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Communication

Fluorination

Borosilicate Activation of (Difluoroiodo)toluene in the *gem*-Difluorination of Phenyldiazoacetate Derivatives

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Abstract: A combined experimental and computational investigation was conducted to identify a mild and effective Lewis-acidic activator for $TolIF_2$ in the *gem*-difluorination of diazo compounds. Computationally, borosilicate, a common constituent of laboratory glassware, was found to spontaneously activate $TolIF_2$, and an extensive experimental survey confirmed borosilicate as the most effective activator to date. The key to realizing this borosilicate-activated reaction was the use of high purity $TolIF_2$, which is prepared by a reproducible, multigram-scale synthesis.

Introduction

The benefits of incorporating fluorine into pharmaceutical and agrochemical agents are widely recognized. Fluorine is routinely employed as a biostere for hydrogen, which alters the lipophilicity, metabolic stability and chemical reactivity of biologically active compounds.[1] Fluorination of organic molecules is a significant obstacle that has challenged researchers for decades and, as evidenced by the relative scarcity of fluorine-containing natural products, even Nature only has a minimally evolved biochemistry of fluorine.[2] Elemental fluorine is the simplest electrophilic fluorinating agent, though it reacts explosively with organic compounds. Hypervalent polyfluorides of other strongly electronegative elements, such as XeF_2,[3] ClF_3,[4] BrF_3,[5] IF_5[6] and SF_4,[7] are also extremely oxidizing and violently reactive with water, such that only XeF_2[8] is regularly used in synthesis.[9,10]

The 1950's discovery of SF_4 as a selective deoxygenative fluorination reagent[11] was timely due to emerging interest in (and the increasing significance of) novel fluorinating agents. Less volatile, more controllable derivatives of SF_4, [e.g. DAST[12] (**1**) and Deoxo-Fluor[13] (**2**), Figure 1], were significant, but as fuming liquids they remain challenging to handle owing to their sensitivity to water and their tendency decompose on standing. Recently XtalFluor-E (**3**) and XtalFluor-M (**4**) were reported to be highly effective deoxofluorination salts synthesized by treating DAST with $BF_3{\cdot}OEt_2$.[14]

Iodine (poly)fluorides of increased stability and practicality over IF_5 have also been developed, such as the hypervalent iodoarene-derived fluorides **5**[15] and **6** [(difluoroiodo)toluene, $TolIF_2$].[16] Contrary to $PhICl_2$ (**7**) which has been widely used as chlorine-transfer agent for over a century,[17] (difluoroiodo)toluene has only recently become popular as a fluorination reagent.[18] While polyfluorides **1**–**4** react to generate sulfonyl fluoride waste (Figure 1),[12,19] iodanes **6** and **7** generate iodobenzene and halide ion byproducts. These halide nucleophiles can be trapped when iodanes **6** or **7** react with ambiphilic diazoesters, giving *gem*-dihalide products [Equations (1) and (2)].[20,21] This chemistry parallels the reactivity between diazo compounds and elemental halogens, and because $TolIF_2$ reacts as a surrogate for elemental fluorine, it provides a facile and economical means to synthesize biologically-relevant difluorides.

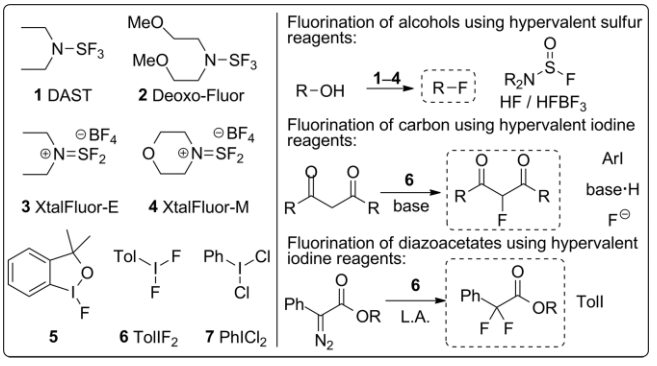

Figure 1. Structure and reactivity profiles of hypervalent sulfur- and iodine-based fluorination reagents.

