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Tetra-*n*-butylammonium Fluoride as an Efficient Transesterification Catalyst for Functionalizing Cyclic Carbonates and Aliphatic Polycarbonates

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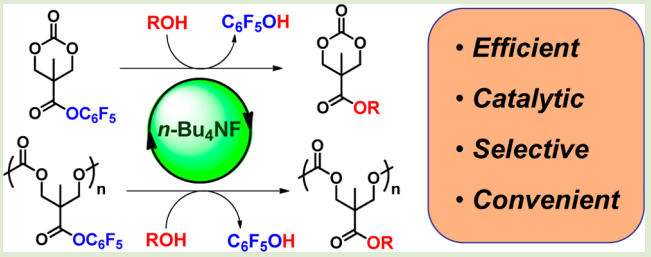
Supporting Information

ABSTRACT: We have developed a general method for the functionalization of cyclic carbonate monomers having a pentafluorophenyl ester substituent at the 5-position (MTC-OC_6F_5), as well as the postpolymerization modification of the subsequent polymer, poly(MTC-OC_6F_5), with alcohols. The transesterifications are achieved under mild conditions using catalytic tetra-*n*-butylammonium fluoride (TBAF) as the nucleophilic acyl transfer agent. As an organic-soluble form of fluoride, TBAF loadings as low as 5 mol % were sufficient in bringing about high conversions at room temperature. The mild reaction conditions preserved the integrity of the sensitive carbonate moieties even without the use of Schlenk techniques. In addition to commercial TBAF solutions, we also found solid-supported forms of TBAF to be effective for transesterification, thus enabling facile postreaction workup and purification. More importantly, with only minor adjustments to the reaction conditions, we show that TBAF also promotes the postpolymerization modification of poly(MTC-OC_6F_5), whereby fluoride-mediated transesterification with various alcohols proceeded quantitatively across the pendant pentafluorophenyl esters. Synthesizing a series of pendant ester-functionalized polycarbonates from a common precursor polymer was previously unattainable with existing methods, an issue that is now resolved by the current work.



Owing to their biocompatibility, degradability, and low toxicity, aliphatic polycarbonates have received considerable attention as a promising platform for polymer-based therapeutics, drug and gene delivery, and imaging contrast agents. These polycarbonates can be synthesized with a high degree of control via ring-opening polymerization (ROP) of cyclic carbonates by organocatalytic, anionic, cationic, coordination−insertion, or enzymatic methods.[1−10] The incorporation of diverse functionality into aliphatic polycarbonates has been accomplished through the ROP of functionalized cyclic carbonate monomers[11−17] and via the postpolymerization modification of polycarbonates.[15,18−24] Examples of the latter strategy include the use of "click reactions" based on thiol−ene chemistry by Dove and co-workers[21] as well as Sanyal et al.[20] Recently, we also reported the preparation of functionalized polycarbonates via postpolymerization modification of pendant activated esters, whereby primary amines reacted quantitatively with the pentafluorophenyl esters to give amides.[24] The postpolymerization modification of pentafluorophenyl esters was similarly employed in a previous work by Gibson et al.,[23] albeit on a more robust poly(methacrylate) backbone. In both cases, the use of pentafluorophenyl esters was limited to amide bond formation via reaction with amines. Unfortunately, using less nucleophilic alcohols does not afford the corresponding esters. Currently, aliphatic polycarbonates with pendant esters are prepared via the ROP of prefunctionalized cyclic carbonate monomers.[25] There are several shortcomings associated with this route: (1) there are various monomers that are unsuitable for direct polymerization due to functional group incompatibilities, (2) this method cannot generate libraries of polycarbonates with identical chain lengths and polydispersities but with variable side chain esters, and (3) the preparation of ester-functionalized cyclic carbonates from MTC-OC_6F_5 necessitates the use of stoichiometric amounts of Proton-sponge (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine) or the highly hygroscopic and poorly soluble CsF as a promoter.[25,26] Herein, we present a general method that addresses these issues, not only offering an improved route to cyclic carbonate monomers but also enabling the facile postpolymerization modification of poly(MTC-OC_6F_5) with alcohols. Specifically, we have found that tetra-*n*-butylammonium fluoride (TBAF) is a mild and efficient nucleophilic acyl

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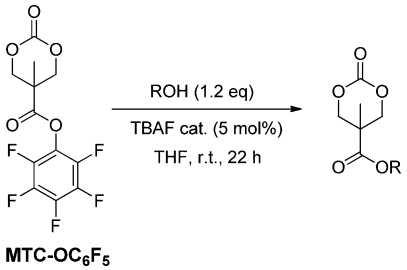
transfer catalyst for transesterification between pentafluorophenyl esters and alcohols in the presence of a sensitive carbonate functionality.

