

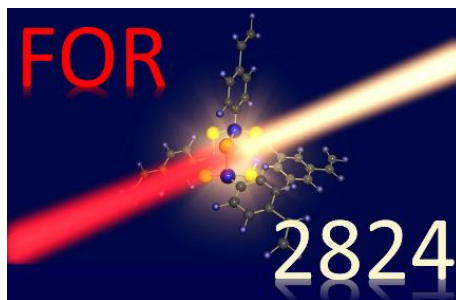
Synthesis and Characterization of Functionalized Diamondoids-Nonlinear optical studies

Gowrisankar Saravanan Ph.D

Group Seminar

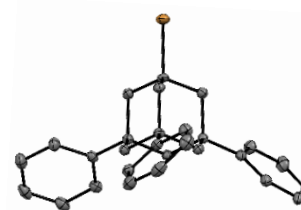
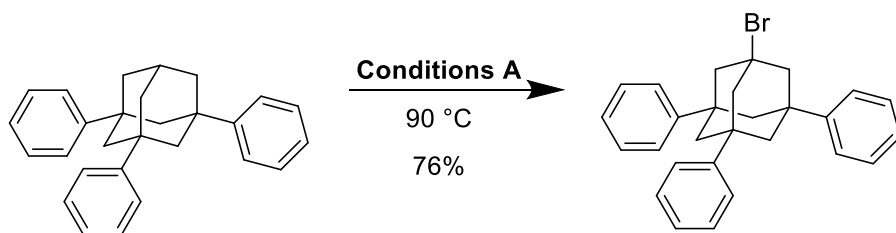
9th April 2021

*Institute of Organic Chemistry
Justus Liebig University Giessen*

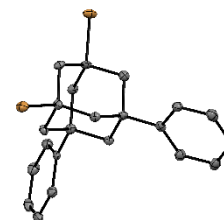
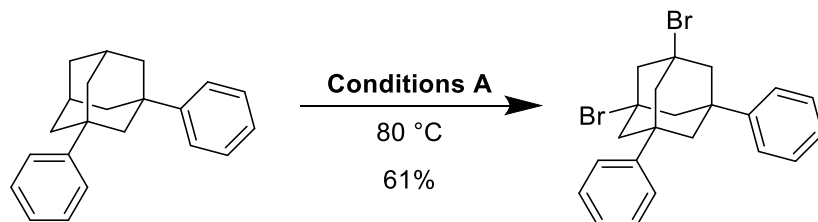




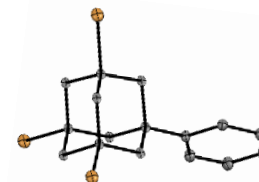
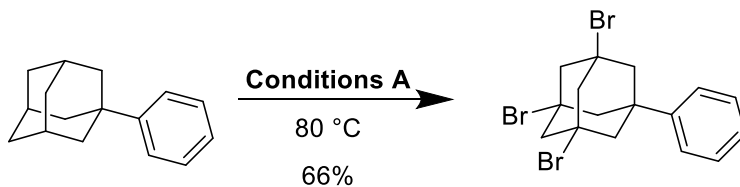
- ❖ Examine the effect of Br substitution (AdPh_3Br , AdPh_2Br_2 , AdPhBr_3 , and AdBr_4) on WLG/SHG.
 - Improve compound purity through recrystallization and sublimation.
 - Determination of crystal structure through powder X-ray diffraction (Powder XRD) and single-crystal X-ray diffraction (single-crystal XRD) of AdPh_4 , BrAdPh_3 , and AdBr_4 .
- ❖ Determine the effect of electron withdrawing/donating groups on aryl substitution of the organic (-C-)/inorganic (-S-Sn-) adamantane derivatives on WLG/SHG.
 - 4-CN, 4-OMe, 3-F, 4-F, 4-NMe₂, CH₂=CH₂COOMe, CH=NPh
 - Compute the HOMO-LUMO gaps (B3LYP-D3(BJ), 6-31G(d,p), BP86/dhf-TZVP).
- ❖ Optimization of the reaction conditions for Meta selective C-H Adamantylation.



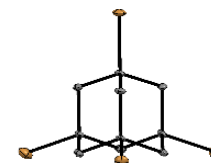
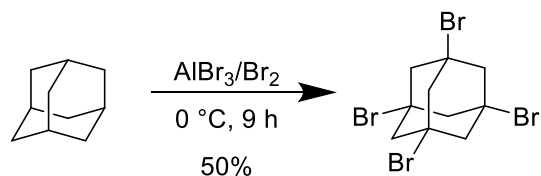
Trigonal (R-3)
Monoclinic (P21/n)



Monoclinic (C2/c)



Triclinic (P-1)

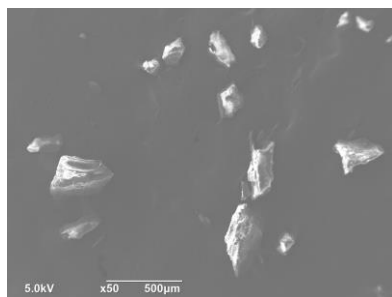
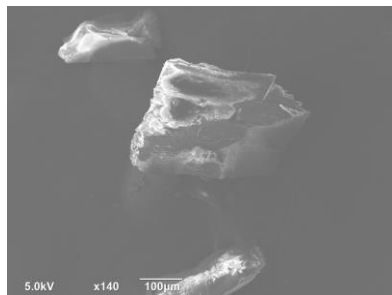
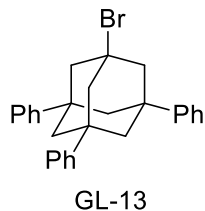


Tetragonal (P21/n)

Conditions A: CBr_4 , Bu_4NBr (cat), $\text{C}_6\text{H}_5\text{F}$, 50% NaOH , 12-24 h.



SEM study



Rigid Multivalent Scaffolds

propionyl-spaced amine function for conjugation of effectors and three carboxylic acids for attachment of ligands. It should be noted that no chromatography is necessary for purification of compounds **13–18** because all of them can easily be purified by crystallization.

Summary and Conclusion

In summary, we report efficient syntheses of new adamantane scaffolds. Both routes are short and give the target compounds **12** and **18** in good yields. These scaffolds have been designed to orient three carboxylic acids in a strictly defined tripodal geometry for the conjugation of cell surface binders. In addition, a primary amine allows the conjugation of the scaffold to an effector molecule that is pointing away from the ligands and is therefore unlikely to interfere with the binding process. We are currently evaluating the potential of these scaffolds for various multivalent ligand receptor interactions. It should be noted that our scaffolds are providing a strictly defined tripodal recognition motif (for surfaces) in combination with a fourth binding motif with all four functionalities easily addressable by standard conjugation techniques. Unlike other systems of that sort,²¹ no rigidifying (hydrophobic) aromatic spacers are needed, making

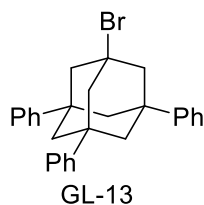
JOC Article

gel, EtOAc/hexane, 6:4, *R_f* 0.78) to give 65 mg of **11** as a colorless solid (83%). ¹H NMR (CDCl₃, 600 MHz) δ 3.65 (s, 9H), 2.03–1.89 (m, 12H); ¹³C NMR (CDCl₃, 125 MHz) δ 175.9, 52.4, 52.1, 43.2, 42.0, 38.8; HRMS (ESI) calcd for C₁₆H₂₄NO₆ [M + H]⁺ 326.1604, found 326.1598.

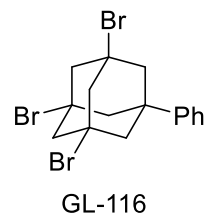
1-Bromo-3,5,7-triphenyladamantane 14. To a solution of 1,3,5-triphenyladamantane **13** (0.20 g, 0.55 mmol), tetrabromomethane (0.73 g, 2.2 mmol), and tetrabutylammoniumbromide (0.02 g, 0.06 mmol) in 5 mL of fluorene was added 3 mL NaOH (wt 50%) and the resulting reaction mixture was heated to 75 °C for 24 h. The solvent was evaporated in vacuo; the crude product was suspended in water and extracted three times with 20 mL of dichloromethane each time. The combined organic layers were dried over Na₂SO₄ and filtered and the solvent was evaporated in vacuo to give the bromide **14**. After crystallization from hexane/ethyl acetate (1:1), 26 g (0.49 mmol; 89%) of **14** was isolated as a yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.23–7.35 (m, 15H), 2.14 (d, 3H, ²J = 13.4 Hz), 2.14 (d, 3H, ²J = 13.4 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 147.8, 128.7, 126.7, 125.0, 65.2, 52.8, 46.7, 42.3; HRMS (EI) calcd for C₂₈H₂₇Br; MS [M]⁺ 442.1296, found 442.1297.

1,3,5-Triphenyl-7-(2-cyanoethyl)adamantane 15. A solution of 1-bromo-3,5,7-triphenyladamantane **14** (0.50 g, 1.13 mmol), acrylonitrile (0.18 g, 3.39 mmol), tributylstannane (0.65 g, 2.26 mmol),

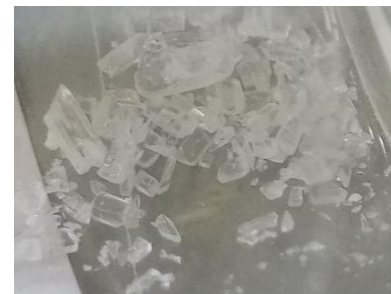




Sublimation/
Crystallization



Double
recrystallization



Colour of the compound is yellow or result of contamination?
Purification through column chromatography.



Elemental analysis (CHN)

AdBr₄**GL_158-2C***Molecular weight: 451.8220**Molecular formula: C₁₀H₁₂Br₄*

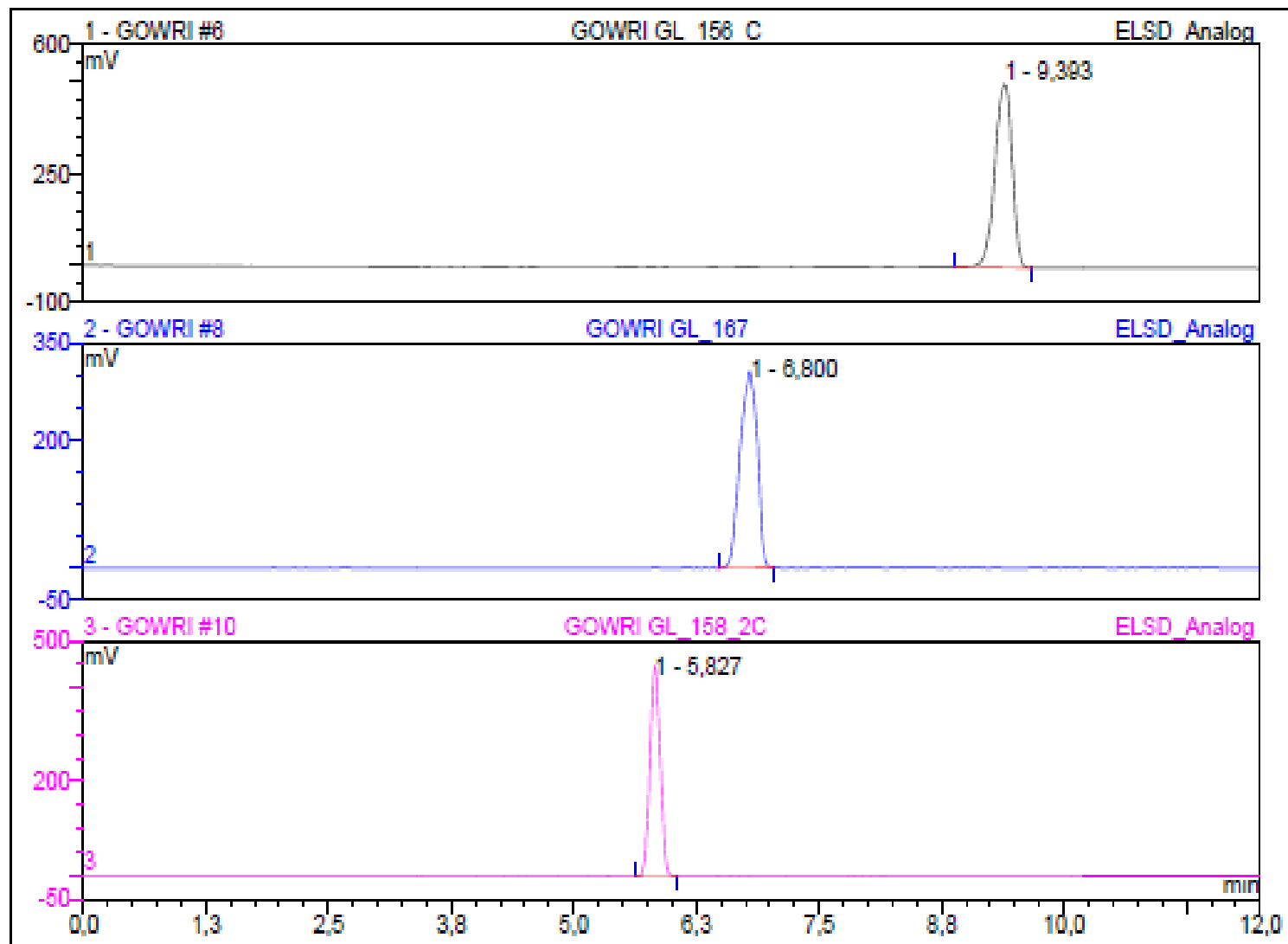
	Theoretical weight (%)	Observed weight (%)		
		1 st run	2 nd run	Average
% N	-	-	-	
% C	26.58	26.76	26.70	26.73
% H	2.68	2.66	2.70	2.68
Error Difference: C% = 0.005%, H% = 0%				