In analogy to the activation of sulfur polyfluorides with $BF_3{\cdot}OEt_2$, Lewis acid activation of $TolIF_2$ was required to bolster its reactivity with phenyl diazoacetates (Equation 2). Unfortunately, inconsistent yields and poor functional group compatibilities were found for the fluorination reactions employing the previously reported activator $BF_3{\cdot}OEt_2$.[22] Gouverneur and coworkers reported similar outcomes in their *gem*-difluorination reactions of **11** (Equation 3).[23] The highly variable yields in these two studies appeared to derive from the poor compatibil-

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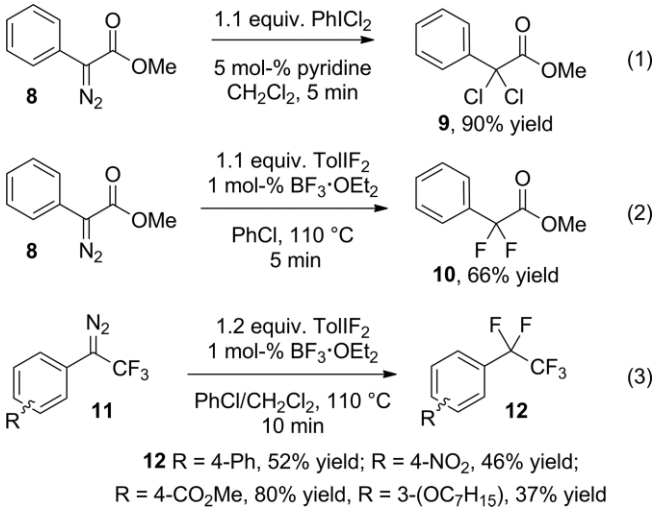
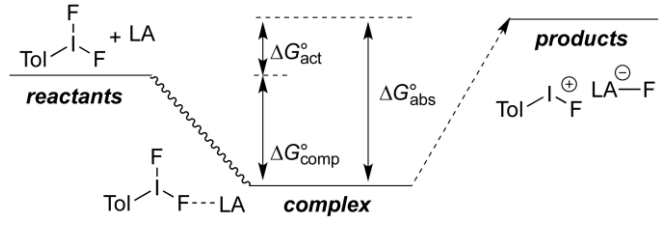


ity between BF_3·OEt_2 and electron-rich functional groups. To overcome this obstacle we conducted a combined experimental and computational exploration for milder Lewis-acidic activators of $TolIF_2$. Here we report the results of the investigation, and show that borosilicate glassware is a highly effective initiator for the *gem*-difluorination reaction.

Results and Discussion

The computational studies were based on a two-step activation of $TolIF_2$: complex formation between **6** and a Lewis acid (LA), followed by heterolytic fluoride abstraction to generate the iodonium ion pair (Table 1). The Gibbs' energies for $TolIF_2$ activation ($\Delta G°_{act}$) were calculated as the sum of the energies of complex formation ($\Delta G°_{comp}$) and fluoride abstraction ($\Delta G°_{abs}$). The energy for the BF_3-mediated iodane activation was calculated as a reference to facilitate identification of viable Lewis acid candidates (Table 1, entry 1).[24] Though most gave significantly higher values for $\Delta G°_{act}$ than did BF_3 (entries 2–4), TiF_4 was promising ($\Delta G°_{act}$ = 24.7 kcal mol^{-1}, entry 5). Because a slow reaction was also observed without BF_3·OEt_2,[21] we also investigated a borosilicate-like cluster (Figure 2, inset) which predicted spontaneous fluoride abstraction ($\Delta G°_{act}$ = –8.2 kcal mol^{-1}, entry 6). This computational result showed that complex formation derives from shared electron density between the Lewis-basic F 2p orbital and the Lewis-acidic B 2p orbital (Figure 2), resulting in an increase in the I–F bond length from 2.04 Å to 2.27 Å.[25,26] This indicates that borosilicate is significantly more Lewis acidic towards $TolIF_2$ than BF_3·OEt_2.[27] Calculations show that this stems from the local geometry of the boron centre in borosilicate, where the non-optimal dihedral angles between donor (O 2p) and acceptor (B 2p) orbitals enhance boron's Lewis acidity.[28,29]

