Doubly Destabilized Carbocations. Strong Aryl Delocalization and the Attenuation of Rate Decelerating Effects of CF_3 and CN Groups

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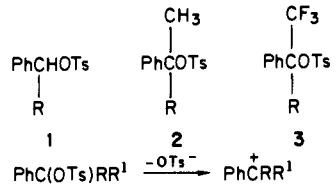
Abstract: Solvolysis rates of $ArC(CF_3)_2OTs$ in CF_3CO_2H give an excellent correlation $\log k = -10.7\sigma^+ - 8.69$, and a point for the *p*-Me_2N compound derived from the rate of the *p*-nitrobenzoate also fits this correlation, giving a span of 10^{19} in reactivity. Limiting values of ρ^+ of −10 to −12 for generation of benzylic cations in the gas phase and solution have been reached. Rate ratios $k(ArCH(OTs)CF_3)/k(ArC(CF_3)_2OTs)$ increase from 2.4 to 54 with decreasing aryl donor power; these $k(H)/k(CF_3)$ ratios are much less than typical values of 10^6 in more stabilized systems. Displacement of the *p*-MeO group occurs in solvolysis of *p*-$MeOC_6H_4C(CF_3)_2OTs$ (**9**) in EtOH and CD_3OH. Trifluoroacetolysis of $ArC(OTs)(CF_3)CN$ (Ar = *p*-Tol (**13**) and Ph) gives $\rho^+ = -12.1$, and for **13** in different solvents the reactivity is greater than *p*-TolCH(OTs)CF_3 by factors of 8.6 to 175. This is the first observation of $k(CN)/k(H)$ ratios greater than 1.0. All these results, plus the rather modest dependence of the rates on solvent polarity ($m = 0.76$ for **9** and 0.66 for **13**), are interpreted in terms of carbocationic transition states and intermediates in which the charge is largely delocalized onto the aryl group.

Previous studies have shown that the replacement of an α-hydrogen in a benzylic tosylate by a CF_3 or CN group results in a large rate decrease ($k_H/k_{CF_3} = 2 \times 10^5$ for both **1** and **2**, and $k_H/k_{CN} = 88$ for **2**) in solvolyses leading to carbocations (eq 1).[1-3]



(1)

These rate decelerations are ascribed to the strong electron-withdrawing effect of these groups that destabilize the developing carbocations (σ_p^+ for CF_3 and CN equals 0.61 and 0.66, respectively).[2,3] The smaller deceleration in the case of the CN derivative, despite the large σ_p^+ value for this group, evidently reflects the possibility of resonance electron donation by this group in situations of high electron demand.[2,3]

It was surprising therefore, that in the presence of one CF_3 group a second strongly electron withdrawing substituent gave a much smaller rate deceleration ($k_H/k_{CF_3} = 54$ and $k_H/k_{CN} = 1.1$ for **3**).[4a,b] This nonadditivity of substituent effects was contrary to the trends observed in alkene protonations, in which the effect of substituents was shown to be cumulative.[5]

Three possible causes for the attenuation of the destabilizing effect of these substituents in **3** were considered:[4a] (i) strong electron donation by the group R; (ii) ground-state strain in **3** that was relieved on solvolysis; and (iii) strong charge delocalization onto the aryl group. In the preliminary communication a firm conclusion regarding the relative importance of these factors was not reached.[4a]

Table I. Rates of Solvolysis of *p*-Nitrobenzoate **4** and Tosylates **10** and **13**[a]

substrate	T, °C	solvent	k_1, s^{-1}	ΔH^* (kcal/mol)	ΔS^* (eu)
4	25	97 HFIP	1.09×10^{-3}		
	25	97 TFE	2.04×10^{-5}		
	25	70 TFE	2.02×10^{-4}		
	25	50 TFE	2.49×10^{-4}		
	25	60 EtOH	1.48×10^{-4}		
	25	80 EtOH	4.47×10^{-5}		
	74.6	100 EtOH	6.20×10^{-4}	21.4	−11.9
	60.6	100 EtOH	1.84×10^{-4}		
	50.5	100 EtOH	5.68×10^{-5}		
	25.5	100 EtOH	3.19×10^{-6}		
10	71.7	TFA	6.36×10^{-4}		
	64.8		2.53×10^{-4}		
	50.4		6.41×10^{-5}		
	42.4		2.44×10^{-5}		
	25.0[b]		2.79×10^{-6}	22.7	−7.8
13	25.0	TFA	5.30×10^{-4}		
	25.0	97 TFE	2.47×10^{-5}		
	73.8	80 EtOH	3.74×10^{-4}		
	62.6		1.04×10^{-4}		
	44.2		1.26×10^{-5}		
	25.0[b]		9.74×10^{-7}	24.3	−4.5
	95.2	100 EtOH	1.87×10^{-4}		
	85.0		5.54×10^{-5}		
	64.8		6.83×10^{-6}		
	25.0[b]		3.38×10^{-8}	25.9	−5.8

[a] Rates measured by UV; duplicate runs at each temperature ±5%. [b] Calculated from data at other temperatures.

Subsequently, an analysis of the molecular structures of **1-3** (R = CF_3) and **3** (R = CN) obtained by X-ray crystallography led to the conclusion that although these structures were significantly distorted from tetrahedral geometries at the carbinyl center there was no evidence for a decisive role of ground-state strain in determining the relative reactivities.[4b] The possibility that the CF_3 group may become electron donating to carbocations which have no other donor groups has also been examined recently by calculations[4c] of the geometry and energy of $CF_3CH_2^+$ that are significantly advanced over previous theoretical studies.[4d-f] No CF_3 donor effects that could explain these results were found.[4c] The work reported herein provides good evidence for a major role for electron donation by the aryl group in attenuating the de-

(1) (a) Allen, A. D.; Jansen, M. P.; Koshy, K. M.; Mangru, N. N.; Tidwell, T. T. *J. Am. Chem. Soc.* **1982**, *104*, 207-211. (b) Allen, A. D.; Ambidge, I. C.; Che, C.; Micheal, H.; Muir, R. J.; Tidwell, T. T. *Ibid.* **1983**, *105*, 2343-2350.

