

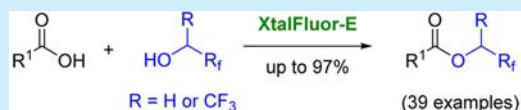
Direct Esterification of Carboxylic Acids with Perfluorinated Alcohols Mediated by XtalFluor-E

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S Supporting Information

ABSTRACT: The direct esterification of carboxylic acids with perfluorinated alcohols mediated by XtalFluor-E is reported. The corresponding polyfluorinated esters are obtained in moderate to excellent yields with a broad range of carboxylic acids, including aromatic, heteroaromatic, aliphatic, and nonracemic chiral substrates, using only a slight excess (2 equiv) of the perfluorinated alcohol. Control experiments indicate that the reaction does not proceed through the formation of an acyl fluoride but most likely through a (diethylamino)difluoro- λ^4 -sulfanyl carboxylate intermediate.

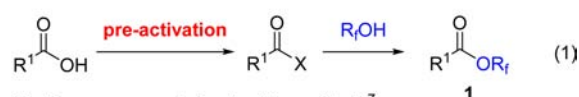


Perfluorination of an organic compound can profoundly modify its physicochemical properties.¹ Within the large family of perfluorinated molecules, polyfluorinated esters with the fluorine located on the alkoxy chain (e.g., **1** in Scheme 1)

Scheme 1. Previous Work and the Current Method

Previous work

Pre-activation of the carboxylic acid⁶



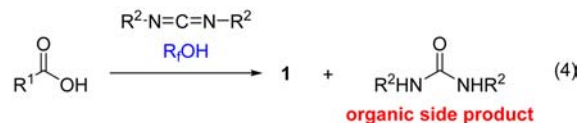
Continuous removal of water (Dean-Stark)⁷



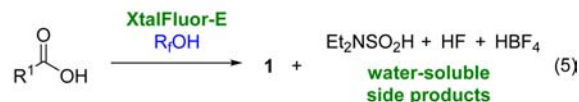
Fischer esterification⁸



Steglich esterification⁹



This work: In situ activation using XtalFluor-E



have found applications in medicinal chemistry,² as monomers for the synthesis of perfluorinated polymers,³ and in organic chemistry as substrates and/or reagents⁴ as well as for other usages.⁵

They are generally prepared through preactivation of the carboxylic acid (mostly as the acyl chloride, i.e., X = Cl) prior to the reaction with the polyfluorinated alcohol (Scheme 1, eq 1).⁶

From a practical aspect, a method that would obviate this preactivation step would be highly desirable. In that regard, the use of a Dean–Stark apparatus (Scheme 1, eq 2)⁷ and synthesis through a Fischer esterification reaction (Scheme 1, eq 3)⁸ have been described occasionally. However, in the former case, the perfluorinated alcohol is used in large excess, while in the latter, it is used as the solvent, which limits the utility of this approach to low-molecular-weight perfluoroalcohols. Finally, a Steglich esterification using carbodiimide reagents has been explored (Scheme 1, eq 4).⁹ Although this approach is more straightforward, the use of carbodiimide reagents leads to the formation of urea byproducts that are sometimes difficult to separate from the desired product.

A few years ago, the research team of Cossy and our group independently reported the synthesis of amides from carboxylic acids mediated by (Et₂NSF₂)BF₄ (XtalFluor-E).^{10–13} In this reaction, XtalFluor-E served to activate the carboxylic acid in situ prior to the attack by the amine. Although XtalFluor-E was primarily developed for the deoxofluorination of alcohols, we hypothesized that because of the low nucleophilicity of perfluorinated alcohols,^{14,15} selective activation of the carboxylic acid over the perfluorinated alcohol with XtalFluor-E could be possible, thus leading to a direct synthesis of **1** (Scheme 1, eq 5).^{13e} Herein we report the direct esterification, mediated by XtalFluor-E, of a broad range of carboxylic acids using only a slight excess of various perfluorinated alcohols. Notably, and as opposed to the use of diimide reagents, this system generates water-soluble side products, which facilitates purification.

