The Chemistry of Professor Craig Jon Hawker

Craig Jon Hawker Ph.D.

Research Interests:
synthetic polymer chemistry, nanomaterials, dendrimer, radical polymerization, biomaterials.

Born on January 11, 1964 in Queensland, Australia

Education

University of Queensland, Australia. B.Sc. 1981-1984
Cambridge University, UK. Ph.D. 1985-1988
Professor Sir A.R. Battersby (Biosynthesis of Vitamin B12 – Model Studies)
Cornell University, Postdoc 1988-1990
Professor J.M.J. Fréchet (dendrimer synthesis)

Academic Appointments

Queen Elizabeth II Research Fellow – University of Queensland. 1990-1993
Research Staff Member – IBM Almaden Research Center. 1993-2004
Professor of Materials, Chemistry, and Biochemistry – UCSB, 2004-2016
Clarke Professor – UCSB, 2013-Present
Director, Dow Materials Institute – UCSB, 2013-Present
Director, California Nanosystems Institute – UCSB, 2013-Present

Mentored around 200 Graduate Students and Postdocs
Recipient of dozens of awards
Approximately 450 publications and 50 patents.
Founder of Olaplex LLC and Tricida, Inc.

The Chemistry of Professor Craig Jon Hawker - Outline

I. Dendrimer Chemistry

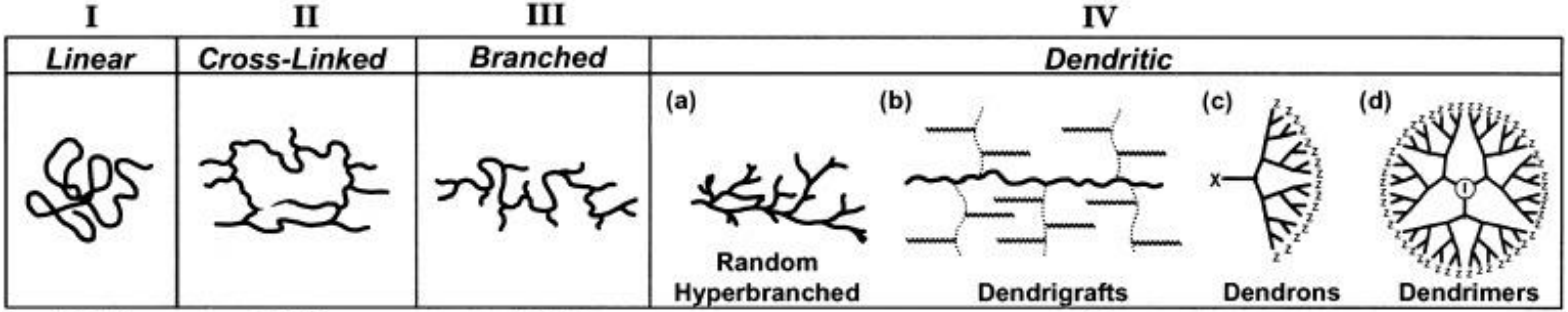
II. Nitroxide & Alkoxyamine Mediated “Living” Radical Polymerization

III. “Living” Radical Polymerization by Light

IV. Click Chemistry in Polymerizations and Bioapplications

V. Industrial Success and Olaplex

Major Macromolecular Architectures



I	II	III	IV
1930's	1940's	1960's	Present
Plexiglass, Nylon	Rubbers, Epoxies	Low Density Polyethylene Metallocene-Based Polyolefins	

Biomedical
- nano-drugs
- gene expression
- immuno diagnostics
- controlled delivery

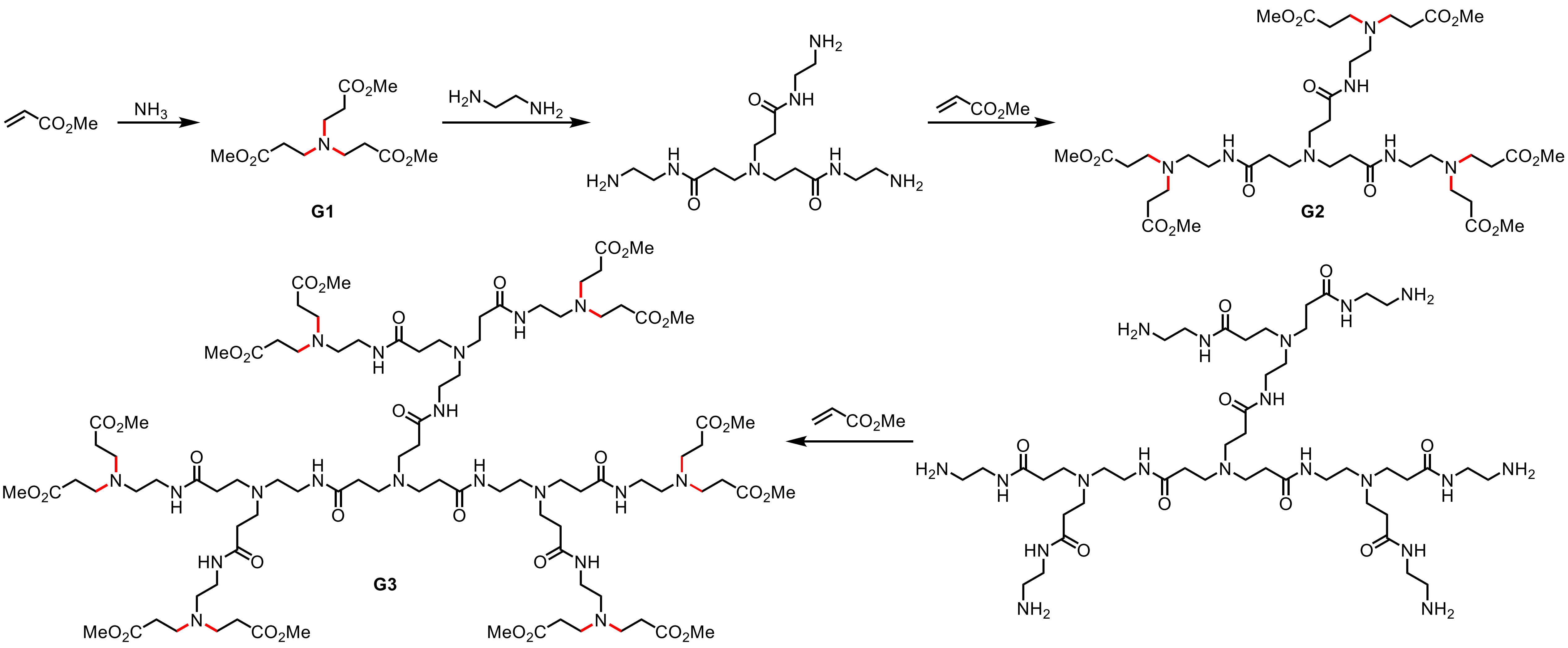
Electronics
- light harvesting
- 3-D conductivity
- quantum dots

Sensors
- chemical
- biological

Coatings
- fast cure, low viscosities

J. Polym. Sci. Part A: Polym. Chem. **2002**, 40, 2719.

Dendrimer Synthesis: Divergent Approach



Reactive groups increases exponentially after each generation.

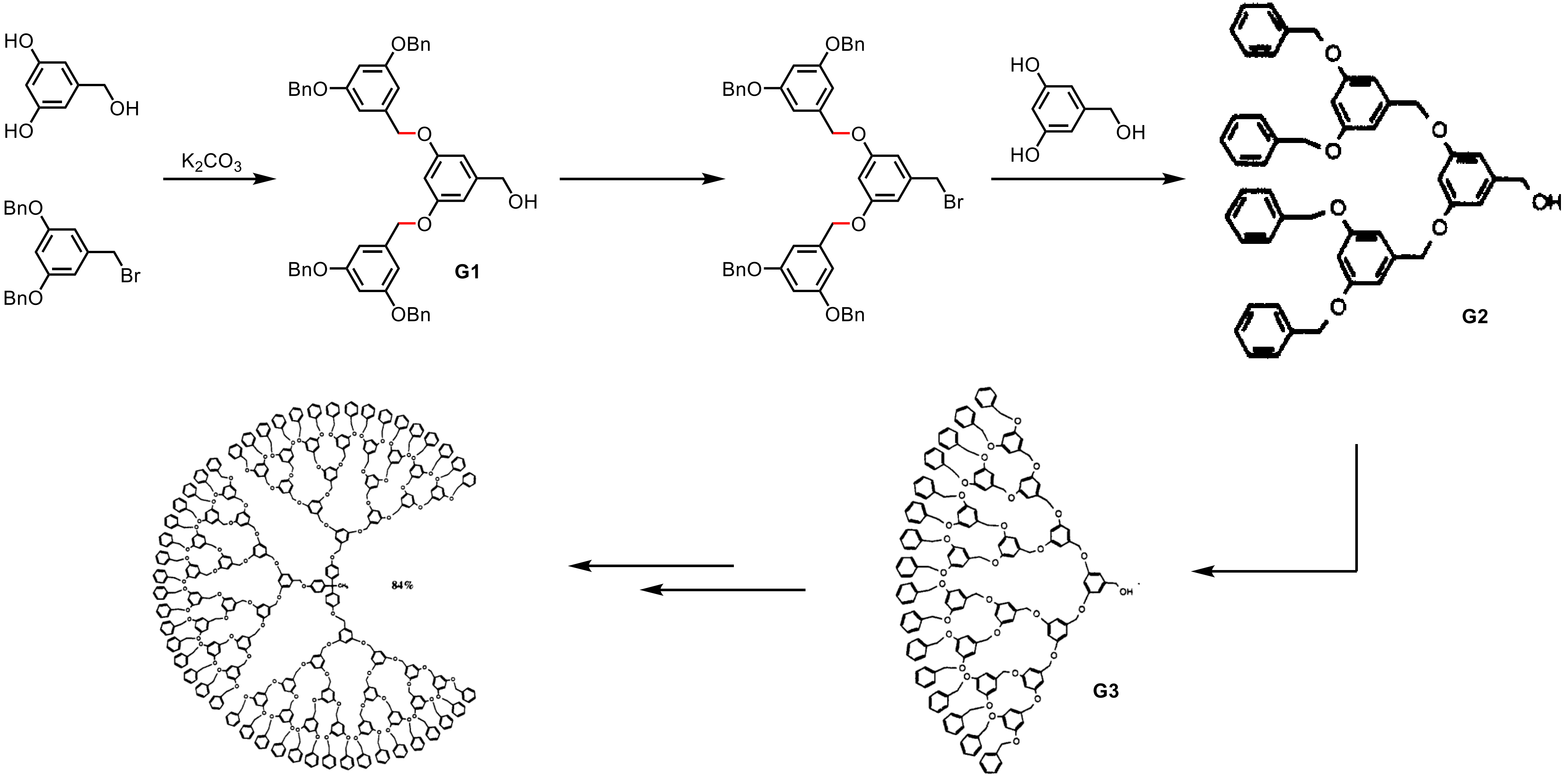
Incomplete reaction at chain terminal lead to imperfections or failure sequences in the next generation.

