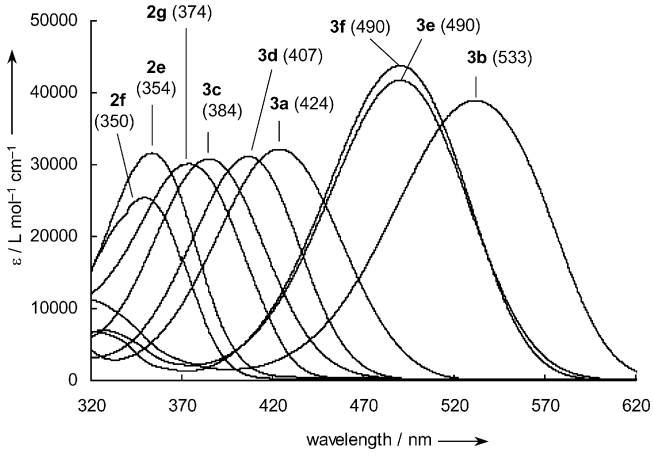


Figure 1. UV/Vis spectra of the quinone methides **2e**–**g** and **3a**–**f** in DMSO, λ_{max} [nm] in parentheses. Molar decadic absorption coefficient ε for **2e**: 31600, **2f**: 25400, **2g**: 30100, **3a**: 32200, **3b**: 39000, **3c**: 30800, **3d**: 31100, **3e**: 41700, **3f**: 43800 $L\,mol^{-1}\,cm^{-1}$.

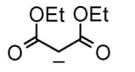
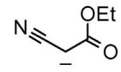
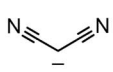
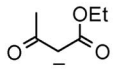
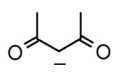
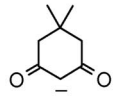
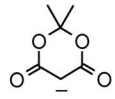
Kinetic Measurements

The reactions of the quinone methides **2e**–**g** and **3c**–**f** with the carbanions **9a**–**h** (Table 1) were followed photometrically in DMSO at 20 °C. To obtain pseudo-first-order conditions, solutions of the quinone methides were mixed with an excess (10–100 equiv.) of the nucleophiles **9a**–**h**. Each reaction was studied with at least four different nucleophile concentrations (for details, see the Supporting Information). The decays of the absorptions of the electrophiles were followed by stopped-flow or conventional UV/Vis spectroscopy, depending on the rates of the reactions. From the fit of the absorbance A_t to the exponential function $A_t = A_0 \exp(-k_{obs}t) + C$, we were able to derive the first-order rate constants k_{obs}. Plots of the first-order rate constants k_{obs} (s^{-1}) vs. the nucleophile concentrations were linear with slopes k_2 ($L\,mol^{-1}\,s^{-1}$) and negligible intercepts (Figure 2). The second-order rate constants k_2 for the reactions derived by this method are listed in Table 1.

Correlation Analysis

The *E* parameters for **2e**–**g** and **3c**–**f** were calculated from the second-order rate constants k_2 of their reactions with the carbanions **9a**–**h** and the previously reported *N* and *s* parameters for **9a**–**h** (Table 1). For this purpose, the squares

Table 1. Second-order rate constants k_2 ($L\,mol^{-1}\,s^{-1}$) for the reactions of the quinone methides **2e**–**g** and **3c**–**f** with the carbanions **9a**–**h**[a] in DMSO at 20 °C.

QMs	Nucleophiles and nucleophilicity parameters N (and s)								E[c]
									
	9a[b]	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**	**9h**	
	21.54 (0.62)	20.22 (0.65)	19.62 (0.67)	19.36 (0.67)	18.82 (0.69)	17.64 (0.73)	16.27 (0.77)	13.91 (0.86)	
2e		3.10×10^3	1.12×10^3	6.91×10^2	4.79×10^2	6.50×10^1			–15.03
2f		7.65×10^3	2.44×10^3	1.57×10^3	1.10×10^3	1.52×10^2			–14.50
2g		1.21×10^4	3.40×10^3	1.84×10^3	1.49×10^3	1.86×10^2	2.15×10^1		–14.36
3c				9.88×10^4	9.29×10^4	1.93×10^4	1.65×10^3	4.97×10^1	–11.87
3d	1.34×10^3	3.30×10^2	1.54×10^2				8.86×10^{-1}		–16.38
3e	3.48×10^2		4.34×10^1				2.69×10^{-1}		–17.18
3f	1.28×10^3		1.87×10^2						–16.36

[a] For all kinetic measurements, the salts **9**-K^+ were used. For N and s parameters (in DMSO) of **9a** see ref.[22], for **9b**–**h** see ref.[11]. [b] ***CAUTION:* Because of explosion hazards,[23] the isolation of 9a-K^+ should be avoided!** [c] Calculated from Equation (1); see section "Correlation Analysis".

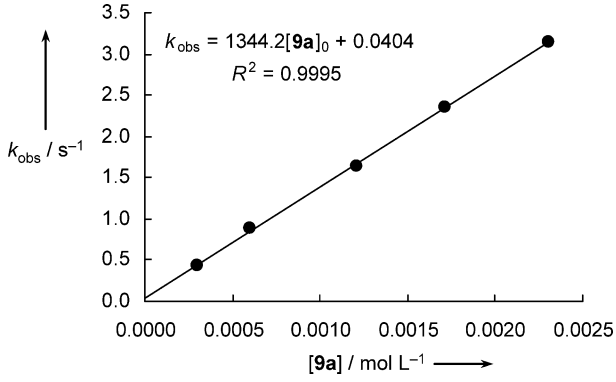


Figure 2. Determination of the second-order rate constant k_2 ($L\,mol^{-1}\,s^{-1}$) for the reaction of **3d** with **9a** in DMSO at 20 °C.

