Tetrakis(dimethylamino)ethylene as a Useful Reductant of Some Bromodifluoromethyl Heterocycles. Application to the Synthesis of New *gem*-Difluorinated Heteroarylated Compounds

Conrad Burkholder and William R. Dolbier, Jr.

Department of Chemistry, University of Florida, P.O. Box 117200, Gainesville, Florida 32611-7200

Maurice Médebielle*

Université Denis Diderot (Paris 7), Laboratoire d'Electrochimie Moléculaire, UMR CNRS 7591, 2 Place Jussieu, 75251 Paris Cedex 05, France

Received February 4, 1998

The cyclic voltammetry of the reductive cleavage of some bromodifluoromethyl heterocycles and of the oxidation of the tetrakis(dimethylamino)ethylene was investigated in *N*,*N*-dimethylformamide and acetonitrile, at an inert electrode. The systematic investigation of the kinetics of the electrochemical reduction of this series of bromodifluoromethyl compounds provides clear evidence of a concerted electron-transfer−bond-breaking mechanism. Application of the theory of the dissociative electron transfer allowed the estimation of the carbon−halogen bond dissociation energy and the standard potential of the reaction. On the basis of the electrochemical experiments, the tetrakis(dimethylamino)ethylene (TDAE) was found to be an effective reductant of the 2-(bromodifluoromethyl)benzoxazole (**1**) and of the 5-(bromodifluoromethyl)-3-phenyl-1,2,4-oxadiazole (**4**). A stepwise electron transfer with a difluoromethyl radical as intermediate is assumed to take place in this reaction. Under mild conditions, the generated difluoromethyl heterocyclic anion was efficiently trapped with aromatic and heterocyclic aldehydes **7**−**17** and ketones **18** and **19**. In this way, the corresponding β,β-difluoro-α-heteroarylated alcohols **20**−**38** were obtained in moderate to good yields and the compounds **20**, **21**, and **23**−**27** were tested against the HIV-1 virus.

There is an increasing interest in organofluorine chemistry for the synthesis of new *gem*-difluorinated compounds in view of the potential biological properties of such molecules.[1] Many selectively fluorinated analogues of biologically important compounds have exhibited dramatic enhancement in their biological activity.[2] Very recently, highly desirable new methodologies for the synthesis of interesting *gem*-difluoromethylene compounds, using free-radical difluoromethylene radicals[3] as well as new nucleophilic difluoromethylene synthons,[4] have been published.

Trifluoromethyl-substituted heterocycles have received considerable interest because of their potential biological properties, and a large number of such heterocycles have been synthesized during the past decade.[5] However, there are few reports on the synthesis of halodifluoromethyl heterocycles,[6] and as far as we know, there exists no general method to prepare them. Such halodifluoromethyl heterocycles would be very useful starting materials to build new difluorinated heterocycles as it is anticipated that the carbon−halogen bond should be quite reactive in single-electron-transfer (SET) reactions, both chemically and electrochemically.

The reverse transcriptase (RT) of the human immunodefficiency virus type 1 (HIV-1) has been, to date, one of the main targets in medicinal chemistry, and the search of new drugs that may be useful for chemotherapeutic intervention in acquired immunodefficiency syndrome (AIDS)[7] is ongoing. The currently approved antiretroviral compounds (AZT, ddI, ddC, d4T) are nucleoside analogues, all of which inhibit competitively the RT enzyme, leading to chain termination during the process of reverse transcription. Unfortunately, the clinical usefulness of these drugs is limited by side effects, toxicities, and drug resistance.[8] Several specific non-nucleoside reverse transcriptase inhibitors (NNRTIs), first discovered by random screening (HEPT, TIBO, αAPA, nevirapine, BHAP...), have also been evaluated in monotherapy protocol trials; however, these trials had to be discontinued due to rapid emergence of viral resistance.[8,9] At the present time, it is generally considered that the use of NNRTIs in combination with other agents (nucleosides, protease inhibitors...) remains a viable alternative in AIDS chemotheraphy.[9] A large number of these NNRTIs are heterocycles or fused

* To whom correspondence should be addressed. Fax: +33 (0) 1. 44. 27. 76. 25. E-mail: mauricem@paris7.jussieu.fr.

(1) Tozer, M. J.; Herpin, T. *Tetrahedron* **1996**, *52*, 8619.

(2) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991.

(3) (a) Médebielle, M. *Tetrahedron. Lett.* **1996**, *37*, 5119. (b) Médebielle, M. *Tetrahedron. Lett.* **1995**, *36*, 2071. (c) Qiu, Z.-M.; Burton, D. J. *J. Org. Chem.* **1995**, *60*, 5570. (d) Itoh, T.; Ohara, H.; Emoto, S. *Tetrahedron Lett.* **1995**, *36*, 3531. (d) Buttle, L. A.; Motherwell, W. B. *Tetrahedron Lett.* **1994**, *35*, 3995. (e) See also ref 1.

(4) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *J. Org. Chem.* **1996**, *61*, 166 and references therein.

(5) Burger, K.; Wucherpfennig, U.; Brunner, E. *Adv. Heterocycl. Chem.* **1994**, *60*, 1.

(6) (a) Luo, B.-H.; Guan, H.-P.; Hu, C.-M. *Synlett* **1997**, 1261. (b) Goure, W. F. *J. Heterocycl. Chem.* **1993**, *30*, 71. (c) South, M. S.; Van Sant, K. A. *J. Heterocycl. Chem.* **1991**, *28*, 1017. (d) Hamper, B. C. *J. Fluorine Chem.* **1990**, *48*, 123. (e) Morimoto, K.; Makino, K.; Yamamoto, S.; Sakata, G. *J. Heterocycl. Chem.* **1990**, *27*, 807. (f) Fujii, S.; Kimoto, K.; Maki, Y. *Rep. Gov. Ind. Res. Inst. Nagoya.* **1986**, *35(3)*, 117−29; *Chem. Abstr.* **1987**, *106*, 156352j.

(7) Connoly, K. J.; Hammer, S. L. *Antimicrob. Ag. Chemotheraphy.* **1992**, *36*, 509.

(8) Kilby, J. M.; Saag, M. S. *Infect. Ag. Diseases* **1994**, *3*, 313.

(9) Romero, D. L. *Annu. Rep. Med. Chem.* **1994**, *13*, 123.

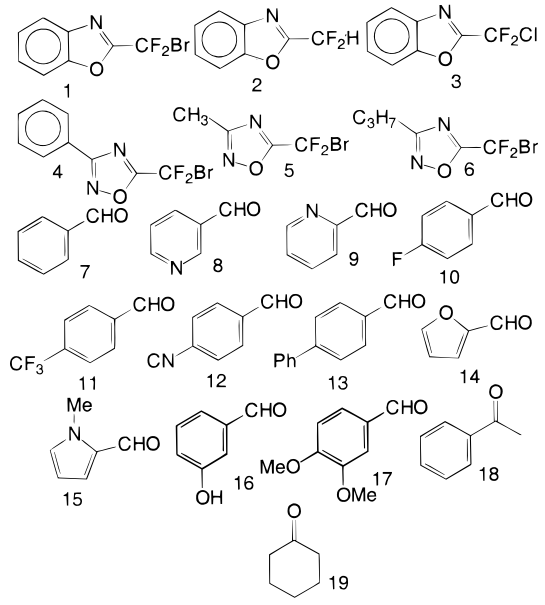
S0022-3263(98)00201-1 CCC: $15.00
Published on Web 07/07/1998

heterocycles;[10] however, it is surprising that no *gem*-difluorinated heterocycles (some molecules containing one or two fluorine atoms on the rings are reported) were synthesized in these studies and screened as HIV-1 specific reverse-transcriptase inhibitors. Such heterocycles, due to the presence of a difluoromethylene moiety, often recognized as a key in biological activity, would be, therefore, worth designing for biological screening.

Tetrakis(dimethylamino)ethylene (TDAE) has an ionization potential of 6.13 eV[11] and has a reducing power close to zinc.[11] There are a limited number of reports on the use of TDAE in organofluorine synthesis; Carpenter[12a] has shown that TDAE reacts with fluorinated polyhalogenated compounds such as 1,1,1-trifluoropentachloropropane ($CF_3CCl_2CCl_3$) and 1,1,1,4,4,4-hexafluorotetrachlorobutane ($CF_3CCl_2CCl_2CF_3$) to produce the corresponding olefins ($CF_3CCl{=}CClCF_3$ and $CF_3CCl{=}CCl_2$) by loss of the two vicinal chlorine atoms; perfluoroheptyl iodide ($C_7F_{15}I$) reacts with TDAE by replacement of the iodide with a hydrogen. Later, Carpenter[12b] extended the use of the TDAE for the defluorination of fluorinated triazoles under more drastic conditions (at 100 °C). Pawelke et al.[13a] then demonstrated that, at low temperatures, TDAE and CF_3I form a charge-transfer complex that can act as a nucleophilic trifluoromethylating agent in polar solvents; in such a way, some (trifluoromethyl)boron [$(CF_3)_3BNHEt_2$] and -silicon compounds [CF_3SiMe_3 and $Me_2Si(CF_3)_2$] were obtained in reasonable yields. Later, the methodology was extended to the synthesis of *N*-(trifluoromethyl)dialkylamines (R_2NCF_3) through the reduction of CF_2Br_2 in the presence of secondary amines[13b] and also for the synthesis of (fluoromethyl)silicon derivatives through the reduction of $CFBr_3$ in the presence of organochlorosilanes $R_{4-n}SiCl_n$.[13c] Very recently, Chambers et al.[14a] elegantly demonstrated that TDAE could act as a useful defluorination reagent of fluorinated alkenes to yield a fluoride salt $[TDAE]^{2+}2F^-$ that is soluble in a wide range of organic solvents. In addition, stable fluorinated anions of TDAE have been isolated using this process.[14b] Finally, TDAE can react with anhydrous unsaturated fluorocarbons to produce "in situ", powerful fluoride-ion sources. These fluoride anions were used for oligomerization and polyfluoroalkylation reactions.[14c] These studies involving TDAE are probably electron-transfer reactions, with formation of charge-transfer complexes. However, in these TDAE studies, no examples have been reported of the generation of a difluoromethyl heterocyclic anion that could be used in synthetic applications.