Selected optimization data using 5-phenylvaleric acid (**2**) with 2,2,2-trifluoroethanol (TFE) are reported in Table 1. The use of a slight excess of XtalFluor-E with Et₃N (2.5 equiv) and TFE as the solvent provided the desired ester **3** in 68% yield (Table 1, entry 1). Product **3** was obtained in 75% yield with a 1:1 TFE/CH₂Cl₂ mixture (Table 1, entry 2). Further dilution to 1:9 provided an improved yield of 88% (Table 1, entry 3).

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Table 1. Optimization Results for the Esterification of 5-Phenylvaleric acid (2) with TFE Using XtalFluor-E^a

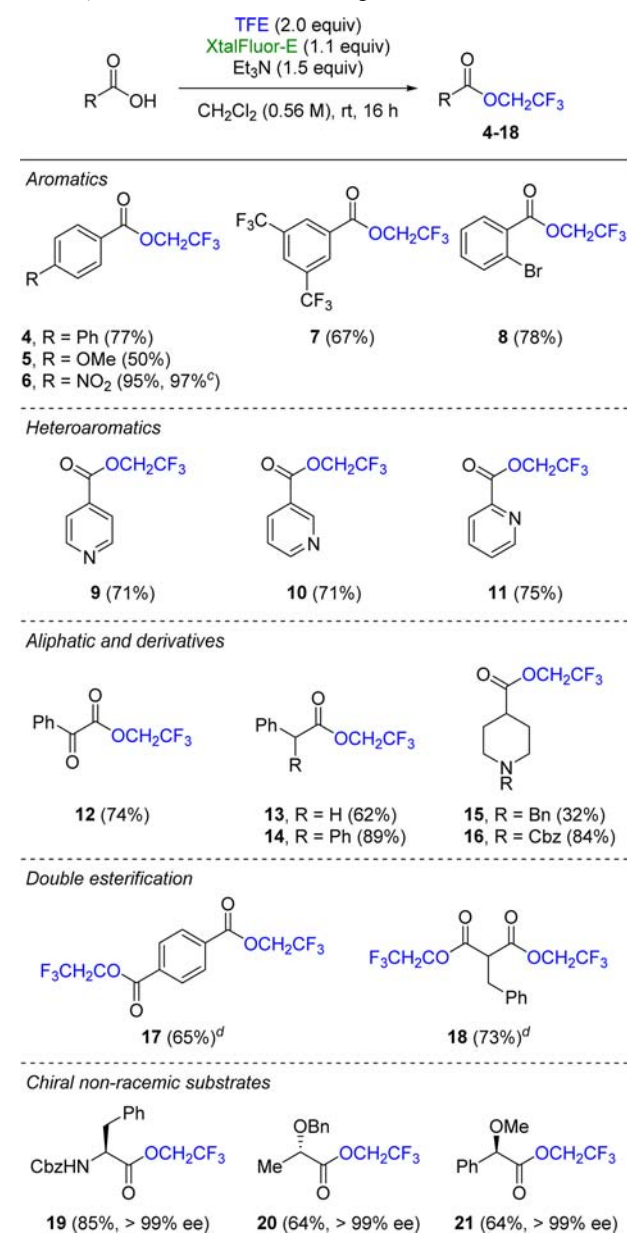
entry	y	solvent	yield (%) ^b
1	2.5	TFE	68
2	2.5	TFE/CH ₂ Cl ₂ (1:1)	75
3	2.5	TFE/CH ₂ Cl ₂ (1:9)	88
4	2.5	TFE/THF (1:9)	80
5	2.5	TFE/toluene (1:9)	60
6	2.5	TFE/EtOAc (1:9)	74
7	2.5	TFE/CH ₃ CN (1:9)	58
8	0	TFE/CH ₂ Cl ₂ (1:9)	60 ^c
9	1	TFE/CH ₂ Cl ₂ (1:9)	89
10	1.5	TFE/CH ₂ Cl ₂ (1:9)	90
11	1.5	TFE (2 equiv) in CH₂Cl₂	84
12	1.5	TFE (1.2 equiv) in CH ₂ Cl ₂	55

^aSee the [Supporting Information](#) for the detailed experimental procedures. The optimized conditions are shown in bold. ^bIsolated yields. ^cEstimated by NMR analysis of the crude reaction mixture.

