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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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From Olefination to Alkylation: In-Situ Halogenation of Julia–Kocienski Intermediates Leading to Formal Nucleophilic Iodo- and Bromodifluoromethylation of Carbonyl Compounds

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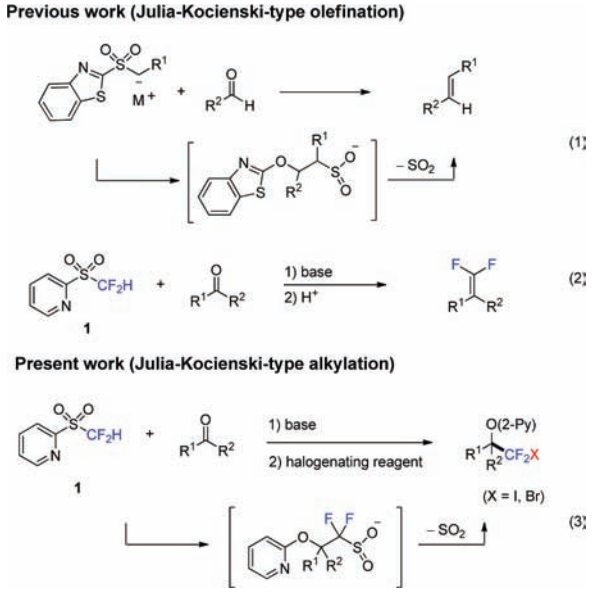
Supporting Information

ABSTRACT: Iodo- and bromodifluoromethylated compounds are important synthetic intermediates and halogen-bond acceptors. However, direct introduction of $-CF_2I$ and $-CF_2Br$ groups through nucleophilic addition is particularly challenging because of the high tendency of decomposition of CF_2Br^- and CF_2I^- to difluorocarbene. In this work, we have developed a formal nucleophilic iodo- and bromodifluoromethylation for carbonyl compounds. The key strategy of the method is the halogenation of in situ-generated sulfinate intermediates from the Julia–Kocienski reaction to change the reaction pathway from the traditional olefination to alkylation. Interesting halogen–π interactions between the halocarbon and aromatic donors were observed in the crystal structures of the products. The method could also be extended to the introduction of other fluorinated groups, such as $-CFClBr$, $-CFClI$, $-CFBr_2$, and $-CFMeI$, which opens up new avenues for the synthesis of a wide range of useful fluorinated products.

Selective introduction of fluorinated moieties into organic molecules can often impart beneficial properties, and therefore, fluorinated compounds have found wide applications as pharmaceuticals and materials.[1] Among them, iodo- and bromodifluoromethylated compounds are of vital importance because they are valuable synthetic intermediates[2] for many other biologically important compounds containing difluoromethylene (which is known to be isosteric and isopolar to an ethereal oxygen)[3] as well as candidates for investigating halogen bonding.[4] Despite these important applications, their preparation still largely relies on multistep modifications of CF_2I- and CF_2Br-containing substances, such as XCF_2COOEt (X = Br, I),[5] which seriously decreases the synthetic efficiency and diversity. On the other hand, nucleophilic fluoroalkylation has proved to be an efficient and reliable route to fluorinated compounds, as exemplified by the remarkable success of nucleophilic trifluoromethylation of diverse bioactive molecules with the Ruppert–Prakash reagent (Me_3SiCF_3).[6] Thus, it is very appealing to develop the analogous nucleophilic iodo- and bromodifluoromethylation methods. However, the introduction of $-CF_2I$ and $-CF_2Br$ groups through nucleophilic addition is particularly challenging, mainly because of the much faster decomposition of CF_2Br^- and CF_2I^- to difluorocarbene (CF_2:) than that of CF_3^-. As a result, direct nucleophilic iodo- and bromodifluoromethylations of carbonyl compounds, such as simple aldehydes and ketones,[7] have not been achieved to date, and indeed, an efficient preparation of *gem*-difluorinated cyclopropenes using Me_3SiCF_2Br as a difluorocarbene precursor was recently disclosed by us.[8]

