Dendrimer Synthesis

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Fluoride-Promoted Esterification with Imidazolide-Activated Compounds: A Modular and Sustainable Approach to Dendrimers**

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Abstract: *Based on the growing demand for facile and sustainable synthetic methods to structurally perfect polymers, we herein describe a significant improvement of esterification reactions capitalizing on 1,1′-carbonyldiimidazole (CDI). Cesium fluoride was shown to be an essential catalyst for these reactions to reach completion. This approach was successfully applied to the synthesis of structurally flawless and highly functional polyester dendrimers employing traditional and accelerated growth strategies. A sixth generation bis-MPA dendrimer with a molecular weight of 22.080 Da and 192 peripheral hydroxy groups was isolated in less than one day of total reaction time. Large quantities of dendrimerswere obtained in high yields (>90%) using simple purification steps under sustainable conditions. The fluoride-promoted esterification (FPE) via imidazolide-activated compounds is wide in scope and constitutes a potentially new approach toward functional polymers and other materials.*

The new technological breakthroughs that are needed to sustain our modern society rely heavily on the production of highly complex molecules, which is often achieved by demanding, multi-step synthetic strategies with a large consumption of resources. Subsequently, researchers are continuously investing great efforts into the development of robust reactions that simplify the formation of complex molecules, thereby facilitating the transfer from basic research to commercial availability. A clear example is the concept of "click chemistry" introduced by Sharpless.[1] This concept comprises a family of chemical reactions that proceed efficiently under mild conditions, are regioselective, and show a high tolerance toward different functional groups and solvents. In materials science, polymer chemists often capitalize on verified synthetic concepts that generate complex macromolecular structures. As the synthesis of "flawless" dendrimers is challenging, they represent ideal test candidates for highly reliable chemical reactions. Thus, to enable the transfer of click chemistry from the synthesis of small molecules to more complex macromolecules, the applicability of the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) was originally demonstrated by the formation of a library of dendrimers.[2]

Biocompatible and biodegradable aliphatic polyesters based on 2,2-bismethylolpropionic acid (bis-MPA) as the building block belong to the most versatile dendritic polymers, and arrays of dendritic structures have been successfully synthesized. Synthetic methodstoward bis-MPA-based scaffolds are characterized by mild reaction conditions and high yields. Traditional synthetic approaches to these scaffolds are based on the use of the coupling reagent *N*,*N*′-dicyclohexylcarbodiimide (DCC), either for the in situ activation of an acetal-protected bis-MPA monomer[3] or for the generation of the anhydride derivative,[4,5] followed in both cases by the reaction with a free hydroxy group of the framework. Although these protocols are highly efficient, they are limited by tedious purification steps, excessive loss of reagents, and controversial reaction conditions, including the use of toxic pyridine, 4-(dimethylamino)pyridine (DMAP), and 4-(dimethylamino)pyridinium-4-toluenesulfonate (DPTS) along with carcinogenic chlorinated solvents.[6] An attractive alternative is the use of 1,1′-carbonyldiimidazole (CDI) as a coupling reagent, as it meets the three requisites for medicinal chemistry, that is, it has a wide utility and scalability, and is "green".[7] CDI has been successfully employed in the synthesis of a library of dendrimers based on, for example, polyurethane, polycarbonate, and polyamide,[8–12] and for post-functionalization purposes.[13–14] However, the synthesis of dendrimers based on polyester was thus far less successful, with low yields and long reaction times.[15]

We herein propose an efficient, scalable, and sustainable esterification approach with CDI as the coupling reagent and cesium fluoride (CsF) as an essential catalyst. The efficiency and robustness of the reaction were benchmarked by the synthesis of a library of structurally diverse bis-MPA dendrimers through a divergent growth approach. The strategy relies on the in situ generation of imidazolide-activated monomers in ethyl acetate and their efficient use in esterification reactions with the hydroxy groups of the macromolecular scaffolds (Scheme 1).

