

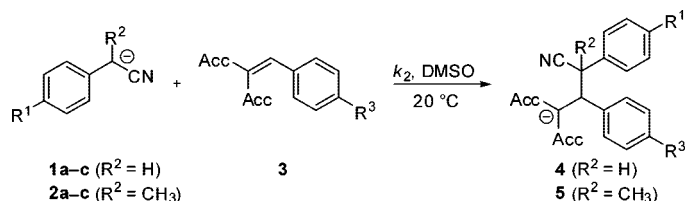
## Nucleophilicities of the Anions of Arylacetonitriles and Arylpropionitriles in Dimethyl Sulfoxide

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The rates of the reactions of the colored para-substituted phenylacetonitrile anions **1a–c** and the phenylpropionitrile anions **2a–c** with Michael acceptors (**3a–u**) were determined by UV–vis spectroscopy in DMSO at 20 °C. The reactions follow second-order kinetics, and the corresponding rate constants  $k_2$  obey the linear-free-energy relationship  $\log k_2(20\text{ }^\circ\text{C}) = s(N + E)$ , from which the nucleophile-specific parameters  $N$  and  $s$  of the carbanions **1a–c** and **2a–c** have been derived. With nucleophilicity parameters from  $19 < N < 29$ , they are among the most reactive nucleophiles which we have so far parametrized. In DMSO, the nucleophilicity of the *tert*-butoxide anion is comparable to that of the *p*-cyanophenylacetonitrile anion **1b**.

### Introduction

The comparison of the nucleophilicities of different classes of compounds is of considerable importance for our understanding of organic reactivity. The most comprehensive nucleophilicity scale presently available is based on the reactions of benzhydrylium ions and structurally related quinone methides with different nucleophiles.<sup>1</sup> With this method, we have been able to directly compare  $n$ -nucleophiles (amines, alcohols, phosphanes),  $\pi$ -nucleophiles (alkenes, arenes, organometallics), and  $\sigma$ -nucleophiles (hydride donors) with each other.<sup>1–4</sup> Re-

cently, we investigated the reactivities of different carbanions<sup>5–10</sup> including trifluoromethylsulfonyl-stabilized carbanions,<sup>6</sup> phenylsulfonyl-stabilized carbanions,<sup>7</sup> nitronates,<sup>8,9</sup> as well as the bis(4-nitrophenyl)methyl anion<sup>10</sup> and demonstrated that their additions to benzhydryl cations and structurally related quinone methides can be described by eq 1, where  $E$  is an electrophile-specific parameter and  $N$  and  $s$  are nucleophile-specific parameters.

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

Vice versa, the second-order rate constants  $k_2$  for the reactions of carbanions with Michael acceptors<sup>11–14</sup> have been used to determine the electrophilicities of these electron-deficient  $\pi$ -systems.

Because UV–vis spectroscopy is an efficient method to determine reaction rates, we have selected a set of colored benzhydrylium ions,<sup>2</sup> quinone methides,<sup>4</sup> and benzyldiene malonates<sup>14</sup> as reference electrophiles for characterizing the

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(1) (a) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77. (b) Mayr, H.; Ofial, A. R. In *Carbocation Chemistry*; Olah, G. A., Prakash, G. K. S., Eds.; Wiley: Hoboken, NJ, 2004; pp 331–358. (c) Ofial, A. R.; Mayr, H. *Macromol. Symp.* **2004**, *215*, 353–367. (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.

(2) 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.

(3) Mayr, H.; Patz, M. *Angew. Chem.* **1994**, *106*, 990–1010; *Angew. Chem., Int. Ed.* **1994**, *33*, 938–955.

(4) Lucius, R.; Loos, R.; Mayr, H. *Angew. Chem.* **2002**, *114*, 97–102; *Angew. Chem., Int. Ed.* **2002**, *41*, 91–95.

(5) Bug, T.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 12980–12986.

(6) Berger, S. T. A.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2007**, *129*, 9753–9761.

(7) Seeliger, F.; Mayr, H. *Org. Biomol. Chem.* **2008**, *6*, 3052–3058.

(8) Bug, T.; Lemek, T.; Mayr, H. *J. Org. Chem.* **2004**, *69*, 7565–7576.

(9) Phan, T. B.; Mayr, H. *Eur. J. Org. Chem.* **2006**, 2530–2537.

(10) Berger, S. T. A.; Lemek, T.; Mayr, H. *ARKIVOC* **2008**, x, 37–53.

**SCHEME 1. Phenylacetonitrile Anions 1a–c, Phenylpropionitrile Anions 2a–c, and Their pK<sub>aH</sub> Values in DMSO**

R	pK <sub>aH</sub>	R	pK <sub>aH</sub>
<b>1a</b> CF <sub>3</sub>	18.1 <sup>a</sup>	<b>2a</b> H	23.0 <sup>b</sup>
<b>1b</b> CN	16.0 <sup>b</sup>	<b>2b</b> CN	<sup>c</sup>
<b>1c</b> NO <sub>2</sub>	12.3 <sup>b</sup>	<b>2c</b> NO <sub>2</sub>	<sup>c</sup>

<sup>a</sup> From ref 16a. <sup>b</sup> From ref 16b. <sup>c</sup> pK<sub>aH</sub> values in DMSO not available.

reactivities of a large variety of nucleophiles. On the other hand, we do presently not yet have a comprehensive set of colored nucleophiles, which might be employed for the systematic investigation of the reactivities of electrophiles. So far, only colored carbanions of relatively low nucleophilicity ( $N < 20$ ) have been characterized.<sup>5–10</sup>

In view of the frequent use of cyano substituted carbanions in organic synthesis, we have selected the carbanions **1a–c** and **2a–c** for systematic studies of the relationship between structure and nucleophilic reactivity of highly reactive carbanions.<sup>15</sup>

Although the correlations between nucleophilicity ( $N$ ) and basicity (pK<sub>aH</sub>) of carbanions are not of high quality,<sup>6</sup> the pK<sub>aH</sub> values of the phenylacetonitrile anions **1a–c** and that of the phenylpropionitrile anion **2a** (Scheme 1) suggested that these carbanions have considerably higher reactivities than  $\alpha$ -nitro- and  $\alpha$ -trifluoromethylsulfonyl-stabilized benzyl anions.

