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Electrophilic Reaction Media

Lewis Acid Catalyst Free Electrophilic Alkylation of Silicon-Capped π Donors in 1,1,1,3,3,3-Hexafluoro-2-propanol**

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The electrophilic alkylation of π donors most often implies the use of Lewis acid catalysts for the generation of reactive electrophilic species from covalent precursors.[1] A promising alternative to this procedure has recently been suggested in studies by Mayr and co-workers.[2,3] In particular, it was disclosed that cationic intermediates generated by solvolysis of S_N1-active substrates in polar solvents, such as acetone/water, acetonitrile/water, 2,2,2-trifluoroethanol (TFE), or 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), can be trapped by π nucleophiles (activated arenes, heteroarenes, or enol ethers) provided the nucleophilicity of the latter is higher than that of the solvent system.[3]

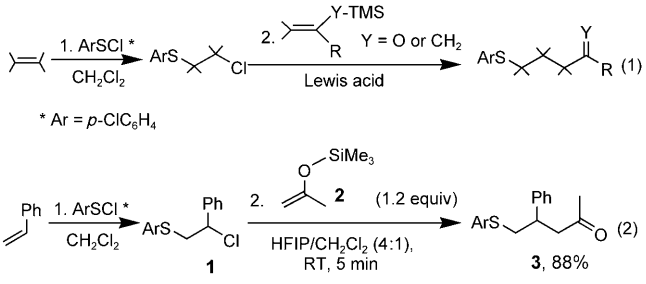
Herein[4], we show that a similar approach can be extended well beyond the scope of purely solvolytic reactions, and might also be applicable for elaboration of the Lewis acid free protocols for a diverse set of reactions, such as β-arylthioalkylation of π donors,[5a] Hosomi–Sakurai acetal allylation,[5b] the Mukaiyama aldol reaction,[5c] and Sakurai–Mukaiyama conjugate additions.[5d–f]

Since the use of HFIP as a reaction medium was found to be a factor of crucial importance for performing these transformations (see below), it is appropriate to briefly discuss the specific physical properties of HFIP and some aspects of its preparative utilization relevant to this subject.[6a,b]

HFIP is well-known as a polar solvent[7] of high ionizing power[8] and low nucleophilicity.[9] Notably, in sharp contrast to the majority of other polar solvents, HFIP is capable of strongly solvating anions but not cations, as was deduced from both conductometric studies[10] and gas-phase determination of the anion-binding energy.[11] HFIP also serves as a powerful hydrogen-bond donor, as was demonstrated not only by the spectral studies and calorimetric measurements,[12] but also by the isolation of extremely stable complexes with a number of nucleophilic species.[13]

The above properties of HFIP make it an optimal solvent for the generation of persistent carbocations and cationic radicals from various precursors and under a fairly diverse set of reaction conditions.[14] A considerable amount of experimental data also attests to the usefulness of HFIP as a medium for synthetically useful reactions, such as C–O cleavage of oxiranes with O, N, or S nucleophiles under neutral conditions,[6a] or in certain C–C bond-forming transformations such as arene *p*-methoxybenzylation,[3a] Diels–Alder cycloaddition,[6a] or cationic cyclization.[15]

As was demonstrated in previous studies by our group, the interaction of β-chloroalkyl arylthioethers with Lewis acids leads to the formation of electrophilic species capable of reacting with a number of silicon-capped π donors, to give the respective products of β-arylthioalkylation (Scheme 1, [Eq. (1)]).[5a]



Scheme 1. β-Arylthioalkylation of Si-capped π donors. TMS = trimethylsilyl; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

Owing to the low nucleophilicity and highly ionizing properties of HFIP, complemented by its capacity to effectively solvate chloride anions, it might be anticipated that this solvent could be useful both as a medium and as a Lewis acid substitute in this reaction. The validity of these expectations was fully confirmed for the model reaction of the adduct **1** (formed in situ by the interaction of styrene with *p*-chlorophenylsulfenyl chloride) with 2-silyloxypropene **2**. The introduction of an excess of HFIP to a solution of these components in CH_2Cl_2 at 20 °C resulted in a rapid, slightly exothermic reaction, furnishing the β-arylthioalkylation adduct **3** as the sole product, isolated in 88% yield (Scheme 1, [Eq. (2)]).

