



HAL
open science

Tetramethylammonium fluoride

Jean-Bernard Behr, Fabien Massicot

► **To cite this version:**

Jean-Bernard Behr, Fabien Massicot. Tetramethylammonium fluoride. Encyclopedia of Reagents for Organic Synthesis, 2017. <hal-03545117>

HAL Id: hal-03545117

<https://hal.science/hal-03545117v1>

Submitted on 23 Feb 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

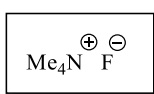
Contributor's Details

Jean-Bernard Behr & Fabien Massicot

Université de Reims Champagne-Ardenne, Institut de Chimie Moléculaire de Reims, CNRS UMR 7312, UFR des Sciences Exactes et Naturelles, 51687 Reims Cedex 2, France. Fax: (+)33 326913166. E-mail: jb.behr@univ-reims.fr

Reagent Details

Tetramethylammonium Fluoride



[373-68-2] C₄H₁₂FN (MW 93.14)

Alternate Name(s): TMAF

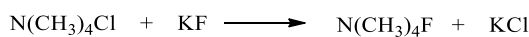
Physical Data: anh. TMAF : mp_{dec.} 170°C.¹ The crystal structure of TMAF,4H₂O was determined.²

Solubility: TMAF is highly soluble in water and alcohols with which it might form solvates.¹ Strong interactions with the solvent occur with most solvents in which TMAF is soluble. It is partially soluble in chlorinated hydrocarbons but tends to undergo chlorine-fluorine exchange.³ It reacts with acetonitrile via proton abstraction during solubilisation. Dissolving TMAF in formamide, acetone or nitromethane is accompanied by modifications of ¹⁹F NMR signals upon time. The most inert solvent for TMAF is CHF₃.

Form Supplied in: anh. TMAF, white crystalline solid (hygroscopic); commercially available. TMAF,4H₂O, colorless solid; commercially available.

Analysis of Reagent Purity: ¹⁹F NMR (in CHF₃), δ -107 ppm; ¹⁹F NMR (in H₂O), δ -119 ppm; ¹⁹F NMR (in CD₃CN), δ -74 ppm; ¹⁹F NMR (in (CD₃)₂SO), δ -75 ppm; ¹H NMR (CH₃CN), δ 3.1 ppm (*J*¹H¹⁴N = 0.6 Hz).^{1,3-5} For infrared and Raman spectra of solid anhydrous TMAF, see reference 1.

Preparative Methods: several methods for the synthesis of TMAF can be found in literature, which are based mainly on two approaches. A first one involves the neutralization of N(CH₃)₄OH with HF⁶ and the second approach implies a metathetical step⁷ resulting in ion exchange such as :



The difficulties with these processes are the removal of traces of water and of impurities (HF₂⁻ or Cl⁻, depending on the reaction). Several improved procedures for the preparation of pure anhydrous TMAF are reported.⁸⁻¹⁰

Purification: recrystallization from iPrOH.¹

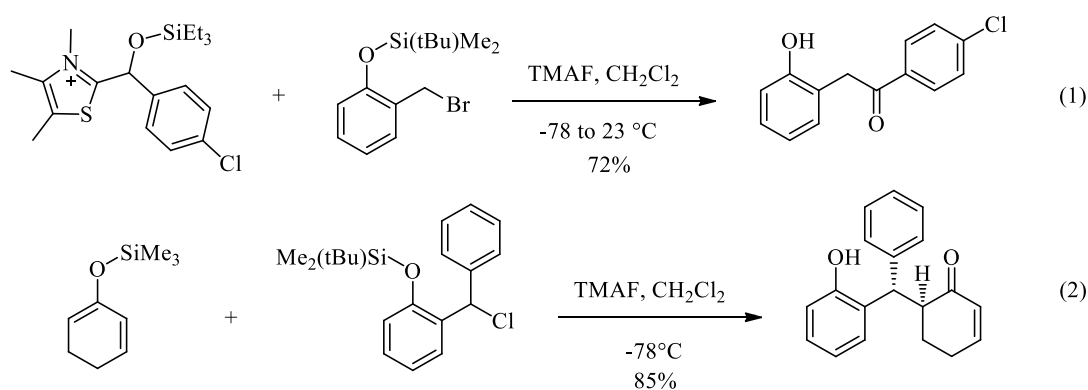
Handling, Storage, and Precautions: TMAF is a moisture-sensitive compound and should be stored under anhydrous conditions in a refrigerator and kept under argon. It is strongly basic and should be used with care in a fume hood.