(2) (a) Gassman, P. G.; Guggenheim, T. L. *J. Org. Chem.* **1982**, *47*, 3023-3026. (b) Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 4138-4143.

(3) (a) Gassman, P. G.; Tidwell, T. T. *Acc. Chem. Res.* **1983**, *16*, 279-285. (b) Tidwell, T. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 20-32.

(4) (a) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1983**, *105*, 5961-5962. (b) Kanagasabapathy, V. M.; Sawyer, J. F.; Tidwell, T. T. *J. Org. Chem.* **1985**, *50*, 503-509. (c) Charpentier, M.; Fossey, J.; Tidwell, T. T.; Wolfe, S. *Can. J. Chem.*, submitted for publication. (d) Paddon-Row, M. N.; Santiago, C.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6461-6563. (e) Reynolds, W. F.; Dais, P.; MacIntyre, D. W.; Topsom, R. D.; Marriott, S.; Nagy-Felsobuki, E. v.; Taft, R. W. *Ibid.* **1983**, *105*, 378-384. (f) Paddon-Row, M. N.; Houk, K. N.; Tidwell, T. T. *Tetrahedron Lett.* **1982**, *23*, 383-386.

(5) (a) Nowlan, V. J.; Tidwell, T. T. *Acc. Chem. Res.* **1977**, *10*, 252-285. (b) Koshy, K. M.; Roy, D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 357-363. (c) Allen, A. D.; Shahidi, F.; Tidwell, T. T. *Ibid.* **1982**, *104*, 2516-2518.

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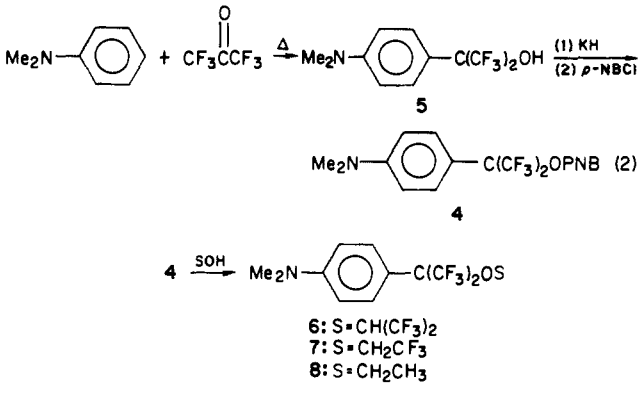
stabilizing influences of CF_3 and CN in doubly destabilized systems.

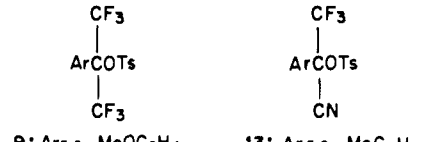
Results

1-(*p*-(Dimethylamino)phenyl)-1-(trifluoromethyl)-2,2,2-trifluoroethyl *p*-nitrobenzoate (**4**) was prepared through the intermediacy of the known alcohol **5**[6a] by the sequence shown in eq 2. The reaction of **4** in various solvents gave good first-order rate



behavior as monitored by UV spectroscopy, and the derived rate constants are reported in Table I. Reaction of **4** in solutions of HFIP and TFE, each containing 1.1 equiv of Et_3N, and in EtOH gave the corresponding ethers **6–8**, respectively, as the only observed products. In the absence of the Et_3N, minor additional products that were not identified were observed in HFIP and TFE, but the rates were the same in the presence or absence of Et_3N.

The tosylates **9–12** were prepared by reaction of the corresponding alcohols[6] with KH followed by TsCl in ether,[4b] and tosylates **13** and **14** were obtained by reaction of the carbinols with TsCl in pyridine.[4b]



9: Ar = *p*-$MeOC_6H_4$
10: Ar = *p*-MeC_6H_4
11: Ar = *p*-FC_6H_4
12: Ar = *p*-Ph
13: Ar = *p*-MeC_6H_4
14: Ar = Ph

These derivatives also gave good first-order rate constants for solvolysis, and results for **10** and **13** are included in Table I. Rate data for **9**, **11**, **12**, and **14** were reported previously.[4a]

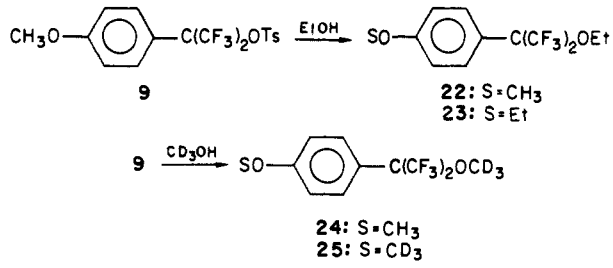
Reaction products from **9–14** in selected pure solvents were examined, and the substitution products **15–21** were observed.

15 X = *p*-MeO; S = CF_3CH_2
16: X = *p*-Me; S = CF_3CH_2
17: X = *p*-Me; S = CF_3CO
18: X = *p*-F; S = CF_3CO
19: X = H; S = CF_3CO
20: X = *p*-Me; S = CF_3CH_2
21: X = H; S = CF_3CO

Unexpectedly reaction of **9** in EtOH gave a mixture of **22** and **23** in a ratio of 50/50 as determined by VPC separation and isolation. Similarly **9** in CD_3OH gave **24** and **25** in a ratio of 69/31 as analyzed by the relative intensity of their respective mass spectral M^+ peaks at 291 and 294.

