Doctoral Dissertation

Study on Development of a New Photoreactive Framework for Photoreleasing Various Functionalities and its Photoreactivity

多様な官能性化合物の光放出能を有する新規光反応性骨格の開発

およびその光反応性に関する研究

September 2022

Graduate School of Science and Technology

Nara Institute of Science and Technology

Liu Haiying

Table of Contents

List of Abbreviations

Ar	Aryl
Ac	Acetyl
Abs	Absorbance
Acetyl	Acetyl
LDA	Lithium diisopropyl amide
UV	Ultraviolet
DCM	dichloromethane
DMSO	Dimethylsulfoxide
DMF	*N, N*-Dimethylformamide
Et	Ethyl
GC	Gas chromatography
IR	Infrared absorption spectrometry
Me	Methyl
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
Ph	Phenyl
rt	Room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
DIPC	*N*,*N*′-Diisopropylcarbodiimide
bpy	2,2'-Bipyridyl
DABCO	1,4-diazabicyclo[2.2.2]octane

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-Dimethylaminopyridine
UV-vis	Ultra violet-visible
PPG	Photoremovable protecting group
NQ	1,4-Napthoquinone
NQ-Ar	2-arylnaphthalene-1,4-dione
NQ-Ar-OH	2-aryl-3-(hydroxymethyl)naphthalene-1,4-dione
NQ-Ph-N_2	2-(diazomethyl)-3-phenylnaphthalene-1,4-dione

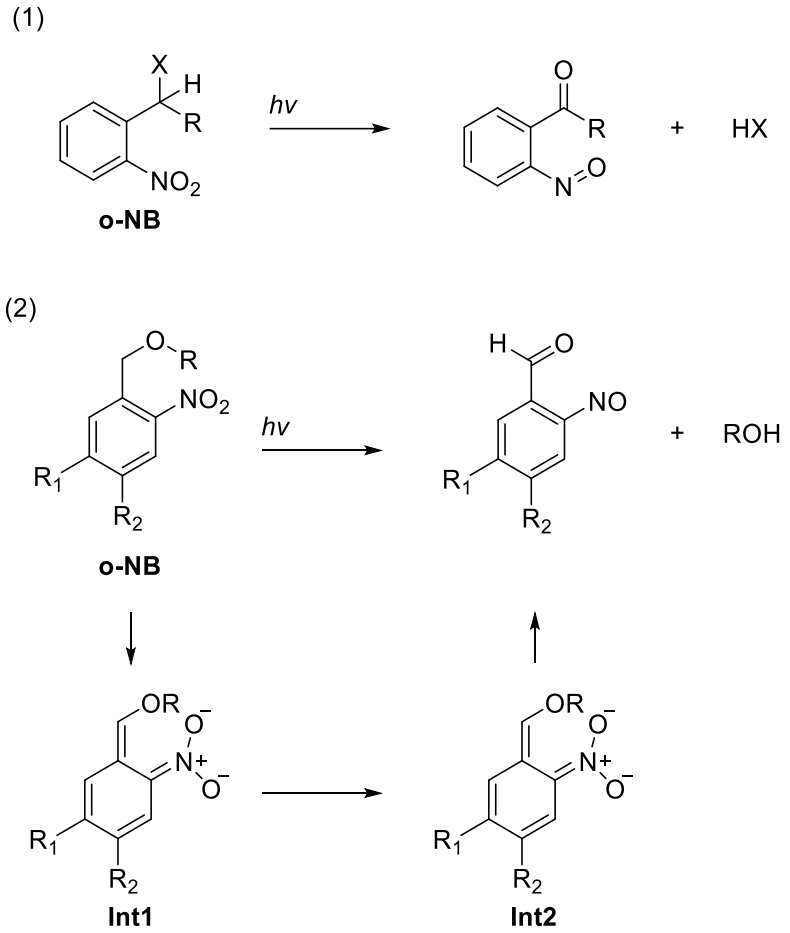
General Introduction

1. Photoremovable Compounds

Photoremovable groups allow for the temporally and spatially controlled release of reactive substances only by photoirradiation without the need for adding other chemicals.[1] A photoremovable protecting group (PPG) functions much as any other protecting group, except that its release step is triggered by irradiation with light. There is the additional advantage of mild and neutral reaction conditions. Following early reports on PPGs for use in organic synthesis by Barltrop,[2] Barton,[3] Woodward,[4] Sheehan[5] and their co-workers, more and more photoremovable compounds were developed.

o-Nitrobenzyl derivatives (*o*-NB) make up a family of general-purpose PPGs that have been developed since the 1960s and are still widely used.[6] The photoirradiation of *o*-NB esters usually yields carboxylic acid, accompanied by an *o*-nitrosobenzaldehyde.[7] Frechet and co-workers expanded the *o*-NB photoremovable framework to yield organic bases by employing *o*-nitrobenzyl carbamates of amines and diamines, which then result in the release of the respective alkylamines.[8] Then, *o*-NB variants were used for alcohol releasing[9] and peptide releasing[10]. Recent developments have focused on the design of *o*-

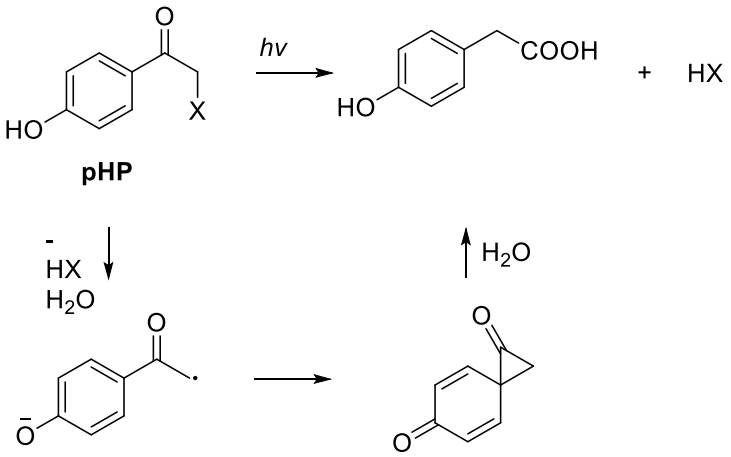
NB-based protecting groups with a red-shifted absorption to allow photolysis to occur using two-photon excitation techniques.[11] Linkers and protecting groups based on *o*-NB chemistry can usually be cleaved in minutes when exposed to 300−365 nm. (Scheme 0.1)



Scheme 0.1 Photoirradiation reaction and postulate pathway of *o*-NB derivatives.

p-Hydroxyphenacyl (Scheme 0.2) has emerged as a promising candidate.[12] Advantageous properties are the hydrophilicity of the *p*HP ligand, the high quantum

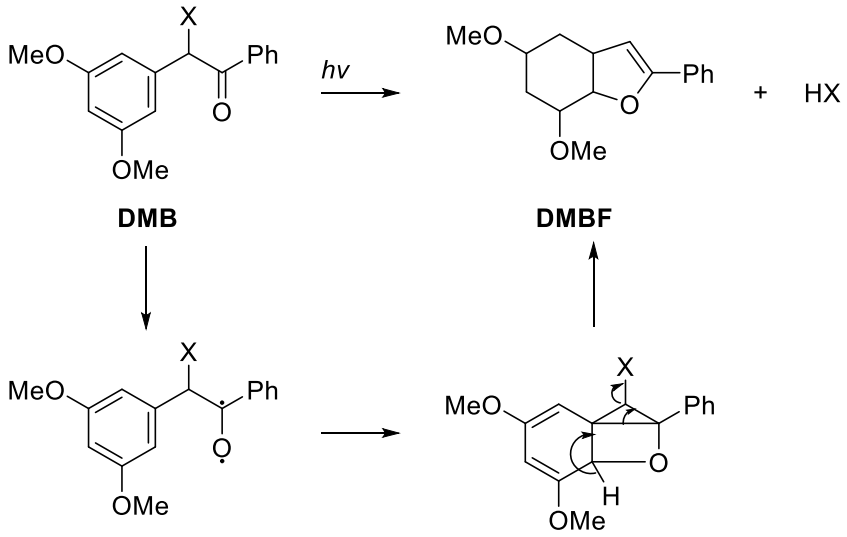
yields, and the unusually clean reaction that yields only one significant byproduct. *p*-Hydroxyphenacyl monophosphates are available either through the displacement of *p*HP Br (X= Br).[13] *p*-Hydroxyphenacyl phosphoric acids can be coupled with ADP or GDP through their imidazolium salts to provide the protected nucleotides *p*HP ATP[14, 15] and *p*HP GTP[16] respectively. Of the leaving groups thus far explored, sulfonates,[17] phosphates,[18] and carboxylates,[19] are the most efficacious and most commonly encountered.



Scheme 0.2 Photoirradiation reaction of *p*HP derivatives.

During their ground-breaking studies on benzoin acetates, Sheehan and Wilson determined that the 3′,5′-dimethoxybenzoin (Scheme 0.3: DMB, X= OAc) derivative performed best as a PPG of acetate.[20] The expected product 2-phenyl-5,7-

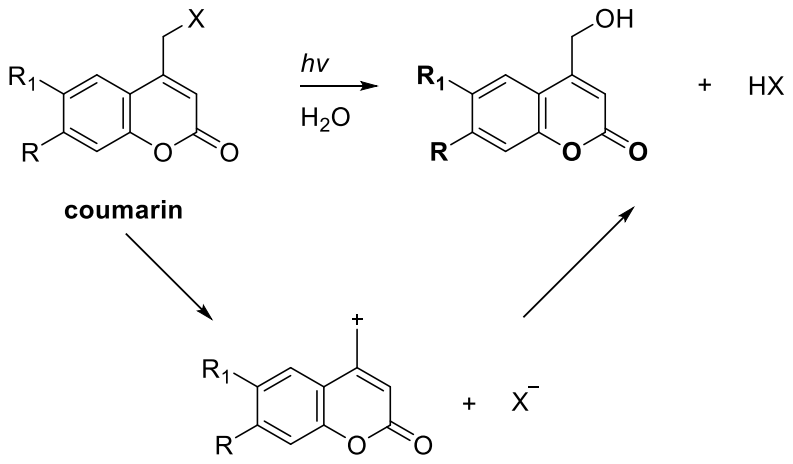
dimethoxybenzofuran (Scheme 0.3: DMBF) was formed in quantitative yield. Time-resolved work on DMB derivatives was performed by the groups of Trentham,[21] Wan,[22] Simon,[23] Wirz,[24] and Phillips[25].



Scheme 0.3 Photoirradiation reaction of DMB derivatives.

Coumarin (2H-chromen-2-on) is a secondary metabolite that was first isolated from the Tonka bean in 1820.[26] The development of coumarins as a new class of photoremovable protecting groups began with the discovery of Givens that the (coumarin-4-yl)methyl group exhibits photoreactivity, enabling the release of phosphate esters (Scheme 0.3).[27] Analogous to alcohols, the release of amines from coumarin-4-methyl carbamates (X= NR) proceeds uneventfully, although, at a slower rate.[28] As in the

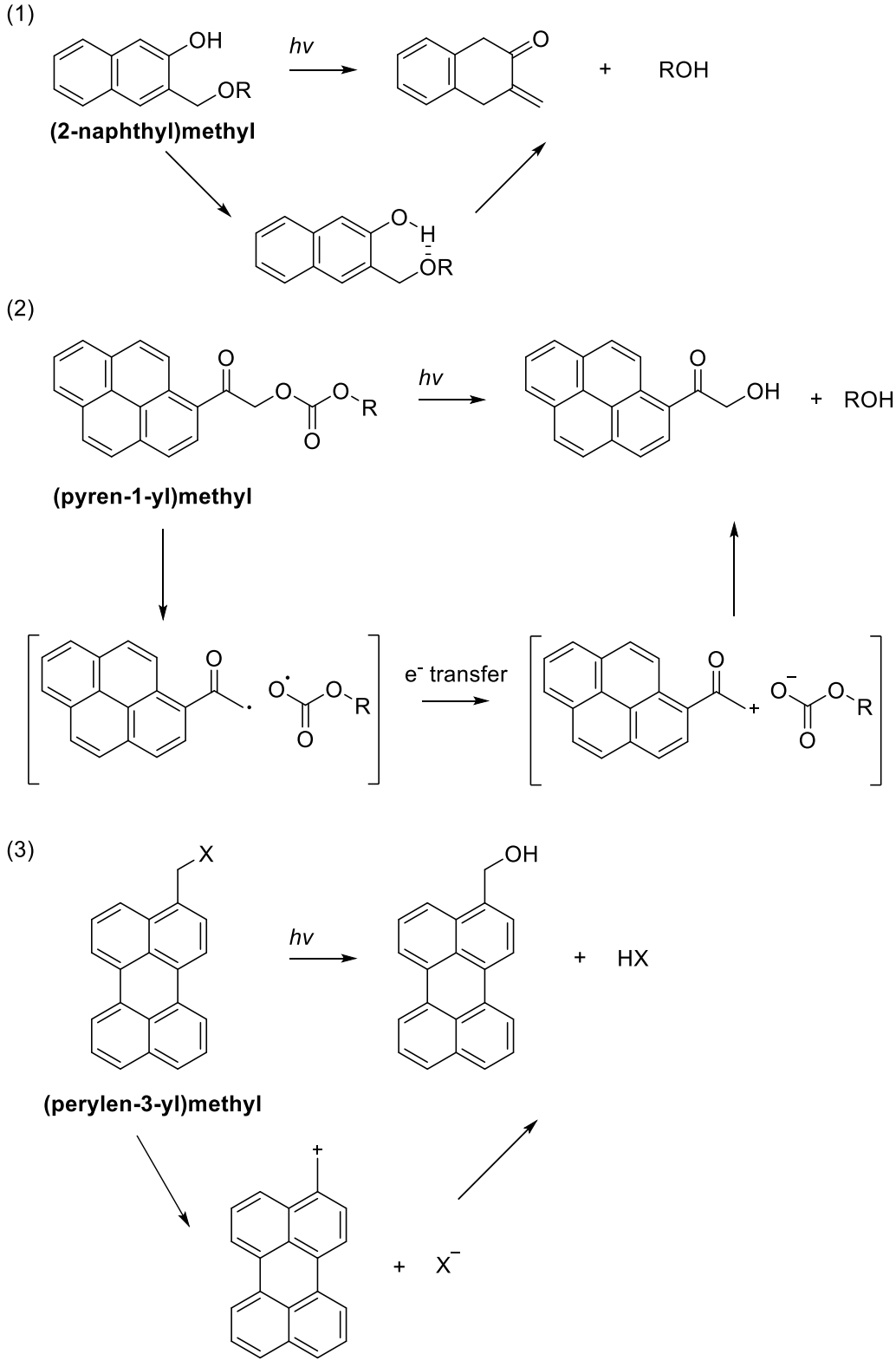
case of carbamates, the rate-limiting step is the decarboxylation of the released carbamate anion, which is more strongly dependent on the pH and on the nature of the released amine or amino acid. In general, coumarin-based PPGs offer several advantages: 1) high molar absorption coefficients at wavelengths above 350 nm, (2) high photorelease efficiencies, (3) acceptable stabilities in the dark, (4) fast photolysis kinetics, and (5) practically useful 2-photon excitation cross sections. Furthermore, their spectroscopic, photochemical, and other relevant properties (e.g., solubility and conjugation) can easily be tuned by varying the substituents on the coumarin ring.



Scheme 0.4 Photoirradiation reaction of coumarin derivatives.