2.6.3 Body of Text

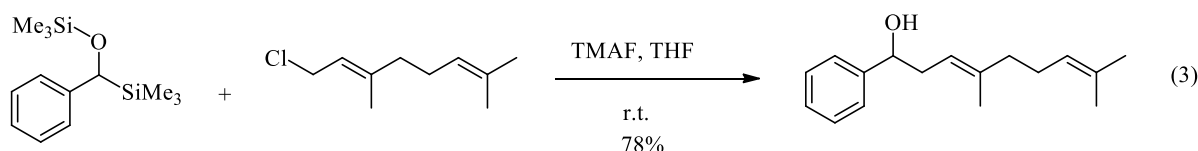
Quaternary ammonium fluorides are typically used in various organic reactions such as desilylation, fluoride-promoted elimination or nucleophilic substitution. These reagents may be considered as organic soluble sources of “naked” fluoride ion, the reactivity of which is clearly dependent on its environment (hydrated state, counteranion). Among the tetraalkylammonium fluorides, TMAF offers the advantage that it is easily available in strictly anhydrous conditions unlike its homologues, which are susceptible to elimination upon water removal by heating.

Desilylating reagent.

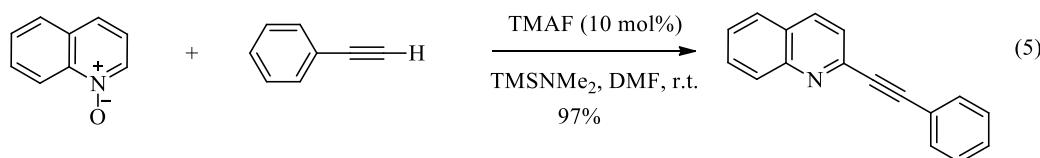
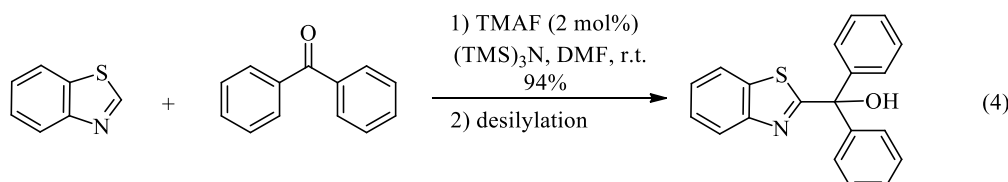
Due to the high affinity of fluorine for silicon (Si-F , $139 \text{ kcal}\cdot\text{mol}^{-1}$), quaternary ammonium fluorides are frequently used for the cleavage of silyl protecting groups. TMAF, used under strictly anhydrous conditions, allowed subsequent nucleophilic acylations (eq 1) and Michael additions of enolates (eq 2) to take place.^{11,12} TMAF proved superior than other fluoride sources to generate the expected carbonyl anion (umpolung process) from silylated thiazolium carbinols (eq 1). The originality of these approaches lies in the simultaneous formation of both nucleophilic and electrophilic species via TMAF-mediated desilylation of protected alcohols.



