Reduction of 20. A solution of 40 mg of **20** in 1 mL of $CDCl_3$ was admixed with 60 mg of triphenylphosphine. ^1H NMR analysis after 1 h showed the presence of **8** (δ 3.67, s) and of formaldehyde (δ 9.75, s) in a molar ratio of 1.25:1.0.

3-Methoxy-3-(1-methoxyethenyl)-1,2-dioxolane (21): colorless liquid; ^1H NMR ($CDCl_3$, TMS) δ 3.27 (s, 3 H), 3.64 (s, 3 H), 4.24 (d, J = 2.77 Hz, 1 H), 4.51 (d, J = 2.79 Hz, 1 H), ABXY system with δ_A 2.78, δ_B 2.79, δ_X 4.15, δ_Y 4.31 and J_{AB} = 6.97, J_{AX} = 7.07, J_{AY} = 6.79, J_{BX} = 7.47, J_{BY} = 7.19, J_{XY} = 6.51 Hz; ^{13}C NMR ($CDCl_3$, TMS, -20 °C) δ 46.71 (t, J = 153.60 Hz), 50.43 (q, J = 143.11 Hz), 55.10 (q, J = 144.21 Hz), 69.80 (ddt, J = 150.37, 147.67, and 2.54 Hz), 84.38 (dd, J = 164.72 and 157.55 Hz), 106.06 (s), 156.32 (s).

Reduction of 21. When a solution of 260 mg of **21** in 10 mL of $CDCl_3$ was admixed with a solution of 432 mg of triphenylphosphine in 30 mL of $CDCl_3$, a vigorous reaction occurred, as evidenced by heating of the sample. ^1H NMR analysis after 1 day showed that **21** had completely disappeared and that methanol and **24** had been formed. The mixture was concentrated in vacuo at room temperature, and the residue was separated (15 g of silica gel; pentane/diethyl ether, 2.3:1) to give 118 mg (56%) of **24**.

2-Methoxy-3-oxo-5-hydroxy-1-pentene (24): colorless liquid; ^1H NMR ($CDCl_3$, TMS) δ 2.94 (t, J = 5.48 Hz, 2 H), 3.66 (s, 3 H), 3.90 (t, J = 5.45 Hz, 2 H), 4.53 (d, J = 2.83 Hz, 1 H), 5.25 (d, J = 2.83 Hz, 1 H); ^{13}C NMR ($CDCl_3$, TMS) δ 40.26 (t, J = 126.52 Hz), 56.43 (q, J = 144.68 Hz), 57.75 (tt, J = 144.16 and 3.78 Hz), 91.29 (dd, J = 164.21 and 160.02 Hz), 158.32 (s), 197.78 (s); IR (film) 3400 (broad; OH), 1720 (C=O) cm^{-1}; El-MS m/z (%) 130 (8) $[M]^+$, 86 (87) $[M - CH_3CH{=}O]^+$, 73 (43) $[COCH_2CH_2OH]^+$, 57 (100) $[CH_2{=}COCH_3]^+$, 44 (3) $[CH_3CH{=}O]^+$, 43 (85) $[CH_3CO]^+$.

Ozonolysis of 25 on Polyethylene. When 451 mg (5.13 mmol) of **25** on 40 g of polyethylene was ozonized for 3 h, one obtained 378 mg of a liquid residue. ^1H NMR analysis showed the presence of *cis*-**27** (13%; δ 5.93, s),[5] *trans*-**27** (15%; δ 6.08, s),[5] *cis*-**28** (20%), and *trans*-**28** (31%). Separation of the residue (20 g of silica gel; pentane/diethyl ether, 17:1) gave 85 mg (8%) of *trans*-**27** (^1H NMR δ 3.65, s, and 6.08, s; mp 64-65 °C; lit.[5] mp 66 °C), 79 mg (8%) of *cis*-**28**, and 128 mg (13%) of trans-**28**.

***cis*-3,5-Dimethoxy-1,2,4-trioxolane (*cis*-28):** colorless liquid; ^1H NMR ($CDCl_3$, TMS) δ 3.52 (s, 6 H), 6.01 (s, 2 H); ^{13}C NMR ($CDCl_3$, TMS, -20 °C) δ 52.01 (qd, J = 143.17 and 2.64 Hz), 114.73 (ddq, J = 203.89, 5.03, and 3.15 Hz).

***trans*-3,5-Dimethoxy-1,2,4-trioxolane (*trans*-28):** colorless solid; mp 39-41 °C; ^1H NMR ($CDCl_3$, TMS) δ 3.41 (s, 6 H), 6.16 (s, 2 H); ^1H NMR ($CDCl_3$, TMS, -20 °C) δ 51.79 (qd, J = 143.17 and 2.64 Hz), 112.76 (ddq, J = 198.86, 5.03, and 3.78 Hz).

Reduction of 28. A solution of *cis*- and *trans*-**28** in $CDCl_3$ was admixed with a solution of triphenylphosphine in $CDCl_3$ and kept at room temperature for 2 days. ^1H NMR analysis showed the signals of methyl formate at δ 3.77 (d, J = 0.8 Hz) and δ 8.06 (q, J = 0.8 Hz).

Ozonolysis of 30 on Polyethylene. Compound **30** (972 mg, 11.3 mmol) (prepared by elimination of methanol from 1,1-dimethoxy-2-methylpropane;[18] δ 1.54, 1.60, 3.53, 5.74) on 80 g of polyethylene was ozonized for 4 h. Then, the mixture was evacuated at room temperature and 10^{-2} Torr, and the products were collected in two consecutive cold traps kept at -30 °C (trap 1) and at -78 °C (trap 2), respectively. ^1H NMR analysis showed that the product of trap 1 (130 mg of colorless liquid) contained 53% of **29** (δ 1.65, s), 11% of **33a** (δ 1.35, s and 1.80, s), and 4% of **33b** (δ 1.46, s), along with methyl formate and acetone; the product of trap 2 (737 mg, colorless liquid) contained 20% of **32** (δ 1.47, s),[6] along with methyl formate, acetone, and unreacted **30**. Separation of the product from trap 1 (15 g of silica gel; pentane/diethyl ether, 30:1) gave 14 mg (ca. 1%) of **29** and 10 mg (0.6%) of **33a**.

3-Methoxy-5,5-dimethyl-1,2,4-trioxolane (29): colorless liquid; ^1H NMR ($CDCl_3$, TMS) δ 1.49 (s, 3 H), 1.65 (s, 3 H), 3.45 (s, 3 H), 5.97 (s, 1 H); ^{13}C NMR ($CDCl_3$, TMS, -20 °C) δ 21.7, 24.4, 52.1, 109.9, 112.8. The data are consistent with those reported.[5]

Ozonolysis of 34 on Polyethylene. Compound **34** (870 mg, 8.4 mmol) on 73 g of polyethylene was ozonized for 7 h. Then, the mixture was evacuated at room temperature and 10^{-2} Torr, and the products were collected in two consecutive cold traps kept at -40 °C (trap 1) and at -75 °C (trap 2), respectively. ^1H NMR analysis showed that the product of trap 1 (230 mg, colorless liquid) contained 58% of **32** (δ 1.47, s),[6] along with acetone and methyl acetate, and the product of trap 2 (413 mg, colorless liquid) contained acetone and methyl acetate. Separation of the product from trap 1 by PGC (glass column, 0.7 × 540 cm, 5% methylsilicone OV 101 on Chromosorb G; 80 °C) gave 103 mg (9%) of ozonide **32**. It was identified on the basis of the identity of its ^1H and ^{13}C NMR and its MS data with those reported.[6]

After evacuation was completed, the residual polyethylene was extracted with ether, the extract was concentrated, and from the residue 15 mg (0.8%) of **33b** was isolated by column chromatography (60 g of silica gel; pentane/diethyl ether, 10:1).

Ozonolysis of 34 in Pentane. A solution of 430 mg (4.2 mmol) of **34** in 30 mL of pentane was ozonized to completion at -75 °C. ^1H NMR analysis of the concentrated crude product showed the presence of acetone (18%), methyl acetate (60%), and **33b** (22%), to the exclusion of the expected ozonide **35a**.

Supplementary Material Available: 250-MHz ^1H NMR spectra of compounds **6**, **7**, **11**, **12**, **18**, **20**, **21**, **24**, *cis*-**28**, *trans*-**28**, and **29** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(18) Howard, W. L.; Jacobsen, E. C.; Newton, R. A. *J. Org. Chem.* 1961, *26*, 3574.

Ambident Behavior of Ketone Enolate Anions in S_NAr Substitutions on Fluorobenzonitrile Substrates

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2,6-Difluorobenzonitrile was found to be a suitable substrate for studying carbon versus oxygen nucleophilic attack by enolate anions of weakly acidic ketones. The influence of the nucleophile structure and the solvent are investigated. The charge control character of the reaction and the influence of the substrate are discussed.

