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Nucleophile Assisting Leaving Groups: A Strategy for Aliphatic ^{18}F-Fluorination

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Abstract

A series of arylsulfonate nucleophile assisting leaving groups (NALGs) were prepared in which the metal chelating unit is attached to the aryl ring via an ether linker. These NALGs exhibited significant rate enhancements in halogenation reactions using metal halides. Studies with a NALG containing a macrocyclic ether unit suggest that rate enhancements of these nucleophilic halogenation reactions are facilitated by stabilization of charge in the transition state rather than through strong pre-complexation with metal cation. In several cases, a primary substrate containing one of the new leaving groups rivaled or surpassed the reactivity of triflates when exposed to nucleophile but was otherwise highly stable and isolable. These and previously disclosed chelating leaving groups were used in ^{18}F-fluorination reactions using no-carrier-added [^{18}F]fluoride ion ($t_{1/2}$ = 109.7 min, β^+ = 97%) in CH_3CN. Under microwave irradiation and without the assistance of a cryptand, such as K2.2.2, primary substrates with select NALGs led to a substantial improvement (2 to 3 fold) in radiofluorination yields over traditional leaving groups.

Introduction

We have previously reported on the development of new chelating leaving groups capable of facilitating nucleophilic reactions involving metal salts[1] and titanium(IV) complexes.[2] We have termed such groups nucleophile assisting leaving groups (NALGs) arguing that the rate enhancement afforded by these designed leaving groups is primarily due to stabilizing interactions with a metal-nucleophile pair in the course of a reaction to lower the transition state energy of the rate limiting step.[3] For example, in the case of substrate **A**, it is expected that the negative charge imparted to the leaving group moiety (LG) by an incoming nucleophile (Nuc^-) in transition state **C** should provide a more favorable chelation complex relative to its neutral precursor ligand **B** (scheme 1).[4] Depending on the specific nucleophilic reaction mechanism, metal chelation in the transition state should reduce the energy of activation (Ea_1) of NALG substrates relative to substrates containing traditional leaving groups. Without the added stabilizing effect of nucleophilic salt chelation with a nearby multidentate ligand, the energy of activation (Ea_2) for reactions involving traditional leaving groups (leading to a transition state such as **D**) is expected to be higher ($Ea_2 > Ea_1$).

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Our initial arylsulphonate NALG design **E** consisted of an oligoether (also macrocyclic) unit connected to the aryl ring *ortho* to the sulphonate via an ester linking unit (Scheme 1). NALGs **E** were prepared in one pot starting from very low cost materials and proved to be useful leaving groups in a number of reactions [1,2,5] and in a recent total synthesis.[6] However, crystal structure studies of these original NALGs demonstrated that the carbonyl of the ester linker is out of conjugation with the arylsulfonyl ring.[1] We argued that since this chelated conformation is not ideal, further nucleophilic reaction rate gains might be realized with NALG systems devoid of the ester carbonyl. Also, the aryl ether linker in **F** should possess broader chemical stability than a carboxyl ester for applications as a leaving group in complex synthesis. In this report, we describe the synthesis and nucleophilic reaction performance of new NALGs **F** whereby the chelating moiety is connected to an arylsulfonyl ring by an ether linkage. These new ether-linked NALGs, along with others that we have previously described, have been examined for their effectiveness in nucleophilic radiofluorination using $K^{18}F$ for eventual application in preparing radiotracers for positron emission tomography (PET).

Results and Discussion

Evidence for stabilized TS hypothesis

Our previous studies with NALG systems suggest their rate of reaction with metal halides to produce alkyl halides is not heavily dependent on the chelating ability of the *ortho* oligo-ether unit attached to the leaving group. A useful comparison would be NALG **1** containing a 12-crown-4 chelating unit with NALG **10** which possesses a linear unit containing the same number of Lewis basic oxygens (table 1, entries 6 and 7). The time required for both substrates to be completely converted to bromide product **2** indicates that they proceed at very similar rates despite the substantial difference (10^3) in their intrinsic lithium cation chelating abilities.

One explanation for this small rate difference in the bromination of reactions of NALGs **1** and **10** might be that the 12-crown-4 unit of **1** is hindered from effectively chelating lithium cation by its aryl sulfonate unit. Other Lariat systems have been known to exhibit similar side arm restrictions relative to their parent crown compounds.[7] To explore this possibility, NALG **1** was examined by ^1H NMR in the presence of a non-nucleophilic lithium salt ($LiBF_4$). Our titration curves following known protocols[8] clearly established that **1** rapidly chelated lithium cation (scheme 2). Thus we conclude that the superior chelating ability of 12-crown-4 over tetraethylene glycol holds in our NALG systems.

The lithium cation is expected to be available for chelation of the sulfonate unit of **1** in the transition state since 12-crown-4 is known to hold this cation in a perched rather than buried position.[6] Therefore, we surmise that the failure of NALG **1** to provide highly superior leaving group ability over linear NALG systems such as **10** may be due to an inability of the crown ether to effectively present the lithium cation in transition states such as **C** (scheme 1). Others have observed a preference for straight-chain chelators (podands) over crown ethers in nucleophilic processes arguing that a chelating macrocycle draws a cation into its cavity and away from the reactive site.[9] Another possibility may be that the carbonyl group linking the 12-crown-4 unit to phenyl sulfonate in **1** does not afford the conformation mobility required for the macrocyclic chelating unit to assist in the nucleophilic reaction. In this regard, the superior flexibility of our NALGs containing acyclic chelating units may be better poised to stabilize the growing negative charge in transition state **C** despite their poor chelating abilities. Nonetheless, we surmised that even the acyclic chelator systems would benefit from a change in linkage to the arylsulfonyl moiety.