The synthetic methods that we had previously developed for preparing functionalized cyclic carbonate monomers from MTC-OC_6F_5 employs either substoichiometric/superstoichiometric amounts of CsF[25] or equimolar quantities of Proton-sponge to promote transesterification[26] since alcohols are too weakly nucleophilic compared to primary amines to displace pentafluorophenol without assistance. However, the use of either additive suffers from practical problems. In the case of CsF, relatively high loadings (usually exceeding 0.25 equiv and as high as 1.33 equiv) of the salt are typically required to give higher product yields. This is probably due to the poor solubility of CsF in the reaction solvent (THF). In addition, CsF is also extremely hygroscopic, rendering benchtop usage less convenient. In the case of Proton-sponge, a stoichiometric quantity of the base is usually required. This creates purification difficulties in many cases, especially upon reaction scale-up, since a large amount of waste is generated in the process. Also, conditions involving stoichiometric amounts of base frequently result in some degree of undesirable carbonate ring opening and consequently diminished isolated yields. To make matters worse, both CsF and Proton-sponge were found to be ineffective as promoters for the postpolymerization transesterification of poly(MTC-OC_6F_5). The main issues were the incomplete conversion of the pendant pentafluorophenyl esters (e.g., 50% conversion) as well as a significant degree of hydrolysis.[16]

In our search for an alternative transesterification catalyst that would work for both our monomer and polymer systems, we began by screening common nucleophilic acyl transfer catalysts such as 4-(dimethylamino)pyridine[27] and *N*-methylimidazole.[28] Unfortunately, both reagents were found to be ineffective. We then considered TBAF, as this represented an organic-soluble form of fluoride that was inexpensive and commercially available as a 1.0 M solution in THF. Gratifyingly, we found that TBAF catalyzed transesterification between MTC-OC_6F_5 and various alcohols (Scheme 1) to the desired

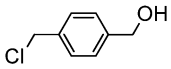
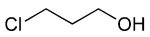
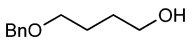
Scheme 1. General Synthesis of Functionalized Cyclic Carbonates via TBAF-Catalyzed Transesterification



esters in high conversions without causing ring opening. Conversions were determined by ^{1}H NMR spectroscopy, based on the relative integration values of methylene protons on the products versus MTC-OC_6F_5. The chemical shifts of the ester products were compared and verified against literature values.[11,12,16,17,21,25,29,30]

Effective catalytic loadings were several times lower than with CsF. Using just 5 mol % of TBAF (as a 1.0 M solution in THF) with respect to pentafluorophenyl ester, good conversions with several different alcohols were achieved within the first 3 h of reaction (Table 1), and over 70% conversion was obtained in all cases after overnight stirring at room temperature (20 °C).

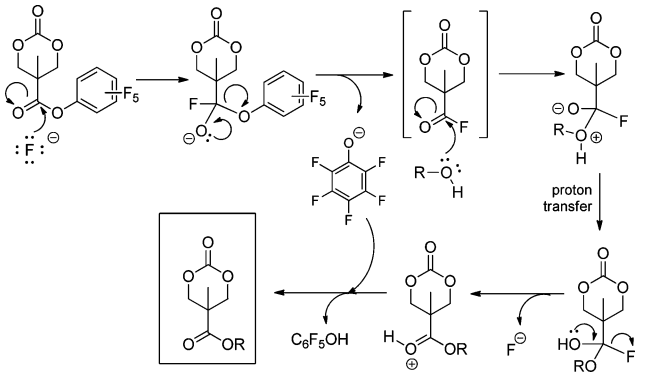
Table 1. Relative Conversions to Functionalized Cyclic Carbonates Using TBAF (1.0 M in THF) as the Catalyst[a]

Entry	ROH	Conv. at 3h (%)	Conv. at 22h (%)
1		59	77
2		64	79
3[b]		54	71
4		80	92
5		62	75
6		65	82
7		57	71

[a]Concentrations: [carbonate] = 0.547 M, [alcohol] = 0.655 M, [TBAF] = 0.0273 M; volume of solvent = 0.56 mL. [b]With bulky *t*-BuOH, stoichiometric TBAF was required for effective conversion.