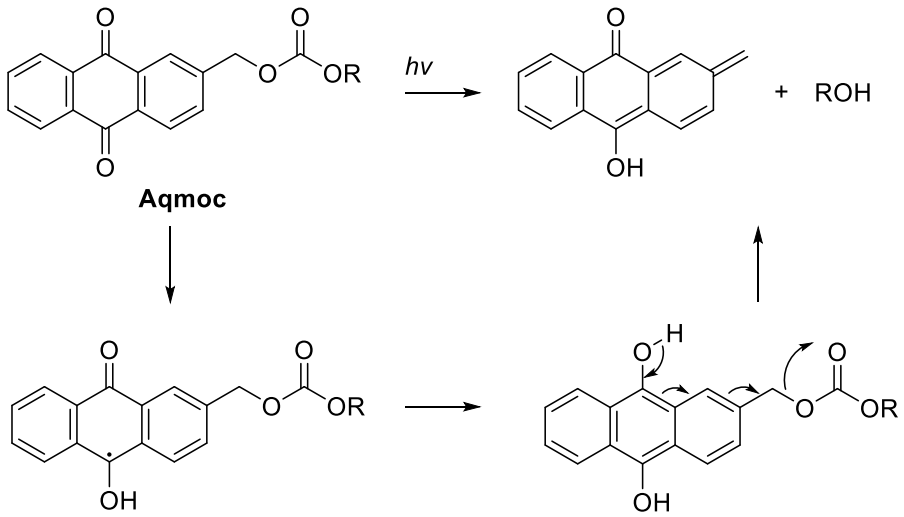
The majority of trityl- and benzyl-based PPGs require irradiation with light of rather a short wavelength to achieve efficient substrate release. To shift the caging chromophore

absorbance to longer wavelengths, the photocleavage of several polyaromatic analogues of the benzyl protecting group, including (2-naphthyl)methyl,[29] (anthracen-9-yl)methyl,[30] (pyren-1-yl)methyl,[31] (perylen-3-yl)methyl,[32] and (phenanthren-9-yl)methyl,[33] was explored. (Scheme 0.5) These cages have significant absorbance at 350 nm and show weak to moderate fluorescence.



Scheme 0.5 Photoirradiation reaction of trityl- and benzyl-based PPGs.

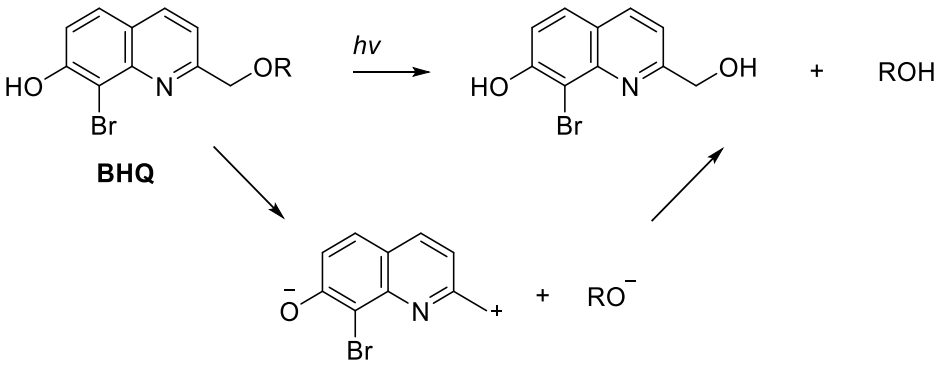
The common drawback of polyaromatic PPGs is their poor aqueous solubility. Addressing this problem, Furuta and co-workers have developed the anthraquinon-2-ylmethoxycarbonyl cage (Scheme 0.6: Aqmoc), which undergoes fairly efficient photocleavage at 350 nm and has good aqueous solubility.[34]



Scheme 0.6: Photoirradiation reaction of Aqmoc derivatives.

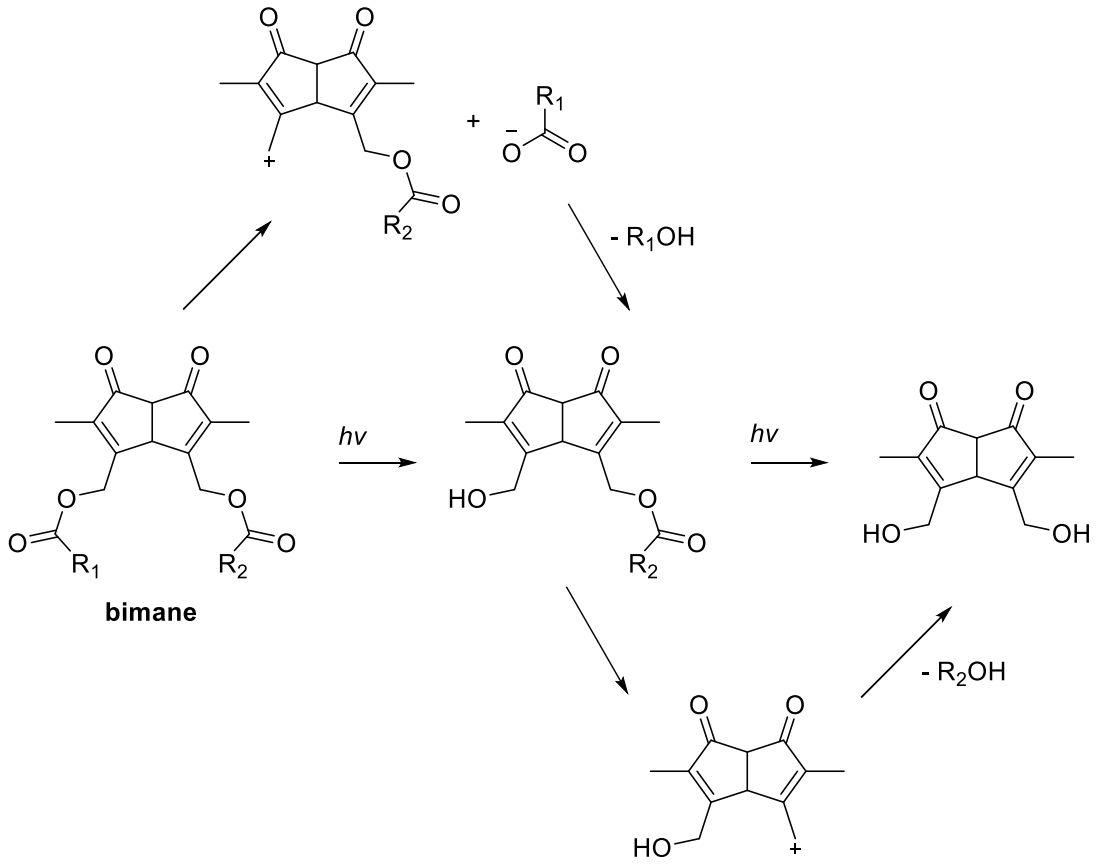
Dore and co-workers developed heteroaryl-based PPG for carboxylic acids, (8-bromo-7-hydroxyquinoline-2-yl)methyl (BHQ).[35] It is noteworthy that this group can be removed under two-photon excitation conditions. BHQ-caged carboxylates, phosphates, and diols are efficiently released under simulated physiological conditions using single-photon and two-photon activation.[36] Replacing the bromine substituent in BHQ with a cyano group ((8-cyano-7-hydroxyquinoline-2-yl)methyl, CyHQ) results in a significant

red-shift of the chromophore. However, none of the (quinoline-2-yl)methyl derivatives had higher sensitivity toward two-photon absorption than the parent BHQ group. (Scheme 0.7)



Scheme 0.7: Photoirradiation reaction of BHQ derivatives.

Chaudhuri and co-workers reported bimane as FPRPG for caging single and dual (same and different) carboxylic and amino acids, which release the caged acids simultaneously on exposure to UV ($\lambda \geq 365$ nm) and visible light ($\lambda \geq 410$ nm) irradiation.[37] (Scheme 0.8)

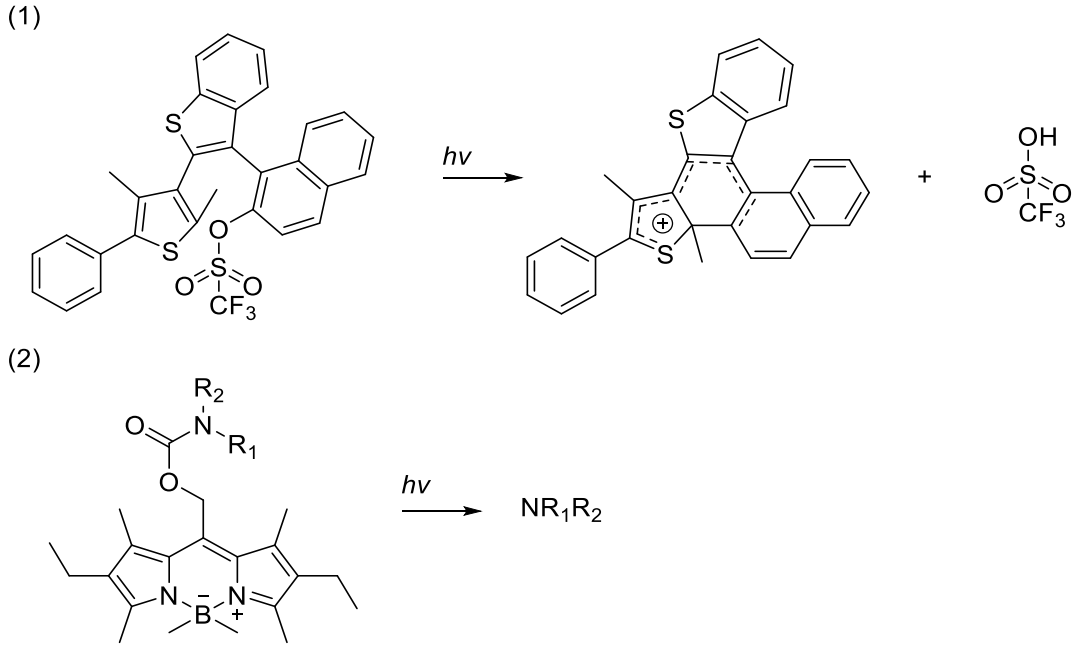


Scheme 0.8: Photoirradiation reaction of bimane derivatives.

2. Application of Photoremovable Compounds

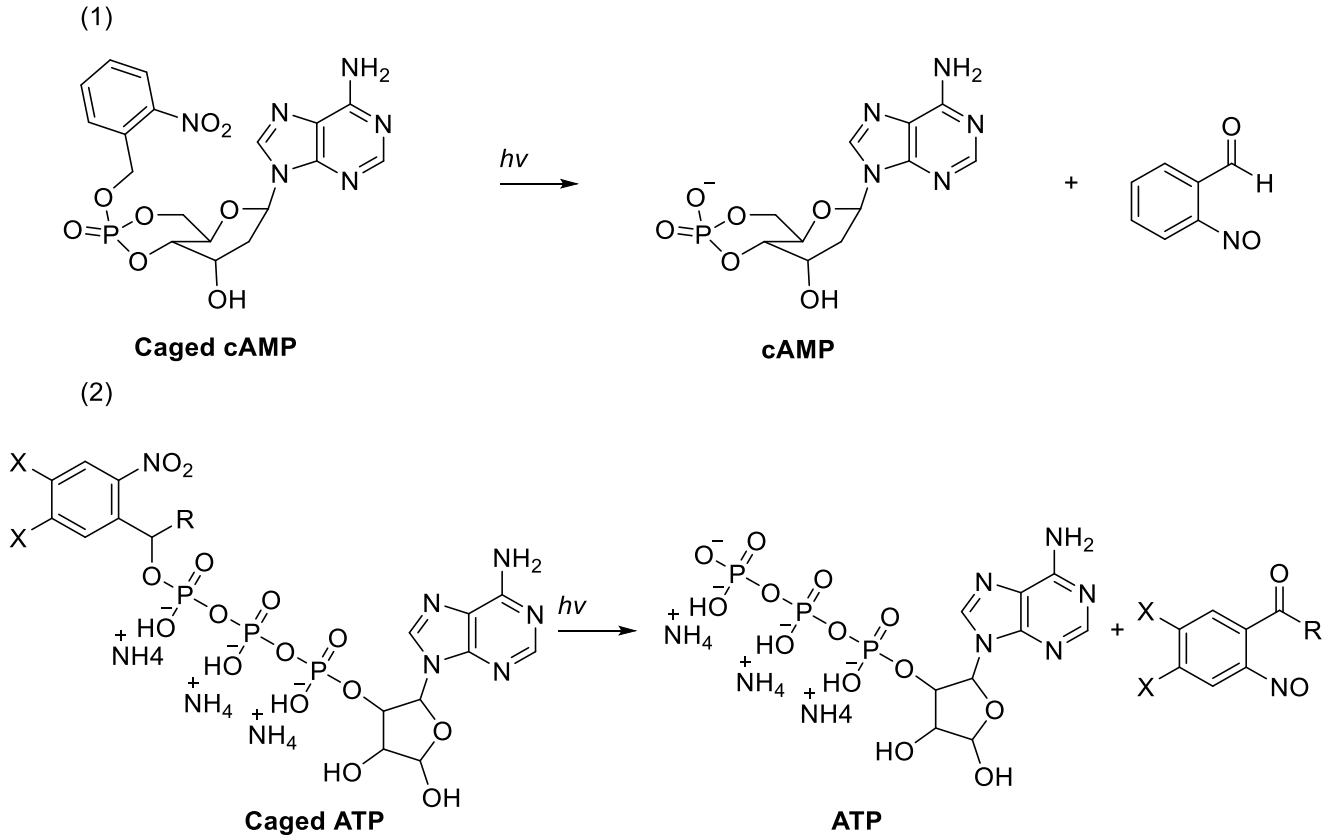
Phototriggered reactions have been extensively studied in organic synthetic chemistry and photochemistry since such reactions are widely used in industrial and medical applications as well as in stimulating biological systems. PPGs have been applied in many areas involving organic compounds: protective groups for organic synthesis, generators of acids or bases for polymerization initiation, and caging bioactive molecules. During a

synthetic sequence, most of these functionalities are blocked and released when selective chemical manipulation needs to be performed.[38] In the last decade, people found that polymers can be prepared by photopolymerization, and then intensive research has been devoted to the synthesis and utilization of photoactive molecules that can generate a base or an acid upon irradiation.[39] Photoacid generators (PAGs) are compounds capable of triggering a polymerization process by releasing acids upon exposure to light.[40] Mizutsu and co-workers reported a self-contained PAG based on a photo-chromic terarylene.[41] (Scheme 0.9 (1)) It showed that the photochemical quantum is much higher than obtained with most previous PAGs. Sitkowska and co-workers described a series of easily accessible, visible-light-sensitive BODIPY(PPGs) for primary and secondary amines, can be efficiently uncaged in vitro with visible light.[42] (Scheme 0.9 (2))



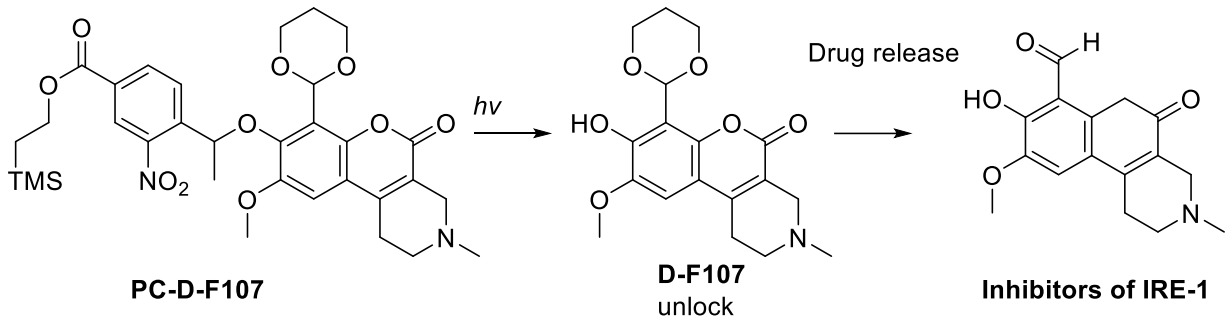
Scheme 0.9: Application for photo-acid or base generator.

