

Electrophilicities of  $\alpha$ -Chlorinating  
Agents Used in Organocatalysis

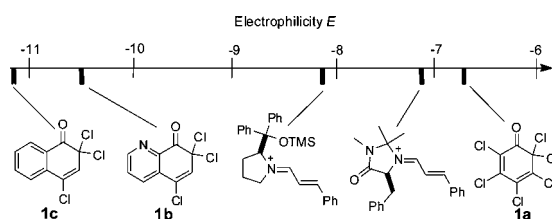
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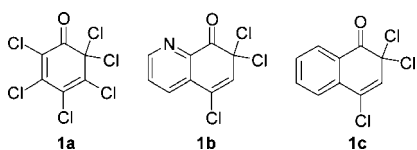
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## ABSTRACT



Kinetics of the reactions of the chlorinating agents **1a–c** with  $\pi$ -nucleophiles have been studied to include these compounds in our comprehensive electrophilicity scale.

Nucleophilic substitutions of C–Cl bonds are an important method for the stereocontrolled generation of C–C, C–N, and C–O bonds.<sup>1</sup> For that reason, enantioselective constructions of stereogenic centers carrying a chlorine substituent are of eminent importance for organic synthesis. Among various methods developed for this purpose, organocatalytic  $\alpha$ -halogenations of carbonyl compounds have been found to be particularly efficient, and the polychloroquinone derived reagents **1a–c** belong to the most frequently used chlorinating agents.<sup>2</sup>



During our efforts to rationalize scope and limitations of organocatalytic processes, we have previously characterized nucleophilicities and carbon basicities of frequently used

organocatalysts such as amines and phosphanes.<sup>3</sup> Using the linear free energy relationship (eq 1), where  $E$  is an electrophile-specific parameter, and  $N$  and  $s$  are nucleophile-specific parameters,<sup>4</sup> we have furthermore characterized nucleophilicities of substrates for iminium-catalyzed reactions, e.g., pyrroles,<sup>5c</sup> indoles,<sup>5b</sup> and sulfur ylides,<sup>5e</sup> as well as the nucleophilicities of enamines<sup>5a</sup> and the electrophilicities of iminium ions,<sup>5d</sup> key intermediates of organocatalytic reactions.

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

In previous reviews on scope and limitations of eq 1 we have stated that this correlation, which was initially derived for reactions of carbocations with olefins,<sup>4a–c</sup> cannot be expected to hold for halogenation reactions, because bridging

(2) Reviews: (a) France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475–479. (b) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (d) Czekelius, C.; Tzschucke, C. C. *Synthesis* **2010**, 543–566, and references cited therein.

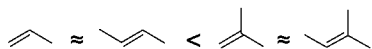
(3) (a) Kempf, B.; Mayr, H. *Chem.—Eur. J.* **2005**, *11*, 917–927. (b) Baidya, M.; Kobayashi, S.; Brotzel, F.; Schmidhammer, U.; Riedle, E.; Mayr, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6176–6179. (c) Baidya, M.; Mayr, H. *Chem. Commun.* **2008**, 1792–1794. (d) Baidya, M.; Horn, M.; Zipse, H.; Mayr, H. *J. Org. Chem.* **2009**, *74*, 7157–7164. (e) Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. *Eur. J. Org. Chem.* **2009**, 6379–6385.

(1) (a) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; John Wiley & Sons: New York, 2007. (b) House, H. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972. (c) De Kimpe, N.; Verhé, R. *The Chemistry of  $\alpha$ -Haloketones,  $\alpha$ -Haloaldehydes, and  $\alpha$ -Haloamines*; John Wiley & Sons: New York, 1988.

electrophiles ( $\text{Br}_2$ ,  $\text{Cl}_2$ ,  $\text{RS}^+$ ) are known to follow a different selectivity pattern as nonbridging electrophiles (Scheme 1). As shown in Scheme 1, the reactivities of CC double bonds

**Scheme 1.** Relative Reactivities of Alkenes toward Various Electrophiles (from ref 6)

Reactivity order toward non-bridging electrophiles ( $\text{R}^+$ ,  $\text{H}_3\text{O}^+$ ).