Table 1. Gibbs' energies of complex formation ($\Delta G°_{comp}$), fluoride abstraction ($\Delta G°_{abs}$), and activation ($\Delta G°_{act}$) between $TolIF_2$ and Lewis acidic additives.[a]



Entry	Lewis acid[b]	$\Delta G°_{comp}$ [kcal mol^{-1}]	$\Delta G°_{abs}$ [kcal mol^{-1}]	$\Delta G°_{act}$ [kcal mol^{-1}]
1	BF_3·OEt_2	14.9	44.5	59.4
2	AlF_3	128.4	44.8	173.2
3	GaF_3	64.5	44.8	104.9
4	FeF_3	73.4	63.9	137.3
5	TiF_4	–21.9	46.6	24.7
6	borosilicate	–57.7	49.6	–8.2

[a] Calculations were conducted at the B3LYP/6-311+G(d,p) level of theory using a 6-311G* basis set for iodine.

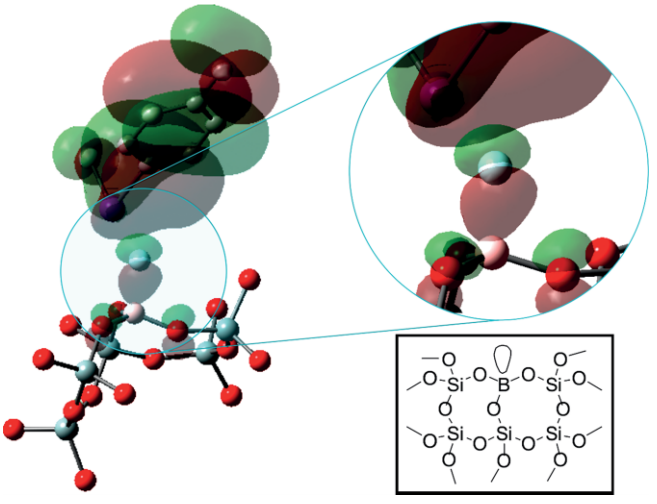
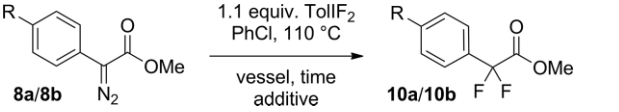


Figure 2. Highest occupied molecular orbital (HOMO) for the borosilicate·$TolIF_2$ complex. Magnification shows the boron atom with substantial orbital overlap with the Lewis-basic fluorine. Inset: borosilicate (bsg) cluster used in molecular modelling.

A borosilicate flask-activated *gem*-difluorination reaction would be a major improvement over the use of BF_3·OEt_2 as an activator. A previous attempt of this reaction only proceeded in 40 % yield in 2 hours (Table 2, entry 1), but the experiment was

Table 2. Control experiments for the *gem*-difluorination of phenyldiazoacetates using various silicates as activating agents for $TolIF_2$.