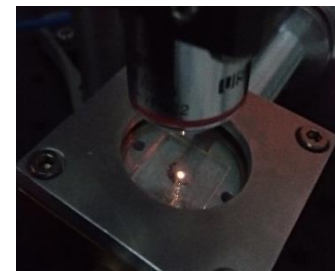
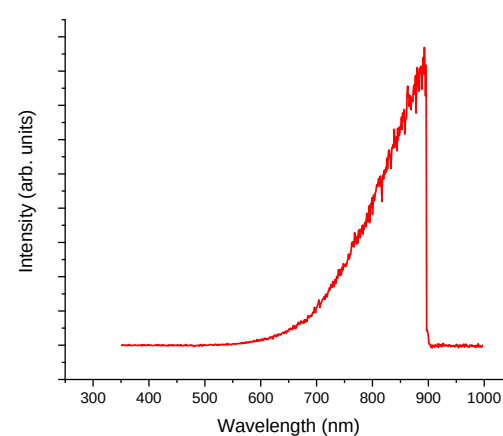
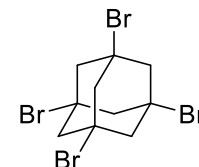
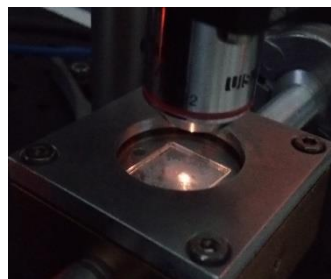
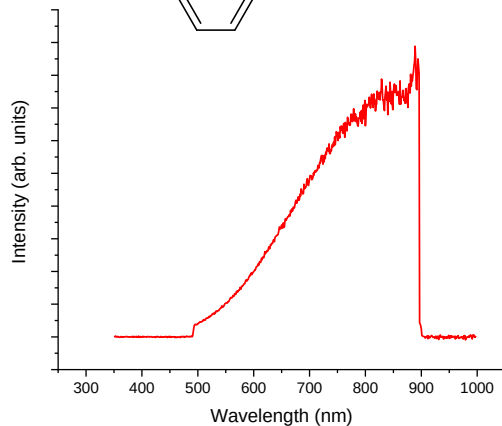
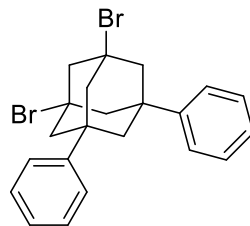
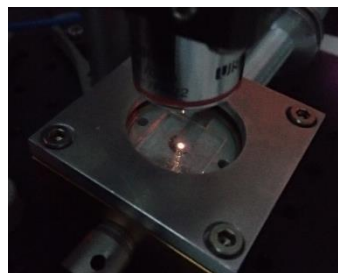
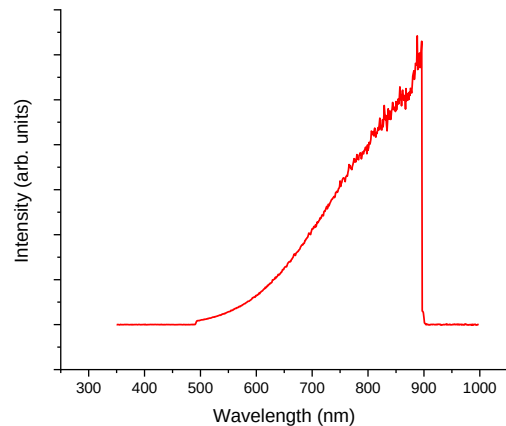
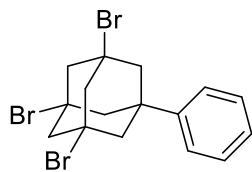
AdBrPh₃**GL_156-C***Molecular weight: 443.4280**Molecular formula: C₂₈H₂₇Br*

	Theoretical weight (%)	Observed weight (%)		
		1 st run	2 nd run	Average
% N	-	-	-	
% C	75.84	75.91	75.77	75.84
% H	6.14	6.11	6.15	6.13
Error Difference: C% = 0.0%, H% = 0.001%				

AdBr₃Ph**GL_167***Molecular weight: 449.0240**Molecular formula: C₁₆H₁₇Br₃*

	Theoretical weight (%)	Observed weight (%)		
		1 st run	2 nd run	Average
% N	-	-	-	
% C	42.80	42.75	42.77	42.76
% H	3.82	3.74	3.68	3.71
Error Difference: C% = 0.09%, H% = 0.029%				



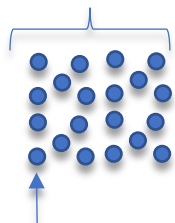


- Upon irradiation with 980 nm laser light, the powders produce broad WLG (Red). Filter window 500–900 nm was used

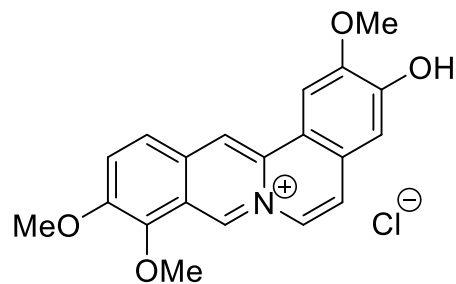
WLG measured by Gowri. Ball mill was used for making amorphous.



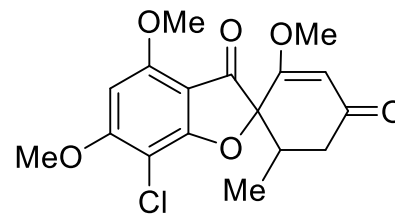
Powder XRD



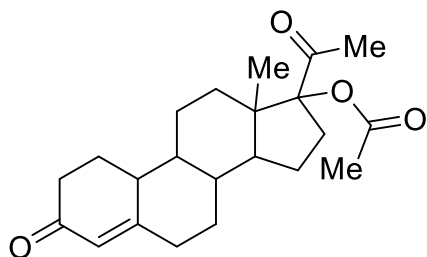
Single crystal XRD



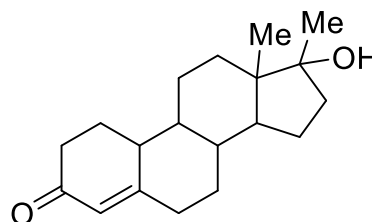
Jatrorrhizine chloride



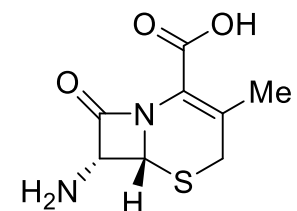
Griseofulvin



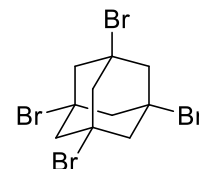
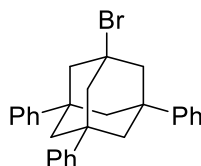
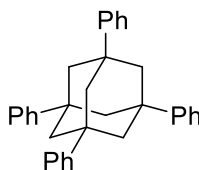
Gestonoronacetate