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New aryl ether NALGs

As an alternative to the carbonyl linker of our previous NALGs, we turned to aryl ether systems in an effort to develop simple and convenient chelating leaving groups. Although this type of connection might diminish the electron withdrawing capacity of the arylsulfonyl moiety, it was thought that the Lewis basicity of the aryl ether oxygen would provide additional chelating ability, possibly offsetting its negative electronic effect.

Beginning with cheap and commercially available 4-substituted and 2,4-disubstituted phenols, a series of small oligo-ethyleneglycol tosylates were appended to the phenolic hydroxyl group to give aryl ethers **3** in good yields (scheme 3). With the *para*-position blocked by either a *tert*-butyl or a fluoro group, the reaction of **3** with chlorosulfonic acid initially gave desired product **4** in low yields (20–40%) most likely due to the formation of significant amount of sulfonic acid product. The addition of a chlorinating agent (thionyl chloride) significantly improved the yields presumably by converting sulfonic acid products to desired sulfonyl chlorides **4**. Intermediates **4** were then isolated and purified by aqueous workup followed by silica gel flash chromatography leading to high isolated yields (72–88%).

Using 3-phenylpropanol as a model substrate for a series of reaction rate studies, attempts to form sulfonates **11** – **18** with DMAP activation were unsuccessful. However, the conversion of 3-phenylpropanol to the alkoxide using NaH followed by addition of **4** and DMAP gave good yields of sulfonates **11** – **18** (and **11a** – **18a**). This procedure has also been used with success to form a wide variety of sulfonates from hindered secondary alcohols.[2] Despite the high reactivity of these aryl ether NALGs towards metal halides, they are remarkably stable compounds. By contrast, triflates (especially primary) are generally more reactive towards Lewis basic agents and some are not isolable by silica gel chromatography. NALG substrates, on the other hand, are easily purified by flash chromatography and can be stored for extended periods at room temperature.

In order to easily rank a variety of leaving groups using room temperature reactions in a convenient solvent such as acetone, we chose to study bromination reactions of substrates **11** – **19** to form 3-phenyl-1-bromopropane (**2**) using the quite soluble LiBr salt. For ready comparison, we also examined the brominations of our previously-disclosed ester NALG system (compounds **7** – **10** and **1**)[1] under the same conditions. Despite the near ubiquity of bromination reactions with LiBr, conditions involving even non-hindered primary tosylate substrates are often quite forcing[10] even with highly polar solvents such as DMF or NMP.[11] Indeed, primary tosylate **5** required 32 h for conversion to the corresponding bromide **2** in acetone at room temperature.[12] Substrate **6** containing the triflate leaving group, which is considered to be among the best nucleofuges,[13] required 2 h under the same conditions although other analogous brominations sometimes entail refluxing in acetone.[14]

In general, the bromination reaction of NALGs **11** – **13** containing a *tert*-butyl group *para* to the oligoethylene oxide chelating unit (table 1, entries 8 – 10) reacted more slowly than their ester analogs (entries 3 – 5). This modest rate decrease was likely due to the fact that both the *tert*-butyl and ether linkage in **11** – **13** release electron density into the arylsulfonyl ring destabilizing partial negative charge of the sulfonate leaving group in the transition state. These experiments also indicate that the carbonyl unit in NALGs such as **7** – **10** likely contributes a modest electron-withdrawing effect even though our previous crystallographic studies demonstrated that the carbonyl lies orthogonal to the plane of the aryl ring.[1]

As observed in our previous studies with ester NALGs,[1] an increase in the number of ether oxygens of the NALG sidearm, translates into stepwise increases in the rate of bromination. In each series (table 1), **7** – **10**, **11** – **13**, **14** – **16**, and **17** – **18**, addition of the second ethylene oxide unit exerts the greatest rate enhancement, leading to between double and triple the

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reaction rate. However, the addition of a fourth ethylene oxide unit gives only a relatively moderate rate enhancement (compare **9** and **10**).

Our original hypothesis that reaction rate gains would result from the replacement of a carboxyl linker with an ether does not appear to be supported by our data. Nonetheless, we reasoned that the more robust aryl ether NALG could be made practical through the introduction of electron withdrawing groups to offset the electron donation property of the ether linker. Indeed, the introduction of fluoro groups (NALGs **14** – **18**) led to substantial gains in the bromination reaction rate relative to *tert*-butyl NALGs (**11** – **13**). The combination of one or two fluoro groups with a chelating arm of three ethylene glycol units, NALGs **16** and **18** (entry 15), led to a reaction rate nearly 20 times greater than that of tosylate **5** and equivalent to that of triflate **6**.

