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Ring-opening Copolymerization of Maleic Anhydride with Functional Epoxides to Yield Poly(propylene fumarate) Analogues Capable of Post-polymerization Modification

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Abstract: Three functional epoxides were copolymerized with maleic anhydride to yield degradable poly(propylene fumarate) analogues. The polymers were modified post-polymerization and post-printing with “click”-type addition reactions or UV deprotection in order to attach bioactive species or increase the hydrophilicity. Successful dye attachment, induced wettability and improved cell spreading show the viability of these analogues in biomaterials applications.

Degradable polyesters have been used widely in regenerative medicine applications.[1],[2],[3],[4] While many of these materials have enjoyed clinical and commercial success, efforts to broaden the scope of chemical, mechanical and degradation properties have proven challenging.[3],[5],[6] The most widely used synthetic polyesters in biomedical applications are poly(*L*-lactic acid) (PLLA),[7],[8],[9],[10] poly(lactic acid-*co*-glycolic acid) (PLGA) and poly(ε-caprolactone) (PCL).[11],[12] However, as a consequence of long degradation times, acidic degradation products and limited handles for post-polymerization modification, new materials with well-defined properties and easily accessible functional handles are needed.[13]

Another widely investigated degradable polyester is poly(propylene fumarate) (PPF). PPF is resorbable upon degradation and contains an alkene group in its backbone, which facilitates photochemical crosslinking and 3D printing *via* stereolithographic methods.[14] PPF has generated substantial interest for use as patient specific bone scaffolds as its modulus when crosslinked is near that of cancellous bone.[15] Despite its potential in regenerative medicine, PPF lacks inherent osteoconductive and osteoinductive properties known to stimulate bone growth. Previous studies have shown that PPF scaffolds preloaded with a number of pharmaceuticals, short peptide chains and biologically active molecules help promote cell attachment, growth, differentiation and proliferation.[16],[17],[18] However, most reports of PPF functionalization are non-specific, physical interactions. Thus, covalent, regioselective and concentration specific methods for attaching bioactive molecules would be advantageous, but these opportunities are limited as few bioactive species are able to survive thermal processing, photochemical printing and/or post-printing irradiation processes.

Due to the highly quantitative yields, rapid orthogonal addition and mild reaction conditions,[19] “click”-type addition reactions have been used widely to form polymer-bioactive molecule conjugated compounds.[20],[21] The addition of bioactive molecules in order to enhance cell attachment, growth and proliferation *via* “click” chemistry has been demonstrated in multiple studies using a Huisgen 1,3-dipolar cycloaddition.[22],[23] Additionally, with the appropriate reactive handle, these reactions can be performed post-polymerization or post-printing so that bioactive conjugates are not subjected to harsh processing or irradiation. Thus, incorporating reactive handles at the chain end or within the backbone may afford a route to “click” modifiable PPF analogues. [24],[25]

Traditionally, PPF has been synthesized *via* step-growth polymerization, which requires both elevated temperature and reduced pressure and typically results in modest yields, broad molecular mass distribution ($Đ_M$) and byproducts that must be removed prior to use.[26] Various copolymerization strategies of epoxides, anhydrides and lactones have been investigated previously to produce a wide range of polyesters.[27],[28],[29],[30] Recently, PPF was synthesized using an alternating ring-opening copolymerization (ROCOP) of maleic anhydride (MA) and propylene oxide (PO) to produce poly(propylene maleate) (PPM), which was subsequently isomerized to produce PPF.[31],[32],[33],[34] This approach results in a much higher degree of control of the material properties and the use of two monomer species offers multiple sites for post-polymerization chain functionalization. We recently demonstrated the utility of magnesium 2,6-*di*-*tert*-butyl-4-methylphenoxide ($Mg(THF)_2(BHT)_2$) in the production of end-functionalized PPF *via* ROCOP.[25] In this study, both Megastokes® 673-azide dye and a GRGDS peptide were attached to the propargyl functionalized chain-end after scaffold crosslinking to demonstrate the feasibility of using the reactive handles and “click” type reactions for post-printing bioconjugate addition.

