JOC Article

Electrophilic Fluorinating Reagent Mediated Synthesis of Fluorinated α-Keto Ethers, Benzil, and 6,6′-Dialkoxy-2,2′-bipyridines

Sudha Manandhar, Rajendra P. Singh, Gary V. Eggers, and Jean'ne M. Shreeve*

Department of Chemistry, University of Idaho, Moscow, Idaho 83844-2343

jshreeve@uidaho.edu

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Interactions of various fluorinated and nonfluorinated alcohols with *trans*-stilbene in the presence of electrophilic reagents were studied. Under neat conditions, reactions of *trans*-stilbene (**1**) with fluorinated alcohols, R_fOH (R_f = CF_3CH_2-, CFH_2CH_2-, $CF_3CF_2CH_2$-, $CF_2H(CF_2)_3CH_2$-, $(CF_3)_2CH$-, $(CF_3)_3C$- (**2a**−**f**) in the presence of an electrophilic reagent, 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) or *N*,*N*-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (MEC-31), gave α-keto ethers (**3a**−**f**) and benzil (**4**) in good to moderate yields. α-Keto ether and benzil formation was very much dependent on the reaction time, the degree of fluorination of the alcohols, and whether a solvent such as CH_3CN, DMF or DMA was utilized. In solution, α-keto ethers and benzil did not form. Interestingly, under neat conditions, nonfluorinated alcohols, ROH (R = CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH_2CH_2CH_2CH_2$-) (**5g**−**k**) did not react with *trans*-stilbene in the presence of MEC-31 but gave 6,6′-dialkoxy-2,2′-bipyridines (**6g**−**k**), regioselectively, in excellent isolated yields. On the other hand, fluorinated alcohols did not react with MEC-31. Reaction of MEC-31 with an excess of diethylene glycol (**7**) gave the bipyridine derivative (**8**) in 88% isolated yield. Reaction of **8** either with diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) readily produced the corresponding difluoro derivative (**9**) in 85% isolated yield. All new compounds have been characterized by spectroscopic and elemental analysis.

Introduction

Synthetic and structural aspects of organofluorine compounds derived directly from nonfluorinated precursors by using fluorinating agents have been the focal points of vigorous research as evidenced by the appearance of a large number of publications.[1] Because fluorine is the element with highest electronegativity and its van der Waals radius is close to that of hydrogen, the incorporation of a fluorine atom or a fluorine-containing group into organic molecules alters their physical, chemical, and biological properties dramatically, making them suitable for diverse applications in material sciences and agrochemistry as well as in the pharmaceutical industry.[2−5] The biological activity and numerous commercial applications of organofluorine compounds have encouraged interest in developing synthetic methods for selective and efficient incorporation of fluorine or fluorinated groups into organic compounds under mild reaction conditions. Recently, there have been several reports for the preparation of useful organic compounds mediated by electrophilic reagents.[6] We have found new applications of Selectfluor and of MEC-31 in the preparation of

* To whom correspondence should be addressed. Fax: 208-885-9146.

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(2) For the general applications of organofluorine compounds, see: *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds.; Plenum: New York, 1994.

(3) For the use of organofluorine compounds in medicinal and biomedical chemistry, see: (a) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (b) *Organic Chemistry in Medicinal Chemistry and Biomedical Applications*; Filler, R., Ed.; Elsevier: Amsterdam, 1993. (c) Welch, J. T.; Eswaraksrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991. (d) Filler, R.; Kirk, K. Biological Properties of Fluorinated Compounds. In *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M.; Pavlath, A. E.; Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 1011−1022. (e) Elliot, A. J. Fluorinated Pharmaceuticals. In *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M.; Pavlath, A. E.; Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 1119−1125. (f) Sholoshonok, V. A., Ed. *Enantiocontrolled Synthesis of Organo-Fluorine Compounds: Stereochemical Challenge and Biomedical Targets*; John Wiley and Sons: 1999.

(4) For the use of organofluorine compounds in agrosciences, see: (a) Cartwright, D. Recent Developments in Fluorine-Containing Agrochemicals. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds.; Plenum: New York, 1994; pp 237−257. (b) Lang, R. W. Fluorinated Agrochemicals. In *Chemistry of Organic Fluorine Compounds II*; Hudlicky, M.; Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 1143−1148.

(5) The ability of fluorine to change the properties of organic molecules has been discussed extensively elsewhere. For example, see: Smart, B. E. *Characteristics of C−F Systems*. In *Organofluorine Chemistry*: *Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds.; Plenum: New York, 1994; pp 57−82.