Relative nucleophilicities of carbanions derived from  $\alpha$ -substituted phenylacetonitriles **2** toward methyl iodide and other alkyl halides in liquid ammonia have previously been investigated by competition experiments.<sup>17</sup>

Recent studies of the oxidative nucleophilic substitution of hydrogen revealed that the phenylpropionitrile anion **2a** and its derivatives add to nitrobenzene and some nitrobenzene derivatives in liquid ammonia to form persistent  $\sigma^H$ -adducts, from which hydride was abstracted when treated subsequently with KMnO<sub>4</sub>.<sup>18</sup> When these  $\sigma^H$ -adducts were combined with dimethyldioxirane, replacement of the nitro group by hydroxyl took place prior to rearomatization, and the corresponding phenols were isolated as major products.<sup>19</sup>

(11) (a) Lemek, T.; Mayr, H. *J. Org. Chem.* **2003**, *68*, 6880–6886. (b) Kaumanns, O.; Mayr, H. *J. Org. Chem.* **2008**, *73*, 2738–2745.

(12) Seeliger, F.; Berger, S. T. A.; Remennikov, G. Y.; Polborn, K.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 9170–9180.

(13) Berger, S. T. A.; Seeliger, F. H.; Hofbauer, F.; Mayr, H. *Org. Biomol. Chem.* **2007**, *5*, 3020–3026.

(14) Kaumanns, O.; Lucius, R.; Mayr, H. *Chem.—Eur. J.* **2008**, *14*, 9675–9682.

(15) (a) Collier, S. J.; Langer, P. In *Science of Synthesis*; Murahashi, S.-I., Ed.; Thieme: Stuttgart, 2004; Vol. 19, Chapter 19.5.15, pp 403–425. (b) Murahashi, S. I. In *Science of Synthesis*; Murahashi, S.-I., Ed.; Thieme: Stuttgart, 2004; Vol. 19, Chapter 19.5.14, pp 345–402. (c) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747–789. (d) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035–2077. (e) Fleming, F. F.; Gudipati, S. *Eur. J. Org. Chem.* **2008**, 5365–5374.

(16) (a) Bordwell, F. G.; Bausch, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 1979–1985. (b) Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J.; Bares, J. E. *J. Phys. Org. Chem.* **1988**, *1*, 209–223.

(17) Smith, H. A.; Bissell, R. L.; Kenyon, W. G.; MacClarence, J. W.; Hauser, C. R. *J. Org. Chem.* **1971**, *36*, 2132–2137.

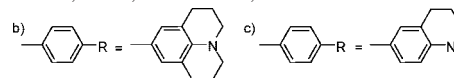
(18) (a) Makosza, M.; Stalinski, K.; Klepka, C. *Chem. Commun.* **1996**, 837–838. (b) Makosza, M.; Stalinski, K. *Chem.—Eur. J.* **1997**, *3*, 2025–2031. (c) Makosza, M.; Stalinski, K. *Tetrahedron* **1998**, *54*, 8797–8810. (d) Makosza, M.; Stalinski, K. *Synthesis* **1998**, 1631–1634.

(19) (a) Adam, W.; Makosza, M.; Zhao, C.-G.; Surowiec, M. *J. Org. Chem.* **2000**, *65*, 1099–1101. (b) Adam, W.; Makosza, M.; Stalinski, K.; Zhao, C.-G. *J. Org. Chem.* **1998**, *63*, 4390–4391.

**TABLE 1. Michael Acceptors 3a–u and Their Electrophilicity Parameters  $E$**

Electrophile		R	$E^a$
	<b>3a</b>	OMe	-12.18
	<b>3b</b>	NMe <sub>2</sub>	-13.39
	<b>3c</b>	Me	-15.83
	<b>3d</b>	OMe	-16.11
	<b>3e</b>	NMe <sub>2</sub>	-17.29
	<b>3f</b>	jul <sup>b</sup>	-17.90
	<b>3g</b>	H	-10.11
	<b>3h</b>	OMe	-11.32
	<b>3i</b>	NMe <sub>2</sub>	-13.56
	<b>3j</b>	jul <sup>b</sup>	-14.68
	<b>3k</b>	OMe	-10.37
	<b>3l</b>	NMe <sub>2</sub>	-12.76
	<b>3m</b>	NO <sub>2</sub>	-17.67
	<b>3n</b>	CN	-18.06
	<b>3o</b>	<i>m</i> Cl	-18.98
	<b>3p</b>	H	-20.55
	<b>3q</b>	Me	-21.11
	<b>3r</b>	OMe	-21.47
	<b>3s</b>	NMe <sub>2</sub>	-23.1
	<b>3t</b>	thq <sup>c</sup>	-23.4
	<b>3u</b>	jul <sup>b</sup>	-23.8

<sup>a</sup> Electrophilicity parameters  $E$  of **3a–f** were taken from ref 4, of **3g–j** from ref 13, of **3k,l** from ref 12, and of **3m–u** from ref 14.

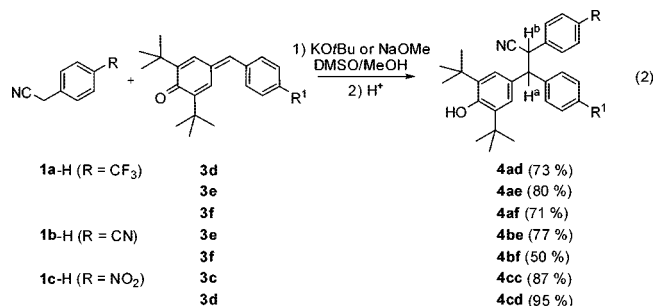


We will now report on the kinetics of the reactions of the phenylacetonitrile anions **1a–c** and the phenylpropionitrile anions **2a–c** with the electrophiles **3a–u** (Table 1) in DMSO at 20 °C. The second-order rate constants  $k_2$  will subsequently be used to derive the nucleophile-specific parameters  $N$  and  $s$  of the carbanions **1a–c** and **2a–c**.

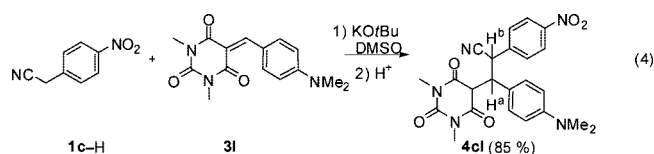
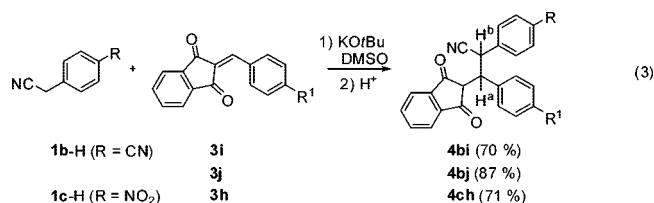
**Results and Discussion**

**Product Studies.** Products of representative combinations of nucleophiles with electrophiles have been characterized. The phenylacetonitrile anions **1a–c**, which were generated from (**1a–c**)-H with KO-*t*-Bu in DMSO or DMSO/MeOH mixtures, reacted with the quinone methides **3c–f** to give the addition products **4ad–4cd** (eq 2) in good yields. Their <sup>1</sup>H NMR spectra showed doublets for H<sup>a</sup> and H<sup>b</sup> at  $\delta = 4.11–4.54$  ppm and a signal for the hydroxy group. Generally, two sets of signals in the <sup>1</sup>H NMR spectra of the products **4** indicated the formation of almost equal amounts of two diastereomers.