However, in order to adopt a functional backbone strategy in the production of PPF,[35],[36],[37] either PO or MA must be modified. The functionalization of MA significantly alters the reactivity of the alkene group,[38] which will decrease or sacrifice the ability of PPF to undergo photo-crosslinking reactions. Alternatively, epoxides can be modified easily to incorporate a pendent functional group

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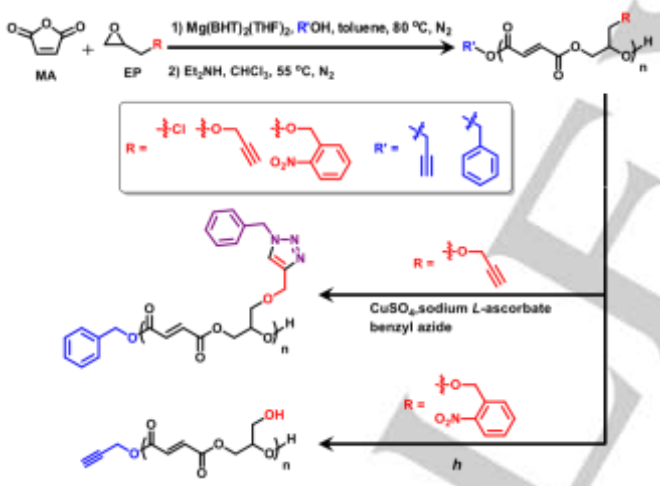
into the chain.[39],[40] Using a functional monomer approach, the stoichiometry of the respective epoxide can be controlled and multifunctional polymer chains are possible.[41],[42],[43] Herein, we utilize ROCOP of MA and functional epoxides to produce a series of chlorine, propargyl and *o*-nitrophenyl functionalized PPF analogues that can undergo post-polymerization and post-print type reactions for the rapid attachment of bioactive conjugates. While epichlorohydrin (EC) has been demonstrated in the literature to copolymerize with MA,[31],[33],[44] so far no example has been shown to introduce propargyl or *o*-nitrophenyl moieties into PPF analogues.

In order to explore the viability of $Mg(THF)_2(BHT)_2$ catalyzed ROCOP with functional epoxides (EP), equimolar quantity of EC and MA were copolymerized under sealed, dry and inert conditions, using benzyl alcohol as an initiator at a 2 M concentration in toluene. The reaction mixture was heated at 80 °C for 24 hours (**Scheme 1**). After quenching, the solution was precipitated into an equimolar quantity of warm (40 °C) hexanes in order to remove residual MA and catalyst. The recovered polymer, poly(epichlorohydrin maleate) (PEM), was characterized using ^{1}H NMR spectroscopy. As a consequence of the difference in chemical structure compared to PPM, the proton resonances corresponding to the methylene adjacent to the chlorine atom are shifted downfield to δ = 3.75 ppm rather than δ = 1.25 ppm, which corresponds to the pendent methyl group of PPM.



Scheme 1. Synthesis and post-polymerization modification of poly(propylene fumarate) analogues that incorporate functional epoxides using magnesium 2,6-*di-tert*-butyl-4-methylphenoxide.

Following a previously reported procedure, PEM was isomerized using diethylamine.[45] The resonance corresponding to the alkene protons at δ = 6.32 ppm shifted downfield to δ = 6.90 ppm, which confirmed the change from *cis* to *trans* stereochemistry. Two separate resonances appeared at δ = 4.40-4.60 ppm as a consequence of regiochemical differences during the ring-opening of epichlorohydrin, which resolves to a greater extent after isomerization (**Figure S4A**).

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-ToF MS) was used to determine the repeat unit molecular mass and end-group fidelity. Before isomerization, one major distribution was observed by MALDI-ToF MS, which corresponds to a benzyl alcohol-initiated chain and a 190 Da repeat unit corresponding to EC and MA (**Figure S4B**). The successful synthesis of poly(epichlorohydrin fumarate) (PEF) demonstrates that this polymerization can be used to copolymerize modified epoxides with MA without unwanted side reactions.

