Reviews

Aryl- and hetaryl-containing amide anions in reactions of aromatic nucleophilic substitution

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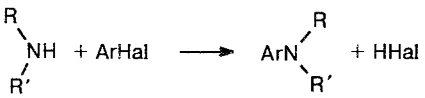
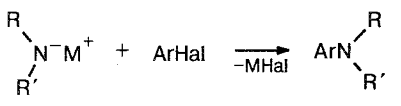
The results of kinetic studies of S_NAr reactions of *p*-nitrohalobenzenes, hexafluorobenzene, and pentafluoropyridine with aryl-, diaryl-, and hetarylamide anions under homogeneous conditions (in dimethyl sulfoxide) and under conditions of phase transfer catalysis (in toluene) are analyzed. The increase in the Brönsted coefficient β_{Nu} in reactions of amide anions in DMSO as the electrophilicity of the substrate increases and steric hindrance in nucleophiles decreases may result from a higher degree of charge transfer from a nucleophile to a substrate in the transition state. The possibility of replacement of the S_NAr by the SET mechanism in these reaction is discussed.

Key words: aryl-containing amide anions, aryl halides, S_NAr reactions, phase transfer catalysis, Brönsted coefficient.

It is well known that the functionalization of arenes is largely based on the replacement of halogen atoms in haloarenes under the action of various nucleophiles. The introduction of an amino group into arenes is most often carried out using ammonia, primary or secondary amines (Eq. (1)) and, much more rarely, their alkaline metal salts (Eq. (2)).[1]



$$RR'NH + ArHal \longrightarrow ArNRR' + HHal \quad (1)$$



$$RR'N^-M^+ + ArHal \xrightarrow[-MHal]{} ArNRR' \quad (2)$$

M = K, Na, Li

The reactivity of amide anions (see Eq. (2)) is much higher than that of uncharged amines. It was of great interest to study the peculiarities of their nucleophilic behavior under various conditions.

Therefore, the goal of this work was to study the quantitative regularities of the nucleophilic substitution of halogen atoms in arenes under the action of alkaline salts of amide anions generated from aryl-, diaryl-, and hetarylamines both in a highly polar medium (DMSO) and in a low polar medium (toluene) under conditions of phase transfer catalysis.

The choice of aryl halides ArHal (*p*-nitrofluorobenzene, hexafluorobenzene, and pentafluoropyridine) as substrates was determined by the fact that their electrophilicities differ significantly, the steric effect at the reaction center remaining constant. It is known that

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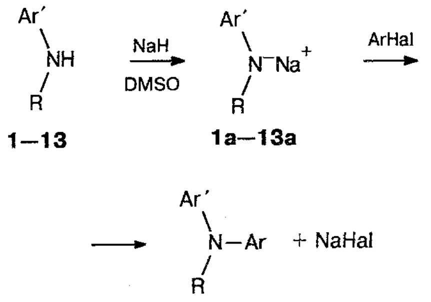
passing from *p*-nitrofluorobenzene and hexafluorobenzene to pentafluoropyridine leads to a 10^7-fold increase in the rate of their reactions with the methoxide ion in methanol.[2] The effect of the leaving group, halide ion, has been studied for *p*-nitrofluoro- and *p*-nitrochlorobenzenes, since it is known that one of the important criteria of the S_NAr reaction mechanism is the change in the reactivity on passing from fluorine to chlorine.[3]

The series of nucleophiles were selected in such a way that the steric effects of the N-anionic centers were constant within each series. It seems possible to use nucleophiles containing fluorine atoms in the *ortho*-position to the reaction center and their hydrogen analogs in the same series, since the steric constants of phenyl and *o*-fluorophenyl group differ insignificantly.[4] Combining polyfluoroaryl-containing compounds and their hydrogen analogs within the same series of nucleophiles made it possible to expand considerably the range of their basicity.