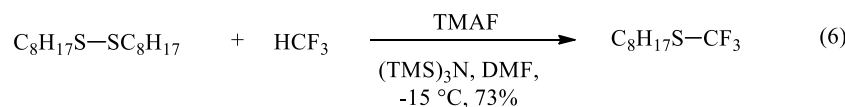
An analogous umpolung strategy with silylated thiazolium carbinols was applied to produce β -nitro ketones by using nitroalkenes as electrophiles.¹³ A silyloxy anion could be generated likewise (umpolung process) from α -silyl silylethers with TMAF to form new carbon-carbon sp^3 - sp^3 bonds by reaction with primary halides (eq 3).¹⁴ In this reaction, the use of TMAF as Lewis base circumvent issues that arise from strongly basic conditions usually required for the generation of such unusual nucleophiles.



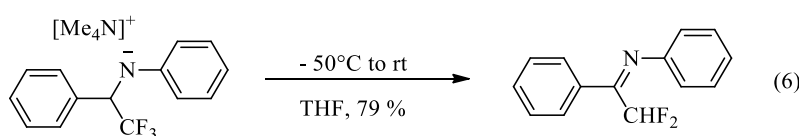
Organocatalytic functionalizations of heteroarenes (eq 4) and heteroaromatic *N*-oxides (eq 5) were achieved using *in situ* generated amide bases by desilylation of aminosilanes with TMAF in catalytic amount.^{15,16}



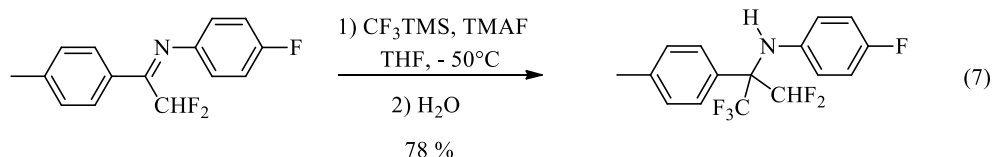
A similar strategy has been followed with TMAF and tris(trimethylsilyl)amine to perform nucleophilic trifluoromethylations of carbonyl compounds and disulfides from fluoroform (eq 6).¹⁷



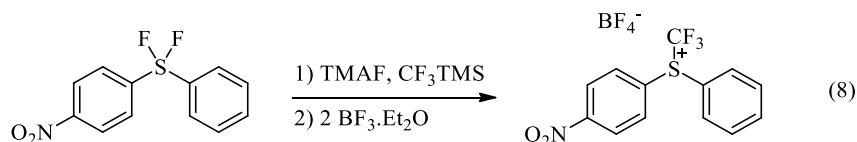
Surprisingly, unlike its equivalents TBAF or TBAT, TMAF has been scarcely used as initiator in trifluoromethylation reactions of carbonyl compounds from the fairly generalized trifluoromethyltrimethylsilane (Ruppert-Prakash reagent). The lower solubility, highly hygroscopic and strongly basic character of TMAF could explain this apparent under-utilization. Nevertheless, TMAF served as key reagent in a series of mechanistic investigations to uncover the nature of the reactive intermediates in fluorine-initiated trifluoromethylations with Me_3SiCF_3 .¹⁸⁻²¹ In addition, TMAF was used efficiently, either in catalytic or in stoichiometric amount, to drive trifluoromethylation of non-activated aldimines.^{22,23} Initial addition of trifluoromethide to aldimines at low temperature afforded the expected trifluoromethylated amide salt, which upon warming to room temperature underwent fluorine elimination to yield a difluoromethyl-ketimine (eq 6).