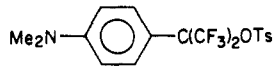
Discussion

The response of the rates of solvolysis of these derivatives to the electron supply of the aryl substituents is an important measure



of the electronic effects in these systems. Rates for the bis(trifluoromethyl) tosylates **9–12** in TFA at 25 °C give an excellent correlation with the σ_p^+ constants: $\log k = -10.7\sigma^+ - 8.69$, $r = 0.999$. This result provides strong evidence of a powerful electron-donating effect by the aryl substituents.

The inclusion of the *p*-(dimethylamino)-substituted derivative **26** in this set of substrates would provide a critical test of electronic effects in this system because of the great donor power of this group. For this comparison of the *p*-nitrobenzoate **4** to the tosylates **9–12** an estimate of the relative leaving group ability $k(OTs)/k(OPNB)$ is required. Such estimates must be interpreted with caution because of the complex interplay of structural, solvent, and temperature effects on reactivity, but with this caveat a useful analysis is possible. Four independent estimates of this ratio derived from literature sources[7-11] (see Appendix) are 5.7×10^8, 4.4×10^7, 9.4×10^6, and 2×10^9 from which a rounded value of 10^8 may be selected.



26

The measured value of 0.470 s^{-1} for **9** in TFA can be converted to $k_1 = 10^{10}$ s^{-1} for the desired substrate **26** with use of the above ratio of 10^8 and an estimated value of 220 for $k(\mathbf{4})/k(\mathbf{9})$ in TFA. Measured rate ratios $k(\mathbf{4})/k(\mathbf{9})$ at 25 °C are 220 (HFIP), 10^3 (TFE), 6 (80% EtOH), and 9 (100% EtOH), and the value for HFIP is the best choice for estimating the rate in TFA.

The appropriate value of σ_p^+ for the Me_2N substituent is an item of some interest, and a value of −1.74 derived from solvolytic data[12a] appears most suitable for comparison in the present case, and preferable to a recently reported value of −2.15 based on ketone basicities.[12b]

Use of $k_1 = 10^{10}$ s^{-1} for **26** in TFA and $\sigma_p^+ = -1.74$ gives a point with an excellent fit to the correlation derived from the other four substituents.[13] From this result we conclude that there is a very powerful electron demand that is not attenuated throughout a 10^{19} range in solvolytic reactivity. There were several debateable assumptions made in deriving the coordinates of the point for **26**, but because of the vast range of reactivities covered this conclusion is not highly sensitive to the value of k_1, which could be as low as 10^7 s^{-1} without changing the interpretation.

The magnitude of the ρ^+ value of −10.7 is large, but not significantly greater than those for secondary tosylates ArCH(OTs)CF_3 of −6.7 to −11.9 in various solvents[1b] and that of −11.6

(6) (a) Knunyants, I. L.; Gambaryan, N. P.; Ch'ing-yun, C.; Rokhlin, E. M. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1962**, 684–692. (b) Reines, S. A.; Griffith, J. R.; O'Rear, J. G. *J. Org. Chem.* **1970**, *35*, 2772–2777. (c) Livshits, B. R.; D'yachenko, I. A.; Palii, V. P.; Gambaryan, N. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 614–618. (d) Farah, B. S.; Gilbert, E. E.; Litt, M.; Otto, J. A.; Sibilia, J. P. *J. Org. Chem.* **1965**, *30*, 1003–1006.

(7) (a) Goering, H. L.; Briody, R. G.; Sandrock, G. *J. Am. Chem. Soc.* **1970**, *92*, 7401–7407. (b) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *Ibid.* **1985**, *107*, 4513–4519.

(8) A Y_{OTs} values in 70% acetone of 0.38 was extrapolated from data for 10–60% acetone given in the following: Bentley, T. W.; Carter, G. E. *J. Org. Chem.* **1983**, *48*, 579–584. Bentley, T. W.; Carter, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 5741–5747.

(9) $k(t\text{-BuCl})/k(t\text{-BuOPNB})$ is 2.6×10^4 at 25 °C in 80% acetone.[10]

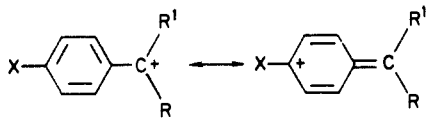
(10) (a) Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1956**, *78*, 2770–2777. (b) Brown, H. C.; Dickason, W. C. *Ibid.* **1969**, *91*, 1226–1228. (c) Brown, H. C.; Ravindranathan, M.; Chloupek, F. J.; Rothberg, I. *Ibid.* **1978**, *100*, 3143–3149. (d) Brown, H. C.; Rao, C. G. *J. Org. Chem.* **1980**, *45*, 2113–2116.

(11) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper and Row: New York, 1981; p 340.

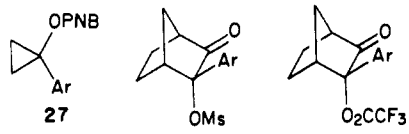
(12) (a) Brown, H. C.; Rao, C. G.; Ravindranathan, M. *J. Am. Chem. Soc.* **1978**, *100*, 7946–7953. (b) Azzaro, M.; Gal, J. F.; Geribaldi, S. *J. Chem. Soc., Perkin Trans. 2* **1984**, 771–774.

(13) The correlation including all five points is $\log k = -10.7\rho^+ - 8.71$, $r = 0.9999$.

for $ArCH_2OMs$ in HFIP.[14b] Among other destabilized sulfonates[14a] the ρ^+ for $ArCH(OMs)PO_3Et_2$ is −10.1,[14b] and the range of −10 to −12 appears to be at least a temporary ceiling on the magnitude of ρ^+ values for benzylic solvolyses. A plausible interpretation of this behavior is that a lower limit has been reached for positive charge buildup on the benzylic carbon in the transition state and that additional electron-withdrawing substituents have no further effect. Thus in the pair of resonance structures shown the charge is effectively delocalized completely on the ring for the substituent pairs R, R¹ = H, H; CF_3, H; and CF_3, CF_3, and the ρ^+ values for these systems are near the limit.