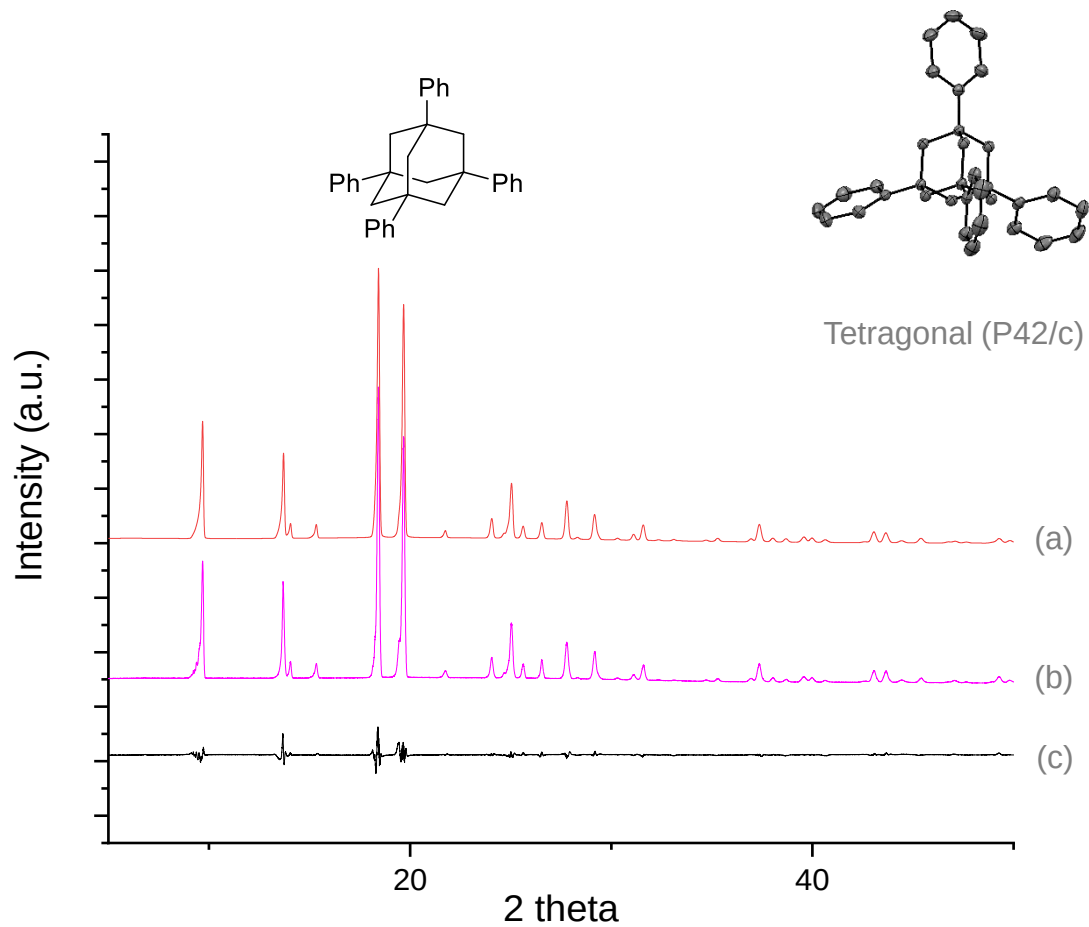


Normethisterone

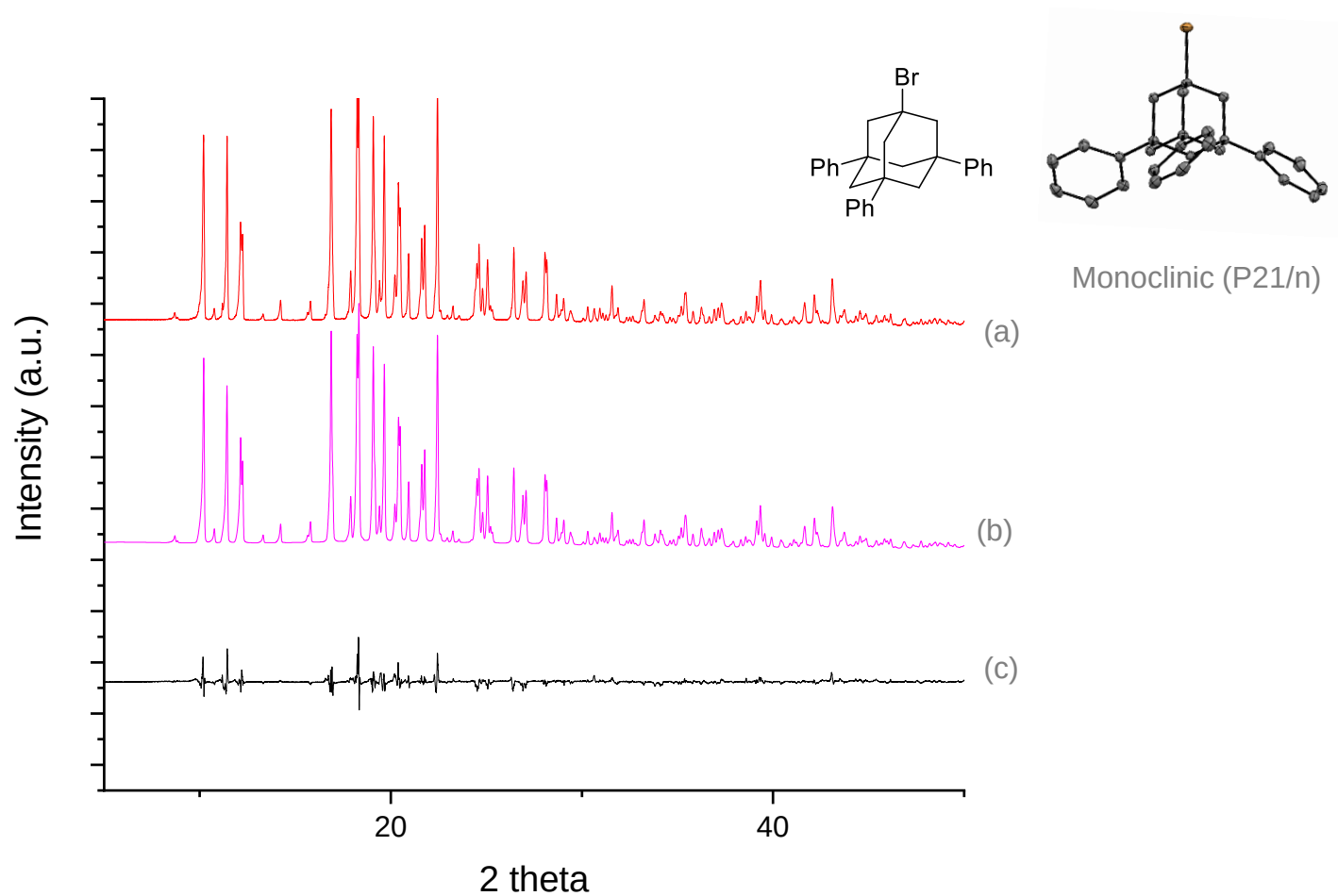


7-amino-3-desacetoxy
cephalosporanic acid

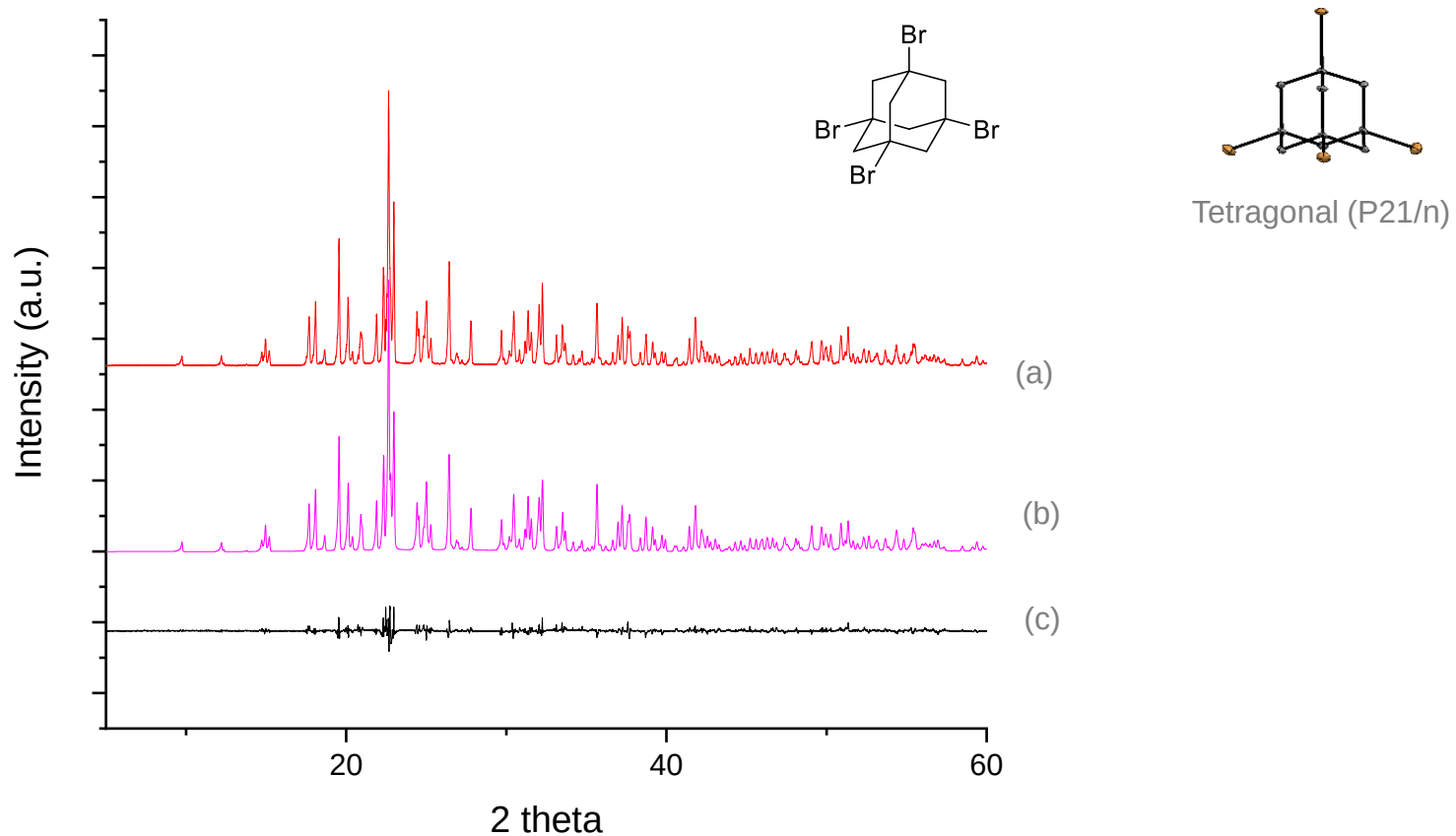




- (a) Measured pattern (**Red**) from powder XRD
- (b) Refinement powder XRD (**Magenta**) from Single crystal XRD
- (c) Difference between measured pattern and refinement pattern (**Black**).



- (a) Measured pattern (Red) from powder XRD
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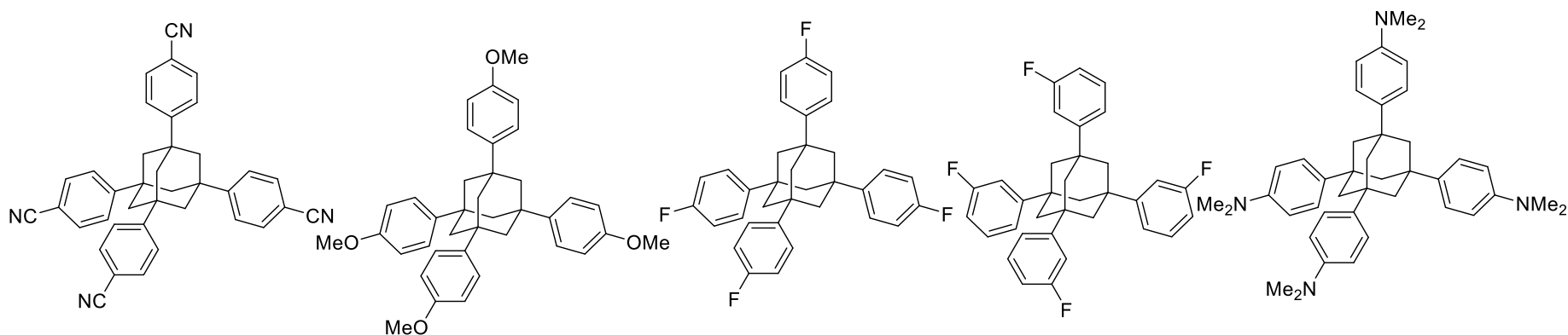


- (a) Measured pattern (Red) from powder XRD
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- (c) Difference between measured pattern and Refinement pattern (Black).

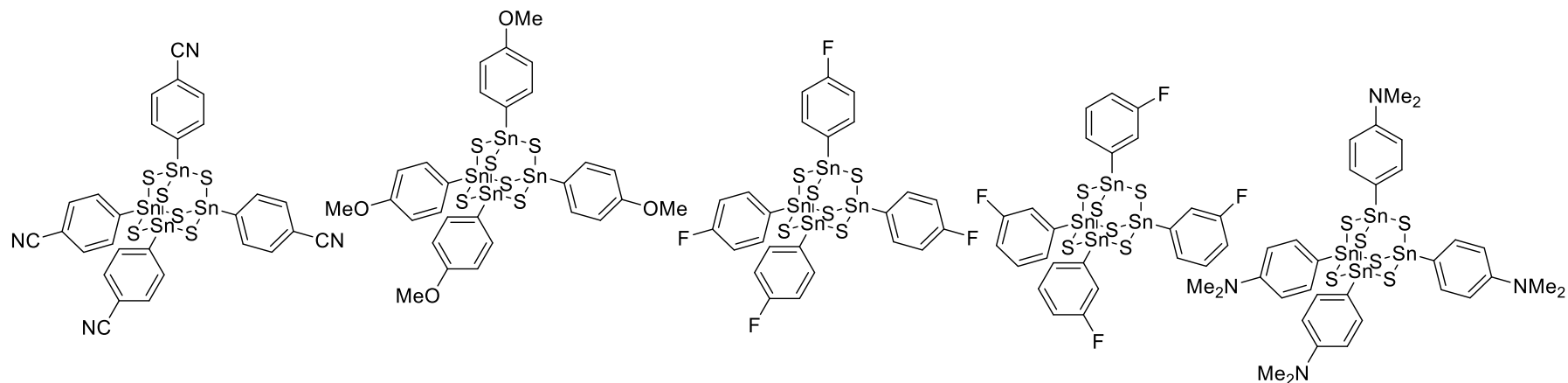
Determine the Hammett series (HOMO-LUMO gaps)



Organic Compounds



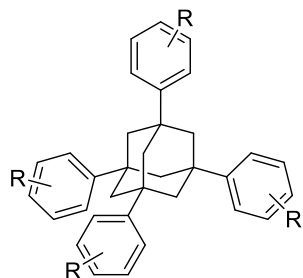
Inorganic Clusters



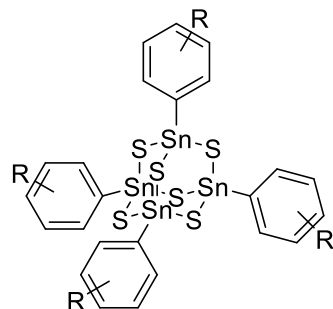
Determine the Hammett series (Organic compounds(-C-))



Natural Population Charge Analysis

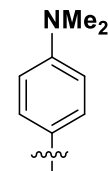
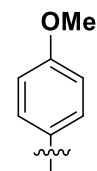
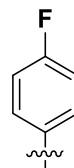
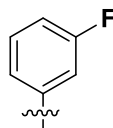
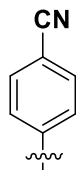
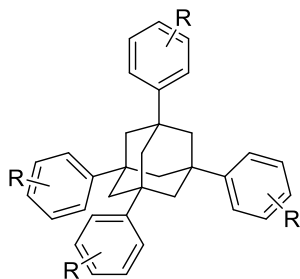


Hammett σ	+0.66	+0.34	+0.06	-0.27	-0.83
Avg. q (C tet)	+0.52	+0.57	+0.54	+0.39	+0.40
Avg. q (CH₂)	-0.26	-0.29	-0.28	-0.19	-0.20
Total q (Core)	+0.52	+0.56	+0.48	+0.40	+0.44