Using other cosolvents (THF, toluene, EtOAc, and CH₃CN) instead of CH₂Cl₂ provided lower yields (58–80%) (Table 1, entries 4–7). Running the reaction in the absence of Et₃N provided a considerably lower yield as estimated by NMR analysis of the crude reaction mixture (Table 1, entry 8), but 1.5 equiv seemed to be the optimal amount (Table 1, entries 9 and 10). Finally, the amount of TFE could be reduced to 2 equiv without a major effect on the outcome (Table 1, entry 11), although further reducing it to 1.2 equiv resulted in a lower yield (Table 1, entry 12). The conditions shown in Table 1, entry 11 were chosen as the optimized ones.

With those conditions in hand, the esterification of other carboxylic acids was investigated, and the results are shown in Scheme 2. Various aromatic carboxylic acids provided the desired esters 4–8 in moderate to excellent yields. The reaction could also be performed on a gram scale, as illustrated by the esterification of 1.00 g of 4-nitrobenzoic acid in 97% yield. Interestingly, the TFE esters of all regioisomers of picolinic acid (9–11) could be obtained in good yields (71–75%). A β-keto carboxylic acid such as phenylglyoxylic acid reacted well, providing ester 12 in 74% yield. Aliphatic carboxylic acids could also be used as substrates for this transformation, as illustrated by the use of derivatives of phenylacetic acid and isonipecotic acid. In the latter case, a Cbz protecting group is preferred over a benzyl group, probably because of the reduced basicity of the nitrogen. Phthalic acid and a benzylmalonic acid could both be bisesterified to provide 17 and 18, respectively, in good yields when the stoichiometry of the reagents was adjusted accordingly. The reaction could be extended to nonracemic chiral carboxylic acids. For instance, Cbz-protected L-phenylalanine could be esterified with TFE to provide ester 19 in 85% yield. Likewise, the reactions of O-benzyl-(S)-lactic acid and O-methyl-(R)-mandelic acid provided esters 20 and 21, respectively, in good yields. In all cases, chiral HPLC analyses showed no loss of enantiopurity.

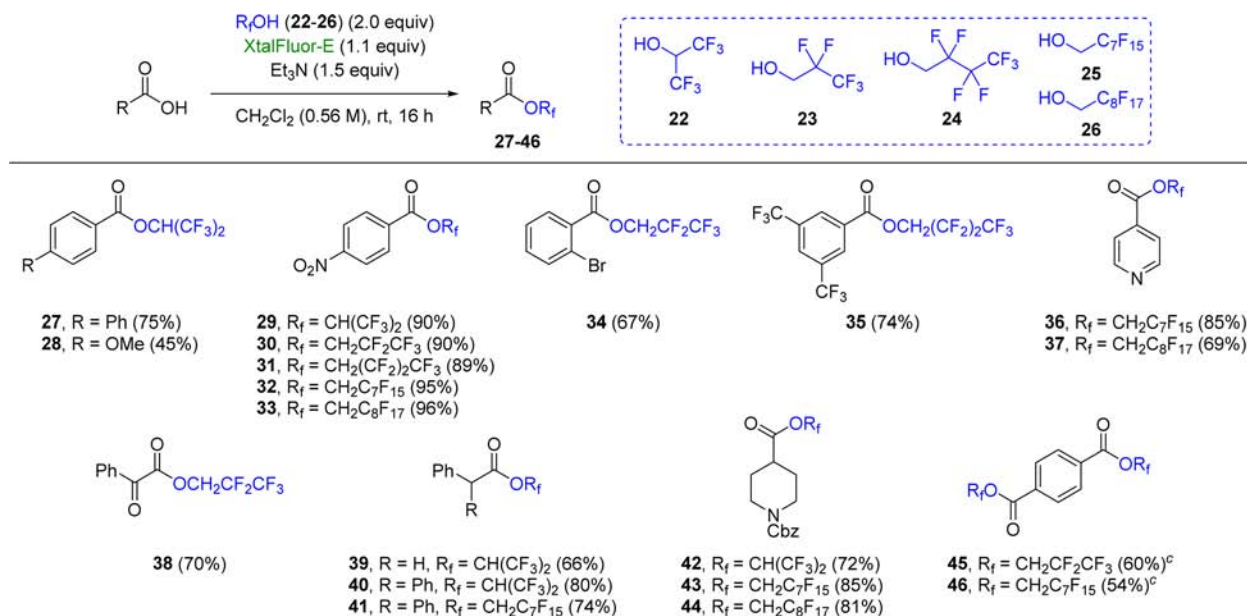
To further extend the utility of this transformation, esterification with other perfluorinated alcohols was explored, as shown in Scheme 3. For that purpose, 1,1,1,3,3,3-hexafluoro-