For pairs of substituents with somewhat greater electron-donor powers the magnitude of ρ^+ is rather less, as in the following pairs: CH_3, H (−3.0 to −6.3);[7b] CH_3, CF_3 (−7.46);[15] and CH_3, CN (−6.70).[2a] Similarly, ρ^+ values for 1-arylcyclopropyl *p*-nitrobenzoates (**27**)[10c] and the bicyclic α-aryl derivatives **28**[14c] and **29**[14d] are −7.07, −5.69, and −7.1, respectively. The magnitude of ρ^+ for **27** is the largest that has been observed for a geometrically destabilized system,[3b] while the intermediate from **28** and **29** is tertiary and can be stabilized by positive charge delocalization onto the carbonyl.



27 **28** **29**

Further evidence that these ρ^+ values are near limiting value comes from studies of gas-phase equilibrium basicities of styrenes and α-methylstyrenes, which have ρ^+ values of −10.9 and −9.4, respectively.[16] Similar measurements for arylalkynes give ρ^+ = −10.0.[16c]

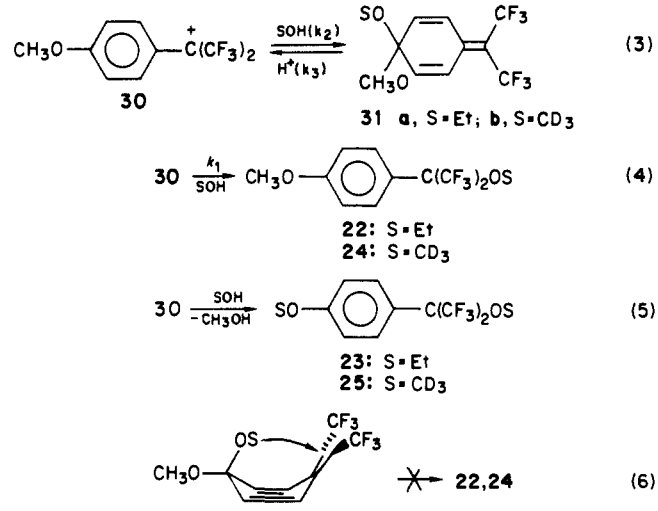
$$ArCR{=}CH_2 + H^+ \rightleftarrows Ar\overset{+}{C}RCH_3$$

$$R = H, CH_3$$

The ratio $k(ArCH(OTs)CF_3)/k(ArC(CF_3)_2OTs)$ as a function of the aryl substituent provides another measure of the degree of electron transfer to the ring. Thus for Ar = *p*-$MeOC_6H_4$ this ratio is between 2.4 and 5.2 (6 solvents) but for Ar = *p*-Tol and Ar = *p*-Ph it increases to 22 and 54, respectively.[17] Thus there is a direct relationship between the electron-donor power of the aryl ring and the degree to which the decelerating ability of the second CF_3 is diminished.

The rates of **9** as a function of solvent polarity are correlated by the equation $\log k = 0.76Y_{OTs} - 3.30$, showing a lesser dependence on the solvent than in the case of the model 2-adamantyl tosylate. There have been numerous other examples of the same phenomenon (*m* less than 1.0) in benzylic and other conjugated systems,[1b,7b,14,18] and we have argued[1b] that this is interperetable in terms of a lesser effect of solvent polarity in highly delocalized systems.[19]

Scheme I



The rates of the α-cyano derivatives **13** and **14** show some similar behavior to the $(CF_3)_2$ derivatives **9–12**. Thus the solvent dependence for **13** is $\log k = 0.66Y_{OTs} - 6.11$ ($r = 0.991$) and for **13** and **14** in TFA $\log k = -12.1\sigma^+ - 7.01$. The rather low value of *m* and the large magnitude of ρ^+ are both consistent with a high degree of electron delocalization in these substrates.

Strikingly, the cyano derivative **13** is *more* reactive than the corresponding hydrogen compound *p*-TolCH(OTs)CF_3[1b] in all the solvents studied: $k(CN)/k(H)$ = 8.6 (TFA), 22 (TFE), 46 (80% EtOH), and 175 (100% EtOH). This is evidently the first demonstration of an α-cyano carbocation system that is formed more rapidly than the hydrogen analogue and is a vivid example of how the expected electron-withdrawing effect of this group can be attenuated. The distinct increase in the ratio above with decreasing solvent polarity is notable and may arise from stronger π-donation by cyano in the less ionizing solvents.

For **14** the $k(CN)/k(H)$ ratio is 0.9, so only with *p*-tolyl as the aryl donor is the cyano giving net acceleration of the reaction. Evidently there is significant electron delocalization in the carbocation onto both the aryl ring and the cyano group, but the respective contributions of the two π-donors to the total stabilization in this cross-conjugated system cannot now be specified with certainty.

The formation of the products **23** and **25** in which the CH_3O group of **9** is replaced by EtO or by CD_3O on solvolysis in EtOH and CD_3OH, respectively, gives further evidence of the major buildup of positive charge on the intermediate ion in these reactions. Evidently these products arise by the sequence of Scheme I in which the intermediate carbocation **30** undergoes competitive attack by solvent at C_4 of the ring to form **31** or at C_α to give **22–25**.

The possibility of product formation by a 1,5-shift as shown in eq 6 can be excluded, as particularly in the case of **31b** shift of the CH_3O and CD_3O should be equally likely, and the product of the former process was not observed.