In our search for a new and robust synthetic methodology toward complex aliphatic polyesters, three main hurdles were identified: 1) to eliminate the use of an anhydride-activated bis-MPA monomer in order to reduce the loss of the valuable and derivatized bis-MPA unit, 2) to avoid the use of controversial DMAP, DPTS, pyridine, and CH_2Cl_2, and 3) to surpass the robustness of the current anhydride method with regard to scalability and versatility. To overcome these limitations, CDI was used as a mild and versatile coupling reagent that fulfils all desired requirements for dendrimer and

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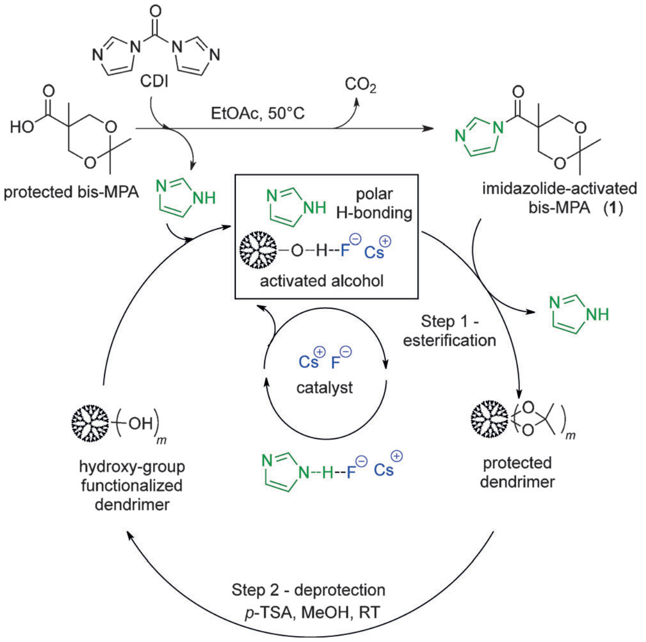


Scheme 1. Two-step synthesis of bis-MPA dendrimers through the FPE approach, depicting the important role of imidazole and CsF.

green chemistry. CDI is commercially available in kilogram quantities and cheap, and releases CO_2 and imidazole as unique by-products.

The acetonide-protected bis-MPA monomer was reacted with one equivalent of CDI in EtOAc for 1 h at 50 °C to generate the corresponding activated imidazolide (**1**) with around 100 % conversion, along with free imidazole and CO_2 (Scheme 1). While the intermediate could be successfully isolated through simple precipitation, an in situ reaction with hydroxy groups was pursued, as it eliminates time-consuming purification steps and the excessive use of resources. An interesting aspect of the in situ acylation with CDI is the polar H-bonding nature of the leaving group, imidazole, which is capable of solubilizing hydroxy-functionalized dendrimers of higher generations. This aspect overcomes one of the main obstacles in the divergent growth approach toward bis-MPA dendrimers, and the released imidazole becomes a good alternative to pyridine, which is traditionally used in large quantities in anhydride-promoted esterifications.[6] Thus, in contrast to earlier reports on the use of CDI as reagent in the synthesis of dendrimers,[8–12] we exploited its use in the large-scale synthesis of dendrimers by a divergent growth approach. However, this growth approach is known for challenging conversions of the dendrimers of higher generations and typically requires the use of DMAP as a catalyst.[5] Alkali metal fluorides have been widely studied in organic synthesis for base-assisted substitution reactions, proceeding under essentially neutral conditions.[16] Cesium fluoride (CsF) proved to be an attractive candidate, given its high activity and moderate solubility in organic solvents. Importantly, to our knowledge, the influence of fluoride anions together with imidazolide-activated acids on esterification reactions has to date not been reported.

Trimethylolpropane (TMP) was chosen as a model substrate for the in situ reaction with the activated monomer **1** (Scheme 2). TMP and a catalytic amount of CsF (0.2 equiv per OH group) were added to a solution of **1** (1.5 equiv per OH group) in EtOAc. The reaction reached completion within 30 min at 50 °C. Excess imidazolide monomer **1** was quenched with water, and a simple work-up through washing with $NaHCO_3$ (aq.) afforded the first-generation acetonide-protected dendrimer TMP[G1](acet)$_3$ (**2**) as a white solid in 92 % yield. The subsequent deprotection was carried out under simple conditions, that is, in 1 h at room temperature in MeOH using *p*-TSA (10 wt %) as acidic catalyst. The solution was then filtered through an Amberlyst A21 column to remove the catalyst, followed by evaporation, which quantitatively afforded dendrimer TMP[G$_1$](OH)$_6$ (**3**) as a white solid (Scheme 2 A). The iterative growth/deprotection steps of bis-MPA dendrimers through FPE was carried out with unprecedented efficiency, and the sixth-generation monodisperse dendrimer TMP[G$_6$](OH)$_{192}$ (**13**) was obtained in less than 24 h total reaction time and with yields of more than 90 % on a 50 g scale (Figure 1, Table 1). All reactions were followed by ^1H and ^{13}C NMR spectroscopy and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (see the Supporting Information).