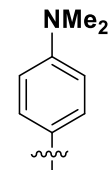
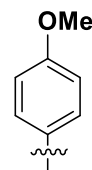
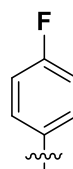
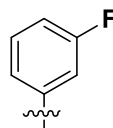
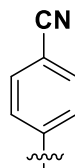
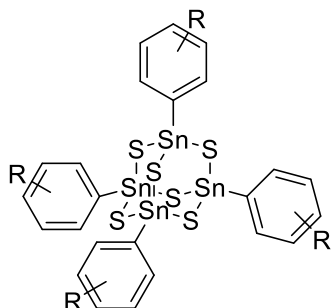


	+0.66	+0.34	+0.06	-0.27	-0.83
Hammett σ	+0.66	+0.34	+0.06	-0.27	-0.83
Total q (Sn)	+5.31	+5.32	+5.28	+5.35	+5.37
Total q (S)	-4.00	-4.05	-3.96	-4.16	-4.25
Total q (Sn-S)	+1.31	+1.27	+1.33	+1.19	+1.12

BP86/dhf-TZVP

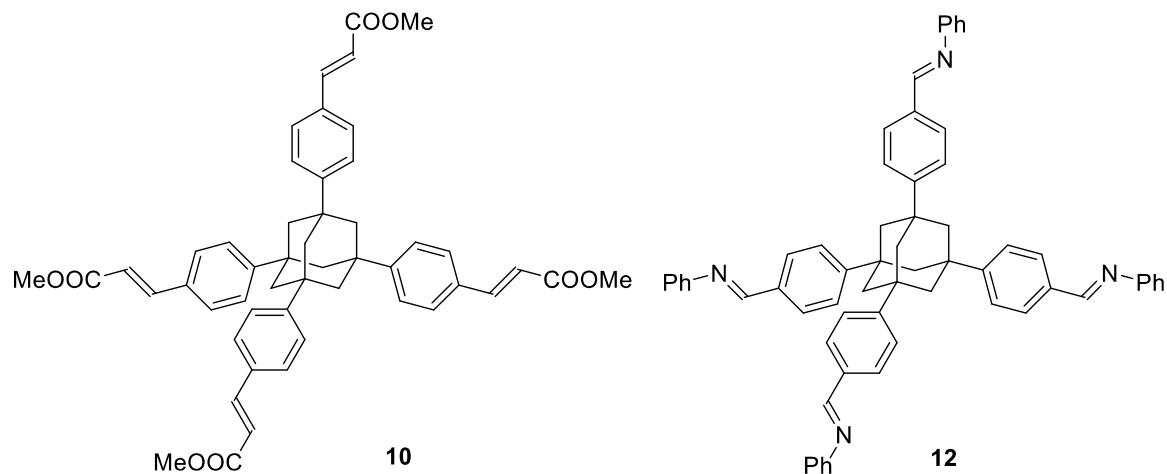


σ	+0.66	+0.34	+0.06	-0.27	-0.83
Gap: eV	+3.87	+4.52	+4.39	+4.05	+3.54



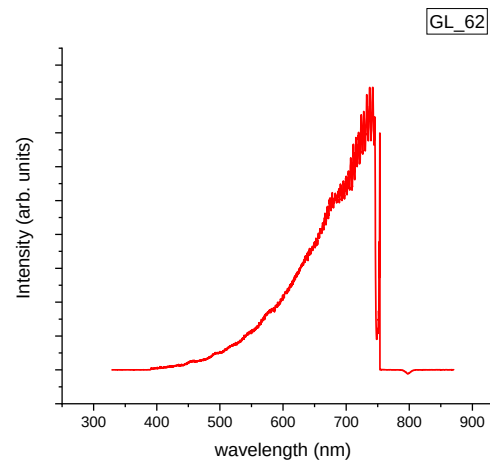
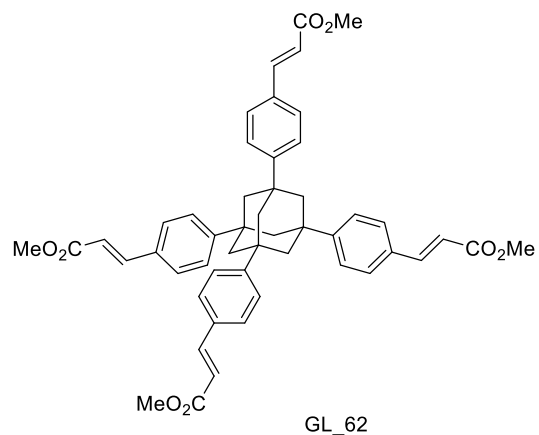
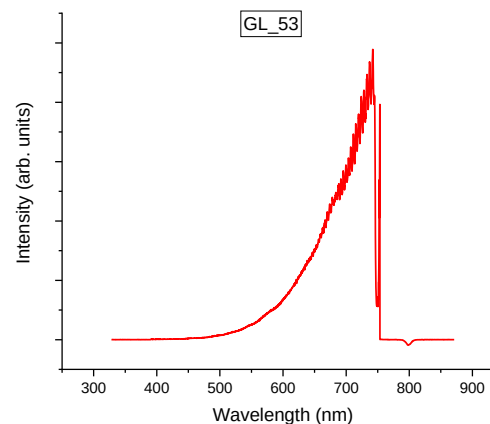
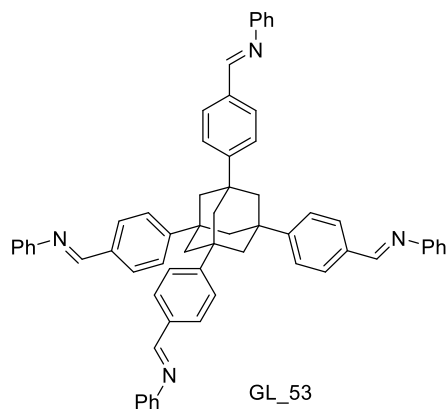
σ	+0.66	+0.34	+0.06	-0.27	-0.83
Gap: eV	+3.22	+3.22	3.16	+2.83	+2.01

BP86/dhf-TZVP



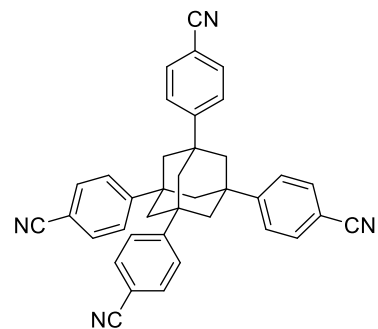
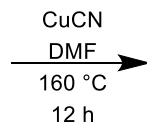
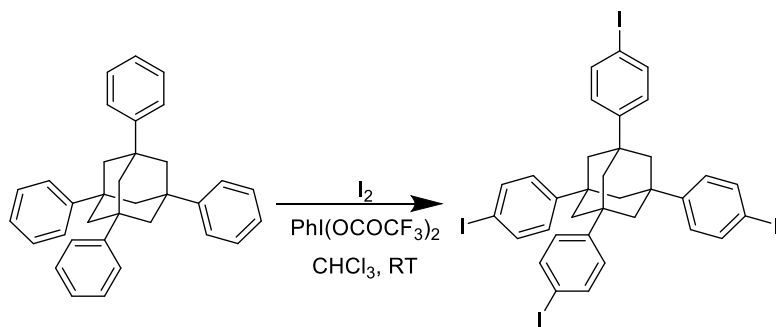
Compounds	HOMO – LUMO energy gap / eV
10	4.36
12	4.20

B3LYP-D3(BJ)/6-31G(d,p)

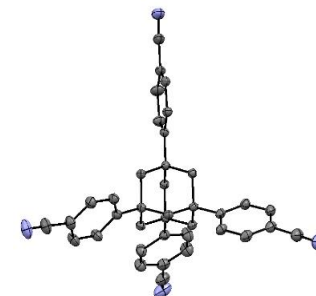


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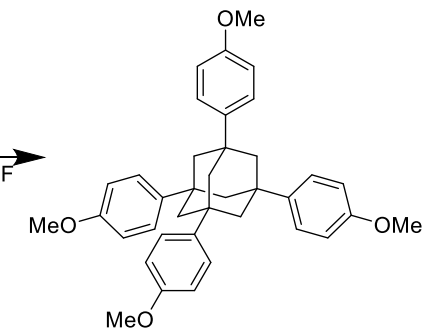
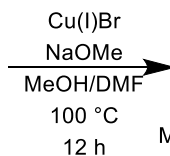
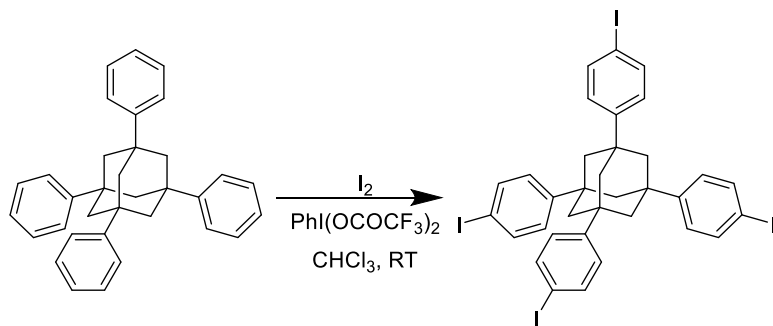
Synthesis of the following compounds



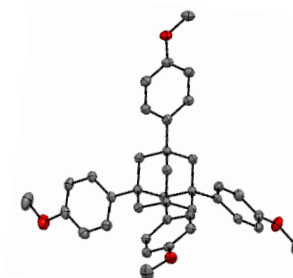
1,3,5,7-Tetrakis(4-CN-Phenyl)adamantane



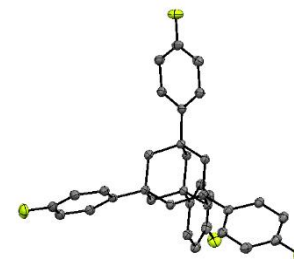
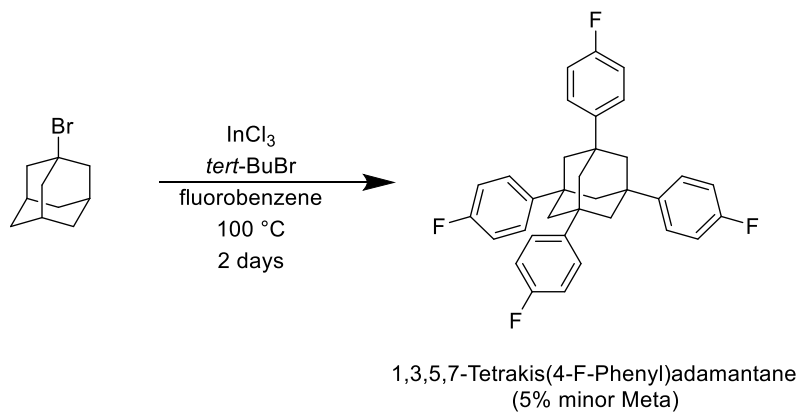
Monoclinic ($P2_1/n$)



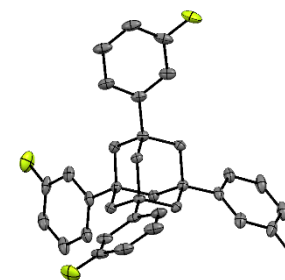
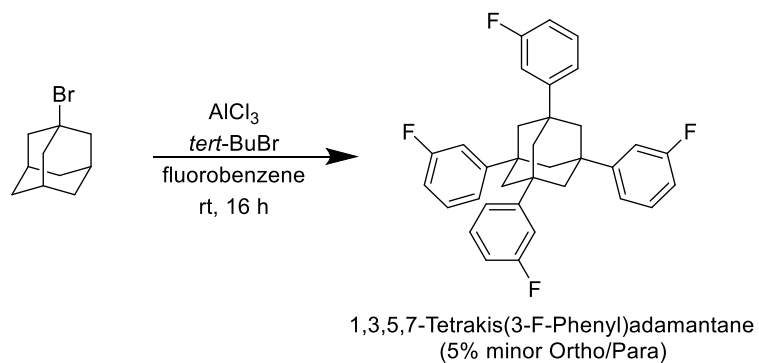
1,3,5,7-Tetrakis(4-MeO-Phenyl)adamantane



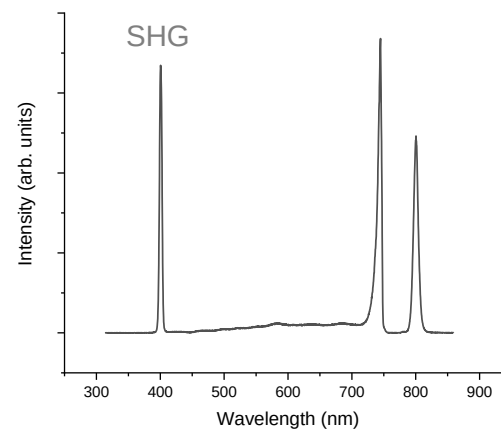
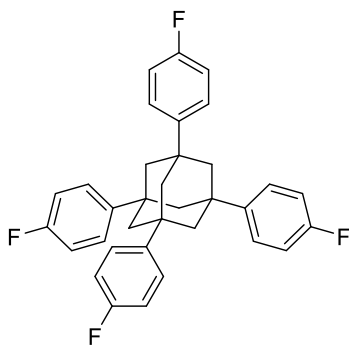
Monoclinic ($P2_1/n$)