In the course of studies in the field of aromatic nucleophilic substitution reactions with ketone enolate anions,[1] we had occasion to carry out an S_NAr reaction[2] between 2,6-difluorobenzonitrile (**1a**) and the anion derived

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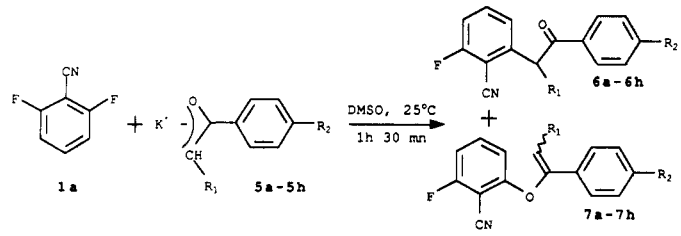
Table I. S_NAr Reactions of Para- (5a,b,d,e,i) and α- (5f–h,j) Substituted Acetophenones with 2,6-Difluorobenzonitrile



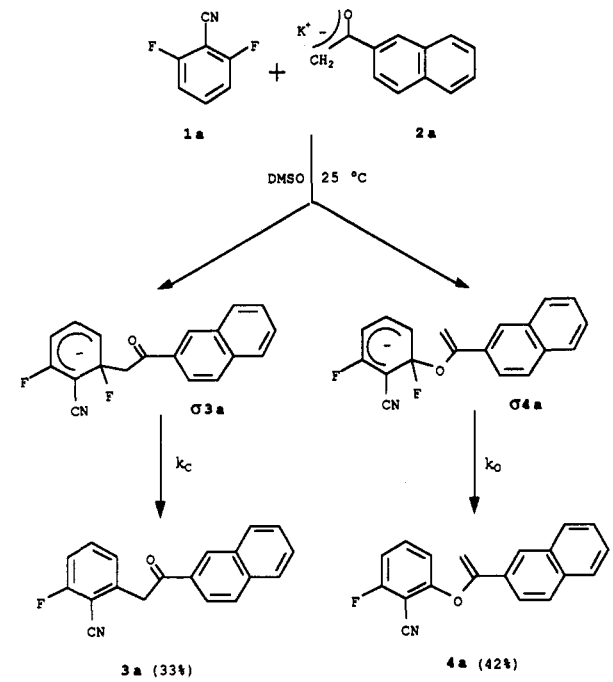
entry	Nu	R_1	R_2	l_O[a]	l_C[a]	P[b]	Y_O[c]	Y_C[c]	S[d]	log S
1	**5a**	H	Br	−0.575	−0.488	1.178	31	31	1	0
2	**5b**	H	F	−0.576	−0.490	1.175	44	53	0.83	−0.079
3	**5c**	H	H	−0.579	−0.494	1.173	41	41	1	0
4	**5d**	H	OMe	−0.575	−0.493	1.167	25	39	0.65	−0.187
5	**5e**	H	O^-	−0.626	−0.541	1.157	7	19	0.37	−0.434
6	**5f**	Me	H	−0.550	−0.550	1.000	30	14	1.34[f]	0.382
7	**5g**		[e]	−0.556	−0.519	1.072	55	20	2.75	0.439
8	**5h**	Ph	H	−0.462	−0.435	1.062	28	3	8.5	0.938
9	**5i**	H	NH_2	−0.577	−0.495	1.165	0	0		
10	**5j**		[g]	−0.531	−0.594	0.894	90	7.5	12	1.08

[a] l_O and l_C are the partial charges on the oxygen and carbon sites of the nucleophile, calculated by semiempirical methods (cf. Experimental Section). [b] $P = l_O/l_C$ is the polarity index. [c] Y_O and Y_C are, respectively, the yields of O-aryl (**7**) and C-aryl (**6**), calculated as a mean value from three ^1H NMR measurements (cf. Experimental Section). [d] $S = Y_O/Y_C$. [e] **5g** is 6-methoxytetralone. [f] $S < Y_O/Y_C$ is due to di-C-arylated product **9** formation, see ref 14. [g] **5j** is isobutyrophenone.

from 2-acetonaphthone (**2a**) in DMSO at 25 °C (Scheme I). Together with the expected C-arylated product **3a** (33%), we isolated the O-arylated product **4a** (42%). This result was unexpected and surprising in that ketone enolate anions were reported to give C-arylated product by S_NAr mechanism.[3] In contrast to the well-documented ambident behavior of these nucleophiles in alkylation reactions,[4] there was in the literature only one study by Kurts and co-workers dealing with C- versus O-arylation of ketone enolates. The authors reported[5a] the O-arylation of ethyl acetoacetate anion and studied the influence of different factors[5b–f] with the same nucleophile. They finally used other enolate anions all derived from highly acidic ketones[6] (pK_A ranging from 7 to 13) known to be readily O-arylated.[7]

The ambident behavior of enolate anions derived from weakly acidic ketones, such as **2a** (pK_A slightly lower than that of acetophenone: 19.1[8]) is not frequently documented,[9] due to the scarcity of aromatic substrates with a marked affinity for the oxygen site of ketone enolate anions.[10] Thus, our fortuitous observation of the formation of **4a** prompted us to initiate the investigations reported here.

Scheme I. σ Complex Intermediates and Products from S_NAr Reaction of Acetonaphthone Enolate Anion with 2,6-Difluorobenzonitrile



Results and Discussion

In our efforts to elucidate factors which govern the competition between C- and O-arylation of the strongly basic enolate anions, we have considered the effects of

(1) Beugelmans, R.; Bois-Choussy, M. *J. Org. Chem.* **1991**, *56*, 2518.

(2) For recent book and review on S_NAr reactions, see: (a) Terrier, F. In *Nucleophilic Aromatic Displacement: The role of the nitro group*; VCH: New York, 1991; Chapter 1. (b) Paradisi, C. Arene Substitution via Nucleophilic Addition to Electron Deficient Arenes. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 4, pp 423–450.

(3) (a) Masatamo, H.; Genji, H.; Seitaro, S. *Chem. Lett.* **1986**, 173. (b) *Ibid.* **1986**, 31. (c) Hitomi, S.; Tsutomu, K.; Yoshiki, Y. *Ibid.* **1983**, 193. (d) Saburo, S.; Hiroshi, I.; Tokuji, O.; Sanya, A.; Shiro, I. *Ibid.* **1982**, 597.

(4) (a) Zook, H. D.; Miller, J. A. *J. Org. Chem.* **1971**, *36*, 1112. (b) Zook, H. D.; Russo, T. J.; Ferrand, E.; Slotz, D. S. *J. Org. Chem.* **1968**, *33*, 2222. (c) Heiszwolf, G. J.; Kloosterziel, H. *Rec. Trav. Chim. Pays-Bas* **1970**, *89*, 1153.

(5) (a) Kurts, A. L.; Kogan, G. O.; Bundel, Y. G. *Vestn. Mosk. Univ., Ser. 2: Khim.* **1981**, *22*, 86; *Chem. Abstr.* **1981**, *95*, 6042y. (b) *Ibid.* **1981**, *22*, 187; *Chem. Abstr. 95*, 60925b. (c) Kurts, A. L.; Davydov, D. V.; Bundel, Y. G. *Ibid.* **1982**, *23*, 483; *Chem. Abstr.* **1983**, *98*, 53328t. (d) *Ibid.* **1983**, *24*, 73; *Chem. Abstr.* m1983, *98*, 197719u. (e) *Ibid.* **1983**, *24*, 385; *Chem. Abstr.* **1983**, *99*, 174995y. (f) *Ibid.* **1984**, *25*, 68; *Chem. Abstr.* **1984**, *100*, 209307h.

(6) Davydov, D. V.; Kurts, A. L.; Bundel, Y. G. *Vestn. Mosk. Univ., Ser. 2: Khim.* **1984**, *25*, 292; *Chem. Abstr.* **1984**, *101*, 170329k.

(7) Previous reports on O-arylation of highly acidic ketones: (a) Beringer, F. M.; Forgione, P. S.; Yudis, M. D. *Tetrahedron* **1960**, *8*, 49. (b) Zacharova, O. V.; Blasov, V. M.; Jacobson, C. G. *Isv. Ann. SSSR, Ser. Khim.* **1974**, *7*, 1670. (c) Jawdosiuk, M.; Kmiotek-Starzynska, I. *Polish. J. Chem.* **1979**, *53*, 2259.

(8) Zook, H. D.; Kelly, W. L.; Posey, I. Y. *J. Org. Chem.* **1968**, *33*, 3477.

(9) A study on ambident behavior of weakly acidic ketone in S_NAr *gas-phase* reactions was recently published: Frericks, I. L.; Koning, L. J.; Nibbering, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 9119.

(10) In a recent review (Buncel, E.; Dust, J. M.; Park, K. T.; Renfow, R. A.; Strauss, M. J. Reactions of ambident nucleophiles with nitroaromatics electrophiles and superelectrophiles. *Nucleophilicity*; American Chemical Society: Washington, DC, 1987; pp 369–382), the authors outlined the fact that the carbon site of enolate anions has a much greater basicity than the oxygen site toward activated aromatics (such as dinitro or trinitro benzenes).

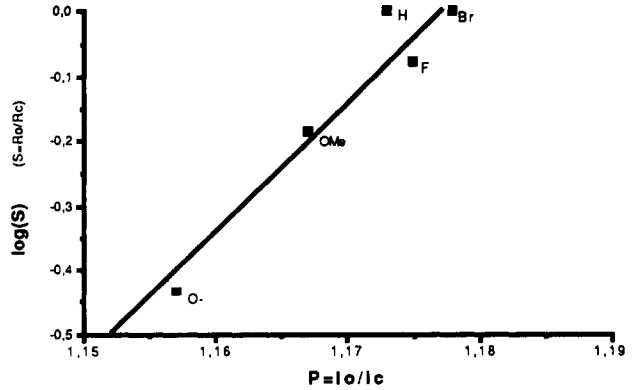
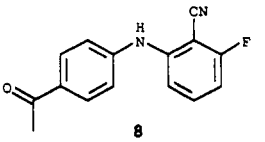


Figure 1. Plot of the selectivity index log S versus the polarity index P for para-substituted acetophenones.

enolate structure, solvent, and substrate structure.

a. Influence of the Enolate Structure. Electronic Effects. The formation of the less thermodynamically stable compound **4a** in DMSO suggests a kinetic control[11] as is the case of reactions of enolate anions with activated alkyl substrates in aprotic dipolar solvents.[4c,12] To confirm this hypothesis and to evaluate the charge-controlled character of the reaction, we have studied the behavior of a series of para-substituted acetophenones (Table I, entries 1–5) where R_2 exerts solely electronic effects. The data collected in Table I show that there is no obvious correlation between the yields of O-arylated products **7a–e** (Y_O) or C-arylated products **6a–e** (Y_C) with the partial charges[13] of the corresponding site (l_O or l_C). However, the allopolarization concept proposed by Gompper[12] predicts that the orientation of attack of the enolate anion is better described by the so-called polarity index $P = l_O/l_C$. P was proposed as a measure of the charge control character of the reaction and so, high values of P favor the nucleophile attack by the site which carries the greater charge (in this case the oxygen). The plot of log S ($S = Y_O/Y_C$) versus P in Figure 1 shows that this is the case for C/O competition in arylation of enolates: Δ log S is roughly proportional to ΔP (the correlation coefficient is 0.93). Assuming that the kinetics of the reaction is second order (in both O-attack (k_O) and C-attack (k_C)) and that Y_C and Y_O are the final yields (no evolution of the reaction was observed after 30 min), one can easily demonstrate that $Y_O/Y_C = k_O/k_C$. Thus, the proportionality between log S (= log (k_O/k_C)) and P implies a direct relationship between the difference in activation energies of C- and O-attack and the polarity index, and hence provides strong evidence that the reaction is charge controlled.