Mass spectrometric analysis of the product in CD_3OH gives a 69/31 ratio for the M^+ ions derived from **24** and **25**. The ratio of the products **22/23** or **24/25** is predicted by a steady-state analysis of eq 3–5 to be $2k_1/k_2$, and thus in CD_3OH $k_2 = 0.9k_1$ while in EtOH the product ratio was 1/1 so $k_2 = 2k_1$. The greater proportion of attack by EtOH at the ipso ring carbon may arise from steric hindrance to attack of the larger nucleophile at the α-position, or it could be due to subtle electronic effects.

In conclusion the doubly destabilized substrates **4** and **9–14** show some remarkable properties, including an enormous span of 10^{19} in reactivity as a function of the aryl substituents, values of ρ^+ of great magnitude but not exceeding an apparent limiting

(14) (a) Creary, X. *Acc. Chem. Res.* **1985**, *18*, 3–8. (b) Creary, X.; Underiner, T. L. *J. Org. Chem.* **1985**, *50*, 2165–2170. (c) Creary, X. *J. Am. Chem. Soc.* **1981**, *103*, 2463–2465. (d) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938–3945.

(15) Liu, K.-T.; Kuo, M.-Y.; Sheu, C.-F. *J. Am. Chem. Soc.* **1982**, *104*, 211–215.

(16) (a) Harrison, A. G.; Houriet, R.; Tidwell, T. T. *J. Org. Chem.* **1984**, *49*, 1302–1304. (b) Hartman, K. N.; Lias, S.; Ausloos, P.; Rosenstock, H. M.; Schroyer, S. S.; Schmidt, C.; Martinsen, D.; Milne, A. *A Compendium of Gas-Phase Basicity and Proton Affinity Measurements*; U.S. Department of Commerce: Washington, DC, 1979; NBSIR 79-1977. (c) Marcuzzi, F.; Modena, G.; Paradisi, C.; Giancaspro, C.; Speranza, M. *J. Org. Chem.* **1985**, *50*, 4973–4975.

(17) Values for R = CF_3 are from this work and those for R = H are from ref 1b.

(18) Allen, A. D.; Girdhar, R.; Jansen, M. P.; Mayo, J. R.; Tidwell, T. T. *J. Org. Chem.*, in press.

(19) No systematic study of the effect of solvent on the rates of solvolysis of *p*-nitrobenzoate esters is available so an analysis of the rate dependence of **4** on solvent has not been undertaken.

value of about −12, the occurrence of ipso substitution by solvent at C_4 of the aryl ring, and $k(CN)/k(H)$ ratios as large as 175. These diverse results are all interpretable in terms of the intermediacy of benzylic carbocations with a very high degree of positive charge delocalization onto the aryl ring.

Experimental Section

Fluorinated solvents and reagents were purchased from Aldrich and were purified as reported previously.[1,4b] Reactions were carried out under N_2 in glassware that had been oven or flame dried. Liquid chromatographic purifications were carried out with use of glass columns or a Chromatotron centrifugal radial thin-layer chromatograph from Harrison Research. ^1H and ^{19}F NMR spectra were measured on Varian T-60 and XL-200 instruments, respectively.[20] Elemental analyses are by Galbraith Laboratories.

The preparations of **12** and **14** were described previously.[4b] The carbinols p-$XC_6H_4C(CF_3)_2OH$ with X = Me_2N (**5**), OMe (**32**), Me (**33**), and F (**34**) were prepared by known[6] methods, while p-$MeC_6H_4C(CF_3)(CN)OH$ (**35**) was prepared from the ketone by using our previous procedure.[4b] Tosylates **9–11** were prepared from the carbinols by reaction with KH and then TsCl in ether[4b] and the p-nitrobenzoate **4** was prepared by the same general procedure with KH and then p-NBCl in ether. The cyano tosylate **13** was prepared from the carbinol, TsCl, and pyridine.[4b]

Kinetic measurements were made by UV as described previously.[1b]

1-Aryl-1-(trifluoromethyl)-2,2,2-trifluoroethanols. Aryl bromide (40 mmol) was added dropwise to Mg (42 mmol) in 40 mL of ether with a few crystals of I_2 in a 2-necked flask equipped with a dry ice condenser and a magnetic stirrer with spontaneous refluxing. Hexafluoroacetone was generated by dripping hexafluoroacetone sesquihydrate (13.7 g, 74 mmol) into P_2O_5 (35 g) with magnetic stirring at a rate such that no cloudy vapor evolved and was swept into the solution of ArMgBr by a slow stream of N_2. After addition was complete the solution was stirred overnight, aqueous HCl was added, the product was extracted with ether which was dried and evaporated, and the carbinols were obtained by vacuum distillation.

1-(*p*-(Dimethylamino)phenyl)-1-(trifluoromethyl)-2,2,2-trifluoroethanol (5). A mixture of hexafluoroacetone sesquihydrate (9.2 g, 50 mmol) and *N,N*-dimethylaniline (4.85 g, 40 mmol) was refluxed 17 h, dissolved in ether, washed with NaCl solution, dried, the ether evaporated, and the product was recrystallized from pentane. Yield 83%; mp 75.5–77.5 °C (lit.[6a] mp 75–76 °C); IR (CCl_4) 3605 cm^{-1} (OH); ^1H NMR (CCl_4) δ 2.98 (s, 6, 2 CH_3), 3.32 (s, 1, OH), 6.57–7.53 (q, 4, Ar); ^{19}F NMR (C_6D_6) δ 2.17; mass spectrum m/e (rel intensity) 287 (57, M^+), 218 (100, $M^+ - CF_3$), 148 (54, p-$Me_2NC_6H_4CO^+$).