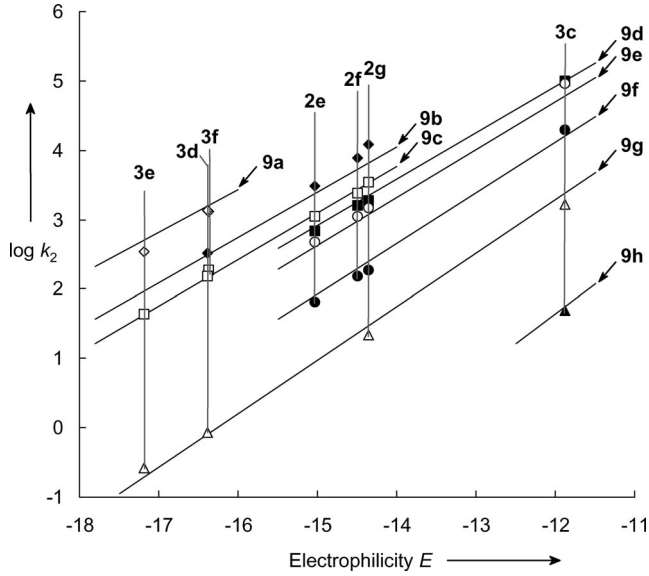


Figure 3. Plot of $\log k_2$ for the reactions of the quinone methides **2e**–**g** and **3c**–**f** with the carbanions **9a**–**h** in DMSO vs. the electrophilicity parameters E of **2e**–**g** and **3c**–**f** (Table 1). The depicted correlation lines are those derived in refs[11, 22] from the reactions of the carbanions **9a**–**h** with the so far established reference electrophiles. The electrophilicity parameters for **2e**–**g** and **3c**–**f** result from a best fit of the second-order rate constants in Table 1 to the fixed correlation lines of the carbanions **9a**–**h** (see text).

of the deviations between calculated and experimental rate constants [$\Delta^2 = \Sigma(\log k_2 - s(N + E))^2$] were minimized using a nonlinear solver software.[24] The resulting E parameters for the quinone methides **2e**–**g** and **3c**–**f** are listed in the last column of Table 1.

Figure 3 illustrates that the second-order rate constants for the reactions of the quinone methides **2e**–**g** and **3c**–**f** with the carbanions **9a**–**h** match satisfactorily the previously reported $\log k_2$ vs. E correlation lines for the reactions of these carbanions with benzhydrylium ions and other quinone methides.

In order to compare the reactivities of these quinone methides with those of the parent compounds **o-QM** and **p-QM**, we used the rate constants determined by Freccero[3] and Kresge[5b,5d] (in water at 25 °C) for the reactions of these quinone methides with a series of different n-nucleophiles with known N and s parameters (water, chloride, bromide, primary and secondary amines, and amino acids).[3] As required by Equation (1), a linear plot of $(\log k)/s$ vs. N was obtained for both **o-QM** and **p-QM**, with a slightly better correlation for the *para*-substituted quinone methide (Figure 4). The E parameters for **o-QM** (E = –3.1) and **p-QM** (E = –5.2) were subsequently calculated by the same error minimization method[24] described above for **2e**–**g** and **3c**–**f**. The electrophilicity parameters for **o-QM** and **p-QM** thus determined are considered preliminary because the nucleophiles investigated do not belong to the set of reference nucleophiles[10a,10b] and the temperature has not been cor-

rected to 20 °C. Please note that application of Equation (1) enforces a slope of 1.0 for the correlation lines in Figure 4. A better fit would be obtained if an additional electrophile-specific slope parameter would be introduced as previously shown for S_N2 reactions.[13b] It turned out that the rate constants were reproduced by Equation (1) within an error limit of a factor of 4, even though the reaction of **o-QM** with Cys^{2-} ($k_2 = 1.3 \times 10^8$ L mol^{-1} s^{-1}) may already be attenuated by its vicinity to the diffusion limit.

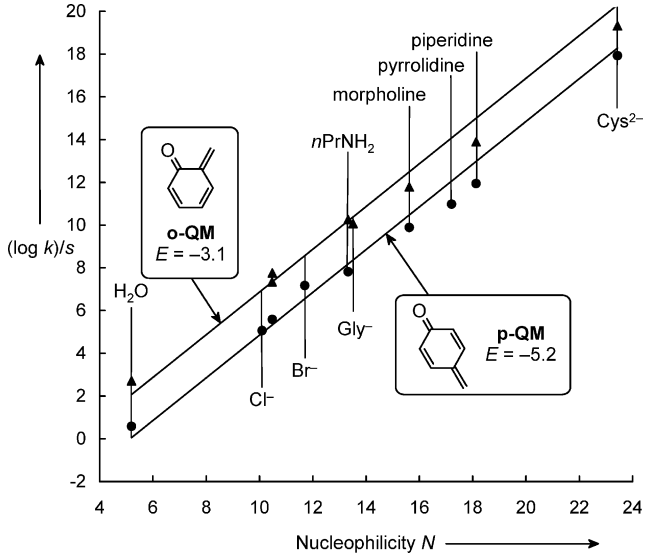


Figure 4. Preliminary determination of the electrophilicity parameters E according to Equation (1) for **o-QM** and **p-QM** from the kinetics of their reactions with water, chloride, bromide, primary and secondary amines, and amino acids in aqueous solution (at 25 °C, for amines and Gly^- at pH 12.0, for Cys^{2-} at pH 12.2; see the Supporting Information for the employed rate constants k from refs.[3,5b,5d] as well as reactivity parameters N and s from ref[10h]).