In the case of *p*-aminoacetophenone (**5i**) (entry 9) neither C- nor O-attack was detected and the only product formed was **8** (50%) resulting from N-arylation by the amino group.



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Steric Effects. In contrast to the above results, no correlation could be established between log S and P for ketone enolates where $R_1 \neq H$ (Table I, entries 6–8, 10). Compound **5f** (R_1 = Me, entry 6), for instance, has a much smaller P value (1.000) than **5c** (entry 3, P = 1.173), but the O-arylated product **7f** is predominant (S = 1.34,[14] compared with S = 1 for **5c**). This result suggests that the orientation of attack is also controlled by steric interactions. The methyl substituent in **5f** increases steric hindrance at the carbon site, favoring thus the attack on the more accessible oxygen site (Y_O = 30%). The predominance of steric over electronic effects is confirmed by assays on **5g** and **5h** (entries 7 and 8) where a marked increase of $S = Y_O/Y_C$ with the size of R_1 (H < Me < $-(CH_2)_2-$ < Φ) was observed, consistent with Zook's results[4b] in the alkylation of α-acetophenones. Entry 10 shows the dramatic effect of steric hindrance when the carbon nucleophilic site is disubstituted. In spite of the small size of the two substituents (methyl groups) on isobutyrophenone (**5j**), the O-arylated product **7j** is largely predominant (S = 12). Note also that deoxybenzoin (**5h**) gives a particularly large S value (entry 8). This high selectivity (R_C = 3%) can hardly be explained solely by steric interactions and probably arises from the high acidity of this ketone (pK_A of **5h** is 16.1[8]).

b. Influence of the Solvent. We focused our study on the influence of solvent polarity.[15] In a model reaction between acetophenone and **1a** (Table II), the highest yield of O-arylation (Y_O = 41%) was obtained from the most

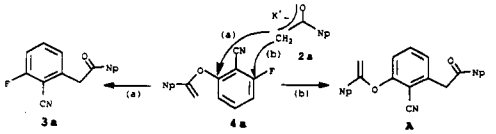
Table II. S_NAr Reactions of Acetophenone with 2,6-Difluorobenzonitrile in Various Solvents

1a + **5c** $\xrightarrow{\text{solvent}}$ **6c** (C-aryl) + **7c** (O-aryl)

entry	solvent	$E_T^N(30)^a$	$Y_O{}^b$	$Y_C{}^b$	Y^c	S^d
1	Et_2O	0.117	1	4.5	5.5	0.22
2	THF	0.207	9	29	38	0.31
3	HMPT	0.315	36	40	76	0.89
4	DMSO	0.444	41	41	82	1

[a] Normalized E_T^N-values, taken from ref 16, p 408. [b] Y_O and Y_C are, respectively, the yields of O-aryl (**7c**) and C-aryl (**6c**), calculated as a mean value from three ^1H NMR records of the mixture (cf. Experimental Section). [c] $Y = Y_O + Y_C$ is the overall yield of the S_NAr reaction. [d] $S = Y_O/Y_C$.

(11) A reviewer pointed out the problem of O/C-arylated products interconversion. The only possibility for such a process is the C attack of the enolate **2a** on the O-arylated product **4a** following path a below (where Np is 2-naphthyl):

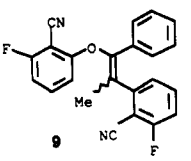


We can reasonably rule out the possibility of thermodynamic control by considering that (i) attack on fluorinated sites is much faster than on oxygenated sites in S_NAr reactions (refs 2a and 20) which means that path b on the above scheme is preferred, and (ii) the diadduct product **A** was never observed in our reactions.

(12) Gompper, R.; Wagner, H. U. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 321.

(13) Calculations were made by InsightII and MOPAC programs; see Experimental Section for more details.

(14) Together with the expected C- and O-arylated products (**6f** and **7f**), we isolated, in 10% yield, the di-C/O-arylated product **9** resulting from the O-attack of **6f** on the substrate **1a**. Therefore, the total yield of C-attack on **1a** becomes 14 + 10 = 24%, and hence S = Yo/24 = 30/24 = 1.34.



9

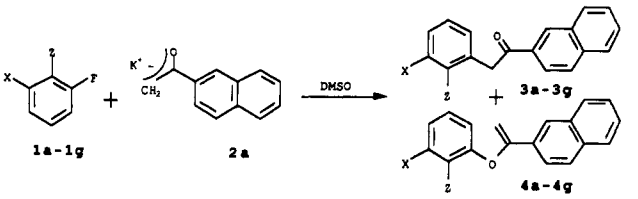
(15) The hydrogen-bonding ability of the solvent is known to have some influence on the course of ambident enolate reactions (Kurts, A. L.; Dem'yanov, P. I.; Macias, A.; Beletskaya, I. P.; Reutov, O. A. *Tetrahedron Lett.* **1968**, 3679). We looked at this point by adding up to 5 equiv of water in DMSO and observed no significant change in the C/O ratio. This result is consistent with Heiszwolf findings (ref 4c) and is believed to be linked to the good ability of DMSO as hydrogen-bond acceptor.

polar solvent (entry 4, DMSO), and the selectivity index (log S) correlated well with the normalized solvent parameter values E^{T}_{N}.[16] This result is consistent with previous findings in C/O competitive alkylation of enolates[4c,12] revealing that dipolar aprotic solvents favor attack at the center of greater charge density (i.e., the oxygen). This phenomenon is believed to be directly linked to the capacity of the solvent to solvate the enolate counterion,[17] which is preferentially coordinated with the oxygen (i.e., "the freer the oxygen, the larger the O/C ratio"[18]). However, it is noteworthy that the two-step S_NAr reactions behave similarly to the single-step alkylation reactions: the C/O competition could only occur in the first step of the S_NAr mechanism, and consequently, the observed influence of the polarity on the O/C ratio suggests that the addition step of the mechanism is rate determining, as is generally found to be the case in S_NAr reactions. As expected, the overall reactivity decreases with the polarity of the solvent: Y dropped from 82% for DMSO (entry 4) to 5.5% for diethyl ether[19] (entry 1).

c. Influence of the Substrate Structure. A rationalization of O-arylation of ketone enolate anions **2a** and **5a–j** by substrate **1a** can be made based upon Miller's[20] prediction (confirmed latter by theorical calculations[21]) that electron-withdrawing groups at the ipso position stabilize σ complexes. Accordingly, σ**4a** (Scheme I) which has an oxygen atom on the tetrahedral carbon is more stable than σ**3a** which has a carbon substituent at the ipso position. The symbiosis effect[22] could also be considered: for a given molecular frame, geminal groups of similar nature (in the HSAB meaning) exert a stabilizing effect on the whole structure. The σ complex intermediate σ**4a**, originating from O-attack of the enolate, has fluorine and oxygen atoms (both hard bases) on the same tetrahedral carbon, while the σ complex σ**3a** from the C-attack has geminal hard and soft atoms. The transition state corresponding to σ**4a** is thus assumed to have a smaller free energy of activation than that corresponding to σ**3a** and consequently O-attack will be faster than C attack ($k_O \gg k_C$). However, the formation of O-arylated products could not be accounted for solely by the nature of the leaving group and the whole structure of the substrate must be considered. For this purpose, we investigated (1) the influence of the meta substituent X and (2) the effect of the Z activating group (Table III).