In the three aryl ether series of compounds (table 1), **11** – **13**, **14** – **16**, and **17** – **18**, the rate of bromination is influenced by the substituent on aromatic ring *meta* to the sulfonyl group and follows the order: *tert*-butyl < mono-F < di-F. As may be expected, an electron donating group reduces while an electron-withdrawing group accelerates the rate of bromination.

We recently described stereoretentive halogenation and azidation reactions using Ti(IV) reagents with the 8-quinoline sulfonate (quisylate) leaving group.[2b] While this leaving group only possesses one chelating heteroatom, the rigid geometry of the 8-quinoline system appears to allow for more ideal chelation. The reaction of phenylpropyl quisylate substrate **19** with LiBr gave a significantly enhanced bromination rate of 4 h (entry 16) rivaling ester and ether NALGs containing two ethylene oxide units.

Application to ^{18}F-labeling

The substantially enhanced rate observed in the reaction of NALG containing substrates towards bromination especially in aryl ether systems (such as **16**) encouraged us to test whether such advantages might also be realized in nucleophilic radiofluorination for possible applications in preparing radiotracers for PET. PET is a powerful imaging modality for clinical research[15] and drug development.[16] Fluorine-18 (^{18}F, $t_{1/2}$ = 109.7 min) is one of the most widely used positron emitting radioisotopes because [^{18}F]fluoride ion in large quantity and high specific radioactivity can be made from a cyclotron through the proton irradiation of ^{18}O-enriched water.[17] Nucleophilic radiofluorination of aliphatic compounds remains an important labelling method.[17,18]

A number of strategies have been used to overcome the inherent limitation of fluoride ion as a nucleophile including the use of phase transfer catalysts such as the widely-used amino-ether cryptand Kryptofix 2.2.2 (K2.2.2) which serves to capture the metal counter ion (generally K^+) and to separate it from [^{18}F]fluoride ion, thereby enhancing its nucleophilicity. K2.2.2 must be removed from the final product due to its toxicity.[19] A few recent reports describe successful fluorination strategies that involve a significant deviation from the widely used and standard $^{18}F^-$, K2.2.2-K^+/CH_3CN conditions.[16] These include *tert*-butylammonium fluoride[20] (TBAF) in tertiary alcohol solvents[21] and KF with imidazolium-ionic liquids.[22] However, we reasoned that a well-designed leaving group may obviate the need for cryptand and solvent substitutions relative to the $^{18}F^-$, K2.2.2-K^+/CH_3CN system while still achieving rapid ^{18}F-incorporation.

Our initial studies involved the use of the NALG esters of 3-phenylpropanol. However, the fluorination product proved too volatile (bp = 70 °C/10 mmHg) for convenient handling in our radiosynthesis apparatus where the reaction was heated for 5 × 2 min at 90 W (reaching 130 °C) under microwave condition or at 130 °C for 10 min under thermal condition. Thus we prepared analogs of compounds **1**, **5**, **7** – **10**, **11**, **13**, **16**, and **19** containing a 4-*tert*-butyl group

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on the phenyl ring (table 2). As expected, radiofluorinated product **20,** resulting from the *tert*-butyl containing substrates was far easier to handle and measure.

Typical ^{18}F radiosynthesis procedures call for the use of M^{18}F obtained by adding poorly nucleophilic and weak bases to the proton irradiated [^{18}O]water.[23]

In our previous work, we demonstrated that NALGs **1** containing a 12-crown-4 moiety exhibited a substantial rate enhancement with lithium halide salts over sodium or potassium salts.[1] NALGs containing linear oligoether arms also showed some preference for the lithium cation. Thus we adapted standard procedures to form Li^{18}F and reacted this with several NALGs under various conditions in an attempt to produce **20** (table 2). Contrary to our results using LiBr in acetone (table 1), we observed no fluorination product using Li^{18}F with substrates **5a**, **1a**, and **16a** in acetone, acetonitrile, DMF, or DMSO. In the reaction of **1a** in acetonitrile, several bases were used to prepare Li^{18}F including Li_2CO_3, LiOH, and LiOAc, none yielding desired product **20**.

We have previously observed that highly polar solvents cancel the "NALG effect" by effectively competing with the oligoether arm of a NALG in chelating the metal of a nucleophilic salt. A highly solvated cation is not likely to participate in stabilizing transition states such as **C** (scheme 1). Thus we interpret the poor reactivity of **1a** and **16a** in DMF and DMSO to be the result of over-solvation. In less polar solvents such as acetonitrile and acetone, the poor reactivity of **1a** and **16a** was likely due to the poor solubility of Li^{18}F or the formation of tighter ion pair in these solvents.

With K_2CO_3 and K2.2.2, desired product **20** was obtained with a variety of NALG substrates under both thermal and microwave conditions (table 2) in good radiochemical yields (decay-corrected, $n > 2$). In most cases, NALGs performed significantly worse than the tosylate leaving group. With the cryptand tightly complexing the potassium cation of K^{18}F, *ortho* chelating units of our NALG substrates sterically hinder the approach of the K2.2.2/K^{18}F complex to the electrophilic site of the substrate. As expected, the radiochemical yields were much better with microwave irradiation than under thermal heating.[24] Here, as well, the phase transfer catalyst K2.2.2 cancelled the NALG effect. In the absence of K2.2.2, product **20** was only obtained under microwave conditions (table 2). Our benchmark substrate **5a** gave a radiochemical yield (RCY) of 9% under these conditions (table 2, entry 1).