(3)

Ar = 4-$NO_2C_6H_4$, C_6F_5, 4-C_5F_4N; Hal = F, Cl
Ar′, R = Ph, Ph (**1**, **1a**); 3-ClC_6H_4, Ph (**2**, **2a**); C_6F_5, H (**3**, **3a**); 4-$NO_2C_6H_4$, H (**4**, **4a**); 4-C_5F_4N, H (**5**, **5a**); 4-$NO_2C_6H_4$, Ph (**6**, **6a**); 4-CNC_6F_4, H (**7**, **7a**); 4-C_5F_4N, Ph (**8**, **8a**); 4-CNC_6F_4, Ph (**9**, **9a**); 4-MeC_6F_4, C_6F_5 (**10**, **10a**); C_6F_5, C_6F_5 (**11**, **11a**); 4-ClC_6F_4, C_6F_5 (**12**, **12a**); 4-C_5F_4N, C_6F_5 (**13**, **13a**)

Table 1 presents the acidity of aryl-, diaryl-, and hetaryl amines (**1—13**) in the gas phase and in DMSO solution. It follows from these data that the range of basicity of the related amide anions (**1a—13a**) (Eq. (3)) is ~16 p*K* units in DMSO and 37 kcal mol^{-1} in the gas phase. A good correlation between the acidity in the gas phase ($\Delta_g G^0$) and that in DMSO (p*K*) for compounds **1**, **3—9**, **11**, and **13** is found (Eq. (4)), confirming that the steric and solvation effects of substituents upon a change in the basicity are proportional for anions **1a—13a** in both media. Therefore, when the transition state in an S_NAr reaction in reached, the energy consumption for desolvation of these anions should also change proportionally to the change in the anion basicity. Hence, one may expect that the Brönsted dependence between the nucleophilicity and the basicity would be fulfilled.

$$pK = 0.40\ \Delta_g G^0 - 111.96\ (r = 0.986,\ n = 8) \qquad (4)$$

Table 1. Acidity of aryl-, diaryl-, and hetarylamines (**1—13**) in the gas phase ($-\Delta_g G^0$) and in DMSO solution (pK_{DMSO})[a]

Compound	$-\Delta_g G^0$/kcal mol^{-1}	pK_{DMSO}
Ph_2NH (**1**)	348.3[5]	25.55[7,b]
3-ClC_6H_4NHPh (**2**)	—	24.1[7,b]
$C_6F_5NH_2$ (**3**)	341.3[6]	23.1[8]
4-$NO_2C_6H_4NH_2$ (**4**)	336.2[5]	21.5[9,b]
4-$NC_5F_4NH_2$ (**5**)	332.6[6]	19.2[8]
4-$NO_2C_6H_4NHPh$ (**6**)	328.3[5]	17.45[7,b]
4-$CNC_6F_4NH_2$ (**7**)	326.2[6]	17.9[10]
4-NC_5F_4NHPh (**8**)	—	15.1[c]
4-CNC_6F_4NHPh (**9**)	—	14.7[c]
4-$MeC_6F_4NHC_6F_5$ (**10**)	—	13.3[10]
$(C_6F_5)_2NH$ (**11**)	316.5[6]	12.6[10]
4-$ClC_6F_4NHC_6F_5$ (**12**)	—	12.0[10]
4-$NC_5F_4NHC_6F_5$ (**13**)	310.9[6]	9.4[10]

[a] Relative scale with 9-phenylfluorene as the standard, pK_{st} 18.5. [b] Calculated with respect to the relative scale. [c] Determined by M. I. Terekhova and A. S. Petrov using the known method.[11]

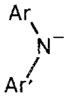
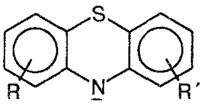
Table 2 presents the rate constants of second-order reactions of anions **3a—5a** and **7a** with *p*-nitrofluoro- and *p*-nitrochlorobenzenes in DMSO.[12,13] As can be seen from these data, the fluoro-derivative reacts much faster than the chloro-derivative, in accordance with the criterion for S_NAr addition-elimination reactions.[3,14] The rate constants obey the Brönsted equation, log*k* = β_{Nu} + const, where the sensitivities of the reaction rates to changes in basicity are similar (*cf.* the β_{Nu} coefficients in Table 3). However, the β_{Nu} coefficient is determined not only by the nature of the leaving group but also by properties of the nucleophile. It follows from a comparison of the β_{Nu} coefficients for the reaction between anions with different structures and *p*-nitrohalobenzenes (see Table 3) that the β_{Nu} value for the less electronegative group, the chlorine atom, increases in the case when the steric effect in the anion decreases when passing from arylamines to phenothiazines. It is known that the transition from cyclic to related acyclic anions results in an increase in of steric hindrance in the course of the formation of the transition state in S_N2 reactions.[15]

Table 2. Rate constants of reactions of anions obtained from anilines (**3a—5a** and **7a**) with 4-$FC_6H_4NO_2$ and 4-$ClC_6H_4NO_2$ in DMSO[12,13]

Anion	$k \cdot 10^3$/L mol^{-1} s^{-1}	
	4-$FC_6H_4NO_2$[a]	4-$ClC_6H_4NO_2$[b]
3a	143.0	111.0
4a	29.6	33.2
5a	7.6	11.2
7a	4.8	4.3

[a] 25 °C. [b] 60 °C.