One alternative strategy for constructing $-CF_2I$ and $-CF_2Br$ groups is to halogenate a difluoromethylene-containing sulfinate ($-CF_2SO_2M$, M = metal).[9] Typically, these fluoroalkyl sulfinates are generated through sulfinatodehalogenation reactions.[9] Therefore, the method is limited to the transformation between different perfluoroalkyl halides via the sulfinate intermediates.[10] A more appealing access to sulfinates is through Smiles rearrangement in the Julia–Kocienski reaction between heteroaryl sulfones and carbonyl compounds; however, the sulfinate intermediates in this case are generally labile species that spontaneously decompose to the corresponding alkenes (eqs 1 and 2 in Scheme 1).[11] Despite the availability of abundant studies of the reaction mechanism, the sulfinate intermediates in Julia–Kocienski olefinations had not been

Scheme 1. Julia–Kocienski-Type Olefination and Alkylation



Received: February 17, 2012
Published: March 16, 2012

   dx.doi.org/10.1021/ja301601b | J. Am. Chem. Soc. 2012, 134, 5790–5793

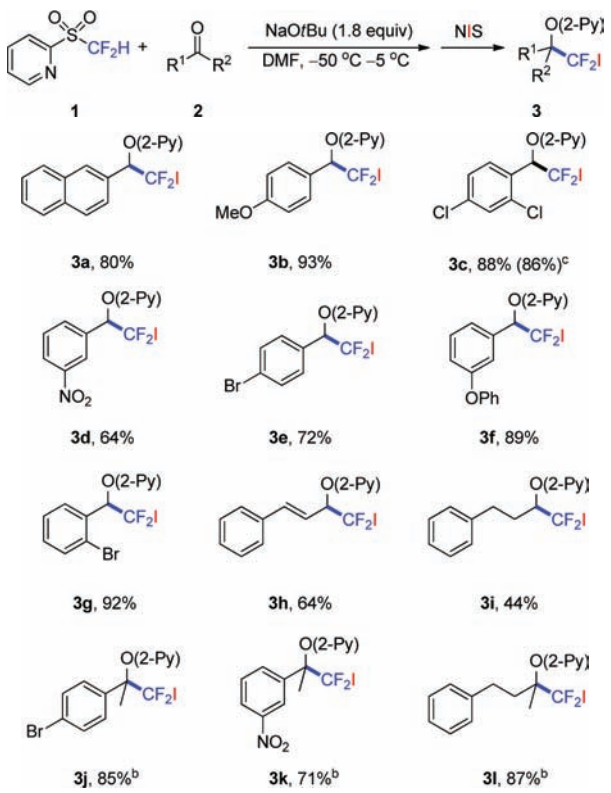
monitored or isolated.[12] In 2010, during our investigation of difluoroolefination with difluoromethyl 2-pyridyl sulfone (**1**), we found that the difluorinated sulfinate intermediate could be both characterized by ^{19}F NMR spectroscopy and trapped with CH_3I to afford the corresponding sulfone at low temperature.[13] We therefore surmised that the classical Julia−Kocienski olefination reaction could probably be transformed into formal nucleophilic iodo- and bromodifluoromethylation reactions if we could succeed in halogenating the in situ-generated sulfinate intermediates (eq 3 in Scheme 1).

We first attempted the reaction of **1** with 2-naphthaldehyde (**2a**) using *t*-BuOK as a base and then quenched the reaction mixture with elemental iodine at −20 °C. After simple workup, we isolated the desired product **3a** in 54% isolated yield, with 2-(2,2-difluorovinyl)naphthalene being a major byproduct. Fluoroalkyl radical was reported to be involved in the halogenation of fluoroalkylsulfinates, while the *β*-pyridinoxyl difluoromethyl radical generated in this case (after the evolution of SO_2) is likely to decompose into an alkene, as reported in a recent paper.[14] Therefore, the difluoroalkene could be produced through both anionic and radical pathways. We surmised that the counterion (M^+ = Li^+, Na^+, K^+) would significantly influence the stability of the difluoromethylsulfinate intermediate as a result of the different M−O bond strengths, and the free radical pathway to the difluoroalkene could be minimized by increasing the rate of halogenation of the difluoromethyl radical. Fortunately, changing the base to *t*-BuONa significantly enhanced the stability of the in situ-generated sulfinate intermediate, and using more powerful *N*-iodosuccinimide (NIS) as the iodinating reagent completely inhibited the formation of the undesired difluoroalkene.

With the optimized reaction conditions (reactant molar ratio **1**/**2**/*t*-BuONa/NIS = 1:1.2:1.8:4) in hand, we examined the substrate scope of the novel iododifluoromethylation reaction. The results are summarized in Table 1. The reaction tolerates various substituents on the aryl aldehyde and is also amenable to aliphatic and *α*,*β*-unsaturated aldehydes. For ketones, the difluorosulfinate intermediates are very unstable, and the iodination should proceed at −20 °C to inhibit the facile generation of difluoroalkenes. The current reaction could be performed on a gram scale (3.7 g for the preparation of **3c**) without any significant impact on the yield.