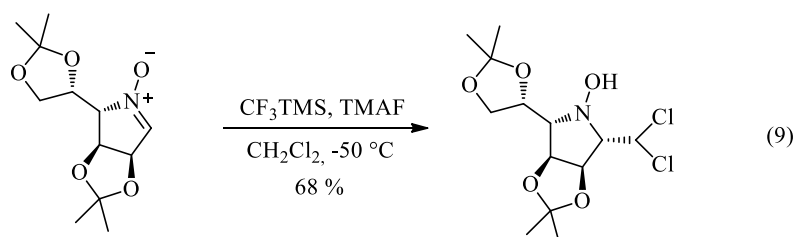
Such ketimines also react with Me_3SiCF_3 in the presence of 1 equiv. of TMAF to form amines with trifluoromethyl and difluoromethyl groups attached to the same carbon atom. (eq 7)



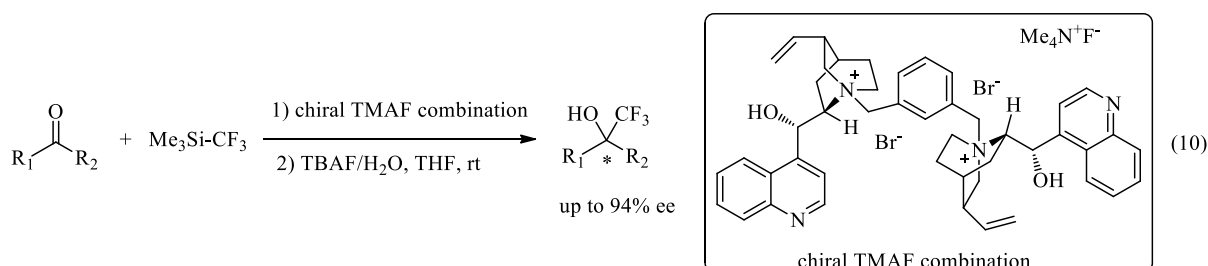
A nice polarity inversion of the trifluoromethyl group was also achieved with TMAF and CF_3TMS through the preparation of diaryltrifluoromethylsulfonium salts. (eq 8) Such systems might be considered as electrophilic reagents, which contain an electropositive $\text{CF}_3 \delta^+$ group.²⁴



In the absence of a suitable electrophile, the decomposition of the kinetically unstable $[\text{CF}_3^-]$ generates either difluorocarbene by removing of a fluoride anion or HCF_3 via proton abstraction from neighboring acidic species. This latter reactivity of trifluoromethide was exploited in the synthesis of a series of 2-(dichloromethyl)-hydroxylamines. Indeed, the trifluoromethyl anion prepared from TMAF and CF_3TMS in CH_2Cl_2 at -50°C is able to generate dichloromethide through proton-abstraction from the solvent. With chiral carbohydrate-derived nitron, addition proceeded with good stereoselectivity.²⁵ (eq 9)