Scheme 2. Results for the Esterification of Various Carboxylic Acids with TFE Using XtalFluor-E^{a,b}

^aSee the [Supporting Information](#) for the detailed experimental procedures. ^bIsolated yields are shown. ^cThe reaction was performed on a 5.98 mmol scale (i.e., 1.00 g of the acid). ^dTFE (4.0 equiv), XtalFluor-E (2.2 equiv), and Et₃N (3 equiv) were used instead.

2-propanol (HFIP, 22), 2,2,3,3,3-pentafluoro-1-propanol (PFPOH, 23), 2,2,3,3,4,4,4-heptafluoro-1-butanol (24), 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-1-octanol (25), and 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-1-nonanol (26) were used. A wide range of carboxylic acids could be esterified (or bisesterified in the case of phthalic acid) to provide the corresponding esters 27–46 in moderate to excellent yields (45–96%).

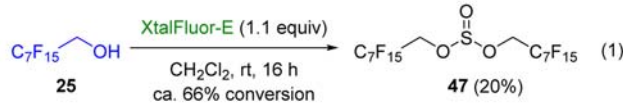
To gain insight into the reaction mechanism, a series of control experiments were run. First, we reacted 25 with XtalFluor-E, omitting the carboxylic acid and Et₃N (Scheme 4, eq 1). A moderate conversion of 66% was obtained, and NMR analysis of the crude reaction mixture revealed the formation of

Scheme 3. Selected Results for the Esterification of Various Carboxylic Acids with Perfluorinated Alcohols Using XtalFluor-E^{a,b}

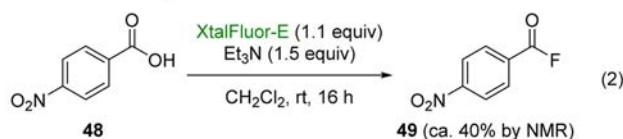
^aSee the Supporting Information for the detailed experimental procedures. ^bIsolated yields are shown. ^c23 or 25 (4.0 equiv), XtalFluor-E (2.2 equiv), and Et₃N (3 equiv) were used instead.

Scheme 4. Control Experiments and Mechanistic Hypothesis^a

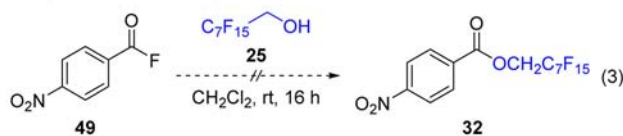
Reaction of perfluorinated alcohol 25 with XtalFluor-E



Formation of an acyl fluoride from 48



Attempted reaction of acyl fluoride 49



Mechanistic hypothesis^b



^aSee the Supporting Information for the detailed experimental procedures. ^bThe counterions have been omitted for clarity.