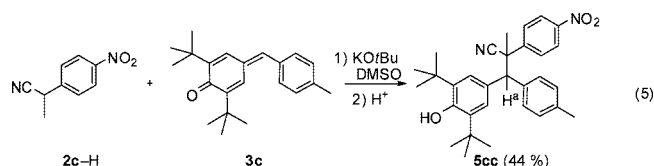
The reactions of the carbanions **1b,c** with the benzylidene indandiones **3h–j** and of **1c** with the benzylidene barbituric



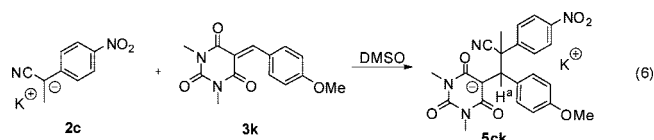
acid **3l** showed the analogous formation of the addition products as a mixture of two diastereomers ( $\approx 1:1$ , eqs 3 and 4).



The reaction of the phenylpropionitrile anion **2c** with the quinone methide **3c** yielded **5cc** as a 1:1 pair of diastereomers, indicated by two singlets for H<sup>a</sup> at  $\delta = 3.95$  and 4.04 ppm, and for the hydroxy group at  $\delta = 5.04$  and 5.20 ppm (eq 5).



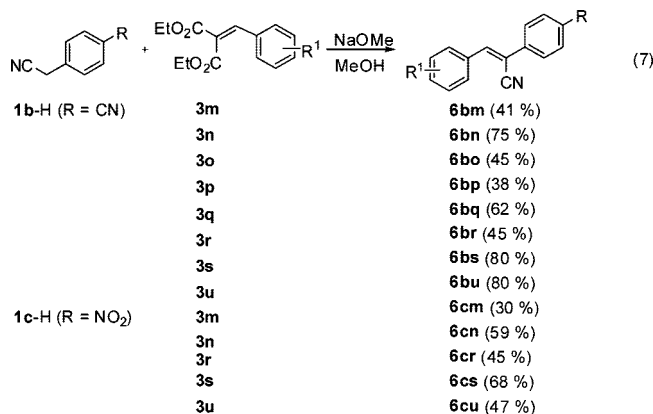
The reaction of the carbanion **2c** with **3k** was investigated by <sup>1</sup>H NMR spectroscopy, which shows the formation of equal amounts of diastereomers of the anionic adduct **5ck** (eq 6).



In contrast, the reactions of the benzylidene malonates **3m–u** with the carbanions **1b,c** in methanol resulted in the formation of  $\alpha$ -cyano stilbenes **6bm–6cu** via Michael addition, proton shift, and retro-Michael addition (eq 7). Compounds **6** were previously employed for the determination of  $H_R$ -acidity scales.<sup>20</sup>

**Kinetics.** The rates of the reactions of the carbanions **1a–c** and **2b–c** with the electrophiles **3a–u** were determined photometrically under first-order conditions by using either the nucleophile or the electrophile in high excess as specified in Table 2.

Because of the large  $pK_a$  value of *t*-BuOH in DMSO (29.4 or 32.2 from refs 21 and 22, respectively), all carbanions listed



in Scheme 1 ( $pK_{aH} < 23.0$ ) should be generated quantitatively when the corresponding CH acids were treated with 1 equiv of KO-*t*-Bu. Analogously, the deprotonation of (**1a–c**)-H and (**2a–c**)-H should also be quantitative with 1 equiv of the phosphazene base P<sub>4</sub>-*t*-Bu ( $pK_{BH^+} = 30.2$ ).<sup>23</sup> In order to verify the complete deprotonation of the CH acids (**1a–c**)-H, KO-*t*-Bu was added stepwise to solutions of (**1a–c**)-H and **2a**-H in DMSO. UV-vis spectroscopy showed that in all cases, the limiting absorbances of the corresponding carbanions were achieved after the addition of one equivalent of KO-*t*-Bu, indicating quantitative deprotonation of these CH acids. While the absorbance of **1c** was persistent under these conditions, the absorbances of the carbanions **1a** and **1b** decreased slowly, when only 1 equiv of KO-*t*-Bu was added (Figures S1–S3, Supporting Information). Persistent absorbances of the carbanions **1a,b** could be observed, however, when they were generated from their conjugate acids (**1a,b**)-H with 2 equiv of KO-*t*-Bu. The unsubstituted phenylpropionitrile anion **2a**, which was also formed quantitatively with 1 equiv of KO-*t*-Bu or P<sub>4</sub>-*t*-Bu, was not even persistent when generated with an excess (2–3 equiv) of base (Figure S4, Supporting Information).

The kinetic experiments with the nitro-substituted carbanions **1c** and **2c** were unproblematic: Because of their stability, stock solutions of the potassium salts **1c-K** and **2c-K** were employed. On the other hand, solutions of the reactive carbanions **1a,b** and **2a,b** were generated immediately before the kinetic experiments by treatment of the corresponding CH acidic compounds with strong bases, and the kinetic investigations were restricted to reactions with active electrophiles, which proceeded faster than the decomposition of the carbanions.

For all reactions described in Table 2, first-order rate constants  $k_{obs}$  (s<sup>-1</sup>) were obtained by least-squares fittings of the monoexponential function  $A_t = A_0 \exp(-k_{obs}t) + C$  to the time-dependent absorbances  $A$  of the minor components. Plots of  $k_{obs}$  versus the concentrations of the compounds used in excess were generally linear with negligible intercepts and the second-order rate constants  $k_2$  (L mol<sup>-1</sup> s<sup>-1</sup>) as slopes (Figure 1, Table 2). Some exceptions are discussed below.