After successfully synthesizing a chlorine functionalized PPF analogue, "clickable" and UV-sensitive epoxides containing an alkyne or *o*-nitrophenyl group were synthesized. Glycidyl propargyl ether (GPE) and 2-(((2-nitrophenyl)methoxy)methyl)oxirane (NMMO) were synthesized using a phase transfer agent catalyzed system.[46] The copolymerization of these monomers with MA was conducted following the same synthetic procedure as that of PEF (**Scheme 1**). It should be noted that propargyl alcohol was used as the initiator for poly(NMMO fumarate) (PNMMOF) synthesis in place of benzyl alcohol since the proton resonances of the benzyl alcohol and *o*-nitrophenyl groups coincide. ^{1}H NMR spectroscopic analysis of the resultant poly(GPE fumarate) (PGPEF) and PNMMOF, showed proton resonances at δ = 2.49 ppm and δ = 7.35-8.15 ppm, which correspond to the protons from the propargyl alcohol alkyne and aromatic *o*-nitrophenyl protons, respectively (**Figures 1, S7**).

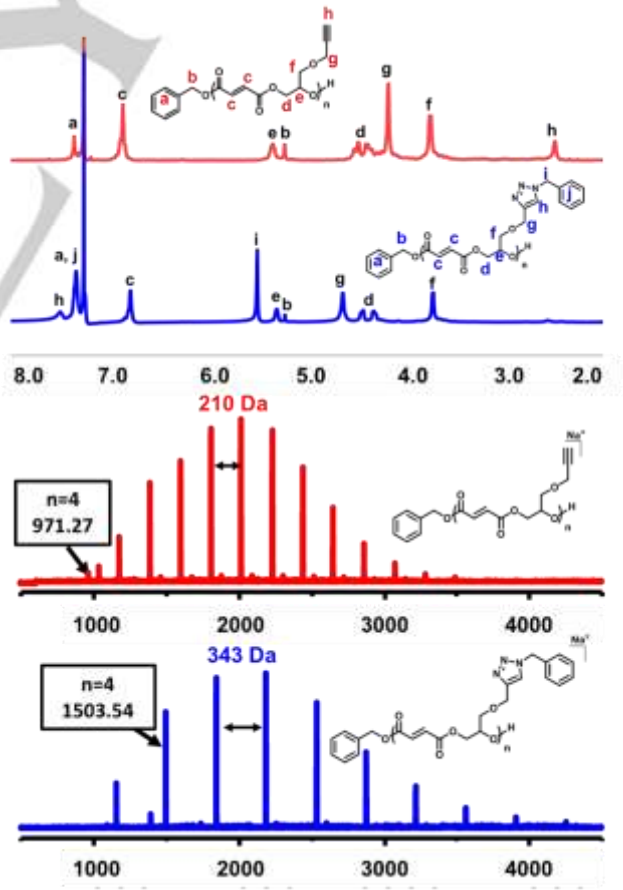


Figure 1. Comparison of ^{1}H NMR spectra and MALDI-ToF MS plots before and after CuAAC of PGPEF and benzyl azide.

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MALDI-ToF MS analysis of each polymer further confirmed the end-group fidelity and molecular mass of the repeat units for PGPEF (210 Da) and PNMMOF (307 Da) (**Figures 1, S9**). The distributions were also used to determine the molecular mass of each polymer. Each polymer showed no ether linkages in the backbone according to the mass spectra, indicating that no homopolymerization of epoxide occurred even when using epoxides with higher reactivity.

Additionally, different monomer feed ratios and targeted molecular masses within the expected 3D printable range was investigated (**Table 1**). It is worth noting that as the steric bulk of the epoxides increases, the glass transition temperature (T_g) decreases. This implies that pendent functional groups from comonomer functionalization can be used to modify the T_g of the polymer and produce room-temperature fluid PPF analogues. This is advantageous as current, printable PPF resin formulations contain ~50% solvent, reactive diluent and other fillers.[15]

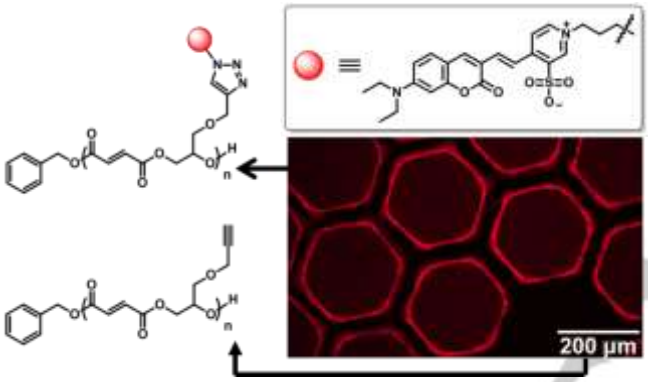

Figure 2. Fluorescence microscopy image of Megastokes® 673-azide dye attached PGPEF thin film. Under 673 nm filter at 10x magnification with TEM grid as mask, the dark regions correspond to the PGPEF film areas that were covered by the TEM grid, the red shows the areas of the PGPEF film exposed to the dye.