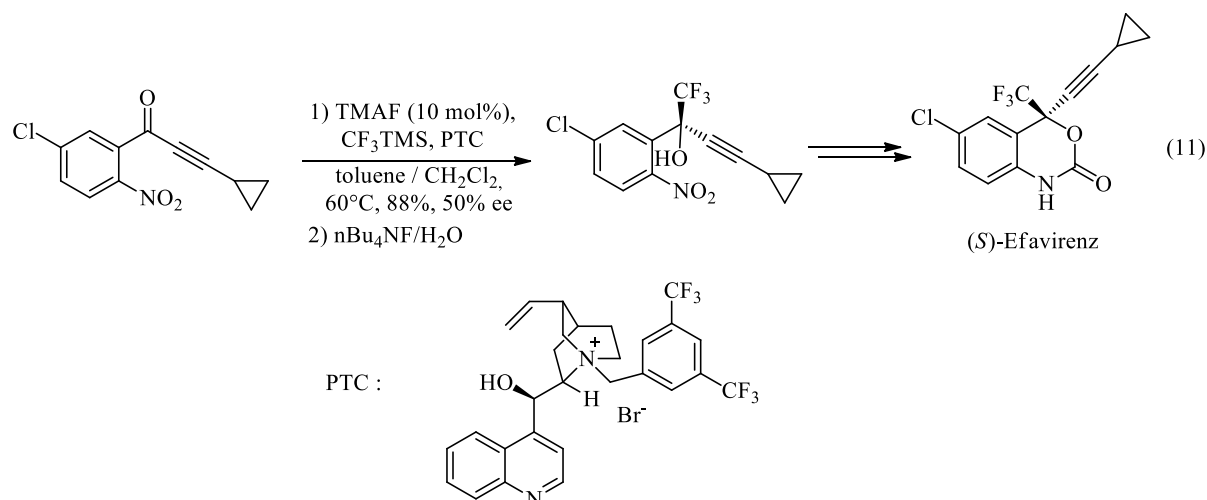


TMAF was used in combination with sterically demanding ammonium bromide of cinchona alkaloid-derived phase-transfer catalyst (PTC) to perform enantioselective trifluoromethylation of aryl ketones, furnishing tetrasubstituted aryl trifluoromethyl alcohols in high yield and high enantioselectivity (up to 94% ee).²⁶ (eq 10)

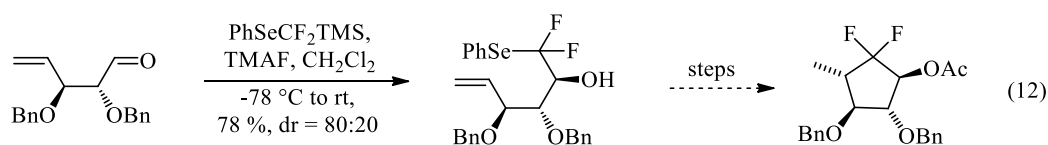


This method was extended with success to other prochiral substrates like aryl aldehydes and alkynyl ketones.^{27,28} A nice application of this reaction is the enantioselective synthesis of (*S*-)

efavirenz, a non-nucleoside reverse transcriptase inhibitor administered as a first-line treatment against HIV.²⁹ (eq 11)



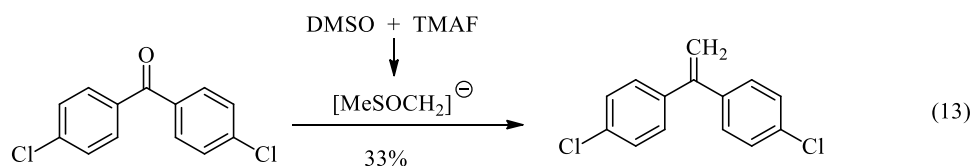
Tetramethylammonium fluoride was also used with success in the diastereoselective addition of PhSeCF₂TMS to carbohydrate-derived aldehydes.³⁰ (eq 12)



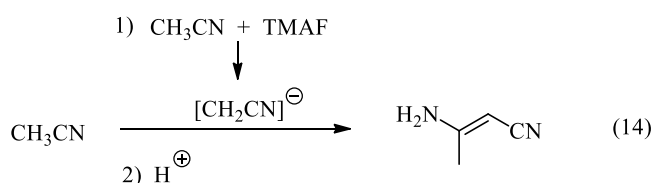
This reaction was examined under various conditions and TMAF appeared as the most appropriate mediator. Selenofluorinated compounds were obtained in satisfactory yields and in 80 : 20 diastereomeric ratio with most substrates. Subsequent tin-hydride radical cyclisation afforded difluorinated analogues of 5-deoxypentofuranoses.

Use as a base.^{31,32}

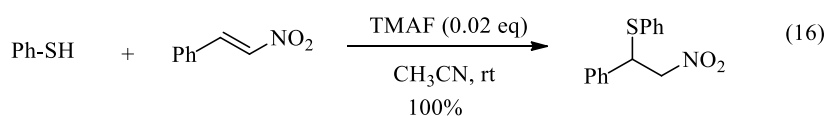
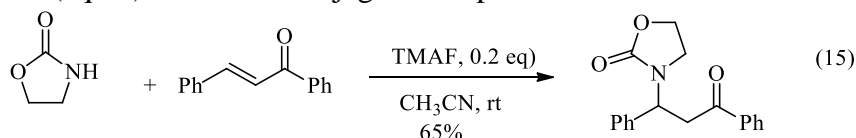
The basicity of the fluoride anion is commonly considered weak (HF, pK_a=3.2). However, under anhydrous conditions TMAF can deprotonate even very weakly CH-acidic substrates through enhanced reactivity of the “naked” F⁻ anion. Activation of DMSO occurred under anhydrous conditions in the presence of TMAF to afford an adduct with 4,4'-dichlorobenzophenone, certainly via addition of the [MeSOCH₂]⁻ carbanion (eq 13). TMAF reacts similarly to strong bases such as NaH, PhLi or MeOK, which were employed towards the same substrate.³³