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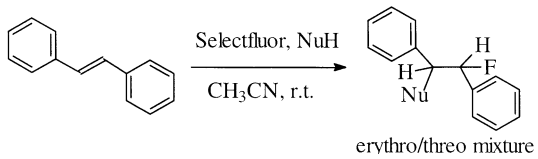
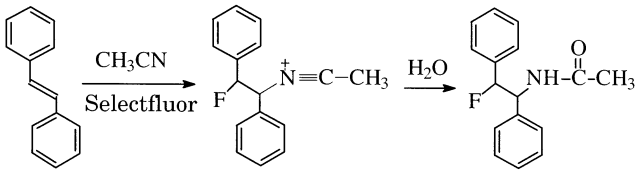
SCHEME 1



SCHEME 2



various fluorinated α-keto ether derivatives as well as 6,6′-dialkoxy-2,2′-bipyridines in good to excellent isolated yields.

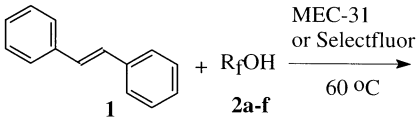
1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Selectfluor) and *N*,*N*-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (MEC-31) are well-known electrophilic reagents that are effective in introducing fluorine into an organic molecules.[1a,7] Recently, we have reported[8] a new application of Selectfluor in the formation of nitrogen−fluorine bonds by displacing nitrogen−hydrogen bonds. The chemistry of nonfluorinated alcohols with *trans*-stilbene in the presence of Selectfluor was reported.[9] *trans*-Stilbene was reacted with Selectfluor in the presence of weak nucleophilic reagents (NuH, Nu = OMe, OH, OAc) in acetonitrile produced *erythro/threo* mixtures of monofluorinated compounds (Scheme 1). We were interested in using fluorinated alcohols in order to synthesize the corresponding polyfluorinated ethers. Surprisingly, the reaction did not proceed when fluorinated alcohols were used under reaction conditions identical to those described in Scheme 1 in the presence of solvent. At the end of the reaction, amide formation was observed[10] arising from the reaction of Selectfluor and *trans*-stilbene with the solvent acetonitrile, followed by hydrolysis with aqueous workup (Scheme 2). However, when the reaction was carried out in the absence of solvent, a completely new chemistry was observed.

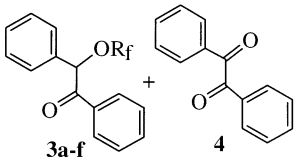
In our continuing efforts to introduce fluorine into organic compounds nucleophilically as well as electrophilically,[11] we report a new route to fluorinated α-keto ethers, benzil, and 6,6′-dialkoxy-2,2′-bipyridine compounds mediated by electrophilic fluorinating reagents.

Results and Discussion

Reaction of Fluorinated Alcohols and *trans*-Stilbene with Selectfluor/MEC-31. As shown in Scheme 1, the reaction of Selectfluor with *trans*-stilbene in the presence of excess methanol led to the formation of a mixture erythro and threo isomers of the corresponding methoxy fluorinated products in good yield.[9] Under similar reaction conditions, the reaction with ethanol also produced erythro/threo mixtures in good yield. But when we attempted to extend this chemistry to polyfluoro alcohols under similar reaction conditions with Selectfluor or with MEC-31 in the presence of *trans*-stilbene in acetonitrile as a solvent, analogous fluorinated ethers were not obtained. Solvent was then excluded. When the reaction of *trans*-stilbene (**1**) was carried out with Selectfluor in excess trifluoroethanol (**2a**) at 25 °C, the formation of α-keto ether (**3a**) was observed as the major product and benzil (**4**) as a minor product but both in low yields (Table 1). Upon heating at 60 °C for 48 h, the yield of **3a** and **4** improved only slightly. When MEC-31 was used at 60 °C for 24 h, the yield of the α-keto ether (**3a**) was found to be higher.

SCHEME 3





a: $R_f = CF_3CH_2$- , **b**: $R_f = CFH_2CH_2$- , **c**: $CF_3CF_2CH_2$- , **d**: $R_f = HCF_2(CF_2)_3CH_2$- , **e**: $R_f = (CF_3)_2CH$- , **f**: $R_f = (CF_3)_3C$-

The yields of the α-keto ether and benzil were found to be a function of the extent of fluorination of the alcohol used (Table 1). Under similar reaction conditions, various fluorinated alcohols (**2b**−**f**) were converted into the corresponding α-keto ethers (**3b**−**f**) in moderate to good yields (Scheme 3, Table 1). Perfluoro-*tert*-butyl alcohol produced mostly benzil in 90% yield and traces of α-keto ether were detected by GC/MS.

On the basis of the literature, the reaction mechanism for the formation of α-keto ether is likely similar to that reported by Rozen[12] where aromatic alkenes were reacted with alcohols in the presence of elemental fluorine to produce α-keto ethers.

Reaction of nonfluorinated alcohols with MEC-31. Reaction of nonfluorinated alcohols under similar reaction conditions gave completely different products

(6) Stavber, S.; Jereb, M.; Zupan, M. *J. Chem. Soc., Chem. Commun.* **2002**, 488−489. (b) Stavber, S.; Kralj, P.; Zupan, M. *Synlett* **2001**, 1152−1154.