As part of our ongoing effort in the synthesis of new fluorinated compounds with potential biological and synthetic applications,[15] we wish to report a novel use of tetrakis(dimethylamino)ethylene, as an electron donor, to generate stable difluoromethyl heterocyclic anions,[16] which can be utilized to react with various aldehydes and ketones in the synthesis of new β,β-difluoro-α-heteroarylated alcohols. The major objective of this work was to prepare a large spectrum of compounds for biological screening against HIV-1. However, this quest also led to the discovery of a new, general method for the in situ preparation of heteroaromatic difluoromethyl anions, which can participate in predictable reactions which have considerable synthetic utility.

Substrates **1**−**6**, 2-(bromodifluoromethyl)benzoxazole (**1**), 2-(difluoromethyl)benzoxazole (**2**), 2-(chlorodifluoromethyl)benzoxazole (**3**), 5-(bromodifluoromethyl)-3-phenyl-1,2,4-oxadiazole (**4**), the 5-(bromodifluoromethyl)-3-methyl-1,2,4-oxadiazole (**5**), 5-(bromodifluoromethyl)-3-propyl-1,2,4-oxadiazole (**6**), aldehydes **7**−**17**, benzaldehyde (**7**), 3-pyridinecarboxaldehyde (**8**), 2-pyridinecarboxaldehyde (**9**), 4-fluorobenzaldehyde (**10**), α,α,α-trifluorobenzaldehyde (**11**), *p*-cyano benzaldehyde (**12**), 4-biphenylcarboxaldehdye (**13**), 2-furfural (**14**), *N*-methyl-2-carboxaldehyde (**15**), 3-hydroxybenzaldehyde (**16**), 3,4-dimethoxybenzaldehyde (**17**), and ketones such as acetophenone (**18**) and cyclohexanone (**19**) were used. The



corresponding alcohols are numbered **20**, **21**, etc. Compounds are shown in Charts 1 and 2.

(10) Selected examples. (a) Nevirapine: Merluzzi, V. J.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shin, C.-K.; Eckner, R. J.; Koup, R. A.; Sullivan, J. L. *Science* **1990**, *250*, 1411. (b) TIBO: Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M. J.; Breslin, H. J.; Raeymaeckers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. *Nature* **1990**, *343*, 470. (c) Ateviridine: Romero, D. L.; Busso, M.; Tan, C. K.; Reusser, F.; Palmer, J. R.; Poppe, S. M.; Aristoff, P. A.; Downey, K. M.; So, A. G.; Resnick, L.; Tarpley, W. G. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8806. (d) A pyridinone derivative (L-697, 661): Hoffman, J. M.; Smith, A. M.; Rooney, C. S.; Fisher, T. E.; Wai, J. S.; Thomas, C. M.; Bamberger, D. L.; Barnes, J. L.; Williams, T. M.; Jones, J. H.; Olson, B. D.; O'Brien, J. A.; Goldman, M. E.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Andersen, P. S. *J. Med. Chem.* **1993**, *36*, 953 and references cites therein. (e) Indole derivatives: Young, S. D.; Amblard, M. C.; Britcher, S. F.; Grey, V. E.; Tran, L. O.; Lumma, W. C.; Huff, J. R.; Schleif, W. A.; Emini, E. E.; O'Brien, J. A.; Pettibone, D. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 491.

(11) Wiberg, N. *Angew. Chem.* **1968**, *20*, 809.

(12) (a) Carpenter, W. *J. Org. Chem.* **1965**, *30*, 809. (b) Carpenter, W. *J. Org. Chem.* **1966**, *31*, 789.

(13) (a) Pawelke, G. *J. Fluorine Chem.* **1989**, *42*, 429. (b) Pawelke, G. *J. Fluorine Chem.* **1991**, *52*, 229. (c) Bürger, H.; Moritz, P. *Organometallics* **1993**, *12*, 4930.

(14) (a) Briscoe, M. W.; Chambers, R. D.; Mullins, S. J.; Nakamura, T.; Vaughan, J. F. S.; Drakesmith, F. G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3115. (b) Chambers, R. D.; Vaughan, J. F. S.; Mullins, S. J.; Nakamura, T.; Roche, A. J. *J. Fluorine Chem.* **1995**, *72*, 231. (c) Chambers, R. D.; Gray, W. K.; Korn, S. T. *Tetrahedron* **1995**, *51*, 13167.

(15) (a) Médebielle, M.; Pinson, J.; Savéant, J.-M. *Electrochim. Acta* **1997**, *42*, 2049. (b) Xu, Y.; Dolbier, W. R., Jr.; *J. Org. Chem.* **1997**, *62*, 6503. (c) Médebielle, M.; Oturan, M. A.; Pinson, J.; Savéant, J.-M. *J. Org. Chem.* **1996**, *61*, 1331. (c) Médebielle, M. *Tetrahedron. Lett.* **1996**, *37*, 5119. (d) Dolbier, W. R., Jr.; Burkholder, C. R.; Abboud, K. A.; Loehle, D. *J. Org. Chem.* **1994**, *59*, 7688.

(16) A preliminary account of this work has been published: Burkholder, C.; Dolbier, W. R., Jr.; Médebielle, M. *Tetrahedron. Lett.* **1997**, *38*, 821.

Chart 1

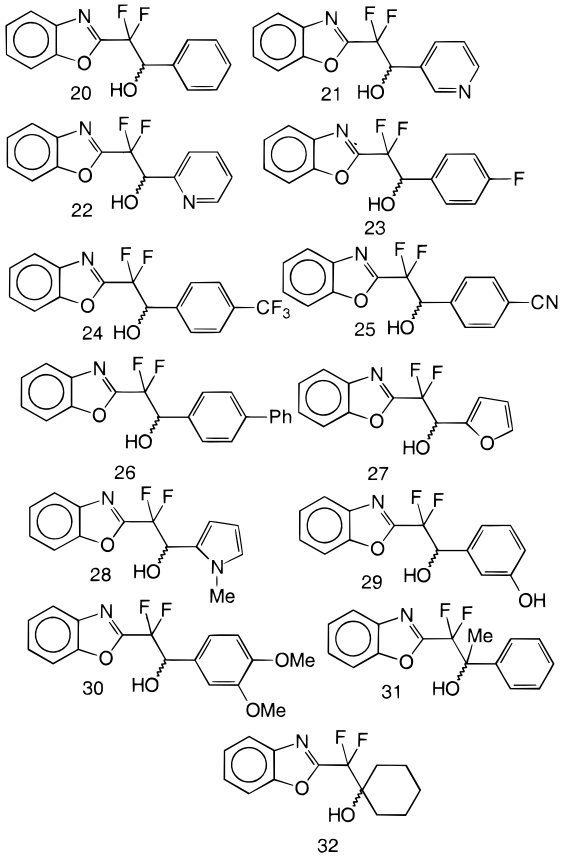
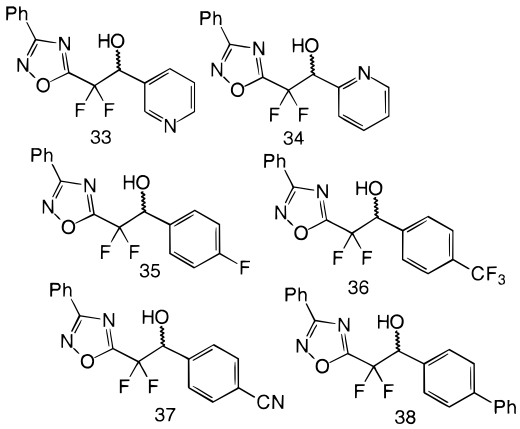


Chart 2



Results and Discussion

In CH_3CN, electrochemical oxidation of TDAE occurs in two reversible one-electron oxidation steps, to $[TDAE]^{+}$ and $[TDAE]^{2+}$ at −0.78 and −0.61 V vs SCE (standard potential, $E° = (E_{pa} + E_{pc})/2$) (Figure 1a).[17a] However, in DMF, a two-electron reversible wave is observed at −0.62V vs SCE (standard potential, $E° = (E_{pa} + E_{pc})/2$ (Figure 1b).[17b] The superposition of the two one-electron steps points out that considerable conformational changes take place upon oxidation,[18a] and this effect is enhanced in DMF. Indeed, evidence of a restricted rotation about the $C-NMe_2$ bond has been found for the radical cation of TDAE.[19] In addition, AM1 calculations[19a] for $[TDAE]^{\cdot+}$ suggest that the positive charge might be distributed over the two molecular halves—in full agreement with the ^1H coupling constants obtained by ESR and especially ENDOR spectroscopy, respectively.[19b,c]

