

Convergent Synthesis of Geometrically Disassembling Dendrimers using Cu(I)-Catalyzed C–O Bond Formation

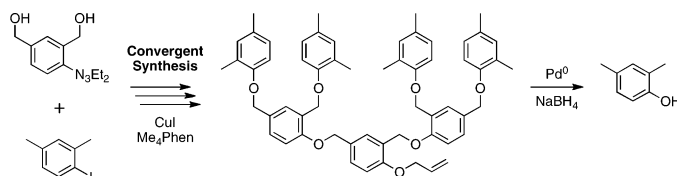
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Received September 1, 2010

ABSTRACT



The convergent synthesis of geometrically degradable dendrimers based on the 2,4-bis(hydroxymethyl)phenol subunit is presented. The key step of the synthetic scheme involves the CuI/3,4,7,8-tetramethyl-1,10-phenanthroline-catalyzed coupling of aryl iodides and alcohols. The synthesis and disassembly of these compounds is discussed.

Dendrimers¹ are a widely studied class of globular polymeric materials with applications ranging from nanomaterials² to drug delivery.^{3,4} The ability to control the degradation of dendrimers has gained much attention in recent years due to attractive potential applications in nanomedicine and materials chemistry.⁵ Of particular interest is the preparation of geometrically disassembling (a.k.a. self-immolative) dendrimers^{3,6} that represent an efficient cleavage process where multiple disassembly pathways within the dendrimer subunit are triggered by a single stimulus. Disassembling systems, both dendritic and polymeric, have been applied to drug loading and release,⁷ detectors,⁸ signal amplifiers,⁹ and de-

gradable nanoparticles.¹⁰ To date, the synthesis of our geometrically disassembling dendrimers has followed divergent methods. While viable for preparing materials up to the second-generation,¹¹ complications such as poor solubility and incomplete reactions at the periphery¹² make the divergent route less desirable for producing higher-generation dendrimers of suitable purity. Generating large quantities of these compounds will require convergent synthetic strategies.¹³ In addition, a convergent strategy for preparing these disassembling systems would allow the installation of the trigger moiety at the final stage of the synthesis.

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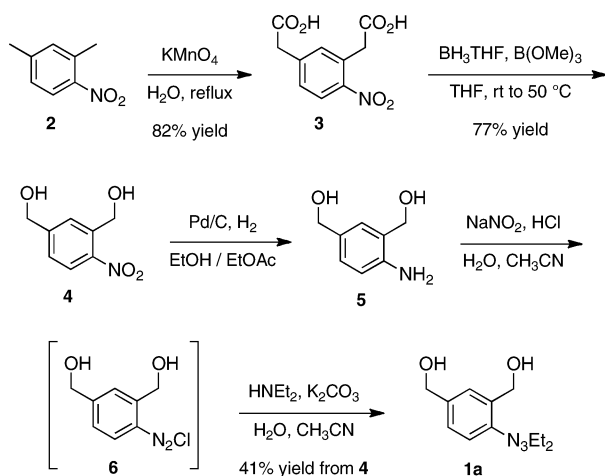
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Herein we report a convergent synthetic route using the Cu(I)-catalyzed coupling of aryl halides and alcohols to prepare geometrically degradable dendrimers based on the 2,4-bis(hydroxymethyl)phenol subunit.¹¹ While Cu(I)-catalyzed Ullmann-type¹⁴ coupling reactions of aryl halides and alcohols have been known for some time,¹⁵ most reports require the use of large excesses of alcohols¹⁶ and/or high temperatures,¹⁷ making these protocols undesirable when coupling valuable alcohols or temperature-sensitive functional groups. A recent report by Buchwald demonstrated improved coupling yields with only slight excesses of substrates by including Me₄Phen¹⁸ in the reaction mixture.¹⁹ This system served as the basis of our convergent synthetic route.