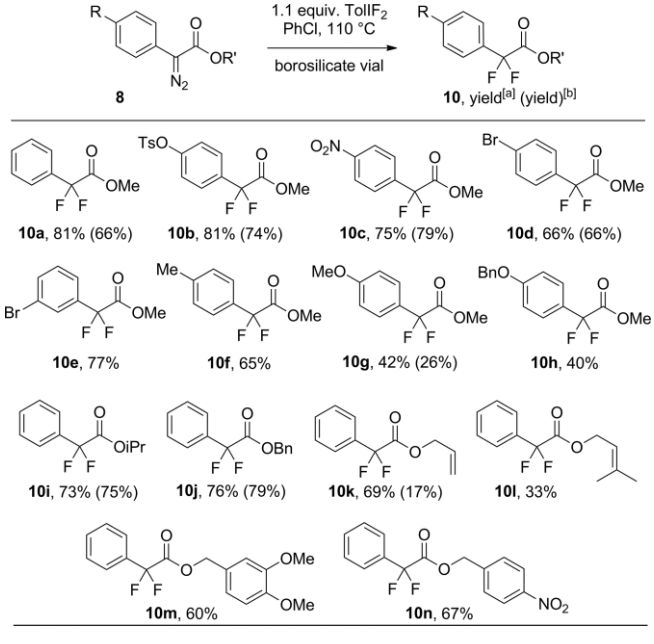


Entry	Substrate	Vessel	Additive (5 wt.-%)	Time	Yield[a]
1	**8a** R = H	bsg[b]	–	2 h	10a 40 %
2	**8a** R = H	bsg	–	10 min	**10a** 81 %[c]
3	**8b** R = OTs	bsg[d]	–	8 min	**10b** 81 %[c]
4	**8b** R = OTs	PFA	–	1 h	–
5	**8b** R = OTs	Nalgene	–	1 h	–
6	**8b** R = OTs	PFA	borosilicate	10 min	**10b** 76 %[c]
7	**8b** R = OTs	PFA	SiO_2 gel	1 h	–
8	**8b** R = OTs	PFA	Pasteur pipette	1 h	–
9	**8b** R = OTs	PFA	quartz	1 h	–
10	**8b** R = OTs	silanized borosilicate	–	10 min	**10b** 67 %[c]

[a] Isolated yield. [b] Borosilicate flask. [c] Glyoxylate isolated in ca. 15 % yield. [d] New glassware used. PFA: 4 mL of PFA (Teflon^{TM}) vial.

repeated and gave **10b** in 81 % yield over 10 min (entry 2). This improvement is a consequence of using pure $TolIF_2$ in the reaction,[26] indicating the importance of reagent quality to realizing rapid and efficient activation by the borosilicate glassware.[30] To rule out surface impurities being responsible for the improved reactivity, newly purchased glassware and stir bar were used in the reaction, and gave **10b** in 81 % yield (Table 2, entry 3). Experiments conducted in Nalgene and PFA vials failed, though addition of 5 wt.-% ground borosilicate to a reaction in PFA gave **10b** in 76 % yield (entries 4–6). Reactions performed in boron-free silicates, such as silica gel, Pasteur pipette glass, and ground quartz failed (entries 7–9), which strongly supports boron's role in the activation process. Use of a silanized borosilicate vial gave **10b** in 76 % yield (entry 10), indicating that passivating the glass surface fails to impede the *gem*-difluorination reaction.

Similar improvements in reaction efficacy were also realized for diazoacetates **8a**–**f**, with the products being recovered in equal or greater yield than under $BF_3{\cdot}OEt_2$ activation (Scheme 1). The improvements realized for the aryl ether substrates **8g** (R = 4-OMe) and **8h** (R = OBn) were less than anticipated, presumably because aryl ethers are labile under the reaction conditions. The novel reaction conditions were equally effective for substrates **8i**–**n**, with a dramatic improvement in chemoselectivity and reaction efficacy being realized for the allyl ester (**8k**) and 3,4-dimethoxybenzyl ester (**8m**) substrates. Overall, the reactions carried out under borosilicate catalysis were rapid, operationally simple, and moderate-to-good yielding. Importantly, borosilicate activation of $TolIF_2$ was sufficiently mild to enable us to elucidate the possibility of a subtle, though important discrepancy in the stability of aryl ether substitution on the arene (**8g**) and ester (**8m**) functional groups.



Scheme 1. *gem*-Difluorination of phenyldiazoacetate using borosilicate activation. [a] Isolated yield. [b] Yield using 1 mol-% $BF_3{\cdot}OEt_2$.

Based on our computational studies and experimental observations, a plausible mechanism is proposed for the fluorine transfer reaction (Figure 3). Activation of the iodane gives an ion pair between the iodonium ion and the borosilicate–fluoride complex (F-bsg). Attack by the diazoester **8** at the electrophilic iodine produces **A**, which could reductively eliminate iodotoluene to give **B**. Computationally, the initial fluoride abstraction is irreversible,[31] therefore we propose **B** to expel nitrogen, possibly by anchimeric assistance from the carbonyl[15,32] or electron-rich arene groups, and give benzylic cation **C**.[33] Should this cation be sufficiently Lewis acidic, it could abstract fluoride from $TolIF_2$ and regenerate the original iodonium ion pair.