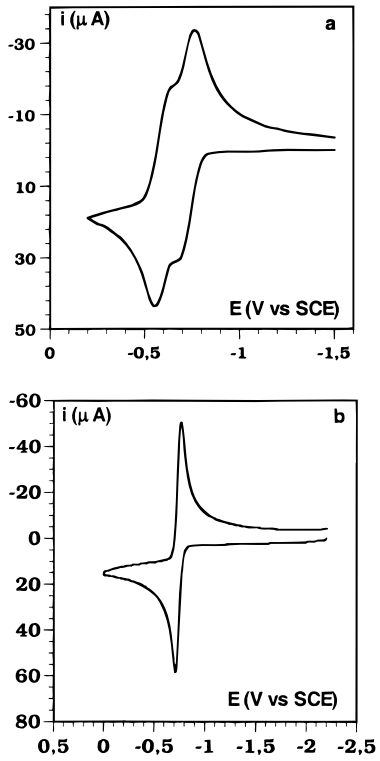


Figure 1. Cyclic voltammetry of tetrakis(dimethylamino)-ethylene (TDAE): (a) C = 4.3 mM in CH_3CN + 0.1 M Et_4NBF_4 at 20 °C, (b) C = 3.0 mM in DMF + 0.1 M Et_4NBF_4 at 20 °C. Scan rate: 0.2 V/s.

Cyclic voltammetry of 2-(bromodifluoromethyl)benzoxazole **1**[20] (in anhydrous DMF + 0.1 M Et_4NBF_4) shows two successive reduction waves; the first one is irreversible (up to 500 V/s), corresponding to the uptake of 1.5 electrons (as compared with the one-electron oxidation wave of the ferrocene) and located at −1.36 V vs SCE (E_p = peak potential at 0.2 V/s on a glassy carbon electrode). This reduction step corresponds to the cleavage of the C−Br bond and to the formation of the 2-(difluoromethyl)benzoxazole **2** as the reduction product (Figure 2a). The other irreversible wave, located at a more negative potential (E_p = −2.12V vs SCE at 0.2 V/s), is attributed to the reduction of this compound as was shown by comparison with an authentic sample (Figure 2b).[20] As expected, the 2-(chlorodifluoromethyl)benzox-

(17) (a) This observation is comparable to values of −0.53 and −0.68V vs SCE: Fox, J. R.; Foxman, B. M.; Guarrera, D.; Miller, J. S.; Calabrese, J. C.; Reis, A. H., Jr. *J. Mater. Chem*. **1996**, *6*, 1627. (b) This observation is comparable to value of −0.57 V vs SCE: Bock, H.; Jaculi, D. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 305.

(18) Such phenomena has already been observed for the 1,4,5,8-tetrakis(dimethylamino)naphthalene: (a) Kirsch, A.; Krieger, C.; Staab, H.; Neugebauer, F. A. *Tetrahedron. Lett*. **1994**, *35*, 8365. (b) Barth, T.; Krieger, C.; Neugebauer, F. A.; Staab, H. A. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1028. Other related studies: (c) Evans, D. H.; Hu, K. *J. Chem. Soc. Faraday Trans*. **1996**, *92*, 3983. (d) Evans, D. H.; Hu, K. *J. Electroanal. Chem*. **1997**, *423*, 29. (e) Evans, D. H.; Hu, K. *J. Phys. Chem*. **1996**, *100*, 3030.

(19) (a) Tanaka, K.; Sato, T.; Yamabe, T. *J. Phys. Chem*. **1996**, *100*, 3980. (b) Reference 10 in: Bock, H.; Borrmann, H.; Havlas, Z.; Oberhammer, H.; Ruppert, K.; Simon, A. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1678. (c) Bock, H.; Hierholzer, B. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 1069. (d) See ref 11.

(20) The synthesis of the halodifluoromethyl heterocycles will appear in a forthcoming paper: Burkholder, C.; Dolbier, W. R., Jr.; Médebielle, M. Submitted.

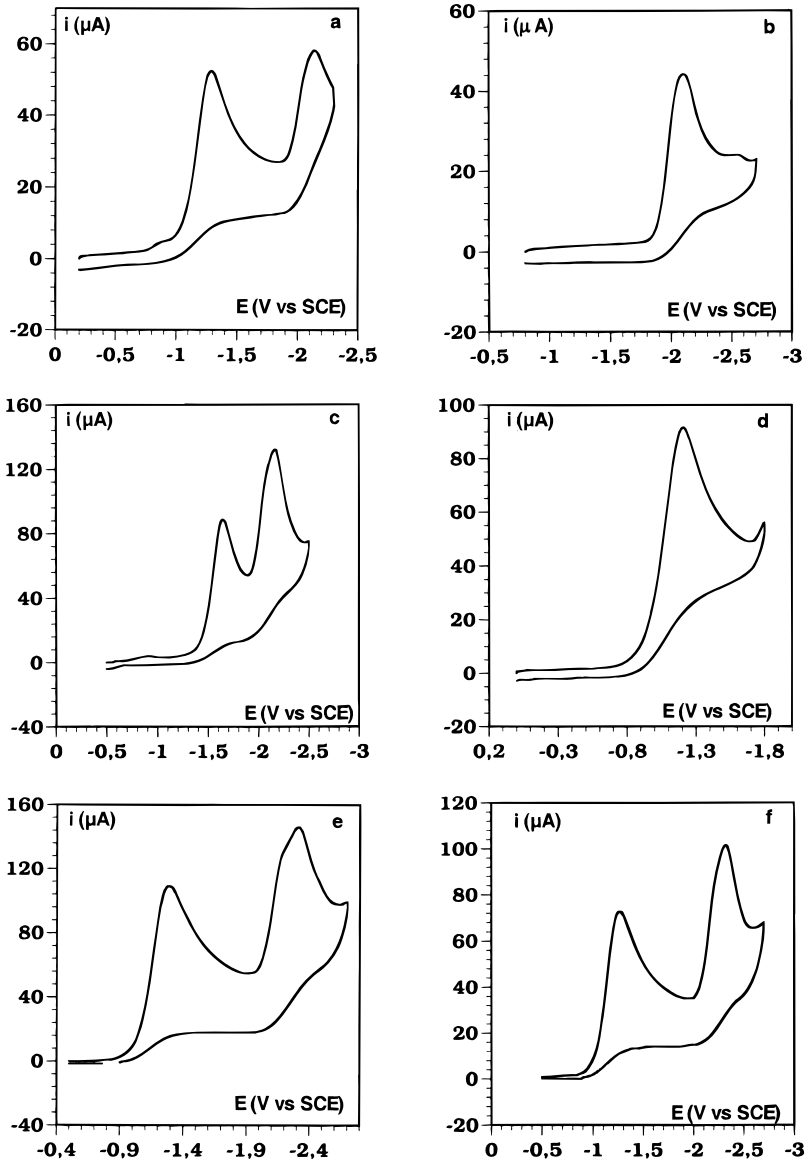


Figure 2. Cyclic voltammetry of the halodifluoromethyl heterocycles derivatives **1**−**6**: (a) 2-(bromodifluoromethyl)benzoxazole (**1**) (C = 1.65 mM); (b) 2-(difluoromethyl)benzoxazole (**2**) (C = 1.16 mM); (c) 2-(chlorodifluoromethyl)benzoxazole (**3**) (C = 3.94 mM); (d) 5-(bromodifluoromethyl)-3-phenyl-1,2,4-oxadiazole (**4**) (C = 4.21 mM); (e) 5-(bromodifluoromethyl)-3-methyl-1,2,4-oxadiazole (**5**) (C = 4.33 mM); (f) 5-(bromodifluoromethyl)-3-propyl-1,2,4-oxadiazole (**6**) (C = 3.28 mM); in DMF + 0.1 M Et_4NBF_4 at 20 °C. Scan rate: 0.2 V/s.

azole **3**[20] was found to be irreversibly reduced at a more negative potential than **1**, close to −1.66 V vs SCE (E_p at 0.2V/s on a glassy carbon electrode, Figure 2c). The bromodifluoromethyl oxadiazole compounds **4**−**6**[20] were found to be reduced at more positive potential than the benzoxazole derivative **1** (Figure 2d−f); for example, the compound **4** is irreversibly reduced (in anhydrous DMF + 0.1 M Et_4NBF_4) at −1.20 V vs SCE (E_p at 0.2 V/s on a glassy carbon electrode) followed by a small irreversible wave located at a more negative potential close to −2.0 V vs SCE (Figure 2d). The cyclic voltammetric data of the halodifluoromethyl heterocycles **1** and **3**−**6** are collected in the Table 1.