As mentioned above, we were not able to obtain persistent solutions of the carbanion **2a**. When its reactions with **3s** (used as the minor component) were followed photometrically,

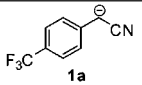
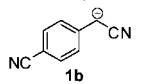
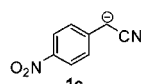
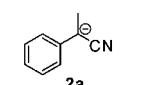
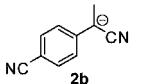
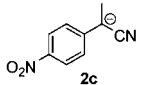
(21) Arnett, E. M.; Small, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 808–816.

(22) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295–3299.

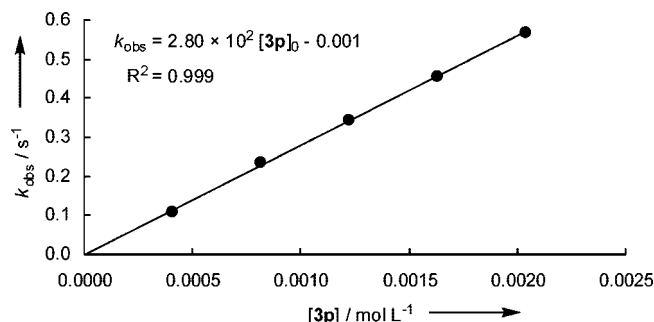
(23) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G. Z.; Peters, E. M.; Peters, K.; v. Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, 1055–1081.

(20) Kroeger, D. J.; Stewart, R. *Can. J. Chem.* **1967**, *45*, 2163–2171.

**TABLE 2.** Second-Order Rate Constants  $k_2$  for the Reactions of the Phenylacetone Anions **1a–c** and the Phenylpropionitrile Anions **2a–c** with the Michael Acceptors **3a–u** in DMSO at 20 °C

Nucleophile	Electrophile	$\lambda$ / nm <sup>a</sup>	$k_2$ / M <sup>-1</sup> s <sup>-1</sup> <sup>b</sup>
 <b>1a</b> $N = 27.28; s = 0.50$	<b>3d</b>	<b>3d</b> / 440	$4.04 \times 10^5$
	<b>3e</b>	<b>3e</b> / 486	$8.24 \times 10^4$
	<b>3f</b>	<b>3f</b> / 521	$5.45 \times 10^4$
	<b>3e</b>	<b>3e</b> / 486	$1.10 \times 10^4$
	<b>3f</b>	<b>3f</b> / 521	$6.59 \times 10^3$
	<b>3i</b>	<b>3i</b> / 490	$1.61 \times 10^6$
 <b>1b</b> $N = 25.11; s = 0.54$	<b>3j</b>	<b>3j</b> / 523	$3.94 \times 10^5$
	<b>3j</b>	<b>3j</b> / 523	$4.09 \times 10^{5c}$
	<b>3m</b>	<b>1b</b> / 394	$1.70 \times 10^4$
	<b>3m</b>	<b>1b</b> / 398	$1.64 \times 10^{4c}$
	<b>3m</b>	<b>1b</b> / 398	$1.60 \times 10^{4c,d}$
	<b>3m</b>	<b>1b</b> / 398	$1.86 \times 10^{4c,e}$
	<b>3n</b>	<b>1b</b> / 394	$8.87 \times 10^3$
	<b>3o</b>	<b>1b</b> / 397	$2.81 \times 10^3$
	<b>3p</b>	<b>1b</b> / 397	$2.80 \times 10^2$
	<b>3q</b>	<b>1b</b> / 394	$1.54 \times 10^2$
 <b>1c</b> $N = 19.67; s = 0.68$	<b>3a</b>	<b>3a</b> / 400	$1.29 \times 10^{5c}$
	<b>3c</b>	<b>3c</b> / 380	$4.19 \times 10^2$
	<b>3c</b>	<b>3c</b> / 400	$4.43 \times 10^{2c}$
	<b>3d</b>	<b>3d</b> / 400	$3.43 \times 10^2$
	<b>3d</b>	<b>3d</b> / 400	$3.26 \times 10^{2c}$
	<b>3h</b>	<b>3h</b> / 388	$5.23 \times 10^5$
	<b>3l</b>	<b>3l</b> / 560	$4.17 \times 10^4$
	<b>3m</b>	<b>1c</b> / 537	$2.51 \times 10^{1f}$
	<b>3n</b>	<b>1c</b> / 537	$9.98^g$
	 <b>2a</b> $N = 28.95; s = 0.58$	<b>3f</b>	<b>3f</b> / 524
<b>3s</b>		<b>3s</b> / 405	$3.05 \times 10^{3g}$
<b>3s</b>		<b>3s</b> / 410	$2.87 \times 10^{3g}$
<b>3s</b>		<b>3s</b> / 400	$3.12 \times 10^3$
<b>3s</b>		<b>3s</b> / 400	$3.09 \times 10^{3h}$
<b>3s</b>		<b>3s</b> / 400	$3.15 \times 10^{3i}$
<b>3t</b>		<b>3t</b> / 405	$1.86 \times 10^{3g}$
<b>3t</b>		<b>3t</b> / 405	$1.69 \times 10^{3h}$
<b>3t</b>		<b>3t</b> / 405	$1.50 \times 10^3$
<b>3u</b>		<b>3u</b> / 405	$9.90 \times 10^{2g}$
<b>3u</b>		<b>3u</b> / 405	$8.54 \times 10^2$
<b>3u</b>		<b>3u</b> / 405	$9.82 \times 10^{2h}$
 <b>2b</b> $N = 25.35; s = 0.56$	<b>3b</b>	<b>3b</b> / 533	$7.73 \times 10^{6j}$
	<b>3e</b>	<b>3e</b> / 488	$4.54 \times 10^{4j}$
	<b>3e</b>	<b>3e</b> / 488	$3.20 \times 10^4$
	<b>3f</b>	<b>3f</b> / 524	$2.51 \times 10^{4j}$
	<b>3m</b>	<b>2b</b> / 403	$1.08 \times 10^4$
	<b>3m</b>	<b>2b</b> / 403	$1.15 \times 10^4$
	<b>3n</b>	<b>2b</b> / 403	$5.68 \times 10^3$
	<b>3o</b>	<b>2b</b> / 403	$2.44 \times 10^3$
	<b>3p</b>	<b>2b</b> / 403	$1.19 \times 10^3$
	 <b>2c</b> $N = 19.61; s = 0.60$	<b>3a</b>	<b>3a</b> / 410
<b>3c</b>		<b>3c</b> / 375	$2.04 \times 10^{2k}$
<b>3d</b>		<b>2c</b> / 590	$9.61 \times 10^{1k}$
<b>3g</b>		<b>2c</b> / 590	$5.22 \times 10^5$
<b>3h</b>		<b>2c</b> / 590	$1.15 \times 10^5$
<b>3k</b>		<b>2c</b> / 590	$1.88 \times 10^5$
<b>3l</b>		<b>2c</b> / 590	$9.12 \times 10^3$