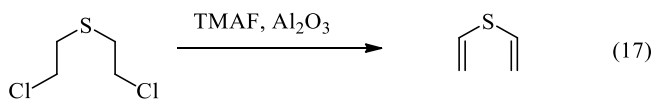
With acetonitrile, deprotonation results in the formation of [CH₂CN]⁻ which, upon addition to CH₃CN yields *trans*-3-aminobut-2-enitrile (eq 14).^{1,3}



TMAF has also been demonstrated as an efficient catalyst for the conjugate addition of oxazolidinone (eq 15) or thiols (eq 16) to various conjugate acceptors.³⁴

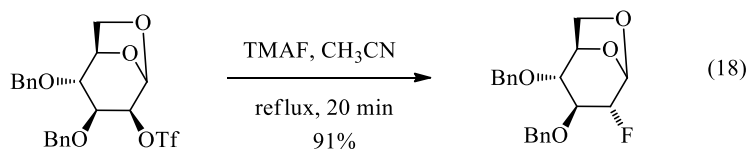


TMAF supported on alumina exhibit strong reactivity towards 2,2'-dichloroethylsulfide to afford the elimination product divinyl sulfide (eq 17). Such a reactivity could be applied in the context of instantaneous detoxification of chemical warfare agents.³⁵

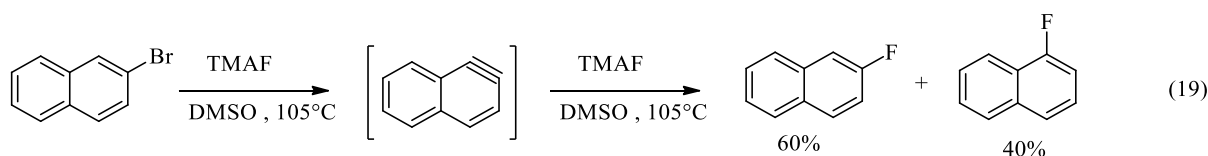


Use as a nucleophilic fluoride source.

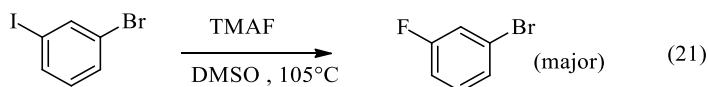
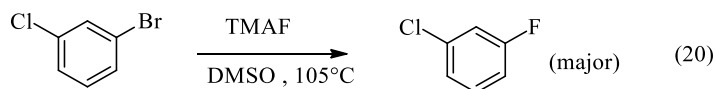
Under anhydrous conditions, the nucleophilicity/basicity balance of F⁻ in TMAF is clearly shifted towards basicity, impeding the use of this reagent as a fluorinating agent in S_N reactions. However, CHCl₃ and CH₂Cl₂ readily react with TMAF at room temperature undergoing halogen exchange.³ With chloroform the reaction is quite fast and affords the three possible exchange products CHCl₂F, CHClF₂ and CHF₃. TMAF was also shown to give good yields in the fluorination reaction of sugar-derived triflates (eq 18)^{36,37} or cyclic sulfates.^{38,39} However the efficiency of this transformation was clearly substrate-dependent and it could not find wide application.