(1) In model reactions with the acetonaphthone enolate

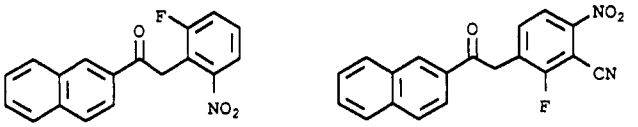
Table III. S_NAr Reactions of Acetonaphthone with Substrates 1a–g



entry	substrate	X	Z	δ^a	$Y_O{}^b$	$Y_C{}^b$	S^c
1	**1a**	F	CN	0.218	42	33	1.27
2	**1b**	OMe	CN	0.206	4	36	0.11
3	**1c**	H	CN	0.194	5	30	0.17
4	**1d**	NMe_2	CN	0.189	0	23	0
5	**1e**	NO_2	CN	0.179	0	0	X
6	**1f**	F	NO_2	0.239	6	21	0.14[d]
7	**1g**	H	NO_2	0.232	5	33	0.14

[a] Partial charge of the fluorinated site on the substrate, calculated by semiempirical methods (cf. Experimental Section). [b] Y_O and Y_C are, respectively, the yields of O-aryl and C-aryl products, calculated as a mean value from three ^1H NMR records of the mixture (cf. Experimental Section). [c] $S = Y_O/Y_C$. [d] $Y > Y_O + Y_C$ and $S < Y_O/Y_C$ are due to side reactions (see text).

we observed that Y_O decreases dramatically when the meta substituent X is OMe, H, or NMe_2, while Y_C remains nearly constant (Table III, entries 1–4). The changes in S correlate quite well with the partial charge[13] (δ) of the fluorinated reaction site: O-attack of the enolate anion is thus favored with highly polarized substrates. This result is consistent with HSAB considerations and confirms also the hypothesis of a charge-controlled reaction. The nitro derivative **1e** (entry 5) undergoes neither O- nor C-attack of the enolate anion on the fluorinated site. The main products, **10** (3%) and **11** (18%), result, respectively, from CN^- and hydride displacement[23] by the carbon site of the enolate. A contribution of several effects might explain



10 **11**

this preferential attack: (i) Attack on activated unsubstituted positions is known from kinetic measurements[24] to be faster than ipso attack, and the intermediates were successfully trapped for synthetic purposes.[25] (ii) The fluorinated site of **1e** is weakly activated compared to **1a** (as shown by $\delta_{(1e)} = 0.179$), while the CN site, which is ortho to the nitro group, becomes reasonably polarized (partial charge for CN site is 0.050 for **1e** and −0.061 for **1a**). (iii) The electronic cloud in the vicinity of the leaving group favors H and CN displacement over attack at the fluorinated site.

(2) The CN substituent—considered to be a moderate to good activating group[26]—was replaced by NO_2, a

(16) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; reviewed and enlarged edition; Weinheim: Basel (Schweiz), Cambridge, New York, 1988.

(17) Reviews including several references on solvent effects: (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (b) Shevelev, S. A. *Russ. Chem. Rev.* **1970**, *39*, 844.

(18) Le Noble, W. J.; Morris, H. F. *J. Org. Chem.* **1969**, *34*, 1969.

(19) As suggested by a reviewer, the heterogeneous conditions in the case of diethyl ether and THF (see Experimental Section) undoubtly play a crucial role in the reactivity and in the O/C arylation ratio of the enolate anion. Thus, Kornblum et al. (Kornblum, N.; Lurie, A. P. *J. Am. Chem. Soc.* **1959**, *81*, 2705) have clearly shown that the C-alkylation of potassium phenoxide salts is related to the heterogeneity of the reaction, while the O-alkylation is a result of homogeneous conditions. In our case, the small O/C ratios found with these two solvents (entries 1 and 2) are certainly the combined result of low polarity and heterogeneity. These reactions could be homogenized by using appropriate cation complexing agents. However, Kurts et al. (ref 5b) have shown that their addition strongly influences the ambident behavior of the acetoacetate anion in S_NAr reactions. Therefore, the use of such agents does not seem to be suitable for our studies on solvent polarity.

(20) Miller, J. *Aromatic nucleophilic substitutions*; Elsevier: New York, 1968.

(21) Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 6430.

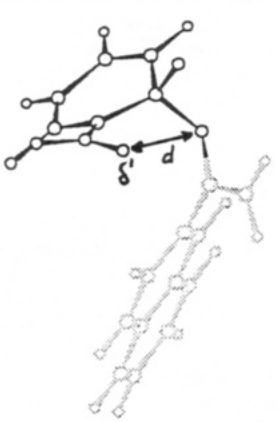
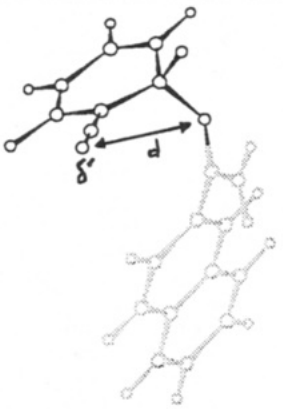
(22) This principle has been successfully used for the understanding of the C/O competition in alkylation of enolate anions: Pearson, R. G.; Songstad, J. *J. Org. Chem.* **1967**, *32*, 2899.

(23) A similar hydride displacement by enolate anions derived from weakly acidic ketones has been observed in *p*-chloronitrobenzenes. A decrease in the "H displacement product" yield was noted under inert atmosphere together with an increase under oxygen stream. These results suggests an oxidation process in the second step of the reaction mechanism (decomposition of the σ complex), which constitutes a fundamental difference with the S_NAr mechanism. Masatamo, H.; Genji, H.; Seitaro, S. *Heterocycles* **1982**, *17*, 177. Aromatic hydride displacements of this kind were recently described in ref 2b.

(24) Terrier, F. *Chem. Rev.* **1982**, *82*, 77.

(25) (a) Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282. (b) Rajanbabu, T. V.; Chenard, B. L.; Petti, M. A. *J. Org. Chem.* **1986**, *51*, 1704. (c) Rajanbabu, T. V.; Reddy, G. S.; Fukunaga, T. *J. Am. Chem. Soc.* **1985**, *107*, 5473.

Table IV. Minimized Structures[a] of Substrates 1a and 1f and Their Corresponding σ Complexes[b] σ4a and σ4f Originating from O-attack of Acetonaphthone Enolate

	σ4f	σ4a	1a	1f
				
d (Å)	3,39	4,21	3,55	3,17
δ'	-0,442	-0,253	-0,048	-0,309
θ(c)	25	X	X	101

[a] By the Mopac program, see Experimental Section. [b] For the sake of clarity, the naphthylethylene residue of σ4a and σ4f was drawn in shadowed lines. [c] Angle between the plane of the nitro group and the phenyl ring in deg.

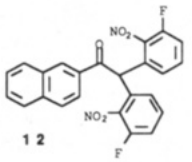
stronger and more commonly used electron-withdrawing group in S_NAr studies.[2a] Thus, the derivative **1f** was reacted with acetonaphthone enolate anion **2a** (Table III, entry 6). As shown by the δ values, replacement of CN by NO_2 increases the polarity of the reaction site by approximately 10%. Entries 1–5 show that a slight change in polarity (δ decreased by 5-, 11-, and 13%, respectively, for **1b**, **1c**, and **1d**) has a considerable influence on the C/O product distribution. Therefore, a *S* value greater than that obtained with **1a** (1.27) was expected for **1f**. However, Y_O dropped to 6%, while the overall yield of C-attack[27] on **1f** reached 42%, giving a particularly low value of *S* (0.14).

This unexpected oxygen reactivity could be rationalized by stereoelectronic considerations. The minimized[13] structure of **1f** shows that the plane of the nitro moiety has an angle of ca. 80° with the phenyl ring and attributes a partial charge of −0.309 on each oxygen (Table IV). Thus, the site of attack on **1f** lies in highly negatively charged surroundings[28] due to the proximity of the two oxygens (ca. 3.17 Å). Therefore, the attack by the more charged site of the enolate anion (oxygen) on the substrate **1f** would be hindered by electrostatic repulsion with the neighboring oxygen atoms of the nitro groups.[29] On the other hand, the nitrogen atom of the CN group of **1a** is poorly charged (−0.048) and quite far away (3.55 Å) from the reaction site. This explains the dramatic decrease of Y_O (from 42% of **4a** to 6% of **4f**). These considerations, which take starting reactants into account, are supported by molecular modeling studies[13] of the σ complexes which originate from the O-attack of **1a** and **1f** (respectively, **σ4a** and **σ4f**, Table IV) which indeed provides a more accurate description of the reaction transition state. Negative charges developed on the oxygen atoms of the nitro group of **σ4f** (respectively, −0.437 and −0.442) remain greater than the partial charge on the cyano nitrogen atom of **σ4a** (−0.253). Hence, we can postulate that, in the transition state of σ complex formation, the nitro moiety is more charged compared with the cyano group. Thus, the transition state corresponding to the oxygen site approach on **1f** will be higher in energy than that resulting from O-attack on **1a**.

The relative affinities of **1a** and **1f** toward the oxygen site of the enolate anion could also be described by considering the London attractive forces between the ortho substituent (CN or NO_2) on the aromatic substrates and the incoming sites of enolate anion. Such interactions were supposed to be rate controlling in some particular S_NAr reactions[30] (the so-called ortho effect). The carbon atom of the enolate, being the softer, is more polarizable than the oxygen atom. On the other hand, the NO_2 moiety is considered, in general,[31] to be more polarizable than the CN group. This was confirmed in our case by calculating the changes of the global charges of these groups during the addition step of the S_NAr mechanism.[32] Therefore,

(26) Miller, J.; Parker, A. J. *Aust. J. Chem.* **1958**, *11*, 302.

(27) Together with the expected C- and O-arylated products, we isolated in 21% yield, the di-C-aryl product (11) resulting from the C-attack of **3f** on the substrate **1f**. Therefore, the total yield of C-attack on **1f** becomes 21+21 = 42%.



12

(28) This observation is consistent with *ab initio* calculations on nitrobenzene which indicated that rotation of the nitro group by 90° from the planar form resulted in a decrease of the electrostatic potential at the sides of the ring, especially at positions ortho to the nitro group: Politzer, P.; Lane, P.; Jayasuriya, K.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1987**, *109*, 1899.

(29) The importance of the repulsion between the negative charge on the nucleophile and the electronic cloud of the substrate framework in the vicinity of the reaction site was outlined in a quantitative treatment of S_NAr reactions: Bartoli, G.; Todesco, P. E. *Acc. Chem. Res.* **1977**, *10*, 125.

(30) Bunnett, J. F. *J. Am. Chem. Soc.* **1957**, *79*, 5969.

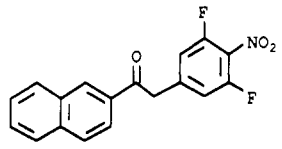
(31) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.