Examination of the cyclic voltammograms reveals a broad wave for the first reduction step, with a small value of the transfer coefficient α (close to 0.30) derived from the value of the peak width $E_{p/2} - E_p$ [E_p = peak potential; $E_{p/2}$ = half-peak potential: $\alpha = RT/F(1.85/E_{p/2} - E_p)$], characteristic of a reductive cleavage under kinetic control of a heterogeneous electron-transfer reaction.[21] The fact that the transfer coefficient α is significantly smaller than 0.5 (see Table 1) is a first indication that the reduction mechanism of these halodifluoromethyl compounds follows a concerted mechanism. Indeed, according to the theory of dissociative electron transfers,[22a,c]

Table 1. Determination of C−X Bond Dissociation Energies, Standard Potentials, and Intrinsic Barrier Free Energies from the Peak Potentials of the Halodifluoromethyl Heterocycles undergoing Dissociative Electron Transfer[a]

compd	$-E_p$ (V/SCE)	D (eV)	$-E°$ (V/SCE)	$\Delta G_0^{\ddagger}$ (V)	α
1	1.36	2.19	0.485	0.81	0.34
3	1.66	2.62	0.29	0.93	0.37
4	1.20	2.06	0.355	0.78	0.32
5	1.28	2.11	0.405	0.79	0.34
6	1.26	2.10	0.395	0.78	0.32

[a] Glassy carbon electrode, in DMF + 0.1 M Et_4NBF_4 at 20 °C. Scan rate = 0.2 V/s.

the intrinsic barriers are usually large because they are mostly governed by the dissociation energy of the bond being broken. It follows that the reduction takes place at a potential much more negative than the dissociative electron-transfer standard potential, $E°$ (RX/R$^{\cdot}$ + X^{-}), and therefore, the transfer coefficient (symmetry factor)[22]

$$\alpha = 0.5[1 + (E - E°)/4\Delta G_0^{\ddagger}]$$

should be significantly lower than 0.5. The large distance separating the first peak from the second (where the reduction of the dehalogenated products occurs) peak at low scan rate also constitutes a good indication of a concerted mechanism. Under these conditions, we can reasonably conclude that the reduction of the halodifluoromethyl heterocycles is a dissociative electron-transfer reaction in which the electron transfer and the bond breaking steps are concerted

$$RCF_2X + 1e \rightarrow RCF_2^{\cdot} + X^{-}$$

We may then use the dissociative electron-transfer theory developed by Savéant[22] to estimate the homolytic dissociation energy D_{RX} of the C−X bonds. For this purpose, we employed the same strategy recently applied to benzyl and other arylmethyl halides,[23] for *N*-halosultams,[24] and for α-substituted acetophenones.[25] For compounds following a concerted mechanism, the D_{RX} may be derived from the value of the peak potential and the value of the standard potential for the oxidation of the leaving group, $E°$ (X$^{\cdot}$/X^{-}):

$$D_{RX} = -^2/_3[E_p - E° (X^{\cdot}/X^{-})] + C$$

with $C = 0.3$[24,25b] and $E°$ (X$^{\cdot}$/X^{-})= 1.44 V (X = Br) and 1.79 V (X = Cl) vs SCE in DMF.[25b]

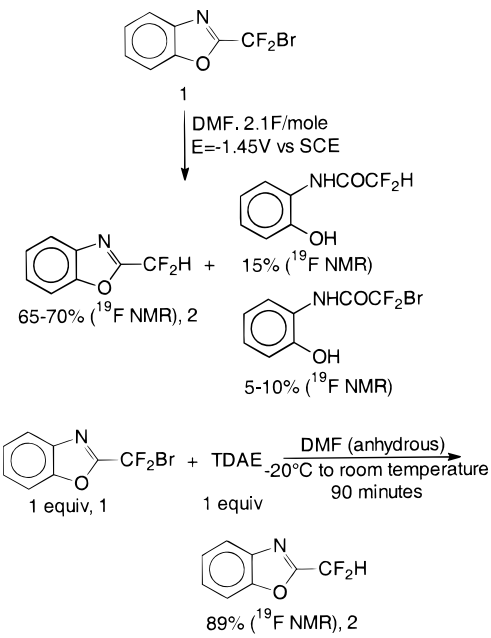
The standard potential for the dissociative electron-transfer reaction is a function of the bond dissociation energy, D_{RX}, of the standard potential $E°$ (X$^{\cdot}$/X^{-}) and of an entropic term $-T\Delta S$; for the same halogen, $C' = E°$ (X$^{\cdot}$/X^{-}) $- T\Delta S$, is about constant whatever the exact structure of the molecule ($C' = 2.33$ eV for X = Cl and 1.705 eV for X = Br):[24]

$$E° (RX/R^{\cdot} + X^{-}) = -D_{RX} + C'$$

The resulting values of the D_{RX} and the values of the standard potential E° (RX/R$^{\cdot}$ + X^{-}) of the compounds **1** and **3**−**6**, are collected in Table 1.

Preparative electrolysis of **1** ($C = 5.74$ mM in anhydrous DMF + 0.1 M Et_4NBF_4) at −1.45 V vs SCE on a carbon felt cathode gave after the consumption of 2.1 F/mol the 2-(difluoromethyl)benzoxazole **2** in 65−70% yield (^{19}F NMR); the side products, which represent the remaining balance material, were the *N*-(2-hydroxydifluoromethyl)amide (15%, ^{19}F NMR) and the *N*-(2-hydroxybromodifluoromethyl)amide (5−10%, ^{19}F NMR) resulting from the hydrolysis of the starting material and of the reduction product (Scheme 1). Then the question was posed: could we generate a stable and reactive difluoromethyl heterocyclic anion, chemically and/or electrochemically? The preparative electrolysis of **1** in the absence of any electrophile indicated that indeed the difluoromethyl anion had been produced. However, a preparative electrolysis of **1** ($C = 5.74$ mM in anhydrous DMF + 0.1 M Et_4NBF_4) in the presence of an excess of **7** ($C = 28.7$ mM) at −1.45 V vs SCE on a carbon felt cathode gave as major product only **2** ($Y = 65\%$ by ^{19}F NMR), with only traces of the alcohol **20** ($Y = 10\%$ by ^{19}F NMR). Apparently, the difluoromethyl anion, under those conditions, is not sufficiently reactive to react efficiently with benzaldehyde. Subsequent attempts to generate the 2-(difluoromethyl)benzoxazole anion via exchange with *n*-BuLi in THF at −78 °C resulted only in decomposition of the 2-(difluoromethyl)benzoxazole lithium derivative. Attempts to form an organozinc intermediate from **1** using activated zinc in anhydrous DMF, at room temperature or at 70 °C, resulted only in the formation of **2** in 10% yield (^{19}F NMR), the major isolated material being the unreacted starting material with some formation of amides. Our studies on the cyclic voltammetry of TDAE as well as on the bromodifluoromethyl heterocycles at this point prompted us to try the TDAE as a milder and conceptually different synthetic electron-transfer reagent. Initially, 0.25 equiv of TDAE and 1 equiv of **1** were mixed together for 1 h in anhydrous DMF at −20 °C and a deep red color immediately developed, probably due to the formation of a charge-transfer complex (as already observed in previous studies[13,14]). The solution (which slowly became orange) was warmed to room temperature and, after 1 h at this temperature, was filtered (to remove the [TDAE]$^{2+}$2Br^{-}), hydrolyzed, and worked up. ^{19}F NMR analysis of the crude product clearly showed the formation **2** in 45% yield with 50% of unreacted starting material and no

Scheme 1



(21) Andrieux, C. P.; Savéant, J.-M. Electrochemical Reactions. In *Investigation of Rates and Mechanisms of Reactions, Techniques of Chemistry*; Bernasconi, C. F., Ed.; Wiley: New York, 1986; Vol. VI/4E, Part 2, pp 305−390.

(22) (a) Savéant, J.-M. Dissociative Electron Transfer. In *Advances in Electron-Transfer Chemistry*; Mariano, P. S., Ed.; JAI Press: New York, 1994; Vol. 4, p 53. (b) Savéant, J.-M. *J. Am. Chem. Soc.* **1987**, *109*, 6788. (c) Savéant, J.-M. *J. Am. Chem. Soc.* **1992**, *114*, 10595.

(23) Andrieux, C. P.; Le Gorande, A.; Savéant, J.-M. *J. Am. Chem. Soc.* **1992**, *114*, 6892.

(24) Andrieux, C. P.; Differding, E.; Robert, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1993**, *115*, 6592.

(25) (a) Andrieux, C. P.; Savéant, J.-M.; Tallec, A.; Tardivel, R.; Tardy, C. *J. Am. Chem. Soc.* **1996**, *118*, 9788. (b) Andrieux, C. P.; Savéant, J.-M.; Tallec, A.; Tardivel, R.; Tardy, C. *J. Am. Chem. Soc.* **1997**, *119*, 2420.