Tetragonal (I-4)



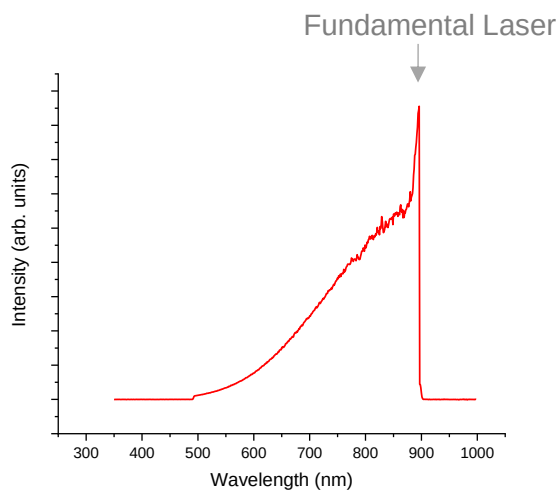
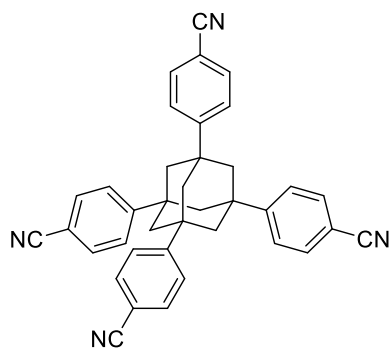
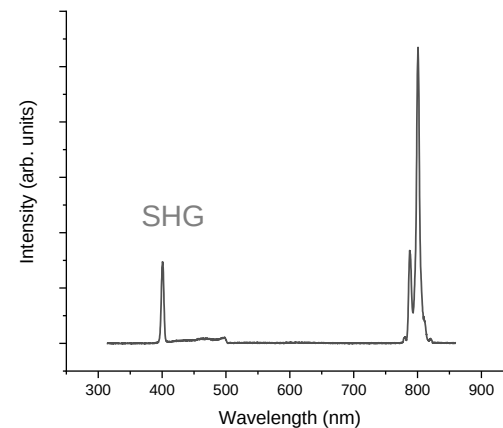
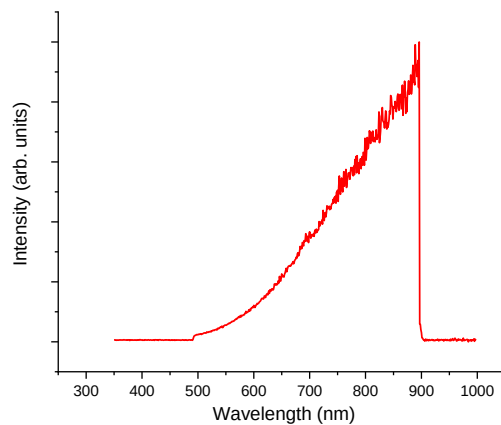
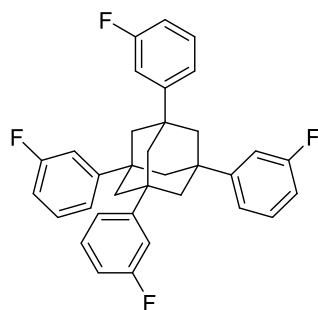
Tetragonal (P-4)



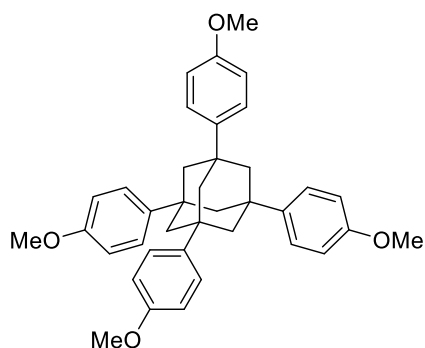
After WL measurement



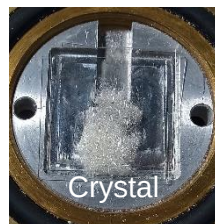
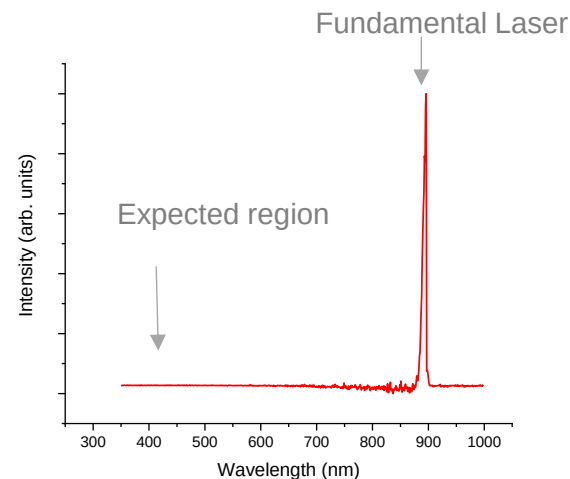
- WLG measured by Gowri. SHG measured by Mr. Marius Müller (Prof. Chatterjee).



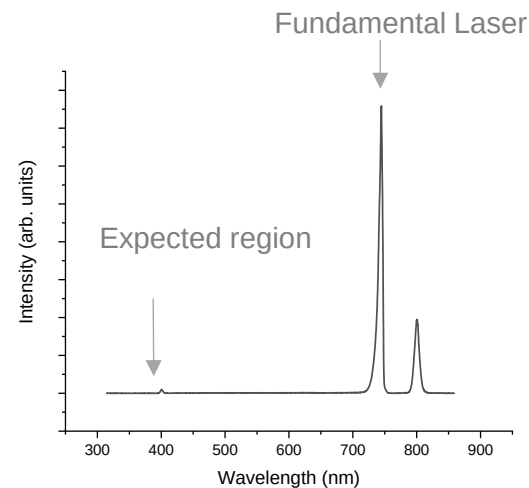
- Upon irradiation with 980 nm laser light, the powders produce broad WLG (**Red**). Single crystal give SHG (**Black**). Filter window 500–900 nm was used.



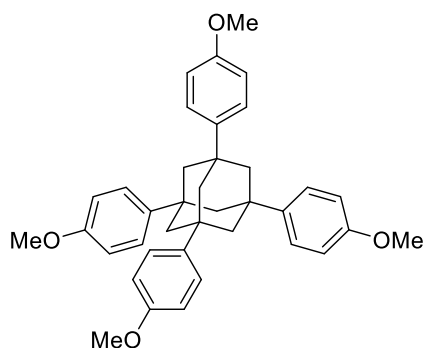
In principle amorphous does show WLГ



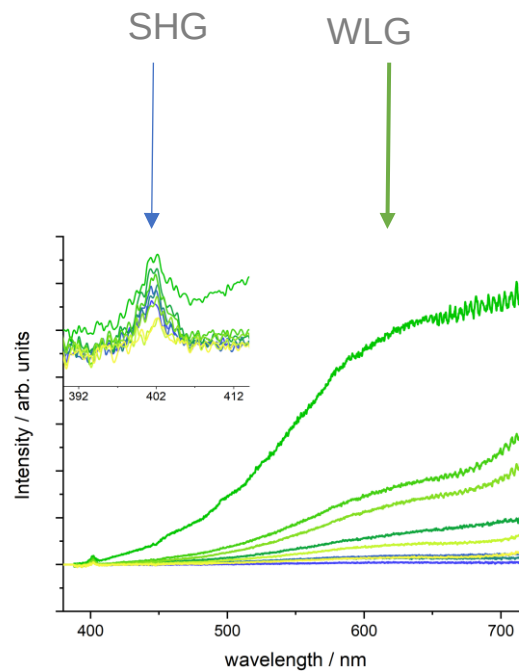
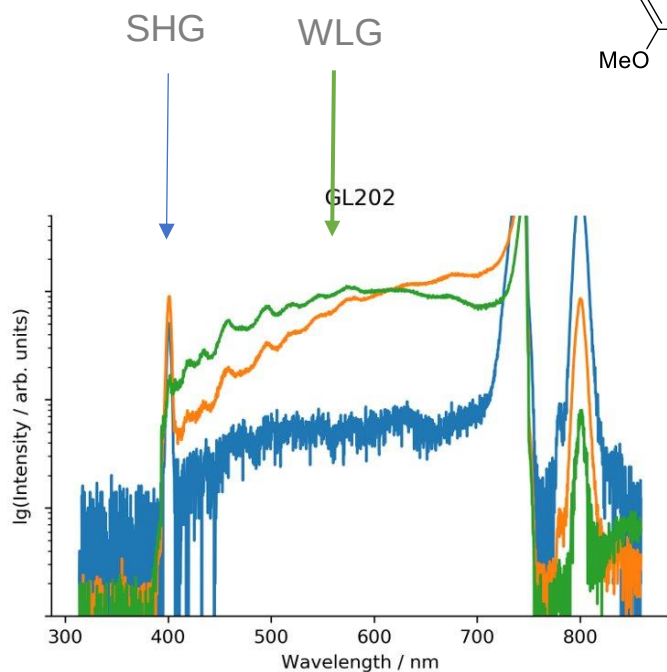
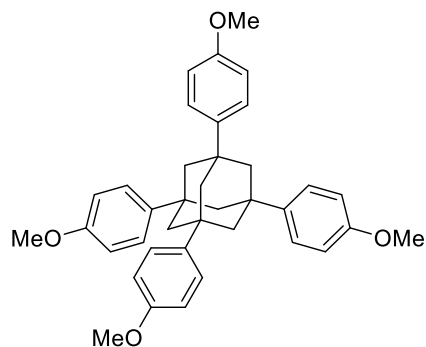
In principle crystal does show SHG



- Upon irradiation with 980 nm laser light, the powders produce broad WLГ (Red). Single crystal give SHG (Black). Filter window 500–900 nm was used.

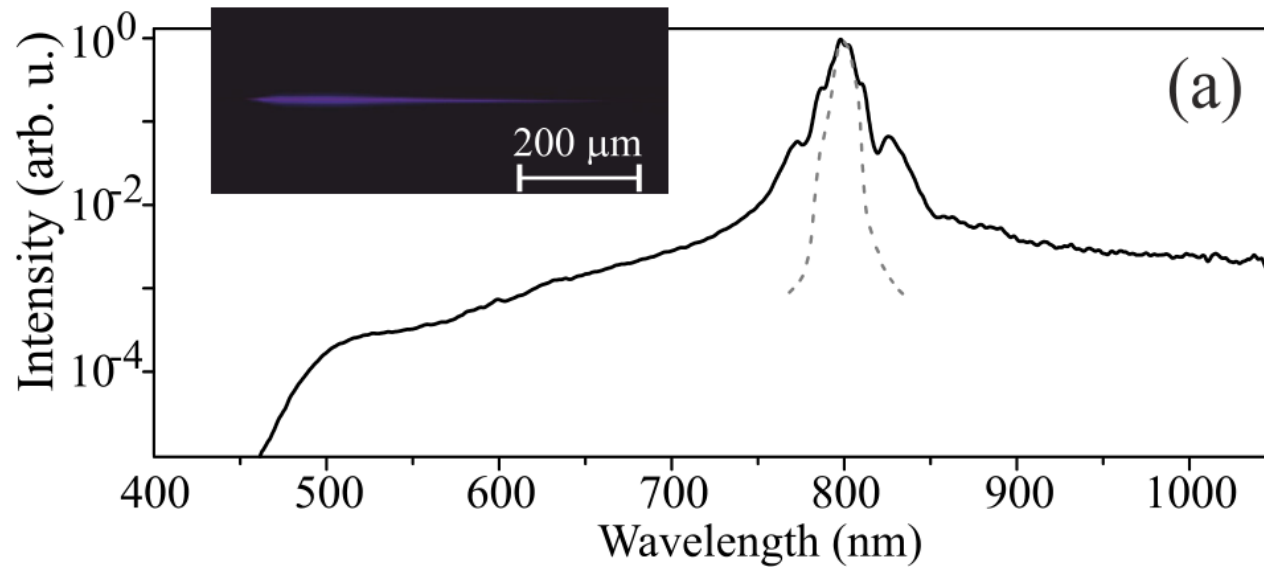


- Upon irradiation of laser light, the powder is moving away.