Table 3. Brönsted coefficients β_{Nu} for S_NAr reactions of monoaryl-, diaryl-, and phenothiazinide anions with *p*-fluoro- and *p*-chloronitrobenzenes in DMSO at 25 °C

Anion	Substrate	β_{Nu}
 (**1a**, **2a**, **6a**, **9a**)	1-F-4-$NO_2C_6H_4$	$0.24^{12,a}$
$ArNH^-$ (**3a**—**5a**, **7a**)	1-Cl-4-$NO_2C_6H_4$ 1-F-4-$NO_2C_6H_4$	$0.26^{13,b}$ $0.28^{12,c}$
	1-F-4-$NO_2C_6H_4$ 1-Cl-4-$NO_2C_6H_4$	0.51^{14} 0.70^{14}

[a] $\log k_F = 0.24pK - 6.49$ ($r = 0.997$, $n = 4$). [b] At 60 °C. [c] $\log k_F = 0.28pK - 7.44$ ($r = 0.988$, $n = 4$).

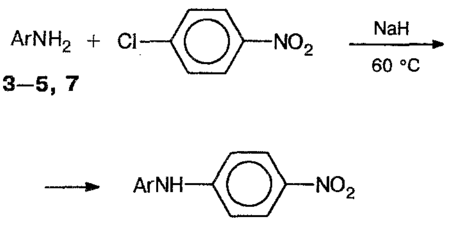
The study of the kinetics of the reactions of anions generated from anilines with *p*-nitrochlorobenzene in low polar toluene under conditions of phase transfer catalysis (dicyclohexano-18-crown-6 as the catalyst, sodium hydride as the base) showed that the reactivity of anions is more than 2 orders of magnitude higher (200—400-fold) in DMSO than in toluene (Table 4).[13] Such behavior can be explained by the different structure of the nucleophilic species in these two media; nucleophiles exist as free ions in DMSO and as ionic pairs in toluene. Good Brönsted correlations with similar β_{Nu} coefficients were obtained for both media:

$$\log k_{PhMe} = 0.31\ pK_{DMSO} - 10.42\ (r = 0.991,\ n = 4), \quad (5)$$

$$\log k_{DMSO} = 0.26\ pK_{DMSO} - 7.03\ (r = 0.996,\ n = 4). \quad (6)$$

This means that the type of species (free ions or ionic pairs) only slightly affects the sensitivity of nucleophiles to the changes in basicity.

Table 4. Rate constants of the reactions of anions **3a**—**5a** and **7a** with *p*-nitrochlorobenzene in toluene under conditions of phase transfer catalysis and in DMSO[13]



Nucleophile	$k\cdot10^3$/L mol^{-1} s^{-1}		k_{DMSO}/k_{PhMe}
	PhMe	DMSO	
3a	0.599	111.0	185
4a	0.118	33.2	281
5a	0.0282	11.2	397
7a	0.0139	4.25	306

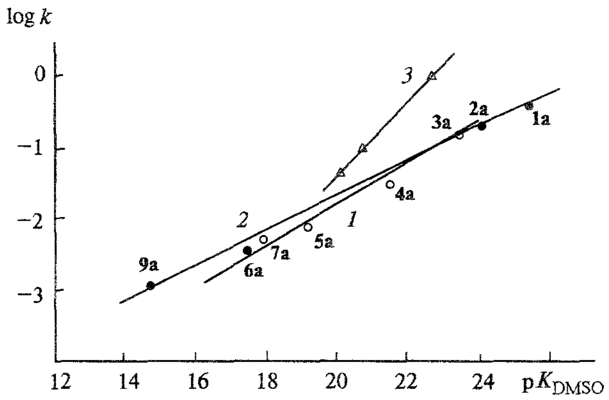


Fig. 1. Brönsted relations for the reactions between *p*-nitrofluorobenzene and anions generated from arylamines (**3a**—**5a** and **7a**) (*1*, β_{Nu} = 0.28), diarylamines (**1a**, **2a**, **6a**, **9a**) (*2*, β_{Nu} = 0.24), and phenothiazines (*3*, β_{Nu} = 0.51) in DMSO at 25 °C.[12,24]

The kinetics of the reactions of the anions generated from aryl- (**3a**—**5a** and **7a**) and diarylamines (**1a**, **2a**, **6a**, and **9a**) with *p*-nitrofluorobenzene are described by Brönsted equations; both are straight lines that practically coincide (Fig. 1, lines *1* and *2*).[12] The latter fact indicates that the influence of steric factors on the reactivity of these anions is nearly the same. Both reaction rate constants (see Fig. 1, line *3*) and β_{Nu} coefficients (see Table 3) increase noticeably with decrease in steric hindrance when passing from diaryl and monoaryl anions to cyclic phenothiazinide anions in reactions with *p*-nitrohalobenzenes.