In general, we found that our chelating groups provided significantly less rate enhancement with K^{18}F in acetonitrile than our previous studies with LiBr in acetone (table 1). NALG **1a** was essentially unreactive towards potassium fluoride even under microwave conditions. It is likely that the macrocycle unit only served to provide steric hindrance to the nucleophilic salt given the very poor affinity of 12-crown-4 for the potassium cation. With ester NALGs **7a** – **10a**, we observed a marked preference for three ethylene oxide units in the side chain. Thus, **9a** gave an average RCY of 22% (entry 4), a 2-to-3 fold enhancement relative to tosylate **5a** (entry 1). Importantly, attempts to fluorinate the triflate of 3-(*tert*-butylphenyl)-propanol were hampered by the instability of this compound to purification[25] and to reaction conditions. This underscores the utility of our chelating leaving groups whose reactivity is more directed towards the nucleophilic salt. To our knowledge, the fluorination of **9a** is the highest reported radiochemical yield of a primary substrate using K^{18}F/CH_3CN unassisted by additives, such as a cryptand.

Although the reasons for additional rate enhancement afforded by three ethylene oxide units in **9a** are unclear, a similar preference was observed with the aryl ether NALGs (entry 8 *vs.* 7). However, the addition of an electron-withdrawing fluorine in NALG **16a** (also containing three ethylene oxide units) did not improve the radiochemical yield (entry 9 *vs.* 8). Similar to our

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bromination experiments (table 1), quisylate **19a** significantly enhanced fluorination of the primary substrate relative to tosylate giving an RCY of 19%.

Conclusion

Studies with substrate **1** containing a 12-crown-4 moiety accord with the concept that a NALG chelating unit enhances metal halide substitution reactions through stabilization of charge in the transition state rather than through strong pre-complexation with metal cations. Based on this principle, the ideal NALG should contain a linker which allows its chelating unit to stabilize the transition state effectively. To this end, a new series of NALGs were synthesized in which the chelating units were attached to the aryl ring *via* an ether linkage. In addition, we prepared NALGs with electron-withdrawing fluorines on the aryl ring. In some cases, these new NALGs were more reactive towards LiBr than our previous systems suggesting that future variation of the linker element may provide additional rate enhancements. These and previously disclosed NALGs were then evaluated for their effectiveness in ^{18}F-fluorination, an application requiring fast and high yield reactions. Under microwave irradiation, several NALGs especially those with three ethylene oxide units in the chelating arm exhibited useful reactivity towards K^{18}F. Importantly, this reactivity was achieved in the absence of a cryptand which significantly increases the efforts necessary to purify radiolabeled samples for use in medical imaging applications. With this stand-alone reactivity, we believe that our NALG systems hold promise for solid phase applications especially those involving the synthesis of ^{18}F-labeled PET imaging agents.

Experimental Section

General Procedure for preparation of aryl ether derivatives 3

To an ice-cooled suspension of NaH (1.5 equiv) in *N*,*N*- dimethylformamide, the phenol derivative (1.0 equiv) was added slowly followed by stirring for 30-60 min. The tosylate derivative (1.5 equiv) of oligoethylene glycol was then added and reaction mixture was heated to 60-65 °C for 16-18h followed by cooling and quenching with aqueous HCl (2 M) and water dilution. The mixture was extracted three times with ether. The organic layer was dried over anhydrous sodium sulphate and concentrated. Purified product was obtained by flash column chromatography using hexane-ethyl acetate as the eluent. Reaction yields varied from 85-96%.

General Procedure for preparation of sulfonyl chloride derivatives 4

Aryl ether derivative (1.0 equiv) was added over 30 min to neat chlorosulfonic acid (5.0 equiv) cooled to 0 °C. After complete addition, the reaction mixture was stirred at room temperature for 3-6 h. The reaction mixture was then re-cooled to 0 °C and *N*,*N*-dimethylformamide (5.5 equiv) was added slowly followed by thionyl chloride (10.0 equiv). The reaction mixture was heated at 60-65 °C for 2 h and cooled to 0 °C and then added slowly to a mixture of ice and ether with constant stirring. The ether layer was extracted and aqueous layer was washed twice with ether. The ether washings were collected, washed with saturated sodium bicarbonate solution, and dried over anhydrous sodium sulphate. Purified product was obtained by flash column chromatography using hexane-ethyl acetate as the eluent. Reaction yields varied from 60-85%. 2-(2-(2-(2-Methoxyethoxy)ethoxy)ethoxy-5-fluorobenzene-1-sulfonyl chloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (dd, *J* = 7.45, 3.15 Hz, 1H), 7.41-7.36 (m, 1H), 7.18-7.15 (dd, *J* = 9.22, 3.93 Hz, 1H), 3.35-3.33 (m, 2H), 3.97-3.95 (m, 2H), 3.79-3.77 (m, 2H), 3.67-3.63 (m, 4H), 3.56-3.53 (m, 2H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 153.7, 153.1-153.0 (d, *J* = 2.50 Hz, 1C), 123.9-123.7 (d. *J* = 22.85 Hz, 1C), 116.3-116.1 (d, *J* = 27.31 Hz, 1C), 116.0-115.9 (d, *J* = 7.28 Hz, 1C), 71.7, 70.8, 70.5, 70.3, 70.0, 69.1, 58.9; HRMS (CI +) calc. for $C_{13}H_{18}ClFNaO_6S$ $[M+Na]^+$: 379.0389. Found: 379.0393.