Figure 5 summarizes the electrophilicities E of all quinone methides so far characterized by Equation (1). The electrophilic reactivities of the parent quinone methides **o-QM** and **p-QM** are comparable to those of stabilized carbocations (tropylium ion, $E = -3.7$),[10b] i.e., they are more electrophilic than Terrier's superelectrophiles which have so far been considered the strongest neutral nucleophiles.[25] In contrast, the substituted *para*-quinone methides **2** and **3** are much less reactive ($-18.0 < E < -11.5$) comparable to other Michael acceptors[22,26] or electron-deficient arenes.[12g,25,27]

The influence of different 2,6-substituents R on the electrophilicity of aryl-substituted quinone methides can be illustrated by comparing the 4-(dimethylamino)phenyl-substituted compounds **2b**, **3e**, **3f**, and **3b** (Scheme 9).

Replacement of the *tert*-butyl groups in **2b** by methyl (→ **3f**), causes an increase of electrophilicity by one order of magnitude. Though alkoxy groups commonly have a much stronger +M-effect than alkyl groups, the methoxy substituted quinone methides **3d** and **3e** show similar reactivities as the corresponding *tert*-butyl-substituted compounds (**2c** and **2b**).

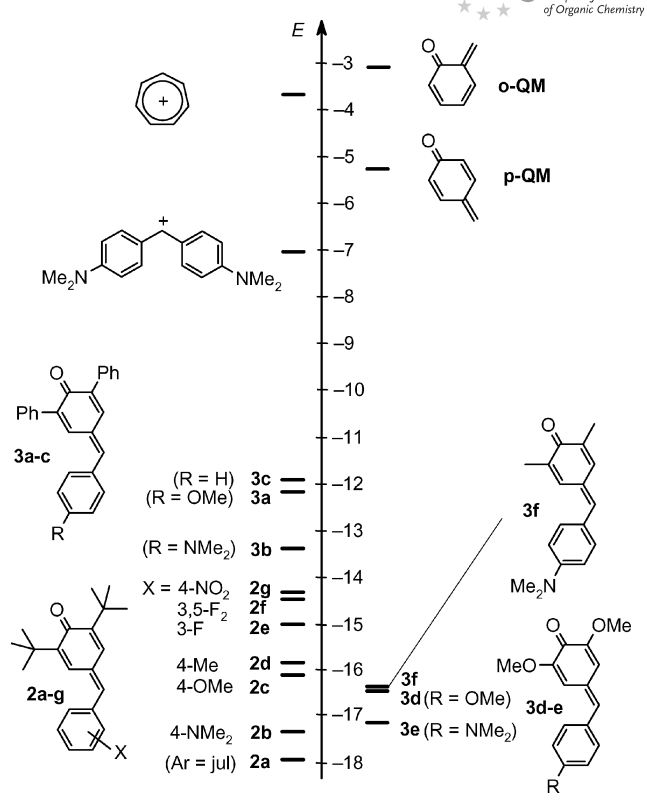
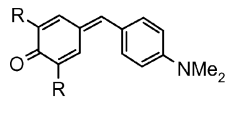


Figure 5. Comparison of the electrophilicities E of the new quinone methides **2e**–**g** and **3c**–**f** with those of the previously reported analogues **2a**–**d** and **3a**,**b**. For "jul"-substituent see **2a** in Scheme 1.



	R	E
2b	*t*Bu	–17.29
3e	MeO	–17.18
3f	Me	–16.36
3b	Ph	–13.39

Scheme 9. Electrophilicity parameters E of 4-(dimethylamino)-phenyl-substituted quinone methides.

The much weaker electron-donating ability of phenyl compared to alkyl or alkoxy groups is reflected in an increase of the electrophilicity of **3b** by a factor of 10^4 compared to the reactivity of **2b**, **3e** or **3f**.

With the characterization of the electrophilicity E for compounds **2e**–**g**, reactivity parameters for seven di-*tert*-butyl-substituted quinone methides are available, in which the substituent X at the phenyl ring varies from strongly electron-donating (X = 4-NR_2) to strongly electron-accepting (X = 4-NO_2).

Figure 6 shows a linear correlation with Hammett's σ^+ parameters. The slope of 1.20 corresponds to a reaction constant $\rho = 1.20$ for the reaction with a nucleophile of $s = 1$ and to $\rho = 0.84$ for the reaction with a nucleophile of $s = 0.7$.

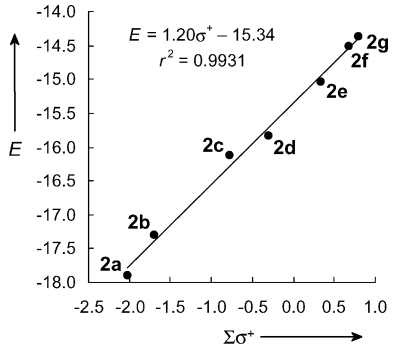


Figure 6. Correlation of the electrophilicity parameter E of the quinone methides **2a**–**g** with Hammett's $\Sigma\sigma^+$ parameters. σ^+ for **2b**–**g**: ref.[28], σ^+ for **2a**: ref.[10a].

Conclusions

The newly developed syntheses of compounds **3a** and **3b** reported in this article provide a straightforward access to these compounds whose electrophilicities are in between those of **1a** and **2d** (Scheme 1). These compounds and several other novel quinone methides described in this article represent a group of colored electrophiles which are structurally related to benzhydrylium ions and, therefore, are valuable reference compounds for the characterization of nucleophiles.