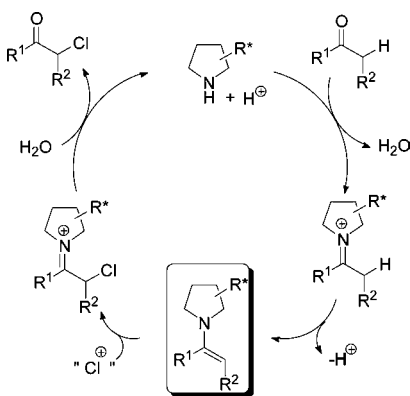


Reactivity order toward bridging electrophiles ( $\text{Cl}_2$ ,  $\text{Br}_2$ ).



toward nonbridging electrophiles are hardly affected by alkyl groups at the position of electrophilic attack but are strongly increased by alkyl groups at the new carbenium center.<sup>6</sup> In contrast, reactivities toward bridging electrophiles are increased almost equally by alkyl groups at both termini of the double bond.

**Scheme 2.**  $\alpha$ -Chlorinations of Carbonyl Compounds Catalyzed by Secondary Amines



As illustrated in Scheme 2, enamines have been suggested to be the key intermediates in organocatalytic chlorinations of carbonyl compounds.<sup>2</sup> Because chloro-bridging does not occur in  $\beta$ -chloro-substituted iminium ions, we had speculated that the relative reactivities of enamines and other electron-rich  $\pi$ -systems toward “ $\text{Cl}^+$ ” may follow the same reactivity order as toward carbenium ions, with the consequence that the  $N$  and  $s$  parameters of the  $\pi$ -nucleophiles **2a–m** (Table 1) which have been derived from the rates of their reactions with benzhydrylium ions can also be used to describe the rates of their reactions with the electrophiles **1a–c**.

As shown in Scheme 3 for the reaction of 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one (**1a**) with the indole **2a**, the silyl enol ether **2c**, and the enamine **2g**, the chlorine transfer step is associated with the conversion of the cyclohexadienone chromophore of **1a** ( $\lambda_{\text{max}} = 378$  nm) into

**Table 1.**  $N$  and  $s$  Parameters of the Employed Nucleophiles

| nucleophile | $N$       | $s$   | solvent | ref                      |    |
|-------------|-----------|-------|---------|--------------------------|----|
|             | <b>2a</b> | 5.75  | 1.23    | $\text{CH}_2\text{Cl}_2$ | 5b |
|             | <b>2b</b> | 5.85  | 1.03    | $\text{CH}_2\text{Cl}_2$ | 4b |
|             | <b>2c</b> | 6.57  | 0.93    | $\text{CH}_2\text{Cl}_2$ | 4b |
|             | <b>2d</b> | 8.23  | 0.81    | $\text{CH}_2\text{Cl}_2$ | 4b |
|             | <b>2e</b> | 8.69  | 1.07    | $\text{CH}_3\text{CN}$   | 5c |
|             | <b>2f</b> | 9.00  | 0.98    | $\text{CH}_2\text{Cl}_2$ | 4b |
|             | <b>2g</b> | 9.96  | 0.79    | $\text{CH}_2\text{Cl}_2$ | 5a |
|             | <b>2h</b> | 10.61 | 0.86    | $\text{CH}_2\text{Cl}_2$ | 4b |
|             | <b>2i</b> | 10.76 | 0.87    | $\text{CH}_2\text{Cl}_2$ | 5a |
|             | <b>2j</b> | 11.40 | 0.83    | $\text{CH}_2\text{Cl}_2$ | 4b |
|             | <b>2k</b> | 12.56 | 0.70    | $\text{CH}_2\text{Cl}_2$ | 4b |
|             | <b>2l</b> | 12.90 | 0.79    | $\text{CH}_2\text{Cl}_2$ | 5a |
|             | <b>2m</b> | 13.41 | 0.82    | $\text{CH}_2\text{Cl}_2$ | 5a |