Switching on molecule's bioactivity by light is an attractive idea in several respects. The application of photoremovable compounds in "cage" compounds has been recognized as a powerful tool in an arsenal of life science methods since photolabile cAMP[43] and ATP[44] analogues were introduced. (Scheme 0.10)

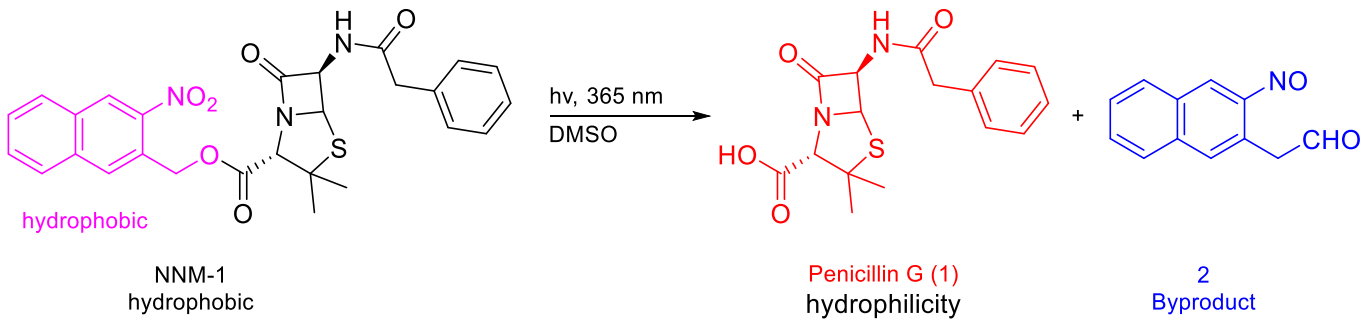


Scheme 0.10 Application for caged cAMP and ATP.

Shao and co-workers have demonstrated a unique prodrug strategy that can be used to enhance the efficacy of salicylaldehyde-based inhibitors of IRE-1.[45] It is the first report that the 1,3-dioxane acetal protecting group on a salicylaldehyde-based compound can be stabilized by installing a photolabile group on its ortho-hydroxy position. (Scheme 0.11)



Scheme 0.11 The application for drug release.

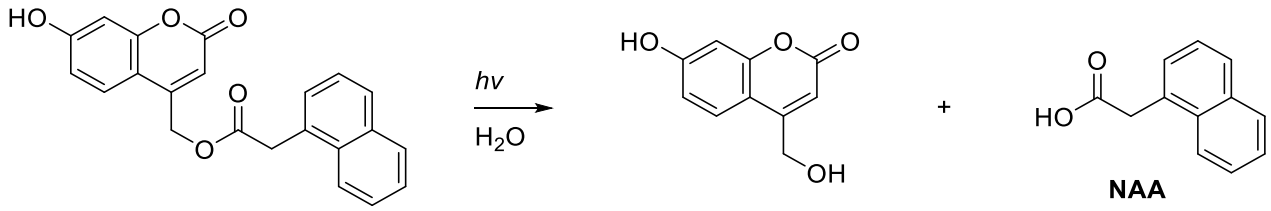


Scheme 0.12 Application for drug delivery.

The antibiotic penicillin G cannot be completely incorporated into hydrophobic lipid membranes owing to its hydrophilicity.[46] Through modification with a hydrophobic and photolabile protecting group, penicillin G was effectively incorporated into liposomes and released by photoirradiation at 365 nm. (Scheme 0.12)

Six coumarin-caged compounds of 1-naphthaleneacetic acid (NAA) comprising different substituents on the coumarin moiety were synthesized and evaluated for their photophysical and chemical properties as light-responsive controlled-release plant root

stimulators.[47] (Scheme 0.13)



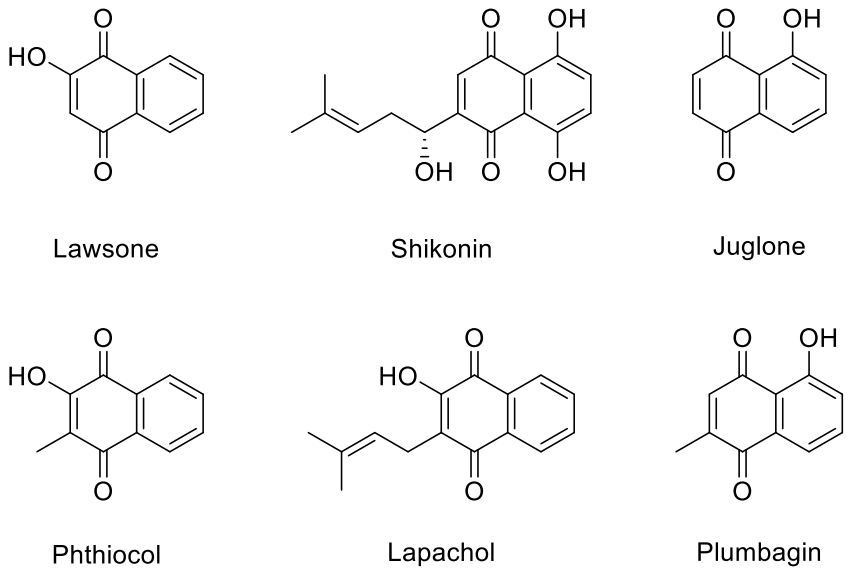
Scheme 0.13: Application for plant root stimulator.

3. Naphthoquinone

Quinone compounds are famous as cellular co-factors and natural products.[48] Meanwhile, many articles disclosed various photochemical properties and chemical transformations of quinone, the most popular being the intermolecular photochemical reductions.[49]

Among quinones, naphthoquinone moieties widely existed in a variety of plants[50-52], fungi[53] and some animals[54, 55]. For instance, lawsone, shikonin, juglone, phthiocol, lapachol, and plumbagin are naturally occurring which showed us extensive biological activities, including antibacterial, antifungal, antiviral, antiparasitic, antiplasmodial, anti-inflammatory, antiproliferative, and DNA interaction.[56-61] (Scheme 0.14)

Naphthoquinone has attracted significant attention as an electron and hydrogen atom acceptor in both organic chemistry and biochemistry.[62] In general, "primary" quinones are widely distributed as electron acceptors, while "secondary" quinoid metabolites (by rapid reoxidation of the semiquinone) play a defence role by generating reactive oxygen species (ROS) through redox cycling, which is related to the various biological application.[63]



Scheme 0. 14: Chemical structures of 1,4-naphthoquinone derivatives.

Naphthoquinone is also well known for the plenty of chemical transformations, which are derived from 1,4-naphthoquinone with an aromatic ring and a free position in conjugation to one of the carbonyls. Therefore, it has been applied to various reactions,

such as Diels-Alder reactions[64], additional cycloadditions[65], amination[66], allylation[67], Thiele-Winter acetoxylation[68].

4. This work

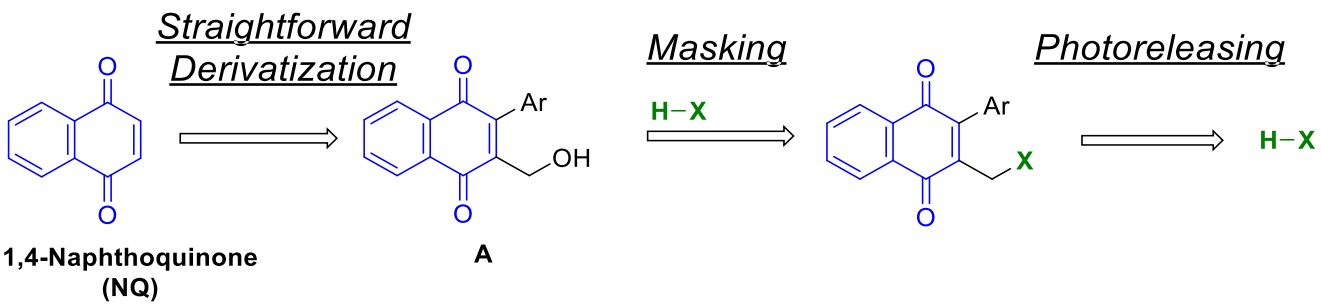
There are some requirements for an effective photoremovable compound. First, one photoremovable molecular can protect and photorelease several types of active groups. Second, the photoreleasing takes place in the no bio-damage region. The irradiation by an IR light can effectively circumvent the limitation of biomedical applications, as UV irradiation is constrained by its toxicity and very low tissue penetration power. Third, it is necessary for the photoprotecting group that can be synthesized by a simple and economic synthetic strategy.

Although there are lots of papers that reported the photoirradiation properties can be modified by changing different substituents in the photoresponse mother ring. Developing a universal synthetic strategy that would allow a platform for photoremovable groups that have photochemically versatile reactivities for releasing various functionalities continues to be a challenge.

To overcome such a challenge, this doctoral research focused on the use of the commercially available 1,4-naphthoquinone (NQ), as a starting material to produce

potential photoresponsible cores. NQ, which has unique photochemical properties regarding 330–600 nm light has the potential to become a photoremovable scaffold. Second, the reactive functional groups contained by NQ (one C=C double bond conjugated with two carbonyl groups) enable the derivatization of NQ. Here I focus on the synthesis of a new NQ-based photoreactive core **A** and the development of a method that permits the synthesis of **A** in a straightforward and diversity-oriented way. (Scheme 0.15)

In chapter 1, I focus on the development of the simple and diversity-oriented synthetic strategy of the NQ photoreactive core A. In chapter 2 the NQ-based photoremovable compounds, which were synthesized by using NQ photoreactive core A with various functional groups will be synthesized. In chapter 3, the photoreactivity of NQ-based photoremovable compounds will be tested. And the photoreaction pathway will be discussed. The standard photoreaction conditions also will be evaluated.



Scheme 0.15: Research hypothesis.

5. References

1. Klan, P.; Solomek, T.; Bochet, C. G.; Blanc, A.; Givens, R.; Rubina, M.; Popik, V.; Kostikov, A.; Wirz, J. *Chem. Rev.* **2013,** *113*, 119-191.

2. Barltrop, J. A.; Schofield, P. *Tetrahedron Lett.* **1962,** *16*, 697-699.

3. Barton, D. H. R.; Chow, Y. L.; Cox, A.; Kirby, G. W. *J. Chem. Soc.* **1965,** *654*, 3571-3578.

4. Patchornik, A.; Amit, B.; Woodward, R. B. *J. Am. Chem. Soc.* **1970,** *92*, 6333-6335.

5. Sheehan, J. C.; Wilson, R. M. *J. Am. Chem. Soc.* **1964,** *86*, 5277-5281.

6. Zhao, H.; Sterner, E. S.; Coughlin, E. B.; Theato, P. *Macromolecules* **2012,** *45*, 1723-1736.

7. Sofia, M. J.; Allanson, N.; Hatzenbuhler, N. T.; Jain, R.; Kakarla, R.; Kogan, N.; Liang, R.; Liu, D.; Silva, D. J.; Wang, H.; Gange, D. Anderson, J.; Chen, A.; Chi, F.; Dulina, R.; Huang, B.; Kamau, M.; Wang, C.; Baizman, E.; Branstrom, A.; Bristol, N.; Goldman, R.; Han, K.; Longley, C.; Midha, S.; Axelrod, H. R. *J. Med. Chem.* **1999,** *42*, 3193-3198.

8. Cameron, J. F.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1991,** *113*, 4303-4313.

9. Specht, A.; Goeldner, M. *Angew. Chem. Int. Ed. Engl.* **2004,** *43*, 2008-2012.

10. Marinzi, C.; Offer, J.; Longhi, R.; Dawson, P. E. *Bioorg. Med. Chem.* **2004,** *12*, 2749-2757.

11. Aujard, I.; Benbrahim, C.; Gouget, M.; Ruel, O.; Baudin, J. B.; Neveu, P.; Jullien, L. *Chem. Commun.* **2006,** *12*, 6865-79.

12. Park, C.H.; Givens, R. S. *J. Am. Chem. Soc.* **1997,** *119*, 2453-2463.

13. Givens, R. S.; Stensrud, K.; Conrad, P. G., 2nd; Yousef, A. L.; Perera, C.; Senadheera, S. N.; Heger, D.; Wirz, J. *Can. J. Chem.* **2011,** *89*, 364-384.

14. Givens, R. S.; Weber, J. F. W.; Jung, A. H.; Park, C.-H. In *Methods Enzymol.*, Academic Press: 1998; Vol. 291, pp 1-29.

15. Geibel, S.; Barth, A.; Amslinger, S.; Jung, A. H.; Burzik, C.; Clarke, R. J.; Givens, R. S.; Fendler, K. *Biophys. J.* **2000,** *79*, 1346-1357.

16. Klán, P.; Šolomek, T.; Bochet, C. G.; Blanc, A.; Givens, R.; Rubina, M.; Popik, V.; Kostikov, A.; Wirz, J. *Chem. Rev.* **2013,** *113*, 119-191.

17. Kötting, C.; Gerwert, K. *J. Chem. Phys.* **2004,** *307*, 227-232.

18. Remeš, M.; Roithová, J.; Schröder, D.; Cope, E. D.; Perera, C.; Senadheera, S. N.; Stensrud, K.; Ma, C.-c.; Givens, R. S. *J. Org. Chem.* **2011,** *76*, 2180-2186.

19. An, H. Y.; Kwok, W. M.; Ma, C.; Guan, X.; Kan, J. T.; Toy, P. H.; Phillips, D. L. *J. Org. Chem.* **2010,** *75*, 5837-5851.

20. Sheehan, J. C.; Wilson, R. M.; Oxford, A. W. *J. Am. Chem. Soc.* **1971,** *93*, 7222-7227.

21. Corrie, J. E. T.; Trentham, D. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2409-2417.

22. Corrie, J. E. T. *Tetrahedron lett.* **1998,** *54*, 5407-5416.

23. Pirrung, M. C.; Ye, T.; Zhou, Z.; Simon, J. D. *Photochem.Photobiol.* **2006,** *82*, 1258-1264.

24. Bisht, R.; Singh, S.; Krishnamoorthy, K.; Nithyanandhan, J., *J. Phys. Chem.* **2018,** *17*, 835-845.

25. Kwok, W. M.; Ma, C.; Matousek, P.; Parker, A. W.; Phillips, D.; Toner, W. T.; Towrie, M.; Umapathy, S. *J. Phys. Chem. A* **2001,** *105*, 984-990.