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General procedure for esterification reactions to give 11 – 18

To a cooled (0 °C) suspension of sodium hydride (2.0 equiv) in dichloromethane (0.2 M) was added 3-phenyl-1-propanol (1.5 equiv) under argon. After 1 h of stirring aryl sulfonyl chloride (1.0 equiv) and 4-(dimethylamino)pyridine (1.0 equiv) were added to the previous solution. The reaction was maintained at room temperature for 4-6 h. Following completion, the reaction mixture was quenched with DI water and extracted several times with dichloromethane. The collected organic extracts were concentrated and the resulting oil was purified by silica gel chromatography (using ethyl acetate/hexanes as eluent). Reaction yields varied from 50 - 85%. 3-Phenylpropyl-2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy-5-fluorobenzene-1-sulfonate (16). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (dd, *J* = 7.79, 3.17 Hz, 1H), 7.33-7.26 (m, 3H), 7.22-7.19 (m, 1H), 7.16-7.14 (m, 2H), 7.12-7.09 (dd, *J* = 9.15, 3.98 Hz, 1H), 4.28-4.26 (m, 2H), 4.23-4.20 (t, *J* = 6.20 Hz, 2H), 3.93-3.90 (m, 2H), 3.76-3.73 (m, 2H), 3.65-3.62 (m, 4H), 3.56-3.54 (m, 2H), 3.38 (s, 3H), 2.74-2.71 (t, *J* = 7.39 Hz, 2H), 2.06-2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 154.3, 153.0 (d, *J* = 2.26 Hz, C), 140.3, 128.3, 128.2, 126.0, 122.0-121.8 (d, *J* = 22.82 Hz, 1C), 118.0-117.7 (d, *J* = 26.47 Hz, 1C), 115.5-115.4 (d, *J* = 7.41 Hz, 1C), 71.7, 70.7 (2), 70.5, 70.3, 69.7, 69.2, 58.9, 31.3, 30.6; HRMS (ESI+) calc. for $C_{22}H_{29}FNaO_7S$ $[M+Na]^+$: 479.1510. Found: 479.1507.

General procedure for substitution reactions (Table 1)

To a solution of lithium bromide (4.0 eq) at RT in acetone-d_6 (0.08 M) was added NALG-esters (1.0 equiv). The reaction was maintained at room temperature until completion (2 - 12 h, see Table 1) which was determined by the point at which starting material resonance peaks were no longer visible in the ^{1}H NMR of the reaction mixture. Following completion, the reaction mixture was concentrated under vacuum, quenched with DI water, and extracted several times with ether. The collected organic extracts were concentrated and the resulting oil was purified by silica gel chromatography (using pure hexane as eluent). Reaction yields were > 95%.

General procedure for [^{18}F]Fluoride ion drying and fluorination of NALGs under microwaves (Table 2)

A model 521 instrument for accelerated microwave chemistry microwave cavity (Resonance Instruments, Inc) was securely mounted on the Synthia MKII platform inside a lead-shielded hot cell.[26] The time and power control was located outside the hot cell and linked to the cavity through a RF coaxial cable. A glass reaction V-vial (1 ml) was equipped with a screw-on cap and Tuf-Bond teflon/silicone septum and a vent needle that was connected to a glass vial (20 ml) to collect the solvents and a charcoal trap to retain any volatile break through radioactivity. The V-vial containing NCA (no-carrier-added) [^{18}F]fluoride ions (10-100 mCi) in $H_2{}^{18}O$ (20-100 μl, obtained by irradiating 95 atom% [^{18}O]water for 120 min with a 17 MeV, 20 μA proton beam), K_2CO_3/K2.2.2 or K_2CO_3 only (100-600 μl stock solution of 0.5 mg K_2CO_3 and 5.0 mg K2.2.2, or 0.5 mg K_2CO_3 only in 9:1 CH_3CN and H_2O mixture) and CH_3CN (400 μl) was placed in the microwave cavity. Microwave heating at 90 W in 3 × 2 min pulses was applied under N_2 gas flow (200 ml/min) which speeded up the removal of azeotropic mixture of H_2O and CH_3CN. The temperature reading by the optical sensor reached 130 °C when the liquid volume was over 0.5 ml. The temperature reading gradually decreased to 50-60 °C as solvents evaporates. The heating cycle was repeated twice, and each time fresh CH_3CN (500 μl) was added. At the end of drying, the vent needle was removed. NALG precursor (5.0 mg) in CH_3CN was introduced in the closed V-vial and irradiated with 90 W microwave power in 5 × 2 min pulses. The reaction temperature reached 130 °C during microwave irradiation and decreased to 60-70 °C when microwave irradiation ceased. The reaction mixture was diluted with water (0.7 ml) and purified by HPLC on a reverse phase column (Luna C18, 10 μ, 100 Å, 250 × 10 mm id). The flow rate was 4 ml/min. The mobile phase was isocratic CH_3CN-10