(32) The polarizability of a Z substituent within a given frame is directly linked with its ability to accommodate charge changes of this frame. In our case, the formation of σ complexes is accompanied by an increase in the charge density on the aromatic substrate. We used the MOPAC program to calculate the changes in $\delta_{NO_2} = \delta_N + \delta_{O_1} + \delta_{O_2}$ and $\delta_{CN} = \delta_C + \delta_N$ from aromatic substrates **1a** and **1f** (respectively, $\delta_{CN} = -0.100$ and $\delta_{NO_2} = -0.121$) to the corresponding σ complexes **σ4a** and **σ4f** ($\delta_{CN} = -0.203$ and $\delta_{NO_2} = -0.330$). Therefore, the amount of charge accommodation is −0.209 for NO_2 and only −0.103 for CN. These calculations are not dependent on the nature of the nucleophilic site of the enolate anion (e.g., the global charges of the CN and NO_2 groups in **σ3a** and **σ3f** are virtually the same as in **σ4a** and **σ4f**).

the most stabilizing effect of London forces is found when the carbon site of enolate anion interacts with the *o*-NO_2 substituent of substrate **1f**. These considerations could thus explain the low affinity of **1f** (and, more generally, *o*-nitro-substituted substrates) for the oxygen site of enolate anions.

2-Fluoronitrobenzene (**1g**) (entry 7, Table III), like **1f**, has a much more polar reaction site than **1a** but the enolate attack is still selectively directed toward the carbon site (S = 0.14). This result confirms that introduction of the nitro group on the ortho position of the reaction site increases its polarity but hinders, to a large extent, the attack of the oxygen site of the nucleophile.

We can finally note the formation of compound **13** (7%) resulting from enolate attack at the para position of the nitro in **1f**.[23] For **1g**, where two positions (ortho and para



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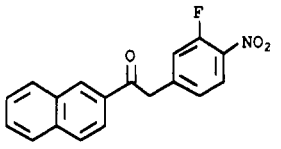
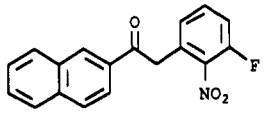


14



3f

to the NO_2 group) are available for hydride displacement,[23] compound **14** (13%) was isolated (attack on the ortho position would lead to **3f** whose spectroscopic data are different from those of **14**, see Experimental Section).

Conclusion. This study is the first one to show that enolate anions from weakly acidic ketones behave as ambident nucleophiles in S_NAr reactions and similarly to alkylation reactions in regard to solvent effects and electronic and steric features of the nucleophile. A first approach to understanding the influence of substrate structure, a key problem, is proposed. The nitro moiety appears to be prejudicial to the approach of the oxygen site of enolate anions and to decrease regioselectivity on the substrate by allowing hydride displacement. The main advantages of the nitrile as activating group for oxygen attack of enolates seem to be linearity and low polarity. Further investigations on C- versus O-arylation competition of ketone enolates could be based upon these observations.

Experimental Section

Computer Calculations. The recent version (2.0.0, June 1991) of InsightII was used on a Silicon Graphics workstation for the molecular modeling of structures. Minimization of the latter and calculation of the partial charges were performed with MOPAC 5.0 using the MNDO parameter set (comparison with the MINDO/3 and AM1 sets was made, and MNDO proved to be the most suitable for our structures). The geometry of all the structures was fully optimized (bond distances, bond angles, and dihedral angles) with restricted Hartree–Fock (RHF) calculations. The minima found were all characterized by calculating their vibrational frequencies, and the six trivial vibrations were acceptably small (less than 30 cm^{-1}). The frequencies and the Z matrix for all the computed structures are available from the authors. The geometrical characteristics (angles and distances) of the minimized structures were taken in from Insight II. The partial charges (Mulliken populations) were directly retriviewed from MOPAC results.

General Procedures. Melting points were recorded on a Reichert apparatus and are uncorrected. IR spectra were measured in CH_2Cl_2, and ^1H NMR spectra ($CDCl_3$, unless otherwise noted; with Me_4Si as an internal standard) were recorded at 200 MHz. The mass spectra and the GCMS analysis were obtained with electron impact ionization at 70 eV.

DMSO and HMPT, purchased from Aldrich, were distilled over CaH_2 and kept under Ar before use. THF was distilled just before use over sodium and benzophenone. Highly pure commercial diethyl ether was dried over sodium wires. KH was purchased from Aldrich as a 35% dispersion in mineral oil.

Starting Materials. 2,6-Difluorobenzonitrile (**1a**), 2-fluorobenzonitrile (**1c**), 2-fluoronitrobenzene (**1g**), and all commercially available acetophenones (**5a–5i**) of acceptable purity were used as purchased. Hydroxyacetophenone (**5e**), a commercially brown material, was recrystallized twice from diethyl ether, giving slightly pink crystals. 6-Methoxy-2-fluorobenzonitrile[33] (**1b**) was obtained by refluxing NaOMe (2.5 equiv) with **1a** in methanol for 2 h. The reaction yielded **1b** (90%) and the dimethoxy derivative (5%). 6-(Dimethylamino)-2-fluorobenzonitrile (**1d**) was prepared by treating **1a** with HMPA according to a method previously described.[34] 2,6-Difluoronitrobenzene (**1f**) was obtained from the corresponding aniline by a literature procedure.[35] Flash chromatography (CH_2Cl_2/heptane (1/1)) followed by distillation (55 °C (0.2 mmHg)) gave **1f** (47%) as a slightly green oil: ^1H NMR δ 7.15 (dd, 2 H, J = 8, 8 Hz), 7.61 (m, 1 H); IR 1614, 1568, 1547 (NO_2), 1480, 1362 (NO_2), 1030 cm^{-1}; MS (EI) m/e 159 (M^+), 143 ($M^+ - O$), 129 ($M^+ - NO$), 113 ($M^+ - NO_2$), 101, 63; HRMS (EI) m/e 159.0122 (159.0132 calcd for $C_6H_3F_2NO_2$). 6-Nitro-2-fluorobenzonitrile (**1e**) was prepared from 6-amino-2-fluorobenzonitrile (**1h**) by the above procedure.[35] Flash chromatography (CH_2Cl_2/heptane/ethyl acetate (6/6/1) yielded yellow crystals whose recrystallization in methanol gave **1e** (40%) as pale yellow crystals: mp = 71–2 °C; ^1H NMR δ 7.75 (dd, 1 H, J = 9, 8 Hz), 7.99 (m, 1 H), 8.25 (d, 1 H, J = 8 Hz); IR 2240 (C≡N), 1604, 1575, 1543 (NO_2), 1493, 1463, 1354 (NO_2), 908 cm^{-1}; MS (EI) m/e 166 (M^+), 150 ($M^+ - O$), 136 ($M^+ - NO$), 120 ($M^+ - NO_2$); HRMS (EI) m/e 166.0186 (166.0179 calcd for $C_7H_3FN_2O_2$). **1h** was prepared by a slight modification of the literature procedure.[34] **1a** (5.56 g, 40 mmol) and DMSO (90 mL) were placed in a strong 1-L bottle, and then dry ammonia (2–3 equiv) was dissolved in the solution. The bottle was hermetically closed and heated at 80 °C in an oil bath. Ammonia was added when the amount of **1h** showed no change (TLC control). After 80 h, CH_2Cl_2 was added and the organic phase was washed several times with water to achieve DMSO removal. Concentration of the organic phase yielded **1h** (5.38 g, 99%) as highly pure (GC) white crystals, mp = 127 °C (CH_2Cl_2). Melting points and spectroscopic data for **1b**, **1d**, and **1h** were identical to those published.[33]

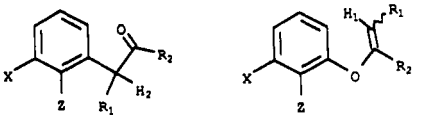
General Method for S_NAr Reactions (Tables I and III). A 35% KH dispersion in mineral oil (126 mg, 1.1 mmol, 1.1 equiv; except for **5e**, 2.2 equiv) was placed in a two-necked, 10-mL round-bottomed flask equipped with a magnetic stirrer and previously dried in the flame and purged with argon. KH was washed twice, under argon, with two 2-mL portions of pentane, and the residual pentane was removed by the argon flow. DMSO (2 mL) was then added under vigorous magnetic stirring. After 10 min H_2 evolution ceased, and the DMSO solution was clear and homogeneous, indicating complete formation of the dimsyl anion. The nucleophile (1 mmol) was then added with stirring. Formation of the enolate was generally slightly exothermic and resulted in a strong yellow coloration of the solution. After 10 min, the substrate (1 equiv, i.e., 1 mL of a 1 M solution in DMSO) was added to the reaction flask. The color of the mixture turned to an intense red except for substrates carrying a nitro group (**1e–1g**) where a dark blue color was observed. The reaction was quenched after 1.5 h by pouring into water (30 mL), and the resulting precipitate was extracted with diethyl ether (3 × 60 mL). In some cases, the precipitate could not be extracted and the aqueous phase was made acidic with 5% HCl. The precipitate dissolved at pH = 5–6 and the extraction could then be achieved.

(33) Hynes, J. B.; Pathak, A.; Panos, C. H.; Okeke, C. C. *J. Heterocycl. Chem.* **1988**, *25*, 1173.

(34) Idoux, J. P.; Gupton, J. P.; Colon, C. *Synth. Commun.* **1982**, *12*, 907.

(35) Roe, A. M.; Burton, R. A.; Willey, G. L.; Baines, M. W.; Rasmussen, A. C. *J. Med. Chem.* **1968**, *11*, 814.