Experimental Section

2,6-Di-*tert*-butyl-Substituted Quinone Methides 2e–g: The quinone methides **2e**–**g** were prepared following a procedure described by Evans et al.:[17] In a Dean–Stark apparatus, a solution of 2,6-di-*tert*-butylphenol and the corresponding benzaldehyde in toluene was heated to reflux. Piperidine was added within 1 h and heating was continued for another 3 h. After cooling just below the boiling point of the reaction mixture, acetic anhydride was added and stirring was continued for 15 min. Then the reaction mixture was poured on ice-water (500 mL) and extracted with CH_2Cl_2 (4 × 200 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude products were purified by column chromatography (3:2, CH_2Cl_2/*n*-hexane) and recrystallized from *n*-hexane.

2,6-Di-*tert*-butyl-4-(3-fluorobenzylidene)cyclohexa-2,5-dienone (2e): From 2,6-di-*tert*-butylphenol (5.16 g, 25.0 mmol), 3-fluorobenzaldehyde (3.10 g, 25.0 mmol), piperidine (4.94 mL, 4.26 g, 50.0 mmol) and acetic anhydride (2.55 g, 50.0 mmol): 4.58 g (59%); yellow crystals; m.p. 86–88 °C (from *n*-hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.30 [s, 9 H, $C(CH_3)_3$], 1.33 [s, 9 H, $C(CH_3)_3$], 6.99 (d, J = 2.4 Hz, 1 H), 7.04–7.18 (m, 3 H), 7.18–7.25 (m, 1 H), 7.37–7.45 (m, 1 H), 7.46 (d, J = 2.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 29.48, 29.51 [2q, $C(CH_3)_3$], 35.0, 35.5 [2s, $C(CH_3)_3$], 115.9 (dd, $^2J_{CF}$ = 21.3 Hz), 116.8 (dd, $^2J_{CF}$ = 22.1 Hz), 126.0 (dd, $^4J_{CF}$ = 3.0 Hz), 127.2 (d), 130.3 (dd, $^3J_{CF}$ = 8.4 Hz), 132.8 (s), 134.8 (d), 138.0 (ds, $^3J_{CF}$ = 8.4 Hz), 140.3 (dd, $^4J_{CF}$ = 2.5 Hz), 148.3 (s), 149.8 (s), 162.8 (ds, $^1J_{CF}$ = 247.2 Hz), 186.5 (s, C=O) ppm. MS (EI): *m*/*z* (%) = 313 (12), 312 (36) [M$^+$], 298 (17), 297 (81), 283 (17), 270 (12), 269 (36), 257 (19), 256 (27), 255 (100). HRMS (EI): calcd. for $C_{21}H_{25}FO$ 312.1889; found 312.1887. $C_{21}H_{25}FO$ (312.43): calcd. C 80.73, H 8.07; found C 80.37, H 8.22.

2,6-Di-*tert*-butyl-4-(3,5-difluorobenzylidene)cyclohexa-2,5-dienone (2f): From 2,6-di-*tert*-butylphenol (5.16 g, 25.0 mmol), 3,5-difluorobenzaldehyde (3.55 g, 25.0 mmol), piperidine (4.94 mL, 4.26 g, 50.0 mmol) and acetic anhydride (2.55 g, 50.0 mmol): 3.91 g (47%); yellow crystals; m.p. 111–113 °C (from *n*-hexane). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.30 [s, 9 H, $C(CH_3)_3$], 1.33 [s, 9 H, $C(CH_3)_3$], 6.84 (tt, $^3J_{HF}$ = 8.7, $^4J_{HH}$ = 2.2 Hz, 1 H), 6.94–6.97 (m, 2 H), 6.97 (d, J = 2.1 Hz, 1 H), 7.03 (s, 1 H), 7.40 (d, J = 2.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 29.47, 29.49 [2q, $C(CH_3)_3$], 35.1, 35.5 [2s, $C(CH_3)_3$], 104.2 (td, $^2J_{CF}$ = 25.4 Hz), 112.8 (ddd, $^2J_{CF}$ = 20.4, $^4J_{CF}$ = 5.4 Hz), 126.7 (d), 133.5 (s), 134.4 (d), 138.6 (td, $^4J_{CF}$ = 2.8 Hz), 138.8 (ts, $^3J_{CF}$ = 9.6 Hz), 148.7 (s), 150.3 (s), 163.0 (dds, $^1J_{CF}$ = 249.7, $^3J_{CF}$ = 13.0 Hz), 186.5 (s, C=O) ppm. MS (EI): *m*/*z* (%) = 331 (18), 330 (40) [M$^+$], 316 (21), 315 (77), 301 (18), 287 (29), 275 (29), 274 (25), 273 (100), 127 (16), 57 (19), 44 (33). HRMS (EI): calcd. for $C_{21}H_{24}F_2O$ 330.1795; found 330.1790. $C_{21}H_{24}F_2O$ (330.42): calcd. C 76.34, H 7.32; found C 76.03, H 7.43.