Encouraged by the success of the iododifluoromethylation reaction, we then extended the reaction to bromodifluoromethylation by using *N*-bromosuccinimide (NBS) as the halogenating reagent. When we carried out the bromodifluoromethylation under the same reaction conditions as shown in Table 1, rather lower yields (<50%) were obtained. It is known that the bromination of sufinates produces sulfonyl bromides, which are more stable than the corresponding sulfonyl iodides. Therefore, sulfonyl bromides could engage in side reactions before being transformed into the desired products. After a quick survey of the reaction conditions, we found that the combination of LiHMDS and $PhMe_3NBr_3$ gave good yields of the products, possibly as a result of the enhanced brominating power and solubility of the reagent. Consequently, we changed the base and modified the reactant ratio to **1**/**2**/LiHMDS/$PhMe_3NBr_3$ = 1:1.2:1.4:4. The data are summarized in Table 2. It was found that similar to iododifluoromethylation, the bromodifluoromethylation of carbonyl compounds **2** proceeded smoothly to afford the desired CF_2Br-containing products **4** mostly in good yields (Table 2).

Table 1. Iododifluoromethylation of Various Carbonyl Compounds 2[a]



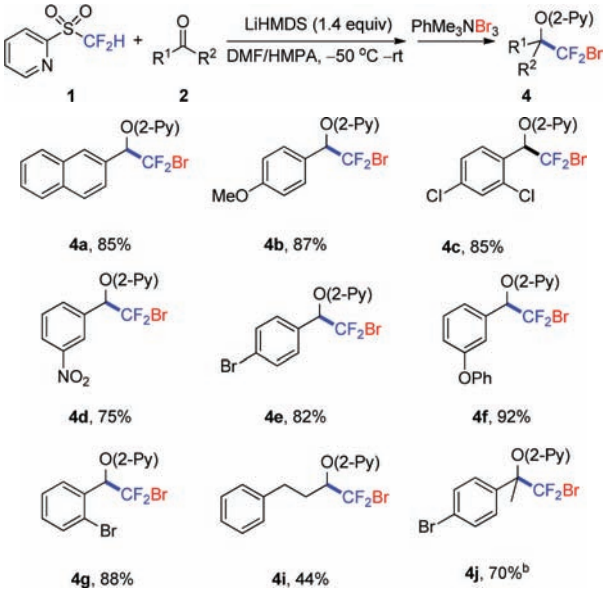
[a]The reaction conditions were as follows: NaO*t*Bu (0.9 mmol) in *N*,*N*-dimethylformamide (DMF) (1 mL) was added to a stirred mixture of **1** (0.5 mmol) and **2** (0.6 mmol) in DMF (2.5 mL) at −50 °C, after which the reaction mixture was allowed to warm to 5 °C and then NIS (2.0 mmol) was added. [b]NIS was added when the reaction mixture had warmed to −20 °C. [c]The reaction was carried out on a 10 mmol scale.

The pyridinoxyl group in the products (**3** and **4**) could be easily transformed to a hydroxyl group by heating with CF_3COOH and subsequent hydrolysis, as shown in Table 3. The current methodology thus provides a highly useful protocol for iodo- and bromodifluoromethylation that is comparable to the previously well-developed trifluoromethylation of carbonyl compounds with Me_3SiCF_3, that is, trifluoromethylation/O-silylation and subsequent desilylation.[6]

Julia−Kocienski reactions are frequently employed in organic synthesis for the highly *E*-selective construction of alkenes.[11] However, the stability and reactivity of the in situ-generated sulfinate intermediates are rarely mentioned in the literature. It might be supposed that difluorosulfinates are more stable than monofluoro- or nonfluorinated ones. To confirm this supposition, we synthesized different 2-pyridyl sulfones (**7**, **8**, **9**, and **14**) and attempted the current reaction. To our surprise, the current iodo- and bromodifluoromethylation reaction smoothly extended to other 2-pyridyl sulfones, giving the corresponding products in good yields, as shown in Table 4. These results indicate that the sulfinates in Julia−Kocienski reactions employing various 2-pyridyl sulfones are relatively stable. Interestingly, the reaction of monofluoromethyl 2-pyridyl sulfone **9** afforded dibromination product **13**, which may be produced by bromination of the C−H bond in the −CHBrF group. For methyl 2-pyridyl sulfone **14**, a different kind of reaction occurred, whose main product was (*E*)-alkene