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mM aqueous $HCOONH_4$ (65:35 v/v). The retention time of the radiolabeled product, 1-(3-[^{18}F]fluoropropyl)-4-*tert*-butyl benzene, was 25 min and was authenticated by co-elution from the column with the corresponding non-radioactive standard, 1-(3-fluoropropyl)-4-*tert*-butyl benzene. Radiochemical yield (decay-corrected) was calculated from the radioactivity of the HPLC fraction at 24-26 min compared to the total radioactivity introduced into the V-vial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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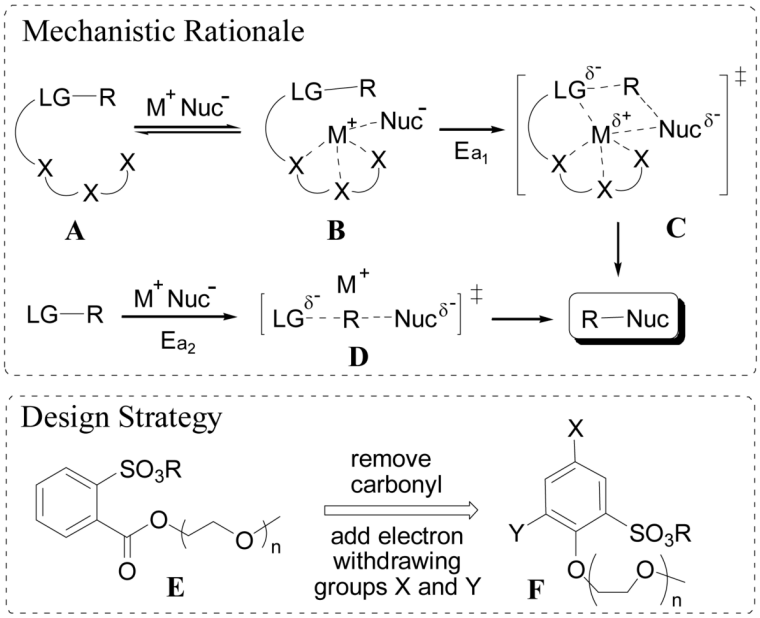
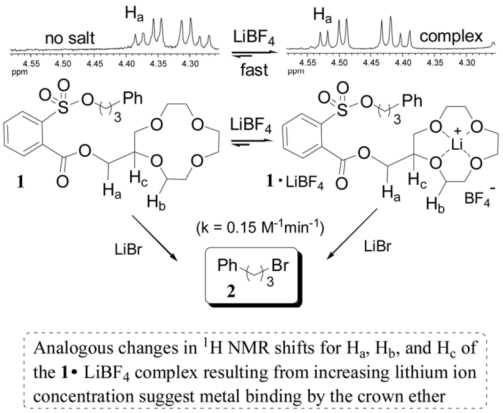
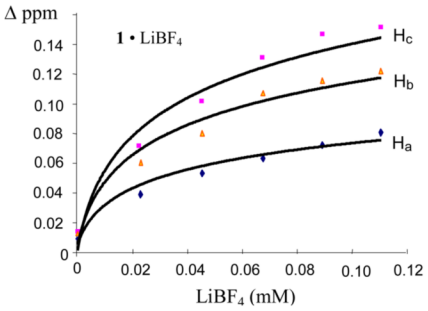


Scheme 1.

Rationale for rate enhancement observed with nucleophile assisting leaving groups (NALGs) and strategies for improvement.





Scheme 2.
Evidence for lithium chelation with NALG **1**.

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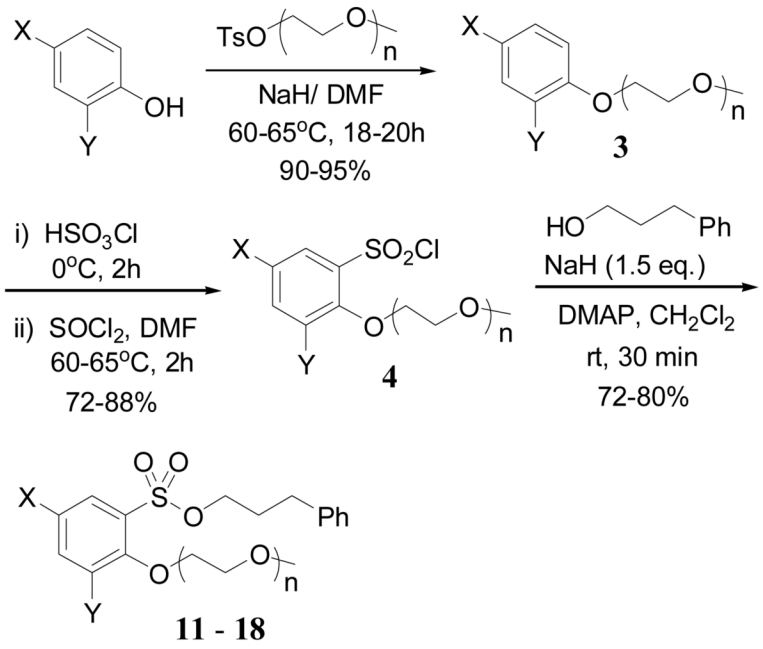

Scheme 3.
Synthesis of second generation NALGs.