1-(*p*-Methoxyphenyl)-1-(trifluoromethyl)-2,2,2-trifluoroethanol (32): yield (chromatographed on Florisil) 72%; mp 94–100 °C (lit.[6d] mp 101–102 °C); IR (CCl_4) 3580 cm^{-1} (OH); ^1H NMR (CCl_4) δ 3.36 (s, 1, OH), 3.82 (s, 3, CH_3), 6.80–7.66 (q, 4, Ar); ^{19}F NMR (C_6D_6) δ 2.07; mass spectrum m/e (rel intensity) 274 (44, M^+), 205 (100, $M^+ - CF_3$), 135 (91, p-$AnisCO^+$).

1-(*p*-Tolyl)-1-(trifluoromethyl)-2,2,2-trifluoroethanol (33): yield 90%, bp 54 °C (9 mmHg) [lit.[6c] bp 69–70 °C (6 mmHg)]; IR (CCl_4) 3600 cm^{-1} (OH); ^1H NMR (CCl_4) δ 2.37 (s, 3, CH_3), 3.14 (s, 1, OH), 7.08–7.60 (q, 4, Ar); mass spectrum m/e (rel intensity) 258 (51, M^+), 189 (100, $M^+ - CF_3$), 119 (99, p-$TolCO^+$).

1-(*p*-Fluorophenyl)-2-(trifluoromethyl)-2,2,2-trifluoroethanol (34): yield 90%; bp 62–64 °C (24 mmHg) [lit.[6c] bp 55–56 °C (6 mmHg)]; IR (CCl_4) 3630 cm^{-1} (OH); ^1H NMR (CCl_4) δ 3.35 (s, 1, OH), 7.0–7.9 (m, 4, Ar); mass spectrum m/e (rel intensity) 262 (32, M^+), 193 (68, $M^+ - CF_3$), 123 (100, p-$FC_6H_4CO^+$).

1-(*p*-Tolyl)-1-cyano-2,2,2-trifluoroethanol (35): yield 50%; mp 73–76 °C; IR (CCl_4) 3610 cm^{-1} (OH); ^1H NMR (CCl_4) δ 2.40 (s, 3, CH_3), 4.40 (s, 1, OH), 7.12–7.56 (q, 4, Ar); mass spectrum, m/e (relative intensity) 215 (18, M^+), 188 (22, $M^+ - HCN$), 146 (81, $M^+ - CF_3$), 119 (100, p-$TolCO^+$); high-resolution mass spectrum 215.0560, calcd for $C_{10}H_8F_3NO$ 215.0558. Anal. Calcd: C, 55.82; H, 3.75; N, 6.51. Found: C, 55.81; H, 3.93; N, 6.61.

1-(*p*-(Dimethylamino)phenyl)-1-(trifluoromethyl)-2,2,2-trifluoroethyl *p*-nitrobenzoate (4): yield 35%; mp 126–127 °C; IR (CCl_4) 1783 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 3.00 (s, 6, 2 CH_3), 6.54–7.27 (q, 4, $Me_2NC_6H_4$), 8.28 (s, 4, $C_6H_4NO_2$); mass spectrum (rel intensity) 436 (31, M^+), 270 (24, M^+ − OPNB), 251 (12, M^+ − F, OPNB), 150 (100, PNB^+); high-resolution mass spectrum 436.0874, calcd for $C_{18}H_{14}F_6N_2O_4$ 436.0858. Anal. Calcd: C, 49.55; H, 3.23; N, 6.42. Found: C, 49.09; H, 3.29; N, 6.06.

(20) The ^1H NMR spectra of the para-disubstituted aryl derivatives were typically AA'XX' quartets.

1-(*p*-Methoxyphenyl)-1-(trifluoromethyl)-2,2,2-trifluoroethyl tosylate (9): yield 30%; mp 64–70 C dec; ^1H NMR (CCl_4) δ 2.45 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 6.8–7.9 (m, 8, overlapping q of 2 Ar); mass spectrum m/e (rel intensity) 428 (28, M^+), 258 (100, $M^+ - OTs$), 239 (16, $M^+ - F, OTs$), 155 (93, Ts^+), high-resolution mass spectrum 428.0505, calcd for $C_{17}H_{14}F_6O_4S$ 428.0517.

1-(*p*-Tolyl)-1-(trifluoromethyl)-2,2,2-trifluoroethyl tosylate (10): yield 40%; mp 90–93 °C; ^1H NMR (CCl_4) δ 2.40 (s, 3, CH_3), 2.46 (s, 3, CH_3), 7.1–7.9 (m, 8, overlapping q of 2 Ar); mass spectrum m/e (rel intensity) 412 (24, M^+), 241 (41, $M^+ - OTs$), 222 (6, $M^+ - F, OTs$), 155 (100, Ts^+); high-resolution mass spectrum 412.0583, calcd for $C_{17}H_{14}F_6O_3S$ 412.0568.

1-(*p*-Fluorophenyl)-1-(trifluoromethyl)-2,2,2-trifluoroethyl tosylate (11): yield 53%; mp 54–78 °C dec; ^1H NMR (CCl_4) δ 2.48 (s, 3, CH_3), 7.0–8.0 (m, 8, 2 Ar); mass spectrum m/e (rel intensity) 416 (18, M^+), 245 (25, $M^+ - OTs$), 155 (100, Ts^+); high-resolution mass spectrum 416.0330, calcd for $C_{16}H_{11}F_7O_3S$ 416.0317. Anal. Calcd: C, 46.16; H, 2.66. Found: C, 46.38; H, 2.69.

1-(*p*-Tolyl)-1-cyano-2,2,2-trifluoroethyl tosylate (13): mp 89–91 °C; ^1H NMR (CCl_4) δ 2.42 (s, 3, CH_3), 2.50 (s, 3, CH_3), 7.2–7.9 (m, 8, overlapping q of 2 Ar); mass spectrum, m/e (relative intensity) 369 (26, M^+), 214 (15, $M^+ - Ts$), 198 (100, $M^+ - TsO$); high-resolution mass spectrum; M^+ obscured by reference peak, calcd for $C_{10}H_7F_3NO$ ($M^+ - Ts$) 214.0480, found 214.0482. Anal. Calcd for $C_{17}H_{14}F_3NO_2S$ (MW 369.37): C, 55.28; H, 3.82; N, 3.79. Found: C, 55.33; H, 3.91; N, 3.77.

