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A Metathesis Route for BODIPY Labeled Polyolefins

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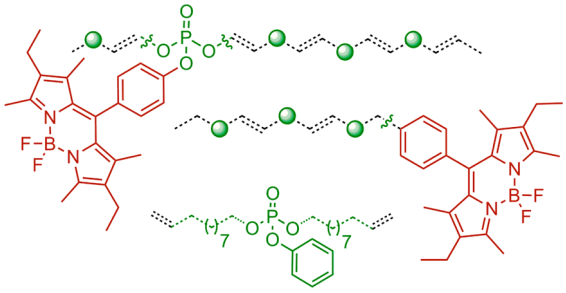
ABSTRACT



It is demonstrated how acyclic diene metathesis polymerization (ADMET) provides an efficient strategy for the labeling of polyolefins. The versatility of phosphorus chemistry allows designing substituted BODIPY monomers or chain stoppers for the synthesis of precise labeled (degradable) polyphosphoesters.

Chemical labeling exhibits great potential for obtaining traceable steadily stained materials for versatile applications such as optical bioimaging and signal amplification in biological diagnostics.[1,2] In the family of organic dyes, the set based on BODIPY (***bo*ron-*dipy*rromethene** or 4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene) has attracted increasing attention over the past decade.[3] BODIPY-based functional materials continuously expand their range of applications because of the unique photophysical properties, such as excellent thermal and photochemical stability, good solubility, and intense absorption profile. BODIPY's chemical robustness allows the design of functional systems for paint, ink compositions, and electroluminescent devices.[4]

One of the main features that makes this organic dye extremely attractive is the possibility to modify its molecular backbone in a straightforward manner. Great potential was recognized for biochemical purposes, resulting in the raised awareness of this stable dye and its use among biologists, for example for the labeling of biomacromolecules such as DNA.[5]

Because of their functionality and similarity to DNA, in recent years synthetic polyphosphoesters have attracted attention in biomaterial science.[6] Typically, polyesters dominate the field and are widely applied in pharmaceutics and medical applications, because of their excellent biocompatibility and degradability.[7]

The structural versatility of phosphorus, combined with a straightforward synthetic approach, allows generating novel functional polymerizable organophosphates.[8] These compounds can undergo acyclic diene metathesis (ADMET)

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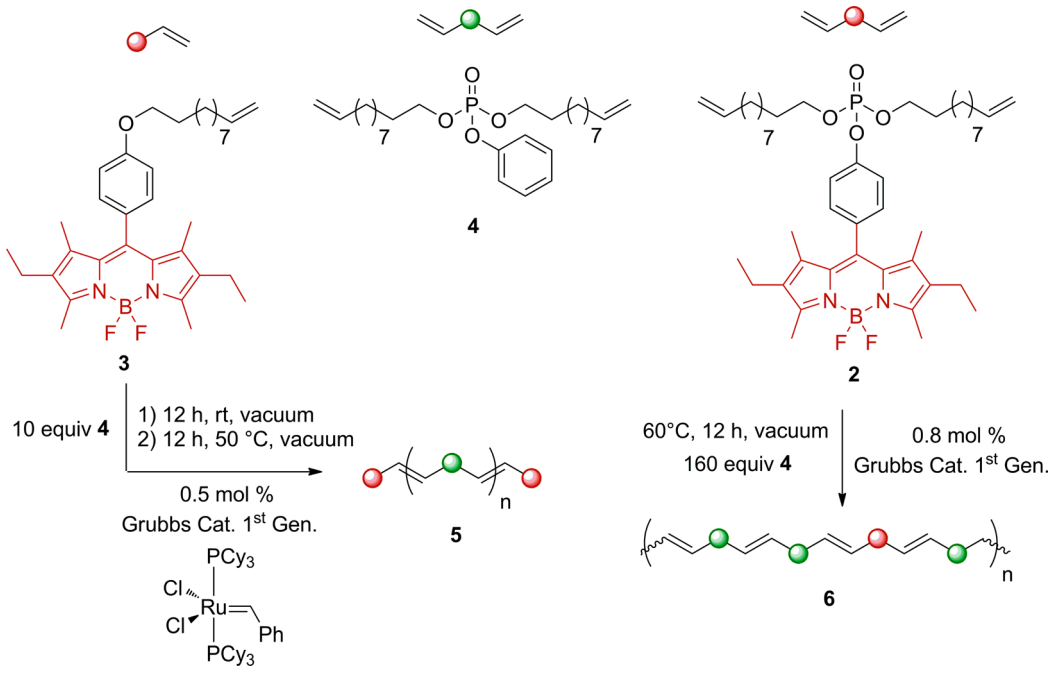
Scheme 1. Metathesis Polycondensation of Phenyl-di-(10-undecenyloxy)-phosphate **4** in Presence of BODIPY Dyes (**2** and **3**)