(7) Baasner, B., Hagemann, X.; Tatlow, J. C. Introduction of Fluorine by N−F Compounds. In *Methods of Organic Chemistry (Houben-Weyl) Organo-Fluorine Compounds*; Furin, G. G., Ed.; Georg Thieme Verlag: New York, 1999; pp 432−499.

(8) Singh, R. P.; Shreeve, J. M. *J. Chem. Soc., Chem. Commun.* **2001**, 1196−1197.

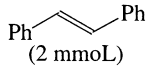
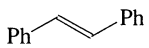
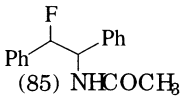
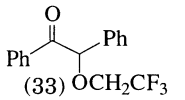
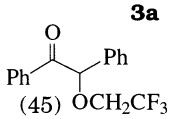
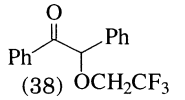
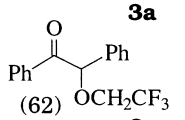
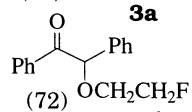
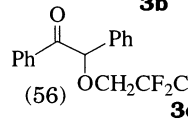
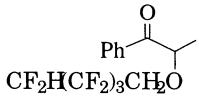
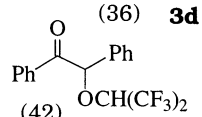
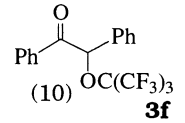
(9) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791−2796. (b) Stavber, S.; Sitler-Pecan, T.; Zupan, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 169−175. (c) Stavber, S.; Sitler-Pecan, T.; Zupan, M. *Tetrahedron Lett.* **1994**, *35*, 1105−1108.

(10) Stavber, S.; Pecan, T. S.; Papez, M.; Zupan, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2247−2248.

(11) Singh, R. P.; Kirchmeier, R. L.; Shreeve, J. M. *Org. Lett.* **1999**, *1*, 1047−1049. (b) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2000**, *65*, 3241−3243. (c) Singh, R. P.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2579−2581. (d) Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2873−2876. (e) Singh, R. P.; Vij, A.; Kirchmeier, R. L.; Shreeve, J. M. *J. Fluorine Chem.* **1999**, *98*, 127−132. (f) Singh, R. P.; Vij, A.; Kirchmeier, R. L;Shreeve, J. M. *Inorg. Chem.* **2000**, *39*, 375−377. (g) Singh, R. P.; Leitch, J. M.; Twamley, B.; Shreeve, J. M. *J. Org. Chem.* **2001**, *66*, 1436−1440. (h) Singh, R. P.; Chakraborty, D.; Shreeve, J. M. *J. Fluorine Chem.* **2001**, *111* (2), 153−160. (i) Singh, R. P.; Shreeve, J. M. *Org. Lett.* **2001**, *3*, 2713−2715. (j) Singh, R. P. Twamley, B.; Shreeve, J. M. *J. Org. Chem.* **2002**, *67*, 1918−1924.

(12) Rozen, S.; Mishani, E.; Kol. M. *J. Am. Chem. Soc.* **1992**, *114*, 7643−7645.

TABLE 1. Reaction of Various Fluorinated Alcohols With *trans*-Stilbene in the Presence of Electrophilic Reagents

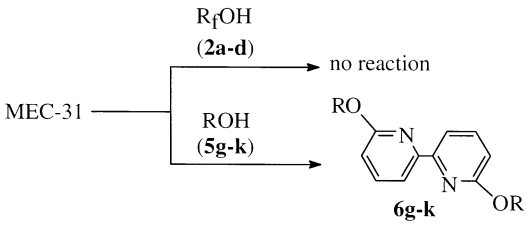
 (2 mmoL)	R_fOH (5ml)	Electrophilic Reagent (2.5 mmoL)	Reaction Conditions	Products (**3a-f**) (Yield, %)	Benzil (**4**) (Yield, %)
	CF_3CH_2OH (1) **2a**	Selectfluor (2.5)	25 °C, 72 h, CH_3CN	 (85)	0
"	CF_3CH_2OH **2a**	Selectfluor	25 °C, 48 h	 (33) **3a**	5
"	CF_3CH_2OH **2a**	MEC-31	25 °C, 48 h	 (45) **3a**	14
"	CF_3CH_2OH **2a**	Selectfluor	60 °C, 48 h	 (38) **3a**	9
"	CF_3CH_2OH **2a**	MEC-31	60 °C, 24 h	 (62) **3a**	21
"	CH_2FCH_2OH **2b**	MEC-31	60 °C, 24 h	 (72) **3b**	25
"	$CF_3CF_2CH_2OH$ **2c**	MEC-31	60 °C, 24 h	 (56) **3c**	35
"	$CHF_2(CF_2)_3CH_2OH$ **2d**	MEC-31	60 °C, 24 h	 (36) **3d**	48
"	$(CF_3)_2CHOH$ **2e**	MEC-31	60 °C, 24 h	 (42) **3e**	52
"	$(CF_3)_3COH$ **2f**	MEC-31	60 °C, 24 h	 (10) **3f**	90