<sup>a</sup> Minor component in the pseudo-first-order kinetics and monitored wavelength. <sup>b</sup> In the presence of 1 equiv of KO<sup>t</sup>Bu. <sup>c</sup> In the presence of 18-crown-6. <sup>d</sup> In the presence of 3 equiv of **1b**-H. <sup>e</sup> Measurement at 25 °C. <sup>f</sup> Reversible reactions, see text and Supporting Information. <sup>g</sup> Deprotonation of acid **2a**-H with P<sub>4</sub>-*t*-Bu phosphazene base. <sup>h</sup> In the presence of 2 equiv of KO<sup>t</sup>-Bu. <sup>i</sup> In the presence of 3 equiv of KO<sup>t</sup>-Bu. <sup>j</sup> Deprotonation of **2b**-H with P<sub>2</sub>-*t*-Bu phosphazene base. <sup>k</sup> In the presence of **2c**-H.



**FIGURE 1.** Determination of the second-order rate constant  $k_2 = 2.80 \times 10^2 \text{ L mol}^{-1} \text{ s}^{-1}$  for the reaction of the *p*-cyanophenylacetone anion **1b** with the Michael acceptor **3p** in DMSO at 20 °C.

exponential decays of the electrophile (**3s**) absorbance were observed. Plots of  $k_{\text{obs}}$  vs the concentration of **2a** (calculated from **[2a-H]** assuming complete deprotonation) were linear, and the slopes, which equal the second-order rate constants  $k_2$ , were almost identical (Table 2), independent of the quantity of the base (1.05 equiv of P<sub>4</sub>-*t*-Bu or 1, 2, or 3 equiv of KO<sup>t</sup>-Bu) used for the deprotonation of **2a**. However, significant negative intercepts of variable magnitude were observed in all cases (Tables S31–S35, Supporting Information), indicating fast and irreversible consumption of certain fractions of the carbanion **2a**. Similar observations, i.e., negative intercepts of variable magnitude and slopes, corresponding to second-order rate constants, which are almost independent of the nature and quantity of base used for the deprotonation of **2a**-H, were made for the analogous reactions of the carbanion **2a** with the electrophiles **3t,u** (see Tables S36–S41, Supporting Information).

On the other hand, significant positive intercepts in plots of the first-order rate constants ( $k_{\text{obs}}$ ) against the concentrations of the major component were observed for the reactions of the *p*-nitrophenylacetone anion (**1c**) with the benzylidene malonates **3m** and **3n**. Positive intercepts are indicative of reversible reactions, and by theory, reflect the rate constants of the reverse reactions.<sup>24</sup> However, as discussed above, the intercepts are also affected by side reactions that we refrain to employ the intercepts of these plots for calculating the rates of the reverse reactions and the equilibrium constants  $K$ .

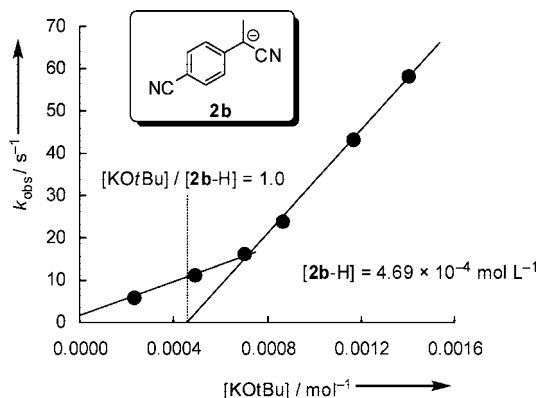
As shown in Table 2, the addition of 18-crown-6 caused only insignificant changes of the second-order rate constants  $k_2$  for the reactions of **1b** with **3j** and **3m** and of **1c** with **3c** and **3d**. These results confirm that ion-pairing is negligible in dilute DMSO solution, in accordance with literature reports<sup>25</sup> and earlier findings of our group.<sup>6,8,26</sup>

**Nucleophilicity of *tert*-Butoxide.** As discussed above, persistent solutions of the more basic carbanions have only been obtained when more than 1 equiv of KO<sup>t</sup>-Bu was used for the deprotonation of the corresponding CH acids. In order to elucidate the influence of excess KO<sup>t</sup>-Bu on the kinetics, we have studied the reaction of **2b** with the quinone methide **3e** in the presence of variable excess of KO<sup>t</sup>-Bu. As shown in Figure 2, the slope of the plot of  $k_{\text{obs}}$  vs  $[\text{KO}^t\text{-Bu}]$  was higher when  $[\text{KO}^t\text{-Bu}] > [\text{2b-H}]$ , and from the different slopes in the range

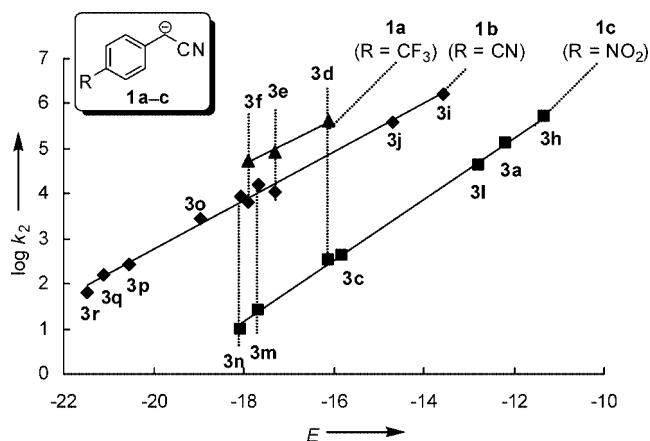
(24) *The Investigation of Organic Reactions and Their Mechanisms*; Maskill, H., Ed.; Blackwell Publishing: Oxford, 2006. (b) Schmid, R.; Sapunov, V. N. *Non-Formal Kinetics*; VCH: Weinheim, 1982.

(25) Binev, I. G.; Tsenov, J. A.; Velcheva, E. A.; Juchnovski, I. N. *J. Mol. Struct.* **1995**, *344*, 205–215.

(26) Lucius, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1995–1997.