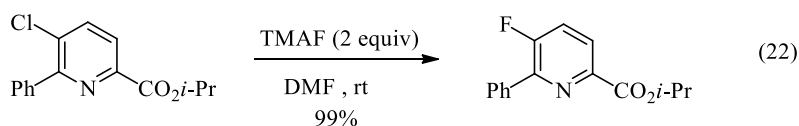
The combination of the high reactivities of TMAF both as a base and as a nucleophile was exploited in the synthesis of fluorinated arenes and heteroarenes. These compounds have been extensively used as building blocks in the synthesis of pharmaceuticals, agrochemicals, dyes and advanced materials.⁴⁰ TMAF effectively converts Aryl-X substrates (typically, X = NO₂, Cl, Br, I, OTf) to Aryl-F. In the light of the results obtained with 2-bromonaphtalene (eq 19), the reaction proceeds via fluorine trapping of an aryne intermediate generated through F⁻ mediated elimination.⁴¹⁻⁴³



In accord with this mechanistic proposal, the reaction of dihalogenobenzene afforded the product rising from elimination of the better leaving group (eq 20 and 21).



Interestingly, analogous transformations were observed with heteroarenes, even at room temperature, in the presence of an excess of anhydrous TMAF (eq 22).⁴⁴



The presence of traces of water completely shut down the transformation since no fluorinated compound was obtained when $\text{NM}_4\text{F}\cdot 4\text{H}_2\text{O}$ was used as the reagent.

References :

- Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J.-a., *J. Am. Chem. Soc.* **1990**, *112*, 7619.
- McLean, W. J.; Jeffrey, G. A., *J. Chem. Phys.* **1967**, *47*, 414.
- Christe, K. O.; Wilson, W. W., *J. Fluor. Chem.* **1990**, *47*, 117.
- Christe, K. O.; Wilson, W. W., *J. Fluor. Chem.* **1990**, *46*, 339.
- Sun, H.; DiMugno, S. G., *J. Am. Chem. Soc.* **2005**, *127*, 2050.
- Klanberg, F.; Muetterties, E. L., *Inorg. Chem.* **1968**, *7*, 155.
- Tunder, R.; Siegel, B., *J. Inorg. Nucl. Chem.* **1963**, *25*, 1097.
- Zheng, Z.; Wu, T.; Zhou, X., *Chem. Commun.* **2006**, 1864.
- Cunico, R. F.; Han, Y.-K., *J. Organomet. Chem.* **1978**, *162*, 1.
- Kolomeitsev, A. A.; Seifert, F. U.; Röschenthaler, G.-V., *J. Fluor. Chem.* **1995**, *71*, 47.
- Mattson, A. E.; Scheidt, K. A., *J. Am. Chem. Soc.* **2007**, *129*, 4508.
- Lewis, R. S.; Garza, C. J.; Dang, A. T. ; Pedro, T. K. A.; Chain, W. J., *Org. Lett.* **2015**, *17*, 2278.
- Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A., *J. Am. Chem. Soc.* **2006**, *128*, 4932.
- Brekan, J. A.; Chernyak, D.; White, K. L.; Scheidt, K. A., *Chem. Sci.* **2012**, *3*, 1205.
- Inamoto, K.; Okawa, H.; Kikkawa, S.; Kondo, Y., *Tetrahedron* **2014**, *70*, 7917.
- Inamoto, K.; Araki, Y.; Kikkawa, S.; Yonemoto, M.; Tanaka, Y.; Kondo, Y., *Org. Biomol. Chem.* **2013**, *11*, 4438.
- Large, S.; Roques, N.; Langlois, B. R., *J. Org. Chem.* **2000**, *65*, 8848.