2,6-Di-*tert*-butyl-4-(4-nitrobenzylidene)cyclohexa-2,5-dienone (2g): From 2,6-di-*tert*-butylphenol (5.16 g, 25.0 mmol), 4-nitrobenzaldehyde (3.78 g, 25.0 mmol), piperidine (4.94 mL, 4.26 g, 50.0 mmol) and acetic anhydride (2.55 g, 50.0 mmol): 5.74 g (68%); yellow solid; m.p. 163–164 °C (from *n*-hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.30 [s, 9 H, $C(CH_3)_3$], 1.34 [s, 9 H, $C(CH_3)_3$], 7.02 (d, J = 2.5 Hz, 1 H), 7.16 (s, 1 H), 7.38 (d, J = 2.5 Hz, 1 H), 7.60 (d, J = 9.0 Hz, 2 H), 8.31 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 29.46, 29.48 [2q, $C(CH_3)_3$], 35.1, 35.6 [2s, $C(CH_3)_3$], 123.9 (d), 126.6 (d), 130.8 (d), 134.35 (d), 134.40 (s), 138.3 (d), 142.3 (s), 147.4 (s), 149.1 (s), 150.7 (s), 186.4 (s, C=O) ppm. MS (EI): *m*/*z* (%) = 340 (14), 339 (38) [M$^+$], 325 (14), 324 (60), 310 (15), 297 (15), 296 (27), 284 (23), 283 (24), 282 (100), 278 (11), 165 (10). $C_{21}H_{25}NO_3$ (339.43): calcd. C 74.31, H 7.42, N 4.13; found C 74.14, H 7.52, N 4.08.

Hydroxybenzhydrols 5a–f. General Procedure: To magnesium turnings (2.6 equiv.) in dry THF (5 mL), a solution of the appropriate *para*-substituted bromobenzene (2.4 equiv.) in dry THF (20 mL) was added dropwise under nitrogen. After refluxing for 75 min, the mixture was cooled to room temperature and a solution of the adequate 4-hydroxybenzaldehyde **4a**–**c** (1 equiv.) in dry THF (20 mL) was added dropwise. After stirring for 12 h, the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl solution (25 mL). The aqueous phase was washed with diethyl ether (2 ×). Then the combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. Crude products with low solubility in diethyl ether were suspended in diethyl ether (100 mL). After 1 h of stirring the purified product was isolated by filtration. Crude products with high solubility in Et_2O were crystallized from diethyl ether/*n*-pentane.

(4-Hydroxy-3,5-diphenylphenyl)(4-methoxyphenyl)methanol (5a): From 4-bromoanisole (2.41 mL, 3.59 g, 19.2 mmol) and 4-hydroxy-3,5-diphenylbenzaldehyde **4a** (2.19 g, 8.00 mmol): 2.54 g (83%); colorless solid; m.p. 117–118 °C (from Et_2O/*n*-pentane). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.18 (s, 1 H, CHO*H*), 3.78 (s, 3 H, OMe), 5.40 (s, 1 H, $OH_{arom.}$), 5.81 (s, 1 H), 6.87 (d, J = 8.6 Hz, 2 H), 7.21–7.57 (m, 14 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 55.3 (q, OMe), 75.5 (d), 113.9 (d), 127.68 (d), 127.73 (d), 128.10 (d), 128.7 (s), 128.8 (d), 129.3 (d), 136.2 (s), 136.4 (s), 137.5 (s), 148.7 (s), 159.0 (s) ppm.

(4-Hydroxy-3,5-diphenylphenyl)[4-(dimethylamino)phenyl]methanol (5b): From 4-bromo-*N*,*N*-dimethylaniline (2.69 g, 13.4 mmol) and 4-hydroxy-3,5-diphenylbenzaldehyde **4a** (1.54 g, 5.60 mmol): 1.74 g (79%); pink solid; m.p. 63–65 °C (from Et_2O/*n*-pentane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.09 (s, 1 H, CHO*H*), 2.92 (s, 6 H, NMe_2),

5.36 (s, 1 H, $OH_{arom.}$), 5.79 (s, 1 H), 6.70 (d, J = 8.8 Hz, 2 H), 7.24–7.56 (m, 14 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 40.6 (q, NMe_2), 75.7 (d), 112.5 (d), 127.5 (d), 127.6 (d), 128.0 (d), 128.5 (s), 128.8 (d), 129.3 (d), 132.0 (s), 136.6 (s), 137.6 (s), 148.4 (s), 150.1 (s) ppm.

(4-Hydroxy-3,5-diphenylphenyl)(phenyl)methanol (5c): From bromobenzene (2.02 mL, 3.01 g, 19.2 mmol) and 4-hydroxy-3,5-diphenylbenzaldehyde **4a** (2.19 g, 8.00 mmol): 2.06 g (73%); colorless solid; m.p. 147–149 °C (from Et_2O/*n*-pentane). ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.28 (d, J = 3.1 Hz, 1 H, CH*OH*), 5.41 (s, 1 H, $OH_{arom.}$), 5.80 (d, J = 2.8 Hz, 1 H), 7.20–7.54 (m, 17 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 75.9 (d), 126.4 (d), 127.5 (d), 127.7 (d), 128.2 (d), 128.5 (d), 128.7 (s), 128.8 (d), 129.3 (d), 136.2 (s), 137.4 (s), 143.8 (s), 148.8 (s) ppm.

(4-Hydroxy-3,5-dimethoxyphenyl)(4-methoxyphenyl)methanol (5d): From 4-bromoanisole (2.41 mL, 3.59 g, 19.2 mmol) and 4-hydroxy-3,5-dimethoxybenzaldehyde **4b** (1.46 g, 8.00 mmol): 1.92 g (83%); colorless solid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.14 (d, ^3J = 3.5 Hz, 1 H, CH*OH*), 3.82 (s, 3 H, OMe), 3.88 (s, 6 H, 2 × OMe), 5.48 (s, 1 H, $OH_{arom.}$), 5.76 (d, ^3J = 3.3 Hz, 1 H), 6.62 (s, 2 H), 6.89 (d, J = 9 Hz, 2 H), 7.30 (d, J = 9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 55.3 (q, OMe), 56.3 (q, 2 OMe), 75.9 (d), 103.3 (d), 113.8 (d), 127.8 (d), 134.0 (s), 135.2 (s), 136.1 (s), 147.0 (s), 159.1 (s) ppm.