26. Murray, R. D. H.; Méndez, J.; Brown, S. A. 1982; p 435−436.

27. Givens, R. S.; Matuszewski, B. *J. Am. Chem. Soc.* **1984,** *106*, 6860-6861.

28. Fonseca, A. S. C.; Gonçalves, M. S. T.; Costa, S. P. G. *Tetrahedron lett.* **2007,** *63*, 1353-1359.

29. Cameron, J. F.; Willson, C. G.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1996,** *118*, 12925-12937.

30. Singh, A. K.; Khade, P. K. *Tetrahedron Lett.* **2005,** *46*, 5563-5566.

31. Furuta, T.; Torigai, H.; Osawa, T.; Iwamura, M. *Chem. Lett.* **1993,** *7*, 1179.

32. Jana, A.; Ikbal, M.; Singh, N. D. P. *Tetrahedron lett.* **2012,** *68*, 1128-1136.

33. Fernandes, A. S. C.; Goncalves, M. S. T.; Costa, S. P. G. *Tetrahedron Lett.* **2007,** *63*, 1353-1359.

34. Furuta, T.; Hirayama, Y.; Iwamura, M. *Org. Lett.* **2001,** *3*, 1809-1812.

35. Fedoryak, O. D.; Dore, T. M. *Org. Lett.* **2002,** *4*, 3419-3422.

36. Zhu, Y.; Pavlos, C. M.; Toscano, J. P.; Dore, T. M. *J. Am. Chem. Soc.* **2006,** *128*, 4267-4276.

37. Chaudhuri, A.; Venkatesh, Y.; Behara, K. K.; Singh, N. D. *Org. Lett.* **2017,** *19*, 1598-1601.

38. Jarowicki, K.; Kocienski, P., Protecting groups. *J. Chem. Soc. Perkin Transactions 1* **2001**, 2109-2135.

39. Zivic, N.; Kuroishi, P. K.; Dumur, F.; Gigmes, D.; Dove, A. P.; Sardon, H. *Angew. Chem. Int. Ed. Engl.* **2019,** *58*, 10410-10422.

40. Tsunooka, M.; Suyama, K.; Okumura, H.; Shirai, M. *J. Photopolym. Sci. Technol.* **2006,** *19*, 65-71.

41. Mizutsu, R.; Asato, R.; Martin, C. J.; Yamada, M.; Nishikawa, Y.; Katao, S.; Yamada, M.; Nakashima, T.; Kawai, T. *J. Am. Chem. Soc.* **2019,** *141*, 20043-20047.

42. Sitkowska, K.; Feringa, B. L.; Szymanski, W. *J. Org. Chem.* **2018,** *83*, 1819-1827.

43. Engels, J.; Schlaeger, E. J. *J. Med. Chem.* **1977,** *20*, 907-911.

44. Kaplan. J. H.; Forbush, B.; Hoffman, J. F. *Biochemistry* **1978,** *17*, 1929–1935.

45. Shao, A.; Kang, C. W.; Tang, C. H.; Cain, C. F.; Xu, Q.; Phoumyvong, C. M.; Del Valle, J. R.; Hu, C. C. *J. Med. Chem.* **2019,** *62*, 5404-5413.

46. Goto, Y.; Ueda, M.; Sugikawa, K.; Yasuhara, K.; Ikeda, A. *RSC. Adv.* **2018,** *9*, 166-171.

47. Kaewchangwat, N.; Thanayupong, E.; Jarussophon, S.; Niamnont, N.;Yata, T.; Prateepchinda, S.; Unger, O.; Han, B. H.; Suttisintong, K. *J. Agric. Food. Chem.* **2020,** *68*, 6268-6279.

48. Dunlap, T.; Chandrasena, R. E. P.; Wang, Z.; Sinha, V.; Wang, Z.; Thatcher, G. R. *J. Chem. Res. Toxicol.* **2007,** *20*, 1903–1912.

49. Walton, D. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **2017,** *139*, 4655−4658.

50. Binder, R. G.; Benson, M.E.; Flath, R.A. *Phytochemistry* **1989,** *28*, 2799- 801.

51. Brigham, L. A.; Michaels, P. J.; Flores, H. E. *Plant Physiol.* **1999,** *119*, 417-428.

52. De Moura, K. C. G.; Emery, F.S.; Neves-Pinto, C.; DoCarmo, M.; Pinto, F.R.; Dantas, A.P.; Salomao, K.; DeCastro, S.L.; Pinto, A.V. J. *Braz. Chem. Soc.* **2001,** *12*, 325-338.

53. Medentsev, A. G.; Akimenko, V. K. *Phytochemistry.* **1998,** *47* 935-959.

54. Wright, D. A. M., C. L.; Dawson, R.; Cutler, H.G. *Environ. Technol.* **2007,** *28*, 1091-1101.

55. Wright, D. A.; Dawson, R.; Cutler, S.J.; Cutler, H.G.; Oranodawson, C.E.; Graneli, E. *Water Res.* **2007,** *41*, 1294-1302.

56. Vaverkova, V.; Vrana, O.; Adam, V.; Pekarek, T.; Jampilek, J.; Petr Babula, P. *Biomed. Res. Int.* **2014**, 461393.

57. Zheng, J.; Hammock, B. D. *Chem. Res. Toxicol.* **1996,** *9*, 904-909.

58. Sawama, Y.; Kawajiri, T.; Asai, S.; Yasukawa, N.; Shishido, Y.; Monguchi, Y.; Sajiki, H. *J. Org. Chem.* **2015,** *80*, 5556−5565.

59. Collins, J. A.; Neil Osheroff, N. *Chem. Res. Toxicol.* **2021,** *34*, 1082−1109.

60. Viana, L. M.; Freitas, M.R.; Rodrigues, S.V.; Baumann, W. Bras. *J. Chem. Eng.* **2003,** *20*, 317-325.

61. Warashina, T. N., Y.; MNoro, T. *Chem. Pharm. Bull.* **2006,** *54*, 14-20.

62. Zhang, Z.; Hao, S.; Zhu, H.; Wang, W. J. *Photochem. Photobiol. B, Biol.* **2008,** *92*, 77–82.

63. Benites, J.; Valderrama, J. A.; Taper, H.; Calderon, P. B. *Chem. Pharm. Bull.* **2009,** *57*, 615—619.

64. Haber, M.; Pindur, U. *Tetrahedron Lett.* **1991,** *47*, 1925-1936.

65. Murase, M. Y., S.; Hosaka, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1991,** *39*, 489.

66. Dong, Y. Mei, T.; Luo, Q.; Feng, Q.; Chang, B.; Yang, F.; Zhou, H.; Shi, Z.; Wang, J.; He, B. *RSC Adv.* **2021,** *11*, 6776-6780.

67. Yadav, J. S.; Reddy, B. V. S.; Swamy, T. *Tetrahedron Lett.* **2003,** *44*, 4861-4864.

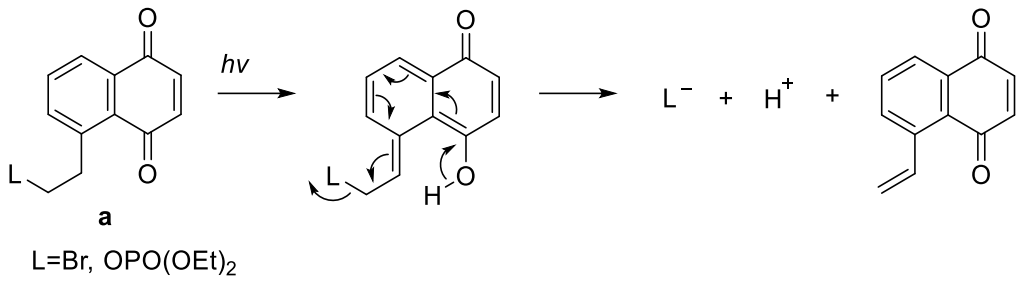
68. Burton, H.; Praill. P. F. G. *J. Chem. Soc.* **1952**, 755.

CHAPTER 1 Design and synthesis of photoremovable protecting group

1.1 Introduction

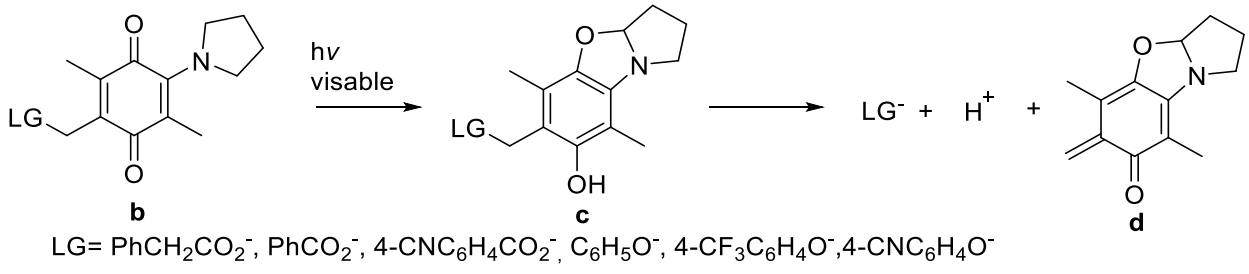
The intermolecular photochemical reductions of quinones and several variants such as an appended amine or sulfide have been well defined since they were first found. Research has shown that the quinone ring plays a key role in mediating photochemical reduction.

Several years ago, Yavor Kamdzhilov and co-workers replaced the methyl group with ethylenyl derivatives as in 5-methyl-1,4-naphthoquinone to yield naphthoquinone derivatives (**a**) (Scheme 1.1).[1] The naphthoquinone derivatives (L= Br and $OPO(OEt)_2$) were irradiated at 313 or 365 nm, which release HBr and $HOPO(OEt)_2$, respectively, in neutral water and acetonitrile in the low microsecond time domain and with high quantum yields. Their advantage is that the photodeprotection occurs cleanly and efficiently in aprotic polar solvents such as acetonitrile. They are promising photoremovable compounds for rapid controlling pH and caging diethyl phosphate functions such as the cyclic nucleotides cAMP and cGMP.



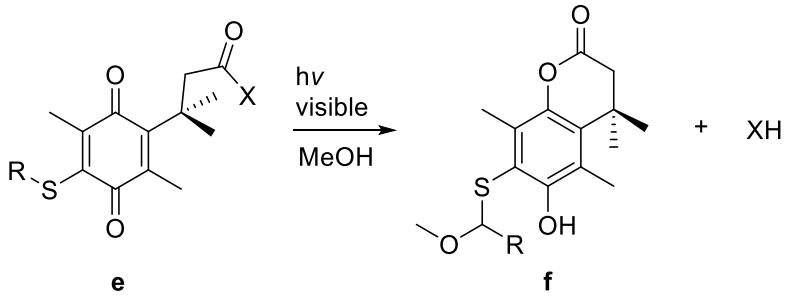
Scheme 1.1 Primary photoreaction of 5-methyl-1,4-naphthoquinone.

A few years ago, dialkylamino-substituted 1,4-benzoquinones have been shown to undergo rearrangement to isomeric benzoxazolines when exposed to sunlight.[2] Then, Yugang Chen and a co-worker found that photolysis of 2-pyrrolidino-1,4-benzoquinones (**b**) offers photocyclization at visible light in the 450–650 nm wavelength region, Scheme 1.2.[3] The postulate of photoreleasing was that the carboxylate leaving groups are rapidly expelled upon photocyclization to the benzoxazolines (**c**) under aqueous conditions. Benzoxazoline (**c**) rapidly releases phenolate groups such as $PhCO_2$ and $PhCH_2CO_2$ and byproduct (**d**) in aqueous media.



Scheme 1.2 Photorearrangement of 2-pyrrolidino-1,4-benzoquinone

Another example is a photochemically initiated trimethyl lock system (**e**) that photoreleases amine and alcohol in quantitative yield at the visible range of light. (Scheme 1.3) The photoreleasing mechanism is described as an intramolecular photochemical quinone reduction followed by a thermal trimethyl lock reaction.[4] The light photochemically induced electron transfer is followed by a critical and irreversible hydrogen transfer, which leads to a net two-electron intramolecular reduction of the quinone. When the photocyclisation starts, the release of alcohol and EtOH is followed. Finally, it offers the releasing group and cyclization byproduct (**f**) under visible light.

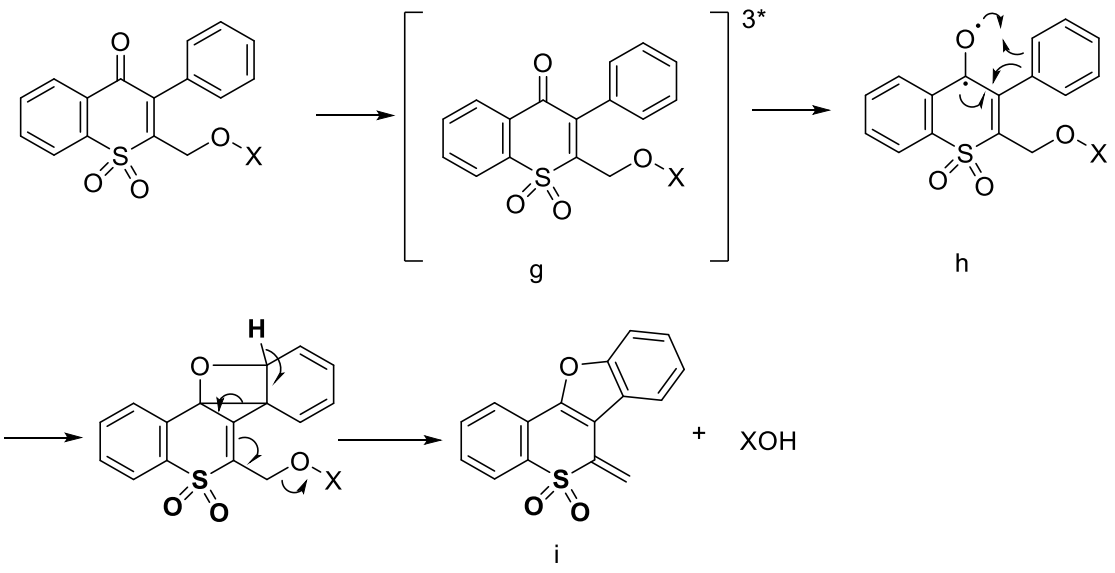


e **f**

Scheme 1.3 Photoreaction of the quinone trimethyl lock.

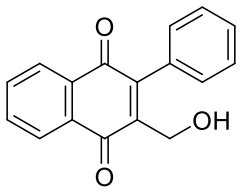
The examples indicated quinone led easily electron and hydrogen transfer by photoirradiation. It is easy to take place the photocyclization in the carbonyl and its ortho substituent due to the photochemical properties of the quinone and carbonyl group.

In our research team, we have also originally developed the thiochromone-based photoresponsible cores and reported that they are competent as a photoremovable framework (Scheme 1.4),[5] however, the multi-step synthesis prevents the derivatization for more effective photoreactivity. According to the thiochromone type framework, the novel 1,4-naphthoquinone framework would follow a carbonyl functionality that is excited by UV irradiation to afford the corresponding triplet state (**g**). Then, the excited carbonyl (**g**) becomes a diradical (**h**) which through Paternò–Büchi type photocyclo-addition with an alkene to offer the furan ring. Then, the aromatization produces the final tetracyclic compound (**i**) and releasing of various groups.[6]



Scheme 1.4 Photoreaction pathway of Thiochromone framework.

Based on the above examples, I selected the 1,4-naphthoquinone moiety as the photoresponse core to design the novel photoremovable framework, as NQ has an electronic property similar to the thiochromone core. Similarly, I planned to introduce phenyl and a hydroxymethyl group onto the C-2 and C-3 positions, respectively, from the similarity with the previous thiochromone-type photoreactive core. The novel NQ-base photoremovable framework was shown in Scheme 1.5.