Table V. ^{1}H NMR Spectroscopic Data for H_1 and H_2 Protons of O- and C-Arylated Products



X	Z	R_1	R_2	product	δ^a	signal^b (J)	product	δ^a	signal^b (J)
F	CN	H	Np^c	**3a**	4.68	s	**4a**	4.96	d (3.0)
								5.49	d (3.0)
OMe	CN	H	Np	**3b**	4.58	s	**4b**	4.85	d (2.4)
								5.41	d (2.4)
H	CN	H	Np	**3c**	4.60	s	**4c**	4.76	d (2.9)
								5.37	d (2.9)
NMe_2	CN	H	Np	**3d**	4.60	s			
F	NO_2	H	Np	**3f**	4.65	s	**4f**	4.95	d (3.1)
								5.46	d (3.1)
H	NO_2	H	Np	**3g**	4.86	s	**4g**	4.95	d (2.9)
								5.46	d (2.9)
F	CN	H	*p*-BrPh^d	**6a**	4.35	s	**7a**	4.66	d (2.8)
								5.19	d (2.8)
F	CN	H	*p*-FPh	**6b**	4.54	s	**7b**	4.79	d (3.0)
								5.30	d (3.0)
F	CN	H	Ph	**6c**	4.56	s	**7c**	4.86	d (2.7)
								5.37	d (2.7)
F	CN	H	*p*-OMePh	**6d**	4.65	s	**7d**	4.73	d (2.6)
								5.22	d (2.6)
F	CN	H	*p*-OHPh	**6e**	4.55	s	**7e**	4.82	d (3.0)
								5.37	d (3.0)
F	CN	Me	Ph	**6f**	5.12	q (6.5)	**7f**	6.01	q (5.7)
F	CN		*e*	**6g**	4.12	dd (3.8, 10)	**7g**	5.56	dd (4.6, 4.6)
F	CN	Ph	Ph	**6h**	5.39	s	**7h**	6.46	s

^{a} Chemical shifts in ppm. ^{b} s for singlet, d for doublet, and q for quartet; coupling constants (J) are in hertz. ^{c} Np for naphthyl. ^{d} Ph for phenyl. ^{e} $R_1\hat{R}_2$ = 6-methoxy, 1-tetralone.

In these cases, there was no hydrolysis of O-arylated product, as shown by comparing the GC analysis of the crude reaction mixture with that of the organic extract from acidic aqueous phase. Kurts and co-workers[5g] have also noticed the stability of O-arylated products under the same conditions. The organic phase was then washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting paste contained in general 20% in weight of residual DMSO which was removed by rotatory evaporation at 50 °C under vacuum (0.2 mmHg). The ^{1}H NMR spectrum of the crude product was recorded before and after removal of DMSO to check the invariance of the O/C ratio (O-aryl products are more volatile than their corresponding C-aryl, but the former were never removed under these conditions; see Calculation of O/C Ratios).

In HMPT, KH and the enolate were partially soluble but the solution became homogeneous immediately after substrate addition. In THF and diethyl ether the mixtures remained heterogeneous during the entire reaction. The procedure was the same except that the pH of the aqueous phase was adjusted to 5–6 before extraction.

Calculation of O/C Ratios. Well-separated and characteristic ^{1}H NMR signals of C- and O-arylated products (Table V) allow accurate integration and thus provide a convenient method for measuring the O/C ratio. The validity of the NMR measurements was checked in two model reactions (**1a** with **5c**, Table I, entry 3 and **1a** with **2a**, Table III, entry 1). The O/C ratio obtained from NMR integration was compared with those obtained (i) by GC (or GCMS) analysis and (ii) by isolation and weighing of the two pure products. In both cases, the results were in agreement, with a mean deviation of 5%, which corresponds approximately to the systematic error of NMR integration. S values of Table I–III correspond to a mean value of three different NMR measurements.

Products Characterization. O-Arylated and C-arylated products are unambiguously distinguished by spectroscopic data.

NMR. For R_1 = H, the two H_1 protons of O-arylated products appear as an A–B system (Table V) easily differentiated from the singlet signal of the two H_2 protons of C-arylated products. For $R_1 \neq$ H, H_1 had always a higher chemical shift than H_2.

IR Spectroscopy. C-Arylated products exhibit a strong carbonyl band in the region 1700–1650 cm^{-1}, while O-arylated products show no signals in this region.

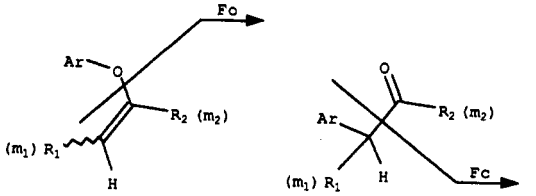


Figure 2. Characteristic fragmentations in mass spectra (EI) of O- and C-arylated products (M_1 and M_2 are m/e values for the fragments R_1 and R_2).

Mass Spectroscopy (electronic impact). The fragmentation patterns allow a clear differentiation to be made between the two products. Thus, fragmentation F_C, α to the carbonyl function of C-arylated products (Figure 2), gives a peak at $m/e = M_2 + 28$; while fragmentation F_O of O-arylated products leads to a peak at $m/e = M_1 + M_2 + 25$. For example, all compounds where R_2 = naphthyl and R_1 = H (Table III) give a fragment at m/e = 155 for C-aryl products and m/e = 153 for O-aryl products.

We report here full characterization of five pairs of C-aryl and O-aryl products, representing the series studied, and all spectroscopic data of the unexpected products.

Reaction of 1a with 5c (Table I, Entry 3). Unreacted **1a** and **5c** were removed under vacuum (see General Procedure), and the remaining crude products were separated on preparative layer chromatography (PLC.) (heptane/ethyl acetate = 100/8) giving, in order of elution, **7c** and **6c**.

2-(Phenylacetyl)-6-fluorobenzonitrile (6c): 98 mg (41%); white crystals; mp 96–7 °C (MeOH); ^{1}H NMR δ 4.56 (s, 2 H), 7.10–7.22 (m, 2 H), 7.47–7.70 (m, 4 H), 8.06 (d, 2 H, J = 8.2 Hz); IR 2234 (C≡N), 1693 (C=O), 1616, 1580, 1475, 1450, 1331, 1214 cm^{-1}; MS (EI) m/e 239 (M^+), 134 ($ArCH_2^+$), 105 ($PhC{=}O^+$), 77 (Ph^+), 51; HRMS (EI) m/e 239.0739 (239.0746 calcd for $C_{15}H_{10}FNO$), 105.0331 (105.0340 calcd for C_7H_5O).

1-Phenyl-1-(2′-cyano-3′-fluorophenoxy)ethene (7c): 98 mg (41%); white needles; mp 119–21 °C (CH_2Cl_2/pentane); ^{1}H NMR δ 4.86 (d, 1 H, J = 2.7 Hz), 5.37 (d, 1 H, J = 2.7 Hz), 6.85 (d, 1 H, J = 6.4 Hz), 6.86 (dd, 1 H, J = 8.5, 8.5 Hz), 7.32–7.38 (m, 3 H), 7.43 (ddd, 1 H, J = 8.5, 8.5, 6.4 Hz), 7.53–7.62 (m, 2 H); IR 2234 (C≡N), 1693 (C=O), 1616, 1580, 1475, 1450, 1331, 1214 cm^{-1}; MS (EI) m/e 239 (M^+), 103 ($PhC^+{=}CH_2$), 77 (Ph^+); HRMS (EI)

m/e 239.0740 (239.0746 calcd for $C_{15}H_{10}FNO$), 103.0539 (103.0548 calcd for C_8H_7).

Reaction of 1a with 5f (Table I, Entry 6). Unreacted **1a** and **5f** were removed under vacuum, and the crude product was purified on PLC (heptane/ethyl acetate = 10/3) giving, as first fraction, a mixture of **6f** and **7f** and then **9**. The first fraction was purified by a second PLC (heptane/methylene chloride = 2/1).

2-(1-Phenyl-2-methylacetyl)-6-fluorobenzonitrile (6f): 35 mg (14%); yellow crystals; mp 55–57 °C (CH_2Cl_2/pentane); ^1H NMR δ 1.59 (d, 3 H, J = 6.5 Hz), 5.12 (q, 1 H, J = 6.5 Hz), 7.09 (dd, 1 H, J = 8.5, 8.5 Hz), 7.17 (d, 1 H, J = 8.5 Hz), 7.40–7.58 (m, 5 H), 7.97 (d, 1 H, J = 7.4 Hz); IR 2232 (C≡N), 1688 (C=O), 1612, 1576, 1473, 1262, 963 cm^{-1}; MS (EI) *m/e* 253 (M^+), 148 ($ArCHMe^+$), 105 ($PhC{=}O^+$), 77 (Ph^+); HRMS (EI) *m/e* 253.0899 (253.0903 calcd for $C_{16}H_{12}FNO$), 105.0333 (105.0341 calcd for C_7H_5O).

1-Phenyl-1-(2′-cyano-3′-fluorophenoxy)propene (7f): 76 mg (30%); white crystals; mp 91–3 °C (CH_2Cl_2/pentane); ^1H NMR δ 1.77 (d, 3 H, J = 7.2 Hz), 6.01 (q, 1 H, J = 7.2 Hz), 6.64 (d, 1 H, J = 8.5 Hz), 6.77 (dd, 1 H, J = 8.5, 8.5 Hz), 7.24–7.39 (m, 4 H), 7.41–7.50 (m, 2 H); IR 2237 (C≡N), 1616, 1593, 1579, 1470, 1288, 1062 cm^{-1}; MS (EI) *m/e* 253 (M^+), 117 ($PhC^+{=}CHMe$), 115, 91; HRMS (EI) *m/e* 253.0892 (253.0903 calcd for $C_{16}H_{12}FNO$), 117.0699 (117.0704 calcd for C_9H_9).