Solvolysis Products from 4. A solution of 100 mg (0.23 mmol) of **4** dissolved in 5 mL of HFIP containing 29.4 mg (0.24 mmol) of Et_3N was sealed in ampules and kept 2 h at 25 °C. The contents were poured into H_2O/ether and extracted with ether; the extact was then washed with $NaHCO_3$, dried, and evaporated. The crude product was recrystallized from pentane at −78 °C to give **6**. The solvolysis of **4** in TFE to give **7** was carried out in a similar fashion at 44 °C for 30 h, and the product was purified by VPC (Carbowax 20M column). The solvolysis of **4** in EtOH for 3 h at 75 °C to give **8** (recrystallized from pentane at −78 °C) was similar except no Et_3N was present.

6: mp 36–37 °C; mass spectrum 437 (M^+); ^1H NMR (CCl_4) δ 3.00 (s, 6, Me_2N), 4.63 (heptet, 1, J = 7 Hz, $CH(CF_3)_2$), 6.6–7.6 (q, 4, Ar). Anal. Calcd for $C_{14}H_{11}F_{12}NO$: C, 38.46; H, 2.54; N, 3.20. Found: C, 38.49; H, 2.60; N, 3.29.

7: Mp 35–37 °C; ^1H NMR (CCl_4) δ 2.99 (s, 6, Me_2N), 3.95 (q, 2, J = 7 Hz, CH_2CF_3), 6.5–7.2 (q, 4, Ar). Anal. Calcd for $C_{13}H_{12}F_9NO$: C, 42.29; H, 3.28; N, 3.78. Found: C, 42.04; H, 3.30; N, 3.69.

8: mp 68–69 °C; ^1H NMR (CCl_4) δ 1.18 (t, 3, J = 7 Hz, CH_2CH_3), 3.0 (s, 6, Me_2N), 3.58 (q, 2, CH_2CH_3), 6.6–7.4 (q, 4, Ar). Anal. Calcd for $C_{13}H_{15}F_6NO$: C, 49.53; H, 4.80; N, 4.44. Found: C, 50.02; H, 5.03; N, 4.43.

Solvolysis Products from 9. A solution of **9** (0.100 g, 0.233 mmol) in 5 mL of 100% freshly distilled TFE was kept at 25 °C for 0.5 h. After aqueous workup the product, which contained only **15** and some residual **9** by ^1H NMR analysis, was separated by VPC (10 mm × 3 m Carbowax 20 M column, 160 °C, retention time 9 min) and **15** was collected: ^1H NMR (CCl_4) δ 3.90 (s, 1, CH_3O), 3.96 (q, 2, J = 7 Hz, CF_3CH_2O), 7.25 (q, 4, Ar). Anal. Calcd for $C_{12}H_9F_9O_2$ (MW 356.20): C, 40.46; H, 2.55. Found: C, 40.48; H, 2.64.

Reaction of **9** (0.100 g, 0.233 mmol) dissolved in 20 mL of 100% EtOH for 24 h at 25 °C and aqueous extraction gave a mixture of **22** and **23** as shown by ^1H NMR. Collection of VPC as above showed the products were presented in equal amounts. **22**: ^1H NMR (CCl_4) δ 1.30 (t, 3, J = 7 Hz, CH_3CH_2), 3.60 (br q, 2, J = 7 Hz, CH_3CH_2), 3.80 (s, 3, CH_3O), 7.14 (q, 4, Ar). Anal. Calcd for $C_{12}H_{12}F_6O_2$ (302.22): C, 47.69; H, 4.00. Found: C, 47.57; H, 4.10. **23**: ^1H NMR (CCl_4) δ 1.30 (t, 3, J = 7 Hz, $CH_3CH_2OC(CF_3)_2$, 1.42 (t, 3, J = 7 Hz, CH_3CH_2OAr), 3.60 (br q, 2, J = 7 Hz, $CH_2OC(CF_3)_2$), 4.02 (q, 2, J = 7 Hz, CH_2OAr), 7.10 (q, 4, Ar). Anal. Calcd for $C_{13}H_{14}F_6O_2$ (316.24): C, 49.37; H, 4.46. Found: C, 49.24; H, 4.53.

Reaction of **9** (40.4 mg, 0.0932 mmol) dissolved in CD_3OH for 10 h at 25 °C and aqueous workup gave the product which was purified by VPC as above and analyzed to be a mixture of **24** and **25** in the ratio 69/31 by he ratio of M^+ peaks at 291 and 294, respectively, in the 70-eV mass spectrum. ^1H NMR δ 3.82 (s, CH_3O), 7.18 (q, 4, Ar). From the integrals of the NMR peaks the mixture was calculated to be a 57/43 mixture of **24** and **25** but this analysis is regarded as being less precise than that for mass spectrometry.

Trifluoroacetolysis Products from 10–12 and 14. A solution of **10** (100 mg, 0.24 mmol) in 1 mL of TFA was heated in an NMR tube for 3 h at 72 °C, and the ^1H NMR solution changed to that of a mixture of **17**, TsOH, and an unidentified material with a characteristic signal at δ 5.40 and an intensity equivalent to about 0.3 protons. The solution was poured into ice water and extracted with ether which was washed with $NaHCO_3$, dried, evaporated, and separated by VPC (10 mm × 3 m OV-17 column,

130 °C, retention time 3 min) to give **17**: ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3, CH_3), 7.30 (s, 4, Ar); IR (CCl_4) 1823 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 354 (98, M^+), 285 (100, $M^+ - CF_3$) 257 (74, $M^+ - CF_3CO$), 241 (46, $M^+ - CF_3CO_2$). The unidentified material showed singlets at δ 5.38 and 7.42 ($CDCl_3$, rel intensity 1:2) but was not examined further.