sulfinate 47 (20%) along with some unidentified XtalFluor-E-related products.^{10b} The fluoride¹⁶ corresponding to 25 was not observed. For comparison, complete conversion in less than 5 min was reported with hydrocinnamyl alcohol.^{10b} The slower

reaction of perfluorinated alcohols with XtalFluor-E likely originates from their impaired nucleophilicity due to the powerful inductive effect of the adjacent fluorine atoms.¹⁴ Next, in two separate experiments, we investigated whether the reaction proceeds through an acyl fluoride, as it has been shown that XtalFluor-E is able to convert a carboxylic acid to an acyl fluoride, albeit slowly in the absence of an external source of fluoride.^{10b} To this end, 4-nitrobenzoic acid (48)¹⁷ was subjected to the reaction conditions without any perfluorinated alcohol. After 16 h, a low conversion of ca. 40% to the corresponding acyl fluoride 49 was determined by NMR analysis (Scheme 4, eq 2). In addition to this slow formation of the acyl fluoride, which is not compatible with the time required for the completion of the esterification reaction, no transformation was observed when independently synthesized acyl fluoride 49 was allowed to react with perfluorinated alcohol 25 (Scheme 4, eq 3). On the basis of those two observations, we discarded the acyl fluoride pathway. Hence, our current working hypothesis is the following: First, deprotonation of the carboxylic acid by Et₃N would lead to the more nucleophilic carboxylate.¹¹ Reaction of the latter with XtalFluor-E would generate (diethylamino)difluoro-λ⁴-sulfanyl carboxylate 50.^{5,6} Under the reaction conditions, the formation of the acyl fluoride would be slower than the reaction of 50 with the perfluorinated alcohol, which would generate the desired perfluorinated ester in addition to diethylaminosulfinyl fluoride.¹⁸

In summary, we have reported the use of XtalFluor-E as an effective promoter for the direct esterification of carboxylic acids using perfluorinated alcohols. The corresponding polyfluorinated esters are obtained in moderate to excellent yields with a broad range of carboxylic acids, including aromatic, heteroaromatic, aliphatic, and nonracemic chiral substrates, using only a slight excess (2 equiv) of the perfluorinated alcohol. Control experiments indicated that the reaction does not proceed through the formation of an acyl

fluoride but most likely through a (diethylamino)difluoro- λ^4 -sulfanyl carboxylate intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b03365](https://doi.org/10.1021/acs.orglett.6b03365).