Table 2. Synthesis of *β,β*-Difluoro-α-heteroarylated Alcohols from the Bromodifluoromethyl Heterocycles

substrate[a]	electrophile	product[b] (%)
1	benzaldehyde **7**	**20** (62)
1	3-pyridinecarboxaldehyde **8**	**21** (57)
4	3-pyridinecarboxaldehyde **8**	**33** (62)
1	2-pyridinecarboxaldehyde **9**	**22** (55)
4	2-pyridinecarboxaldehyde **9**	**34** (60)
1	4-fluorobenzaldehyde **10**	**23** (67)
4	4-fluorobenzaldehyde **10**	**35** (61)
1	α,α,α-trifluoro-*p*-tolualdehyde **11**	**24** (63)
4	α,α,α-trifluoro-*p*-tolualdehyde **11**	**36** (57)
1	*p*-cyanobenzaldehyde **12**	**25** (61)
4	*p*-cyanobenzaldehyde **12**	**37** (57)
1	4-biphenylcarboxaldehyde **13**	**26** (48)
4	4-biphenylcarboxaldehyde **13**	**38** (62)
1	2-furfural **14**	**27** (57)
1	*N*-methyl-2-carboxaldehyde pyrrole **15**	**28**[c]
1	3-hydroxybenzaldehyde **16**	**29**[c]
1	3,4-dimethoxybenzaldehyde **17**	**30**[c]
1	acetophenone **18**	**31** (33)
1	cyclohexanone **19**	**32** (35)

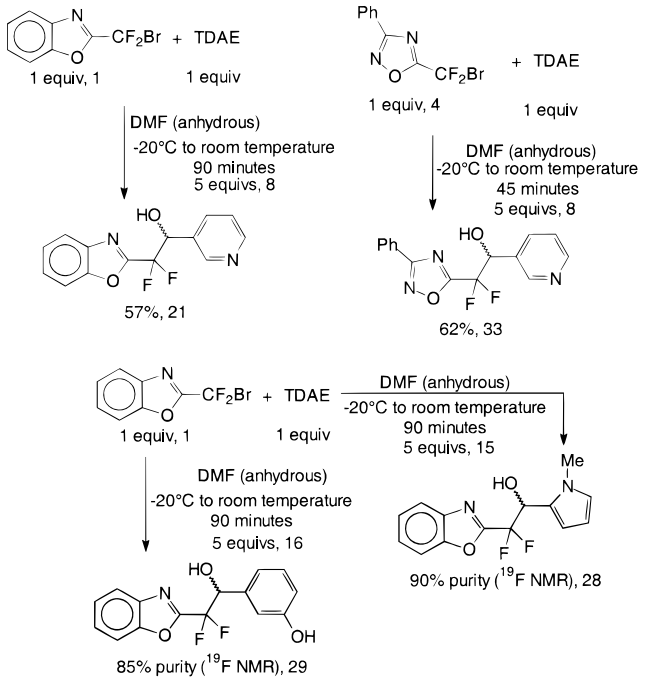
[a] $C_{sub} = 4.01 \times 10^{-3}$ mol + $C_{TDAE} = 4.01 \times 10^{-3}$ mol + $C_{electrophile} = 20.0 \times 10^{-3}$ mol in 10 mL of anhydrous DMF; under nitrogen. [b] Isolated yields. [c] See text and Experimental Section.

trace of amides. Obviously, the generation of the 2-(difluoromethyl)benzoxazole anion had been successful; subsequent experiments demonstrated that an equimolar amount of TDAE was necessary for the complete reduction of the starting bromide **1** and that the reaction was almost complete after 90 min (as checked by TLC). Under these conditions, **2** was obtained in 89% yield (^{19}F NMR, Scheme 1). Under the same conditions, the 2-(chlorodifluoromethyl)benzoxazole **3** was not reduced by TDAE, even after a longer reaction time.

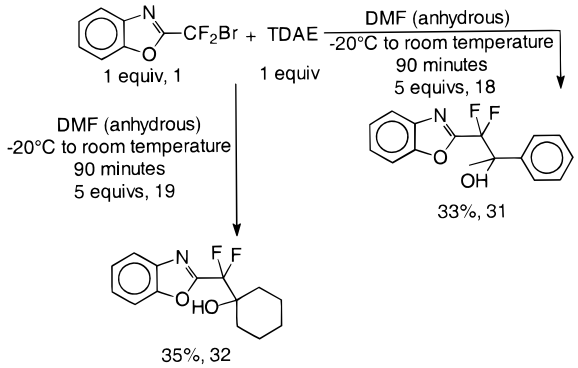
Next, it was demonstrated that the 2-(difluoromethyl)-benzoxazole as well as the 5-(difluoromethyl)-3-phenyl-1,2,4-oxadiazole anions could be efficiently trapped by a series of aromatic aldehydes **7**−**17** and ketones **18** and **19**. Optimization experiments showed that the best yields of the corresponding alcohols **20**−**38** were obtained with a 4−5 molar excess of the electrophile. Formation of the products was monitored by TLC, and the yields were moderate to good (Table 2, Schemes 2 and 3). All the reactions are completed in 1−2 h as determined by TLC. The reactions of **1** and **4** with **8** have been conducted on a larger scale (5−10 g), and it was found that the yields were similar to those obtained on a smaller scale. Usually, the reactions with the oxadiazole derivative **4** are complete in less than 2 h. Most of the *β,β*-difluoro-α-heteroarylated alcohols were isolated after column chromatography or by simple trituration of the crude product with hexane and recrystallization (see the Experimental Section). Electron-rich aldehydes **15**−**17** were less reactive, their reactions being incomplete even after longer reaction times. Moreover, the alcohol products from these reactions were difficult to purify, only being obtained in 80−90% purity after column chromatography (Scheme 2).

The reactions with ketones **18** and **19** gave the corresponding alcohols, albeit in modest yields, after column chromatography. The rather low yields obtained with these ketones could be explained by steric hindrance of the benzoxazole ring (Scheme 3). The alcohol **31** was characterized by a typical AB quartet with a fluorine−fluorine coupling constant close to 276 Hz. The addition of the 2-(difluoromethyl)benzoxazole anion to **19** gave the

Scheme 2



Scheme 3



corresponding alcohol **32** as a single isomer characterized by a singlet ($\delta_F = -117.4$ ppm/$CFCl_3$) in its ^{19}F NMR spectrum. With the alcohols obtained in this work, a possible intramolecular H-bonding between the hydrogen of the hydroxy group and the nitrogen of the benzoxazole (N-3) or the oxadiazole (N-4) rings could be anticipated.[26]

In all of the reactions, the balance of the nonadduct product mixture is **2**, as confirmed by ^{19}F NMR and TLC of the crude reaction.

All of the reactions appear to proceed via the formation of a charge-transfer complex (deep red color) between **1** or **4** and the TDAE at low temperature (−20 °C). Upon raising the temperature, the solution gradually becomes orange and the complex gradually decomposes to generate the 2-(difluoromethyl)heterocyclic anion (and the $[TDAE]^{2+}$), and the putative anion is apparently stable enough to react with aromatic aldehydes and ketones. In all of the experiments, $[TDAE]^{2+}2Br^-$ was recovered by simple filtration at the end of the reaction (in 60−65% yield based on **1** or **4**), demonstrating that the TDAE has been clearly oxidized. A stepwise single electron-transfer mechanism between the TDAE and the starting

(26) Domingues, N. S., Jr.; Krug, C.; Livotto, P. R.; Stefani, V. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1861.

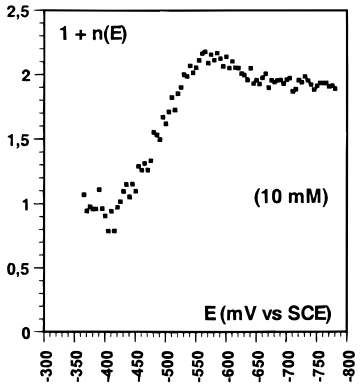
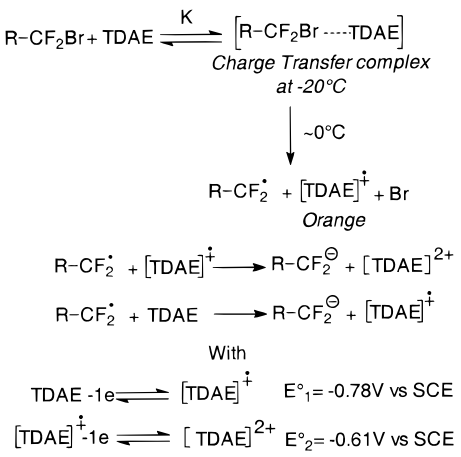


Figure 3. Polarogram of the 2-(difluoromethyl)benzoxazole radical obtained from the parent chloride **3** (the concentration is indicated on the curve) in DMF (+0.1 M Et_4NBF_4) at a gold electrode.

Scheme 4

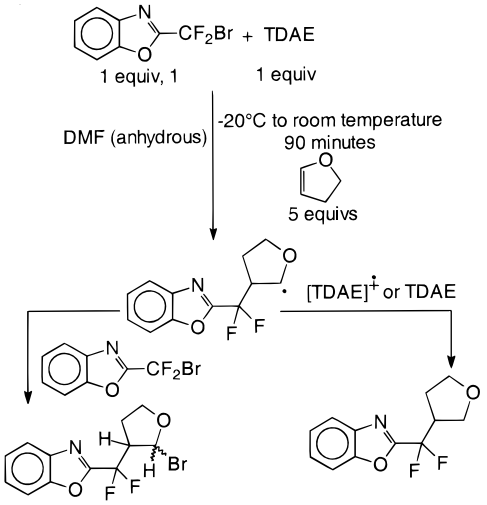


bromides **1** or **4** should occur in all the reactions (Scheme 4).