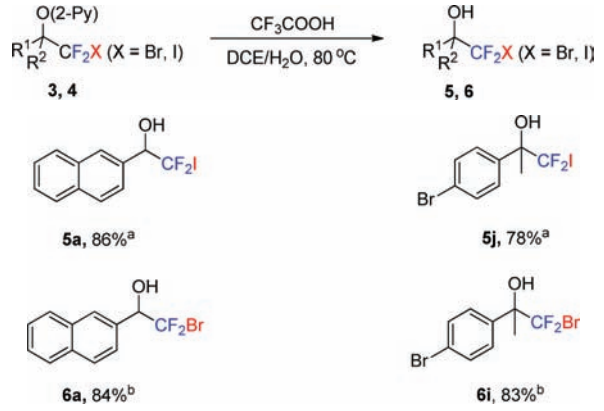
dx.doi.org/10.1021/ja301601b | J. Am. Chem. Soc. 2012, 134, 5790−5793

Table 2. Bromodifluoromethylation of Various Carbonyl Compounds 2[a]



[a]The reaction conditions were as follows: LiHMDS (0.7 mmol) in tetrahydrofuran (0.7 mL) was added to a stirred mixture of **1** (0.5 mmol) and **2** (0.6 mmol) in DMF (2.5 mL) at −50 °C, after which the reaction mixture was allowed to warm to rt and then $PhMe_3NBr_3$ (2.0 mmol) was added. [b]$PhMe_3NBr_3$ was added when the reaction mixture had warmed to 10 °C.

Table 3. Synthesis of Iodo- and Bromodifluoromethylated Carbinols 5 and 6

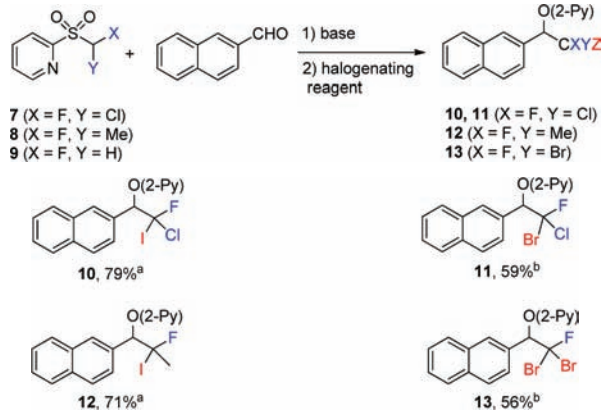


[a]A mixture of **3** (0.25 mmol), H_2O (1 mL), dichloroethane (DCE) (1 mL), and CF_3COOH (1 mL) was heated to 80 °C for 12 h. [b]A mixture of **4** (0.25 mmol), DCE (1 mL), and CF_3COOH (1 mL) was heated to 80 °C for 12 h, after which the crude product was treated with K_2CO_3/MeOH at rt for 2 h.

15 (Scheme 2). The reaction mechanism is proposed to involve an intramolecular nucleophilic attack of an in situ-generated sulfonyl iodide generated from iodination of the sulfinate intermediate, followed by a subsequent ring-opening process. The structure of product **15** was unambiguously confirmed by X-ray crystallographic analysis. The change in the reaction pathway may due to the difference in the stabilities of the nonfluorinated sulfonyl iodide intermediate **16** and fluorinated ones.

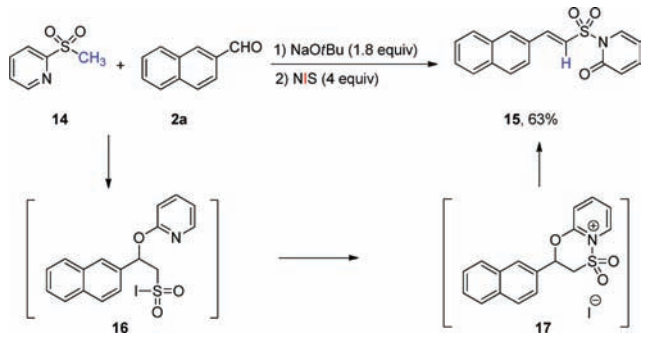
As numerous examples of halogen bonding between R_f-I or R_f-Br and oxygen and nitrogen donors have been reported,[15]

Table 4. Reactions of Various 2-Pyridyl Sulfones (7−9) with 2-Naphthaldehyde 2a



[a]The reaction conditions were the same as in Table 1. [b]The reaction conditions were the same as in Table 2.