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Hiyama, T. In *Organofluorine Compounds: Chemistry and Applications*; Yamamoto, H., Ed.; Springer: New York, 2000 and references therein. (b) *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Horváth, I., Curran, D. P., Eds.; Wiley-VCH: Weinheim, Germany, 2004 and references therein.
- (2) For selected examples, see: (a) Schroeder, G. K.; Wolfenden, R. *Biochemistry* **2007**, *46*, 4037–4044. (b) Yin, W.; Majumder, S.; Clayton, T.; Petrou, S.; VanLinn, M. L.; Namjoshi, O. A.; Ma, C.; Cromer, B. A.; Roth, B. L.; Platt, D. M.; Cook, J. M. *Bioorg. Med. Chem.* **2010**, *18*, 7548–7564. (c) Crocetti, L.; Giovannoni, M. P.; Schepetkin, I. A.; Quinn, M. T.; Khlebnikov, A. I.; Cilibrizzi, A.; Dal Piaz, V.; Graziano, A.; Vergelli, C. *Bioorg. Med. Chem.* **2011**, *19*, 4460–4472. (d) Fuchs, A. V.; Tse, B. W. C.; Pearce, A. K.; Yeh, M.-C.; Fletcher, N. L.; Huang, S. S.; Heston, W. D.; Whittaker, A. K.; Russell, P. J.; Thurecht, K. J. *Biomacromolecules* **2015**, *16*, 3235–3247. (e) Zhang, H.; Xu, X.; Chen, Y.; Qiu, Y.; Liu, X.; Liu, B.-F.; Zhang, G. *Eur. J. Med. Chem.* **2015**, *89*, 524–539.
- (3) For selected recent examples, see: (a) Guo, L.; Jiang, Y.; Qiu, T.; Meng, Y.; Li, X. *Polymer* **2014**, *55*, 4601–4610. (b) Nuhn, L.; Overhoff, I.; Sperner, M.; Kaltenberg, K.; Zentel, R. *Polym. Chem.* **2014**, *5*, 2484–2495. (c) Sun, Q.; Li, H.; Xian, C.; Yang, Y.; Song, Y.; Cong, P. *Appl. Surf. Sci.* **2015**, *344*, 17–26.
- (4) For selected examples, see: (a) Schmidt-Leithoff, J.; Brückner, R. *Helv. Chim. Acta* **2005**, *88*, 1943–1959. (b) Hamada, M.; Inami, Y.; Nagai, Y.; Higashi, T.; Shoji, M.; Ogawa, S.; Umezawa, K.; Sugai, T. *Tetrahedron: Asymmetry* **2009**, *20*, 2105–2111. (c) Monteiro, C. M.; Lourenço, N. M. T.; Afonso, C. A. M. *Tetrahedron: Asymmetry* **2010**, *21*, 952–956. (d) Fang, X.; Li, J.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 3448–3451. (e) Conner, M. L.; Xu, Y.; Brown, M. K. *J. Am. Chem. Soc.* **2015**, *137*, 3482–3485. (f) Curiel Tejada, J. E.; Irwin, L. C.; Kerr, M. A. *Org. Lett.* **2016**, *18*, 4738–4741.
- (5) For selected recent examples, see: (a) Lu, W.; Xie, K.; Chen, Z. x.; Pan, Y.; Zheng, C. m. *J. Fluorine Chem.* **2014**, *161*, 110–119. (b) Sevov, C. S.; Brooner, R. E. M.; Chénard, E.; Assary, R. S.; Moore, J. S.; Rodríguez-López, J.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 14465–14472.
- (6) For example, see refs [2b,c](#), [3c](#), and [4c](#).
- (7) For example, see ref [4a](#).
- (8) For example, see refs [2a,e](#), [4f](#), and [5b](#).
- (9) For example, see ref [4d,e](#).
- (10) (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; Laflamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050–5053. (b) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; Laflamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401–3411. (c) Mahé, O.; L'Heureux, A.; Couturier, M.; Bennett, C.; Clayton, S.; Tovell, D.; Beaulieu, F.; Paquin, J.-F. *J. Fluorine Chem.* **2013**, *153*, 57–60.
- (11) Orliac, A.; Gomez Pardo, D.; Bombrun, A.; Cossy, J. *Org. Lett.* **2013**, *15*, 902–905.
- (12) Mahé, O.; Desroches, J.; Paquin, J.-F. *Eur. J. Org. Chem.* **2013**, *2013*, 4325–4331.
- (13) For other contributions from our group using XtalFluor-E, see: (a) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Org. Biomol. Chem.* **2012**, *10*, 988–993. (b) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Tetrahedron Lett.* **2012**, *53*, 4121–4123. (c) Pouliot, M.-F.; Mahé, O.; Hamel, J.-D.; Desroches, J.; Paquin, J.-F. *Org. Lett.* **2012**, *14*, 5428–5431. (d) Keita, M.; Vandamme, M.; Mahé, O.; Paquin, J.-F. *Tetrahedron Lett.* **2015**, *56*, 461–464. (e) Desroches, J.; Champagne, P. A.; Benhassine, Y.; Paquin, J.-F. *Org. Biomol. Chem.* **2015**, *13*, 2243–2246. (f) Keita, M.; Vandamme, M.; Paquin, J.-F. *Synthesis* **2015**, *47*, 3758–3766.
- (14) Bégue, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18–29.
- (15) For a review of the use of fluorinated alcohols as solvents, cosolvents, or additives in homogeneous catalysis, see: Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, *2007*, 2925–2943.
- (16) Raghavanpillai, A.; Burton, D. J. *J. Fluorine Chem.* **2006**, *127*, 456–470.
- (17) Ochiai, M.; Yoshimura, A.; Hoque, M. M.; Okubo, T.; Saito, M.; Miyamoto, K. *Org. Lett.* **2011**, *13*, 5568–5571.
- (18) (a) Brown, D. H.; Crosbie, K. D.; Darragh, J. I.; Ross, D. S.; Sharp, D. W. A. *J. Chem. Soc. A* **1970**, 914–917. (b) Keat, R.; Ross, D. S.; Sharp, D. W. A. *Spectrochim. Acta, Part A* **1971**, *27*, 2219–2225.