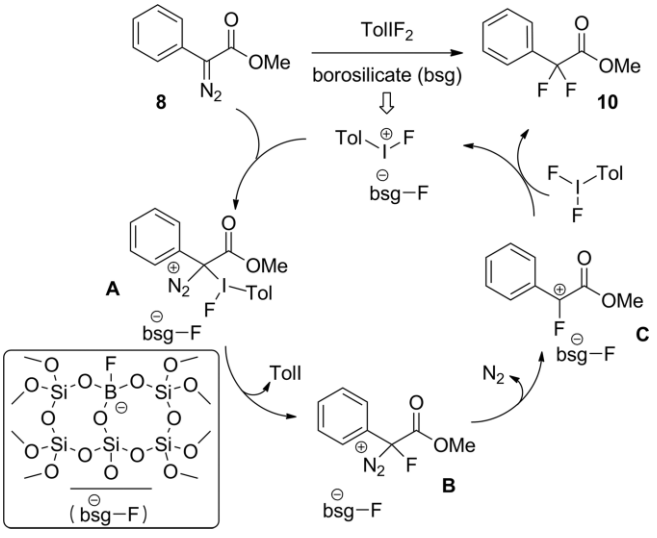


Figure 3. Mechanistic proposal for the borosilicate (bsg)-activated *gem*-difluorination reaction. Inset: anionic borosilicate•fluoride (bsg-F) counterion.

Conclusion

Computational analysis was a valuable complement to our experimental search for mild, highly effective activating agents for the hypervalent iodine reagent $TolIF_2$. Two Lewis acid candidates (TiF_4 and borosilicate glass) were identified as viable leads, and due to the novelty and simplicity of reactions being initiated by the elemental composition of laboratory glassware, borosilicate was further investigated. Computational analysis and control experiments both indicated the boron of borosilicate to be crucial to the improvements realized for the *gem*-difluorination reaction. These studies have clarified the role of the Lewis acid as an activating agent, and the need for high quality $TolIF_2$ in these reactions. We continue to investigate the nature of the activation process and the source of the oxygenation by-products, and these results will be disclosed in due course.

Author Contributions: The manuscript was written by G. K. M. and W. S. H., G. S. S. did the computational work, tested the new Lewis acids candidates and ran the difluorination reactions on most substrates. R. T. repeated and verified key experiments, and characterized various new diazo and difluoride compounds. J. T. synthesized the bulk of the diazo starting materials, and developed the synthesis of $TolIF_2$ that enabled this work.

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Keywords: Fluorine · Diazo compounds · Hypervalent compounds · Iodine · Computational chemistry