**FIGURE 2.** Plot of the observed first-order rate constants  $k_{\text{obs}}$  for the reactions of electrophile **3e** ( $c_0 = 2.00 \times 10^{-5} \text{ mol L}^{-1}$ ) with the nucleophile **2b** against the concentration of KO-*t*-Bu used for the deprotonation of **2b-H** ( $c_0 = 4.69 \times 10^{-4} \text{ mol L}^{-1}$ ) in DMSO at 20 °C.



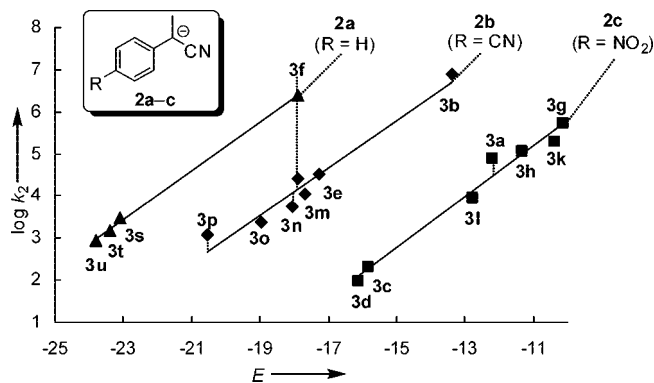
**FIGURE 3.** Plot of  $\log k_2$  for the reactions of the nucleophiles **1a-c** with the electrophiles **3** in DMSO versus their electrophilicity parameters  $E$ .

of  $[\text{KO-}t\text{-Bu}] < [\text{2b-H}]$  and  $[\text{KO-}t\text{-Bu}] > [\text{2b-H}]$  one can derive that KO-*t*-Bu is approximately two times more nucleophilic than **2b**. As a consequence, KO-*t*-Bu cannot be used in excess when nucleophiles with  $N \leq 27$  are investigated. On the other hand, an excess of KO-*t*-Bu used for the deprotonation of **2a-H** will hardly affect the pseudo-first-order rate constant because **2a** reacts considerably faster than KO-*t*-Bu (Figure S6, Supporting Information).

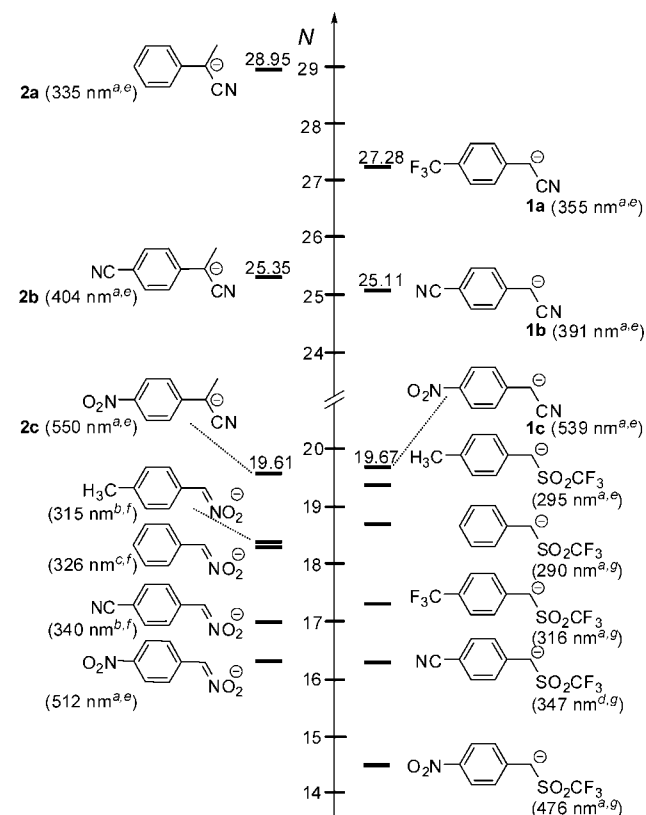
**Correlation Analysis.** In order to determine the nucleophile-specific parameters  $N$  and  $s$  for the phenylacetonitrile anions **1a-c** (Figure 3) and the phenylpropionitrile anions **2a-c** (Figure 4), the logarithmic second-order rate constants  $\log k_2$  of their reactions with electrophiles **3a-u** were plotted against the electrophilicity parameters  $E$  of **3a-u**.

The linear correlations for the reactions of the phenylacetonitrile anions **1a-c** ( $R^2 > 0.98$ , Figure 3) allow us to determine the nucleophile-specific parameters  $N$  and  $s$  for these carbanions.

The correlations for the reactions of the phenylpropionitrile anions **2a-c** ( $R^2 \geq 0.95$ , Figure 4) show larger deviations from linearity than those of the phenylacetonitrile anions **1a-c**. In particular, the reactions of the carbanion **2b** with benzylidene-malonate **3p**, as well as the reaction of carbanion **2c** with quinone methide **3a**, are two times faster than expected. On the other hand, the reactions of **2b** with the benzylidene malonates **3m,n** are approximately two times slower than



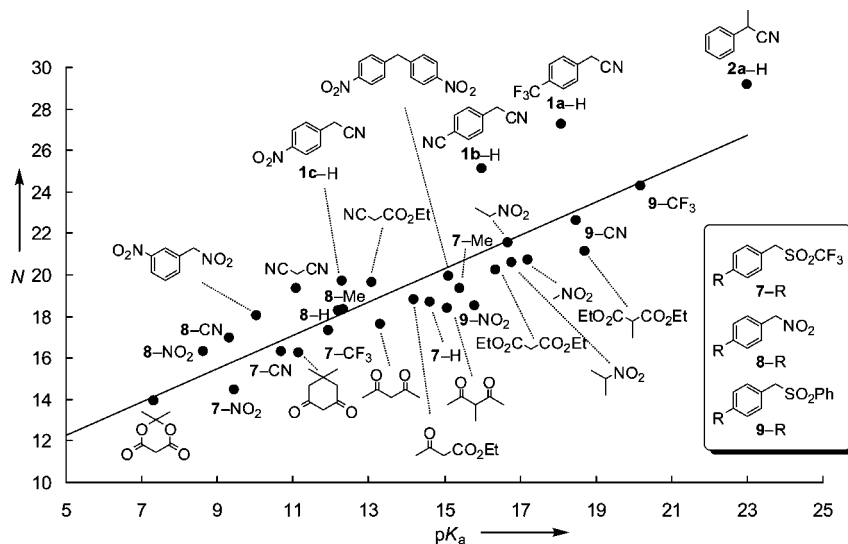
**FIGURE 4.** Plot of  $\log k_2$  for the reactions of the nucleophiles **2a-c** with the electrophiles **3** in DMSO versus their electrophilicity parameters  $E$ .