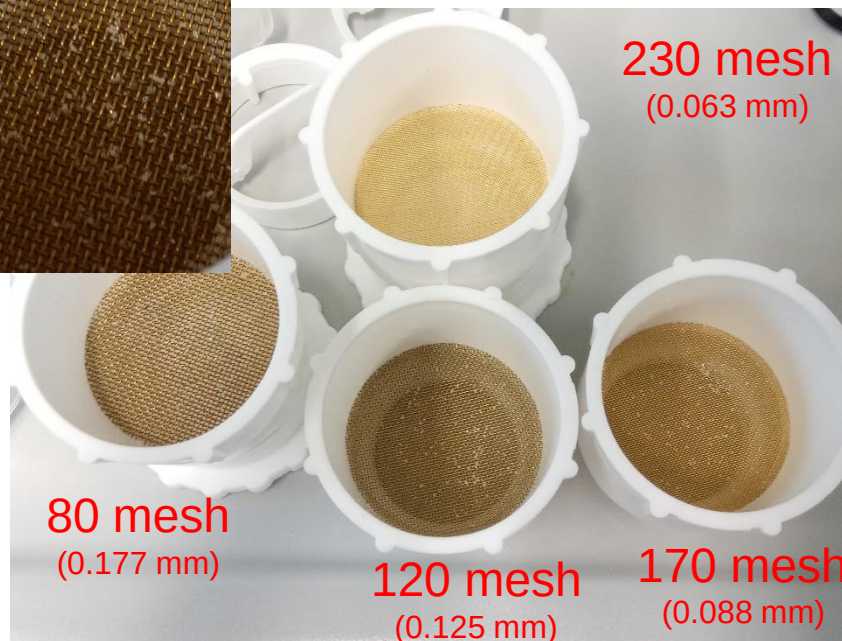
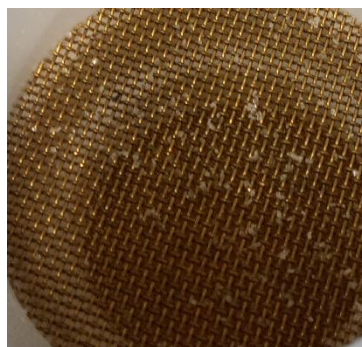
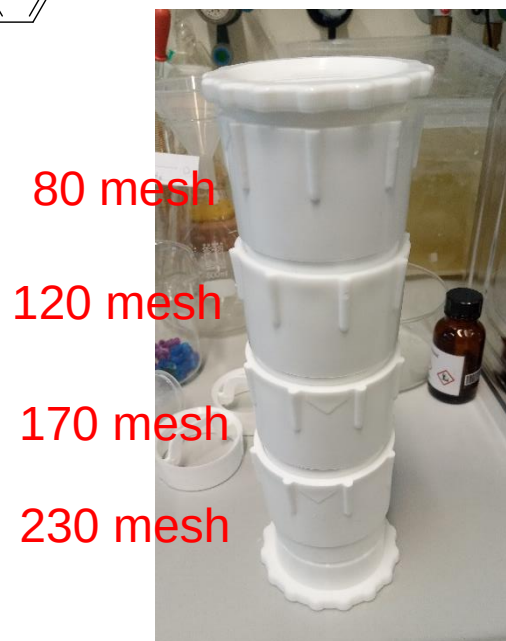
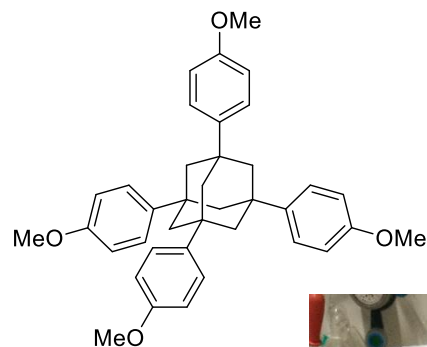
YAG = Yttrium aluminium garnet ($\text{Y}_3\text{Al}_5\text{O}_{12}$)



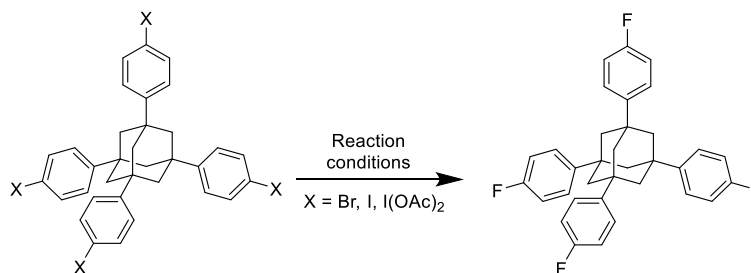
Energy relaxation pathways in ultrafast light-matter interactions.



Need a crystal size is around 0.5 to 1.0 mm

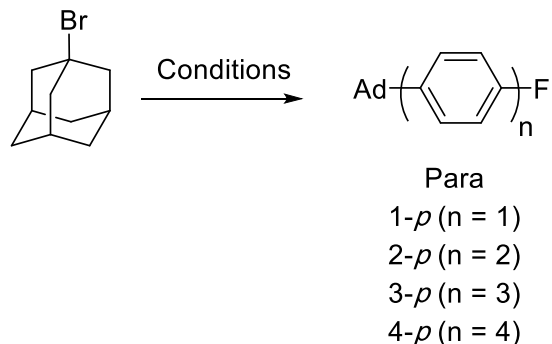


- Bel-Art™ SP Scienceware™ Mini-Sieve Micro sieve Set.



S.No	X	Catalysts	'F'	Conditions	Temp (°C)	Time (h)	Expected Product ^a
1.	I	TBABr	KF	DMF/H ₂ O	130	12	(-)
2.	I	TBABr	LiF	DMF/H ₂ O	130	12	(-)
3.	I	Pd(OAc) ₂	AgF/KF	DMF	135	12	(-)
4.	I	Pd(OAc) ₂	AgF/CsF	DMF	135	12	(-)
5.	I	-	Py.HF	DMF	50	12	(-)
6.	I	-	Py.HF	DMF	90	24	(-)
7.	I(OAc) ₂	Pd(OAc) ₂	CsF	DMF	130	24	(-)
8.	I(OAc) ₂	-	BF ₄	DMF	rt	24	(-)
9.	I	Pd(OAc) ₂ / Xphos (ligand)	KF	Toluene	130	24	(-)
10.	I	Cu(I)Br	KF	DMF	140	24	(-)
11.	I	Cu(I)Br	CsF	DMF	160	24	(-)

^aThe progress of the reaction was monitored by ¹⁹F-NMR. (-) not observed.

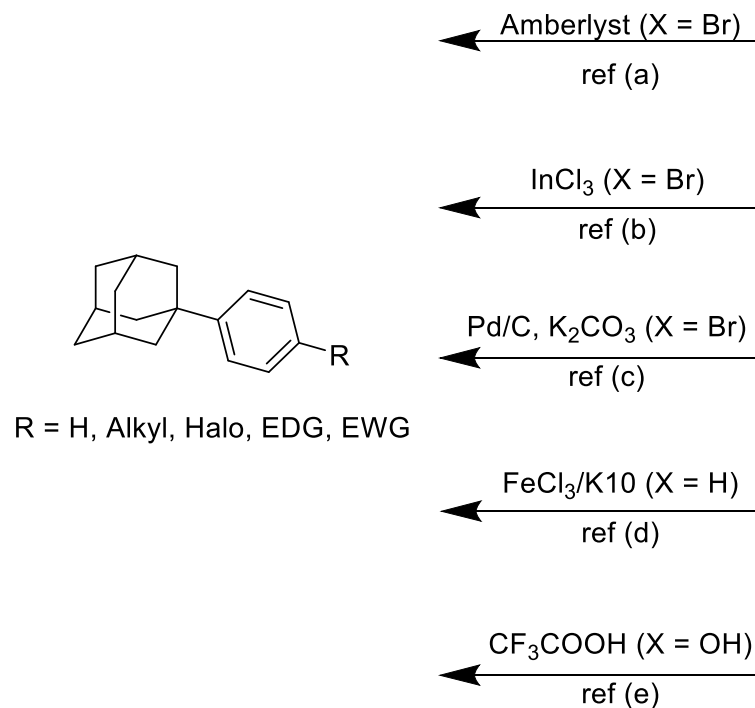


Entry	Catalysts (equiv.)	t-BuBr ^a (equiv.)	Temp. (°C)	Time (h)	Conv. (%)	% isomer distribution	
						Ortho/Para ^b	Meta ^b
1.	CF ₃ CO ₂ H (0.1)	4.0	rt	16	-	(-)	(-)
2.	PCl ₅ (0.1)	4.0	rt	16	-	(-)	(-)
3.	POCl ₃ (0.1)	4.0	rt	16	-	(-)	(-)
4.	MeSO ₂ H (0.1)	4.0	rt	16	-	(-)	(-)
5.	TiCl ₄ (0.1)	4.0	rt	16	-	(-)	(-)
6.	InCl ₃ (0.2)	-	rt	16	100	1- <i>p</i> (97)	(-)
7.	InCl ₃ (0.2)	-	70	16	100	1- <i>p</i> (80), 2- <i>p</i> (10)	(-)
8.	InCl ₃ (0.25)	4.5	100	72	100	4- <i>p</i> (95)	4- <i>m</i> (5)

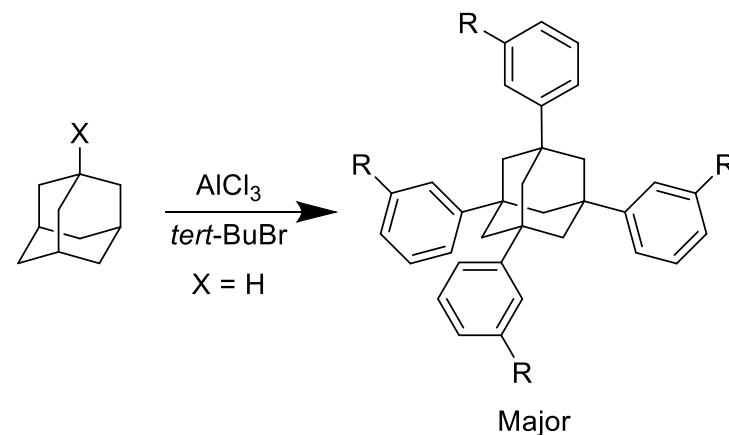
Reaction conditions: Ad-Br (500 mg, 2.33 mmol). ^aFluorobenzene as solvent (3-4 mL). ^bThe progress of the reaction was monitored by ¹⁹F-NMR/GCMS. 1,3,5-Trimethoxybenzene was used as internal standard for ¹H-NMR. (-) not observed.



Known Approach



Our Approach



a) G. A. Olah, B. Török, T. Shamma, M. Török, G. K. S. Prakash, *Catal. Lett.* **1996**, 42, 5.

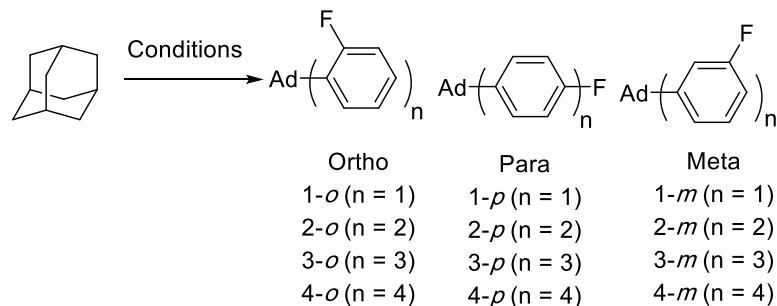
G. A. Olah, O. Farooq, S. M. F. Farnia, A. -H. Wu, *J. Org. Chem.* **1990**, 55, 1516. (some examples for meta selective)

b) P. Mosset, R. Gree, *Synlett* **2013**, 1142.

c) S. Bräse, B. Waegell, A. d. Meijere, *Synthesis*, **1998**, 148.

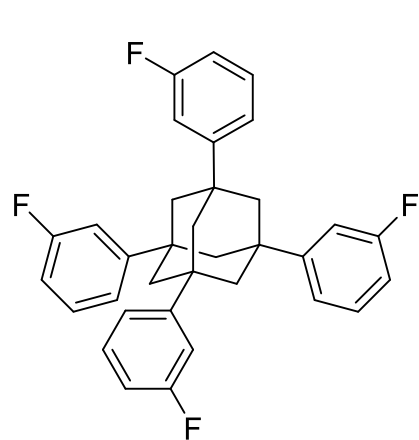
d) S. Chalais, A. Cornélis, A. Gerstmans, W. Kołodziejcki, P. Laszlo, A. Mathy, P. Métra, *Helvetica Chimica Acta*, **1985**, 1196

e) W. A. Sokolenko, N. M. Svirskaya, A. A. Kondrasenko, I. V. Peterson, N. I. Pavlenko, A. I. Rubaylo, *Russian Chemical Bulletin*, **2015**, 64, 246.