than those obtained with fluorinated alcohols. Reaction of *trans*-stilbene (**1**) with anhydrous methanol (**5g**) in the presence of MEC-31 at 60 °C for 24 h did not produce either α-keto ether or benzil. Unreacted *trans*-stilbene was recovered quantitatively along with the formation of 6,6′dimethoxy-2,2′-bipyridine (**6g**) in 95% yield. Compound **6g** was also obtained in 95% yield in a separate reaction where *trans*-stilbene was not used in the reaction. The synthesis of bipyridine derivatives continues to attract attention because of their importance as industrial and medicinal compounds, as analytical reagents, and as ligands for the preparation of metal complexes with catalytic activities.[13] The classical Ullmann reactions requires drastic experimental conditions and in most cases gives low yields of the desired bipyridines. Bipyridines can be also obtained from pyridylphosphine oxides, but the synthesis required several steps. The synthesis of **6g** was reported in the literature by in situ generation of the Ni(0) complex, $Ni[P(C_6H_5)_3]_4$, directly from nickel dichloride, triphenylphosphine and coupling reaction of 2-methoxy-6-halo pyridine.[14] Synthesis of **6g** in the present reaction was found to be excellent in comparison to any reported methods. Under similar reaction conditions, **5h**−**k** were reacted with MEC-31 to obtain the 6,6′-dialkoxy-2,2-bipyridines (**6h**−**k**) in >90% isolated yields (Scheme 4, Table 2). These

(13) Newkome, G. R.; Puckeff, W. E.; Kiefer, G. E.; Gupta, V. K.; Xia, Yuanjiao, Coreil, M.; Hackney, A. *J. Org. Chem.* **1982**, *47*, 7. 4116−4120. (b) Whitchurch, C.; Andrews, A. R. J. *Anal. Chim. Acta* **2002**, *454*, 45−51. (c) Schubert, U. S.; Heller, M. *Chem.-Eur. J.* **2001**, *7*, 5252−5259. (d) Bin, L.; Wang-Lin; Pei, J.; Liu, S.-J.; Lai, Y.-H. Haung, W. *Macromolecules* **2001**, *34*, 7932−7940. (e) Zassinovich, G.; Mestroni, G.; Camus, A. *J. Organomet. Chem.* **1979**, *168*, C37−C38.

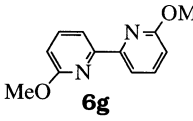
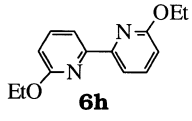
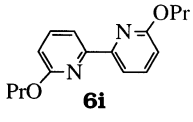
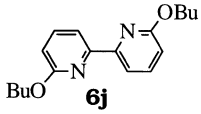
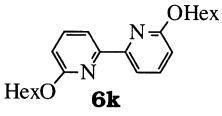
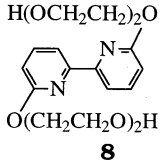
(14) Tiecco, M.; Testaferri, L.; Cianell, D.; Montanucci, M. *Synthesis* **1984**, 736−738.

SCHEME 4



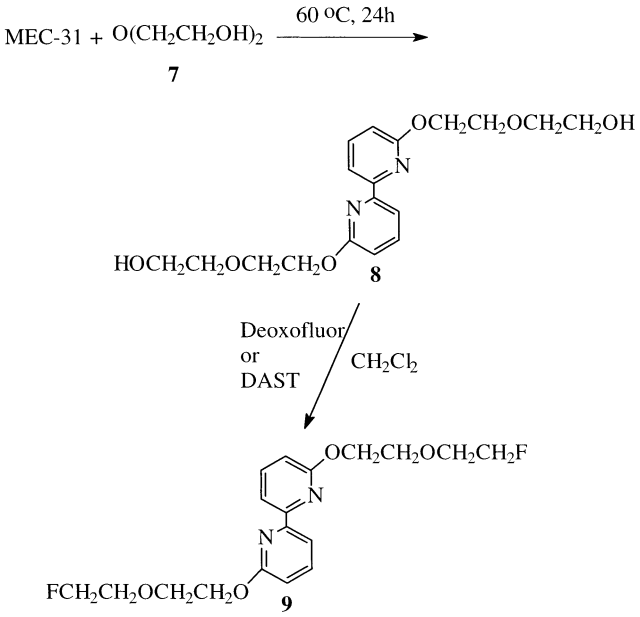
R_f = **a**: CH_2FCH_2- , **b**: CF_3CH_2- , **c**: $CF_3CF_2CH_2$- , **d**: $CF_2H(CF_2)_3CH_2$- ,
R = **g**: CH_3- , **h**: CH_3CH_2- , **i**: $CH_3CH_2CH_2$- , **j**: $CH_3CH_2CH_2CH_2$- , **k**: $CH_3CH_2CH_2CH_2CH_2CH_2$-

TABLE 2. Reaction of Mec-31 With Various Alcohols (60 °C, 24 h)