Our convergent disassembling dendrimer synthesis uses the key compound aryldiethyltriazene diol **1a**. The aryldiethyltriazene functionality can be efficiently transformed into an aryl iodide,²⁰ and so was chosen to act as a masked arylhalide during the coupling reaction. Synthesis of aryldiethyltriazene **1a** began with the oxidation of commercially available 2,4-dimethylnitrobenzene (**2**), followed by reduction of the diacid **3** to give nitrodiol **4** in good yield (Scheme 1). Reduction of

Scheme 1. Synthesis of Diethyltriazene Diol **1a**

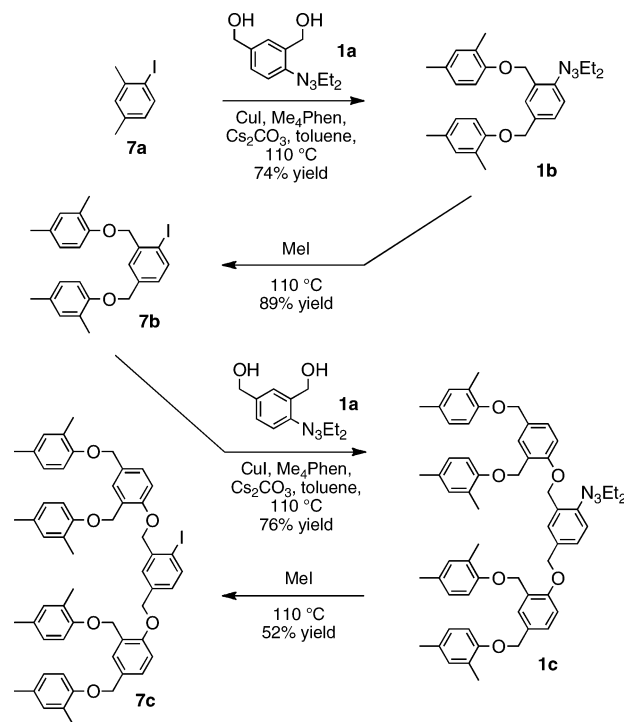


the nitro group of **4** to the corresponding arylamine **5** was accomplished using Pd/C under a H₂ atmosphere. Reaction of crude **5** with NaNO₂ and HCl, immediately followed by addition of HNEt₂ and K₂CO₃, gave the desired aryldiethyltriazene diol **1a** in 41% yield from **4**.

Aryldiethyltriazene diol **1a** was coupled to 4-iodo-*m*-xylene (**7a**) in toluene in the presence of CuI/Me₄Phen/

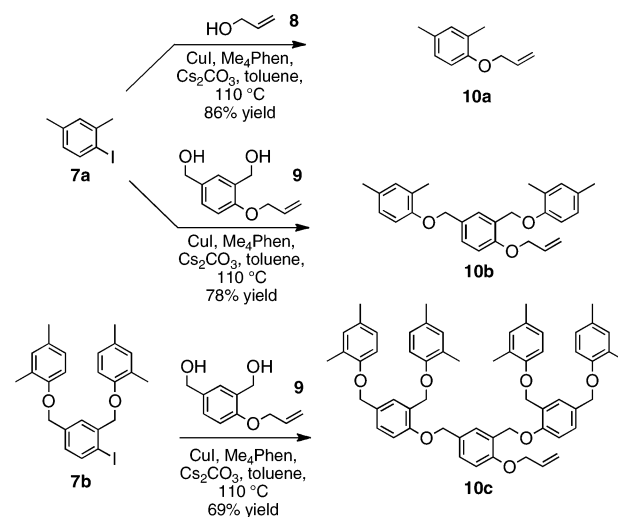
Cs₂CO₃ under air-free conditions at 110 °C for 24 h (Scheme 2).¹⁹ The coupling occurred efficiently, giving first-generation

Scheme 2. Convergent Synthesis of Compounds **1b,c** and **7b,c**



aryldiethyltriazene **1b** in 74% yield. Conversion of **1b** to first-generation aryl iodide **7b** by reaction with CH₃I at 110 °C in a sealed vessel occurred in 89% yield. First-generation aryl iodide **7b** was then reacted with diol **1a** under the same coupling conditions to give second-generation aryldiethyltriazene **1c** in 76% yield. Finally, reaction of **1c** with CH₃I gave second-generation aryl iodide **7c** in 52% yield.²¹