Large excess of reagents required in latter stages.

Mixture of inseparable multi-generation dendrimers.

Tomalia, D. A, et al. Polym. J. 1985, 17, 117.
Tomalia, D. A, et al. Macromolecules 1986, 19, 2466.

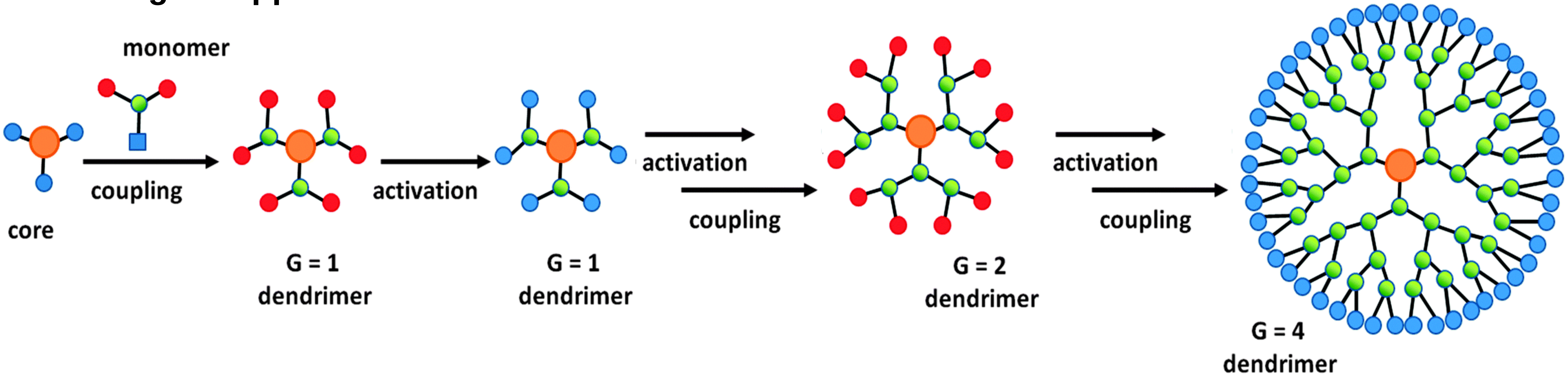
Dendrimer Synthesis: Convergent Approach



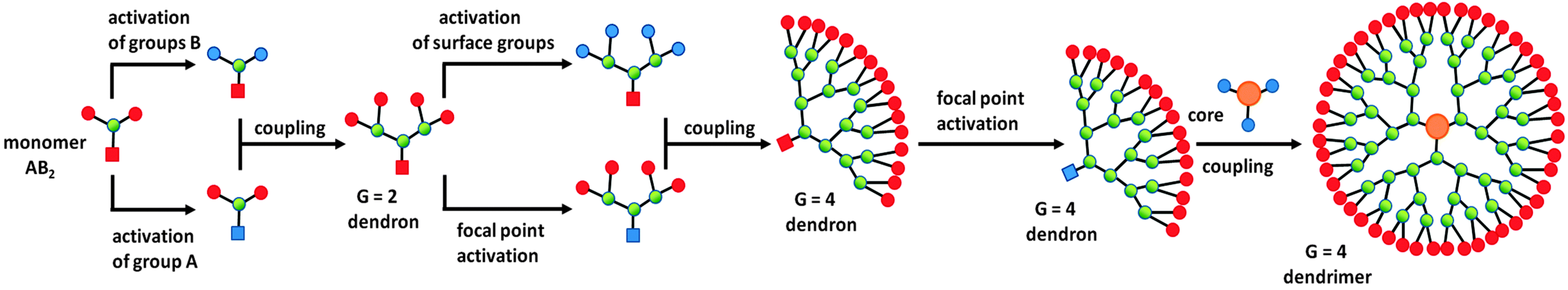
Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1990**, 112, 7638.

Dendrimer Synthesis: Summary

Divergent Approach



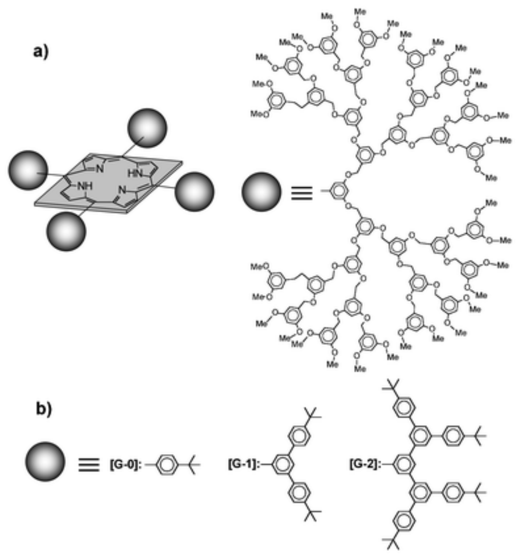
Convergent Approach



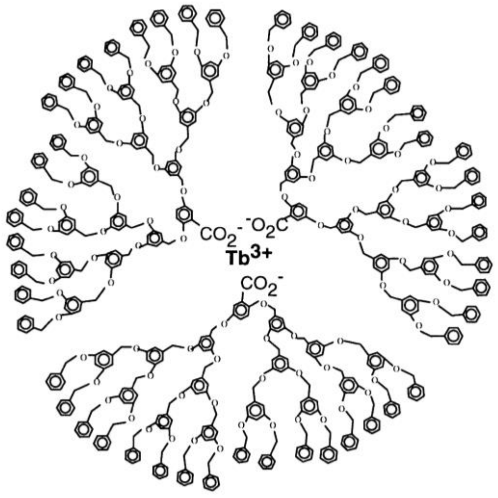
Chem. Rev. **2001**, 101, 123819-123868. *Progress in Polymer Science*. **2013**, 63–235.

Dendrimer Chemistry: Properties and Applications

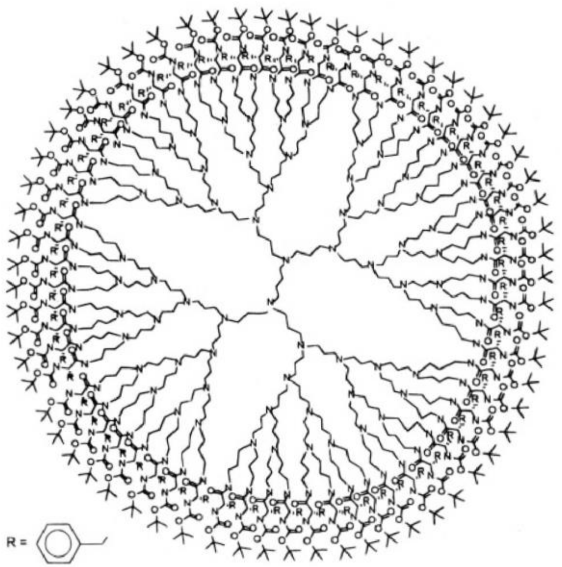
Light Harvest and Emitting	Self-Assembly	Guest Host Chemistry	Biomedical Applications



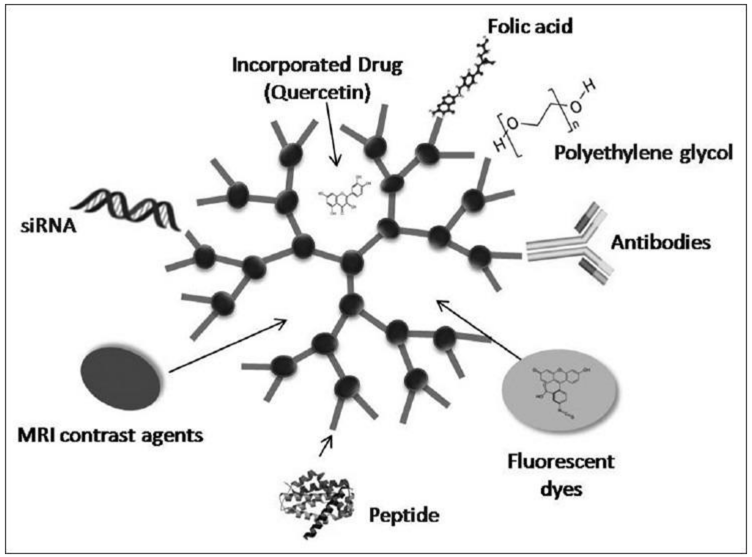
Chem Comm. **2000**, 1701.



Chem. Mater. **1998**, 10, 286.

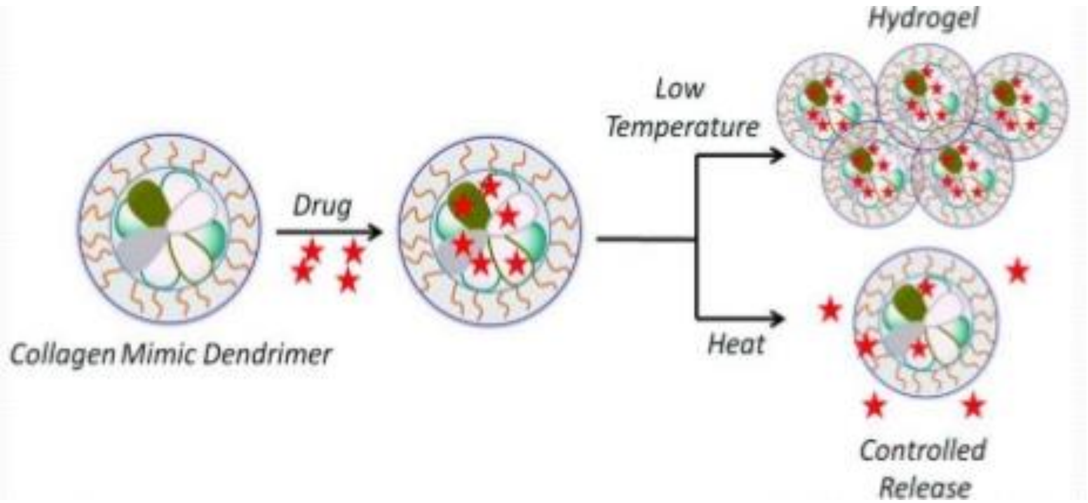


*JACS.***1995**, 117, 4417.



J Pharm Bioallied Sci. **2014,** 6, 139.