NQ photoresponse core

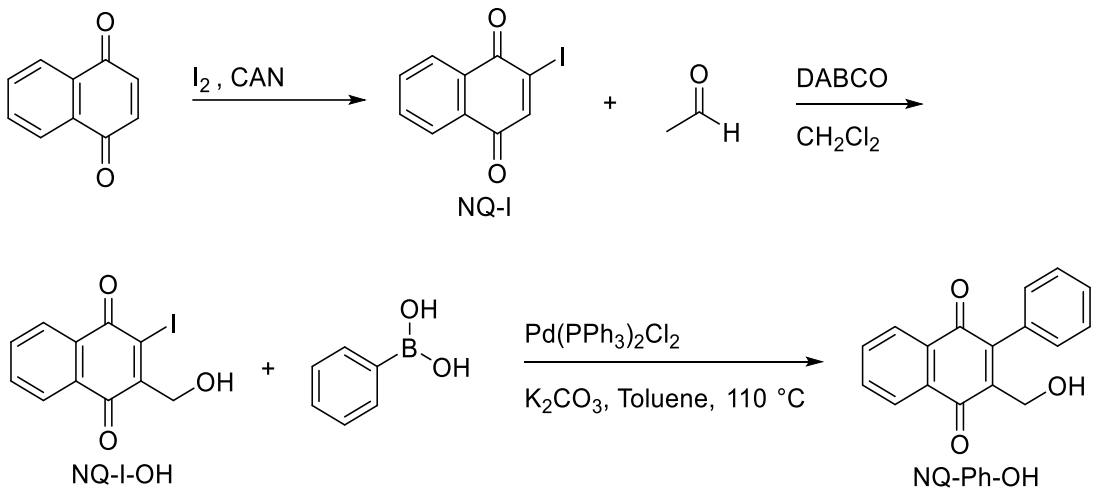
Scheme 1.5 New designed 1,4-NQ based framework

1.2 Stepwise Synthesis of Photoremovable Protecting group NQ-Ph-OH

1.2.1 Synthetic Strategy in Three Steps

At the beginning of the synthesis, I designed the synthetic strategy in a stepwise method, which is achieved by the combination of several conventional reactions. There are three synthetic strategies. One of them is three steps method, which was similar to the

synthetic method of the thiochromone framework.[7] (Scheme 1.6) The first step is the iodination reaction of 1,4-naphthoquinone.[8] Following Baylis Hillman reaction of the resulting iodide compound (**j**) and acetaldehyde offers the compound (**k**).[9] Finally, Suzuki-Miyaura coupling of the intermediate (**k**) with phenylboronic acid afforded the desired 1,4-NQ photoprotecting group.

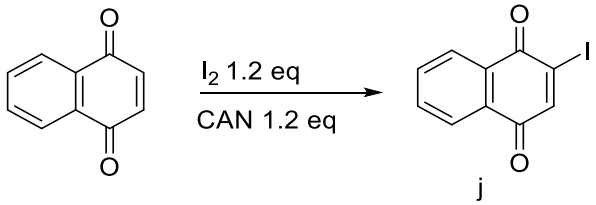


Scheme 1.6 Synthetic strategy of 1,4-NQ based framework in three steps

According to the above plan (Scheme 1.6), we started to synthesize the target compound iodide intermediate (**j**). In the initial attempt, the reaction was carried out in dichloromethane by using 1,4-naphthoquinone, I_2 (iodine) and CAN (Ceric ammonium nitrate) at 60 °C. (Table 1.1) The resulting mixture was purified by a chromatography column to offer the iodide intermediate (**j**) in a 6% yield. (Table 1.1: Entry 1) However,

the yield is too low for preparing an intermediate. In order to elevate the yield, I optimized the reaction condition, the results were shown in Table 1.1. Entry 2 of Table 1.1 shows a yield of 8% when I change the reaction time to 72 h. Then, I evaluated the reaction in MeCN and PhCl at the reflux temperature. As we can see in entries 3 and 4 of Table 1.1, both of them offer the desired iodide (**j**) in 4% of yield when the reaction time is 72 h and 20 h, respectively.

Table 1.1 Synthesis of iodide intermediate **j**.



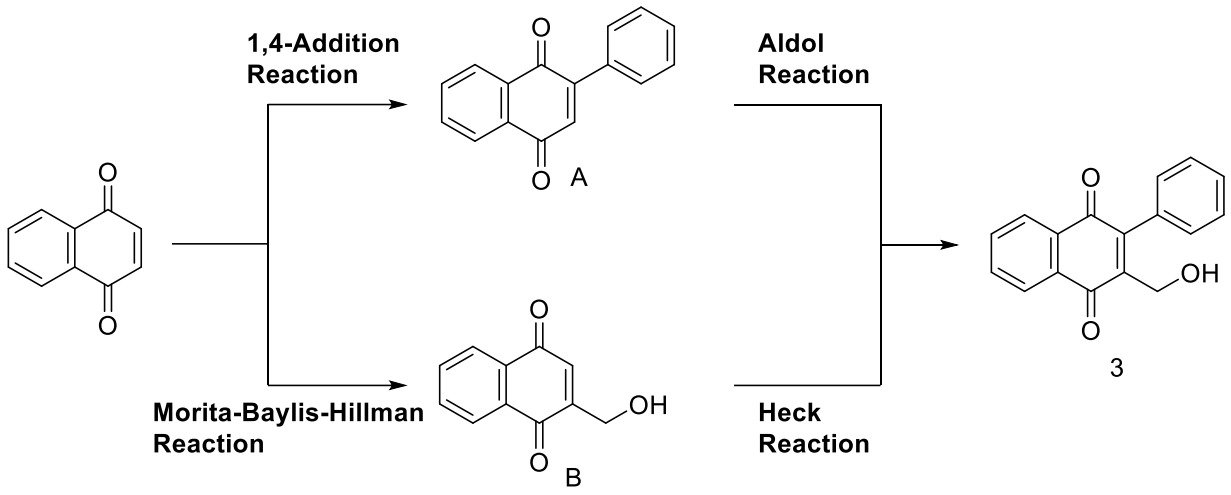
j

Entry	1,4-NQ (mmol)	Solvent	Time (h)	Temp. (°C)	Yield %
1	0.5	DCM	26	60	6
2	0.5	DCM	72	60	8
3	1	MeCN	72	60	4
4	0.5	PhCl	20	100	4
5	0.5	DCE	20	80	0
6	0.5	MeCN	48	80	0

When the temperature is 80 °C as the solvent is DCE or MeCN, the product is a disubstituted iodide compound. Although lots of optimization reactions were tried, the yield is still lower than 10%. For the first intermediate of three steps method, it is not allowed. Then, I changed the synthetic strategy to the two steps synthetic strategy.

1.2.2 Synthetic Strategy in Two Steps

According to the above plan, there are two pathways. (Scheme 1.7) There are four powerful tradition reactions will be applied to this chapter. 1,4-addition is an electrophilic addition reaction of α, β-unsaturated carbonyl.[10-12] Aldol reaction is the nucleophilic addition of a ketone enolate to an aldehyde. Morita-Baylis-Hillman reaction is the coupling of an activated alkene with an electrophile (usually aldehydes or imines) in the presence of a catalyst.[13, 14] Heck reaction is the chemical reaction of an unsaturated halide with an alkene in the presence of a base and a palladium catalyst to form a substituted alkene.[15] In the first pathway, the 1,4-addition of 1,4-naphthoquinone can offer molecular A, reported in high yield. Next, compound **3** can be obtained by the aldol reaction of hydrogenated molecular A with paraformaldehyde. In the second pathway, molecular B can be obtained from the Morita-Baylis-Hillman reaction by using 1,4-naphthoquinone and paraformaldehyde. Finally, compound **3** can be offered from molecular B with iodobenzene by the Heck arylation.

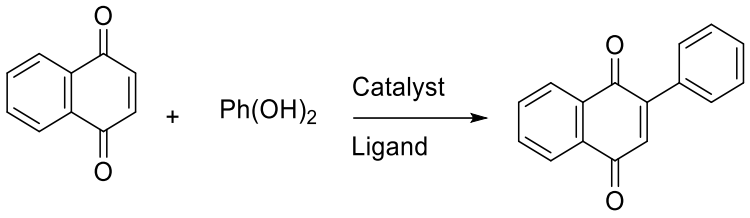


Scheme 1.7 Synthetic strategy of 1,4-NQ framework in two steps.

I started the two steps synthesis with the preparation of Molecular A. At the beginning of the 1,4-addition reaction, the target compound **1** was obtained from 1,4-naphthoquinone with phenylboronic acid in the presence of $[Rh(cod)_2]BF_4$ (cod= 1,5-cyclooctadiene) and R-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) in dioxane/H_2O (10/1) for 23 h. (Table 1.2) The reaction was purified by column chromatography and offered the compound **1** in 68% yield. Next, the reaction was optimized under different solvents, ligands and temperatures as Table 1.2. After the optimization, I found that the reaction of NQ with phenylboronic acid ($PhB(OH)_2$) in the presence of a catalytic amount of palladium acetate and bipyridyl in DMF at 50 °C under air afforded the 2-phenyl-1,4-naphthoquinone (**1**) the best result in 81% yield.[16] Under the condition of Entry 4 in Table 1.2, different phenylboronic reagents were tested for this

reaction. The result shows that the case of triphenylboroxine offered the desired compound **1** in 79% yield, but the case of bis(pinacolato)diboron (PhBpin) could not offer the desired compound (Table 1.2: Entry 6).

Table 1.2 Synthesis of NQ-Ph.

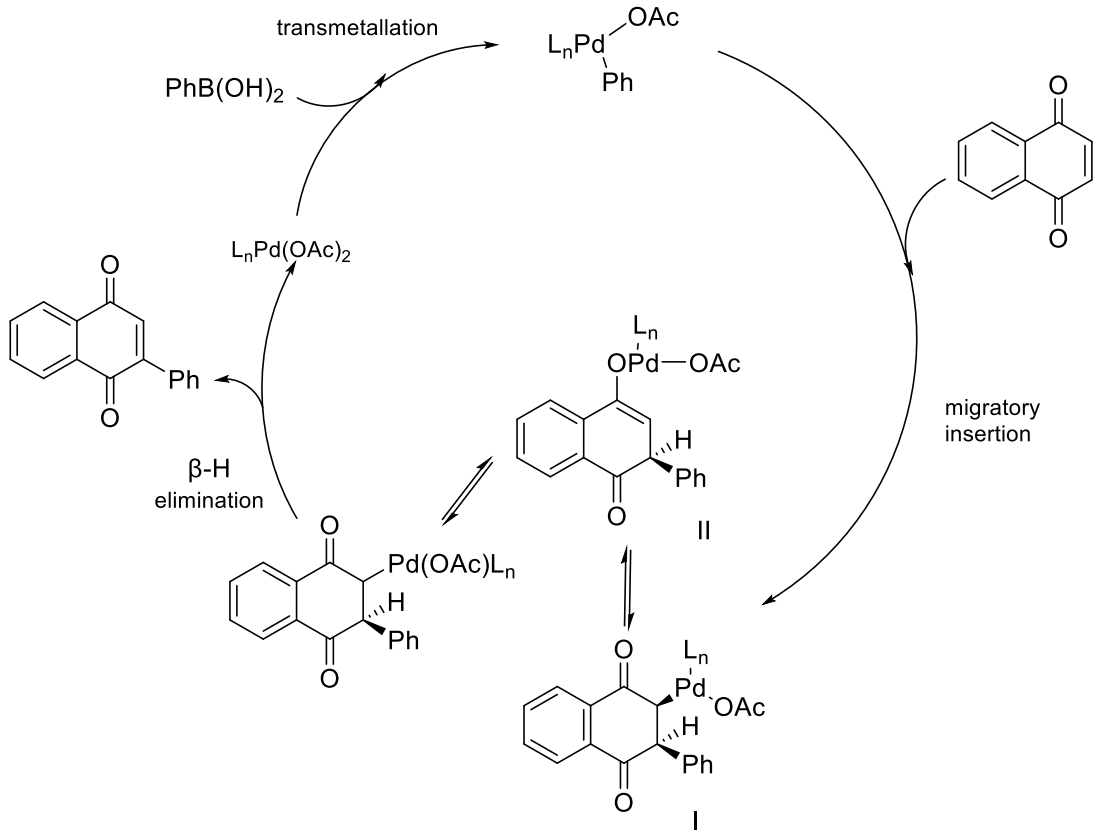


1

Entry	NQ (mmol)	Catalyst	Ligand	Temp. (°C)	Solvent	Time (h)	Yield %
1[a]	0.5	$[Rh(cod)_2]BF_4$ 3 mol%	R-BINAP 3 mol%	100	Dioxane/H_2O (10/1) 3 mL	23	68
2[a]	10	$Pd(OAc)_2$ 5 mol%	Bipyridine 6 mol%	70	DMF 50 mL	17	79
3[a]	1	$Pd(OAc)_2$ 5 mol%	Bipyridine 6 mol%	60	DMF/H_2O (10/1) 3 mL	5	8
4[a]	10	$Pd(OAc)_2$ 5 mol%	Bipyridine 6 mol%	50	DMF 50 mL	20	81
5[a]	1	$Pd(OAc)_2$ 5 mol%	phen 6 mol^	60	DMF/H_2O (10/1) 6 mL	5	23
6[b]	1	$Pd(OAc)_2$ 5 mol%	Bipyridine 6 mol%	50	DMF 50 mL	20	0

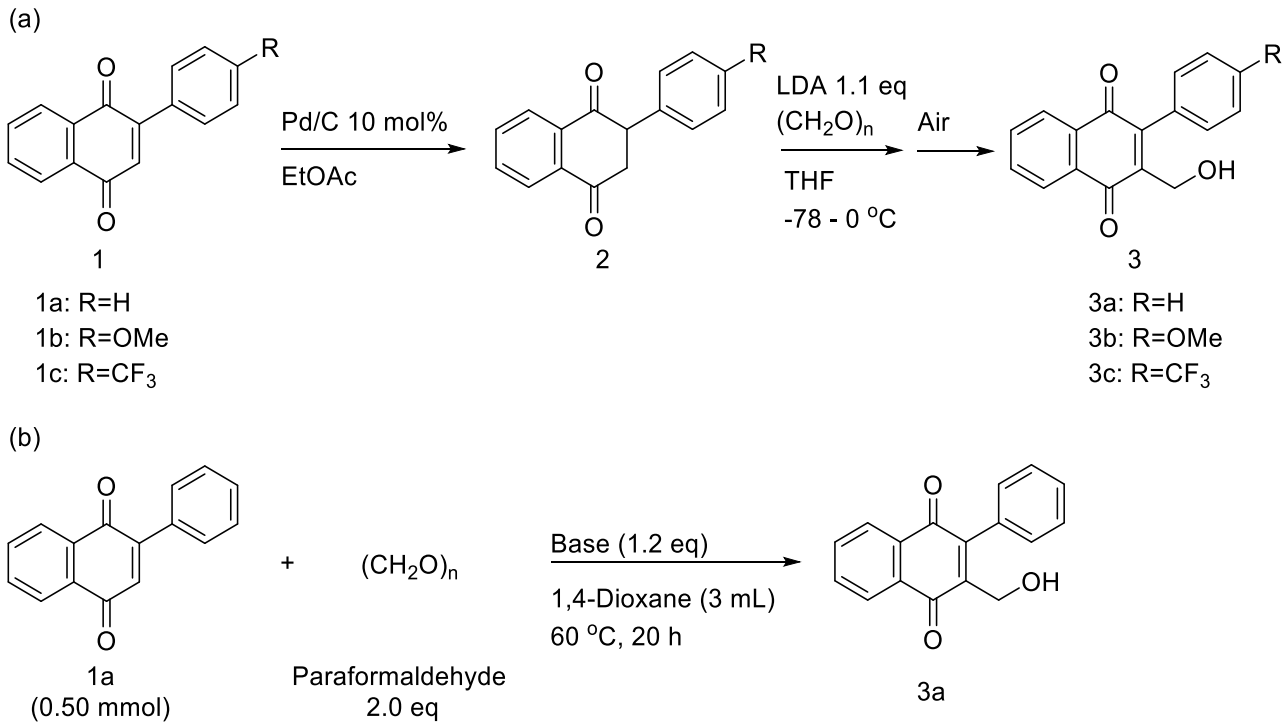
[a]: Boron reagents: $PhB(OH)_2$; [b]: Boron reagents: bis(pinacolato)diboron (PhBpin)

The 1,4-addition reaction pathway of 1,4-naphthoquinone with phenylboronic in the presence of palladium was shown in scheme 1.8. The expected initial step of the catalytic cycle must consist of the transmetallation of the organoboron reagent $ArB(OH)_2$ to the [Pd(II)] species followed by coordination of the boron adduct. Next, the 1,4-insertion of the substituent phenyl generates the Pd intermediate in the β-position. In the insertion progress, there is the isomerization of the Pd-enolate between I and II presumably exists. The final elimination step offers the desired 1,4-addition product **1**.