MEC-31 (2 mmoL)	ROH (5 ml)	Product	Yield (%)
	CF_3CH_2OH **2a**	No reaction	-
"	MeOH **5g**	 **6g**	95
"	EtOH **5h**	 **6h**	92
"	PrOH **5i**	 **6i**	92
"	BuOH **5j**	 **6j**	90
"	HexOH **5k**	 **6k**	90
"	$O(CH_2CH_2OH)_2$ **7**	 **8**	88

reactions show excellent regioselectivity and no other isomers were identified by NMR. Currently, the exact reaction mechanism of the formation of dialkoxy bipyridine regioselectively is unclear but definitely there is a role of [F] in this chemistry. A very similar chemistry of MEC-31 with water has been reported by Umemoto et al.[15] Simple bipyridine was found to be unreactive with methanol under similar reaction conditions.

SCHEME 5



It was also found that secondary and tertiary alcohols did not react with MEC-31 even when attempted at 60 °C for several days. One of the impediments may be the steric hindrance of the alcohols. Also fluorinated alcohols, for example, trifluoroethanol did not react with MEC-31 under conditions similar to those used for nonfluorinated primary alcohols. This is expected due to the lower nucleophilicity of the trifluoroethoxy group. MEC-31 reacted smoothly with excess of diethylene glycol (**7**) to produce **8** in 88% isolated yield. Reaction of **7** with MEC-31 in 1:1 ratio produced only the disubstituted ether (**8**) with none of the bridged species being formed. Reaction of **8** with 2.5 equiv of diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) at room temperature led to the formation of the corresponding fluorinated product (**9**) in 85% isolated yield (Scheme 5).

Conclusion

In summary, new applications of Selectfluor and MEC-31 to produce α-keto ethers and benzil and MEC-31 to form 6,6′-dialkoxy-2,2′-bipyridines are reported. Reactions of *trans*-stilbene with fluorinated alcohols in the presence of Selectfluor or MEC-31 led to the formation of α-keto perfluoroalkylated ethers in good yields. Fluorinated alcohols were found to be unreactive with MEC-31 in the absence of *trans*-stilbene. On the other hand, the reaction of nonfluorinated alcohols with MEC-31 led to the formation of 6,6″-dialkoxy-2,2′-bipyridines in excellent isolated yields. Diethylene glycol also reacted with MEC-31 to produce corresponding 6,6′-disubstituted 2,2′-bipyridine which reacted with DAST or Deoxofluor to give the corresponding fluorinated analogue in good yield.

Experimental Section

General. All the reactions were performed in 25 mL Pyrex glass Schlenk vessels under dry nitrogen and in a moisture free atmosphere. Selectfluor, MEC-31, fluorinated alcohols,

(15) Umemoto, T,; Nagayoshi, M.; Adachi, K.; Tomizawa, G. *J. Org. Chem.* **1998**, *63*, 3379−3385.

trans-stilbene, DAST, Deoxofluor, and nonfluorinated alcohols were used as received. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded in $CDCl_3$ on a spectrometer operating at 300, 282, and 75 MHz, respectively. Chemical shifts are reported in ppm relative to the appropriate standard, $CFCl_3$ for ^{19}F and TMS for ^{1}H and ^{13}C NMR spectra. IR spectra were recorded using NaCl plates for neat liquids and KBr pellets for solids. Mass spectra were measured on an electron impact 70 eV spectrometer. Elemental analyses were performed by Desert Analytics Laboratory, Tucson, AZ.

General Procedure for the Preparation of α-Keto Ethers. In a typical reaction, *trans*-stilbene (2 mmol) and MEC-31 (2.5 mmol) were mixed with the alcohol (5 mL) and heated at 60 °C for 24 h. At the end of the reaction the excess alcohol was recovered by trapping at −195 °C under reduced pressure. To the crude reaction mixture was added methylene chloride, and the solution was washed twice with water. The methylene chloride layer was separated and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed under reduced pressure, and product was purified by thin-layer chromatography.

2-Trifluoroethoxy-2-phenylacetophenone (3a). Yield: 62%; colorless viscous liquid; IR (NaCl film): 3031, 1758, 1494, 1452, 1408, 1276, 1170, 1135, 1049, 977, 752 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ −74.01 (t, 3F, J = 8.5 Hz); ^{1}H NMR ($CDCl_3$) δ 4.48 (q, 2H, J = 8.5 Hz), 5.09 (s, 1H), 7.19−7.34 (m., 10H), ^{13}C NMR ($CDCl_3$) δ 56.50, 60.70 (q, J_{C-C-F} = 36.70 Hz, CH_2CF_3), 122.86 (q, J_{C-F} = 277 Hz, CH_2CF_3),) 127.63, 128.53, 128.77, 137.67, 171.04; MS (EI) *m/z* (species, rel int) 294 (M^+, 14), 275 (M^+ − F, 1), 189 (M^+ − PhCO, 1), 167 [M^+ − (PhCO + HF + 2H), 100], 152 ($PhCHOCH_2CF^+$ + H, 17), 105 ($PhCO^+$, 1.3). Anal. Calcd for $C_{16}F_3H_{13}O_2$: C, 65.29; H, 4.46. Found: C, 65.17; H, 4.53.