- **Dendrimers demonstrate significantly increased solubility compared to linear polymers.**
- **Dendrimers can self-assemble into macromolecules.**
- **Dendrimers exhibit a distinct “interior” that is sterically encapsulated within the dendrimer.**
- **The resulting “dendritic box” allows encapsulation of small molecules and enable drug or gene delivery.**



Dendrimer Chemistry: Drug Delivery

Commercialized dendrimers			
Brand name	Type of dendrimer	Company	Status
Priostar®	PEHAM/PEA	Starpharma	Marketed
Starburst®	PAMAM	Starpharma	Marketed
Astramol®	PPI	Starpharma	Marketed
Polylysine	Poly-L-lysine	Starpharma	Marketed

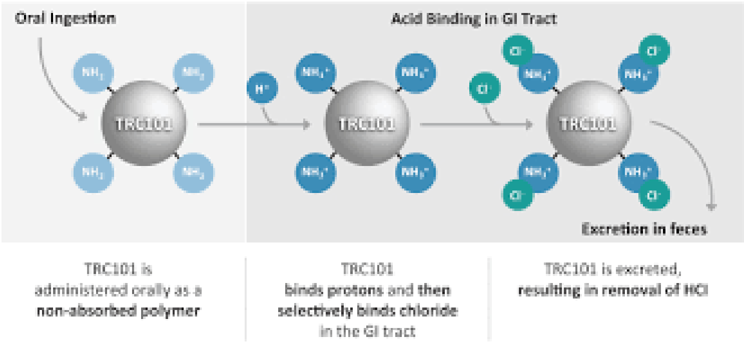
Commercialized/pipeline dendrimer-based products				
Dendrimer	Type of dendrimer	Company	Application	Status
Vivagel®	Poly-L-lysine	Starpharma	Prevent the transmission of HIV and STDs	Clinical trials (phase 3)
Stratus CS®	PAMAM	Dade behring	Cardiac assay diagnostic	Marketed
Superfect®	PAMAM	Qiagen	Transfection agent	Marketed
Priofect™	PAMAM	Starpharma	Transfection agent	Marketed
Alert ticket™	PAMAM	U.S. army lab	Anthrax-detecting agent	Marketed
Dendrimer-docetaxel	ND	Starpharma	Breast cancer treatment	Preclinical
Dendrimer-oxaliplatin	ND	Starpharma	Colon cancer treatment	Preclinical

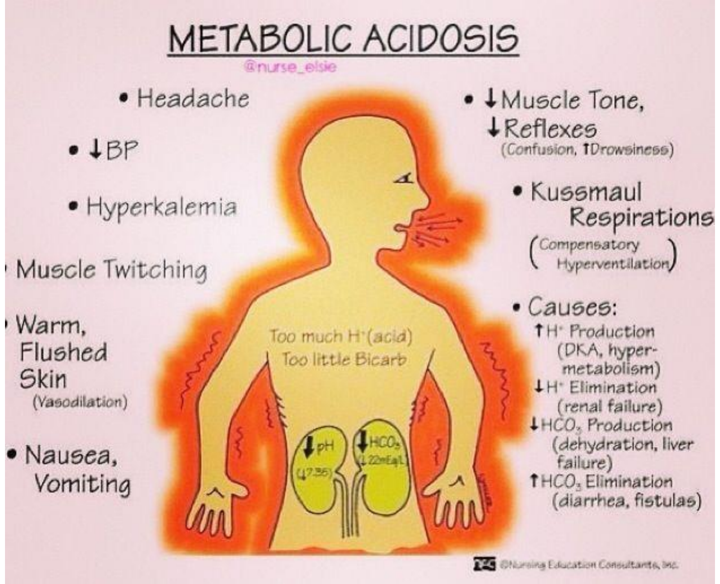
J Pharm Bioallied Sci. **2014,** 6, 139–150

Dendrimer Chemistry: Drug Delivery

Drug	Pharmacology	Dendrimer type	Application
10-hydroxycamptothecin	Anticancer	Carboxylated poly (glycerol-succinic acid)	High cytotoxicity
7-butyl-10-aminocamptothecin	Anticancer	G4.5 poly (glycerol-succinic acid)-COONa	Increased aqueous solubility and 16 fold increased cellular uptake
Paclitaxel	Anticancer	Polyglycerol (G4 and G5)	Increased aqueous solubility
		G4 PAMAM	Increased aqueous solubility, enhanced cytotoxicity
		G3 PAMAM	Improved permeability (12 fold)
		G2 PAMAM	Increased aqueous solubility (3700 fold)
Methotrexate	Anticancer	G2.5 and G3 PAMAM	24-fold increment in cytotoxicity
		G5 PAMAM	Targeted delivery
		G1, G1.5 and G2.5 PAMAM	Enhanced anticancer activity
Doxorubicin	Anticancer	G4 PAMAM	Improved cytotoxicity
		G5 polylysine	Prolonged plasma exposure and diminished drug toxicity
		2, 2 bis (hydroxymethyl) propionic acid (G3)	Long term antitumor activity
Famotidine	Antiulcer	G5 PPI	Improved solubility
Indomethacin	NSAIDs	G5 PPI	Improved solubility
Amphotericin B	Antifungal	G5 PPI	Improved solubility
Rifampicin	Antitubercular	Mannosylated PPI	Sustained release and targeted delivery
Lamivudine	Anti-HIV	Mannosylated PPI	Prolonged drug release up to 144 h
Efavirenz	Anti-HIV	PPI	Targeted delivery
Furosemide	Diuretic	G4 PAMAM	Increased solubility and sustained release
Etoposide	Anticancer	PAMAM	High loading capacity
Erythromycin	Bactericidal antibiotic	G4 PAMAM	Sustained release and improved activity
Zidovudine	Anti-HIV	G4 PPI	Targeted delivery
Ketoprofen	NSAIDs	PAMAM	Improvement of drug permeation through skin
Diflunisal	NSAIDs	PAMAM	Improvement of drug permeation through skin
5-Fluorouracil	Anticancer	G4 PAMAM	Targeted drug delivery
Propanolol	Anti-	Lauroyl-G3 PAMAM	Enhanced basal transport of propranolol

TRICIDA





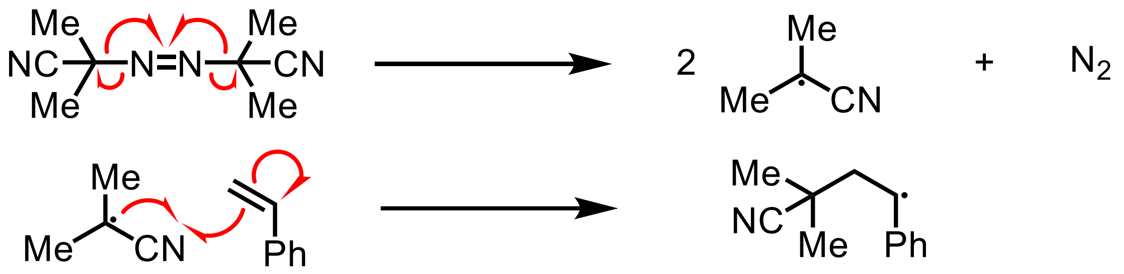
J Pharm Bioallied Sci. **2014,** 6, 139–150

Radical Polymerization

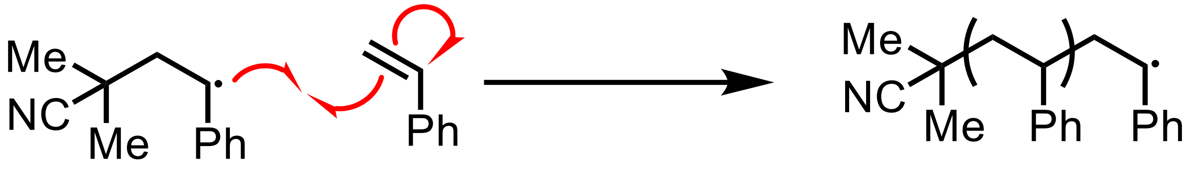
Traditional Radical Polymerization

Initiation

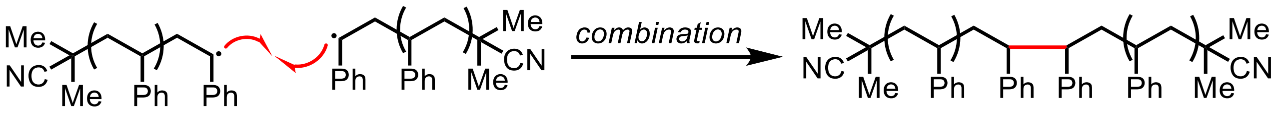
Initiators: AIBN, ROOR, etc



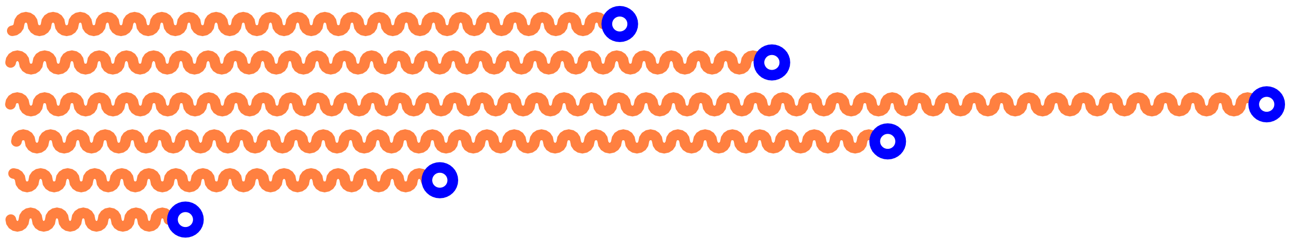
Propagation



Termination

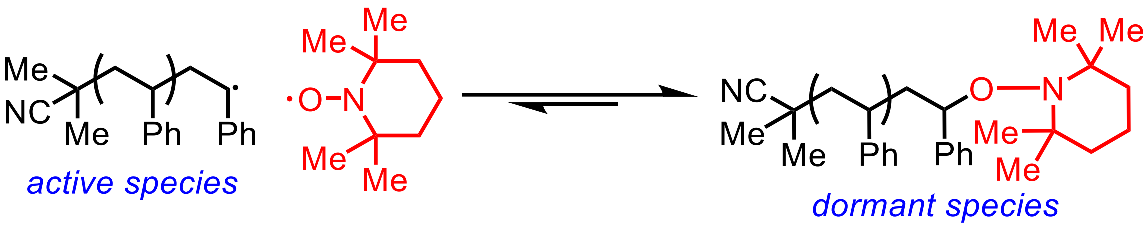


combination, disproportionation, chain transfer



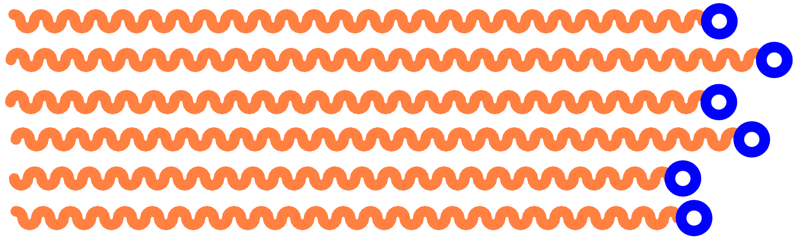
Poor control over molecular weight & polydispersity