Scheme 3. Synthesis of Geometrically Degradable Compounds **10a–c**



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With the aryl iodide dendrons in hand, the next step was the synthesis of the geometrically degradable dendrimers. On the basis of previous work from our lab, the *O*-aryllallyl moiety was chosen as the trigger group.^{11b,22} Compounds **10a–c** were obtained in good yield using the same Cu(I)/Me₄Phen-catalyzed ether formation from aryl iodides **7a** and **7b** (Scheme 3).²³ All reactions proceeded smoothly, producing compounds **10a**, **10b**, and **10c** in 86%, 78%, and 69% yield, respectively. The compounds were easily obtained in high purity as evidenced by NMR, elemental analysis, and GPC. Elution volumes of aryl iodides **7b,c** and degradable compounds **10a–c**, determined by GPC (Figure 1), confirmed

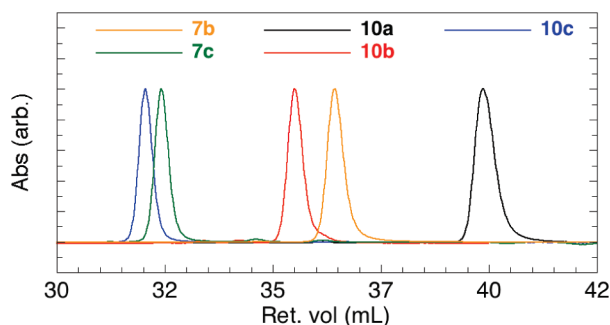


Figure 1. GPC chromatograms of aryl iodides **7b,c** and degradable compounds **10a–10c**.

increasing hydrodynamic size with increasing dendrimer generation.

We investigated the geometric disassembly process by treatment of **10a–c** with a combination of Pd⁰ and NaBH₄, standard conditions for allyl deprotection. Since the byproduct of disassembly was predominantly 2,4-dimethylphenol (**11**), we could readily monitor the reactions by ¹H NMR. Using our previously reported Pd(PPh₃)₄/NaBH₄/DMF

Table 1. Disassembly of Dendrimers **10a–c**

	10a : n = 0				12a : n = 0	
	10b : n = 1				12b : n = 1	
	10c : n = 2				12c : n = 2	
	11					
entry	compd	cat.	solvent	11 ^a	12 ^a	yield ^b
1	10a	Pd(PPh ₃) ₄	DMF	>99	—	93
2	10b	Pd(PPh ₃) ₄	DMF	>96	—	89
3	10c	Pd(PPh ₃) ₄	DMF	>99	—	93
4	10a	Pd/C	THF	55	45	54
5	10b	Pd/C	THF	70	24	70
6	10c	Pd/C	THF	83	9	80

^a Percent relative to reaction mixture determined by ¹H NMR. ^b Purified yield of a 100 mg scale reaction after column chromatography.