Scheme 2. Reaction of Methyl 2-Pyridyl Sulfone 14 with 2-Naphthaldehyde 2a



we became interested in the short contact in the crystal structures of these novel compounds bearing $-CF_2I$, $-CF_2Br$, or $-CFBr_2$ groups. The molecular structures of compounds **3c** and **13** were established by single-crystal X-ray diffraction and are shown in Figure 1. Interestingly, we found that significant

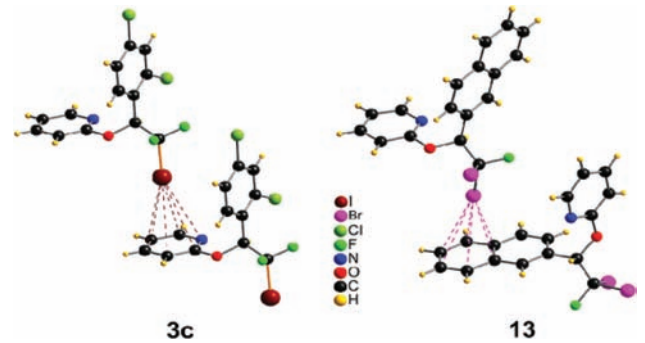


Figure 1. X-ray structures of products **3c** and **13**.

halogen−π interactions exist between $-CF_2I$/$-CFBr_2$ and aromatic donors. For example, The Br atoms of $-CFBr_2$ in compound **13** interact with the naphthalene ring of a neighboring molecule with distances of Br to two C atoms of 3.335 and 3.448 Å, which is in good agreement with the reported results.[15] It is uncommon that halogen−π interactions are more favorable than halogen−N/O interactions in compounds where both types of interaction are possible.

dx.doi.org/10.1021/ja301601b | J. Am. Chem. Soc. 2012, 134, 5790−5793

However, this observation can be partially rationalized by the sterically congested environment around the N and O donors. It is also somewhat surprising that halogen−π interactions between the halocarbon and the heteroaromatic donor were observed in compound **3c**.

In summary, we have reported the unprecedented iodo- and bromodifluoromethylation reactions of carbonyl compounds through a new synthetic strategy, namely, halogenation of the in situ-generated sulfinate intermediates in the Julia−Kocienski reaction to change the reaction pathway from olefination to alkylation. A wide range of aldehydes and ketones were subjected to the present method to give the corresponding iodo- and bromodifluoromethylated products in high yields. Halogen−π interactions between the halocarbon and aromatic donors were observed in the crystal structures of the products. The method could also be extended to the introduction of other fluorinated groups, such as −CFClBr, −CFClI, −$CFBr_2$, and −CFMeI, which opens up a new avenue for the synthesis of a wide range of useful fluorinated compounds. The "hijacking" of the sulfinate intermediates in the Julia−Kocienski reaction for other synthetic applications has been largely ignored in the past, and our work adds new possibilities for further elaboration of this classical reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data for all new compounds, and crystallographic data for **3c**, **13**, and **15** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (20825209, 20832008), the National Basic Research Program of China (2012CB215500), and the Chinese Academy of Sciences. Y.Z. thanks Jian Lü (University of Nottingham) for helpful discussions and processing of Figure 1. J.H. thanks Dr. Jun Xiao (Henkel Corporation) for helpful discussions.

■ REFERENCES

(1) (a) *Organofluorine Compounds: Chemistry and Applications*; Hiyama, T., Ed.; Springer: New York, 2000. (b) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (c) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, U.K., 2004. (d) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U.K., 2006.