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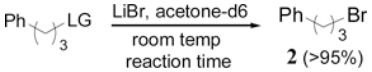
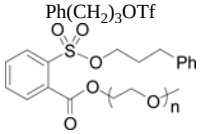
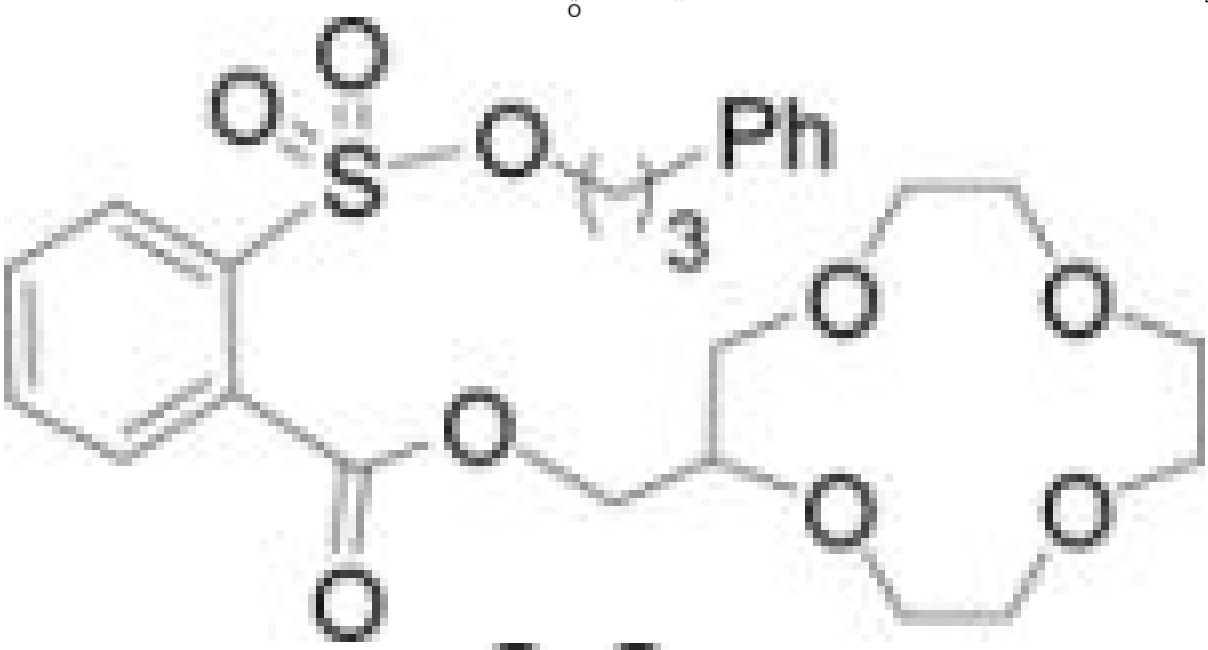
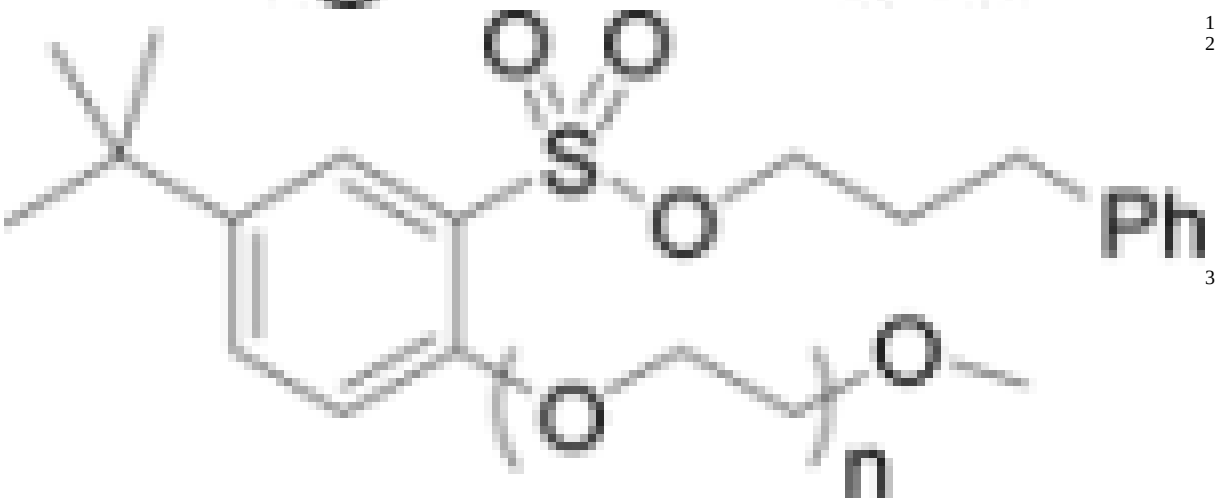
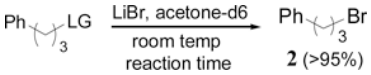
Table 1