1-Phenyl-1-(2′-cyano-3′-fluorophenoxy)-2-(2′-cyano-3′-fluorophenyl)propylidene (9): 37 mg (10%); pale yellow crystals; mp 169–71 °C (MeOH); ^1H NMR δ 2.27 (s, 3 H), 6.79 (dd, 1 H, J = 6.7, 6.7 Hz), 6.96 (d, 1 H, J = 6.7 Hz), 7.01 (d, 1 H, J = 6.8 Hz), 7.12 (dd, 1 H, J = 6.8, 6.8 Hz), 7.16 (s, 5 H), 7.34–7.51 (m, 2 H); IR 2236 (C≡N), 1742, 1616, 1584, 1573, 1468, 1313, 1126, 1098, 982 cm^{-1}; MS (EI) *m/e* 372 (M^+), 236 (M^+ – ArO), 158; HRMS (EI) *m/e* 372.1076 (372.1074 calcd for $C_{22}H_{12}F_2N_2O$), 236.0881 (236.0875 calcd for $C_{15}H_9FN$).

Reaction of 1a with 5i (Table I, Entry 9). PLC (heptane/CH_2Cl_2/MeOH = 50/47/3) gave, in order of elution, **8** and unreacted **5i** (60 mg, 44%).

2-[(*p*-Acetylphenyl)amino]-6-fluorobenzonitrile (8): 138 mg (54%); white crystals; mp 147–9 °C (CH_2Cl_2/pentane); ^1H NMR δ 2.60 (s, 3 H), 6.71 (s, 1 H, NH), 6.73 (dd, 1 H, J = 7.1, 7.1 Hz), 7.17 (d, 1 H, J = 7.5 Hz), 7.22 (d, 1 H, J = 7.5 Hz), 7.43 (dd, 1 H, J = 14.2, 7.1 Hz), 7.98 (d, 1 H, J = 7.5 Hz); IR 3401 (NH), 2226 (C≡N), 1678 (C=O), 1621, 1588, 1522, 1476, 1332, 1180 cm^{-1}; MS (EI) *m/e* 254 (M^+), 239 (M^+ – Me), 165; HRMS (EI) *m/e* 254.0860 (254.0855 calcd for $C_{15}H_{11}FN_2O$); 239.0608 (239.0620 calcd for $C_{14}H_9FN_2O$).

Reaction of 1a with 2a (Table III, Entry 1). Separation was the same as that of the crude from reaction of **1a** with **5c** and gave unreacted **2a** (39 mg, 23%), **4a**, and **3a**.

2-(2-Naphthylacetyl)-6-fluorobenzonitrile (3a): 102 mg (33%); white crystals; mp 160–1 °C (MeOH); ^1H NMR δ 4.68 (s, 2 H), 7.09–7.27 (m, 2 H), 7.47–7.66 (m, 3 H), 7.80–8.10 (m, 4 H), 8.58 (s, 1 H); IR 2236 (C≡N), 1687 (C=O), 1628, 1598, 1579, 1470, 1354, 1324, 1185, 1125 cm^{-1}; MS (EI) *m/e* 289 (M^+), 155 ($NpC{=}O^+$), 127 (Np^+); HRMS (EI) *m/e* 289.0895 (289.0903 calcd for $C_{19}H_{12}FNO$); 155.0488 (155.0496 calcd for $C_{11}H_7O$).

1-Naphthyl-1-(2′-cyano-3′-fluorophenoxy)ethene (4a): 130 mg (42%); white needles; mp = 56–8 °C (MeOH); ^1H NMR δ 4.96 (d, 1 H, J = 3.0 Hz), 5.49 (d, 1 H, J = 3.0 Hz), 6.77–6.85 (m, 2 H), 7.37 (ddd, 1 H, J = 8.7, 8.7, 6.7 Hz), 7.40–7.51 (m, 2 H), 7.64 (dd, 1 H, J = 8.8, 2.1 Hz), 7.74–7.85 (m, 3 H), 8.02 (s, 1 H); IR 2220 (C≡N), 1640, 1620, 1582, 1460, 1228, 1038 cm^{-1}; MS (EI) *m/e* 289 (M^+), 153 ($NpC^+{=}CH_2$), 127 (Np^+); HRMS (EI) *m/e* 289.0908 (289.0903 calcd for $C_{19}H_{12}FNO$); 153.0709 (153.0704 calcd for $C_{12}H_9$).

Reaction of 1e with 2a (Table III, Entry 5). PLC (heptane/ethyl acetate = 5/1) gave, in order of elution, unreacted **2a** (120 mg, 70%), **10**, and a complex mixture, which was separated by a second chromatography (heptane/CH_2Cl_2 = 1/2), affording unreacted **1e** (50 mg, 30%) and **11**.

2-(2-Naphthylacetyl)-3-fluoronitrobenzene (10): 10 mg (3%); yellow crystals; mp 164–6 °C (MeOH); ^1H NMR δ 4.93 (s, 2 H), 7.43–7.53 (m, 2 H), 7.55–7.69 (m, 2 H), 7.88–8.12 (m, 5 H), 8.61 (s, 1 H); IR 1687 (C=O), 1536 (NO_2), 1359 (NO_2) cm^{-1}; MS (EI) *m/e* 309 (M^+), 287, 155 ($NpC{=}O^+$), 127 (Np^+); HRMS (EI) *m/e* 309.0804 (309.0801 calcd for $C_{18}H_{12}FNO_3$).

2-Cyano-3-fluoro-4-(2-naphthylacetyl)nitrobenzene (11): 60 mg (18%); pale yellow crystals; mp 202–4 °C (MeOH); ^1H NMR δ 4.63 (s, 2 H), 7.57–7.69 (m, 2 H), 7.78 (d, 1 H, J = 7.0 Hz), 7.88–8.09 (m, 4 H), 8.19 (dd, 1 H, J = 8.7, 1.8 Hz), 8.60 (s, 1 H); IR 2245 (C≡N), 1688 (C=O), 1541 (NO_2), 1351 (NO_2) cm^{-1}; MS (EI) *m/e* 334 (M^+), 314, 155 ($NpC{=}O^+$), 127 (Np^+); HRMS (EI) *m/e* 334.0756 (334.0754 calcd for $C_{19}H_{11}FN_2O_3$).

Reaction of 1f with 2a (Table III, Entry 6). The crude product (280 mg) was separated on PLC (heptane/ethyl acetate = 5/1) giving, in order of elution, unreacted **2a** (50 mg, 29%), 34 mg of a mixture of **2a**, and **4f**, **13**, **3f**, and **12**. The O-arylated product **4f** was separated from **2a** by a second chromatography (heptane/CH_2Cl_2 = 1/1).

2-(2-Naphthylacetyl)-6-fluoronitrobenzene (3f): 64 mg (21%); yellow crystals; mp 130–2 °C (MeOH); ^1H NMR δ 4.65 (s, 2 H), 7.14 (d, 1 H, J = 8.2 Hz), 7.21 (dd, 1 H, J = 8.4, 8.2 Hz), 7.46 (ddd, 1 H, J = 8.4, 8.4, 5.1 Hz), 7.50–7.67 (m, 2 H), 7.83–7.92 (m, 2 H), 7.93–8.04 (m, 2 H), 8.50 (s, 1 H); IR 1687 (C=O), 1619, 1593, 1538 (NO_2), 1361 (NO_2), 1185, 1125 cm^{-1}; MS (EI) *m/e* 309 (M^+), 261, 155 ($NpC{=}O^+$), 127 (Np^+); HRMS (EI) *m/e* 309.0779 (309.0801 calcd for $C_{18}H_{12}FNO_3$), 155.0490 (155.0496 calcd for $C_{11}H_7O$).

1-(2-Naphthyl)-1-(2′-nitro-3′-fluorophenoxy)ethene (4f): 18 mg (6%); yellow oil; ^1H NMR δ 4.95 (d, 1 H, J = 3.1 Hz), 5.46 (d, 1 H, J = 3.1 Hz), 6.93 (dd, 1 H, J = 6.8, 6.8 Hz), 6.95 (d, 1 H, J = 6.8 Hz), 7.32 (ddd, 1 H, J = 6.8; 6.8, 4.9 Hz), 7.46–7.52 (m, 2 H), 7.67 (dd, 1 H, J = 7.2, 1.5 Hz), 7.79–7.88 (m, 3 H), 8.07 (s, 1 H); IR 1614, 1602, 1542 (NO_2), 1475, 1365 (NO_2), 1133, 1085 cm^{-1}; MS (EI) *m/e* 309 (M^+), 279 (M^+ – NO), 263 (M^+ – NO_2), 169, 153 ($NpC^+{=}CH_2$), 141, 127 (Np^+); HRMS (EI) *m/e* 309.0807 (309.0801 calcd for $C_{18}H_{12}FNO_3$), 153.0704 calcd for $C_{12}H_9$).

α,α′-Bis(2-nitro-3-fluorophenyl)-2-acetonaphthone (12): 94 mg (21%); pale yellow crystals; mp 188–90 °C (MeOH); ^1H NMR δ 6.72 (s, 1 H), 6.98 (d, 2 H, J = 7.7 Hz), 7.27 (ddd, 2 H, J = 8.8, 8.0, 1.2 Hz), 7.48 (ddd, 2 H, J = 7.7, 7.7, 5.2 Hz), 7.53–7.66 (m, 2 H), 7.81–7.91 (m, 2 H), 7.92–8.02 (m, 2 H), 8.47 (s, 1 H); IR 1687 (C=O), 1627, 1614, 1592, 1536 (NO_2), 1475, 1360 (NO_2), 1185 cm^{-1}; MS (EI) *m/e* 448 (M^+), 432 (M^+ – O), 402 (M^+ – NO_2), 172, 155 ($NpC{=}O^+$), 127 (Np^+); HRMS (EI) *m/e* 448.0869 (448.0871 calcd for $C_{24}H_{14}F_2N_2O_5$).