"Living" Radical Polymerization



Discovery of nitroxide radical (TEMPO) as the mediating/control agent:

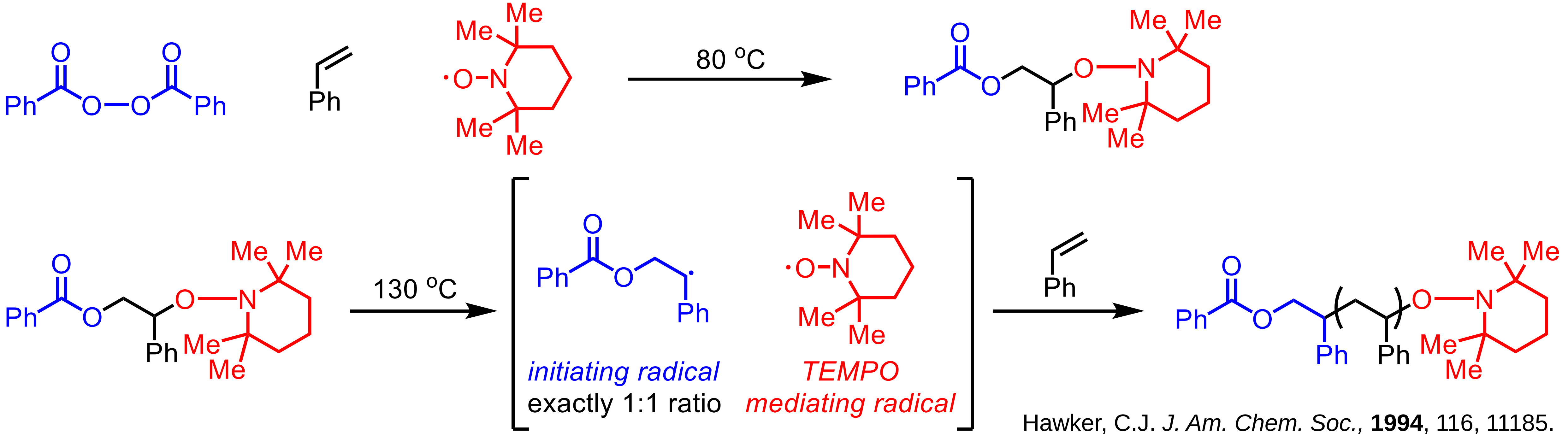
- Does not terminate with itself.
- Does not initiate monomers.
- Only undergo reversible termination of the propagating chain end.
- Minimizes overall propagating radical concentration.
- Minimizes undesired radical reactivity.



Good control over molecular weight & polydispersity

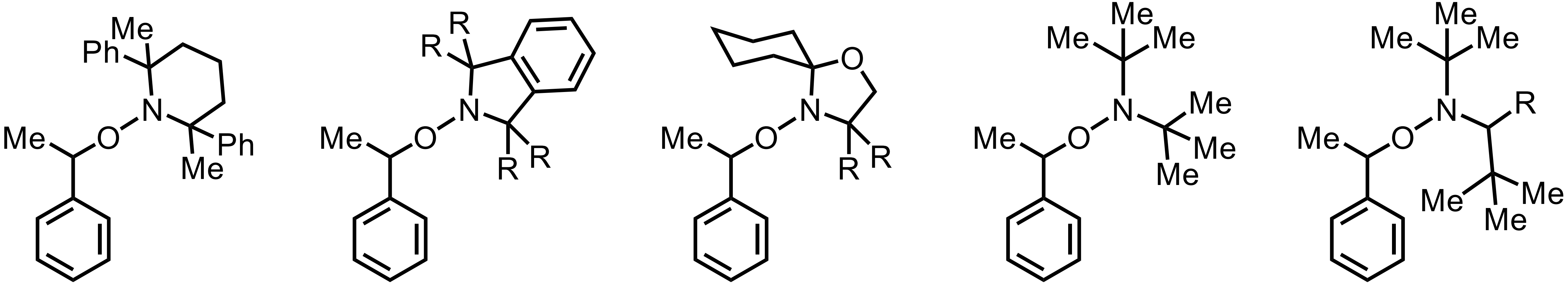
Require precise initiator and nitroxide ratio

"Living" Radical Polymerization – Alkoxyamine as Unimolecular Initiator



Hawker, C.J. *J. Am. Chem. Soc.*, **1994**, 116, 11185.

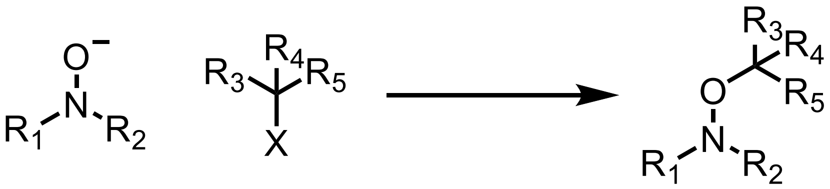
Universal Alkoxyamine for "Living" Free Radical Polymerization



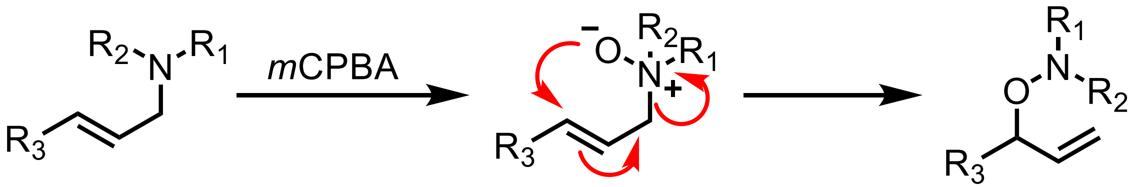
Hawker, C.J. et al. *J. Am. Chem. Soc.*, **1999**, 121, 3904.

"Living" Radical Polymerization – Alkoxyamine Initiator Synthesis and Application