2-Fluoroethoxy-2-phenylacetophenone (3b). Yield: 72%; colorless viscous liquid; IR (NaCl film): 3063, 2954, 1691, 1595, 1492, 1449, 1219, 1124, 1051, 972, 880, 757, 697 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ −223.03 (m, 1F); ^{1}H NMR ($CDCl_3$) δ 3.69 (m, 1H), 3.80 (m, 1H), 4.48 (t, 1H, J = 4.2 Hz), 4.64 (t, 1H, J = 4.2 Hz), 5.68 (s, 1H), 7.19−7.44 (m. 8H), 7.91−7.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 68.8 (d, J_{C-C-F} = 19.84 Hz, CH_2CFH_2), 83.16 (d, J_{C-F} = 169.5 Hz, CH_2CFH_2), 82.49, 85.48, 127.7, 128.54, 128.69, 128.69, 128.94, 129.18, 133.35, 134.97, 135.94, 196.86. MS (EI) *m/z* (species, rel int) 259 (M^+ + H, 25), 195 (M^+ − OCH_2CFH_2, 75), 153 (M^+ − $PhCO^+$, 100), 105 ($C_6H_5CO^+$, 48), 77 ($C_6H_5^+$, 35), 47 (CH_2CFH_2, 10). Anal. Calcd for $C_{16}FH_{15}O_2$: C, 74.39; H, 5.86. Found: C, 74.09; H, 6.29.

2-Pentafluoropropoxy-2-phenylacetophenone (3c). Yield: 56%; colorless viscous liquid, IR (NaCl film): 3066, 1693, 1597, 1449, 1201, 1130, 1101, 1010, 960, 757, 697 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ −83.88 (s, 3F), −123.54 (t, 2F, J_{H-F} = 11.3 Hz); ^{1}H NMR ($CDCl_3$) δ 3.96 (m, 2H), 5.75 (s, 1H), 7.20−7.90 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 65.5 (t, J_{C-C-F} = 26.5 Hz, CH_2-CF_2CF_3), 85.6, 113.0 (triplet of quartets, J_{C-F} = 255 Hz, J_{C-C-F}, 36 Hz), 118.6 (quartet of triplets, J_{C-F} = 286 Hz, J_{C-C-F}, 36 Hz), 127.8, 128.6, 129.0, 129.1, 129.1, 133.6, 134.4, 134.5, 195.4; MS (EI) *m/z* (species, rel int) 345 (M^+ + H, 61), 239 (M^+ − PhCO, 69), 195 (M^+ − $OCH_2CF_2CF_3$, 24),105 ($PhCO^+$, 100), 77 (Ph^+, 22). Anal. Calcd for $C_{17}F_5H_{13}O_2$: C, 59.29; H, 3.81. Found: C, 59.16; H, 3.78.

2-Octafluoropentoxy-2-phenylacetophenone (3d). Product was difficult to separate from benzil by using silica gel thin-layer chromatography. It was characterized along with benzil. Yield: 56% (based on GC); ^{19}F NMR ($CDCl_3$) δ −120.03 (m, 2F), −126.13 (m, 2F), −130.78 (m, 2F), −137.78 (m, 2F); MS (EI) *m/z* (species, rel int) 426 (M^+, 1), 321 (M^+ − PhCO, 85), 195 ([M^+ − $OCH_2(CF_2)_3CF_2H$, 2), 105 ($C_6H_5CO^+$, 100), 77 ($C_6H_5^+$, 28).

2-Hexafluoroisopropoxy-2-phenylacetophenone (3e). Yield: 42%; IR (KBr film): 2965, 1724, 1583, 1424, 1385, 1244, 1195, 1107, 927, 780, 738, 689 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ − 73.29 (d, 6F, J = 6 Hz); ^{1}H NMR ($CDCl_3$) δ 5.26 (s, 1H), 6.68 (sept., 1H, J = 6 Hz), 7.2−7.5 (m. 8H), 7.8−7.9 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 68.2 (septet, J_{C-C-F} = 35 Hz, $CH(CF_3)_2$, 68.5, 119.1 (quartet, J_{C-F} = 284 Hz, $CH(CF_3)_2$, 127.3, 128.53, 129.0, 134.2, 135.6, 137.5, 168.2; MS (EI) *m/z* (species, rel int): 362 (M^+, 1), 324 (M^+- 2F, 1), 322 (M^+ − 2HF, 13), 303 [M^+ − (2HF + F), 10], 254 [M^+ − (CF_3 + HF + F), 4], 253 [M^+ − (CF_3 + 2HF), 27], 105 ($C_6H_5CO^+$, 1), 69 (CF_3+, 3). Anal. Calcd for $C_{17}F_6H_{12}O_2$: C, 56.40; H, 3.30. Found: C, 56.69; H, 3.13.