Similar treatment of **11** gave **18**: ^{1}H NMR (CCl_4) δ 7.0–8.0 (m, Ar); IR (CCl_4) 1830 cm^{-1} (C=O). And **12** gave **19**: ^{1}H NMR (CCl_4) δ 7.46 (s, Ar); IR (CCl_4) 1820 cm^{-1} (C=O).

The analogous reaction of **14** gave **21**: ^{1}H NMR (CCl_4) δ 7.60 (s, Ar); IR (CCl_4) 1825 cm^{-1} (C=O). An authentic sample of **21** was prepared by the reaction of $PhC(CF_3)(CN)OH$[4b] (1 mmol) with 0.75 mL of $(CF_3CO)_2O$ and a drop of pyridine for 2 days at 0 °C followed by evaporation of the solvent.

Trifluoroethanolysis of 13. A solution of **13** (80 mg, 0.22 mmol) and 20 mg (0.32 mmol) of urea in 10 mL of TFE was kept 5 days at 25 °C, poured into ice water–ether, and extracted with ether; the extract was then dried and evaporated and purified by VPC (OV 17 column, 170 °C, retention time 15 min) to give *p*-tolyl-1-cyano-2,2,2-trifluoroethyl 2,2,2-trifluoroethyl ether (**20**) as the only observed product: ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3, CH_3), 3.7–4.0 (m, 2, CH_2CF_3), 7.2–7.6 (q, 4, Ar); mass spectrum *m/e* (rel intensity) 298 (82, $M^+ + 1$), 229 (86, $M^+ - CF_3$), 199 (43, $M^+ - CF_3CH_2O$), 119 (100, $TolCO^+$). Anal. Calcd for $C_{12}H_9F_6NO$ (297.21): C, 48.50; H, 3.05; N, 4.71. Found: C, 48.47; H, 3.25; N, 4.56.

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Appendix: Calculation of *k*(OTs)/*k*(OPNB) Ratios

The rate constant for solvolysis of *p*-AnisCH(OPNB)CH_3 (**36**) at 25 °C in 70% acetone is 4.53 × 10^{-7} s^{-1} (extrapolated from data[7a] at higher temperature) and a rate constant for *p*-AnisCH(OTs)CH_3 (**37**) under the same conditions of 2.6 × 10^2 s^{-1} is obtained from the *mY* correlation log $K = 1.23Y_{OTs} + 1.95$ for **37** derived from calculated log *k* values of **37** in 97% HFIP and 97% TFE of 6.39 and 4.20, respectively. These log *k* values are obtained from the relations log $k = -5.94\sigma^+ + 1.76$ (97% HFIP) and log $k = -5.05\sigma^+ + 0.26$ (97% TFE) for $ArCH(OTs)CH_3$[7b] and the Y_{OTs} value of 0.38 for 70% acetone extrapolated from published data for 10 to 60% acetone.[8] These values give *k*(OTs)/*k*(OPNB) = 5.7 × 10^8.

Combination of the rate ratios *k*(*t*-BuCl)/*k*(*t*-BuOPNB) = 2.6 × 10^4 (80% acetone)[10a,b] and *k*(*exo*-2-NbOTs)/*k*(*exo*-2-NbCl) = 1.7 × 10^3 (60% acetone, Nb = norbornyl)[10c,d] gives *k*(OTs)/*k*(OPNB) = 4.4 × 10^7. Combination of the rate ratio *k*(*t*-BuCl)/*k*(*t*-BuOPNB) = 2.6 × 10^4 (80% acetone)[10a,b] and *k*(*endo*-2-NbOTs)/*k*(*endo*-2-NbCl) = 36 (60% acetone)[10c,d] gives *k*(OTs)/*k*(OPNB) = 9.4 × 10^6. A rate ratio *k*(OTs)/*k*(OPNB) = 2 × 10^9 may be derived from other reported comparisons.[11]

Organic Synthesis with Enzymes. 3.[1] TBADH-Catalyzed Reduction of Chloro Ketones. Total Synthesis of (+)-(*S*,*S*)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid: A Civet Constituent

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Abstract: Highly enantioselective reduction of aliphatic chloro ketones catalyzed by *Thermoanaerobium brockii* alcohol dehydrogenase (TBADH) afforded the corresponding *S* chloro alcohols, which are new and useful chiral bifunctional building blocks. The synthetic potential of these compounds was illustrated by syntheses of several optically pure cyclic ethers. In particular, (*S*)-(+)-5-chloropentan-2-ol was used for the total synthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl) acetic acid, a natural constituent of the perfume material civet. Two of the key steps in the synthesis involve organopalladium chemistry: a Pd(0)-catalyzed intramolecular allylic etherification followed by a Pd(II)-catalyzed Wacker oxidation of the disubstituted olefin.

A most general and reliable approach to the total synthesis of optically active compounds takes advantage of chiral starting materials that are readily available from natural sources. Carbohydrates, tartaric acid, malic acid, lactic acid, amino acids, etc., have been extensively used as a "chiral pool"[2] for preparing a variety of highly functionalized chiral building blocks (chirons[3]). Interestingly, simple aliphatic chirons are less readily available from the above-mentioned chiral pool compounds, as their preparation usually requires multistep removal of functional groups. Enzymes present attractive alternatives for the preparation of new chiral compounds that are not easily derived from natural products.

In the preceding paper we introduced a wide variety of chiral aliphatic secondary alcohols that were efficiently produced by *Thermoanaerobium brockii* alcohol dehydrogenase (TBADH)[4] catalyzed reduction. However, since most of these alcohols possess

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