Further experiments revealed that a similar procedure is also applicable for the preparation of a wide range of compounds analogous to adduct **3**, following the route represented in Scheme 1, [Eq. (1)].[16] Attempts to substitute HFIP for TFE as the reaction medium resulted in a dramatic decrease in the yields of the target products, owing to a side reaction leading to the formation of solvoadducts, such as $ArSCH_2CH(Ph)OCH_2CF_3$. This side product was prepared in nearly quantitative yield upon the treatment of **1** in a CH_2Cl_2/TFE mixture (1:4) with a hindered base, 2,6-di-*tert*-butylpyr-

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idine, and was shown to be totally unreactive toward the selected π donors, even after prolonged heating in the CH_2Cl_2/TFE medium. Notably, in HFIP medium, no competing formation of the respective solvoadducts occurred.

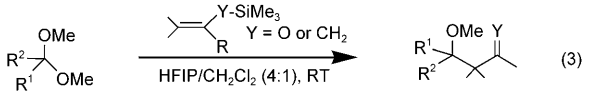
We then investigated the applicability of HFIP as both medium and activator for a number of classical reactions of carbonyl compounds and their acetals, as shown in Table 1 [Eqs. (3–5)], which are carried out using Lewis acid catalysts.[5b–e] Pleasingly, all of these reactions proceeded in HFIP/CH_2Cl_2, under mild conditions without any catalysts, to give the respective adducts in good-to-excellent yields. These results are summarized in Table 1.

The adducts listed were prepared earlier using various Lewis acids and a range of diverse preparative procedures.[1,5f] It is therefore remarkable that, regardless of the nature of the reaction and identity of the reactants, the preparation of all of these adducts was achieved under essentially identical conditions, by merely adding a nucleophile into the solution of the electrophilic component in a CH_2Cl_2/HFIP mixture (1:4) at ambient temperature. Reaction progress was monitored by thin-layer chromatography (for the preparation of **12**, **13**, **22**, and **34**), GC/MS (for **14** and **28**–**33**), or ^{1}H NMR spectroscopy (for **10, 11**, and **19**–**21**), which reveal that, as a rule, complete conversion of the starting electrophile occurred in several minutes. The simple workup required no special treatments and practically pure products could be obtained after removal of the solvent and excess of nucleophile.

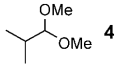
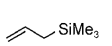
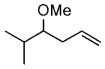
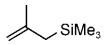
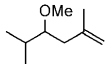
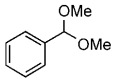
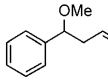
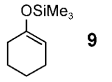
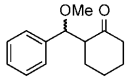
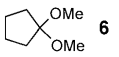
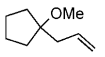
Hosomi-Sakurai acetal allylation[5b] proceeded smoothly for dimethyl acetals of aliphatic and aromatic aldehydes (Table 1, entries 1–3) as well as for cycloalkanone acetals (Table 1, entry 5). The similar reaction of silyl enol ethers resulted in the formation of an aldol-like product. The use of prochiral nucleophile **9** in this reaction afforded the respective adduct **13** as a 1:1 mixture of diastereoisomers (Table 1, entry 4). Reactions of aldehydes, both aliphatic and aromatic, with trimethylsilyl-protected π donors (Mukaiyama aldol reaction[5c]), regardless of the nature of the latter, is accompanied by the transfer of the trimethylsilyl group to give either β-trimethylsiloxycarbonyl compounds (Table 1, entries 6, 8, and 9) or silylated homoallyl alcohols (Table 1, entry 7). Very little diastereoselectivity was detected in the reaction of aldehydes **15** and **16** with silyloxycyclopentene (Table 1, entries 8 and 9). Both cyclic and acyclic conjugated ketones reacted with various π donors under the aforementioned conditions, furnishing the corresponding adducts in good yields (Table 1, entries 10–14). HFIP also promoted reactions with acrylate acceptors (Table 1, entries 15 and 16). No transfer of the trimethylsilyl group occurred in these conjugate addition reactions.

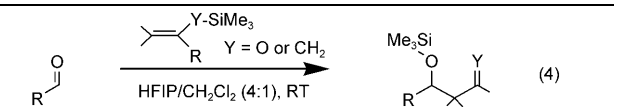
The above results represent proof-of-principle evidence attesting to the promise of the utilizing HFIP as a "magic" solvent to facilitate a range of Friedel–Crafts-type reactions, using covalent reagents in the absence of a Lewis acid catalyst, under essentially neutral conditions. Indeed, HFIP was shown to be a competent substitute for the standard Lewis acid catalysts in promoting two major types of electrophilic additions to π donors; namely, the dissociative type, which involves the removal of the nucleofuge from the covalent precursors (acetals or β-arylthioalkyl ethers), and

Table 1: HFIP-mediated reactions of acetals and carbonyl compounds with π donors.