that of the pentachlorophenolate ion, which absorbs at shorter wavelength ( $\lambda_{\text{max}} = 351$  nm). For that reason, the kinetics of the reactions of **1a**, as well as of 5,7,7-trichloro-8-(7*H*)-quinolinone (**1b**) and 2,2,4-trichloro-1-(2*H*)-naphthalenone (**1c**), with the nucleophiles **2** could be determined photometrically by monitoring the disappearance of the absorbances of **1a–c** at 366–378 nm.

When equimolar amounts of the chlorinated quinones **1a** and the  $N$ -methylindole (**2a**) were combined in  $\text{CH}_3\text{CN}$  at room temperature, the corresponding 3-chloro- $N$ -methylindole was isolated in 81% yield after aqueous workup (Scheme 3). Silyl enol ethers usually gave moderate yields of  $\alpha$ -chlorocarbonyl compounds. For instance, when **1a** was slowly added to a solution of 1-(trimethylsilyloxy)cyclopentene (**2c**) or 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (**2f**) in  $\text{CH}_3\text{CN}$  at room temperature, 2-chlorocyclopentanone and methyl 2-chloroisobutyrate were obtained in low yields. The yields increased to 55% and 51%, respectively, when  $\text{CH}_2\text{Cl}_2$  was used as the solvent. Treatment of **1a** with 1 equiv of

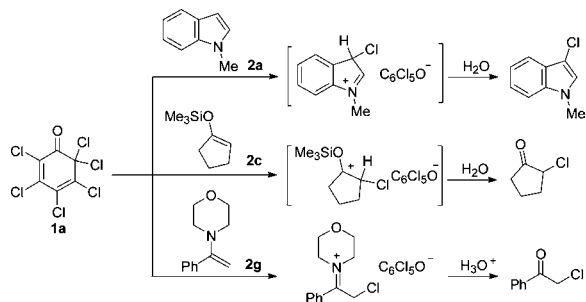
(4) Reviews: (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938–957. (b) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512. (c) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77. (d) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807–1821. (e) Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584–595.

(5) (a) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem.—Eur. J.* **2003**, *9*, 2209–2218. (b) Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. *J. Org. Chem.* **2006**, *71*, 9088–9095. (c) Nigst, T. A.; Westermaier, M.; Ofial, A. R.; Mayr, H. *Eur. J. Org. Chem.* **2008**, 2369–2374. (d) Lakhdar, S.; Tokuyasu, T.; Mayr, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 8723–8726. (e) Lakhdar, S.; Appel, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5034–5037.

(6) Mayr, H. In *Cationic Polymerization: Mechanisms, Synthesis and Applications*; Matyjaszewski, K., Ed.; Marcel Dekker: New York, 1996; pp 51–136.

*N*-(1-phenylvinyl)morpholine (**2g**) in CH<sub>2</sub>Cl<sub>2</sub> gave  $\alpha$ -chloroacetophenone in 78% yield. Under the same conditions, the reactions of the polychlorinated quinones **1b** and **1c** also produced 60% and 65% yields of  $\alpha$ -chloroacetophenone, respectively. Because analogous reaction products can be expected for the combination of **1a–c** with other substrates, product studies have not been performed for all reactions that have been studied kinetically.

