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

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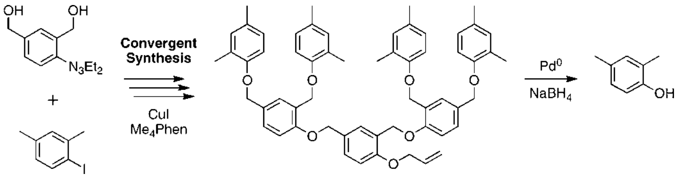
ABSTRACT



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.

Dendrimers[1] are a widely studied class of globular polymeric materials with applications ranging from nanomaterials[2] 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 degradable 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 periphery[12] 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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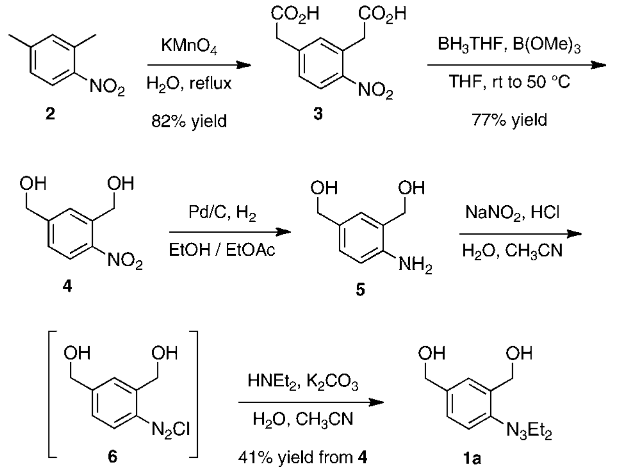
Herein we report a convergent synthetic route using the Cu(I)-catalyzed coupling of aryl halides and alcohols to prepare geometrically degradable dendrimers based on the 2,4-bis(hydroxymethyl)phenol subunit.[11] While Cu(I)-catalyzed Ullmann-type[14] coupling reactions of aryl halides and alcohols have been known for some time,[15] most reports require the use of large excesses of alcohols[16] 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 Me_4Phen[18] in the reaction mixture.[19] This system served as the basis of our convergent synthetic route.

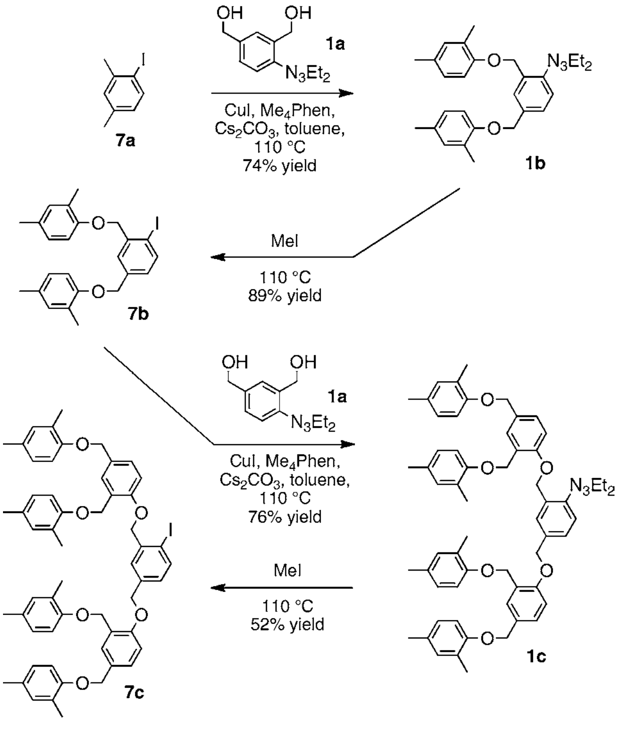
Our convergent disassembling dendrimer synthesis uses the key compound aryldiethyltriazene diol **1a**. The aryldiethyltriazene functionality can be efficiently transformed into an aryliodide,[20] and so was chosen to act as a masked arylhalide during the coupling reaction. Synthesis of aryldiethyltriazene **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 the nitro group of **4** to the corresponding arylamine **5** was accomplished using Pd/C under a H_2 atmosphere. Reaction of crude **5** with $NaNO_2$ and HCl, immediately followed by addition of $HNEt_2$ and K_2CO_3, gave the desired aryldiethyltriazene diol **1a** in 41% yield from **4**.