Scheme 1.8 Reaction pathway for the synthesis of compound **1**

After **1** was quantitatively transformed by Pd/C-catalyzed hydrogenation to 1,4-Adduct **2**, **2** was reacted with paraformaldehyde under the kinetic aldol reaction conditions without any purification since it is easily oxidized under air. As a result, the desired product **3a** was obtained in 82% yield. (Scheme 1.9 (a)) In this two steps method, I synthesized the derivatives of compounds **1a-c** and **3a-c** by changing different substituted arylboronic acids. (Supporting Information (SI)).



Scheme 1.9 Synthesis of compound **3** from **1**.

Next, I tried to synthesize compound **3a** by using compound **1a** with paraformaldehyde under the Baylis Hillman reaction conditions. (Scheme 1.9 (b)) Different bases were tested for this reaction, the result was shown in Table 2. In this reaction, compound **1a** with paraformaldehyde in the presence of NaOMe offers desired compound **3a** in a 16% yield. (Table 1.3)

Basic on this result, the bulky bases showed the lower yields, such as *t*-BuOK, DABCO, DIPEA. It may due to the first step of the Morita-Baylis-Hillman reaction is the addition of the base to the NQ-Ar. Thus, the bulky base is difficult to offer the addition intermediate **1**. (Scheme 1.10) A nother possible reason is that I used paraformaldehyde, it should be active before the reaction. The strong base NaOMe is better for the deprotonation of paraformaldehyde. Therefore, the NaOMe showed the highest yield.

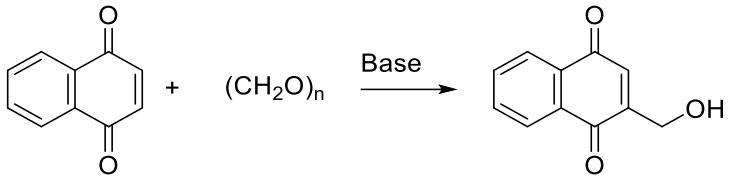
Table 1.3 Base evaluation of Scheme 1.9 (b).

Entry	Base (eq.)	Yield %
1	NaOMe	16
2	*t*-BuOK	0
3	DABCO	<1
4	DIPEA	<1

Then, I continued the second pathway of the two steps method. The first step of the

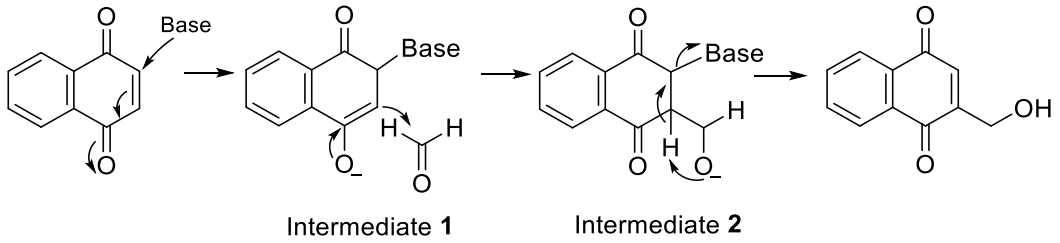
second pathway is the Morita-Baylis-Hillman reaction of 1,4-naphthoquinone. (Table 1.4) The Morita-Baylis-Hillman reaction was carried out in different reaction conditions. Table 1.4 showed the different reaction conditions, including solvent, concentration, base, reaction time, and reaction temperature. In Table 1.4, Entry 6 illustrates the best condition, which offers the desired product (NQ-OH) in a 31% yield.

Table 1.4 Synthesis of NQ-OH.



Entry	$(CH_2O)_n$ (eq.)	Base	Temp. (°C)	Solvent	Time (h)	Yield %
1	1.2	DABCO 10 mol%	50	Dioxane/H_2O (1/1) 5 mL	17	2
2	1.2	DMAP 10 mol%	50	Dioxane/H_2O (1/1) 5 mL	17	1
3	2.0	DABCO 10 mol%	60	Dioxane 5 mL	24	21
4	2.0	DABCO 10 mol%	100	Dioxane 5 mL	24	23
5	1.2	DBU 10 mol%	60	Dioxane 5 mL	20	7
6	2.0	NaOMe 1.2 eq	100	Dioxane 5 mL	24	31
7	2.0	NaOMe 1.2 eq	60	Dioxane 5 mL	24	22

The reaction pathway is shown in scheme 1.10. The first reaction step is a 1,4-addition of the base to the activated alkene to generate the enolate intermediate. In the second step, this enolate intermediate adds to an aldehyde via an aldol addition. Finally, the proton shift generates the final MBH adduct and releases the catalyst via E2 or E1 elimination in the last step.



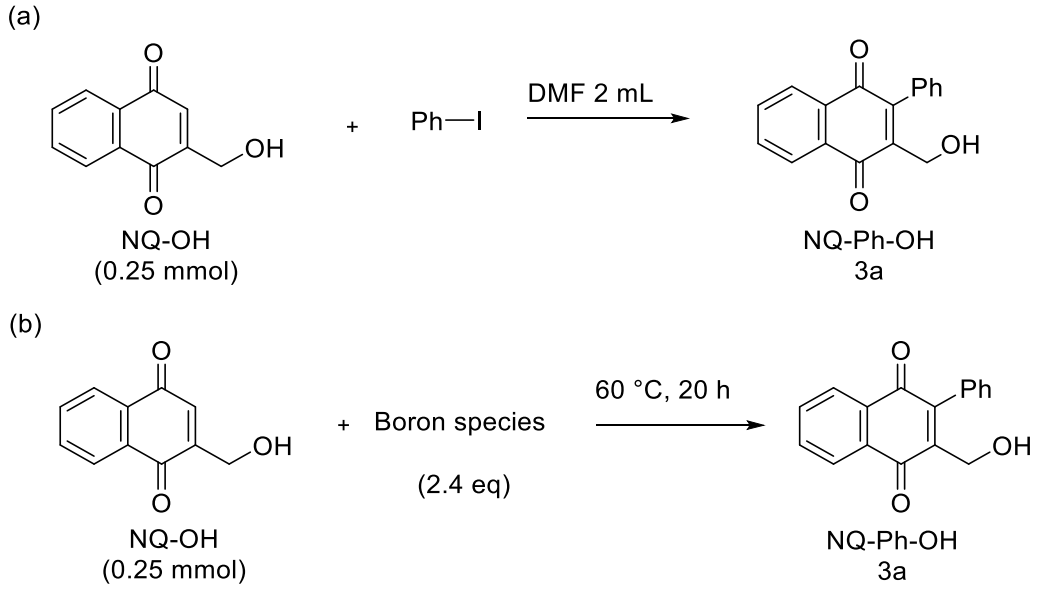
Scheme 1.10 Reaction pathway for the synthesis of NQ-OH.

Next, I tried to the Heck arylation of the NQ-OH. (Scheme 1.11 (a)) Two reaction conditions were evaluated in Table 1.5. However, I failed to obtain the desired compounds **3a**.

Table 1.5 Synthesis of compound **3a** by the Heck reaction of NQ-OH.

Entry	Base (eq.)	Catalyst	Salt (eq.)	Tem. (°C)	Ligand	Time (h)	Yield %
1	$NaHCO_3$ 3.0 eq	$Pd(OAc)_2$ 2 mol%	TBACl 1.0	80	-	20	0
2	-	$Pd(OAc)_2$ 5 mol%	AgOAc 1.5	60	PPh_3 20 mol%	24	0

Then, I changed the method to the 1,4-addition reaction by using the same reaction condition with the synthesis of compound **1**. (Scheme 1.11 (b)) The result demonstrated that the same addition conditions could not offer the desired NQ-Ph-OH.



Scheme 1.11 Synthesis of compound 3a by using NQ-OH

Then, different arylboronic compounds, bases, solvents, temperatures and catalysts were evaluated as Table 1.6. The result shows that the 1,4-addition reaction of NQ-OH with triphenylboroxin $(PhBO)_3$ in the presence of a catalytic amount of $[RhCl(cod)]_2$ (cod= 1,5-cyclooctadiene) and NaOMe in Dioxane at 60 °C afforded the 2-(hydroxymethyl)-3-phenylnaphthalene-1,4-dione (**3a**) in 6% yield.

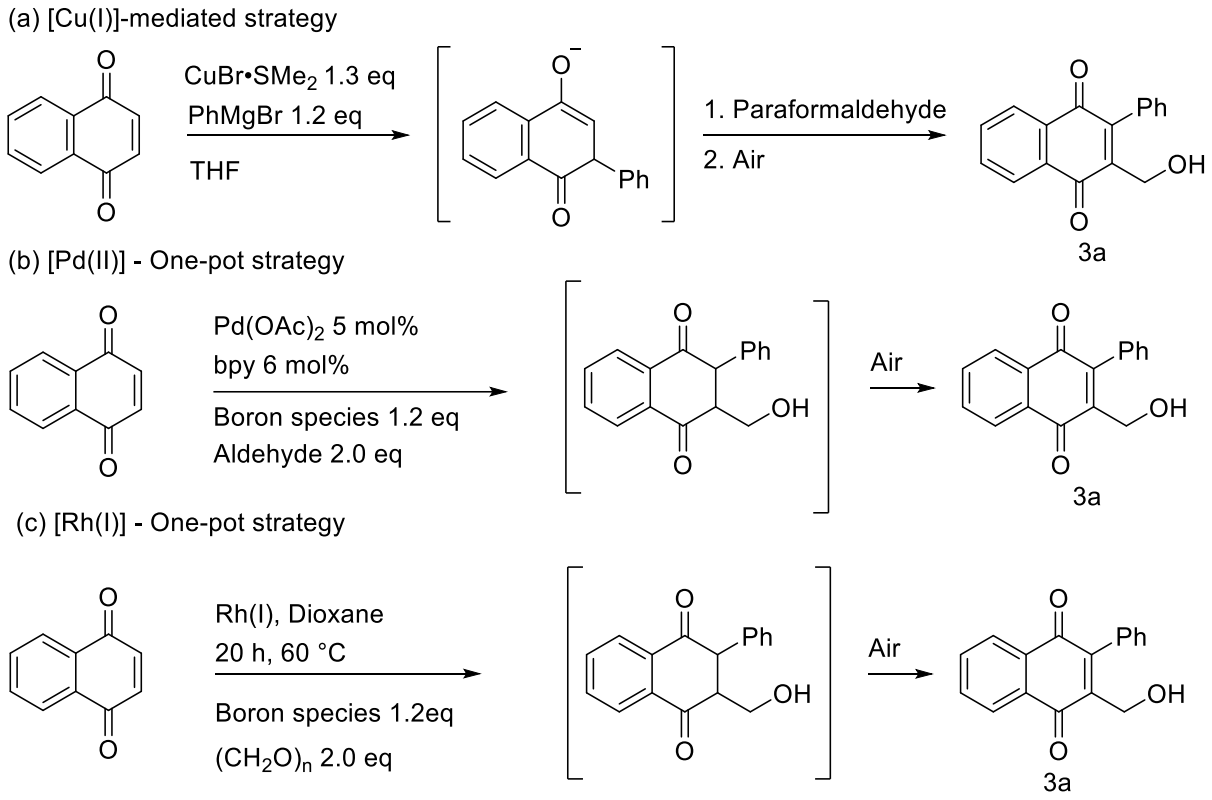
Table 1.6 Synthesis of compound **3a** by the 1,4-addition reaction of compound NQ-OH.

Entry	Boron (eq.)	Catalyst	Ligand	Base (eq.)	Solvent	Yield %
1	$PhB(OH)_2$ 2.4	$[RhCl(cod)]_2$ 3 mol%	-	NaOMe 1.2	Dioxane 3 mL	0
2	$PhB(OH)_2$ 2.4	$Pd(OAc)_2$ 1 mol%	bpy 1.2 mol%	-	DMF 3 mL	0
3	$(PhBO)_3$ 0.8	$Pd(OAc)_2$ 5 mol%	Bipyridine 6 mol%	-	DMF 3 mL	0
4	$(PhBO)_3$ 0.8	$[RhCl(cod)]_2$ 3 mol%	-	NaOMe 1.2	Dioxane 3 mL	6

1.3 One-pot Synthesis of Photoremovable Protecting Group NQ-Ph-OH

At the beginning of the one-shot reaction, I carried out the sequential one-pot operation consisting of the copper(I)-mediated 1,4-addition of phenylmagnesium bromide and the aldol reaction of the in situ-generated enolate with paraformaldehyde as

shown in Scheme 1.12 (a), (copper Grignard) however, the reaction resulted in no formation of **3a** to yield the complex mixture.



Scheme 1.12 One-pot synthetic strategy of compound **3a.**

Next, I tried to synthesize **3a** by the one-pot method catalyzed by a transition-metal complex, which through the sequence of 1,4-addition and aldol reaction. At first, I started this one-pot reaction in different conditions using the catalyst $Pd(OAc)_2$. (Scheme 1.12 (b)) As shown in entry 1, the 1,4-NQ, $Ph(OH)_2$ and paraformaldehyde were used to carry out the one-pot reaction in the presence of $Pd(OAc)_2$ under the 1,4-addition condition.

(Table 1.7) By using phenylboronic acid, different aldehyde and solvents were tested at the same condition with entry 1. Only the 1,4-addition product **1a** was obtained instead of the desired compound **3a**. Then, I considered the failure may relate to the aldol reaction progress dislike water. Therefore, I changed the boron species to triphenylboxine and dehydrated solvents. In the presence of paraformaldehyde, different bases and solvents were evaluated. The result still does not proceed as expected. Then, benzaldehyde and different bases in DMF were used for the Pd (II) system one-shot reaction. There is not desired compound **3a** generated, it proved the low solubility of paraformaldehyde is not the reason. The desired compound **3a** was not obtained in the Pd catalysis one-pot reaction.

Table 1.7 One-pot synthesis of compound **3a** by using Pd(II).