**Scheme 3.** Reactions of **1a** with  $\pi$ -Nucleophiles



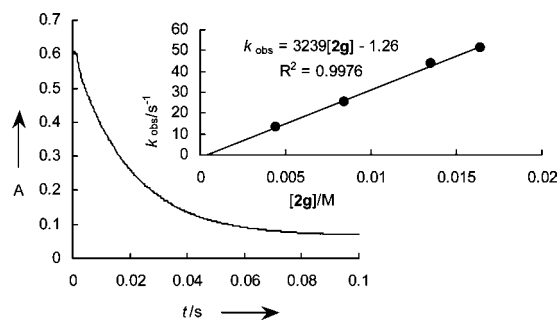
As mentioned above, the kinetics of the reactions of **1a–c** with  $\pi$ -nucleophiles were determined photometrically by following the disappearance of the absorbances of the  $\alpha$ -chlorinating agents at 366–378 nm, using conventional and stopped-flow UV/vis spectrometers. All kinetic experiments were performed at 20 °C in CH<sub>3</sub>CN with a high excess of the nucleophiles **2a–m** in order to achieve first-order conditions (eq 2).

$$-d[1]/dt = k_{\text{obs}}[1] \quad (2)$$

As a consequence, exponential decays of the concentrations of the UV-active electrophiles were observed. The first-order rate constants  $k_{\text{obs}}$  were obtained by least-squares fitting of the time-dependent absorbances of the electrophiles to  $A_t = A_0 e^{-k_{\text{obs}}t} + C$ . Plots of  $k_{\text{obs}}$  versus the concentrations of the nucleophiles [**2**] gave straight lines with the slopes  $k_2$  as shown for one example in Figure 1. The slopes of these plots gave the second-order rate constants  $k_2$  [M<sup>-1</sup> s<sup>-1</sup>], which are summarized in Table 2.

If eq 1 were followed, plots of  $(\log k)/s$  versus  $N$  should be linear with a slope of 1. Figure 2 shows that the reactivities of different classes of compounds, i.e., pyrroles, indoles, enol ethers, and ketene acetals, with the chlorinating agent **1a** are, indeed, linearly correlated with the nucleophilicity parameters  $N$ , but the slope ( $s = 1.25$ ) is slightly larger than 1. Though the nonunity slope might be taken care of by introducing a second, electrophile-specific slope parameter, as previously suggested for the treatment of S<sub>N</sub>2 reactions,<sup>7</sup> we have abstained from introducing an electrophile-specific slope parameter and determined  $E$  by minimizing  $\Delta^2 = \sum(\log k - s(N + E))^2$  with the nonlinear solver “What’s Best!” by

(7) Phan, T. B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3869–3874.



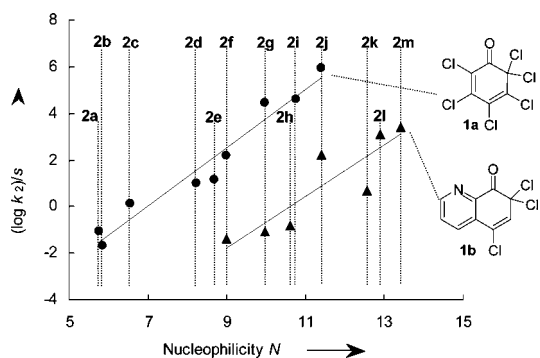
**Figure 1.** Exponential decay of the absorbance at 378 nm during the reaction of **1a** ( $4.19 \times 10^{-4}$  M) with **2g** ( $4.43 \times 10^{-3}$  M) and correlation of  $k_{\text{obs}}$  with the concentrations of **2g** (in the insert).

Lindo systems. In this way a unity slope for the  $(\log k_2)/s$  vs  $N$  plots was enforced. Table S1 in the Supporting Information shows that experimental and calculated rate constants determined in this way agree within a factor of 12. The correlations are of lower quality for the corresponding reactions of **1b** and **1c**, but also in these cases, the deviations between calculated and experimental rate constants are less than a factor of 22, which is quite satisfactory for a three-parameter equation covering a reactivity range of 40 orders of magnitude.