[1] J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Hoboken, NJ, USA, **2008**.
[2] a) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305; b) K. K. J. Chan, D. O'Hagan, in: *Methods in Enzymology*, vol. 516 (Ed.: A. H. David), Academic Press, **2012**, p. 219–235.
[3] a) C. L. Chernick, H. H. Claassen, P. R. Fields, H. H. Hyman, J. G. Malm, W. M. Manning, M. S. Matheson, L. A. Quarterman, F. Schreiner, H. H. Selig, I. Sheft, S. Siegel, E. N. Sloth, L. Stein, M. H. Studier, J. L. Weeks, M. H. Zirin, *Science* **1962**, *138*, 136 ; b) R. Hoppe, W. Dahne, K. M. Rodder, H. Mattauch, *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 599; *Angew. Chem.* **1962**, *74*, 903.
[4] O. Ruff, H. Krug, *Z. Anorg. Allg. Chem.* **1930**, *190*, 270.
[5] P. Lebeau, *Ann. Chim. Phys.* **1906**, *9*, 241.
[6] G. A. Olah, A. E. Pavlath, S. J. Kuhn, *J. Inorg. Nucl. Chem.* **1958**, *7*, 301.
[7] a) F. Brown, P. L. Robinson, *J. Chem. Soc.* **1955**, 3147; b) C. W. Tullock, F. S. Fawcett, W. C. Smith, D. D. Coffman, *J. Am. Chem. Soc.* **1960**, *82*, 539; c) F. S. Fawcett, C. W. Tullock, *Inorg. Synth.* **1963**, *7*, 119.
[8] For uses of XeF_2 in synthesis, see: a) M. Tramsek, B. Zemva, *Acta Chim. Slov.* **2006**, *53*, 105; b) C. A. Ramsden, *ARKIVOC (Gainesville, FL, U.S.)* **2014**, 109; c) M. A. Tius, *Tetrahedron* **1995**, *51*, 6605.
[9] For uses of BrF_3 in synthesis, see: a) T. Shishimi, S. Hara, *J. Fluorine Chem.* **2013**, *145*, 128; b) S. Rozen, *Adv. Synth. Catal.* **2010**, *352*, 2691; c) Y. Hagooly, M. J. Welch, S. Rozen, *Org. Biomol. Chem.* **2011**, *9*, 902; d) U. Farooq, A. Shah, T. Wirth, *Angew. Chem. Int. Ed.* **2009**, *48*, 1018; *Angew. Chem.* **2009**, *121*, 1036.
[10] For uses of IF_5 in synthesis, see: a) T. E. Stevens, *J. Org. Chem.* **1966**, *31*, 2025; b) S. Hara, M. Aoyama, *Synthesis* **2008**, 2510; c) M. Kunigami, S. Hara, *J. Fluorine Chem.* **2014**, *167*, 101; d) N. Yoneda, *J. Fluorine Chem.* **2004**, *125*, 7; e) G. A. Olah, J. Welch, *Synthesis* **1977**, 419.
[11] For uses of SF_4 in synthesis see: a) W. C. Smith, C. W. Tullock, E. L. Muetterties, W. R. Hasek, F. S. Fawcett, V. A. Engelhardt, D. D. Coffman, *J. Am. Chem. Soc.* **1959**, *81*, 3165 ; b) W. R. Hasek, W. C. Smith, V. A. Engelhardt, *J. Am. Chem. Soc.* **1960**, *82*, 543; c) W. C. Smith, *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 467; *Angew. Chem.* **1962**, *74*, 742.
[12] W. J. Middleton, *J. Org. Chem.* **1975**, *40*, 574.
[13] a) G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic, *Chem. Commun.* **1999**, 215; b) M. Yasuda, S. Yoshioka, S. Yamasaki, T. Somyo, K. Chiba, A. Baba, *Org. Lett.* **2006**, *8*, 761.
[14] a) A. L'Heureux, F. Beaulieu, C. Bennett, D. R. Bill, S. Clayton, F. LaFlamme, M. Mirmehrabi, S. Tadayon, D. Tovell, M. Couturier, *J. Org. Chem.* **2010**, *75*, 3401; b) L. N. Markovskii, V. E. Pashinnik, E. P. Saenko, *Zh. Org. Khim.* **1977**, *13*, 1116.
[15] a) G. C. Geary, E. G. Hope, K. Singh, A. M. Stuart, *Chem. Commun.* **2013**, *49*, 9263; b) V. Matoušek, E. Pietrasiak, R. Schwenk, A. Togni, *J. Org. Chem.* **2013**, *78*, 6763.
[16] a) R. F. Weinland, W. Stille, *Justus Liebigs Ann. Chem.* **1903**, *328*, 132; b) W. Bockemuller, *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 522.