or ring-opening metathesis polymerization (ROMP) and thus can be converted into synthetic polyphosphoesters.

To date different strategies for the synthesis of complex BODIPY–polymer conjugates, mostly by anionic or radical polymerization, have been reported.[9] In contrast, little attention was given to the precise incorporation of these dyes into degradable polymers, which has become of particular scientific and application relevance.[1] Different synthetic strategies allow the synthesis of functional BODIPY derivatives via cross-coupling of organometallic compounds,[10] click chemistry,[11] or radical or photochemical polymerizations.[12] To the best of our knowledge, this is the first report on a strategy (Scheme 1) based on ADMET for the facile preparation of precise labeled polymers that further expand the toolbox of biodegradable polyesters based on phosphorus.

A ROMP metathesis strategy for the synthesis of fluorogenic polymers was developed by using norbornene derivatives and suitable fluorophores.[13] However this strategy is limited to only a few monomers that can be polymerized by this technique. Our model system offers many possibilities to design and label various types of polyolefins, because a wide range of functional acyclic diene monomers is available for ADMET[14] in combination with a robust synthetic protocol based on phosphorus oxychloride. Ruthenium-based complexes such as the catalysts of Grubbs provide, furthermore, an efficient and functional-group tolerant tool for olefin metathesis, under mild conditions with quantitative conversion.[15]

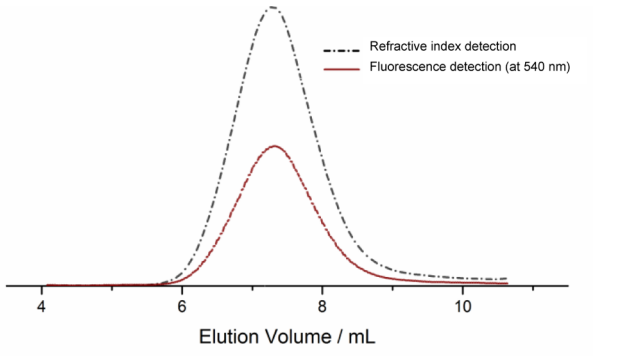


Figure 1. GPC elugram (in THF) for polymer **6** showing the fluorescence (λ = 540 nm) and the refractive index detection.

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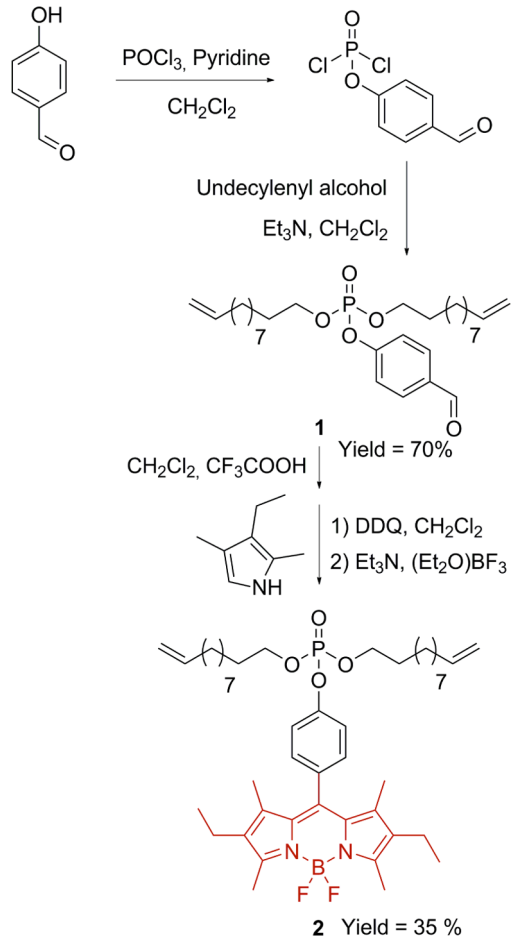
Scheme 2. Synthesis of Polymerizable BODIPY **2**