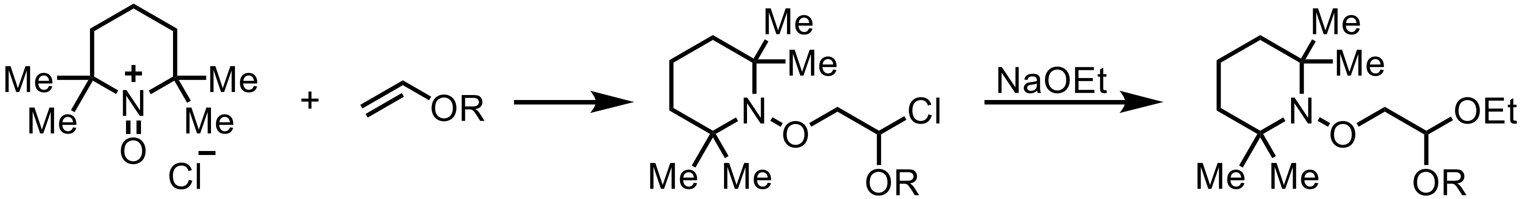
Nucleophilic Substitution



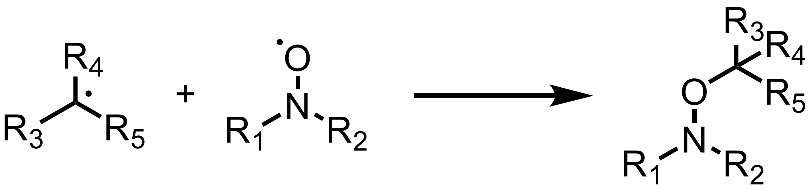
Meisenheimer Rearrangement



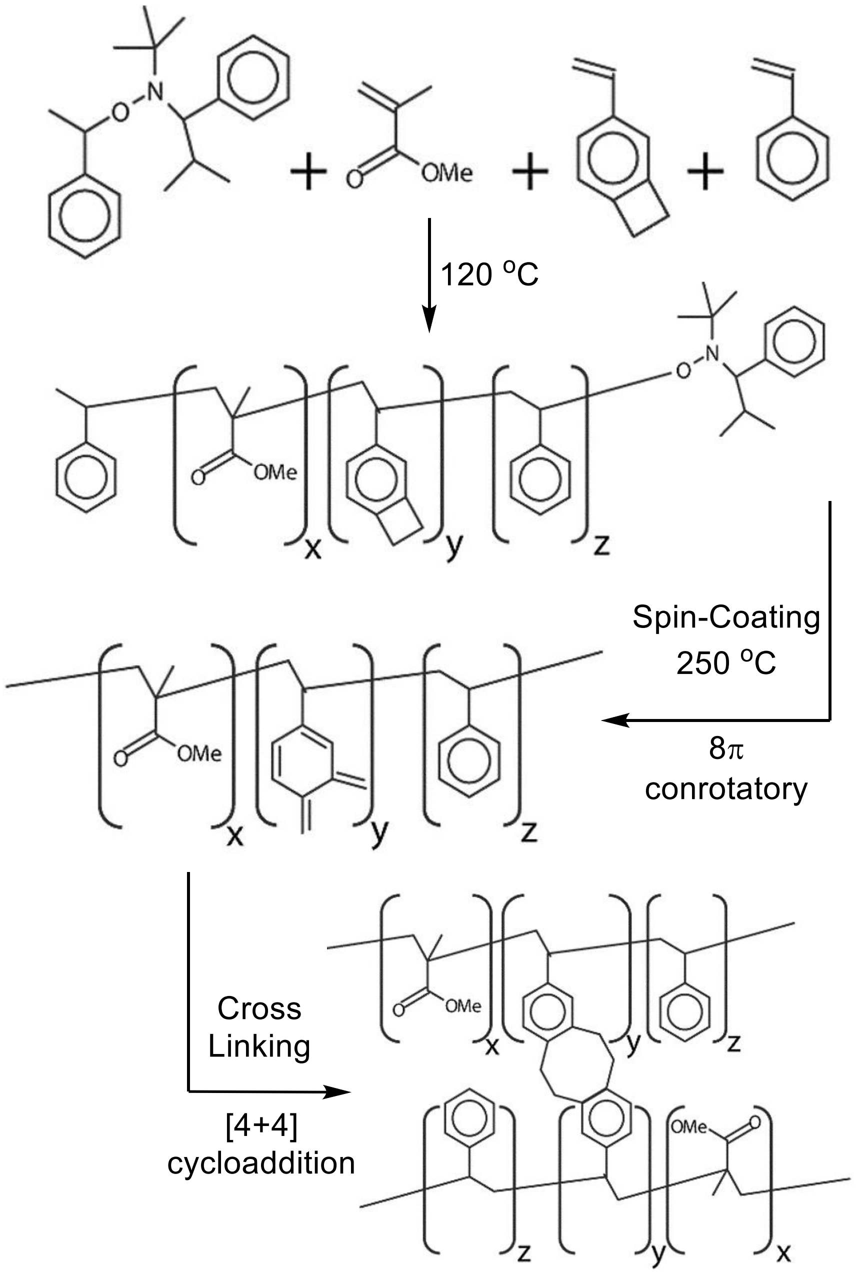
Oxoammonium Salt with an Olefin



Scavaneging of Alkyl Radical by an Aminoxyl Radical

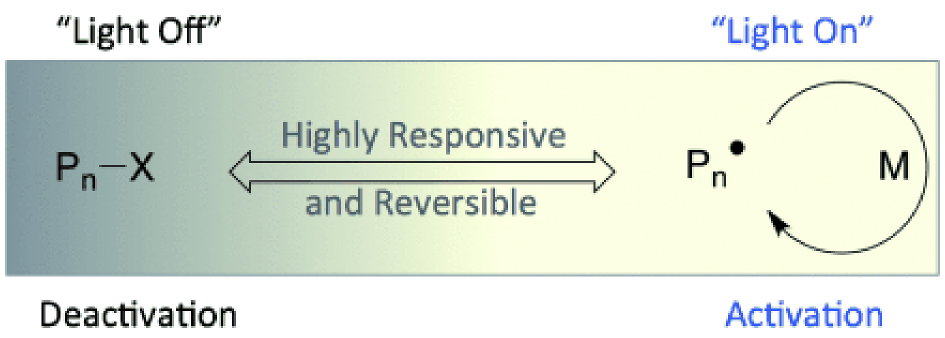


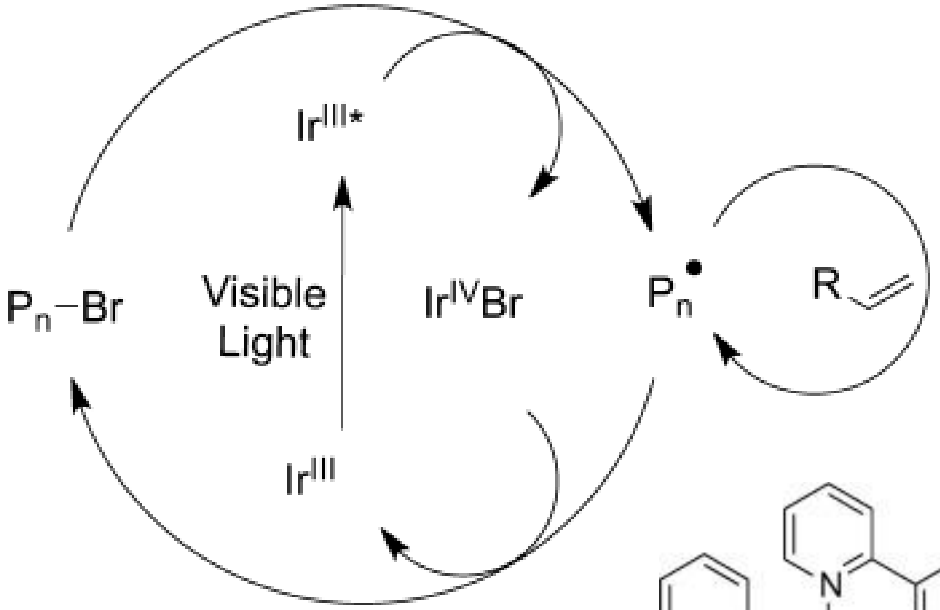
Progress in Polymer Science **2013**, 38, 63.

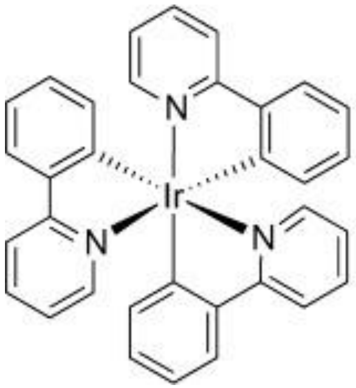


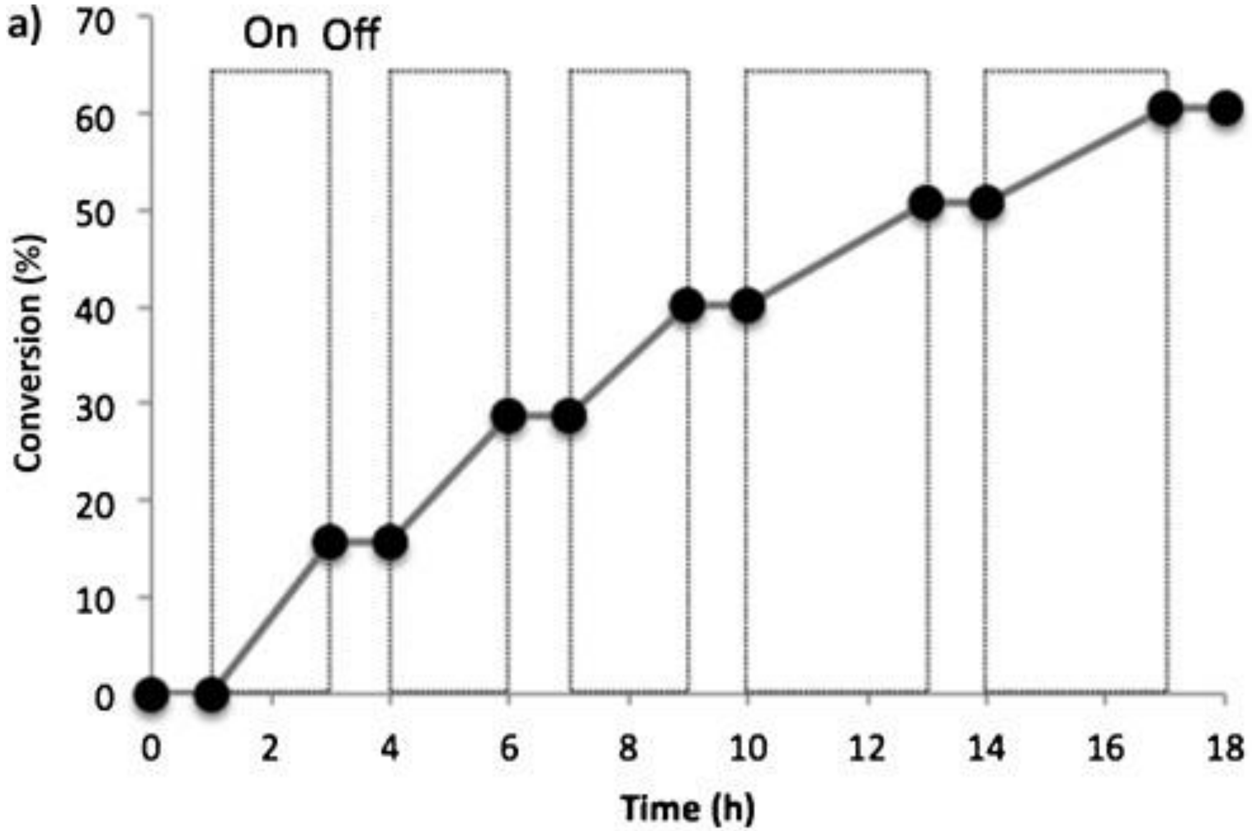
Hawker *et al*. *Science* **2005**, 308, 236.