Entry	boron	Aldehyde	Base eq.	Solvent	Time h	Tem. (°C)	Yield %
1	$PhB(OH)_2$	$(CH_2O)_n$	NaOH 2	Dioxane/H_2O (10/1)	28	100	0
2	$PhB(OH)_2$	formalin	NaOH 2	Dioxane/H_2O (10/1)	24	100	0
3	$PhB(OH)_2$	formalin	NaOH 2	DMF/H_2O (10/1)	27	100	0
4	$(PhBO)_3$	$(CH_2O)_n$	NaOMe 3.6	Dioxane	38	50	0
5	$(PhBO)_3$	$(CH_2O)_n$	NaOMe 3.6	DMF	24	50	0
6	$(PhBO)_3$	PhCHO	NaOMe 3.6	DMF	27	50	0
7	$(PhBO)_3$	PhCHO	CsF 3.6	DMF	27	50	0

Therefore, I changed the catalyst system to Rh[I].[17] (Scheme 1.12 (c)) At first, the reaction was conducted by using 1,4-NQ, 1,3,5-triphenylboroxin, KOH and paraformaldehyde in the presence of $[RhOH(cod)]_2$ (cod= 1,5-cyclooctadiene) to give the target compound **3** in the 3% yield. (Table 1.8) Then, I tried to optimize the reaction condition. The reaction was carried out under the $[RhCl(cod)]_2$ catalyst in the above condition, and the yield of product **3a** was increased to 42%. (Entry 2) The $[RhCl(cod)]_2$ showed the higher efficiency for the one-shot synthesis of compound **3a**. Thus, the reaction was carried out by only changing NaOMe to KOH. However, only 17% **3a** was obtained. Different amount ratio of NaOMe and [Rh(I)] was tested. I found excessive NaOMe (3eq) resulted in 54% yield of 1,4-addition product **1a**, and 3 mol% showed 16% compound **1a** and 15% compound NQ-OH. Next, different boron species were evaluated. Compared to $(PhBO)_3$, desired product **3a** was not obtained by using PhBpin (Bis(pinacolato)diboron) and $PhB(OH)_2$. The reactivity of HCHO gas has been tested, the result showed no generation of desired product **3a**. (Entry 6)

Finally, the standard one-shot reaction conditions were developed as entry 2. Under the $[RhCl(cod)]_2$ (5 mol%) as a catalyst, the reaction of NQ with 1,3,5-triphenylboroxin (1.2 eq), NaOMe (1 eq) and paraformaldehyde (2 eq) resulted in the sequence of 1,4-

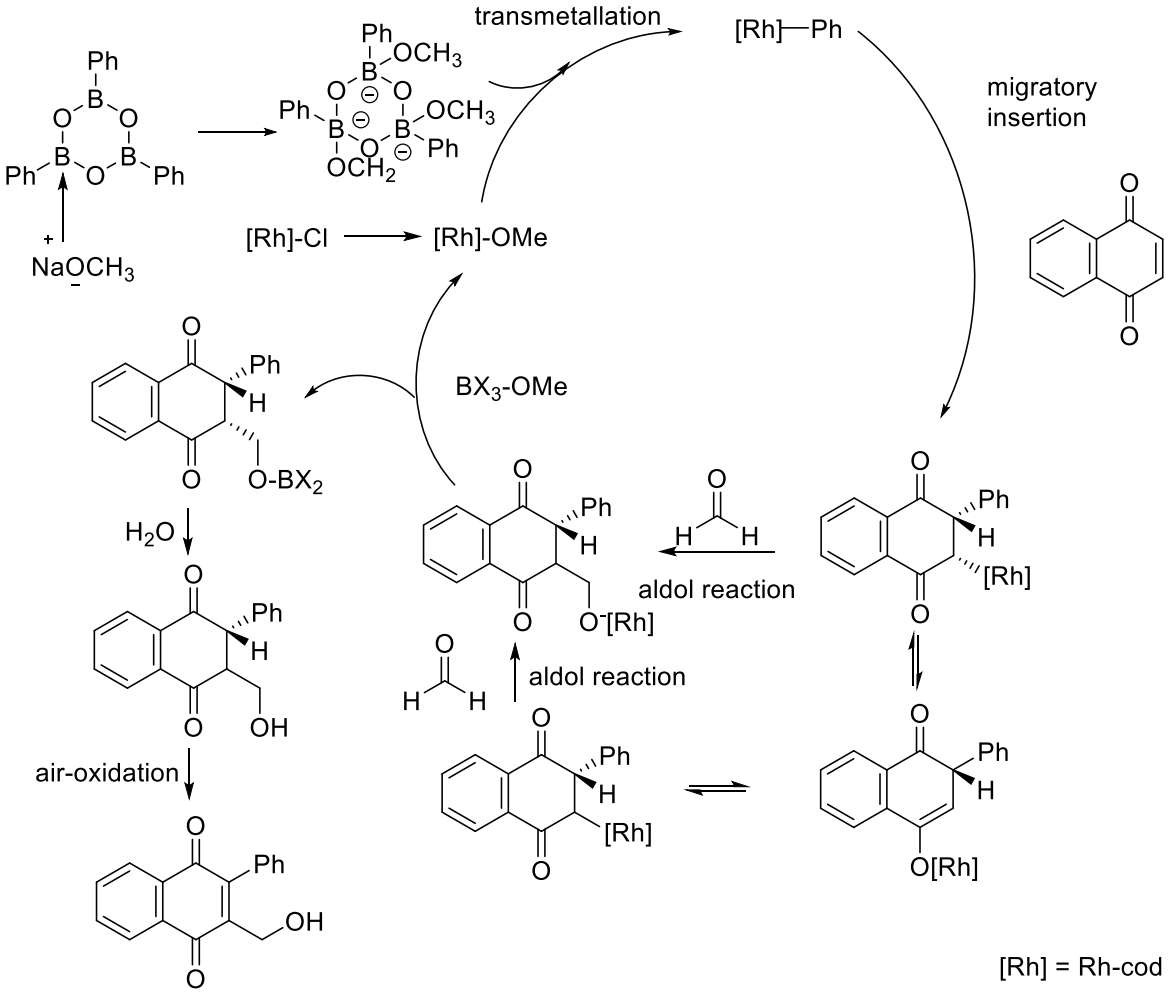
addition and aldol reaction to give the target compound **3a** in highest isolated yield. This method was suitable for the different substituent, and successfully offered the desired 2-(hydroxymethyl)-3-(4-methoxyphenyl) naphthalene-1,4-dione **3b** and 2-(hydroxymethyl)-3-(4-(trifluoromethyl) phenyl) naphthalene-1,4-dione **3c**.

Table 1.8 One-shot synthesis of compound **3a** by using Rh(I).

Entry	Boron eq.	Aldehyde eq.	Base eq.	Catalyst mol%	Yield %
1	$(PhBO)_3$ 1.2	$(CH_2O)_n$ 2	KOH 1	$[RhOH(cod)]_2$ 2.5	1
2	$(PhBO)_3$ 1.2	$(CH_2O)_n$ 2	NaOMe 1	$[RhCl(cod)]_2$ 5	42
3	$(PhBO)_3$ 1.2	$(CH_2O)_n$ 2	KOH 1	$[RhCl(cod)]_2$ 3	17
4	$(PhBO)_3$ 1.2	$(CH_2O)_n$ 2	NaOMe 1	$[RhCl(cod)]_2$ 3	39
5	$(PhBO)_3$ 1.2	$(CH_2O)_n$ 2	NaOMe 3	$[RhCl(cod)]_2$ 1	5
6	$(PhBO)_3$ 1.2	HCHO gas 3	NaOMe 1.2	$[RhCl(cod)]_2$ 3	0
7	$PhB(OH)_2$	$(CH_2O)_n$ 2	NaOMe 1.2	$[RhCl(cod)]_2$ 3	0
8	PhBpin	$(CH_2O)_n$ 2	NaOMe 1.2	$[RhCl(cod)]_2$ 3	0

The reaction assumed pathway was shown in scheme 1.13. It is followed by the sequence of a 1,4-addition reaction and aldol reaction. First, the base (NaOMe) attracts

the boron species and offers the free phenyl to [Rh(I)]. The transmetallation progress gives the [Rh(I)]-Ph complex. Then, the migratory insertion of 1,4-NQ with the [Rh(I)]-Ph complex, results in two isomerization species. Before the elimination step, the paraformaldehyde generated the aldol reaction. Finally, the desired compound **3a** was obtained after oxidation.



Scheme 1.13 Assumed reaction pathway of the one-pot method.

1.4 Summary

Here I reported a novel NQ photoremovable framework **3**. It was successfully synthesized in three methods from the commercially available 1,4-naphthoquinone. The one-pot synthetic method is the 1,4-addition-aldol reaction, where a rhodium complex catalyzes both two carbon-carbon bond-forming reactions, the catalytic cycle consisting of the 1,4-addition of an organorhodium species to an unsaturated ketone and the aldol addition of the resulting rhodium intermediate to an aldehyde. The one-pot reaction showed us a 42% yield of **3a**. The stepwise method is the combination of a 1,4-addition reaction and Morita-Baylis-Hillman reaction or a 1,4-addition reaction and Aldol reaction. The two stepwise methods showed the different yields of compound **3**. In the case of Baylis Hillman's reaction, it offered compound **3a** in 16% yield. In the case of Aldol reaction, compound **3a** was obtained in 82% yield.

Furthermore, compound **3a** can be easily derivatized from 1,4-naphthoquinone and different boron species.

1.5 References

1. Kamdzhilov, Y.; Wirz, J. *Photochem. Photobiol. Sci.* **2007,** *6*, 865-72.

2. Cameron, D. W.; Giles, R. G. F. *Number.* **1965,** *22*, 573-574.

3. Chen, Y., ; Steinmetz, M. G. *J. Org. Chem.* **2006,** *71*, 6053-6060.

4. Walton, D. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **2017,** *139*, 4655-4658.

5. Hikage, S.; Nishiyama, Y.; Sasaki, Y.; Tanimoto, H.; Morimoto, T.; Kakiuchi, K. *ACS Omega.* **2017,** *2*, 2300-2307.

6. Zhang, Y.; Zhang, H.; Ma, C.; Li, J.; Nishiyama, Y.; Tanimoto, H.; Morimoto, T.; Kakiuchi, K. *Tetrahedron Lett.* **2016,** *57*, 5179-5184.

7. Kakiuchi, K.; Zhang, Y.; Tanimoto, H.; Nishiyama, Y.; Morimoto, T. *Synlett.* **2012,** *23*, 367-370.

8. Sharma, J.; Singh, P. K.; Singh, K. P.; Khanna, R. N. *Org. Prep. Proced. Int.* **2009,** *27*, 84-86.

9. Bonin, H.; Fouquet, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2011,** *353*, 3063-3084.

10. She, Z.; Shi, Y.; Huang, Y.; Cheng, Y.; Song, F.; You, J. *Chem. Commun.* **2014,** *50*, 13914-13916.

11. Deb, A.; Manna, S.; Maji, A.; Dutta, U.; Maiti, D. *Eur. J. Org. Chem.* **2013,** *2013*, 5251-5256.

12. Akagi, Y.; Komatsu, T. *Tetrahedron Lett.* **2020,** *61*, 152446.

13. Williams, C.; Porzelle, A.; Schwartz, B.; Gentle, I. *Synlett.* **2005,** *2005*, 2923-2926.

14. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003,** *103*, 811−891.

15. Dounay, B. A.; Overman, L. E. *Chem. Rev.* **2003,** *103*, 2945-2963.

16. Heravi, M. M.; Dehghani, M.; Zadsirjan, V. *Tetrahedron: Asymmetry* **2016,** *27*, 513-588.

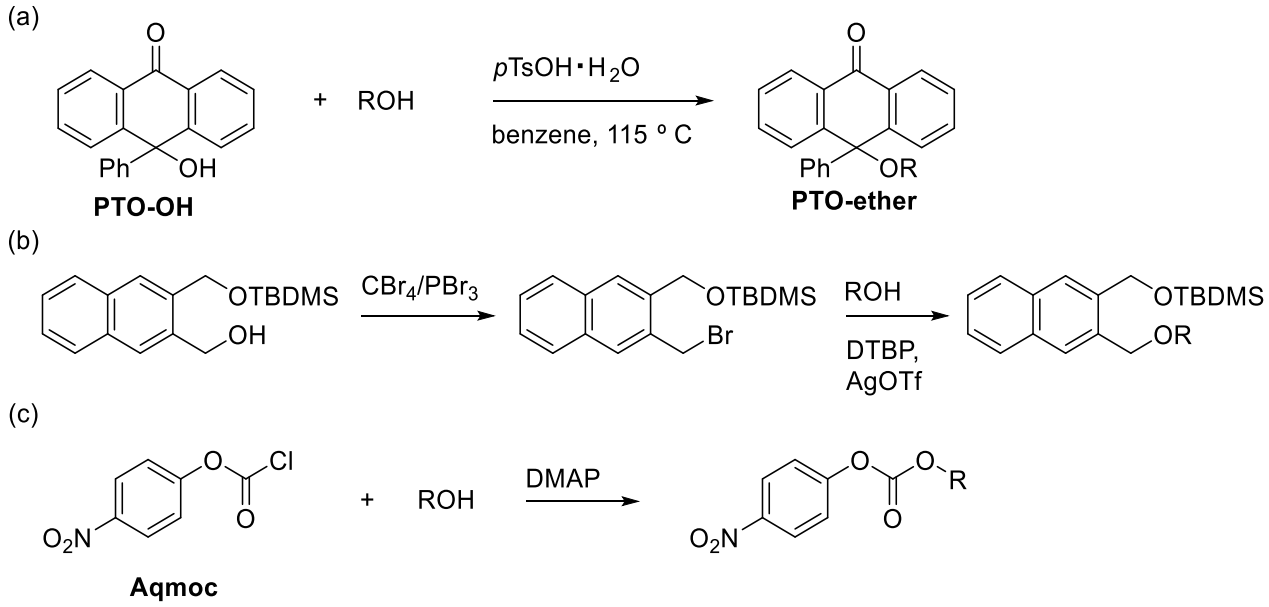
17. Yoshida, K.; Ogasawara, M; Hayash, T. *J. Am. Chem. Soc.* **2002,** *124*, 10984-10985.