As an alternative to the direct chlorine attack at the  $\pi$ -bond of the enamine (Scheme 2 and upper reaction path in Scheme 4), initial *N*-chlorination and subsequent 1,3-sigmatropic shift of chlorine to the carbon atom (lower pathway in Scheme 4) has been suggested.<sup>8</sup> Figure 2 shows that the relative

**Table 2.** Second-Order Rate Constants  $k_2$  for the Reactions of the Polychlorinated Quinones **1a–c** with the  $\pi$ -Nucleophiles **2a–m** in CH<sub>3</sub>CN at 20 °C

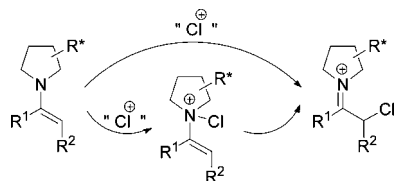
| electrophile | $\lambda_{\text{max}}$ [nm] | nucleophile | $k_2$ [M <sup>-1</sup> s <sup>-1</sup> ] |           |                       |
|--------------|-----------------------------|-------------|------------------------------------------|-----------|-----------------------|
| <b>1a</b>    | 378                         | <b>2a</b>   | $4.01 \times 10^{-2}$                    |           |                       |
|              |                             | <b>2b</b>   | $1.89 \times 10^{-2}$                    |           |                       |
|              |                             | <b>2c</b>   | 1.26                                     |           |                       |
|              |                             | <b>2d</b>   | 6.52                                     |           |                       |
|              |                             | <b>2e</b>   | $1.60 \times 10^1$                       |           |                       |
|              |                             | <b>2f</b>   | $1.36 \times 10^2$                       |           |                       |
|              |                             | <b>2g</b>   | $3.24 \times 10^3$                       |           |                       |
|              |                             | <b>2i</b>   | $1.04 \times 10^4$                       |           |                       |
|              |                             | <b>2j</b>   | $8.76 \times 10^4$                       |           |                       |
|              |                             | <b>1b</b>   | 366                                      | <b>2f</b> | $4.59 \times 10^{-2}$ |
| <b>2g</b>    | $1.38 \times 10^{-1}$       |             |                                          |           |                       |
| <b>2h</b>    | $1.93 \times 10^{-1}$       |             |                                          |           |                       |
| <b>2j</b>    | $6.97 \times 10^1$          |             |                                          |           |                       |
| <b>2k</b>    | 2.91                        |             |                                          |           |                       |
| <b>2l</b>    | $2.82 \times 10^2$          |             |                                          |           |                       |
| <b>2m</b>    | $6.21 \times 10^2$          |             |                                          |           |                       |
| <b>1c</b>    | 375                         |             |                                          | <b>2g</b> | $4.84 \times 10^{-1}$ |
|              |                             |             |                                          | <b>2h</b> | $2.40 \times 10^{-2}$ |
|              |                             |             |                                          | <b>2j</b> | $1.20 \times 10^1$    |
|              |                             | <b>2k</b>   | $3.81 \times 10^{-1}$                    |           |                       |
|              |                             | <b>2l</b>   | $4.85 \times 10^1$                       |           |                       |
|              |                             | <b>2m</b>   | $1.18 \times 10^2$                       |           |                       |



**Figure 2.** Correlation of  $(\log k_2)/s$  with the nucleophilicity parameter  $N$  for the reactions of the chlorinated quinones **1a** and **1b** with the nucleophiles **2** ( $\text{CH}_3\text{CN}$ ,  $20^\circ\text{C}$ ).

reactivities of enamines, silylated enols, and ketene acetals, as well as of pyrroles and indoles toward the chlorinating agents **1a** and **1b**, are the same as toward donor-substituted diarylcarbenium ions, from which the  $N$ -scale has been derived. Though highly reversible  $N$ -attack by diarylcarbenium ions at enamines could not be excluded, it has been demonstrated that the observed second-order rate constants for these reactions reflect the rates of the CC bond-forming step.<sup>5a</sup> As a consequence, the  $N$  and  $s$  parameters in Table 1, including those of enamines, reflect  $\pi$ -nucleophilicities, and the correlations shown in Figure 2 indicate analogous

#### Scheme 4. Ambident Reactivity of Enamines



transition states for electrophilic chlorinations and alkylations of the nucleophiles **2**. In view of these findings, the generality of the suggested  $N$ -attack<sup>8</sup> of electrophilic chlorinating agents at enamines in amine-catalyzed  $\alpha$ -chlorinations of aldehydes should be examined.