Living Polymerization by Light – Ir(III) Photoredox Catalyst



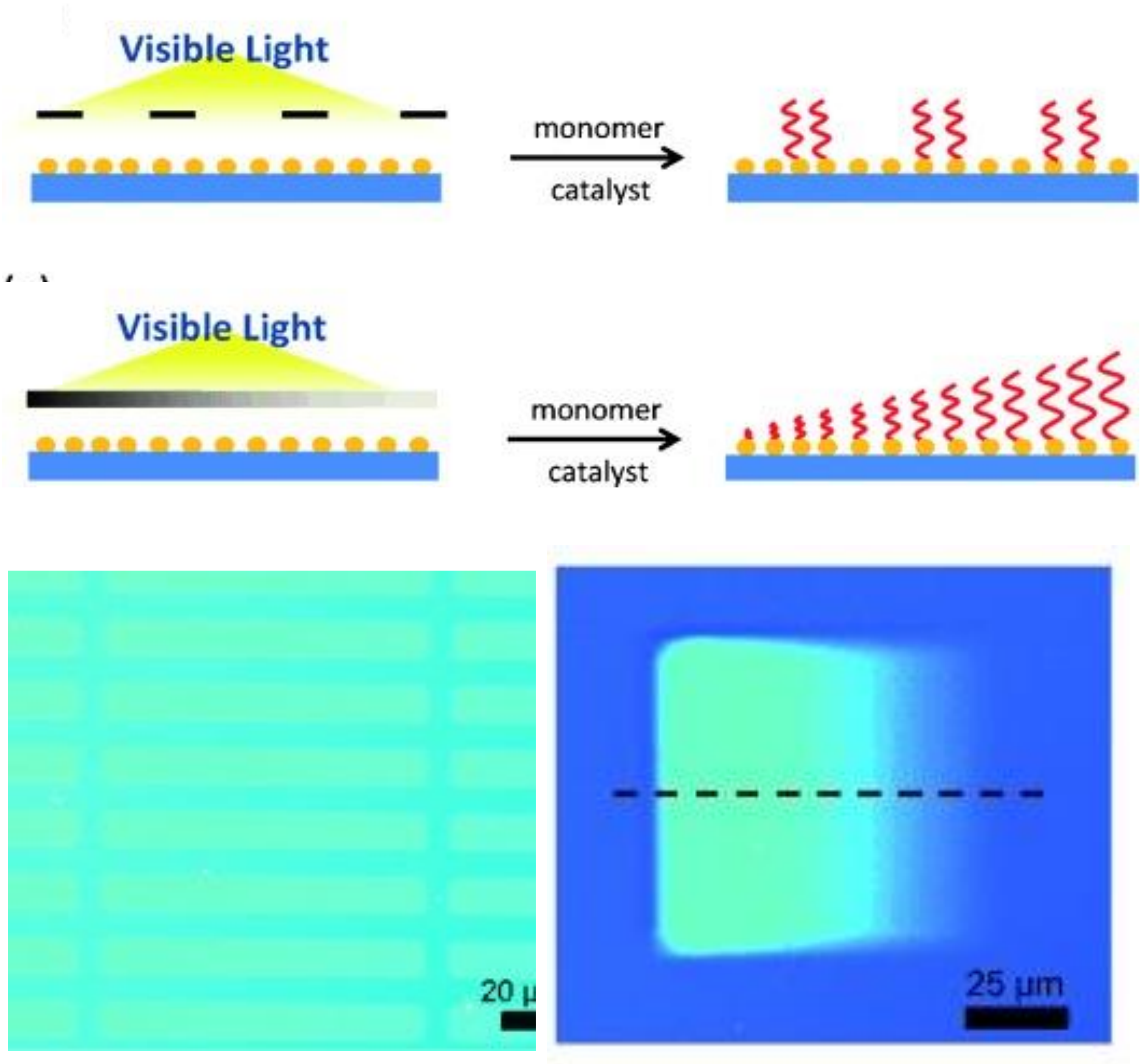


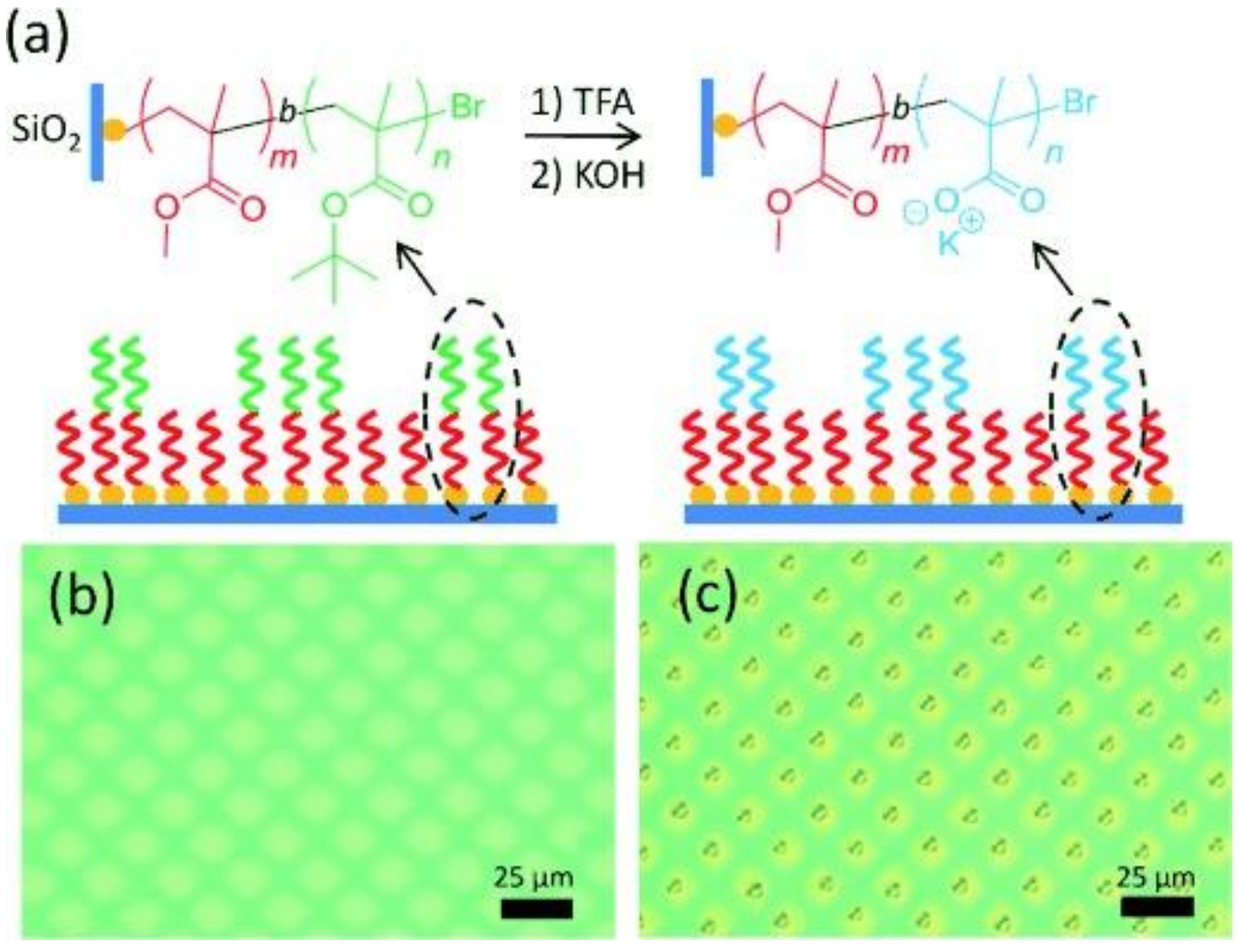




Fors, B.; Hawker, C. *Angew. Chem., Int. Ed.* **2012**, 51, 8850.

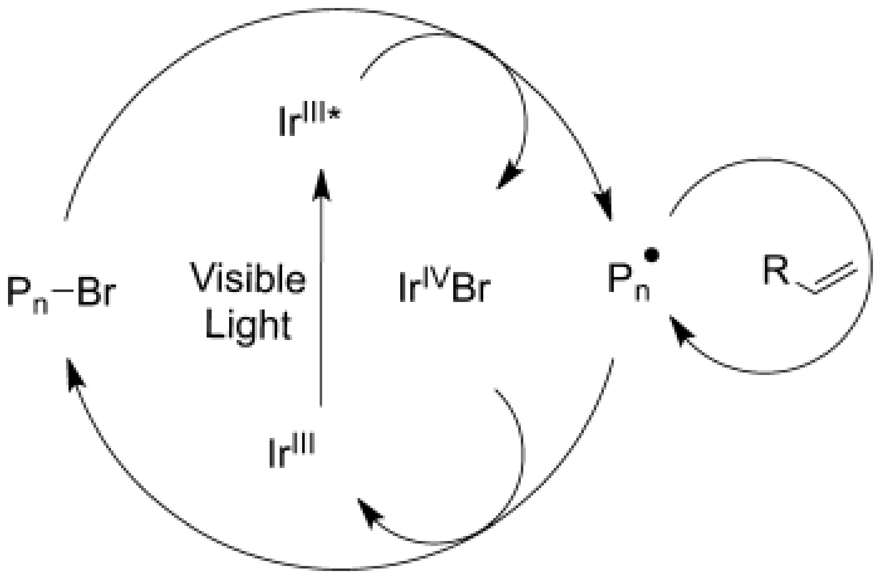
Living Polymerization by Light – Applications

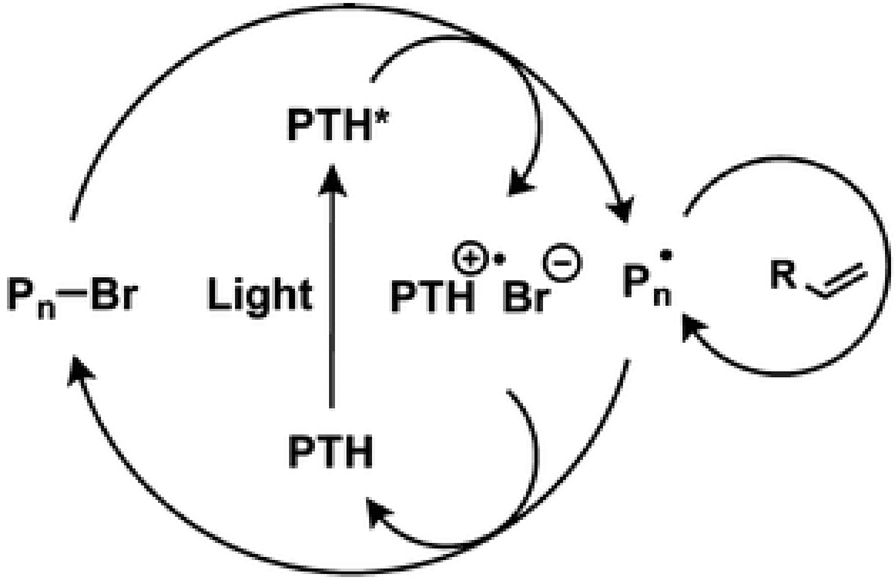


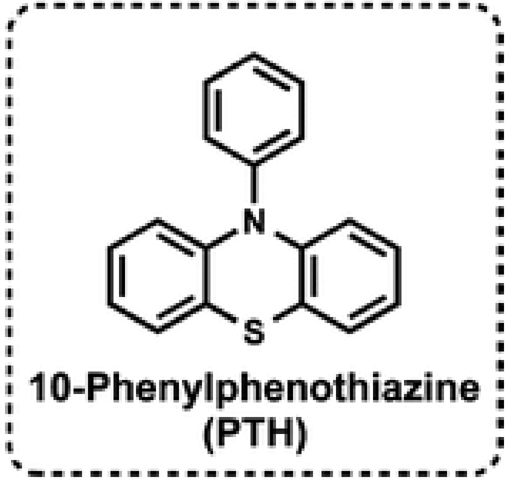


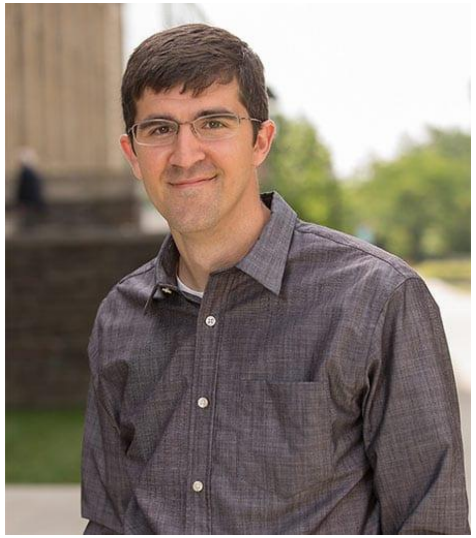
Poelma, J. E.; Fors, B. P.; Meyers, G. F.; Kramer, J. W.; Hawker, C. J. Angew. Chem., Int. Ed. 2013, 52, 6844−6848.

Living Polymerization by Light – Organic Photo Catalyst





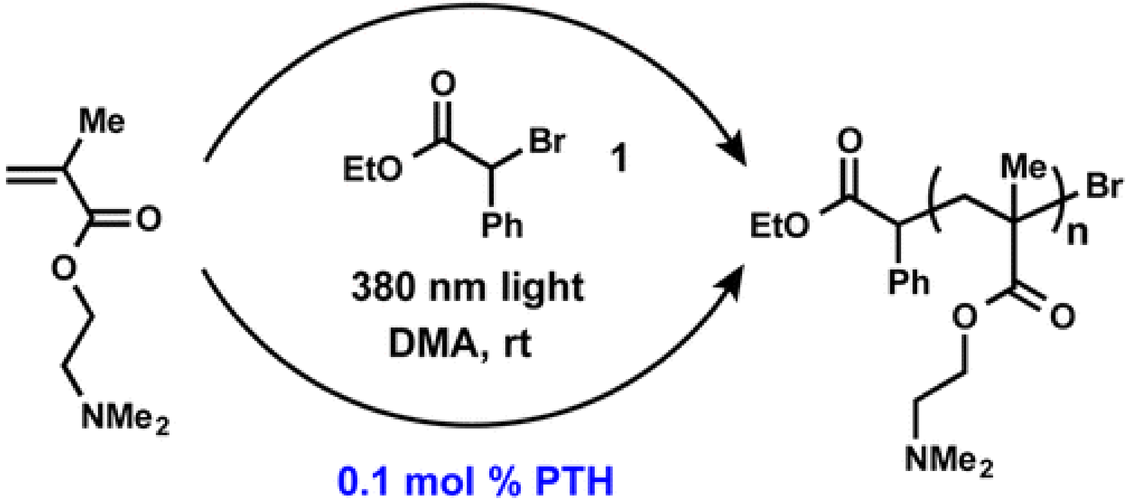




Treat, N. J.; Sprafke, H.; Kramer, J. W.; Clark, P. G.; Barton, B. E.; Read de Alaniz, J.; Fors, B. P.; Hawker, C. J. Metal-Free Atom Transfer Radical Polymerization. J. Am. Chem. Soc. 2014, 136, 16096− 16101.