**FIGURE 5.** Comparison of the nucleophilicity parameters  $N$  of the phenylacetonitrile anions **1a-c** and the phenylpropionitrile anions **2a-c** with those for  $\alpha$ -nitro- and  $\alpha$ -trifluoromethylsulfonyl-stabilized carbanions in DMSO. Key: (a)  $\lambda_{\text{max}}$  in DMSO; (b)  $\lambda_{\text{max}}$  in MeOH; (c)  $\lambda_{\text{max}}$  in DMSO/H<sub>2</sub>O 10:90 (v/v); (d)  $\lambda_{\text{max}}$  in DMSO/H<sub>2</sub>O 30:70 (v/v); (e) this work; (f) see ref 9; (g) see ref 27.

expected. Taking into account that many different classes of Michael acceptors have been used as electrophiles, these deviations can be considered as rather small, and the correlation lines in Figure 4 were employed to determine the nucleophile-specific parameters  $N$  and  $s$  for the phenylpropionitriles **2a-c**.

As expected, electron-withdrawing groups at the para-position of the aromatic ring decrease the nucleophilicities  $N$  of the carbanions **1a-c** and **2a-c**. A comparison between the reactivities of the phenylacetonitrile anions **1a-c** and the phenylpropionitrile anions **2a-c** (Table 2 and Figure 5) shows that replacement of one hydrogen by a methyl group at the  $\alpha$ -carbon of phenylacetonitrile anions does not significantly affect the



**FIGURE 6.** Correlation of the nucleophilicity parameters  $N$  of different carbanions versus the  $pK_a$  values of their corresponding CH acids in DMSO. Overall correlation:  $N = 0.802pK_a + 8.278$ ,  $R^2 = 0.750$  (nucleophilicity parameters  $N$  and  $pK_a$  values used for this diagram are compiled in the Supporting Information).

nucleophilicities. The inductive effect of the methyl group and its steric demand obviously compensate each other resulting in similar reactivities of the analogously substituted carbanions **1b**/**2b** and **1c**/**2c**.

In order to determine reliable nucleophilicity or electrophilicity parameters, reaction partners should be employed, which differ by several orders of magnitude. The correlation lines for compounds **2a–c** fulfill this condition. However, it should be noted that the slopes of the correlation lines for compounds **2a** and **2b** are largely controlled by the reactions with the electrophiles **3f** and **3b**, respectively. The situation for compounds **1b,c** is much better because their  $N$  and  $s$  parameters can be derived from a balanced series of rate constants (Figure 3). Because the parameters  $N$  and  $s$  for carbanion **1a** have only been derived from three rate constants, which differ by less than 1 order of magnitude, the nucleophilicity parameters  $N$  and  $s$  for **1a** should be regarded with caution.

Figure 5 compares the colored  $\alpha$ -acceptor-substituted benzyl anions whose nucleophilicity parameters  $N$  have so far been determined. They cover a reactivity range of almost 15 orders of magnitude. It is obvious that the phenylacetone nitrile anions **1a–c** are much stronger nucleophiles than the analogously substituted  $\alpha$ -triflate and  $\alpha$ -nitro-substituted benzyl anions, whose reactivities have recently been determined.<sup>6,8</sup> Because of the paucity of available data, Hammett plots for the differently substituted phenylacetone nitrile anions **1a–c** and phenylpropionitrile anions **2a–c** are not informative. Figure 5 reveals, however, that variation of the para substituents in both series **1a–c** and **2a–c** have considerably larger effects on the nucleophilic reactivities than in the series of  $\alpha$ -triflate and much more than in the series of  $\alpha$ -nitro substituted carbanions. Obviously, more negative charge is localized in the aromatic rings of the carbanions **1a–c** and **2a–c** than in the corresponding  $\alpha$ -triflate and  $\alpha$ -nitro-substituted benzyl anions.

$pK_a$  values are generally considered to be a useful tool for estimating the nucleophilic reactivities of many compounds. We have already shown that this assumption only holds within groups of structurally closely related nucleophiles.<sup>6,28</sup> For

example, the correlation between nucleophilicities of primary and secondary amines versus their  $pK_{aH}$  values in water is very poor.<sup>28c</sup> Figure 6 shows a moderate correlation between the nucleophilicity parameters  $N$  of carbanions and the  $pK_a$  values of their conjugate CH acids (cf Scheme 1) in DMSO. It is obvious that the phenylacetone nitrile anions **1a–c** and carbanion **2a** are considerably more nucleophilic than expected from the  $pK_a$  values of the corresponding CH acids,<sup>29</sup> indicating the limitation of  $pK_a$  for predicting nucleophilic reactivities. In accordance with earlier reports,<sup>5,8,30</sup> the positive deviations of the cyano-substituted carbanions are indicative of lower intrinsic barriers of their reactions.

## Conclusions

$\alpha$ -Cyano-substituted benzyl anions are several orders of magnitude more nucleophilic than  $\alpha$ -SO<sub>2</sub>CF<sub>3</sub>- and  $\alpha$ -NO<sub>2</sub>-substituted benzyl anions. The high reactivities of the cyano substituted species **1a–c** and **2a–c** are only partially caused by their higher basicities ( $pK_{aH}$ ). Lower intrinsic barriers for the reactions of these carbanions are indicated by positive deviations from the Brønsted plots and also contribute to their high nucleophilicities. Variation of the para substituent in the aromatic ring has a considerably larger effect on the nucleophilicities of **1a–c** and **2a–c** than in the corresponding  $\alpha$ -SO<sub>2</sub>CF<sub>3</sub>- and  $\alpha$ -NO<sub>2</sub>-substituted counterparts, indicating a larger delocalization of the negative charge in the aromatic ring of carbanions **1a–c** and **2a–c**. As colored species of high nucleophilicities, these carbanions complement our series of reference nucleophiles, which can be employed for the photometric determination of electrophilic reactivities.

## Experimental Section

**Arylacetone nitriles (1a–c)-H and Arylpropionitriles (2a–c)-H.** Arylacetone nitriles **1** are commercially available compounds and

(28) (a) Nigst, T. A.; Westermaier, M.; Ofial, A. R.; Mayr, H. *Eur. J. Org. Chem.* **2008**, 2369–2374. (b) Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chem.—Eur. J.* **2007**, *13*, 336–345. (c) Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679–3688.

(29)  $pK_a$  values for **2b** and **2c** have not been reported.