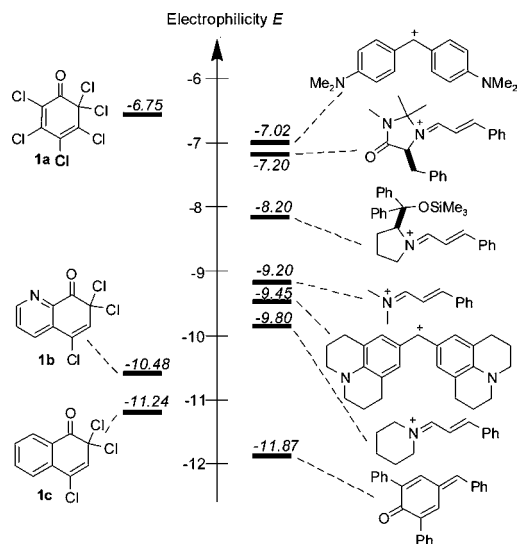
The kinetic data now allow us to include the chlorinating agents into our comprehensive electrophilicity scale (Figure

(8) (a) Halland, N.; Alstrup Lie, M.; Kjærsgaard, A.; Marigo, M.; Schjøtt, B.; Jørgensen, K. A. *Chem.–Eur. J.* **2005**, *11*, 7083–7090. (b) Marquez, C. A.; Fabbretti, F.; Metzger, J. O. *Angew. Chem., Int. Ed.* **2007**, *46*, 6915–6917.

(9) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109.

(10) (a) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531–1532. (b) France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245–4255.

(11) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219–6222.



**Figure 3.** Comparison of the electrophilicities of chlorinated quinones **1a–c** with those of carbon electrophiles.

3), which shows that **1a** is a  $10^4$ - to  $10^5$ -fold stronger electrophile than **1b** and **1c**, comparable to amino-substituted benzhydrylium ions and  $\alpha,\beta$ -unsaturated iminium ions. This reactivity order is in line with the observation that **1a** is a particularly suitable reagent for the imidazolidinone catalyzed  $\alpha$ -chlorination reactions of aldehydes,<sup>9</sup> or  $\alpha$ -chlorinations of acyl chlorides via intermediate ketenes.<sup>10</sup> On the other hand, the more reactive carbanions derived from 1,3-dicarbonyl compounds have been found to react with much better enantioselectivities with the mild chlorinating agent **1b** than with the more reactive electrophile **1a**.<sup>11</sup>

The linear free-energy relationship  $\log k(20^\circ\text{C}) = s(N + E)$  (eq 1) has thus been found to be suitable for predicting the rate constants for the reactions of the chlorinated quinones **1a–c** with  $\pi$ -nucleophiles from the  $E$  parameters of **1a–c** determined in this work and the nucleophile specific parameters  $N$  and  $s$  for **2a–m** reported earlier.<sup>4,5</sup> With these parameters at hand, one can compare the electrophilicities of chlorinated quinones with those of carbon electrophiles, and even more important, use them as a guide for selecting suitable electrophiles for organocatalytic halogenations.

**Acknowledgment.** We thank the Deutsche Forschungsgemeinschaft (Ma 673/21-3) and the Fonds der Chemischen Industrie for financial support. Valuable suggestions by Dr. Armin R. Ofial and Dr. Mahiuddin Baidya are gratefully acknowledged.

**Supporting Information Available:** Details of the product characterization and the kinetic experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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