2,6-Difluoro-4-(2-naphthylacetyl)nitrobenzene (13): 12 mg (3.5%); yellow crystals; mp 138–40 °C (MeOH); ^1H NMR δ 4.49 (s, 2 H), 7.07 (d, 2 H, J = 8.5 Hz), 7.57–7.72 (m, 2 H), 7.88–8.07 (m, 4 H), 8.52 (s, 1 H); IR 1687 (C=O), 1628, 1611, 1542 (NO_2), 1365 (NO_2), 1060 cm^{-1}; MS (EI) *m/e* 327 (M^+), 251, 155 ($NpC{=}O^+$), 127 (Np^+); HRMS (EI) *m/e* 327.0713 (327.0707 calcd for $C_{18}H_{11}F_2NO_3$).

Reaction of 1g with 2a (Table III, Entry 7). PLC (heptane/CH_2Cl_2/ethyl acetate (7/1/1)) gave **4g**, unreacted **2a** (76 mg, 45%), and 137 mg of a mixture of **3g** and **14**. The latter was separated by a second PLC (five migrations with heptane/CH_2Cl_2 = 1/1 were needed to achieve a good separation).

2-(2-Naphthylacetyl)nitrobenzene (3g): 96 mg (33%); pale yellow crystals; mp 129–31 °C (MeOH); ^1H NMR δ 4.85 (s, 2 H), 7.37 (d, 1 H, J = 7.6 Hz), 7.43–7.67 (m, 4 H), 7.85–8.08 (m, 4 H), 8.15 (d, 1 H, J = 8.0 Hz), 8.57 (s, 1 H); IR 1686 (C=O), 1628, 1529 (NO_2), 1470, 1350 (NO_2), 1173, 1125 cm^{-1}; MS (EI) *m/e* 291 (M^+), 155 ($NpC{=}O^+$), 127 (Np^+); HRMS (EI) *m/e* 291.0885 (291.0895 calcd for $C_{18}H_{13}NO_3$), 155.0494 (155.0496 calcd for $C_{11}H_7O$).

1-(2-Naphthyl)-1-(2′-nitrophenoxy)ethene (4g): 14.5 mg (5%); reddish oil: ^1H NMR δ 4.66 (d, 1 H, J = 3.0 Hz), 5.31 (d, 1 H, J = 3.0 Hz), 7.18–7.31 (m, 2 H), 7.46–8.06 (m, 8 H), 8.17 (s, 1 H); IR 1604 (C=C Ar), 1546 (NO_2), 1471, 1355 (NO_2), 1248 cm^{-1}; MS (EI) *m/e* 291 (M^+), 261 (M^+ – NO), 245 (M^+ – NO_2), 153 ($NpC^+{=}CH_2$), 141, 127 (Np^+); HRMS (EI) *m/e* 291.0897 (291.0895 calcd for $C_{18}H_{13}NO_3$), 153.0698 (153.0704 calcd for $C_{12}H_9$).

2-Fluoro-4-(2-naphthylacetyl)nitrobenzene (14): 40 mg (13%), yellow paste which failed to crystallize in various solvents; ^1H NMR δ 4.52 (s, 2 H), 7.20–7.30 (m, 2 H), 7.54–7.70 (m, 2 H), 7.87–8.12 (m, 5 H), 8.53 (s, 1 H); IR 1686 (C=O), 1627, 1612, 1529 (NO_2), 1125 (NO_2), 1060 cm^{-1}; MS (CI) *m/e* 310 (MH^+), 280 (MH^+ – NO); HRMS (EI) *m/e* 309.0802 (309.0801 calcd for $C_{18}H_{12}FNO_3$), 155.0495 (155.0496 calcd for $C_{11}H_7O$).

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Registry No. 1a, 1897-52-5; 1b, 94088-46-7; 1c, 394-47-8; 1d, 96994-73-9; 1e, 143306-27-8; 1f, 19064-24-5; 1g, 1493-27-2; 2a, 93-08-3; 3a, 143306-28-9; 3b, 143306-29-0; 3c, 143306-30-3; 3d, 143306-31-4; 3f, 143306-32-5; 3g, 143306-33-6; 4a, 143306-34-7; 4b, 143306-35-8; 4c, 143306-36-9; 4f, 143306-37-0; 4g, 143306-38-1; 5a, 99-90-1; 5b, 403-42-9; 5c, 98-86-2; 5d, 100-06-1; 5e, 99-93-4; 5f, 93-55-0; 5g, 1078-19-9; 5h, 451-40-1; 5i, 99-92-3; 5j, 611-70-1; 6a, 143306-39-2; 6b, 143306-40-5; 6c, 143306-41-6; 6d, 143306-42-7; 6e, 143306-43-8; 6f, 143306-44-9; 6g, 143306-45-0; 6h, 143306-46-1; 6j, 143306-47-2; 7a, 143306-48-3; 7b, 143306-49-4; 7c, 143306-50-7; 7d, 143306-51-8; 7e, 143306-52-9; 7f, 143306-53-0; 7g, 143306-54-1; 7h, 143306-55-2; 7j, 143306-56-3; 8, 143306-58-5; 9, 143306-57-4; 10, 143306-59-6; 11, 143306-60-9; 12, 143306-61-0; 13, 143306-62-1; 14, 143306-63-2.

Supplementary Material Available: ^{1}H NMR spectra of 1e–f, 3a, 3f–g, 4a, 4f–g, 6c, 6f, 7c, 7f, and 8–14 (19 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Stereoelectronic Control of Facial Selectivity in the Diels–Alder Cycloaddition of Sterically Unbiased 5,5-Diarylcyclopentadienes

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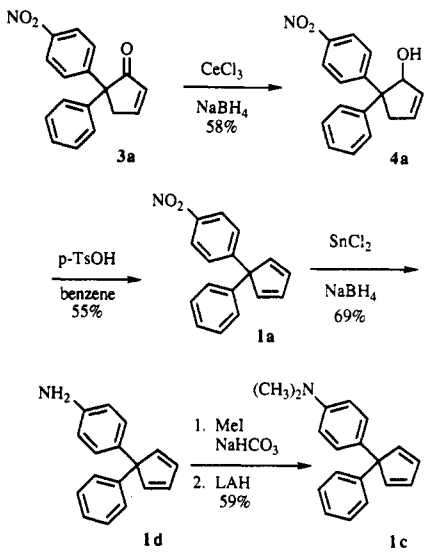
This study provides strong evidence for stereoelectronic control of diastereoselectivity in the Diels–Alder cycloaddition of sterically unbiased 5-(4-X-phenyl)-5-phenylcyclopentadienes 1 (X = NO_2, Cl, and $N(CH_3)_2$) with dimethyl acetylenedicarboxylate (DMAD) producing diastereomeric norbornyl diesters 2 in cis/trans ratios (diester relative to the substituted arene) varying from 68:32 to 38:62 as determined by ^{1}H NMR spectroscopy. The reactions were carried out under both thermal and Lewis acid catalyzed conditions, giving essentially identical selectivities regardless of the conditions used. Structural assignments were made by ^{1}H NMR lanthanide shift reagent studies of the isolated diastereomers, separable by preparative thin-layer chromatography. In each case the dienophile approached the diene from the side opposite the more electron rich aromatic ring as predicted by Cieplak's theory for explaining stereoelectronic control. The observed ratios correspond to an overall energy difference of 0.65 kcal/mol. A Hammet plot of the log (cis/trans) versus the σ_p parameter produced a linear relationship with a correlation coefficient of 0.98. An efficient synthesis of the diarylcyclopentadienes is described.

The role of stereoelectronic effects in controlling diastereoselectivity has, in recent years, been the subject of a growing amount of research.[1] Although steric interactions are thought to be a major factor which determines selectivity in many organic transformations, among them the synthetically important Diels–Alder reaction, it has been less clear to which degree stereoelectronic factors influence diastereoselectivity. A few investigations into the nature of stereoelectronic control of facial diastereoselectivity in the Diels–Alder reaction have been reported. Franck examined the Diels–Alder reaction of various, sterically biased acyclic dienes containing an chiral allylic alkoxy group.[2] le Noble has reported on the Diels–Alder reaction of sterically unbiased 5-fluoroadamantanethione with 2,3-dimethyl-1,3-butadiene which showed that the diene approached the olefin from the face syn to the electron-withdrawing fluoro substituent, in accord with the product predicted by Cieplak theory.[3,4] Fallis has reported studies of Diels–Alder reactions of sterically biased 5-substituted cyclopentadienes.[5]

We have been engaged in an ongoing investigation of the role of stereoelectronic effects in controlling stereoselectivity in a variety of reaction types involving sterically unbiased, yet electronically biased, substrates. We have reported diastereoselectivity in the sodium borohydride reduction of sterically unbiased 2-(4-X-phenyl)-2-phenylcyclopentanones (X = NO_2, Br, Cl, OH, OH, OCH_3, and NH_2) which gave diastereomeric alcohols with stereoselectivities up to 79:21.[6] More recently we reported the results of the osmium-catalyzed cis-dihydroxylations[7]

Scheme I



† Work performed at Department of Chemistry, Boston University, Boston, MA.

(1) An overview of studies concerning stereoelectronic control can be found in the following papers and references therein: (a) Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001–2006. (b) Li, H.; Mehta, G.; le Noble, W. *J. Org. Chem.* **1991**, *56*, 2006–2011. (c) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447–8462. (d) Smith, A. B. III; Dunlap, N. K.; Sulikowski, G. A. *Tetrahedron Lett.* **1988**, *29*, 439–442. (e) Okada, K.; Tomita, S.; Oda, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 459–468.

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