(3)

Entry	Substrate	Nu	Product	Yield
1	 **4**	 **7**	 **10**	83%
2	**4**	 **8**	 **11**	52%[a]
3	 **5**	**7**	 **12**	69%
4	**5**	 **9**	 **13**	82% (d.r. 1:1)
5	 **6**	**7**	 **14**	61%



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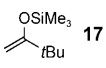
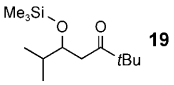
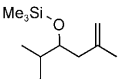
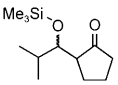
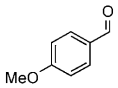
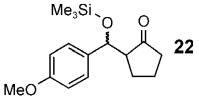
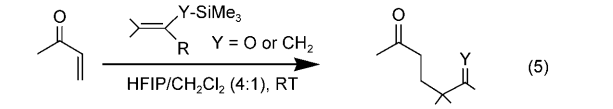
6	 **15**	 **17**	 **19**	51%[a]
7	**15**	**8**	 **20**	88%
8	**15**	 **18**	 **21**	76% (d.r. 1.1:1)
9	 **16**	**18**	 **22**	93% (d.r. 1.5:1)



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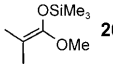
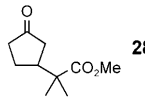
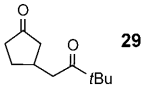
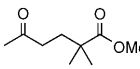
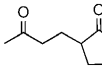
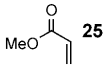
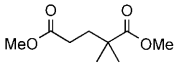
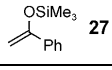
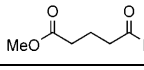
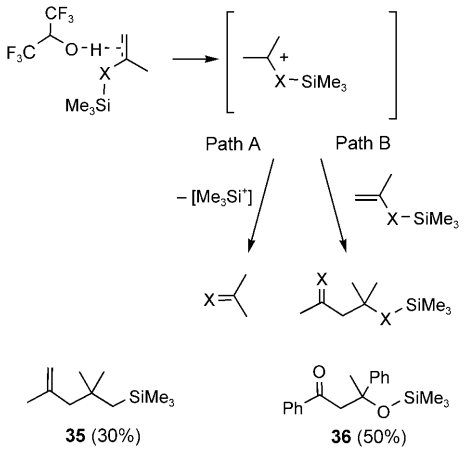
10	 **23**	 **26**	 **28**	89%
11	**23**	**17**	 **29**	53%[a]
12	**23**	**8**	 **30**	83%
13	 **24**	**26**	 **31**	80%
14	**24**	**18**	 **32**	77%[a]
15	 **25**	**26**	 **33**	61%
16	**25**	 **27**	 **34**	25%[a]

[a] The low yield of the adduct is due to the occurrence of side reactions (see Scheme 2).

the associative type, which requires the activation of the carbonyl compounds (aldehydes or α,β-unsaturated enones or enoates).

It may be assumed that this unprecedented activity pattern of HFIP is primarily a result of its well-documented capacity to serve as a very efficient hydrogen-bond donor towards a number of acceptors.[12,13] It is tempting to speculate that the transformation of the starting covalent compounds into the polarized, H-bonded species[17] resulted in a substantial enhancement of their activity as electrophilic reagents. Furthermore, the interaction of these reagents with the covalent π donors should be facilitated by efficient stabilization of the polar transition state by the solvation effects of HFIP, as a highly polar and ionizing solvent.

In the course of this study we came across a rather unexpected reactivity profile of HFIP. Hitherto, HFIP has been known to be an H-bond provider for heteroatomic functional groups.[6a] We disclosed that a similar donation toward a nucleophilic C=C bond may result in a consumption of the π nucleophiles because of the competing side reactions, namely, protodesilylation (Scheme 2, path A) and electrophilic alkylation of a second molecule of the π donor (Scheme 2, path B), with the formation of dimeric products. The dimeric adducts **35** and **36** were isolated as by-products in significant yields in the reactions of acetal **4** with methallylsilane **8** (Table 1, entry 2), and of acrylate **25** with enolate **27** (Table 1, entry 16), respectively. The formation of products resulting from path A (isobutylene from **8** and acetophenone from **27**) was ascertained by ^{1}H NMR spectroscopy of the reaction mixtures.