Thermodynamically, the electron transfer between the starting bromides and the TDAE is clearly favorable, as is indicated by the values of the standard potentials $E°$ ($RX/R^{\cdot} + X^-$) for **1** and **4**, which have been estimated with the Savéant theory for dissociative electron transfer and from the values of the normal potential standards of the two oxidation steps of the TDAE. A photochemical approach for the determination of redox potentials of organic radicals was employed to estimate the reduction potential of the 2-(difluoromethyl)benzoxazole radical. It consists of injecting electrons from a gold electrode by means of a laser pulse or modulated light and then observing their reaction with a substrate introduced to the solution. This method has been successfully applied for the determination of the reduction potentials of benzylic radicals.[27] For our purposes we used as the generating substrate one that is more difficult to reduce than the radical, the 2-(chlorodifluoromethyl)benzoxazole **3** ($E_p = -1.55$ V vs SCE on a gold electrode in DMF + 0.1 M Et_4NBF_4). The typical polarogram of the 2-(difluoromethyl)benzoxazole radical is shown in Figure 3.

From this polarogram, the half-wave reduction potential of the 2-(difluoromethyl)benzoxazole radical was estimated to be −0.485 V vs SCE. Such a value clearly

Scheme 5



indicates that a single electron transfer between this radical and $[TDAE]^{\cdot+}$ or TDAE should occur in our reaction. Evidence of the 2-(difluoromethyl)benzoxazole radical as an intermediate in these reactions was demonstrated by the observation of radical addition to 2,3-dihydrofuran, an electron-rich olefinic substrate. The product, although difficult to purify by column chromatography, was shown (GC/mass and ^{19}F NMR) to be indeed the bromine-radical adduct obtained as a mixture of cis and trans isomers (Scheme 5, see the Experimental Section).

Conclusions

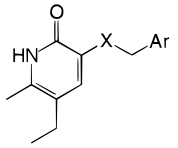
The systematic investigation of the kinetics of the electrochemical reduction of the bromodifluoromethyl compounds provides clear evidence of a concerted electron-transfer−bond-breaking mechanism. The values of the standard potential of the reaction of the halodifluoromethyl heterocycles as well as of the TDAE, and the determination of the reduction potential of the 2-(difluoromethyl)benzoxazole radical, demonstrate that TDAE has the remarkable ability to generate a difluoromethyl radical and a stable difluoromethyl anion in a stepwise mechanism. The present procedure may be utilized as a facile and convenient synthetic method for the synthesis of new *gem*-difluorinated alcohols and should be able to be extended to other electrophiles of biological interest. We are now exploring the TDAE methodology with other electrophiles as well as with other bromodifluoromethylated heterocycles. The various *gem*-difluorinated alcohols synthesized in this work are also expected to be good substrates for further chemical modifications.[28] Among the recent NNRTIs synthesized as HIV-1 specific reverse transcriptase inhibitors, an interesting family of 2-pyridinone derivatives from the Merck Research Laboratories[10d] have been synthesized, and detailed structure−activity-relationship (SAR) have lead to the discovery of some potent candidates for further clinical trials (Chart 3).

The compounds **20** and **21** and **23**−**27** regarded as analogues of the Merck molecules were tested against the HIV-1 virus; unfortunately, thus far, none of them have shown interesting activity.

(27) Hapiot, P.; Konovalov, V.; Savéant, J.-M. *J. Am. Chem. Soc.* **1995**, *117*, 1428.

(28) Hagiwara, T.; Tanaka, K.; Fuchikami, T. *Tetrahedron Lett.* **1996**, *37*, 8187.

Chart 3



X=CH_2, Ar= benzoxazole, IC_{50}=22nM
X=CH_2, Ar= 4,7-dichlorobenzoxazole, IC_{50}=9.6nM

Experimental Section

The electrochemical equipment has been described in ref 29. The synthesis of the starting halodifluoromethyl heterocycles will be described in a forthcoming paper.[20] All the aldehydes and ketones are from commercial origin. Anhydrous DMF and CH_3CN (Fluka Puriss dried over molecular sieve) were used as received. Silica gel (MN Kieselgel 60, 70−230 mesh, Macherey-Nagel) was employed for column chromatography. Analytical TLC was performed with 0.25 mm coated commercial plates (Macherey-Nagel, Polygram SIL G/UV_{254}). All the reactions with air-sensitive compounds were carried out under a nitrogen atmosphere.

NMR spectra were taken in $CDCl_3$ using TMS as the internal standard for ^1H (250.133 Hz). ^{19}F NMR (235.323 Hz) used CCl_3F as internal standard. Melting points are uncorrected.

A representative procedure for the synthesis of the **2-benzoxazol-2-yl-2,2-difluoro-1-phenyl-1-ethanol (20)** is described. Into a three-necked flask equipped with a silica gel drying tube, a thermometer, and a nitrogen inlet was added, under nitrogen at −20 °C, a 10 mL anhydrous DMF solution of **1** (1.0 g, 4.01 mmol) and **7** (2.12 g, 20.05 mmol, 2.03 mL). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.80 g, 4.01 mmol, 0.93 mL). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at −20 °C for 1 h and then warmed to room temperature for 2 h. After this time, TLC analysis (Et_2O/hexane 60:40) clearly showed that the bromide **1** was totally consumed. The orange-red turbid solution was filtered [to remove the octamethyloxamidinium dibromide, 0.93 g (2.60 mmol), 65% based on **1**] and hydrolyzed with 30 mL of H_2O. The aqueous solution was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic solutions were washed with brine (3 × 30 mL) and H_2O (3 × 30 mL) and dried over $MgSO_4$. Evaporation of the solvent left an orange-red viscous liquid (5.08 g) as crude product. ^{19}F NMR analysis of the crude product gave only two products: the desired alcohol with δ −108.7 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 4.9 Hz), −120.5 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 17.4 Hz) and **2** with δ −123 ppm (2F, d, $^2J_{F-H}$ = 55.6 Hz) in the ratio 13:1. The crude product was then triturated with hot hexane (5 × 10 mL, to remove unreacted aldehyde), leaving an orange-red solid, which was purified by silica gel chromatography (Et_2O/hexane 50:50). Further purification by recrystallization (Et_2O/hexane) gave **20** (62%): mp 152−154 °C (white powder); TLC R_f = 0.50 (hexane/Et_2O 60:40); ^1H NMR δ 3.68 (1H, brs, OH), 5.47−5.57 (1H, dd, J = 16.9, 5.3 Hz), 7.37−7.83 (9H, m); ^{19}F NMR δ −108.4 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 5.3 Hz), −119.5 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 16.9 Hz); MS (CI/CH_4) 276 (M + H^+). Anal. Calcd for $C_{15}H_{11}F_2NO_2$: C, 65.45; H, 4.00; N, 5.09. Found: C, 65.32; H, 3.83; N, 5.18.

2-Benzoxazol-2-yl-2,2-difluoro-1-pyridin-3-ylethanol (21). Evaporation of the organic phase left 3.5 g of an orange-red viscous liquid as crude product. Trituration with hot hexane (5 × 10 mL) left an insoluble viscous orange oil that was recrystallized (Et_2O) to give **21** (57%): mp 142 °C (cream powder); TLC R_f = 0.50 (Et_2O); ^1H NMR δ 5.47−5.57 (1H, dd, J = 16.9, 5.6 Hz), 5.70 (1H, brs, OH), 7.28−7.93 (6H, m), 8.50 (1H, d), 8.60 (1H, s); ^{19}F NMR δ −107.9 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 5.2 Hz), −119.6 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 16.9 Hz); MS (CI/CH_4) 277 (M + H^+). Anal. Calcd for $C_{14}H_{10}F_2N_2O_2$: C, 60.87; H, 3.62; N, 10.14. Found: C, 61.02; H, 3.83; N, 10.18.

2-Benzoxazol-2-yl-2,2-difluoro-1-pyridin-2-ylethanol (22). Evaporation of the organic phase left 2.2 g of an orange viscous oil as crude product, which was recrystallized ($CHCl_3$/hexane 1:4) to give after two crops **22** (55%): mp 110−112 °C (cream powder); TLC R_f = 0.50 (EtOAc/hexane 70:30); ^1H NMR δ 5.45−5.53 (1H, dd, J = 16.9, 4.60 Hz), 7.37−7.85 (7H, m), 8.60 (1H, d); ^{19}F NMR δ −106.8 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 4.94 Hz), −122.6 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 16.9 Hz); MS (CI/CH_4) 277 (M + H^+). Anal. Calcd for $C_{14}H_{10}F_2N_2O_2$: C, 60.87; H, 3.62; N, 10.14. Found: C, 60.63; H, 3.61; N, 10.05.

2-Benzoxazol-2-yl-2,2-difluoro-1-(4-fluorophenyl)ethanol (23). Evaporation of the organic phase left 4.83 g of an orange viscous oil as crude product, which was purified by silica gel chromatography (hexane/Et_2O 70:30) to give **23** (67%): mp 160 °C (white solid); TLC R_f = 0.50 (Et_2O/hexane 50:50); ^1H NMR δ 3.78 (1H, d, J = 4.35 Hz), 5.43−5.54 (1H, dd, J = 16.7, 4.96 Hz), 5.70 (1H, brs, OH), 7.05−7.83 (8H, m); ^{19}F NMR δ −109.2 (1F, dd, J_{F-F} = 282 Hz, $^3J_{F-H}$ = 5.2 Hz), −116.8 (1F, brs), −119.6 (1F, dd, J_{F-F} = 282 Hz, $^3J_{F-H}$ = 16.7 Hz); MS (CI/CH_4) 294 (M + H^+). Anal. Calcd for $C_{15}H_{10}F_3NO_2$: C, 61.43; H, 3.41; N, 4.78. Found: C, 61.76; H, 3.32; N, 4.87.