In order to better understand the kinetics involved in FPE, the synthesis of the fourth-generation dendrimer TMP[G$_4$](acet)$_{24}$ (**8**) from TMP[G$_3$](OH)$_{24}$ (**7**) was investigated further. The conversion of **7** (1.3 M initial OH concentration) to **8** was monitored by MALDI-TOF MS (Figure 2). In all experiments, the spectra showed a narrow distribution, with a progressively increasing number-average molecular weight (M_n) and decreasing polydispersity index (PDI) over time (Figure S1 in the Supporting Information). The influence of fluoride anions was studied at various fluoride/hydroxy group ratios, with 0.06–0.24 equivalents of fluoride ions per OH group. The noncatalyzed control reaction reached 93 % conversion after 8 h and failed to reach completion after 18 h. This plateau effect at high conversions could be explained by

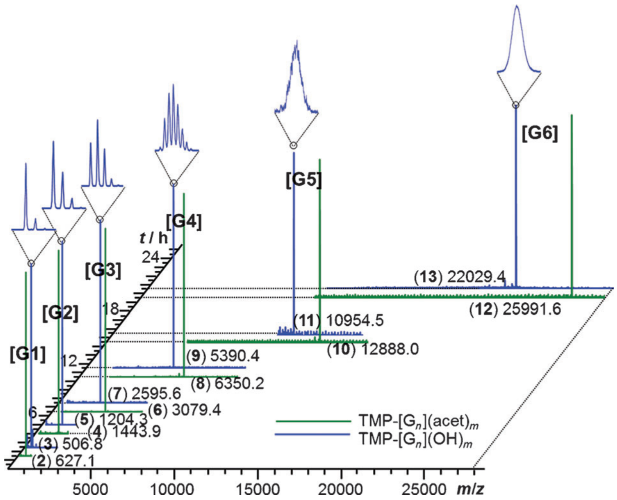
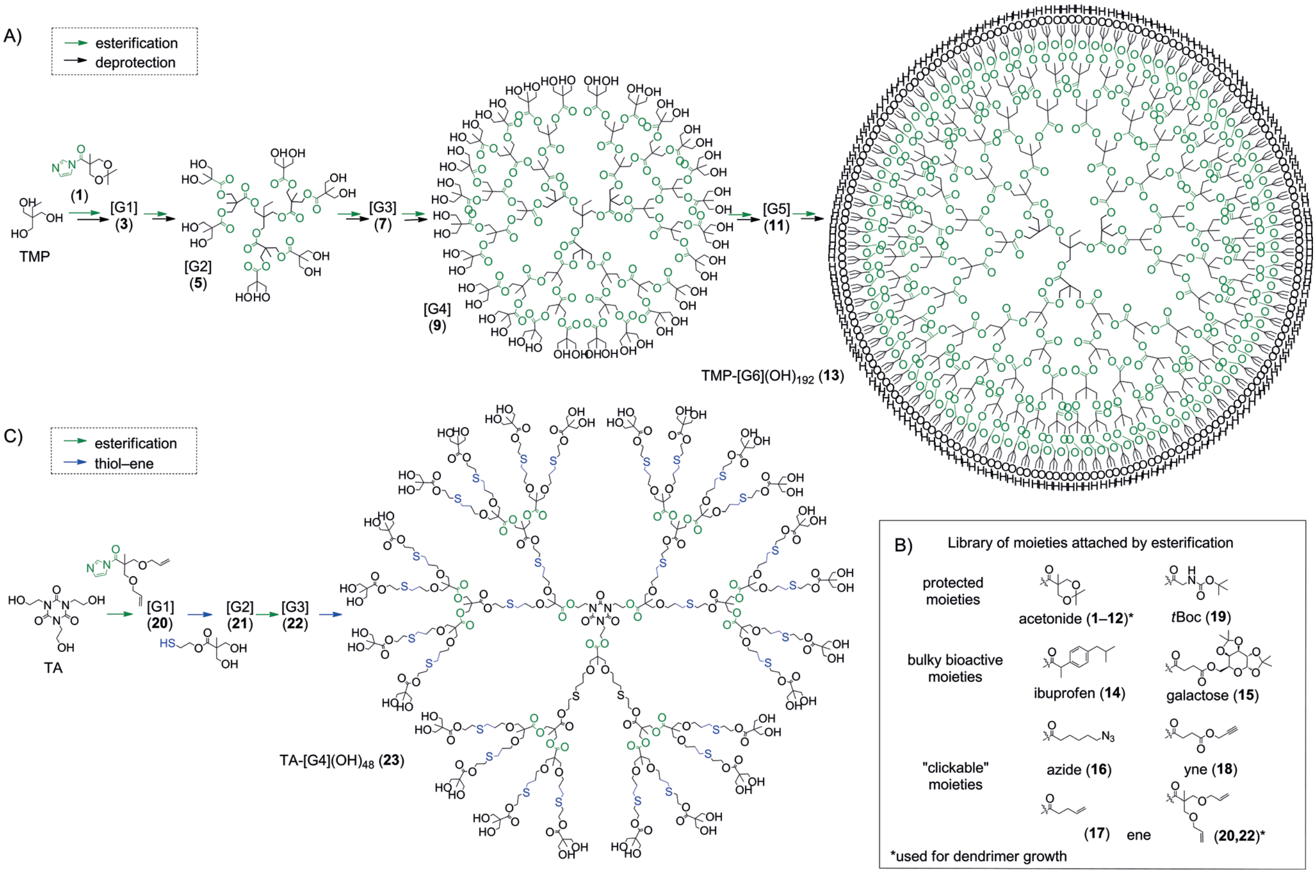