Scheme 2. The protonation of a carbon–carbon double bond by HFIP, and subsequent desilylation (A) or electrophilic alkylation (B).

Monitoring of the solutions of Si-capped nucleophiles, in a CD_2Cl_2/HFIP mixture at room temperature, by ^{1}H NMR spectroscopy revealed that their half-lives in these conditions vary from several minutes (for **17**, **26**, and **27**) up to several hours (for the less-reactive **7** and **8**) and the ratio of desilylated (path A) and dimeric (path B) products depends on the nature of the π nucleophile. The ease with which these reactions occur is especially surprising in view of the low acidity of HFIP ($pK_a = 9.3$, compared to $pK_a = 4.8$ for acetic acid).

The observed phenomenon of a remarkably high protonating capacity of HFIP towards C=C bonds seems to be rather nontrivial and, as such, it merits further in-depth investigation.

In summary, the concept, advanced and validated in the presented study, has potential applicability in a number of other synthetically useful reactions, which are conventionally Lewis acid mediated procedures. Our current studies are aimed at the evaluation of the scope and preparative ramifications of the described novel Lewis acid free protocol for the electrophilic alkylation of various π donors.

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Keywords: electrophilic addition · hydrogen bonds · Lewis acids · silanes · solvent effects

[1] M. Santelli, J.-M. Pons, *Lewis Acids and Selectivity in Organic Chemistry*, CRC, Boca Raton, **1996**, p. 334; see also A. D. Dilman, S. L. Ioffe, *Chem. Rev.* **2003**, *103*, 733.

[2] For a discussion of the basic concepts of this approach, see: a) S. S. Minegishi, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.* **2004**, *126*, 5174; b) B. Denegri, S. Minegishi, O. Kronja, H. Mayr, *Angew. Chem.* **2004**, *116*, 2353; *Angew. Chem. Int. Ed.* **2004**, *43*, 2302; c) H. Mayr, B. Kempf, A. F. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66.

[3] a) M. Hofmann, N. Hampel, T. Kanzian, H. Mayr, *Angew. Chem.* **2004**, *116*, 5518; *Angew. Chem. Int. Ed.* **2004**, *43*, 5402; b) M. Westermaier, H. Mayr, *Org. Lett.* **2006**, *8*, 4791.

[4] Preliminary results of this study were presented at ESOC-2007, Dublin, Ireland (Book of Abstracts, 342).

[5] a) W. A. Smit, M. I. Lazareva, I. P. Smolyakova, R. Caple, *Russ. Chem. Bull. Int. Ed.* **2001**, *50*, 1949; b) A. Hosomi, *Acc. Chem. Res.* **1988**, *21*, 200; c) T. Mukaiyama, *Angew. Chem.* **1977**, *89*, 858; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817; d) T. Mukaiyama, M. Murakami, *Synthesis* **1987**, 1043; e) H. Hosomi, H. Sakurai, *J. Am. Chem. Soc.* **1977**, *99*, 1673; f) K. Narasaka, K. Soai, T. Mukaiyama, *Chem. Lett.* **1974**, 1223; T. Mukaiyama, Y. Sagawa, S. Kobayashi, *Chem. Lett.* **1986**, 1017; g) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**, p. 373.

[6] For a review, see: a) J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, 18; b) I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* **2007**, 2925.

[7] As was calculated from the solvatochromic measurements, the empirical parameter of solvent polarity, $E_N^T = 1.068$ for HFIP. Among 360 solvents tested, HFIP is the sole solvent outside of the range of the scale defined by the limiting values $E_N^T = 0$ (for Me_4Si) and $E_N^T = 1$ (for water), see: C. Reichardt, *Chem. Rev.* **1994**, *94*, 2319.

[8] From the data of solvolytic studies, the ionizing power Y for HFIP is 3.61 (cf. $Y = 3.04$ for HCOOH), see: F. L. Schadt, T. W. Bentley, P. von R. Schleyer, *J. Am. Chem. Soc.* **1976**, *98*, 7667.

[9] According to recent estimates by Mayr and co-workers, the magnitude of the nucleophilicity parameter $N \approx -2.4$ for HFIP, which is much lower than N values for the majority of other polar solvents and synthetically useful π donors (see Refs. [2a, 3a]).