2-Benzoxazol-2-yl-2,2-difluoro-1-[4-(trifluoromethyl)-phenyl]ethanol (24). Evaporation of the organic phase left 1.2 g of a yellow solid as crude product, which was triturated with hot hexane (3 × 20 mL) and recrystallized ($CHCl_3$/hexane 1:4) to give **24** (63%): mp 196 °C (white powder); TLC R_f = 0.50 (EtOAc−hexane 50:50); ^1H NMR δ 3.90 (1H, brs), 5.53−5.60 (1H, dd, J = 17.2, 5.1 Hz), 7.26−7.85 (8H, m); ^{19}F NMR δ −67.08 (3F, s), −108.3 (1F, dd, J_{F-F} = 285 Hz, $^3J_{F-H}$ = 4.94 Hz), −119.6 (1F, dd, J_{F-F} = 285 Hz, $^3J_{F-H}$ = 17.2 Hz); MS (CI/CH_4) 344 (M + H^+). Anal. Calcd for $C_{16}H_{10}F_5NO_2$: C, 55.98; H, 2.91; N, 4.08. Found: C, 56.06; H, 3.05; N, 4.23.

4-(2-Benzoxazol-2-yl-2,2-difluoro-1-hydroxyethyl)benzonitrile (25). Evaporation of the organic phase left 2.8 g of an orange oil that was triturated with hot hexane (3 × 20 mL), leaving an orange solid, which was purified by silica gel chromatography (Et_2O/hexane 70:30) to give **25** (61%): mp 210 °C (yellowish powder); TLC R_f = 0.50 (Et_2O/hexane 50:50); ^1H NMR δ 4.08 (1H, d, J = 4.10 Hz), 5.28−5.60 (1H, dd, J = 17.1, 5.1 Hz), 7.46−7.84 (8H, m); ^{19}F NMR δ −108.2 (1F, dd, J_{F-F} = 285 Hz, $^3J_{F-H}$ = 5.17 Hz), −118.7 (1F, dd, J_{F-F} = 285 Hz, $^3J_{F-H}$ = 16.9 Hz); MS (CI/CH_4) 301 (M + H^+). Anal. Calcd for $C_{16}H_{10}F_2N_2O_2$: C, 64.00; H, 3.33; N, 9.33. Found: C, 64.21; H, 3.01; N, 9.43.

2-Benzoxazol-2-yl-1-biphenyl-4-yl-2,2-difluoroethanol (26). Evaporation of the organic phase left 2.79 g of an orange-yellow oil, which was recrystallized (Et_2O/hexane 1:1) to give **26** (48%): mp 182−184 °C (yellowish plates); TLC R_f = 0.50 (Et_2O/hexane 50:50); ^1H NMR δ 3.68 (1H, brs), 5.50−5.60 (1H, dd, J = 16.7, 5.3 Hz), 7.36−7.84 (13H, m); ^{19}F NMR δ −108.4 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 5.13 Hz), −119.2 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 16.7 Hz); MS (CI/CH_4) 352 (M + H^+). Anal. Calcd for $C_{21}H_{15}F_2NO_2$: C, 71.79; H, 4.27; N, 3.99. Found: C, 71.47; H, 4.23; N, 4.06.

2-Benzoxazol-2-yl-2,2-difluoro-1-furan-2-ylethanol (27). Evaporation of the organic phase left 5.3 g of an orange-red liquid as crude product, which was purified by silica gel chromatography (hexane/Et_2O 70:30) to give **27** (57%): mp 94−96 °C (cream powder); TLC R_f = 0.50 (hexane/Et_2O 50:50); ^1H NMR δ 3.64 (1H, d, J = 7.4 Hz), 5.52 (1H, dd, J = 13.9, 7 Hz), 6.50 (1H, dd, J = 10.1, 3.3 Hz), 6.54 (1H, d, J = 7.3 Hz), 7.28−7.93 (4H, m); ^{19}F NMR δ −107.9 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 5.2 Hz), −119.6 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 16.9 Hz); MS (CI/CH_4) 266 (M + H^+). Anal. Calcd for $C_{13}H_9F_2NO_3$: C, 58.87; H, 3.39; N, 5.28. Found: C, 59.05; H, 3.56; N, 5.56.

2-Benzoxazol-2-yl-2,2-difluoro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanol (28). Evaporation of the organic phase left 2.07 g of a red viscous liquid as crude product, which was purified by silica gel chromatography (hexane/Et_2O 60:40) to give 0.49 g of an orange solid. The solid was shown to contain **28** in

(29) Médebielle, M.; Pinson, J.; Savéant, J.-M. *J. Am. Chem. Soc.* **1991**, *113*, 6872.

90% purity contaminated with an inseparable fluorinated impurity (δ −81.7, d, J = 3 Hz): TLC R_f = 0.50 (Et_2O/hexane 50:50); ^{1}H NMR δ 5.47−5.57 (1H, dd, J = 16.9, 5.6 Hz), 5.70 (1H, brs, OH), 7.28−7.93 (6H, m), 8.50 (1H, d), 8.60 (1H, s); ^{19}F NMR δ −109.2 (1F, dd, J_{F-F} = 273 Hz, $^3J_{F-H}$ = 8.7 Hz), −117.1 (1F, dd, J_{F-F} = 273 Hz, $^3J_{F-H}$ = 15.3 Hz); GC/MS (EI/70 eV) 278 (M^+), 168.

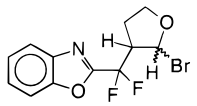
3-(2-Benzoxazol-2-yl-2,2-difluoro-1-hydroxyethyl)phenol (29). Evaporation of the organic phase left 3.5 g of a brown liquid as crude product, which was purified by silica gel chromatography (Et_2O/hexane 60:40) to give 0.68 g of a brownish viscous oil. The viscous oil was shown to contain **29** in 85% purity contaminated with other unidentified fluorinated products: ^{19}F NMR δ −108.1 (1F, dd, J_{F-F} = 272 Hz, $^3J_{F-H}$ = 6.6 Hz), −122.2 (1F, dd, J_{F-F} = 272 Hz, $^3J_{F-H}$ = 16.7 Hz); GC/MS (EI/70 eV) 292 (M^+), 168.

2-Benzoxazol-2-yl-1-(3,4-dimethoxyphenyl)-2,2-difluoroethanol (30). Evaporation of the organic phase left 2.07 g of an orange oil as crude product, which was purified by silica gel chromatography ($CHCl_3$/Et_2O, 70:30 and 90:10) to give 0.33 g of a yellowish viscous oil. The oil was shown to contain **30** in 95% purity: ^{19}F NMR δ −109.5 (1F, dd, J_{F-F} = 271 Hz, $^3J_{F-H}$ = 7.06 Hz), −120.4 (1F, dd, J_{F-F} = 271 Hz, $^3J_{F-H}$ = 16.2 Hz); GC/MS (EI/70 eV) 336 (M^+), 168.

1-Benzoxazol-2-yl-1,1-difluoro-2-phenylpropan-2-ol (31). Evaporation of the organic phase left 3.9 g of an orange oil as crude product, which was purified by silica gel chromatography (hexane/EtOAc 90:10) to give **31** (33.6%): mp 120 °C (white solid); TLC R_f = 0.50 (hexane/EtOAc 80:20); ^{1}H NMR δ 1.89 (3H, s, CH_3), 4.10 (1H, s, OH), 7.31−7.78 (9H, m); ^{19}F NMR δ −111.3 (1F, AB quartet, J_{F-F} = 276 Hz), −113.6 (1F, AB quartet, J_{F-F} = 276 Hz); MS (CI/CH_4) 290 (M + H^+). Anal. Calcd for $C_{16}H_{13}F_2NO_2$: C, 66.43; H, 4.49; N, 4.84. Found: C, 66.14; H, 4.55; N, 4.86.

1-(Benzoxazol-2-yl-2,2-difluoromethyl)cyclohexanol (32). Evaporation of the organic phase left 3.2 g of an orange oil as crude product, which was purified by silica gel chromatography (hexane/EtOAc 85:15) to give **32** (35%): mp 126−128 °C (off-white solid); TLC R_f = 0.50 (hexane/EtOAc 80:20); ^{1}H NMR δ 1.23 (4H, m), 1.60−1.89 (6H, m), 2.78 (1H, s, OH), 7.38−7.83 (4H, m); ^{19}F NMR δ_F = −117.4 (2F, s); MS (CI/CH_4) 268 (M + H^+). Anal. Calcd for $C_{14}H_{15}F_2NO_2$: C, 62.92; H, 5.61; N, 5.24. Found: C, 62.69; H, 5.43; N, 5.32.