2-Tertiary Perfluorobutoxy-2-phenylacetophenone (3f). Product was difficult to separate from benzil by using silica gel thin-layer chromatography. It was characterized along with benzil. Yield: 10% (based on GC); ^{19}F NMR ($CDCl_3$). −74.27 (s, 9F); MS (EI) *m/z* (species, rel int): 341 [M^+ − (CF_3 + HF), 1], 235 [$OC(CF_3)_3^+$, 1].

Benzil (4). In all the reactions, benzil was characterized by comparing melting point, MS, ^{1}H and ^{13}C NMR spectra with an authentic samples.

General procedure for the preparation of 6,6′-dialkoxy-2,2′-bipyridine derivatives: In a typical reaction, MEC-31 (2 mmol) was mixed with the appropriate nonfluorinated alcohol (5 mL) and heated at 60 °C for 24 h. At the end of the reaction the excess alcohol was recovered by trapping at liquid nitrogen temperature under reduced pressure. In the crude reaction mixture, methylene chloride was added and was washed with water two times. The methylene chloride layer was separated and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed under reduced pressure, and the product was purified by flash chromatography.

6,6′-Dimethoxy-2,2′-bipyridine (6g).[14] Yield: 95%; colorless solid, mp = 118 °C; IR (KBr film): 2951, 1579, 1463, 1300, 1265, 1071, 1020, 907, 793, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 6H), 6.69 (d, 2H, J = 8.3 Hz), 7.60 (t. 2H, J = 8.1 Hz), 7.95 (d, 2H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 53.6, 111.3, 114.2, 139.6, 153.9, 163.8; MS (EI) *m/z* (species, rel int): 217 (M^+ + H, 100), 216 (M^+, 62), 201 (M^+ − CH_3, 2), 186 (M^+ − $2CH_3$, 8), 185 (M^+ − OCH_3, 7), 155 (M^+ − $2OCH_3$ + H, 2), 108 (M^+ − $C_5H_3NOCH_3$, 2).

6,6′-Diethoxy-2,2′-bipyridine (6h). Yield: 92%; colorless solid, mp = 69−70 °C; IR (KBr film): 2978, 2895, 1573, 1432, 1384, 1298, 1259, 1145, 1074, 1031, 981, 923, 823, 796 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 6H, J = 7.1), 4.45 (q, 4H, J = 7.02), 6.69 (d, 2H, J = 8.18), 7.63 (t, 2H, J = 8.1), 7.94 (d, 2H, J = 7.7); ^{13}C NMR ($CDCl_3$) δ 15.1, 61.9, 111.4, 113.9, 139.6, 153.9, 163.6; MS (EI) *m/z* (species, rel int) 245 (M^+ + H, 100), 244 (M^+, 28), 229 (M^+ − CH_3, 8), 214 (M^+ − $2CH_3$, 3). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60. Found: C, 68.93; H, 6.67.

6,6′-Dipropoxy-2,2′-bipyridine (6i). Yield: 92%; colorless solid, mp = 60 °C; IR (KBr film): 2964, 2879, 1573, 1435, 1379, 1297, 1263, 1147, 1072, 1006, 982, 908, 848, 796, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 6H, J = 6 Hz), 1.81 (m, 4H, J = 7.05 Hz), 4.33 (t. 4H, J = 6.6 Hz), 6.67 (d, 2H, J = 8.13 Hz), 7.60 (t, 2H, J = 7.83 Hz), 7.92 (d, 2H, J = 7.38 Hz). ^{13}C NMR ($CDCl_3$) δ 11.1, 22.8, 67.7, 111.4, 113.8, 139.5, 154.0, 163.8; MS (EI) *m/z* (species, rel int) 273 (M^+ + H, 100), 272 (M^+, 15), 257 (M^+ − CH_3, 1), 243 (M^+ − $CH_2CH_3^+$, 7), 230 (M^+ − $CHCH_2$-CH_3^+, 4), 43 ($CH_3CH_2CH_2^+$, 7). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40. Found: C, 70.63; H, 7.33.

6,6′-Dibutoxy-2,2′-bipyridine (6j). Yield: 92%; colorless solid, mp = 70 °C; IR (KBr film): 3082, 2953, 2864, 1571, 1433, 1381, 1301, 1252, 1145, 1070, 1027, 985, 843, 799 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 6H, J = 7.3 Hz), 1.47 (m, 4H), 1.75 (m, 4H), 4.36 (t, 4H, J = 6.6 Hz), 6.66 (d, 2H, J = 8.1 Hz), 7.60 (t, 2H, J = 8.0 Hz), 7.89 (d, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.8, 31.6, 65.9, 111.4, 113.8, 139.5, 154.0, 163.8; MS (EI) *m/z* (species, rel int) 301 (M^+ + H, 100), 300 (M^+, 14), 270 (M^+ − $2CH_3$, 3), 257 (M^+ − $CH_2CH_2CH_3^+$, 4), 244 (M^+ − $CHCH_2CH_2CH_3^+$, 1), 57 ($C_4H_9^+$, 4). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05. Found: C, 72.11; H, 7.97.