Bromination reaction times with 3-phenylpropyl substrates containing various leaving groups



entry	structure	ncompound	reaction time (h)[a]
1	$Ph(CH_2)_3OTs$	**5**	32
2	$Ph(CH_2)_3OTf$	**6**	2.0
3	 1	**7**	12
4	2	**8**	5.0
5	3	**9**	3.3
6	4	**10**	2.3
7		**1**	1.3
8	1	**11**	25
9	2	**12**	8.8
10	 3	**13**	6.8



entry	structure	ncompound	reaction time (h)[a]
11		1 **14** (X=H)	10
12		2 **15** (X=H)	4.0
13		3 **16** (X=H)	2.5
14		2 **17** (X=F)	2.5
15		3 **18** (X=F)	1.8
16		**19**	4.5

[a]All brominations were carried out in acetone-d6 noting the time of reaction completion by the disappearance of starting material resonance peaks in the ^{1}H NMR.

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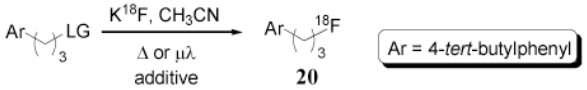
Table 2

[^{18}F]Fluorination of various NALG containing substrates to yield **20** under thermal and microwave heating conditions.



entry	structure	n	compound	% RCY[a] thermal K2.2.2[b]	% RCY[a] microwave K2.2.2	% RCY[a] microwave no K2.2.2
1	$Ar(CH_2)_3OTs$		**5a**	65	76	9
2		1	**7a**	11	34	17
3		2	**8a**	13	49	4
4		3	**9a**	62	79	22
5		4	**10a**	44	66	4

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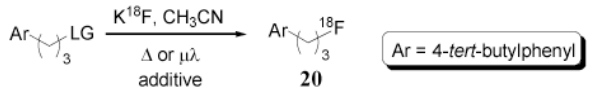
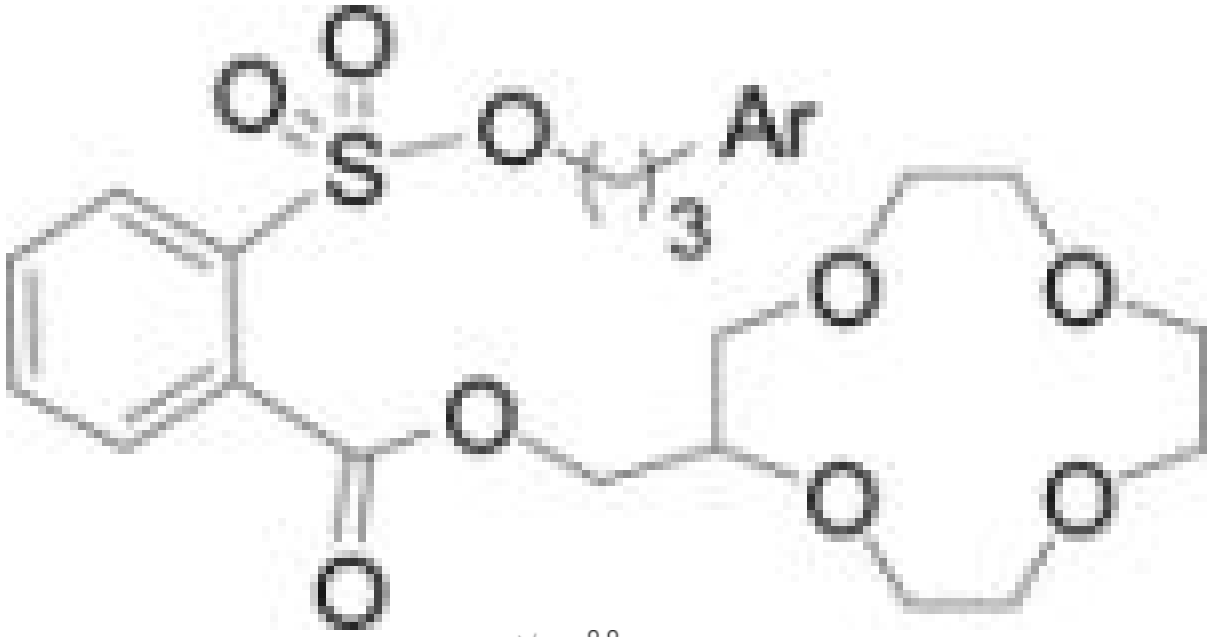
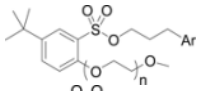
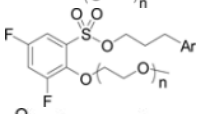
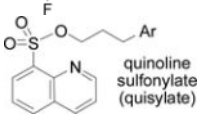


entry	structure	n	compound	% RCY[a] thermal K2.2.2[b]	% RCY[a] microwave K2.2.2	% RCY[a] no K2.2.2
6			**1a**	2	4	0
7		1	**11a**	32	80	0[c]
8		3	**13a**	31	64	16
9		3	**16a**	72	75	12
10	quinoline sulfonylate (quisylate)		**19**	11	64	19

[a] Average decay-corrected radiochemical yield (n ≥ 2)

[b] No product with thermal conditions in the absence of K2.2.2.

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[c]Unidentified radioactive product (7%) obtained at retention time of 14-16 min.