18. Prakash, G. K. S.; Yudin, A. K., *Chem. Rev.* **1997**, *97*, 757.
19. Maggiarosa, N.; Tyrra, W.; Naumann, D.; Kirij, N. V.; Yagupolskii, Y. L., *Angew. Chem. Int. Ed.* **1999**, *38*, 2252.
20. Kolomeitsev, A.; Bissky, G.; Lork, E.; Movchun, V.; Rusanov, E.; Kirsch, P.; Röschenthaler, G. V., *Chem. Commun.* **1999**, 1107.
21. Adams, D. J.; Clark, J. H.; Hansen, L. B.; Sanders, V. C.; Tavener, S. J., *J. Fluor. Chem.* **1998**, *92*, 123.
22. Prakash, G. K. S.; Mogi, R.; Olah, G. A., *Org. Lett.* **2006**, *8*, 3589.
23. Kirij, N. V.; Babazhanova, L. A.; Movchun, V. N.; Yagupolskii, Y. L.; Tyrra, W.; Naumann, D.; Fischer, H. T. M.; Scherer, A., *J. Fluor. Chem.* **2008**, *129*, 14.
24. Yagupolskii, L. M.; Matsnev, A. V.; Orlova, R. K.; Deriabkin, B. G.; Yagupolskii, Y. L., *J. Fluor. Chem.* **2008**, *129*, 131.
25. Behr, J. B.; Chavaria, D.; Plantier-Royon, R., *J. Org. Chem.* **2013**, *78*, 11477.
26. Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T., *Org. Lett.* **2007**, *9*, 3707.
27. Kawai, H.; Mizuta, S.; Tokunaga, E.; Shibata, N., *J. Fluor. Chem.* **2013**, *152*, 46.
28. Kawai, H.; Tachi, K.; Tokunaga, E.; Shiro, M.; Shibata, N., *Org. Lett.* **2010**, *12*, 5104.
29. Kawai, H.; Kitayama, T.; Tokunaga, E.; Shibata, N., *Eur. J. Org. Chem.* **2011**, 5959.
30. Fourrière, G.; Van Hijfte, N.; Lalot, J.; Dutech, G.; Fragnet, B.; Coadou, G.; Quirion, J. C.; Leclerc, E., *Tetrahedron* **2010**, *66*, 3963.
31. Clark, J. H., *Chem. Rev.* **1980**, *80*, 429.
32. Ooi, T.; Maruoka, K., *Acc. Chem. Res.* **2004**, *37*, 526.
33. Adams, D. J.; Clark, J. H.; McFarland, H.; Nightingale, D. J., *J. Fluor. Chem.* **1999**, *94*, 51.
34. Ménand, M.; Dalla, V., *Synlett*, **2005**, 95.
35. Zafrani, Y.; Yehezkel, L.; Goldvaser, M.; Marciano, D.; Waysbort, D.; Gershonov, E.; Columbus, I., *Org. Biomol. Chem.* **2011**, *9*, 8445.
36. Haradahira, T.; Maeda, M.; Kai, Y.; Kojima, M., *J. Chem. Soc. Chem. Commun.*, **1985**, 364.
37. Haradahira, T.; Maeda, M.; Kai, Y.; Kojima, M., *J. Labeled Compd. Radiopharm.*, **1988**, *25*, 721.
38. *J. Org. Chem.* **2013**, *78*, 11 (JOC 1983, *48*, 3507-3510 –
39. Berridge, M. S.; Franceschini, M. P.; Rosenfeld, E.; Tewson, T. J., *J. Org. Chem.* **1990**, *55*, 1211.
40. Liang, T.; Neumann, C. N.; Ritter, T., *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.
41. Grushin, V. V.; Marshall, W. J., *Organomet.*, **2008**, *27*, 4825.
42. Bochat, M.; Clark, J. H., *J. Chem. Soc. Chem. Commun.*, **1993**, 921.
43. Clark, J. H.; Wails, D., *J. Fluor. Chem.* **1995**, *70*, 201.
44. Schimmler, S. D.; Ryan, S. J.; Bland, D. C.; Anderson, J. E.; Sanford, M. S., *J. Org. Chem.* **2015**, *80*, 12137.