Phosphorus oxychloride is a key compound for the synthesis of structural versatile organophosphates. This intermediate can be reacted with a variety of alcohols to obtain functional and polymerizable phosphoaldehyde (**1**, Scheme 2) which is the perfect handle for building the BODIPY moiety onto the olefinic monomer (details on the synthesis of **2** and **3** can be found in the Supporting Information).

As phenyl-di-(10-undecenyloxy)-phosphate **4** is a liquid, it facilitates the bulk-metathesis copolymerization of the olefinic BODIPYs allowing the generation of high molecular weight polymers. In order to ensure covalent labeling of the polymer, **2** or **3** was used as a comonomer or chain stopper, respectively, during the polymerization. The relative amount of **2** allows tailoring the percentage of dye in the polymer, while BODIPY **3** acts as a terminating agent capping the polymer chains to allow adjusting the molecular weight and also the labeling position (at the chain ends in this case).

One important point that should be emphasized here is the possible influence of the polymer chain on the spectroscopic properties of the dye and, conversely, the influence of the dye on the polymer chain conformation. As proven by GPC equipped with a fluorescence detector (Figures 1 and S34), homogeneous labeling of the polymers is achieved. It is possible to tune the percent of labeling by

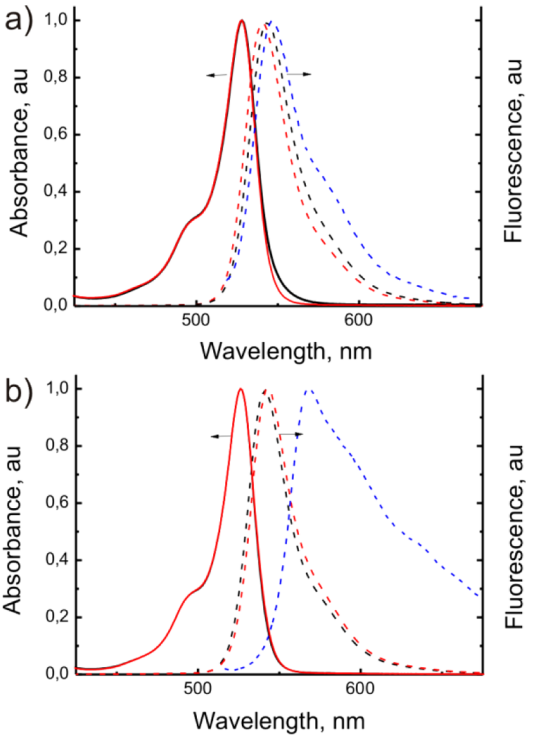
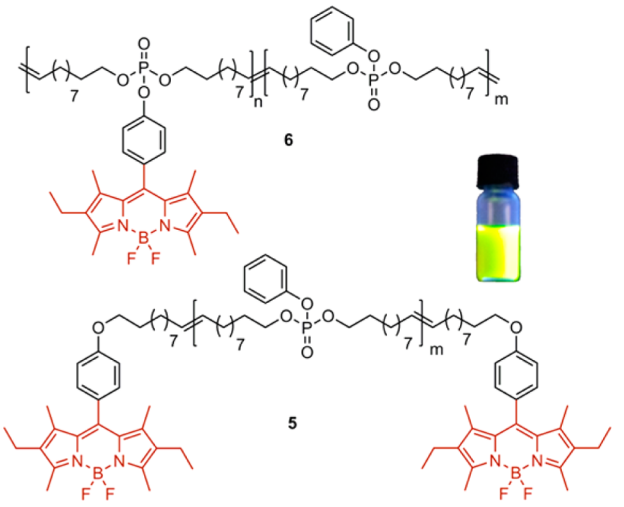