(4-Hydroxy-3,5-dimethoxyphenyl)[4-(dimethylamino)phenyl]methanol (5e): From 4-bromo-*N*,*N*-dimethylaniline (4.80 g, 24.0 mmol) and 4-hydroxy-3,5-dimethoxybenzaldehyde **4b** (1.82 g, 10.0 mmol): 1.29 g (43%); light purple solid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.07 (d, ^3J = 3.5 Hz, 1 H, CH*OH*), 2.94 (s, 6 H, NMe_2), 3.86 (s, 6 H, 2 × OMe), 5.45 (s, 1 H, $OH_{arom.}$), 5.70 (d, ^3J = 3.4 Hz, 1 H), 6.63 (s, 2 H), 6.70 (d, J = 8.8 Hz, 2 H), 7.21 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 40.6 (q, NMe_2), 56.3 (q, OMe), 76.0 (d), 103.2 (d), 112.4 (d), 127.7 (d), 131.9 (s), 133.8 (s), 135.5 (s), 146.9 (s), 150.2 (s) ppm.

(4-Hydroxy-3,5-dimethylphenyl)[4-(dimethylamino)phenyl]methanol (5f): From 4-bromo-*N*,*N*-dimethylaniline (4.80 g, 24.0 mmol) and 4-hydroxy-3,5-dimethylbenzaldehyde **4c** (1.50 g, 10.0 mmol): 1.88 g (69%); light purple solid. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 2.12 (s, 6 H, 2 × Me), 2.83 (s, 6 H, NMe_2), 5.33 (d, J = 4.0 Hz, 1 H), 5.42 (d, J = 4.0 Hz, 1 H), 6.64 (d, J = 8.8 Hz, 1 H), 6.84 (s, 2 H), 7.11 (d, J = 8.8 Hz, 1 H), 7.98 (s, 1 H, $OH_{arom.}$) ppm. ^{13}C NMR ([D_6]DMSO, 101 MHz): δ = 16.7 (q, Me), 40.3 (q, NMe_2), 73.8 (d), 112.1 (d), 123.4 (s), 126.1 (d), 126.9 (d), 134.2 (s), 136.9 (s), 149.3 (s), 151.6 (s) ppm.

Benzhydryl Chlorides 6a,c,d: Under an atmosphere of dry N_2, $SOCl_2$ (1.2 equiv.) in dry CH_2Cl_2 (≈ 5 mL) was added dropwise to a solution of the 4-hydroxybenzhydrol (1 equiv.) in dry CH_2Cl_2 at 0 °C. After stirring at this temperature for 2 h, the solvent was removed under reduced pressure. Because the products were formed nearly quantitatively, they were used for the following step without further purification.

(4-Hydroxy-3,5-diphenylphenyl)(4-methoxyphenyl)methyl Chloride (6a): From **5a** (500 mg, 1.31 mmol) in CH_2Cl_2 (18 mL) and $SOCl_2$ (115 µL, 187 mg, 1.57 mmol): ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.80 (s, 3 H, OMe), 5.44 (s, 1 H, OH), 6.16 (s, 1 H), 6.87 (d, J = 8.8 Hz, 2 H), 7.32–7.57 (m, 14 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 55.3 (q, OMe), 64.2 (d), 113.9 (d), 127.9 (d), 128.8 (d), 128.9 (d), 129.0 (d), 129.3 (d), 129.8 (s), 133.4 (s), 133.7 (s), 137.1 (s), 149.1 (s), 159.3 (s) ppm.

(4-Hydroxy-3,5-diphenylphenyl)(phenyl)methyl Chloride (6c): From **5c** (150 mg, 0.43 mmol) in CH_2Cl_2 (6 mL) and $SOCl_2$ (37 µL, 60.8 mg, 0.51 mmol): ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.44 (br. s, 1 H, OH), 6.16 (s, 1 H), 7.23–7.55 (m, 17 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 64.2 (d), 127.6 (d), 127.9 (d), 128.0 (d), 128.6 (d), 128.8 (s), 128.9 (d), 129.29 (d), 129.34 (d), 133.5 (s), 137.1 (s), 141.0 (s), 149.1 (s) ppm.

(4-Hydroxy-3,5-dimethoxyphenyl)(4-methoxyphenyl)methyl Chloride (6d): From **5d** (1.00 g, 3.46 mmol) in CH_2Cl_2 (40 mL) and $SOCl_2$ (303 µL, 493 mg, 4.15 mmol): ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.81 (s, 3 H, OMe), 3.86 (s, 6 H, 2 × OMe), 5.53 (br. s, 1 H, OH), 6.08 (s, 1 H), 6.64 (s, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 7.32 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 55.3 (q, OMe), 56.4 (q, 2 × OMe), 64.8 (d), 104.8 (d), 113.8 (d), 129.0 (d), 132.3 (s), 133.4 (s), 134.5 (s), 146.8 (s), 159.3 (s) ppm.

Quinone Methides 3a,c,d: Under an atmosphere of dry N_2, the benzhydryl chloride **6** was dissolved in dry CH_2Cl_2 and 1.2–1.3 equiv. of NEt_3 were added. After stirring for 2 h, diethyl ether or *n*-pentane was added. The resulting precipitate was filtered off and dried under reduced pressure.