To ensure this is a viable strategy for bioconjugate addition, it is necessary to prove that the added functionalities are able to undergo post-polymerization modification. For each functional epoxide, one specific, orthogonal post-polymerization modification was selected. The alkyne groups of PGPEF underwent the copper(I)-mediated azide-alkyne cycloaddition (CuAAC) in $CHCl_3$ with benzyl azide or with a fluorescent dye on the surface of a polymer thin film. The *o*-nitrophenyl group in PNMMOF was deprotected by 365 nm UV light with THF as solvent (**Scheme 1**).

After the cycloaddition of benzyl azide, the resultant PGPEF was characterized by MALDI-ToF MS in order to detect the difference in the mass of the repeat unit and the extent of conversion. The repeat unit molecular mass was observed to increase from 210 Da to 343 Da, with the additional 133 Da attributable to the mass of benzyl azide. Moreover, the significant shift to a higher mass region from the same DP peak indicated the addition of benzyl azide group to each alkyne (**Figures 1**). In the ^{1}H NMR spectra, the new proton resonance at δ = 7.50 ppm and disappearance of proton resonance at δ = 2.50 ppm indicated the formation of triazole structure as a consequence of the CuAAC cycloaddition **(Figure S12)**. Fluorescence microscopy was used to image a thin film of PGPEF post-addition which was then compared to a film with no dye attached (**Figure S13**). Also, a TEM grid was used as a mask, which proves that selective dye attachment is achievable (**Figure 2**). As expected, the areas of the thin film exposed to fluorescent dye showed significantly higher intensity under fluorescence microscopy.

For the PNMMOF post-polymerization modification, the photochemical deprotection reaction was monitored by UV/Visible spectroscopy. The maximum absorbance of the starting polymer solution was at 260 nm. After 20 minutes of 365 nm UV treatment, the absorption peak at 260 nm decreased and two new absorption peaks appeared at 290 and 315 nm. This corresponds to the π-π^* transition of the aromatic side product (*o*-nitroso benzaldehyde) which shows that the *o*-nitrophenyl group was cleaved by UV light. However, if the UV light was employed for more than 20 minutes, these two peaks disappeared, which may indicate other photochemical reactions of the aromatic by-product (**Figure 3**).[47] The reaction was further monitored by ^{1}H NMR spectroscopy, which confirmed cleavage of *o*-nitroso benzaldehyde from the polymer backbone (**Figures S14, 15**). After 240 minutes of UV treatment, a different UV absorption curve was observed than that of PPF with a propargyl alcohol end-group, implying that the hydroxyl functionalized polymer, poly(glycidol fumarate) (PGF) was obtained.