Figure 2. UV−visible (solid lines) and fluorescent spectra (dashed lines) for monomeric dyes and the respective polymers. (a) BODIPY **2** in toluene (black), polymer **6** in toluene (red), and thin solid film (blue); (b) BODIPY **3** in toluene (black), polymer **5** in toluene (red), and thin solid film (blue).

tailoring the monomer ratios as both carry electron-rich olefins, leading to random incorporation into the polymer backbone and high molecular weights via ADMET (compare Table S30 in the Supporting Information); the photophysical properties of the dye stay undisturbed after polymerization when the polymer is dissolved in organic solvent (Figure 2 and Table 1). Further, an incorporation efficiency of 100% of **2** and **3** in the polymers was obtained (Table S30). The precise percentage of labeling is crucial to maintain the conformation of the polymer chain, minimizing self-quenching between dyes in close proximity. In a second approach, we used metathesis to selectively label the end groups with **3** that acts as a chain stopper in the polycondensation reaction. In a one-step reaction, this chain stopper was allowed to introduce precisely and homogeneously the fluorescent moieties at the ends of the polymer backbone in a quantitative manner; it can also be used for labeling other compounds by cross metathesis, making it a valuable compound for future work.

More importantly, this strategy allows tailoring the desired molecular weight, as **3** is quantitatively incorporated. Telechelic polymer **5** (M_w 30 000 g/mol, polystyrene standards in THF, PDI = 1.5) with high optical absorptivity per weight of polymer was obtained (Scheme 3). These polymers are promising candidates, for example, to generate fluorescent nanoparticles that could find applications as degradable drug delivery vehicles and to monitor their cell uptake *in vitro*.

Scheme 3. Structures of Labeled Polyphosphoesters Synthesized via ADMET[a]



[a] The vial shows the fluorescence of polymer **6** in toluene.

An important property of the labeled polymer (**5**) is that the fluorescence quantum yield is very similar to the monomer (**3**) in solution but differs in the polymeric film. The decrease of the quantum yield is likely to originate from self-quenching because of the rather high dye content.

The direct copolymerization of **2** allows the high molecular weight labeled polyphosphoester **6** to be generated (M_w 170 000 g/mol, GPC polystyrene standards in THF PDI = 2.1). By this approach, we were able to increase the amount of fluorescent comonomer into the polymer chain **6a** to seven times that in **6**. This tunable labeling keeps the properties of the mother polymer less affected, demonstrating with **6a** the possibility of obtaining a bright material with a high extinction coefficient and strong fluorescence without self-quenching (Table 1).

In summary, two new BODIPY **2** and **3** derivatives have been synthesized which can be used to label polymers and other olefinic compounds via olefin metathesis. The metathesis approach offers the possibility of adjusting the quantity and labeling position at tunable positions, i.e. along the chain or at the chain end—or also via cross metathesis to other compounds. As a model we prepared unsaturated polyphosphoesters which were labeled along the chain or at the chain ends by controlling the molecular weights. This one-step olefin metathesis with mono- or difunctional BODIPY-based dyes is a general protocol to label polymers that can be prepared by ADMET, for example, to follow their cell uptake behavior which is currently under investigation in our group.

Table 1. Summary of Fluorescences of BODIPY Polymer Conjugates in Solution and Film

entry	(λ_{max}) nm	lifetime (τ) ns	quantum yield (η)
6[a]	542	4.8	0.70
6a[a]	542	4.7	0.70
5[a]	542	4.6	0.72
6[b]	547	2.4	0.51
6a[b]	546	0.95	0.09
5[b]	569	0.97	0.10

[a] Solution of polymer in toluene. [b] Polymer film.

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Supporting Information Available. Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.