(30) (a) Bernasconi, C. F.; Zitomer, J. L.; Fox, J. P.; Howard, K. A. *J. Org. Chem.* **1984**, *49*, 482–486. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301–308. (c) Bernasconi, C. F.; Wenzel, P. J. *J. Org. Chem.* **2003**, *68*, 6870–6879.

(27) Goumont, R.; Kizilian, E.; Buncel, E.; Terrier, F. *Org. Biomol. Chem.* **2003**, *1*, 1741–1748.

have been recrystallized from *n*-pentane/MeOH prior to use. Compounds (**2a–c**)-H have been prepared by methylation of the corresponding arylacetonitriles by using methyl iodide as described in the literature.<sup>31</sup>

The synthetic procedures for **4cd** and **6bn** are described as representative examples for the product studies. A complete description for the preparation of all other products **4–6** is given in the Supporting Information.

**3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(4-methoxyphenyl)-2-(4-nitrophenyl)propanenitrile (4cd).** A mixture of **1c**-H (25.0 mg, 154  $\mu$ mol), NaOMe (8.30 mg, 170  $\mu$ mol), and **3d** (50.0 mg, 154  $\mu$ mol) was stirred in MeOH (10 mL) for 1 h under N<sub>2</sub> atmosphere. After workup with diluted acetic acid and chromatography on silica gel (*i*-Hex/EtOAc 4:1, *R<sub>f</sub>* = 0.38), the product was obtained as a yellow foam (71.0 mg, 146  $\mu$ mol, 95% as a mixture of diastereomers in a ratio of 1:1.2). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 1.32, 1.38 (2s, 18 H, 2  $\times$  C(CH<sub>3</sub>)<sub>3</sub>), 3.76, 3.80 (2s, 3 H, OCH<sub>3</sub>), 4.19–4.24 (m, 1 H, CH), 4.51 (d, <sup>3</sup>*J* = 8.4 Hz, 0.50 H, CH), 4.57 (d, <sup>3</sup>*J* = 8.1 Hz, 0.47 H, CH), 5.13, 5.17 (2s, 1 H, OH), 6.78–6.81 (m, 1 H, CH<sub>ar</sub>), 6.85–6.89 (m, 2.20 H, CH<sub>ar</sub>), 6.97 (s, 1 H, CH<sub>ar</sub>), 7.10–7.13 (m, 1 H, CH<sub>ar</sub>), 7.19–7.27 (m, 3 H, CH<sub>ar</sub>) 8.07–8.11 (m, 2 H, CH<sub>ar</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz):  $\delta$  = 30.15, 30.23 (2q, CH<sub>3</sub>), 34.32, 34.35 (2s), 43.64, 43.73 (2d, CH), 55.22, 55.23 (2q, CH<sub>3</sub>), 55.82, 56.07 (2d, CH), 114.07, 114.12 (2d, CH<sub>ar</sub>), 119.13, 119.20 (2s, CN), 123.61, 123.66 (2d, CH<sub>ar</sub>), 124.55, 125.10 (2d, CH<sub>ar</sub>), 128.95, 129.32, 129.43 (3d, CH<sub>ar</sub>, signal for the other diastereomer superimposed), 129.35, 130.08 (s), 131.30, 132.00 (2s), 135.93, 136.12 (2s), 142.44, 142.47 (2s), 147.48, 147.50 (2s), 152.96, 153.26 (2s), 158.69, 158.99 (2d). HR-MS (ESI) [M – H<sup>+</sup>]: calcd 485.2435 (C<sub>30</sub>H<sub>33</sub>N<sub>2</sub>O<sub>4</sub>), found 485.2440.

**4,4'-(Cyanoethene-1,2-diyl)dibenzonitrile (6bn).** Equimolar amounts of **1b**-H (81 mg, 0.57 mmol) and NaOMe were stirred in MeOH, when electrophile **3n** was added subsequently. The resulting precipitate was filtered, washed, and dried to yield the pure product **6bn** as colorless solid (0.11 g, 0.43 mmol, 75%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta$  = 7.98–8.06 (m, 6 H, CH<sub>ar</sub>), 8.09–8.12 (m, 2 H,

CH<sub>ar</sub>), 8.34 (s, 1 H, C=CH). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100 MHz):  $\delta$  = 111.9 (s), 112.8 (s), 116.6 (s), 118.2 (s), 126.8 (d, CH<sub>ar</sub>), 129.8 (d, CH<sub>ar</sub>), 132.7 (d, CH<sub>ar</sub>), 133.0 (d, CH<sub>ar</sub>), 137.5 (s), 143.8 (d, C=CH). MS (EI) *m/z* = 256 (33), 255 (M<sup>+</sup>, 100), 254 (82), 228 (39), 215 (63), 200 (14). HR-MS: calcd 255.0796 (C<sub>17</sub>H<sub>9</sub>N<sub>3</sub>), found 255.0786. Mp: 303–304 °C (dec, lit.<sup>32</sup> 302–303 °C).

**Kinetics.** The reactions of carbanions **1a–c** and **2a–c** were studied in DMSO at 20 °C. The rates of the reactions of carbanions **1a–c** and **2a–c** with the Michael acceptors **3a–u** were determined photometrically under first-order conditions using either a large excess of the electrophiles **3a–u** or of the carbanions **1a–c** and **2a–c** (for details, see the text and Supporting Information), which were generated by deprotonation of the corresponding CH acid (**1a–c**)-H and (**2a–c**)-H by using potassium *tert*-butoxide or Schwesinger's phosphazene bases P<sub>2</sub>-*t*-Bu and P<sub>4</sub>-*t*-Bu.

The reactions were studied with conventional stopped-flow instruments as described earlier. The experiments were initiated by mixing equal volumes of solutions of the base and the CH acidic compounds (**1a–c**)-H and (**2a–c**)-H to generate the corresponding carbanions. After a delay time of *t* = 1 s, the resulting solutions of the carbanions were mixed with equal volumes of solutions of the electrophiles. From the exponential decay of the absorptions of the minor components, first-order rate constants were obtained by least-squares fittings of the monoexponential function  $A_t = A_0 \exp(-k_{\text{obs}}t) + C$  to the absorbance data.

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**Supporting Information Available:** Details of the kinetic experiments, synthetic procedures, and NMR spectra of all characterized compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(31) Bailey, W. F.; Jiang, X.-L.; McLeod, C. E. *J. Org. Chem.* **1995**, *60*, 7791–7795.

(32) Bell, F.; Waring, D. H. *J. Chem. Soc.* **1948**, 1024–1026.