2,6-Diphenyl-4-(4-methoxybenzylidene)cyclohexa-2,5-dienone (3a): From **6a** (313 mg, 780 µmol) in CH_2Cl_2 (10 mL) and NEt_3 (141 µL, 103 mg, 1.01 mmol): 199 mg (70%); yellow solid; m.p. 125–126 °C (from Et_2O). ^1H NMR (CD_2Cl_2, 400 MHz): δ = 3.87 (s, 3 H, OMe), 7.02 (d, J = 8.8 Hz, 2 H), 7.35–7.47 (m, 8 H, $H_{arom.}$), 7.55–7.63 (m, 6 H, $H_{arom.}$), 7.93 (dd, J = 2.6, J = 0.6 Hz, 1 H) ppm. ^{13}C NMR (CD_2Cl_2, 101 MHz): δ = 55.6 (q, OMe), 114.7 (d), 127.8 (d), 127.9 (d), 128.01 (d), 128.02 (d), 128.3 (s), 129.3 (d), 129.4 (d), 130.1 (s), 132.5 (d), 133.0 (d), 137.1 (s), 137.5 (s), 138.3 (s), 140.2 (d), 146.6 (d), 161.7 (s), 183.5 (s, C=O) ppm. MS (EI): *m*/*z* (%) = 366 (16), 365 (18), 364 (64) [M^+], 363 (100). HRMS (EI): calcd. for $C_{26}H_{20}O_2$ 364.1463; found 364.1465.

2,6-Diphenyl-4-benzylidenecyclohexa-2,5-dienone (3c): From **6c** (530 mg, 1.58 mmol) in CH_2Cl_2 (8 mL) and NEt_3 (286 µL, 210 mg, 2.06 mmol): 386 mg (71%); yellow crystals; m.p. 170–172 °C (from CH_2Cl_2/*n*-pentane). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.35–7.61 (m, 17 H, $H_{arom.}$), 7.86 (dd, J = 2.6, J = 0.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 127.97 (d), 128.02 (d), 128.04 (d), 128.07 (d), 129.0 (d), 129.2 (d), 129.3 (d), 129.9 (d), 130.7 (d), 131.8 (s), 132.5 (d), 135.4 (s), 136.3 (s), 136.7 (s), 138.9 (s), 139.7 (d), 140.6 (s), 146.0 (d), 183.8 (s, C=O) ppm. MS (EI): *m*/*z* (%) = 335 (22), 334 (100) [M^+], 333 (70), 256 (22). HRMS (EI): calcd. for $C_{25}H_{18}O$ 334.1358; found 334.1355.

2,6-Dimethoxy-4-(4-methoxybenzylidene)cyclohexa-2,5-dienone (3d): From **6d** (1.07 g, 3.46 mmol) in CH_2Cl_2 (25 mL) and NEt_3 (576 µL, 420 mg, 4.15 mmol): 584 mg (62%); yellow crystals; m.p. 178–180 °C (from CH_2Cl_2/*n*-pentane). ^1H NMR (CD_2Cl_2, 400 MHz): δ = 3.78 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 6.43 (s, 1 H), 6.91 (s, 1 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.12 (s, 1 H), 7.48 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (CD_2Cl_2, 101 MHz): δ = 55.5 (q, OMe), 55.56, 55.57 (2q, 2 OMe), 105.7 (d), 113.1 (d), 114.5 (d), 128.7 (s), 129.0 (s), 132.0 (d), 140.7 (d), 152.1 (s), 153.7 (s), 160.6 (s), 174.8 (s, C=O) ppm. MS (EI): *m*/*z* (%) = 273 (20), 272 (100) [M^+], 271 (19), 254 (17), 243 (41), 242 (30), 241 (16), 226 (28), 211 (22), 196 (15), 171 (16), 169 (18), 143 (22), 128 (20), 115 (53). HRMS (EI): calcd. for $C_{16}H_{16}O_4$ 272.1049; found 272.1052. $C_{16}H_{16}O_4$ (272.30): calcd. C 70.57, H 5.92; found C 70.35, H 5.86.

Quinone Methides 3e,f: Under an atmosphere of dry N_2, the 4-hydroxybenzhydrol (1 equiv.) was dissolved in dry CH_2Cl_2 and cooled to 0 °C. Then ethereal HBF_4 solution (1.1 equiv.) was added at 0 °C. After 5 min, NEt_3 (1.3 equiv.) was added. Stirring at room temperature was continued for 3 h before the mixture was extracted

with water (3 ×). The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure.

2,6-Dimethoxy-4-[4-(dimethylamino)benzylidene]cyclohexa-2,5-dienone (3e): From **5e** (500 mg, 1.65 mmol) in CH_2Cl_2 (40 mL), ethereal HBF_4 (250 μL, 1.81 mmol) and NEt_3 (297 μL, 217 mg, 2.15 mmol): 395 mg (84%); red crystals (from CH_2Cl_2/*n*-pentane); m.p. 163–165 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.07 (s, 6 H, NMe_2), 3.83 (s, 6 H, 2 × OMe), 6.43 (br. s, 1 H), 6.75 (d, J = 8.9 Hz, 2 H), 7.02 (br. s, 1 H), 7.08 (s, 1 H), 7.45 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 40.8 (q, NMe_2), 55.5 (q, OMe), 106.3 (d), 112.1 (d), 113.7 (d), 124.1 (s), 126.4 (s), 132.5 (d), 142.8 (d), 150.9 (s), 174.6 (s, C=O) ppm. HRMS (EI): calcd. for $C_{17}H_{19}NO_3$ 285.1365; found 285.1366.