6,6′-Dihexoxy-2,2′-bipyridine (6k). Yield: 85%; colorless solid, mp = 76 °C; IR (KBr film): 2947, 2918, 1575, 1435, 1303, 1261, 1126, 1074, 1016, 984, 850, 798, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 6H, J = 6.9 Hz), 1.27−1.44 (m, 12H), 1.71−1.80 (m, 4H), 4.34 (t, 4H, J = 6.72 Hz), 6.66 (d, 2H, J = 8.16

Hz), 7.60 (t, 2H, J = 7.59 Hz), 7.89 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4, 23.0, 26.3, 29.5, 32.1, 66.3, 111.4, 113.8, 139.5, 154.0, 163.7; MS (EI) m/z (species, rel int) 357 (M^+ + H, 100), 356 (M^+, 20), 341 ($M^+ - CH_3$, 7), 327 ($M^+ - C_2H_5$, 3), 313 ($M^+ - C_3H_7$, 1), 285 ($M^+ - C_5H_{11}$, 4), 272 ($M^+ - C_6H_{14}$, 5), 188 [$M^+ - (C_{12}H_{26} + 2H)$, 4]. Anal. Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05. Found: C, 73.50; H, 9.27.

6,6′-Bis{[2-(2-hydroxy)ethoxy]ethoxy}-2,2′-bipyridine (8). Compound **8** was prepared by the same procedure as used for **6g**−**k**. Yield: 88%; colorless solid; mp 94 °C; IR (KBr film): 2953, 2887, 1577, 1444, 1300, 1263, 1135, 1063, 1032, 795 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 2H), 3.62 (t, 4H, J = 4 Hz), 3.71 (t, 4H, J = 5.7 Hz), 3.86 (t, 4H, J = 4.8 Hz), 4.55 (t, 4H, J = 4.6 Hz), 6.72 (d, 2H, J = 12.5 Hz), 7.61 (t, 2H, J = 7.7 Hz), 7.88 (d, 2H, J = 12.3 Hz); ^{13}C NMR ($CDCl_3$) δ 62.1, 65.2, 70.0, 72.9, 111.7, 114.2, 139.7, 153.6, 163.2. MS (EI) m/z (species, rel int) 365 (M^+ + H, 1), 220 ($M^+ - C_6H_{10}NO_3$, 100), 219 [$M^+ - (C_6H_{10}NO_3 + H)$, 100], 205 [$M^+ - (C_7H_{11}NO_3 + 2H)$, 40), 203 [$M^+ - (C_6H_{10}NO_3 + OH)$, 56], 165 ($C_9H_{11}NO_2^+$, 56), 57 ($CHCH_2OCH_2^+$, 78). Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64. Found: C, 59.27; H, 6.70.

Preparation of 6,6′-Bis[2-(2-fluoroethoxy)ethoxy]-2,2′-bipyridine (9). Compound **8** (1 mmol) was dissolved in dichloromethane (5 mL), and DAST or Deoxofluor (2 mmol) was added at 25 °C. The reaction was monitored by GCMS and was complete in 15 h. Reaction was quenched by the slow addition of aqueous sodium bicarbonate solution until effervescence had ceased. The dichloromethane layer was separated and dried over anhydrous $MgSO_4$, It was filtered, and removal of solvent afforded the product as a viscous liquid which was purified by chromatography using pentane and dichloromethane mixture (2:1). Yield: 85%; viscous liquid; IR (NaCl film): 1574, 1431, 1298, 1259, 1134, 1048, 930, 798, 725 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ −223.36 (m, 2F); ^{1}H NMR ($CDCl_3$) δ 3.61 (m, 8H), 4.45−4.64 (m, 8H), 6.69−6.75 (m, 2H), 7.57−7.65 (m, 2H), 7.86−7.91 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 64.88, 70.01, 70.50 (d, J = 19.6 Hz), 83.24 (d, J = 169 Hz), 111.39, 113.84, 139.36, 153.25, 162.38. MS (EI) m/z (species, rel int) 369 (M^+ + H, 59), 305 ($M^+ - OCH_2CH_2F$, 14), 278 [$M^+ - (CHCH_2OCH_2CH_2F)$, 12], 277 [$M^+ - CH_2CH_2OCH_2CH_2F$, 3], 258 [$M^+ - (OCH_2CH_2F + CH_2CH_2F)$, 8], 215 ($M^+ - C_6H_{11}O_2F_2$+, 30), 132 ($C_6H_9FO_2$+, 12), 131 ($C_5H_8O_2F^+$, 16), 91 ($CH_2CH_2OCH_2CH_2F^+$, 1), 77 ($C_5H_3N^+$, 17), 47 ($CH_2CH_2F^+$, 69), 45 ($C_2H_5O^+$, 100). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 58.69; H, 6.02. Found: C, 58.53; H, 5.99.

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