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

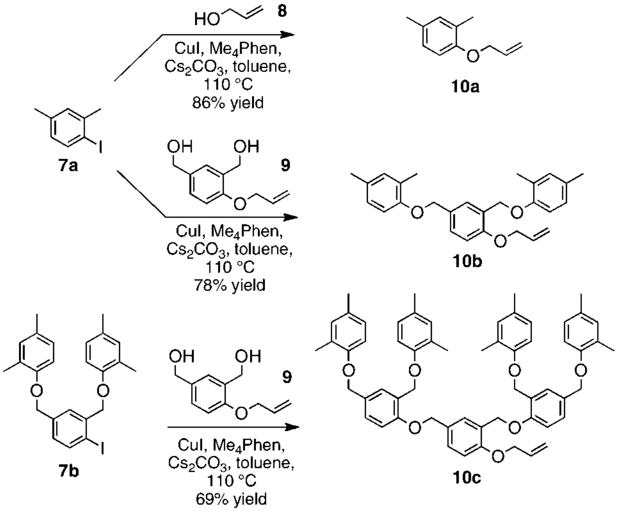


Aryldiethyltriazene diol **1a** was coupled to 4-iodo-*m*-xylene (**7a**) in toluene in the presence of CuI/Me_4Phen/Cs_2CO_3 under air-free conditions at 110 °C for 24 h (Scheme 2).[19] The coupling occurred efficiently, giving first-generation aryldiethyltriazene **1b** in 74% yield. Conversion of **1b** to first-generation aryliodide **7b** by reaction with CH_3I at 110 °C in a sealed vessel occurred in 89% yield. First-generation aryliodide **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 CH_3I gave second-generation aryliodide **7c** in 52% yield.[21]

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



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



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With the aryliodide 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*-arylallyl moiety was chosen as the trigger group.[11b,22] Compounds **10a**−**c** were obtained in good yield using the same Cu(I)/Me$_4$Phen-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 aryliodides **7b**,**c** and degradable compounds **10a**−**c**, determined by GPC (Figure 1), confirmed increasing hydrodynamic size with increasing dendrimer generation.

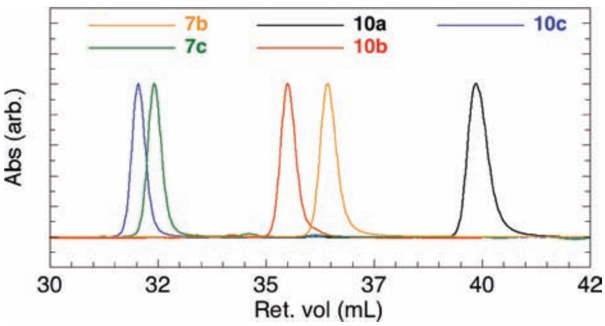
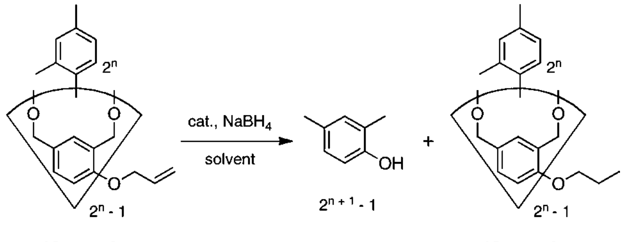


Figure 1. GPC chromatograms of aryliodides **7b**,**c** and degradable compounds **10a**−**10c**.

We investigated the geometric disassembly process by treatment of **10a**−**c** with a combination of Pd^0 and NaBH$_4$, standard conditions for allyl deprotection. Since the byproduct of disassembly was predominantly 2,4-dimethylphenol (**11**), we could readily monitor the reactions by ^{1}H NMR. Using our previously reported Pd(PPh$_3$)$_4$/NaBH$_4$/DMF 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.

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



10a: n = 0
10b: n = 1
10c: n = 2

11

12a: n = 0
12b: n = 1
12c: n = 2

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 ^{1}H NMR. [b] Purified yield of a 100 mg scale reaction after column chromatography.