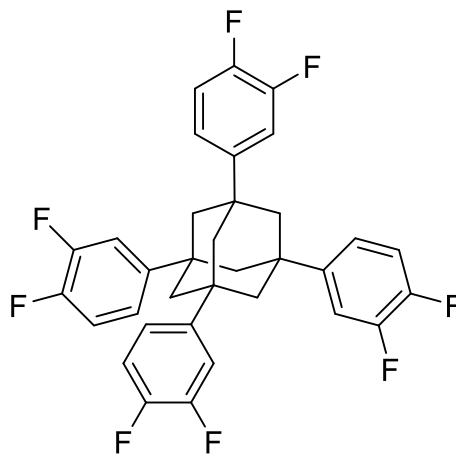


Entry	Catalysts (equiv.)	t-BuBr ^a (equiv.)	Temp. (°C)	Time (h)	Conv. (%)	% isomer distribution	
						Ortho/Para ^b	Meta ^b
1.	AlCl ₃ (0.1)	-	rt	16	100	1- <i>p</i> (11)/2- <i>p</i> (11)	1- <i>m</i> (66)/2- <i>m</i> (11)
2.	AlCl ₃ (0.3)	-	rt	16	100	2- <i>o</i> (2)/2- <i>p</i> (13)	1- <i>m</i> (66)/2- <i>m</i> (19)
3.	AlCl ₃ (0.5)	-	rt	16	100	2- <i>o</i> (2)/2- <i>p</i> (12)	1- <i>m</i> (61)/2- <i>m</i> (24)
4.	AlCl ₃ (0.5)	2.0	rt	16	100	4- <i>o</i> /4- <i>p</i> (20)	4- <i>m</i> (75)
5.	AlCl₃ (0.5)	4.0	rt	16	100	4-<i>o</i>/4-<i>p</i> (13)	4-<i>m</i> (85)
6.	AlBr ₃ (0.5)	4.0	rt	3	100	4- <i>o</i> /4- <i>p</i> (20)	4- <i>m</i> (60)
7.	CF ₃ CO ₂ H (0.1)	4.0	rt	16		(-)	(-)
8.	PCl ₅ (0.1)	4.0	rt	16		(-)	(-)
9.	POCl ₃ (0.1)	4.0	rt	16		(-)	(-)
10.	MeSO ₂ H (0.1)	4.0	rt	16		(-)	(-)
11.	TiCl ₄ (0.1)	4.0	rt	16		(-)	(-)

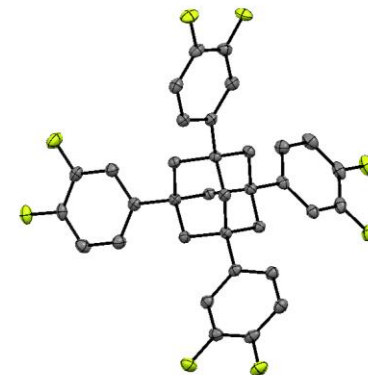
Reaction conditions: Ad-Br/Ad (500 mg). ^aFluorobenzene as solvent (3-4 mL). ^bThe progress of the reaction was monitored by ¹⁹F-NMR/GCMS. 1,3,5-Trimethoxybenzene was used as internal standard for ¹H-NMR. (-) not observed.



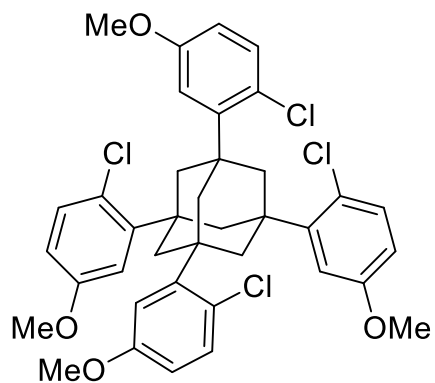
(68%, rt, 16 h)



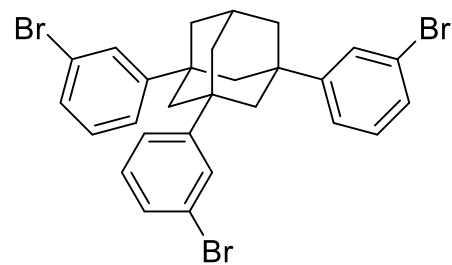
(95%, rt, 16 h)



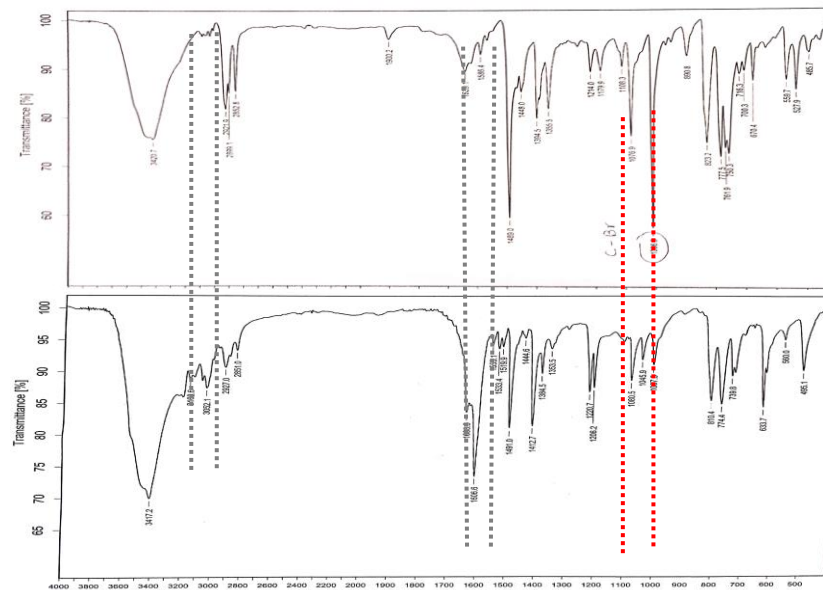
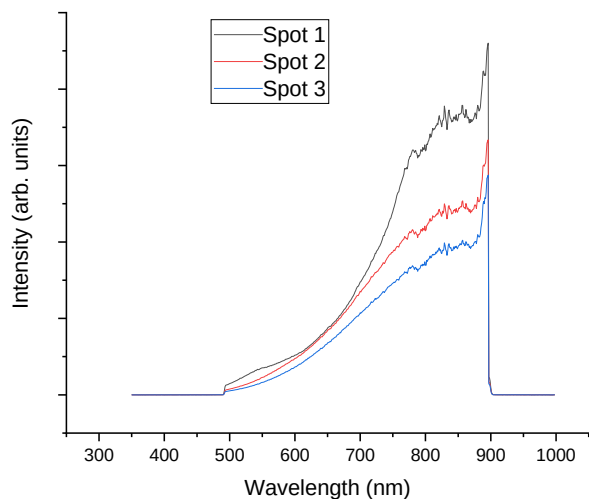
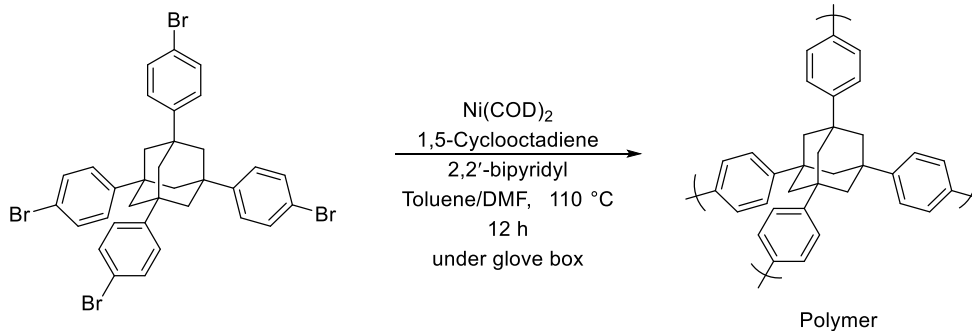
Monoclinic (P21/c)



39%, 70 °C, 16 h
(reconfirm)

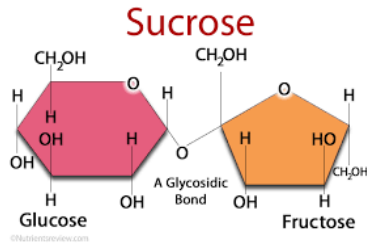


(82%, rt, 16 h)



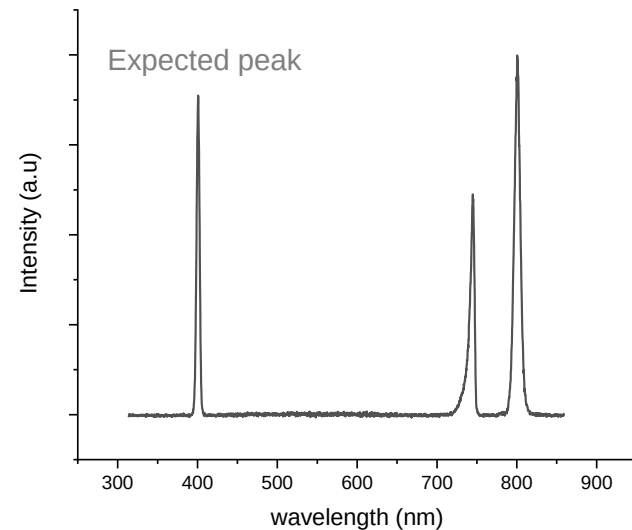
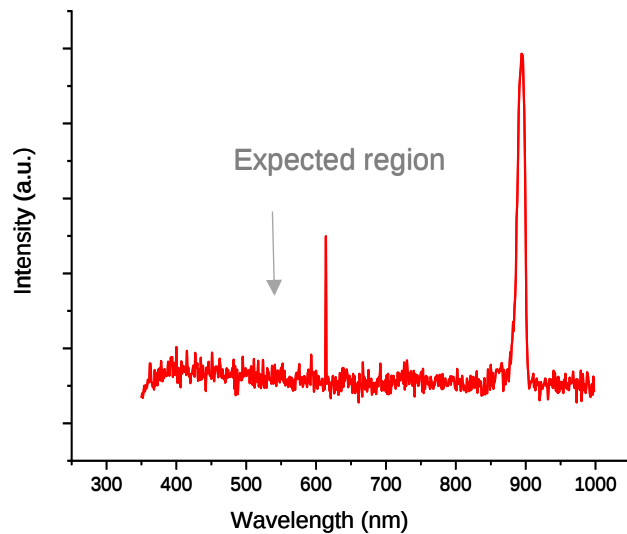
TBPA (Starting material) disappearance of the band at 1076 cm^{-1} which arises from the C–Br oscillation.

New bands appeared near 3050 and 1600 cm^{-1} .



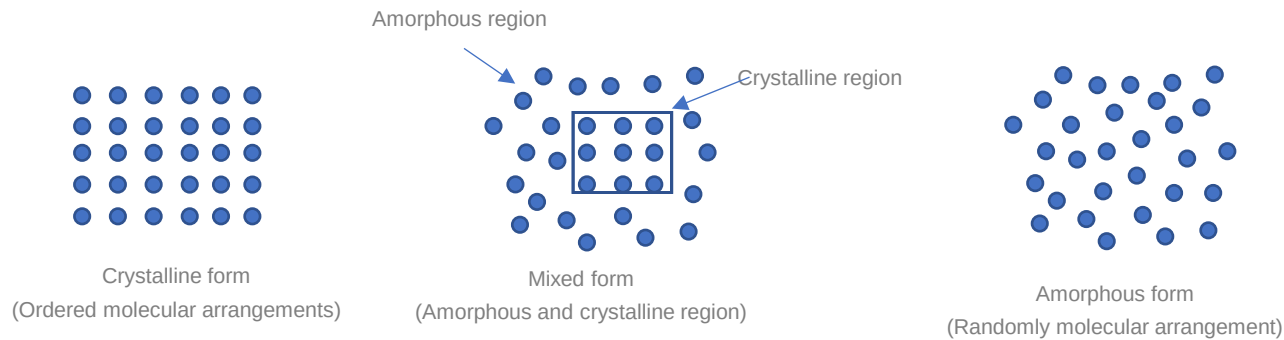
Amorphous

Crystal



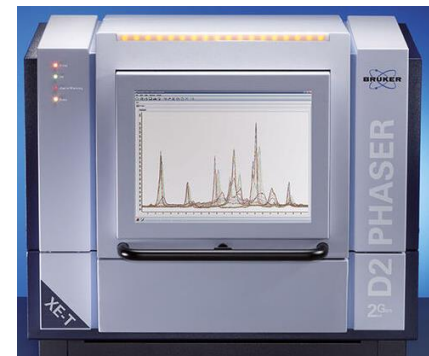
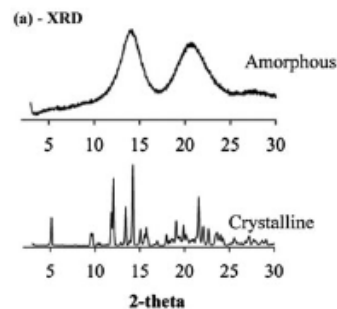
- Upon irradiation with 980 nm laser light, the powders produce broad WLW (Red). Single crystal give SHG (Black). Filter window 500–900 nm was used.