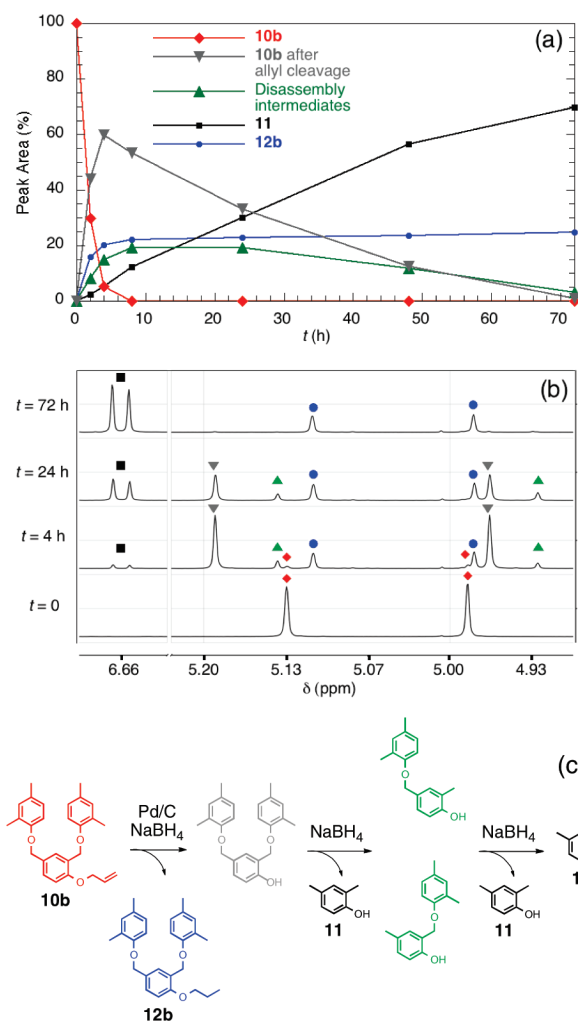


Figure 2. (a) Disassembly of compound **10b** with Pd/C/NaBH₄ in THF monitored by ¹H NMR. (b) Stack plot of selected regions of the ¹H NMR during disassembly of compound **10b** at several time intervals. (c) Proposed disassembly pathway and identity of intermediates of compound **10b** with Pd/C/NaBH₄ in THF.

conditions,^{11b,22,24} we observed nearly quantitative conversion of **10a–c** to **11** within 30 min (Table 1, entries 1–3). Preparative-scale disassembly reactions (100 mg scale) also proceeded smoothly, resulting in purified yields of **11** of 93%, 89%, and 93% from **10a**, **10b**, and **10c**, respectively.

Allyl deprotection of **10a–c** was also accomplished with heterogeneous Pd/C²⁵ as a source of Pd⁰ in THF. The Pd/C/NaBH₄/THF system offers several advantages compared

(21) A typical procedure for Cu(I)-catalyzed C–O bond formation was as follows: Diethyltriazene **1a** (2.00 g, 8.42 mmol), 4-iodo-*m*-xylene (**7a**) (4.90 g, 21.1 mmol), CuI (160 mg, 0.842 mmol), Me₄Phen (398 mg, 1.68 mmol), Cs₂CO₃ (6.86 g, 21.2 mmol), and toluene (3.0 mL) were added to a heavy-walled Schlenk flask. Four cycles of freeze–pump–thaw were performed, followed by sealing the flask and heating to 110 °C with stirring for 72 h. The reaction mixture was cooled to RT, diluted with EtOAc (10 mL), and filtered. The filtrate was washed several times with EtOAc and concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel; CH₂Cl₂:hexanes (3:7)) to give **1b** (2.81 g, 74% yield) as a red glassy solid.

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to Pd(PPh₃)₄/NaBH₄/DMF including lower cost, better catalyst shelf stability, and removal of catalyst from the reaction mixture by filtration, albeit with increased reaction times and lower isolated yields of **11** (Table 1, entries 4–6). The reason for the decreased yields of **11** was elucidated by following the reaction progress of the disassembly of compounds **10a–c** by NMR for the Pd/C/NaBH₄ system in THF. We observed competition between the desired allyl-deprotection/disassembly process and hydrogenation²⁶ of the allyl group to propyl ethers **12a–c** (Table 1).

The disassembly of first-generation dendrimer **10b** could be monitored particularly closely, as the allyl cleavage, hydrogenation to **12b**, disassembly to **11**, and all disassembly intermediates were clearly visible in the benzylic region of the ¹H NMR spectrum throughout the course of the reaction (Figure 2). Interestingly, as the dendrimer generation increased, higher preference for allyl cleavage, and therefore desired disassembly to **11**, was seen (Table 1, entries 4–6). A similar evolution was observed during the disassembly of **10a** and **10c**. Due to the increased complexity of the structure of **10c**, only the disassembly to **11** and appearance of **12c** could be monitored (see Supporting Information). Methods to increase the selectivity of the Pd/C/NaBH₄/THF system are currently under investigation.

In summary, we have demonstrated a new convergent synthetic strategy for the preparation of geometrically disassembling dendrimers utilizing Cu(I)/Me₄Phen-catalyzed

ether formation.¹⁹ Disassembly of the resulting compounds occurs cleanly and rapidly using Pd(PPh₃)₄/NaBH₄ in DMF. We have also introduced the Pd/C/NaBH₄/THF system as a viable method for initiating disassembly with allyl ether triggers. The application of these methods to higher-generation dendrimers and different dendrimer assemblies is currently underway.

Acknowledgment. The authors acknowledge financial support from the National Science Foundation (CHE-0719437). We thank Steve Buchwald for helpful discussions.

Supporting Information Available: Synthetic details and characterization data for all new compounds and ¹H NMR spectra of the disassembly of compounds **10a–c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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