[10] M. A. Matesich, J. Knoefel, H. Feldman, D. F. Evans, *J. Phys. Chem.* **1973**, *77*, 366.

[11] G. W. Caldwell, J. A. Massuchi, M. G. Ikonomou, *Org. Mass Spectrom.* **1989**, *24*, 8.

[12] HFIP was shown to be a much stronger hydrogen-bond donor than phenol towards various acceptors, regardless of the

experimental parameters used to measure this property (calorimetric data, shift in O–H-stretching frequency, hydrogen-bond chemical shifts; see K. F. Purcell, J. A. Stikeleather, S. D. Brunk, *J. Am. Chem. Soc.* **1969**, *91*, 4019). Calculations based upon the Kamlet-Taft generalized solvatochromic equation point to the much higher hydrogen-bond-donor ability of HFIP ($\alpha = 1.96$) than such proton donors as methanol ($\alpha = 0.93$) or acetic acid ($\alpha = 1.09$); see: M. J. Kamlet, J.-L. Abboud, M. H. Abrham, R. W. Taft, *J. Org. Chem.* **1983**, *48*, 2877.

[13] For example, a 1:1 complex of HFIP with THF was stable enough to tolerate distillation at 100 °C; recovery of the alcohol from this complex required its treatment with 20 % oleum; see: W. J. Middleton, R. V. Lindsey, Jr., *J. Am. Chem. Soc.* **1964**, *86*, 4948.

[14] L. Eberson, M. P. Hartshorn, O. Persson, F. Radner, *Chem. Commun.* **1996**, 2105, and references therein.

[15] P. H. Ferber, G. E. Gream, *Aust. J. Chem.* **1981**, *34*, 2217.

[16] A full account of the studies, dealing with elaboration of the preparative methods, will be published shortly.

[17] Studies were carried out, aimed at the evaluation of the effects of HFIP on the parameters of UV/Vis and/or NMR spectroscopy of benzaldehyde acetal **5**, *p*-methoxybenzaldehyde **16**, or cyclopentenone **23**. UV/Vis spectroscopy of solutions of **5** or **16** in HFIP did not disclose any substantial changes indicative of the formation of ionized species. There was a very small shift of the maximum, as compared to the basic spectra in CH_2Cl_2 ($\Delta\lambda_{max} =$ 8–9 nm), whereas the appearance of an intense red-shifted maximum ($\Delta\lambda_{max} = 54$–60 nm) was detected for the methoxycarbenium ion derived from **5** following treatment with boron trihalide or a structurally similar cationic complex of **16** with boron trihalide (c.f. data in H. Mayr, G. Gorath, *J. Am. Chem. Soc.* **1995**, *117*, 7862). The results of the comparative studies of ^1H and ^{13}C NMR spectra for the solutions of **5** or **16** in neat CD_2Cl_2 and a CD_2Cl_2/HFIP (1:10) mixture revealed deshielding effects both for ^1H ($\Delta\delta = 0.2$–0.4 ppm for all protons of **5** and **16**, except CHO in **16**, which underwent an upfield shift, $\Delta\delta =$ 0.15 ppm) and ^{13}C signals ($\Delta\delta = 3.0$ ppm for *C*H(OMe)$_2$ in **5** and 4.8 ppm for CHO in **16**). Although the cause of these effects is far from clear, it is noteworthy that the transformation of **5** or **16** into the respective cationic derivatives resulted in much more dramatic changes in the NMR spectra (see the data in the reference cited above). A noticeable trend was observed upon the comparison of ^{13}C NMR spectra of **23** in neat CD_2Cl_2 and a CD_2Cl_2/HFIP (1:5) mixture. The addition of HFIP resulted in a substantial downfield shift of C1 and C3 signals ($\Delta\delta = 7.0$ and 5.7 ppm, respectively) and an upfield shift for the C2 signal ($\Delta\delta = 1.1$ ppm). Similar, but substantially more strongly expressed, effects were observed earlier for the complexes of conjugated carbonyl compounds with various Lewis acids (for example, $\Delta\delta = 8.3$, -3.3, and 26.1 ppm for C1, C2, and C3, respectively, for the crotonaldehyde–boron trifluoride complex, see: R. F. Childs, D. L. Mulholland, A. Nixon, *Can. J. Chem.* **1982**, *60*, 801).