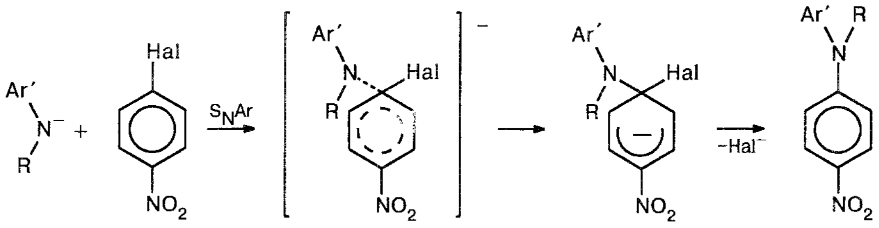
The substrate electrophilicity is yet another significant factor that affects the change in the β_{Nu} coefficient. Figure 2 shows the Brönsted dependences for the reactions of anions generated from arylamines (**3a**—**5a** and **7a**) with *p*-nitrofluorobenzene[12] (line *3*) and hexafluorobenzene[16] (line *4*), and of anions generated from diarylamines (**6a**, **8a**—**13a**) with pentafluoropyridine and hexafluorobenzene (lines *1* and *2*, respectively).[17] It is evident that the reactivities of hexafluorobenzene and pentafluoropyridine are significantly higher in the first and in the second case, respectively, the β_{Nu} coefficient also being significantly increased (see Fig. 2).

Thus, the β_{Nu} coefficient increases with an increase in substrate electrophilicity and with a decrease in steric hindrance in nucleophiles, which can be due to a higher degree of charge transfer from the nucleophile in the transition state of an S_NAr reaction[18] (Scheme 1).

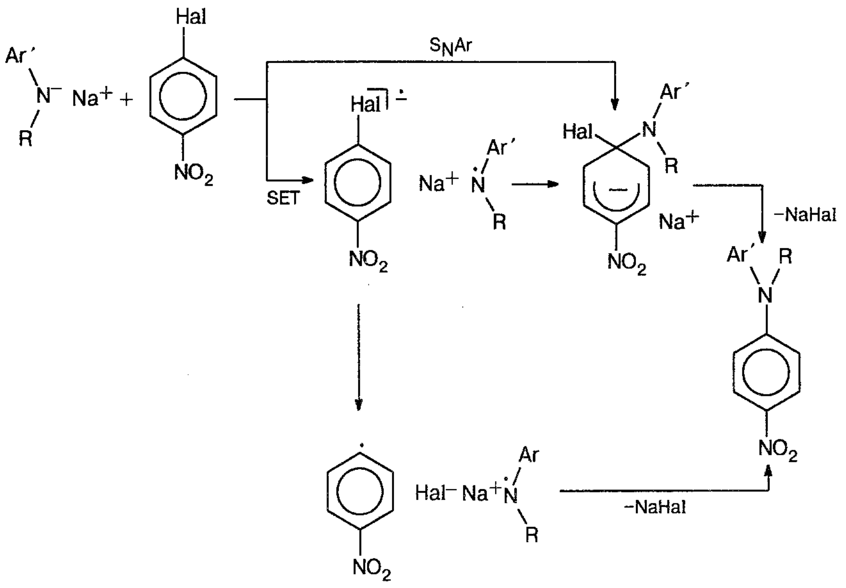
But is electron transfer from an anion to a substrate with the formation of an radical anion possible? Scheme 2 presents the possible pathway for the formation of the final product by the non-chain radical mechanism, assuming that the reactions proceed in a solvent cell.[19,20]

The possibility of this pathway is supported by the

Scheme 1



Scheme 2



fact that the yield of the reaction product, *p*-nitrophenylamine, decreases by ~20 % in the reaction of the most basic anion, diphenylamide anion **1a**, with *p*-nitrofluorobenzene (E_{red} = −1.08 V)[21] in DMSO at 25 °C in the presence of a stronger electron acceptor, *m*-dinitrobenzene (E_{red} = −0.84 V).[21] The reduction potential of *m*-dinitrobenzene in DMSO is more positive, hence it acts as an inhibitor (*cf.* Ref. 19).