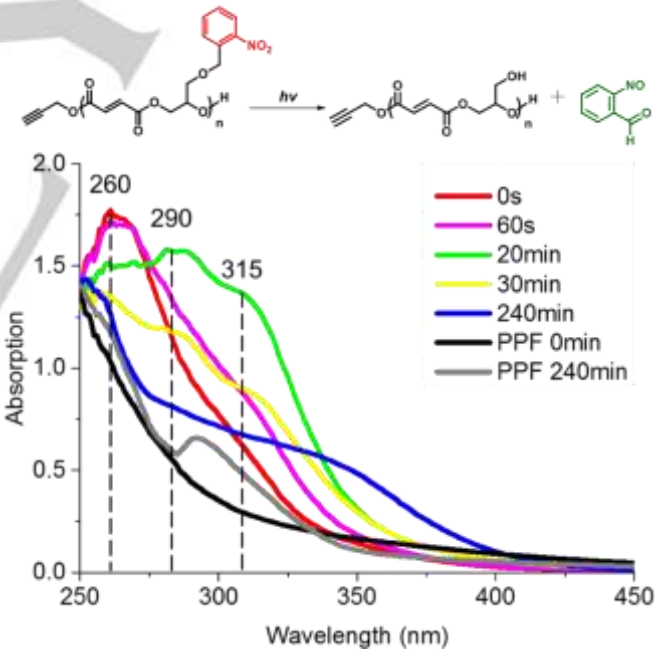

Figure 3. UV/visible spectra during photochemical reaction of PNMMOF as a function of irradiation time. Before the photoreaction, the polymer solution maximum absorption was at around 260 nm, as treatment time increased, the absorption decreased, and peaks emerged at 290 and 315 nm related to the aromatic side products.

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Table 1. Copolymerization of maleic anhydride with different epoxides

Entry	DP	[MA]:[EP]:[I]:[Cat]	Time /h	Conversion$_{MA}$[d] /%	M_n[d] /kDa	M_n[e] /kDa	M_w[e] /kDa	$Đ_M$[e]	T_g/°C
1[a]	10	10:10:1:1	24	85	1.2	2.0	2.9	1.45	10
2[a]	25	25:25:1:1	24	93	3.7	2.6	3.2	1.21	29
3[b]	10	10:10:1:1	24	96	1.3	1.1	1.4	1.29	-5
4[b]	25	25:25:1:1	24	78	2.7	1.5	1.9	1.31	-2
5[c]	10	10:10:1:1	24	65	1.0	2.0	2.3	1.20	11
6[c]	25	25:25:1:1	24	80	1.6	3.3	4.9	1.50	-5

[a] EP = epichlorohydrin. [b] EP = glycidyl propargyl ether. [c] EP = 2-(((2-nitrophenyl)methoxy)methyl)oxirane. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by SEC against poly(styrene) standards.

Additionally, since hydroxyl groups only appear after deprotection, it was expected that the polymer water solubility should change significantly. PNMMOF and the deprotected polymer PGF were put into water for one day at 25 °C. The PGF was fully dissolved to yield a light yellow solution, while PNMMOF remained insoluble. Further evidence was observed from a contact angle measurement. Following deprotection, the water contact angle on the PGF film was 35.1±1.8°, compared to the PNMMOF film which has a contact angle of 58.4±2.0°. The significant decrease of the contact angle value notes an increase in the surface hydrophilicity, which has the potential to enhance cell spreading and adhesion (**Figure 4**).[48] To demonstrate this, mouse calvarial stem cells (MC3T3-E1) were cultured onto PNNMOF and PGF coated glass slides for 48 h. Significantly higher cell spreading was observed on the PGF thin films, showing that the cells can sense the enhanced hydrophilicity of the deprotected polymer (**Figure S16).** Additionally, surface energy measurements showed that compared to PNMMOF surface energy (28.1±4.0 mJ/m^2), PGF thin film has a higher surface energy (48.8±7.4 mJ/m^2) (**Table S2)**.

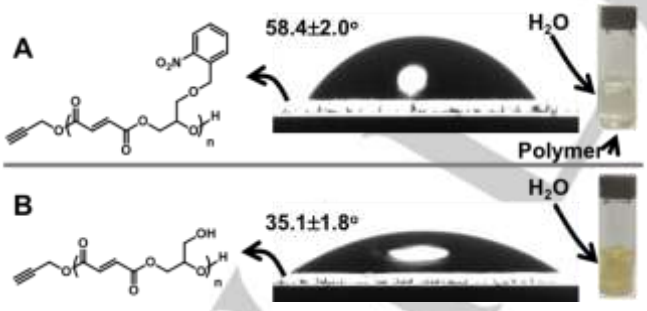

Figure 4. Static contact angle test results. The smaller contact angle of the deprotected polymer film indicated formation of hydroxyl groups. The existence of hydroxyl groups also changed polymer water solubility. The slight yellow color of the polymer water solution shows that the deprotected PNMMOF was released.