Characterize the structure for amorphous and crystalline or mixed structure



- ❖ The common techniques include **X-ray diffraction**, scanning electron microscope, polarized light microscope, thermal analysis (differential scanning calorimetry, thermogravimetry, FT infrared spectroscopy, Raman spectroscopy, solution calorimetry, true density, thermally stimulated current spectrometry, dynamic mechanical analysis).

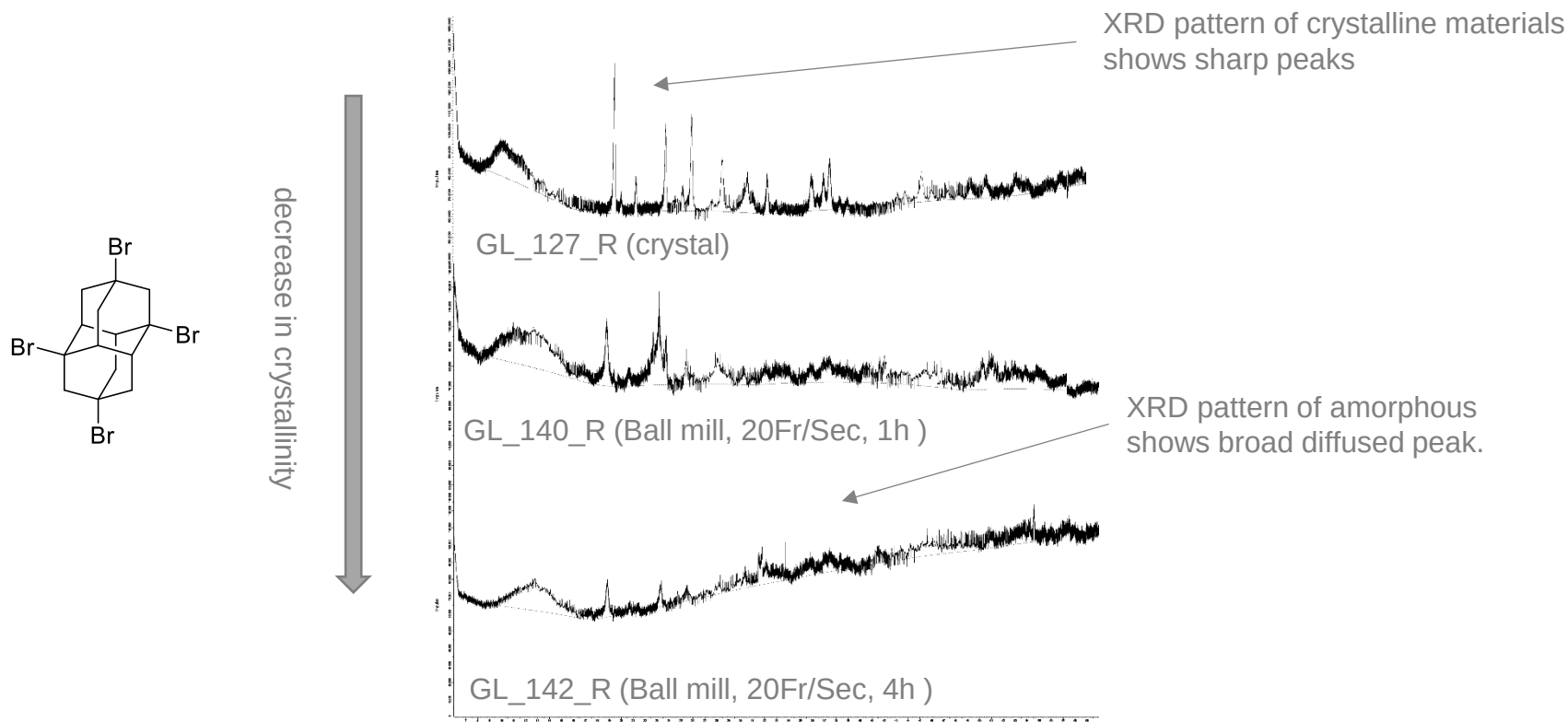
Example: XRD of amorphous and crystalline α -cyclodextrin powders

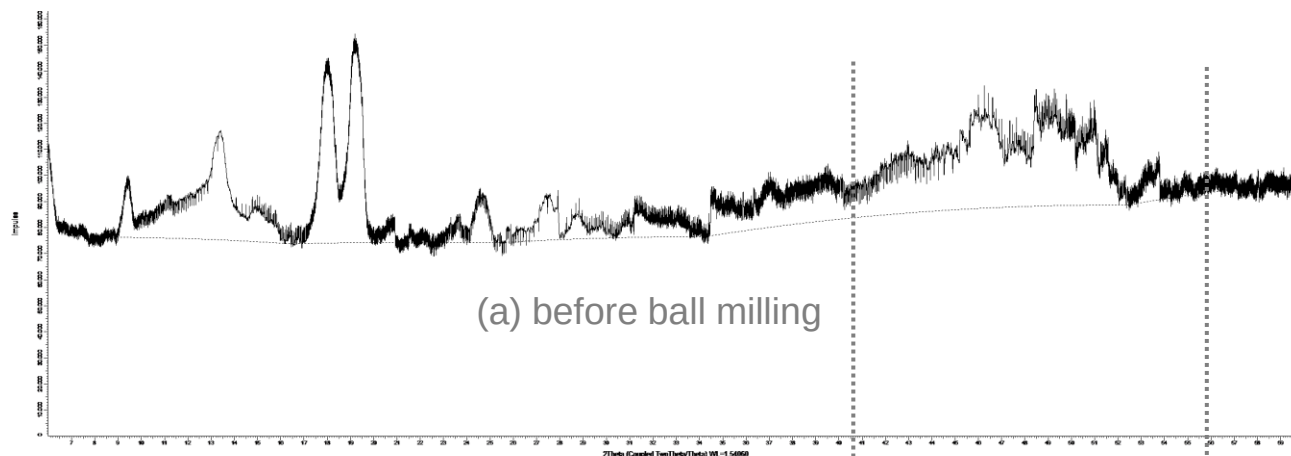


X-ray diffraction (D2 PHASER - best benchtop XRD system)

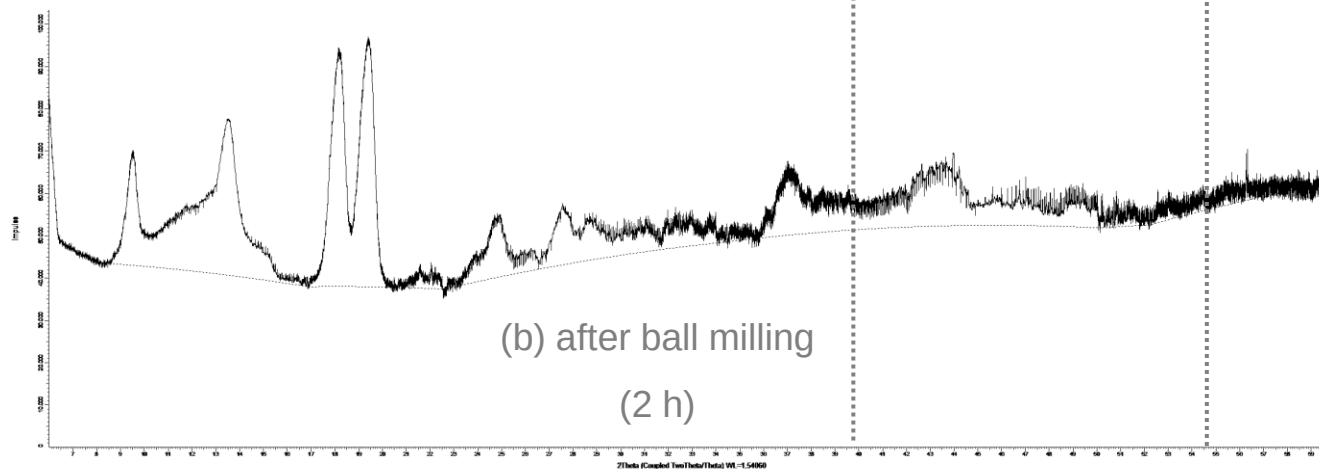
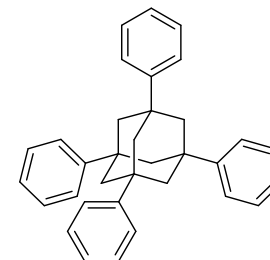


- ❖ After **ball milling** (1– 4 h), we observed a considerable decrease in crystallinity.
- ❖ We use X-ray powder diffraction to characterize the amorphous state. Unfortunately, we do not have necessary tools to quantify the amorphicity/crystallinity.





(a) before ball milling



(b) after ball milling
(2 h)

❖ We observed a small decrease in crystallinity.



- ❖ Bromo substituted adamantane derivatives show WLG.
- ❖ 1,3,5,7-tetrakis(4-methoxyphenyl)adamantane gives supercontinuum generation.
- ❖ Results show that the PXRD technique has approximately the same precision as the Single crystal-XRD technique.
- ❖ Successfully synthesized 1,3,5,7-tetrakis(3-fluoro-phenyl)adamantane in 68% yield as isomer (*meta*) with AlCl_3 as catalyst in combination with *tert*-Butylbromide.
- ❖ Core charge can not change depending on the functional group (-CN, -F, -OMe and -NMe₂, -CH₂=CH-COOMe, -CH=NPH)



Work Packages	months, 1 st year						months, 2 nd year						months, 3 rd year					
	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
WP1: Preparation of aryl-adamantane derivatives																		
WP1: Synthesis of CH ₂ -hetero-adamantane derivatives																		
WP1: Preparation of bridgehead hetero-adamantanes																		
WP2: Computational screening and assessment																		
WP3: Particle size determination																		
WP4: Compound blending studies																		
Writing up, publication																		
WP5: Outlook	Second funding period																	



- ❖ 1. N. W. Rosemann, H. Locke, P. R. Schreiner, S. Chatterjee, *Adv. Optical Mater.* **2018**, 6, 170116.
- ❖ 2. Meta selective C-H Adamantylation of substituted benzene (yet finished)
- ❖ 3. Nonlinear Optical Responses of Inorganic/Organic adamantane cluster of substituted phenyl: DFT and White-Light Generation (yet finished)



- ❖ The synthetic efforts of the Dehnen and our groups will be synced in the sense that all complementary inorganic / organic as well as hybrid structures will be synthesized by these two groups and passed on to the analytical groups.
- ❖ The subsequent physical measurements on nonlinear response upon laser excitation of the new compounds will be carried out in the Chatterjee group, while molecular assemblies will be analyzed with TEM-techniques in the Volz group.
- ❖ Finally, in building a theoretical working model of the non-linear optical effects, our group will closely interact with the theory groups of Mollenhauer and Sanna .





Prof. Peter R. Schreiner
&
Our group (Lab) members
&
Analytical Team



Collaborator:

Mr. Marius Müller (Prof. Chatterjee)

Dr. Juergen Belz (Prof. Volz)

Dr. Benjamin Klee (Prof. Pilgrim)

Mr. Sebastian Schwan (Prof. Mollenhauer)

Dr. Chris (Prof. Dehnen)

Prof. Simone Sanna



Thank you for your kind attention!!!

“Es ist nicht genug zu wissen, man muss auch anwenden;
es ist nicht genug zu wollen, man muss auch tun.”

“Knowing is not enough, we must apply;
Willing is not enough, we must do.”

J. W. von Goethe