Various functional groups such as benzyl chlorides and terminal alkenes were unaffected by the mild conditions. Only in the case of *t*-butyl alcohol (entry 3) was stoichiometric TBAF necessary, but good conversion was still achieved after 22 h despite the significant steric bulk of the nucleophile. Previously, the *t*-butyl-containing monomer could only be accessed via a much harsher acyl chloride route.[17] Another advantage of the current TBAF protocol is the relative lack of side/byproducts formed compared with the Proton-sponge procedure, making for easier purification. This becomes especially important when large-scale monomer synthesis is desired. The transesterification mechanism likely proceeds via an acyl fluoride intermediate that is subsequently attacked by the alcohol nucleophile to give an ester and simultaneously regenerating free fluoride (Scheme 2). Previously, amino acid fluorides have been prepared (e.g., via a cyanuric fluoride route), purified, and isolated for subsequent coupling with amines/alcohols to yield amides/esters.[31] Further examples of fluoride-promoted nucleophilic acyl transfer include transesterifications on phosphonate esters[32] and nucleotide phosphotriesters.[33,34]

Scheme 2. Proposed Mechanism of the TBAF-Catalyzed Transesterification of MTC-OC_6F_5



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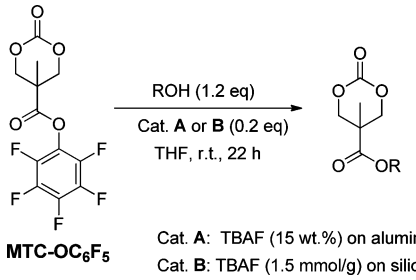
Following the optimization of conditions with TBAF solution, we then explored the possibility of employing solid-supported TBAF sources for transesterification (Scheme 3).

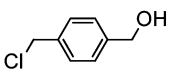
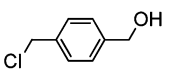
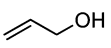
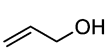
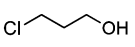
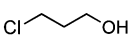
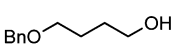
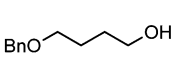
Scheme 3. Functionalizing Cyclic Carbonates via Transesterification with Alcohols, Catalyzed by Solid-Supported TBAF



For this, two commercially available and nonhygroscopic, solid-supported TBAF reagents were screened, namely: TBAF (15 wt %) on alumina and TBAF (1.5 mmol/g) on silica gel. Reactions were likewise performed in THF under ambient conditions without rigorous air and moisture exclusion. The less expensive TBAF/alumina reagent was found to be more effective than the latter, though moderate-to-high yields were also observed with the silica gel supported TBAF. Percentage conversions as judged by ^{1}H NMR were comparable to those obtained with TBAF solution, except in the case of *t*-butyl alcohol, where the steric bulk played a detrimental role. The results of the solid-supported TBAF experiments are given below in Table 2. The attraction behind using a solid-supported catalyst lies in the possibility of simply filtering it off upon reaction completion, obviating the need for column chromatography when large-scale synthesis is involved.