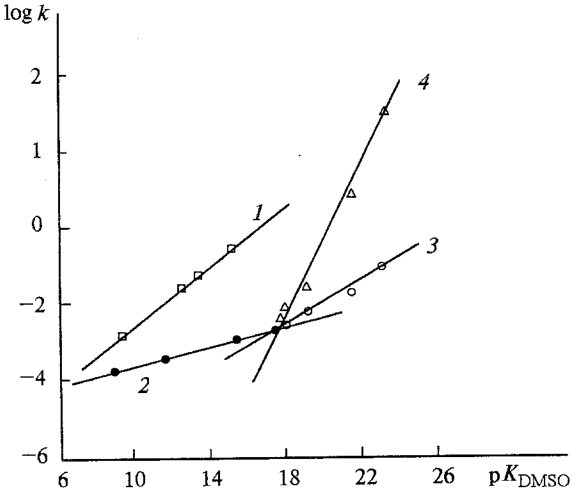
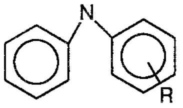
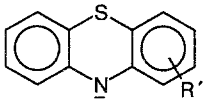


Fig. 2. Brönsted relations for the reactions of anions **9a**, **10a**, **12a**, and **13a** with pentafluoropyridine (*1*, β_{Nu} = 0.47) and hexafluorobenzene (*2*, β_{Nu} = 0.15) and anions **3a—5a** and **7a** with *p*-fluoronitrobenzene (*3*, β_{Nu} = 0.28) and hexafluorobenzene (*4*, β_{Nu} = 0.74) in DMSO at 25 °C.

The reactions of anions studied over a wide range of their basicity (~16 pK units in DMSO) give the β_{Nu} coefficients within the 0.15—0.74 range. These β_{Nu} values correspond to the S_NAr mechanism of reactions between anions and haloarenes, since the reactions proceeding according to the SET mechanism have the β_{Nu} values of ≈ 1.[22] Hence, the higher the value of β_{Nu}, the higher the contribution of the SET process (see Scheme 2).

If this is the case, the rate of nucleophilic substitution should be more sensitive to the oxidation potentials of anions (*cf.* Ref. 23). Table 5 presents the logarithms of the rate constants for the reactions of *p*-nitrofluorobenzene with the anions generated from phenothiazines and diphenylamines as a function of oxidation potentials of these anions. As can be seen from these data, the reaction rate for a series of phenothiazinide ions (for this reaction, the Brönsted coefficient β_{Nu} is 0.51) is more sensitive to the change in oxidation potentials of these anions than in the case of diphenylamide anions (β_{Nu} = 0.24). In addition, the oxidation potentials of pheno-

Table 5. Dependences of the rate constant logarithms $\log k_2 = aE_{ox} + b$ of the reactions of *p*-nitrofluorobenzene with anions generated from diphenylamines[12] and phenothiazines[14] on the oxidation potentials of these anions (E_{ox})[24]

Anion	*a*	*b*	*r*	R	$k_2 \cdot 10^2$/L mol^{-1} s^{-1}	E_{ox}*/V
	−3.4	−0.7	0.988	H	33.0	−0.115
				3-Cl	21.0	0.038
				4-NO_2	0.353	0.490
	−6.8	−1.5	0.952	H	94.1	−0.209
				2-Cl	9.31	−0.035
				3,7-Br_2	4.50	−0.050

Note. The measurements were carried out in DMSO solutions at 25 °C.

* *vs.* the standard hydrogen electrode.

thiazinide ions are more negative (see Table 5) due to higher stability of N-centered radicals.[24]

Thus, the reaction rates of the anions generated from aryl-, diaryl-, and hetarylamines with nitrohalo- and polyhaloarenes are described by the Brönsted equation over a wide range of β_{Nu} coefficients (0.15—0.74). The higher sensitivity of the reaction rate to changes in oxidation potentials of the anions corresponds to a higher value of β_{Nu} coefficient, therefore, at the limiting value of $\beta_{Nu} \approx 1$, one may expect a change from the S_NAr to the SET reaction mechanism.