2,6-Dimethyl-4-[4-(dimethylamino)benzylidene]cyclohexa-2,5-dienone (3f): From **5f** (200 mg, 737 μmol) in CH_2Cl_2 (60 mL), ethereal HBF_4 (110 μL, 811 μmol) and NEt_3 (133 μL, 100 mg, 958 μmol): 149 mg (80%); red needles; m.p. 127–128 °C (from acetonitrile). ^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 2.01 (d, J = 1.1 Hz, 3 H, Me), 2.06 (d, J = 1.2 Hz, 3 H, Me), 3.06 (s, 6 H, NMe_2), 6.75 (d, J = 8.6 Hz, 2 H), 7.05 (br. s, 1 H), 7.07 (s, 1 H), 7.50 (d, J = 8.7 Hz, 2 H), 7.71 (br. s, 1 H) ppm. ^{13}C NMR (CD_2Cl_2, 101 MHz): δ = 16.1, 16.8 (2q, 2 Me), 39.9 (q, NMe_2), 112.0 (d), 123.6 (s), 127.9 (s), 131.5 (d), 133.1 (d), 133.8 (s), 136.2 (s), 139.6 (d), 144.7 (d), 151.6 (s), 186.4 (s, C=O) ppm. MS (EI): *m*/*z* (%) = 254 (17), 253 (100) [M^+], 252 (11). HRMS (EI): calcd. for $C_{17}H_{19}NO$ 253.1467; found 253.1461.

(4-Hydroxy-3,5-diphenylphenyl)[4-(dimethylamino)phenyl]methylbenzenesulfone (8): The alcohol **5b** (200 mg, 506 μmol) and $PhSO_2Na$ (133 mg, 809 μmol, 2 equiv.) were dissolved in 40 mL of a 1:1 mixture of water and acetic acid. Concd. H_2SO_4 (22 μL, 40 mg, 0.40 mmol) was added. After heating to 100 °C for 7 h, the mixture was cooled down and was diluted with water. The precipitate was collected and dried in vacuo; 125 mg (48%); colorless solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.93 (s, 6 H, NMe_2), 5.21 (s, 1 H), 5.42 (s, 1 H, OH), 6.64 (d, J = 8.9 Hz, 2 H), 7.29–7.64 (m, 21 H, $H_{arom.}$), 7.68 (d, J = 7.1 Hz, 2 H, $H_{arom.}$) ppm.

2,6-Diphenyl-4-[4-(dimethylamino)benzylidene]cyclohexa-2,5-dienone (3b): The sulfone **8** (50 mg, 96 μmol) was dissolved in CH_2Cl_2 (20 mL) and shaken with conc. aqueous NaOH (500 μL) for 2 min. To the organic layer, *n*-pentane (80 mL) was added and the resulting precipitate was separated by filtration. The volatile components of the filtrate were removed under reduced pressure: 23.4 mg (65%); dark violet solid; m.p. 189–191 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.07 (s, 6 H, NMe_2), 6.72 (d, J = 8.9 Hz, 2 H), 7.32–7.65 (m, 14 H, $H_{arom.}$), 8.00 (d, J = 2.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 40.0 (q, NMe_2), 112.1 (d), 123.5 (s), 127.4 (d), 127.56 (d), 127.62 (d), 127.9 (d), 129.2 (d), 129.4 (d), 132.8 (d), 133.7 (d), 137.3 (s), 137.8 (s), 139.4 (s), 140.7 (d), 148.1 (d), 151.8 (s), 182.9 (s, C=O) ppm. MS (EI): *m*/*z* (%) = 379 (19), 378 (28), 377 (88) [M^+], 376 (100). HRMS (EI): calcd. for $C_{27}H_{23}NO$ 377.1780; found 377.1794.

Kinetics: All kinetics were studied UV/Vis photometrically. The rates of the slow reactions ($\tau_{1/2} > 10$ s) were determined by using a J&M TIDAS diode array spectrophotometer controlled by Labcontrol Spectacle software and connected to a Hellma 661.502-QX quartz Suprasil immersion probe (5 mm light path) via fibre optic cables and standard SMA connectors. For the evaluation of fast kinetics ($\tau_{1/2} < 10$ s) commercial stopped-flow spectrophotometer systems (Hi-Tech SF-61DX2 or Applied Photophysics SX.18MV-R) were used. The temperature of the solutions was kept constant (20.0 ± 0.1 °C) by using circulating bath thermostats.

Solutions of the quinone methides were mixed with an excess (10–100 equiv.) of the nucleophiles **9a**–**h** in order to achieve kinetics under pseudo-first-order conditions. First-order rate constants k_{obs} (s^{-1}) were obtained by fitting the single exponential $A_t = A_0 \exp(-k_{obs}t) + C$ to the observed time-dependent absorbance (averaged from at least 4 kinetic runs for each nucleophile concentration in the case of stopped-flow experiments). Second-order rate constants k_2 ($L\,mol^{-1}\,s^{-1}$) listed in Table 1 were obtained from the slopes of the plots of k_{obs} vs. the nucleophile concentrations which gave linear correlations with negligible intercepts.

Concentrations and rate constants for the individual kinetic experiments for the reactions of quinone methides with carbanions are given in the Supporting Information.

Supporting Information (see also the footnote on the first page of this article): Details about the kinetic measurements and copies of the NMR spectra are given in the Supporting Information.

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