Having achieved transesterification with monomers using various forms of TBAF, we then addressed the more critical goal of doing the same with the pendant pentafluorophenyl esters of a polycarbonate. Initial experiments employing benzyl alcohol under similar conditions, i.e., 0.05 equiv of TBAF and THF as solvent, gave negligible conversion of the side chains. However, increasing the TBAF loading to 0.75 equiv afforded over 90% substitution of the pentafluorophenols after 24 h, as determined by ^{1}H NMR. This was further improved by using *N*,*N*-dimethylformamide (DMF) as solvent, which gave quantitative conversion of the activated esters to benzyl esters (Scheme 4a). The resulting polycarbonate had a polydispersity index (PDI) of 1.26, slightly higher than that of the precursor polymer (M_n = 21.9 kDa, PDI = 1.18). This modest broadening is likely due to a minor extent of backbone activation and degradation. Postpolymerization modifications with other alcohols (e.g., ethanol, allyl alcohol) under the same conditions were also carried out. Polymer PDI was preserved with EtOH, while some broadening was observed with higher alcohols, especially those with greater steric bulk. Detailed NMR and GPC data/analysis are described in the Supporting Information. Compared with transesterification on cyclic carbonates, a higher loading of TBAF was required to convert the pendant pentafluorophenyl esters of poly(MTC-OC_6F_5), possibly due to: (a) inaccessible reaction sites on the polymer due to conformational and aggregation effects and (b) solution viscosity and reagent diffusion issues. Solid-supported forms of TBAF were completely ineffective as postpolymerization transesterification promoters, likely due to the same reasons

Table 2. Relative Conversions to Functionalized Cyclic Carbonates Using Solid-Supported TBAF Catalysts

Entry	ROH	Catalyst	Conv. at 3h (%)	Conv. at 22h (%)
1a		**A**	62	80
1b		**B**	55	70
2a		**A**	56	75
2b		**B**	46	70
3a		**A**	28	56
3b		**B**	17	33
4a		**A**	72	88
4b		**B**	60	79
5a		**A**	44	74
5b		**B**	44	68
6a		**A**	57	83
6b		**B**	45	75
7a		**A**	41	67
7b		**B**	30	52

cited above. Finally, transesterification on a diblock polymer comprised of a 5 kDa poly(ethylene glycol) block and a short polycarbonate segment was also carried out, whereby all the pentafluorophenyl esters of the latter block were quantitatively converted to benzyl esters (Scheme 4b). In all cases, postpolymerization modification was achieved with minimal-to-modest backbone degradation, as shown by gel permeation chromatography (GPC) analysis (see Supporting Information).

In conclusion, we have developed a general method for the TBAF-catalyzed functionalization of cyclic carbonate monomers and postpolymerization modification of poly(MTC-OC_6F_5) with a wide variety of alcohols under mild conditions. This not only enables the expedient preparation of functionalized cyclic carbonates but also allows for the facile and quantitative chemical modification of the pendant side chains of a precursor polymer. In the case of monomers, no undesirable ring opening was observed, while in the case of polymers, the carbonate-based backbone was also preserved. The methods described above combine synthetic ease with a high degree of control, which will allow higher-order polymeric and supra-

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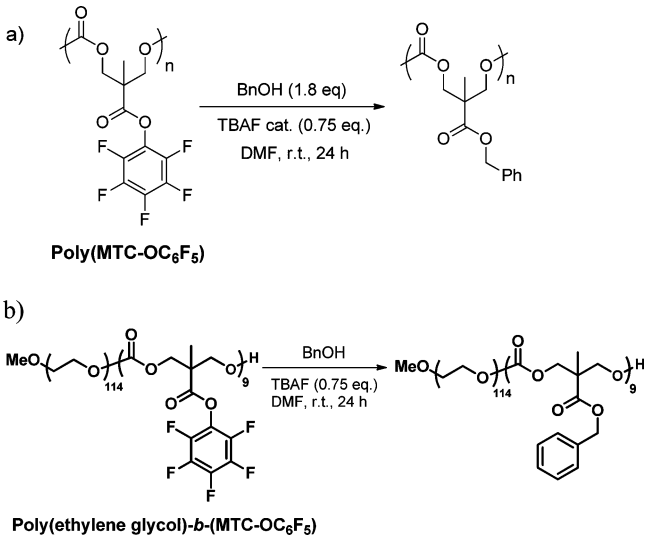
Scheme 4. TBAF-Mediated Postpolymerization Modification of (a) Poly(MTC-OC_6F_5) and (b) a PEG−Polycarbonate Diblock Copolymer



molecular architectures to be realized. In view of the increasing interest and demand for biocompatible and biodegradable materials, it is expected that the new synthetic tools reported herein will help pave the way toward novel and innovative functional polymers.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H NMR spectra, and GPC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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