0.005 mol % $Ir(ppy)_3$

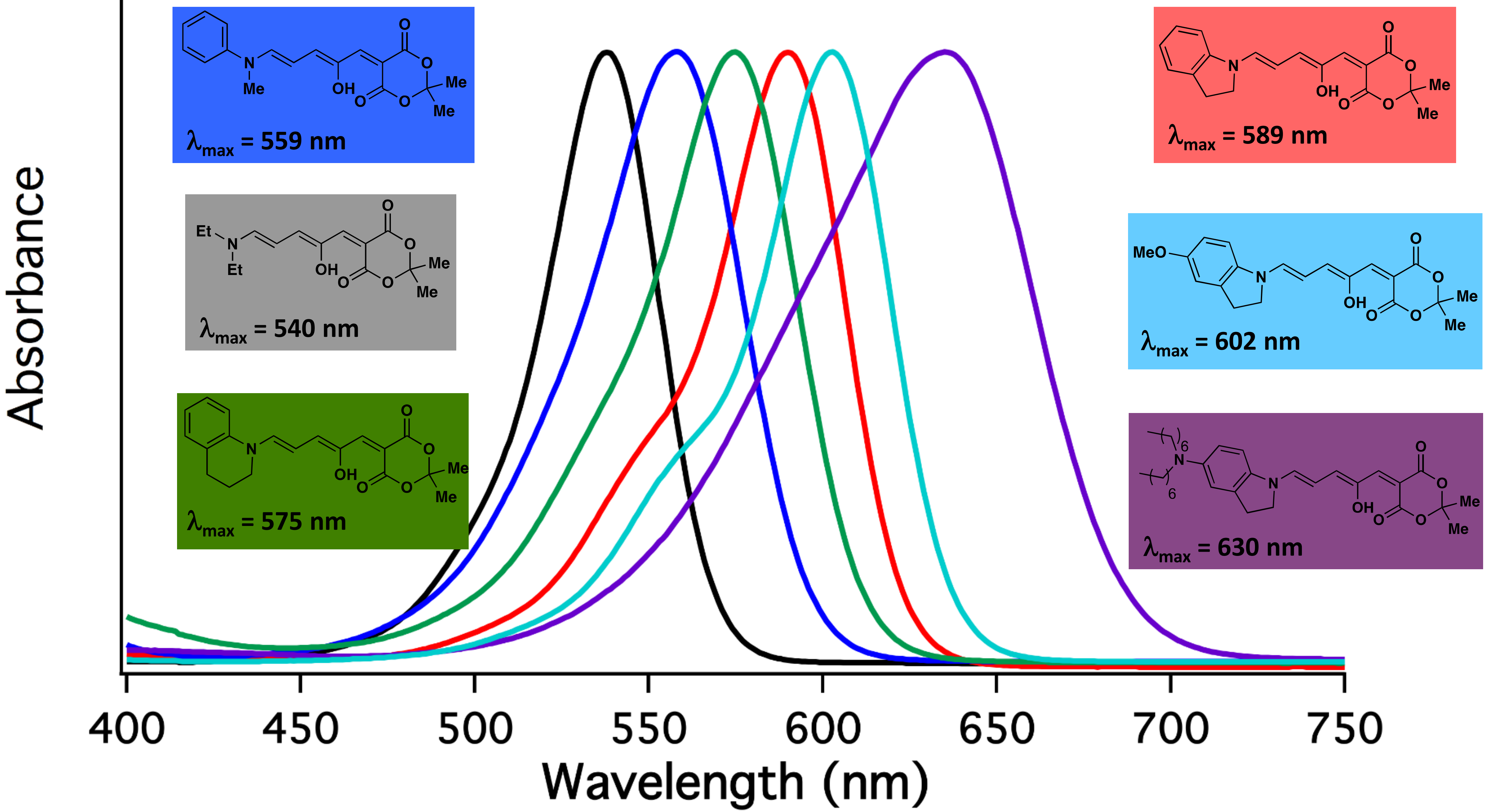
M_n = 9,400 g/mol M_w/M_n = 3.69



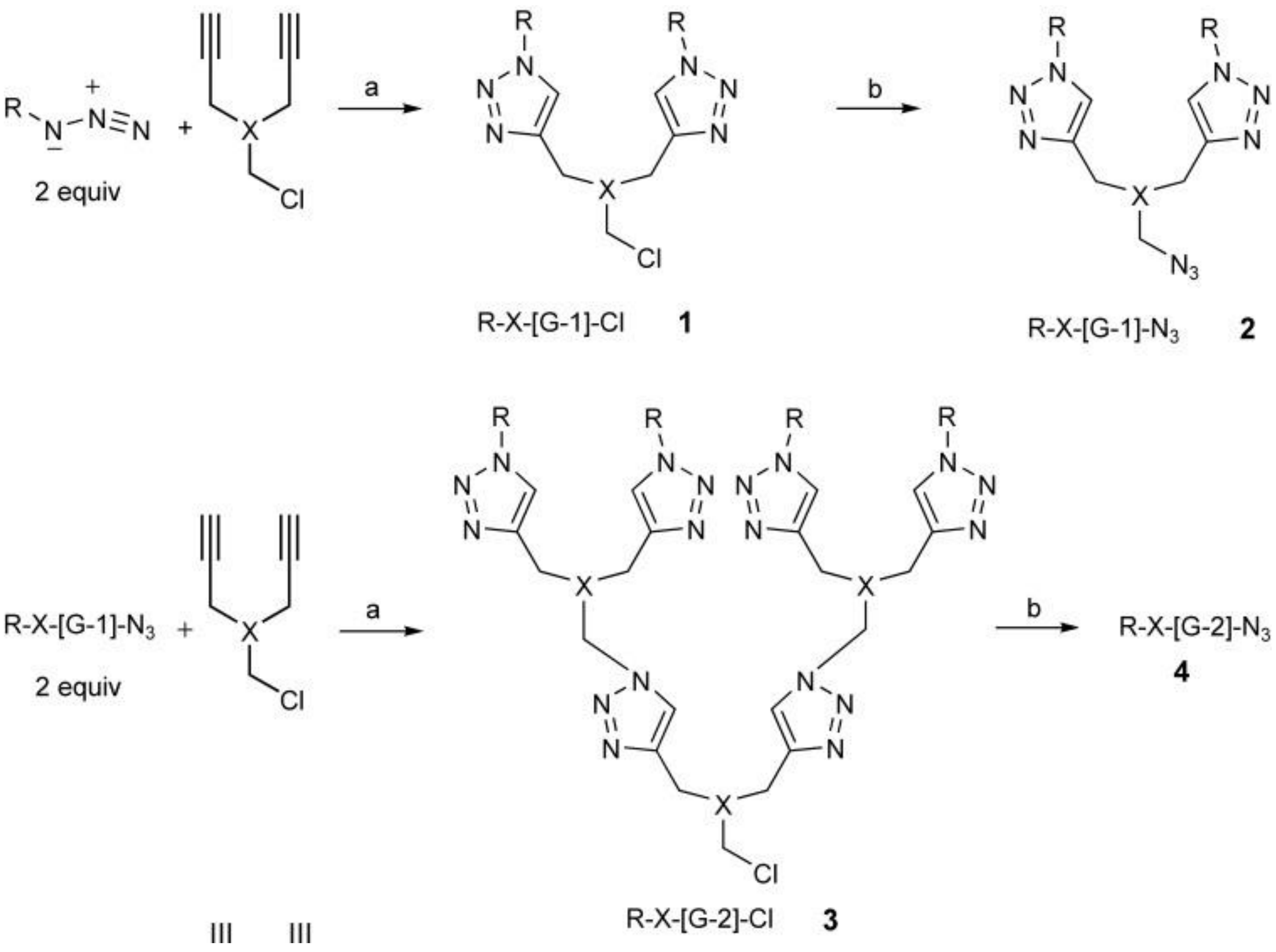
0.1 mol % PTH

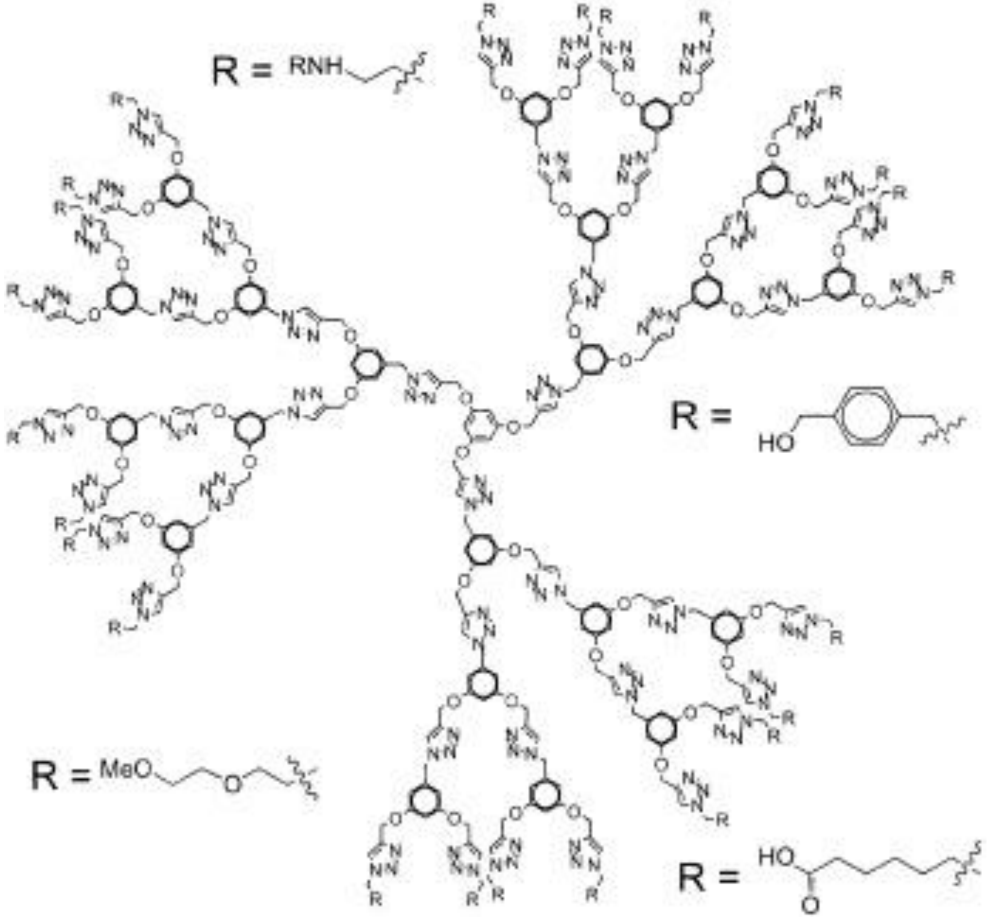
M_n = 8,800 g/mol M_w/M_n = 1.11

Different amines leads to ~90 nm change



Click Chemistry in Polymerization

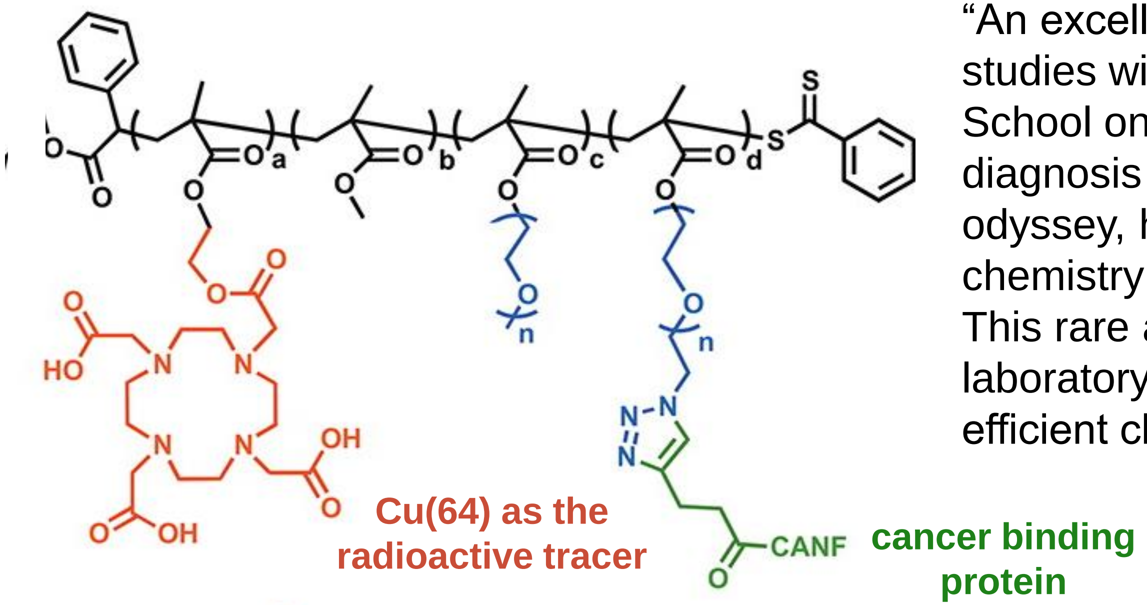


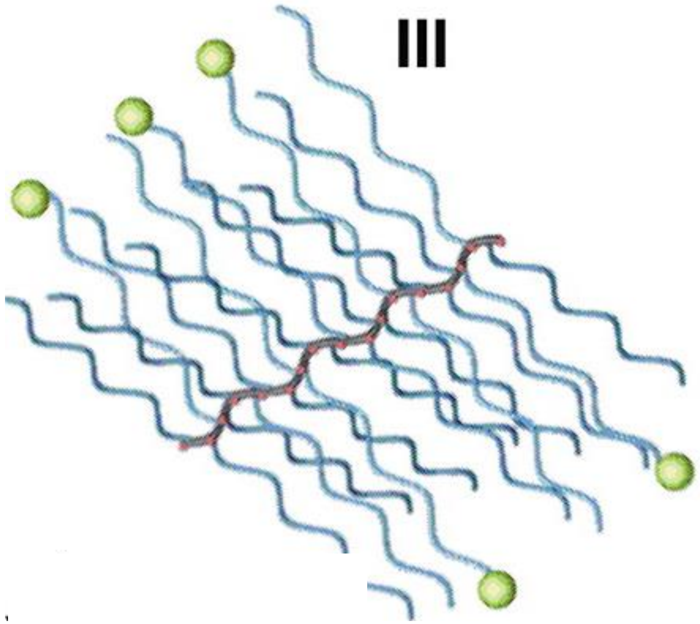


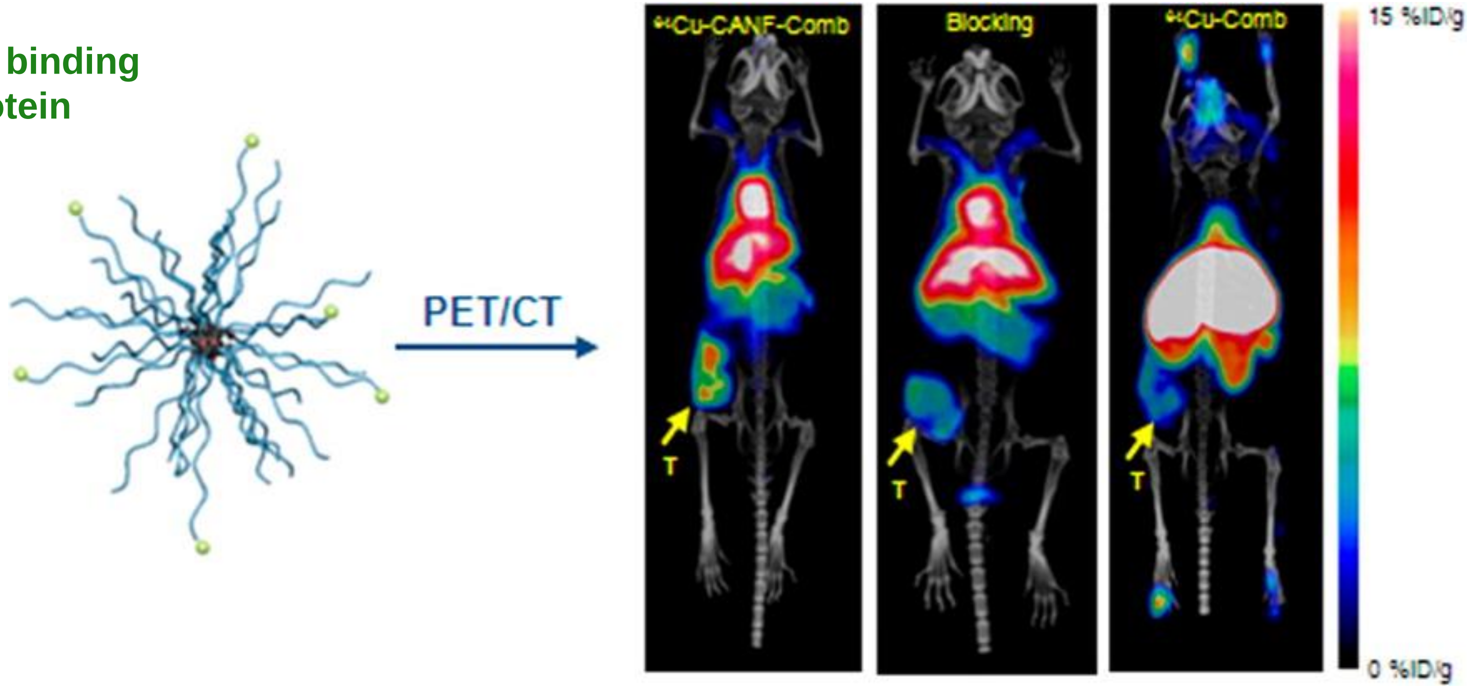
Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928.

Click Chemistry in Polymerization – Applications in Cancer Diagnosis

"An excellent illustration of the impact of this concept is my recent collaborative studies with clinicians led by Professor Pamela Woodard at WashU Medical School on the preparation of multi-functional and multi-valent nanoparticles for the diagnosis and treatment of cardiovascular disease. In 2015, after a ten-year odyssey, human clinical trials on self-assembled nanoparticles based on Click chemistry and