References

1. M. V. Gorelik and L. S. Efros, *Osnovy khimii i tekhnologii aromaticheskikh soedinenii* [*Fundamentals of Chemistry and Technology of Aromatic Compounds*], Khimiya, Moscow, 1992 (in Russian).
2. R. D. Chambers, D. Close, and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1980, 778.
3. F. Terrier, *Nucleophilic Aromatic Displacement — The Influence of the Nitro Group*, Ed. H. Feuer, VCH Publ., New York, 1991.
4. V. I. Galkin and V. I. Cherkasov, *Reakts. Sposobn. Org. Soedin.* [*Reactivity of Organic Compounds*], 1981, **18**, 111 (in Russian).
5. R. W. Taft and F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 463.
6. I. A. Koppel, R. W. Taft, F. Anvia, S.-Z. Zhu, L.-Q. Hu, K.-S. Sung, D. D. DesMarteau, L. M. Yagupolskii, Y. L. Yagupolskii, N. V. Ignatiev, N. V. Kondratenko, A. Y. Volkonskii, V. M. Vlasov, R. Notario, and P. C. Maria, *J. Am. Chem. Soc.*, 1994, **116**, 3047.
7. F. G. Bordwell and D. Algrim, *J. Am. Chem. Soc.*, 1988, **110**, 2964.
8. V. M. Vlasov, G. G. Yakobson, M. I. Terekhova, E. S. Petrov, and A. I. Shatenstein, *J. Fluor. Chem.*, 1980, **16**, 561.
9. F. G. Bordwell, D. Algrim, and N. R. Vanier, *J. Org. Chem.*, 1977, **42**, 1817.
10. V. M. Vlasov, M. I. Terekhova, E. S. Petrov, A. I. Shatenshtein, and G. G. Yakobson, *Zh. Org. Khim.*, 1981, **17**, 2025 [*J. Org. Chem. USSR*, 1981, **17** (Engl. Transl.)].
11. M. I. Terekhova, E. S. Petrov, S. P. Mesyats, and A. I. Shatenshtein, *Zh. Obshch. Khim.*, 1975, **45**, 1529 [*J. Gen. Chem. USSR*, 1975, **45** (Engl. Transl.)].
12. V. M. Vlasov and I. A. Os'kina, *Zh. Org. Khim.*, 1996 (in press).
13. V. M. Vlasov, I. A. Os'kina, D. Landini, and A. Maia, in *The Proc. of the 1st Russian-Italian Workshop on Progress in Fine Chemistry*, Ed. E. Drioli, C.N.R., Rome, 1992, 167.
14. F. G. Bordwell and D. L. Hughes, *J. Am. Chem. Soc.*, 1986, **108**, 5991.
15. F. G. Bordwell and D. L. Hughes, *J. Am. Chem. Soc.*, 1984, **106**, 3234.
16. I. A. Os'kina and V. M. Vlasov, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim.* [*Bull. Sib. Branch Acad. Sci. USSR, Div. Chem. Sci.*], 1984, **4**, 102 (in Russian).
17. V. M. Vlasov and I. A. Os'kina, in *Abstracts of 12th Conf. on Physical Organic Chemistry*, IUPAC, Padova, 1994, 222.
18. A. Pross, *J. Org. Chem.*, 1984, **49**, 1811; S. Hoz, *Acc. Chem. Res.*, 1993, **26**, 69.
19. X.-M. Zhang, D.-L. Yang, and Y.-C. Liu, *J. Org. Chem.*, 1993, **58**, 224; X.-M. Zhang, D.-L. Yang, X.-Q. Jia, and Y.-C. Liu, *J. Org. Chem.*, 1993, **58**, 7350.
20. R. Bacaloglu, A. Blasko, C. A. Bunton, F. Ortega, and C. Zucco, *J. Am. Chem. Soc.*, 1992, **114**, 7708.
21. H. Shalev and D. H. Evans, *J. Am. Chem. Soc.*, 1989, **111**, 2667.
22. F. G. Bordwell, T. A. Cripe, and D. L. Hughes, in *Nucleophilicity*, Ed. J. M. Harris and S. P. McManus, Adv. Chem. Ser., No. 215, Washington DC, 1987, 137.
23. E. Buncel, S. S. Shaik, Ik.-H. Um, and S. Wolfe, *J. Am. Chem. Soc.*, 1988, **110**, 1275.
24. F. G. Bordwell, X.-M. Zhang, and J.-P. Cheng, *J. Org. Chem.*, 1993, **58**, 6410; F. G. Bordwell and J. A. Harrelson, Jr., *J. Org. Chem.*, 1989, **54**, 4893.

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