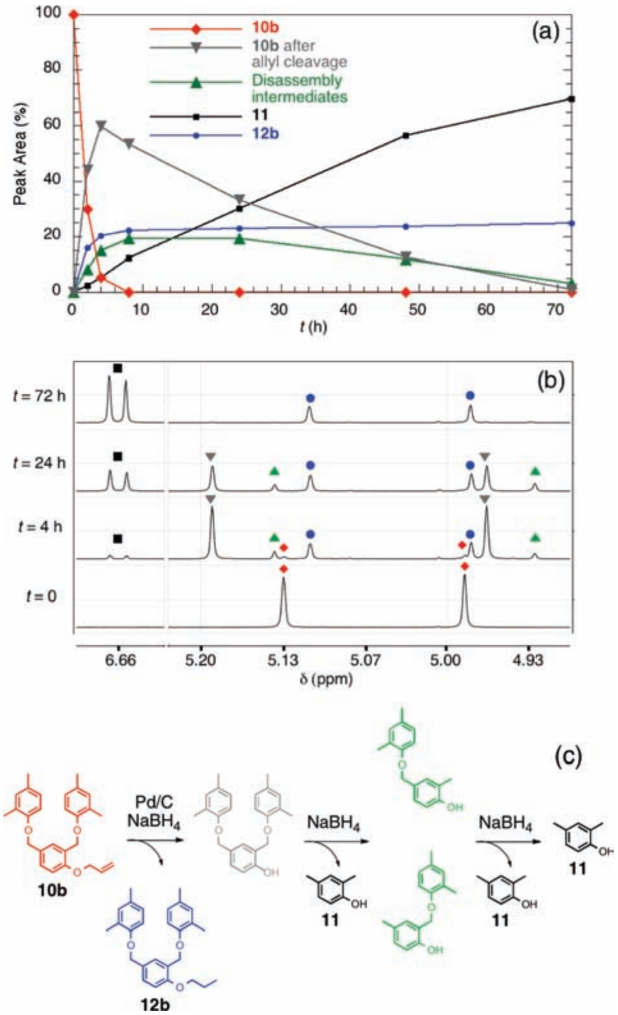


Figure 2. (a) Disassembly of compound **10b** with Pd/C/NaBH$_4$ in THF monitored by ^{1}H NMR. (b) Stack plot of selected regions of the ^{1}H NMR during disassembly of compound **10b** at several time intervals. (c) Proposed disassembly pathway and identity of intermediates of compound **10b** with Pd/C/NaBH$_4$ in THF.

Allyl deprotection of **10a**−**c** was also accomplished with heterogeneous Pd/C[25] as a source of Pd^0 in THF. The Pd/C/NaBH$_4$/THF system offers several advantages compared

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[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), Me$_4$Phen (398 mg, 1.68 mmol), Cs$_2$CO$_3$ (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; CH$_2$Cl$_2$:hexanes (3:7)) to give **1b** (2.81 g, 74% yield) as a red glassy solid.

[22] Li, S.; Szalai, M. L.; Kevwitch, R. M.; McGrath, D. V. *J. Am. Chem. Soc.* **2003**, *125*, 10516.

to $Pd(PPh_3)_4/NaBH_4/DMF$ 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 $Pd/C/NaBH_4$ system in THF. We observed competition between the desired allyl-deprotection/disassembly process and hydrogenation[26] 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 $Pd/C/NaBH_4/THF$ 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)/Me_4Phen-catalyzed ether formation.[19] Disassembly of the resulting compounds occurs cleanly and rapidly using $Pd(PPh_3)_4/NaBH_4$ in DMF. We have also introduced the $Pd/C/NaBH_4/THF$ 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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(23) The formation of the third-generation dendrimer from second-generation aryl iodide **2c** and 2,4-bishydroxymethylphenylallylether (**9**) proved to be problematic, as no third-generation dendrimer was detected in the crude mixture after 21 days of reaction time under the standard reaction conditions.

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(26) Hydrogenation occured as a result of hydrogen evolution from reaction of $NaBH_4$ with the heterogeneous Pd/C catalyst.