[17] C. Willgerodt, *J. Prakt. Chem.* **1886**, *33*, 154.
[18] For uses of $TolIF_2$ in synthesis, see: a) M. Yoshida, K. Fujikawa, S. Sato, S. Hara, *ARKIVOC (Gainesville, FL, U.S.)* **2003**, 36; b) T. Inagaki, Y. Nakamura, M. Sawaguchi, N. Yoneda, S. Ayuba, S. Hara, *Tetrahedron Lett.* **2003**, *44*, 4117; c) W. B. *Motherwell*, M. F. Greaney, D. A. Tocher, *J. Chem. Soc., Perkin Trans. 1* **2002**, *2809*; d) M. A. Arrica, T. Wirth, *Eur. J. Org. Chem.* **2005**, 395; e) P. Conte, B. Panunzi, M. Tingoli, *Tetrahedron Lett.* **2006**, *47*, 273; f) J. Yu, J. Tian, C. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 531; for a summary of its reactivity, see: g) D. M. Lemal, J. Tao, G. K. Murphy, *(Difluoroiodo)toluene*, in: *e-EROS*, **2003**; update: **2016**.
[19] T. J. Tewson, M. J. Welch, *J. Org. Chem.* **1978**, *43*, 1090.
[20] A. Roedig, H. Aman, E. Fahr, *Justus Liebigs Ann. Chem.* **1964**, *675*, 47.
[21] J. Tao, R. Tran, G. K. Murphy, *J. Am. Chem. Soc.* **2013**, *135*, 16312.
[22] a) For activation of $PhIF_2$ with $BF_3{\cdot}OEt_2$, see: N. S. Zefirov, N. S. Samsoniya, T. G. Kutateladze, V. V. Zhdankin, *Zh. Org. Khim.* **1991**, *27*, 220; b) N. S. Zefirov, A. S. Koz'min, T. Kasumov, K. A. Potekhin, V. D. Sorokin, V. K. Brel, E. V. Abramkin, Y. T. Struchkov, V. V. Zhdankin, P. J. Stang, *J. Org. Chem.* **1992**, *57*, 2433.
[23] E. Emer, J. Twilton, M. Tredwell, S. Calderwood, T. L. Collier, B. Liegault, M. Taillefer, V. Gouverneur, *Org. Lett.* **2014**, *16*, 6004.
[24] See the supporting information for the computational and experimental results of all the Lewis acids investigated.
[25] Similar I–F bond elongations were observed for all of the Lewis acid·$TolIF_2$ complexes analyzed in *silico*.
[26] For a crystal structure of $TolIF_2$ see: a) C. F. Ye, B. Twamley, J. M. Shreeve, *Org. Lett.* **2005**, *7*, 3961. For melting points of pure $TolIF_2$, see ref. [26a] and: M. Sawaguchi, S. Ayuba, S. Hara, *Synthesis* **2002**, 1802.
[27] I. B. Sivaev, V. I. Bregadze, *Coord. Chem. Rev.* **2014**, *270*, 75.
[28] a) M. Yasuda, A. Baba, *J. Synth. Org. Chem. Jpn.* **2013**, *71*, 1294; b) M. Yasuda, S. Yoshioka, S. Yamasaki, T. Somyo, K. Chiba, A. Baba, *Org. Lett.* **2006**, *8*, 761.
[29] Glassware acting as a heterogeneous catalyst in fluorination reactions has been reported previously. For an example, see: A. P. Lothian, C. A. Ramsden, M. M. Shaw, R. G. Smith, *Tetrahedron* **2011**, *67*, 2788.
[30] The original result (40 % yield, 2 h) was reproduced by using $TolIF_2$ that had been temperature abused and was turning yellow.
[31] R. Minkwitz, W. Molsbeck, H. Oberhammer, I. Weiss, *Inorg. Chem.* **1992**, *31*, 2104.
[32] a) W. Carpenter, *J. Org. Chem.* **1966**, *31*, 2688; b) T. B. Patrick, J. J. Scheibel, W. E. Hall, Y. H. Lee, *J. Org. Chem.* **1980**, *45*, 4492.
[33] J. Wielgat, Z. Domagala, R. Kolinski, *J. Fluorine Chem.* **1987**, *35*, 643.

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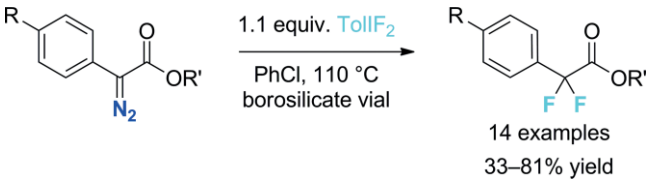

A computational and experimental search for mild Lewis-acidic activators for (difluoroiodo)toluene ($TolIF_2$) has identified borosilicate glass as the most effective activator (to date) in the *gem*-difluorination of phenyl diazoacetate derivatives.

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