(2) For selected examples, see: (a) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (b) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119. (c) Dordonne, S.; Crousse, B.; Bonnet-Delpon, D.; Legros, J. *Chem. Commun.* **2011**, *47*, 5855. (d) Lin, J.-H.; Xiao, J.-C. *Eur. J. Org. Chem.* **2011**, 4536. (e) Colombel, S.; Sanselme, M.; Leclerc, E.; Quirion, J.-C.; Pannecoucke, X. *Chem.—Eur. J.* **2011**, *17*, 5238. (f) Mikami, K.; Tomita, Y.; Itoh, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 3819. (g) Kim, B. M.; San, Q.-Z.; Bhatt, L. R.; Kim, S. K.; Chai, K.-Y. *Bull. Korean Chem. Soc.* **2010**, *31*, 31. (h) Zhu, J.; Zhang, W.; Zhang, L.; Liu, J.; Zheng, J.; Hu, J. *J. Org. Chem.* **2010**, *75*, 5505. (i) Surmont, R.; Verniest, G.; De Kimpe, N. *Org. Lett.* **2009**, *11*, 2920. (j) Yue, X.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 73. (k) Francisco, C. G.; Gonzalez, C. C.; Kennedy, A. R.; Paz, N. R.; Suarez, E. *Chem.—Eur. J.* **2008**, *14*, 6704. (l) Li, Y.; Liu, J.; Zhang, L.; Zhu, L.; Hu, J. *J. Org. Chem.* **2007**, *72*, 5824. (m) Xu, B.; Mashuta, M. S.; Hammond, G. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 7265.

(3) (a) Prakash, G. K. S.; Wang, Y.; Hu, J.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 1361. (b) Blackburn, G. M.; Brown, D.; Martin, S. J.; Parratt, M. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 181. (c) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 913. (d) Blackburn, G. M.; England, D. A.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 930.

(4) For selected examples, see: (a) Cardillo, P.; Corradi, E.; Lunghi, A.; Meille, S. V.; Messina, M. T.; Metrangolo, P.; Resnati, G. *Tetrahedron* **2000**, *56*, 5535. (b) Corradi, E.; Meille, S. V.; Messina, M. T.; Metrangolo, P.; Resnati, G. *Tetrahedron Lett.* **1999**, *40*, 7519. (c) Farina, A.; Meille, S. V.; Messina, M. T.; Metrangolo, P.; Resnati, G.; Vecchio, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 2433. (d) Zhu, S. Z.; Xing, C. H.; Xu, W.; Jin, G. F.; Li, Z. T. *Cryst. Growth Des.* **2004**, *4*, 53.

(5) Osipov, S. N.; Golubev, A. S.; Sewald, N.; Michel, T.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *J. Org. Chem.* **1996**, *61*, 7521.

(6) (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613. (c) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123.

(7) (a) Broicher, V.; Geffken, D. *Arch. Pharm.* **1990**, *323*, 929. (b) Hagiwara, T.; Fuchikami, T. *Synlett* **1995**, 717. (c) Although a direct nucleophilic bromodifluoromethylation of the highly reactive 1,3-dimethylimidazolidine-2,4,5-trione with $TMSCF_2Br$ was reported by Geffken and coworkers as early as 1990, similar reactions with simple aldehydes or ketones have not been achieved to date. We also tried the reaction of $TMSCF_2Br$ and aldehydes with tetrabutylammonium triphenyldifluorosilicate as the nucleophilic catalyst, but no desired product was observed.

(8) Wang, F.; Zhang, W.; Zhu, J.; Li, H.; Huang, K.-W.; Hu, J. *Chem. Commun.* **2011**, *47*, 2411.

(9) Huang, W. Y.; Huang, B. N.; Hu, C. M. *J. Fluorine Chem.* **1983**, *23*, 193.

(10) Cao, H.-P.; Chen, Q.-Y. *J. Fluorine Chem.* **2007**, *128*, 1187.

(11) For reviews of Julia−Kocienski olefination, see: (a) Aissa, C. *Eur. J. Org. Chem.* **2009**, 1831. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2565. (c) Ma, J.; Wang, F.; Wang, J.; You, Q. *Chin. J. Org. Chem.* **2010**, *30*, 1615.

(12) Plesniak, K.; Zarecki, A.; Wicha, J. In *Sulfur-Mediated Rearrangements II*; Schaumann, E., Ed.; Springer: New York, 2007.

(13) (a) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. *Org. Lett.* **2010**, *12*, 1444. (b) Prakash, Olah and co-workers also reported the use of reagent **1** in the synthesis of difluorinated alkanesulfonates. See: Prakash, G. K. S.; Ni, C.; Wang, F.; Hu, J.; Olah, G. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 2559.

(14) Braun, M.-G.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2011**, *133*, 15954.

(15) *Halogen Bonding: Fundamentals and Applications*; Metrangolo, P., Resnati, G., Ed.; Springer: New York, 2007.