LFRP began at Washington University Medical School in St. Louis. This rare achievement of translating a highly functional polymer molecule from the laboratory to the clinic demonstrates the enormous potential of orthogonal and efficient chemical reactions in biomaterials synthesis." – Craig Hawker



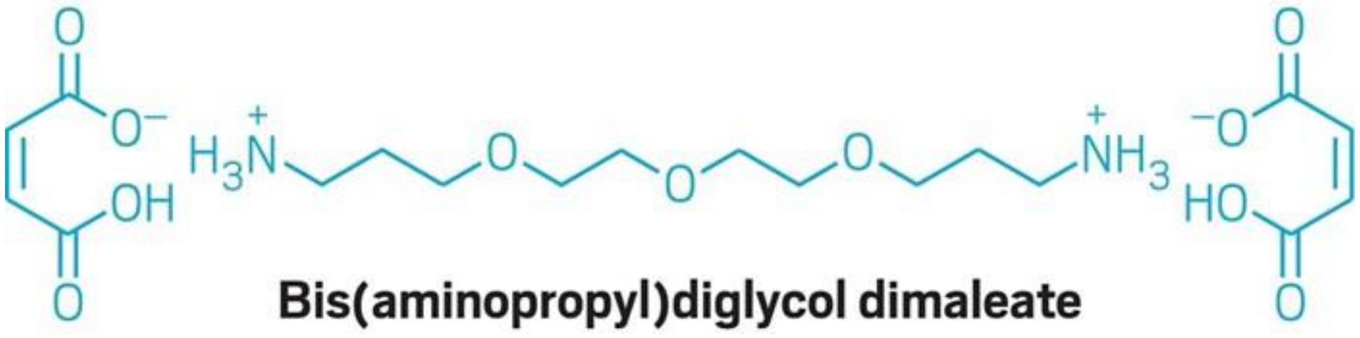




Pharmaceutical Research., **2016**, 33, 2400.
J. Nucl. Med., **2014**, 55, 629.

ACS Nano., **2011**, 52, 738.
J Nucl Med., **2011**, 52, 1956.

Industrial Success - Olaplex



Bis(aminopropyl)diglycol dimaleate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INTELLECTUAL PROPERTY

How a UCSB chemist stood up to L'Oréal in an IP-theft case

Pressly; E.D., Hawker; C.J. *United States Patent* 9,498,419.

Pressly; E.D., Hawker; C.J. *United States Patent* 9,872,821.

Pressly; Eric D., Hawker; Craig J. *United States Patent* 9,144,537.

https://cen.acs.org/policy/intellectual-property/Olaplex-wins-91-million-suit/97/web/2019/08