Representative Procedure for the Reaction of the 2-(Bromodifluoromethyl)benzoxazole (1) in the Presence of the 2,3-Dihydrofuran. Into a three-necked flask equipped with a silica gel drying tube, a thermometer, and a nitrogen inlet were added, under nitrogen at −20 °C, a 5 mL anhydrous DMF solution of **1** (0.5 g, 2.01 mmol) and 2,3-dihydrofuran (0.71 g, 10.05 mmol, 0.77 mL). The solution was stirred and maintained at this temperature for 30 min and then the TDAE (0.40 g, 2.01 mmol, 0.47 mL) was added dropwise (via a syringe). A red color immediately developed with the formation of a white fine precipitate and turned brown as the reaction proceeded. The solution was vigorously stirred at −20 °C for 1 h and then warmed to room temperature for 2 h. After this time, TLC analysis (hexanes−Et_2O 60:40) clearly showed that the bromide **1** was totally consumed. The turbid-brown solution was filtered and hydrolyzed with 15 mL of H_2O. The aqueous solution was extracted with $CHCl_3$ (3 × 15 mL), and the combined organic solutions were washed with brine (3 × 15 mL) and H_2O (3 × 15 mL) and dried over $MgSO_4$. Evaporation of the solvent left a red viscous liquid (0.8 g) as crude product. TLC (hexane/Et_2O, 80:20) and ^{19}F NMR analysis of the crude product gave many products; the major product is **2**, but a new product characterized by a complicated AB pattern was also observed. The crude product was purified by silica gel chromatography (hexane/Et_2O 90:10), leaving 0.58 g of a yellow viscous oil. Further purification by recrystallization ($CHCl_3$/hexane) gave 0.31 g of an orange solid. TLC (hexane/Et_2O 60:40) of this solid gave two inseparable products: ^{19}F NMR δ −104.89 (1F, AB quartet, J_{F-F} = 276 Hz), −108.19 (1F, AB quartet, J_{F-F} = 276 Hz). From the GC/MS (EI/70 eV) spectrum of this solid, we found that the *major* compound is the **2-[(2-bromotetrahydrofuran-3-yl)-difluoromethyl]benzoxazole** probably as a mixture of cis and trans isomers: 319 (M^+), 238 (M − Br), 168.



2,2-Difluoro-2-(3-phenyl[1,2,4]oxadiazol-5-yl)-1-pyridin-3-ylethanol (33). Evaporation of the organic phase left 4.32 g of an orange-red viscous liquid as crude product. Trituration with hot hexane (5 × 10 mL) left an orange-red solid. Further purification by recrystallization ($CHCl_3$/hexane 1:4) gave after two crops **33** (62%): mp 126 °C (yellowish powder); TLC R_f = 0.50 (hexane/Et_2O 60:40); ^{1}H NMR δ 4.72 (1H, brs, OH), 5.48−5.55 (1H, dd, J = 16.2, 6.29 Hz), 7.40−7.55 (4H, m), 7.98−8.67 (5H, m); ^{19}F NMR δ −103.8(1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 6.3 Hz), −116.03 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 16.2 Hz); MS (CI/CH_4) 304 (M + H^+). Anal. Calcd for $C_{15}H_{11}F_2N_3O_2$: C, 59.40; H, 3.63; N, 13.86. Found: C, 59.23; H, 3.70; N, 13.81.

2,2-Difluoro-2-(3-phenyl[1,2,4]oxadiazol-5-yl)-1-pyridin-2-ylethanol (34). Evaporation of the organic phase left 2.87 g of a brown solid as crude product, which was recrystallized ($CHCl_3$/hexane 1:4) to give **34** (60%): mp 160−162 °C (yellowish powder); TLC R_f = 0.50 (hexane/Et_2O 60:40); ^{1}H NMR δ 5.34−5.58 (1H, dd, J = 15.7, 4.94 Hz), 7.38−7.54 (4H, m), 7.90−8.62 (5H, m); ^{19}F NMR δ −106.9 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 4.94 Hz), −116.03 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 15.53 Hz); MS (CI/CH_4) 304 (M + H^+). Anal. Calcd for $C_{15}H_{11}F_2N_3O_2$: C, 59.40; H, 3.63; N, 13.86. Found: C, 59.23; H, 3.57; N, 13.64.

2,2-Difluoro-1-(4-fluorophenyl)-2-(3-phenyl[1,2,4]-oxadiazol-5-yl)ethanol (35). Evaporation of the organic phase left 3.8 g of a yellowish liquid as crude product. Trituration with hot hexane (5 × 10 mL) and recrystallizion (hexane) gave **35** (61%): mp 142 °C (yellow crystals); TLC R_f = 0.50 (hexane/Et_2O 50:50); ^{1}H NMR δ 5.35−5.50 (1H, dd, J = 14.9, 7.4 Hz), 7.07−7.12 (2H, m), 7.48−7.55 (5H, m), 8.10−8.15 (2H, m); ^{19}F NMR δ −106.06 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 7.3 Hz), −112.6 (1F, m), −115.61 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 14.7 Hz); MS (CI/CH_4) 321 (M + H^+). Anal. Calcd for $C_{16}H_{11}F_3N_2O_2$: C, 60.00; H, 3.43; N, 8.75. Found: C, 59.98; H, 3.41; N, 8.87.

2,2-Difluoro-2-(3-phenyl)[1,2,4]oxadiazol-5-yl)-1-[4-(trifluoromethyl)phenyl]ethanol (36). Evaporation of the organic phase left 3.1 g of an orange-yellow viscous liquid as crude product, which crystallized slowly on standing. Further purification by recrystallization (hexane) gave **36** (57%): mp 154−156 °C (white powder); TLC R_f = 0.50 (hexane/Et_2O 50:50); ^{1}H NMR δ 5.48−5.55 (1H, dd, J = 15.7, 6.15 Hz), 7.49−7.69 (7H, m), 8.07−8.10 (2H, m); ^{19}F NMR δ − 67.15 (3F, s), −108.63 (1F, dd, J_{F-F} = 282 Hz, $^3J_{F-H}$ = 6.11 Hz), −119.04 (1F, dd, J_{F-F} = 282 Hz, $^3J_{F-H}$ = 15.3 Hz); MS (CI/CH_4) 371 (M + H^+). Anal. Calcd for $C_{17}H_{11}F_5N_2O_2$: C, 55.13; H, 2.97; N, 7.56. Found: C, 55.00; H, 2.96; N, 7.57.

4-[2,2-Difluoro-1-hydroxy-2-(3-phenyl[1,2,4]oxadiazol-5-yl)ethyl]benzonitrile (37). Evaporation of the organic phase left 4.5 g of an orange-red solid as crude product. Trituration with hot hexane (5 × 10 mL) left an insoluble viscous red-oil, which slowly crystallized on standing. From the hexane solution, 1.5 g of yellowish plates separated that were purified by silica gel chromatography (hexane/Et_2O 80:20) to yield **37** (57%): mp 120 °C (yellowish plates); TLC R_f = 0.50 (hexane/Et_2O 50:50); ^{1}H NMR δ 5.47−5.55 (1H, dd, J = 15.7, 6.01 Hz), 7.71−8.01 (9H, m); ^{19}F NMR δ −107.87 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 5.76 Hz), −119.48 (1F, dd, J_{F-F} = 281 Hz, $^3J_{F-H}$ = 15.9 Hz); MS (CI/CH_4) 328 (M + H^+). Anal. Calcd for $C_{17}H_{11}F_2N_3O_2$: C, 62.38; H, 3.36; N, 12.85. Found: C, 62.76; H, 3.54; N, 13.02.

1′-Biphenyl-4-yl-2,2-difluoro-2-(3-phenyl[1,2,4]oxadiazol-5-yl)ethanol (38). Evaporation of the organic phase left 4.9 g of an orange viscous liquid as crude product. Trituration with hot hexane (5 × 10 mL) and recrystallization (hexane) gave **38** (62%): mp 154−156 °C (yellowish powder); TLC R_f = 0.50 (hexane/Et_2O 60:40); ^{1}H NMR δ 5.44−5.53 (1H, dd, J =

15.31, 6.16 Hz), 7.33−7.77 (7H, m), 8.09−8.13 (2H, m); ^{19}F NMR δ −109.06 (1F, dd, J_{F-F} = 282 Hz, $^3J_{F-H}$ = 6.6 Hz), −119.06 (1F, dd, J_{F-F} = 282 Hz, $^3J_{F-H}$ = 15.3 Hz); MS (CI/CH_4) 379 ($M + H^+$). Anal. Calcd for $C_{22}H_{16}F_2N_2O_2$: C, 69.84; H, 4.23; N, 7.40. Found: C, 69.75; H, 4.31; N, 7.39.

Acknowledgment. We thank Marie-Noelle Rager (ENSCP, Paris) for the ^{19}F NMR spectra and David Clainquart (Université Denis Diderot) for the mass spectra. José Gonzalez is gratefully acknowledged for the photoejection determination of the reduction potential of the 2-(difluoromethyl)benzoxazole radical. M.M, would like to thank the CNRS for a leave of absence at the University of Florida, where most of this work was done. Helpful discussions with Dr. C. P. Andrieux and Prof. J.-M. Savéant are sincerely appreciated. We would like to thank Dr. V. L. Narayanan, Drug Synthesis and Chemistry Branch, and Dr. J. P. Bader, Antiviral Evaluation Branch of the National Cancer Institute, Bethesda, MD, for evaluation of the anti-HIV activity of our compounds.

JO980201+