Figure 1. MALDI-TOF MS spectra of bis-MPA dendrimers from first (**G1**) to sixth (**G6**) generation and the accumulative reaction time for their synthesis. Experimental *m*/*z* values for [M+Na$^+$] are depicted in the figure. Theoretical *m*/*z* values for [M^+]: 602.3 (**2**), 482.2 (**3**), 1418.7 (**4**), 1178.5 (**5**), 3052.5 (**6**), 2571.1 (**7**), 6317.0 (**8**), 5356.2 (**9**), 12 848.0 (**10**), 10 926.5 (**11**), 25 910.0 (**12**), 22 067.0 (**13**).



Scheme 2. Versatility and robustness of the FPE approach in the growth of dendrimers up to the sixth generation (A), postfunctionalization (B), and accelerated growth (C).

Table 1: Comparison of strategies toward acetonide-protected bis-MPA dendrimers. Undesirable and preferred reagents are depicted in red and green, respectively, depending on the criteria for medicinal chemistry.[7]

Coupling reagent	$[G_{max}]$ (M_w)	Reagents and solvents	Purification by	Reaction time [h]/ Yield [%]	Ref.
DCC	G4 (6493)	DPTS CH_2Cl_2	chromatography	24 85	[3]
anhydride	G4 (6437)	Pyr/ DMAP CH_2Cl_2	extraction and chromatography	18 88	[5]
CDI	G6 (25 926)	CsF EtOAc	extraction	3 90	this work

M_w = weight-average molecular weight, Pyr = pyridine.

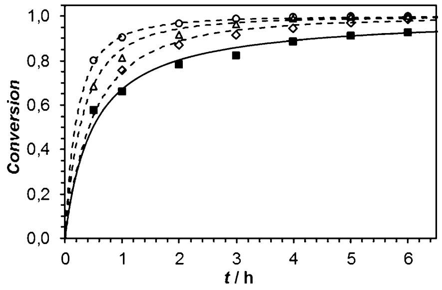


Figure 2. Conversion of TMP[G3](OH)$_{24}$ (**7**) to TMP[G4](acet)$_{24}$ (**8**) versus time for different fluoride/OH ratios: 6% (◇), 12% (△), 24% (○), and no catalyst (■). Data obtained by a Bruker Ultraflex MALDI-TOF (reflector mode, final *m*/*z* calc. 6316.98). Lines depict theoretical fitting through equations in Figure S2.

a second-order dependence on [OH] (Figure 2). A catalytic amount of CsF could overcome these kinetic barriers and push the esterification to full conversion. In catalyzed reactions, a different mechanism seems to prevail at high conversions, based on a more complex rate law. This observation is in agreement with findings suggesting that the strong H-bonding potential of fluoride anions can greatly enhance the nucleophilicity of protic compounds by transferring electron density, in our case, from F^- to the peripheral hydroxy groups of the dendrimer.[16] As depicted in Figures 2 and S3, the reaction rate increases with [CsF], and full conversion was achieved within 2–3 h for the highest concentration.