Finally, as a proof of versatility of this ROCOP method for the production of PPF analogues, statistical terpolymers were synthesized using equimolar EC, GPE and NMMO with the corresponding quantity of MA under the same conditions as above and a targeted DP of 24. After 24 h, 77% monomer conversion of MA was achieved and a 2.2 kDa (M_n, SEC) polymer was obtained. All three EP monomers were confirmed in the resultant polymer *via* ^{1}H NMR spectroscopy and MALDI-ToF MS analysis (**Figure 5 and S10**). Statistical sequencing of the terpolymer was observed through the distribution of repeat unit molecular masses. This tri-functional PPF analogue is presented as a proof of concept and further investigation into functional terpolymers is currently underway.

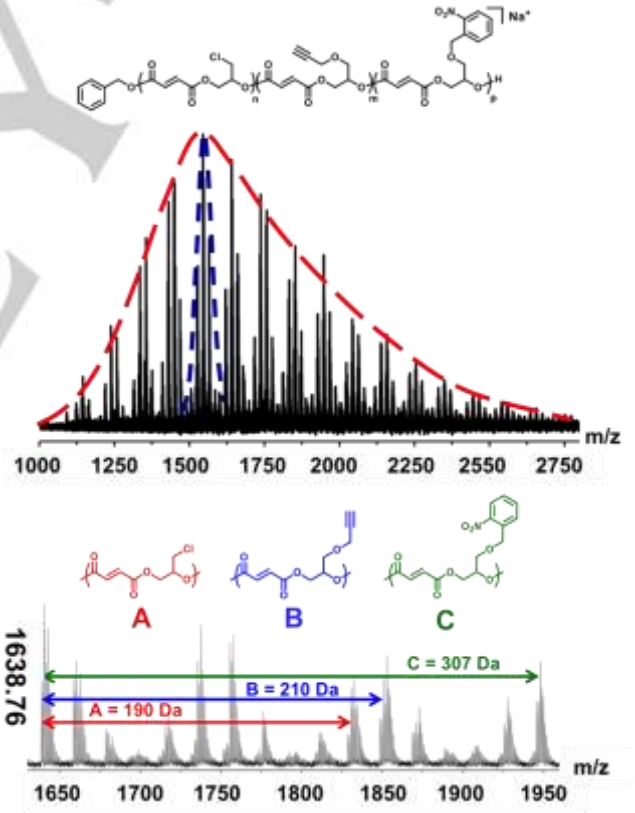

Figure 5. MALDI-ToF MS plots of target DP24 statistical terpolymers.

In summary, a comonomer modification method based on the ROCOP of MA with various epoxides was employed to yield functionalized PPF analogues. The ability to incorporate

functional groups throughout the degradable polymer chain by post-polymerization and post-printing is a significant advantage over previous non-functional PPF. Functional epoxides with chlorine (EC), alkyne (GPE) and *o*-nitrophenyl (NMMO) moieties were copolymerized with MA, which resulted in three functional PPF analogues, PEF, PGPEF and PNMMOF. ^{1}H NMR spectra and MALDI-ToF MS indicated that no non-degradable ether linkages appeared in the polymer backbone. A series of functional analogues at printable molecular masses were synthesized and it was shown that the pendent functionality could be used to modify the T_g of the polymer. This offers the potential to reduce the amount of solvent necessary in PPF resins for stereolithographic printing. Moreover, functional PPF analogues with alkyne and *o*-nitrophenyl moieties were shown to readily undergo post-polymerization modification without unwanted side reactions. Thus, these analogues can be used to attach bioactive species to printed scaffold constructs post-polymerization to enhance bioactivity, overcoming several of the limitations currently associated with PPF.

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Keywords: degradable • ring-opening copolymerization • post-polymerization modification • additive manufacturing

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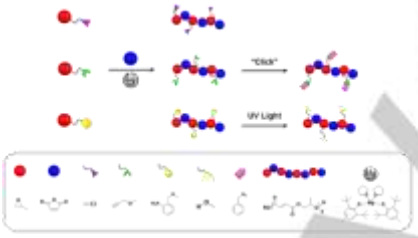
Layout 1:

COMMUNICATION

Polyester functionalization: Poly(propylene fumarate) was functionalized with chlorine, alkyne and nitrophenyl groups *via* ring-opening copolymerization of modified epoxides and maleic anhydride. These polymers can be modified by post-polymerization and post-printing modification.



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Ring-opening Copolymerization of Maleic Anhydride with Functional Epoxides to Yield Poly(propylene fumarate) Analogues Capable of Post-polymerization Modification