Fluoride-assisted substitution reactions are influenced by the relative strength of different electron acceptors in solution through competitive H-bonding.[17] The catalytic effect of fluoride anions in FPE is not inhibited by the presence of significant amounts of imidazoles generated in situ (Figure 2). However, competitive inhibition was observed when a stronger electron acceptor, such as the non-activated acid, was added in excess, and full conversion was not reached after 18 h. Consequently, FPE relies heavily on minimizing the production or presence of competing acids, which would otherwise affect the overall reaction rate.

The fluoride-promoted esterification approach is remarkable, as it delivers a monodisperse sixth-generation dendrimer with 192 peripheral reactive groups in 12 consecutive steps, in less than one day of reaction time and with high yields, simple purifications, and under sustainable conditions. To further demonstrate the versatility of the proposed reaction protocol, dendrimer TMP[G_3]$(OH)_{24}$ (**7**) was chosen as model scaffold for post-functionalization with a library of functional carboxylic acids (Scheme 2B). These were carefully selected to include clickable groups, bioactive ibuprofen, and protected derivatives of galactose and glycine. All carboxylic acids were activated to imidazolide derivatives and then subjected to the established esterification protocol, leading to an array of functionalized pseudo-G4 dendrimers (**14**–**19**) with yields above 90%. In most cases, the esterification reached full conversion within 4 h. For ibuprofen and galactose derivatives, longer reaction times were required, presumably because of the crowded environment in the outer shell toward the end of the reaction. The versatility of the esterification protocol is displayed by the apparent tolerance toward functional groups, including protective groups such as acetonide and *tert*-butyloxycarbonyl (Boc), and reactive groups such as alkenes, alkynes, and azides.

We finally pursued the formation of novel dendrimers through the orthogonal growth approach (Scheme 2C),[18–21] which simplifies and accelerates the synthesis of dendrimers.[20] The orthogonal growth approach capitalizes on two distinctly different monomers (AB_2 and CD_2) that react through two chemoselective reactions. As a result, the dendrimers undergo continuous growth with each reaction step, reaching a fourth-generation dendrimer in four reaction steps. A number of bis-MPA-based dendrimers have been prepared by employing an orthogonal growth approach that combines the selectivity of click chemistry with esterification reactions.[18] In our case, the esterification reaction is combined with UV-initiated thiol–ene coupling (TEC) using imidazolide-activated 3-(allyloxy)-2-((allyloxy)methyl)-2-methylpropanoic acid (iBAPA) as an AB_2 monomer and 2-mercaptoethyl-3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate (HS-bis-MPA) as a complementary CD_2 monomer. 1,3,5-Tris(2-hydroxyethyl)-1,3,5-triazine-2,4,6-trione (TA) was used as a rigid core to react with the the iBAPA AB_2 monomer by esterification (Scheme 2C). The reaction reached completion within 30 min at 50°C in EtOAc. After work-up, the fully activated and allyl-functionalized dendrimer TA[G_1]$(allyl)_6$ (**20**) was isolated as a yellow oil in 98% yield. The growth to the second-generation dendrimer was achieved through TEC with the CD_2 monomer HS-bis-MPA in the presence of photoinitiator Irgacure 691. Complete substitution was achieved after 30 min of exposure to UV light at 365 nm, and the hydroxy-functionalized dendrimer TA[G_2]$(OH)_{12}$ (**21**) was purified by flash chromatography. Iterative growth resulted in bis-MPA dendrimers TA[G_3]-$(allyl)_{24}$ (**22**) and TA[G_4]$(OH)_{48}$ (**23**) with internal thioether linkages in high yields.

In summary, we reported a novel, efficient, scalable, and sustainable esterification approach to advanced macromolecules via imidazolide-activated monomers in the presence of cesium fluoride (CsF) as an essential catalyst. This robust synthetic methodology delivered a library of complex aliphatic polyesters without the loss of valuable and derivatized monomers, and eliminates the need for harmful reagents and solvents. A sixth-generation monodisperse bis-MPA dendrimer with a molecular weight of 22.080 Da and 192 peripheral hydroxy groups was successfully synthesized in less than one day of total reaction time, in high yields, and with simple purification steps. The approach was also successfully employed to generate dendrimers in an accelerated and chemoselective manner.

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