CHAPTER 2 Conjugation of Various Functionalities with NQ-based Photoreactive Framework

2.1 Introduction

To date, scientists have developed many photoremovable compounds, which are derived from the corresponding photoprotecting group with various functionalities. Alcohol, carboxylic acid and amine are the popular functionalities to be protected. The protection efficiency and categories are also important for assessing them. The protection and release of alcohol are usually achieved by transforming them into ether or carbonate. The PTO-ethers were prepared through acid-catalyzed condensation of PTO-OH (9-hydroxy-9-phenyltritylone) with the corresponding alcohols.[1] (Scheme 2.1(a, b)) Therefore, there are lots of etherification methods that can be applied for the protection of various alcohol.[2] The above etherifications were carried out between two alcohols. Another example was converting one of the alcohol into a bromide intermediate, which was then reacted with target alcohols in the presence of silver triflate and di-(tert-butyl)pyridine to produce desired ethers.[3] The Aqmoc carbonates were obtained from the Aqmoc chloroformate and various alcohol.[4] (Scheme 2.1(c)) Some articles also reported that the protected alcohol can be transformed into the corresponding chloroformate as the

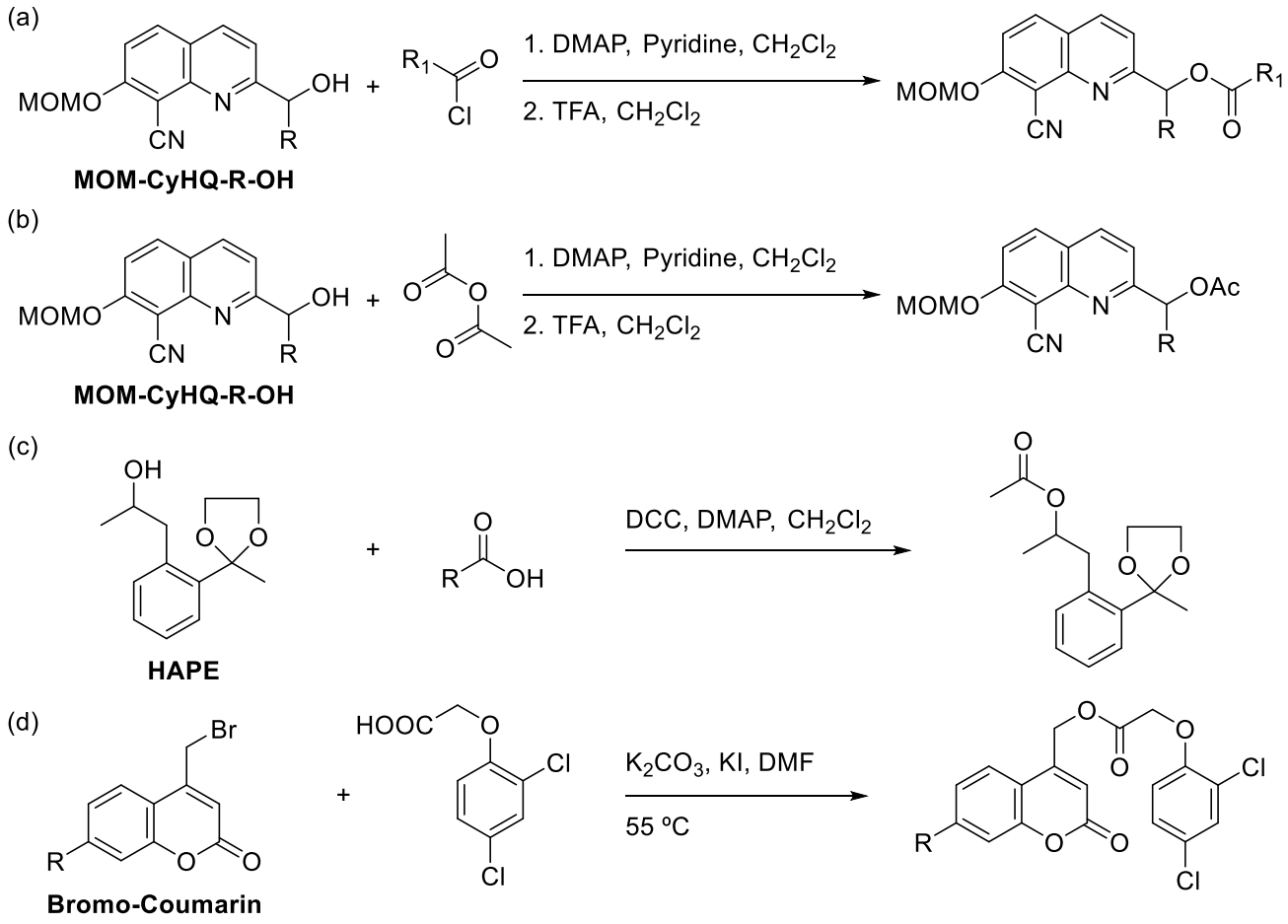
provider of alcohol for the photoreleasing progress.



Scheme 2.1 Protecting strategy for alcohol.

For the photoreleasing of carboxylic acid, the photoremovable compounds based on (8-cyano-7-hydroxyquinolin-2-yl)methyl (CyHQ) with a carboxylic acid group can be obtained by MOM-CyHQ-R-OH in two methods.[5] They are the chloroformalation reaction of chloroformate (Scheme 2.2(a)) and acetylation reaction (Scheme 2.2(b)) of acetic anhydride with the protecting group. The protecting group 1-[2-(2-hydroxyalkyl)phenyl]ethanone (HAPE) is used to protect various carboxylic acids.[6] Protected acids were obtained by treating HAPE protecting group with the acids under the simple esterification reaction. (Scheme 2.2(c)) Direct protection of carboxylic acid

was reported by using coumarin derivatives with Bromo substituent.[7] 4-(bromomethyl)-7-substituted coumarins were treated with a carboxylic acid in the presence of K_2CO_3/KI in dry DMF, resulting in the formation of corresponding caged compounds. (Scheme 2.2(d))

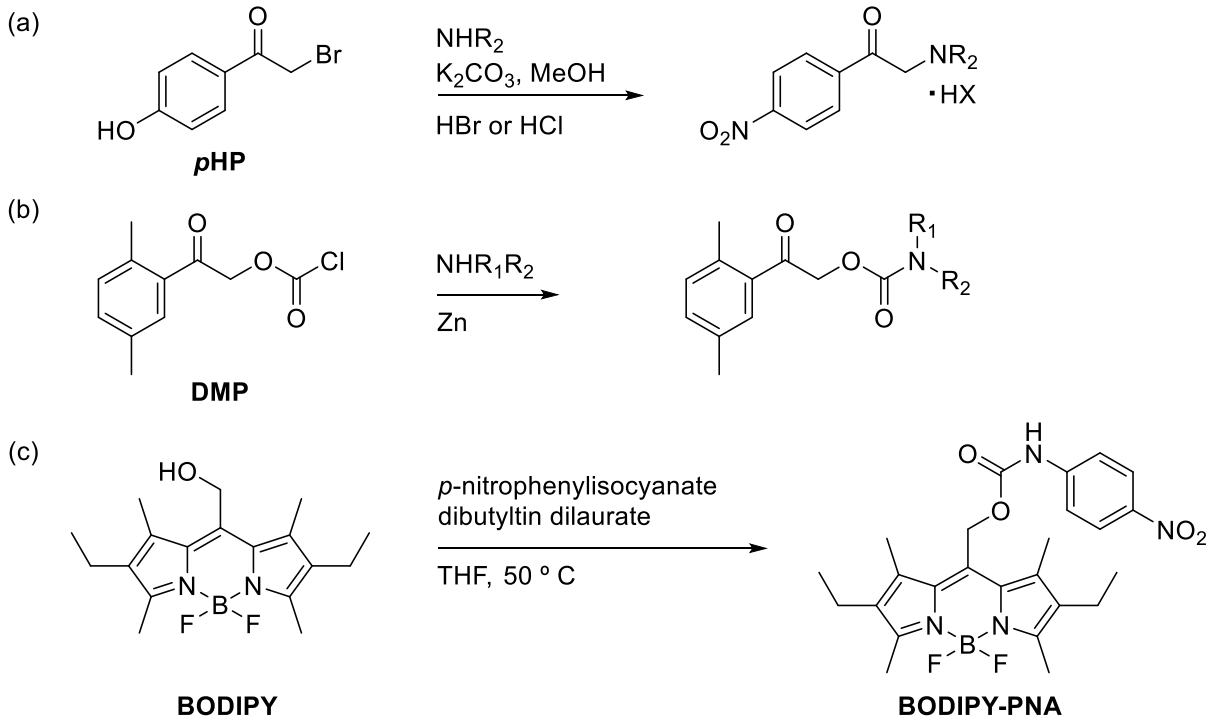


Scheme 2.2 Protecting strategy for carboxylic acid.

Amine has numerous applications in organic chemistry due to its basicity and

nucleophilicity.

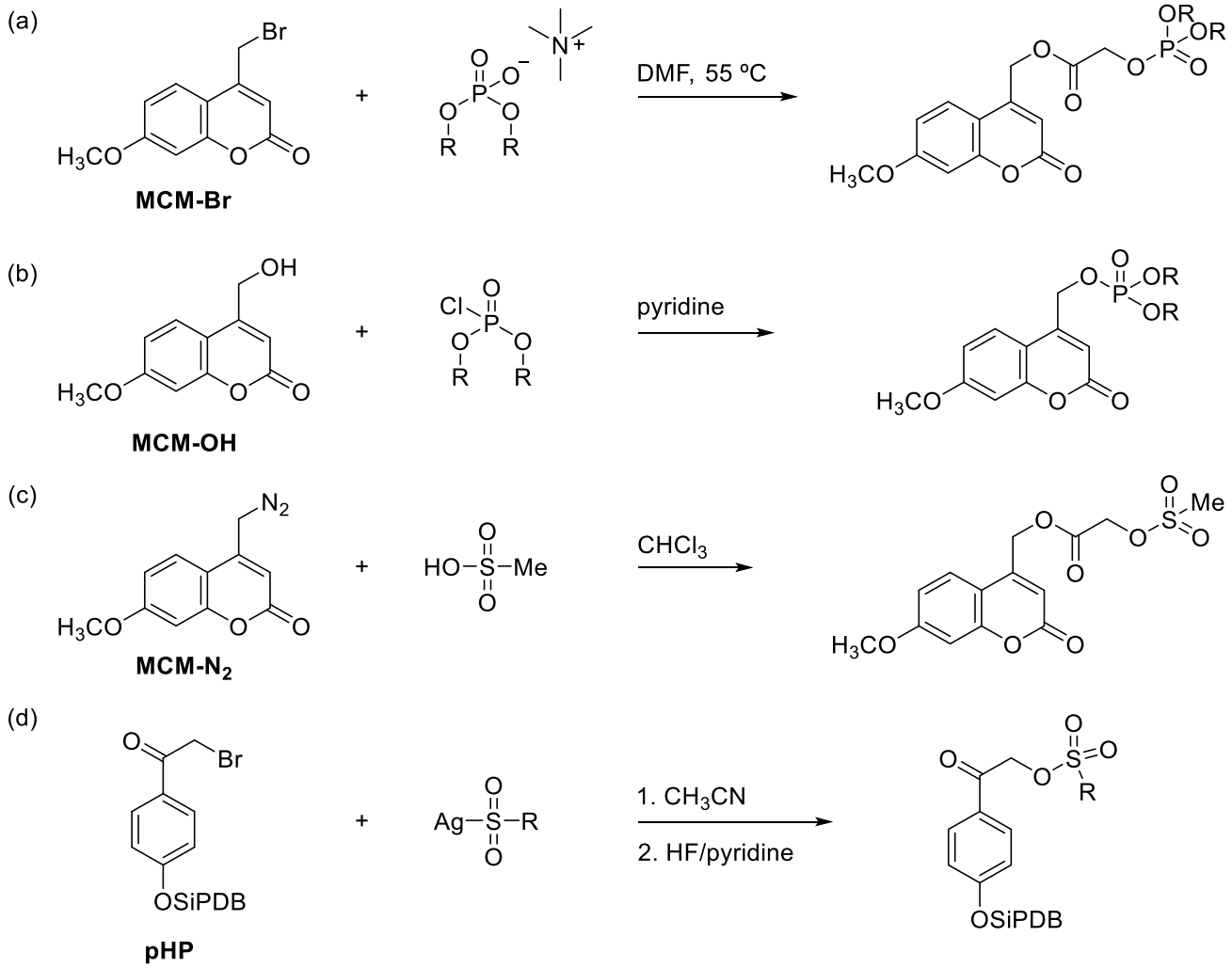
The high reactivity of amine also brings some challenges to the synthetic procedure of organic synthesis. To avoid the side reaction, protecting groups or photoprotecting groups have been used to protect them from the side reaction. For example, the protected amine was prepared by coupling 4-hydroxyphenacyl (*p*HP) bromide with amines in the presence of a base and subsequently acidified with HCl or HBr.[8] (Scheme 2.3 (a)) The amine protection method of the DMP framework is a general method.[9] At first, the 2,5-dimethyl phenacyl (DMP) chloroformate was synthesized from 2,5-dimethylphenacyl alcohol and bis(trichloromethyl) carbonate (BTC). The protected amine was prepared by coupling the DMP chloroformate and the corresponding amine. (Scheme 2.3 (b)) Isocyanate species are electrophiles, which have a high reactive with the alcohols, and amines.[10] Thus, it has been used as the provider of amine in the protection reaction. (Scheme 2.3 (c)) For example, the BODIPY alcohol compound was treated with nitrophenylisocyanate and the catalytic amount of Et_3N, this reaction can offer the desired BODIPY-PNA in high yield.[11]



Scheme 2.3 Protecting strategy for amine.

Phosphates have long held an important formative position in the development of organic photochemistry and a central historic position in caged photochemistry through their cross-disciplinary significance in both biology and chemistry.[12, 13] For the synthesis of caged phosphate acid, it has been used the tetramethylammonium diethyl phosphate with the MCM-Br in DMF. (Scheme 2.4 (a)) The desired phosphate ether was obtained by direct displacement of bromide.[14] The second method is shown in Scheme 2.4 (b), the phosphate ether was synthesized by reaction of diethyl phosphoric acid chloride with the MCM-OH in pyridine.[15]

In the case of sulfonic acid protection, people attempt to obtain MCM mesylate via conversion of MCM-OH with methanesulfonic acid chloride or methanesulfonic acid anhydride led to decomposition. Thus, they transferred the MCM-OH to MCM-N_2, which was esterified with a sulfonic acid to offer the desired sulfonate.[16] An uncommon method is that the sulfonic acid was pretreated with the silver dioxide, followed by the reaction with the pHP to offer the desired sulfonate.[17]



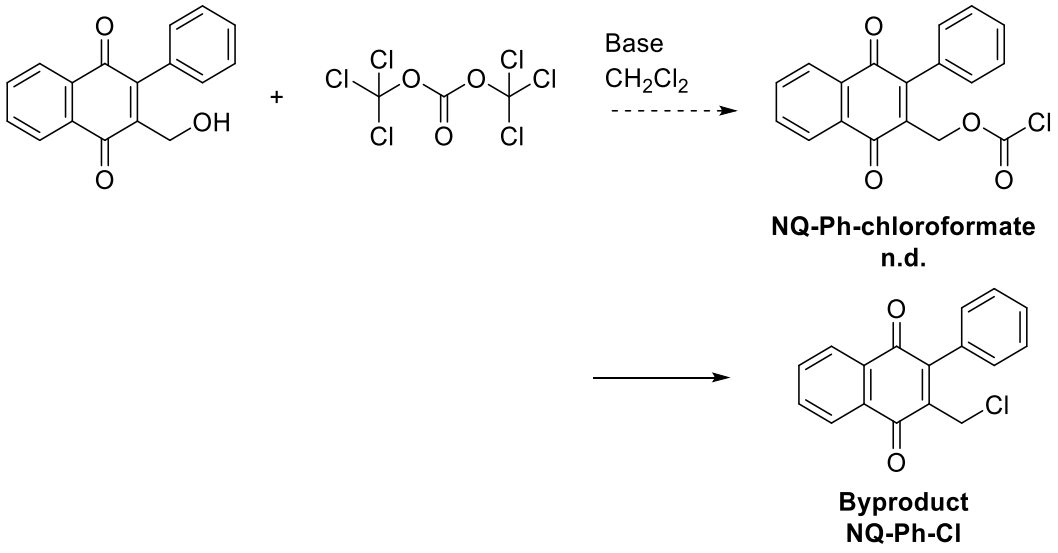
Scheme 2.4 Protecting strategy for phosphate acid and sulfonic acid.

As mentioned in the introduction part of this chapter, I realized that chloroformates are versatile intermediates, which offer simple condition and a high yield in protection.

So far, many lectures reported the protection of alcohols, amines, carboxylic acids and phosphate acids was achieved by a condensation reaction between chloroformate derivatives of the protected group and photoprotecting groups. In this method, various alcohol, amines, and acids need to transfer to their corresponding chloroformate. It is obvious that the direct condensation by using NQ-Ph-OH with various functionalities may show a low yield due to the condensation byproducts. Thus, I designed two synthetic strategies in chapter 2 to protect various functionalities by using the NQ-based photoremovable framework. NQ-Ph-OH (compound **3**) was transferred to its chloroformate in the first method. In this way, a photoremovable protecting group protects various functionalities in a short and unique method. In the second method, various alcohols, amines, and acids are transferred to their chloroformates. In this way, various NQ-Ph-chloroformate species can be directly conjugated with various alcohols and amines as the above-mentioned strategies for alcohol and amine.

2.2 The protection of Various Alcohols, Amines, and Carboxylic acids

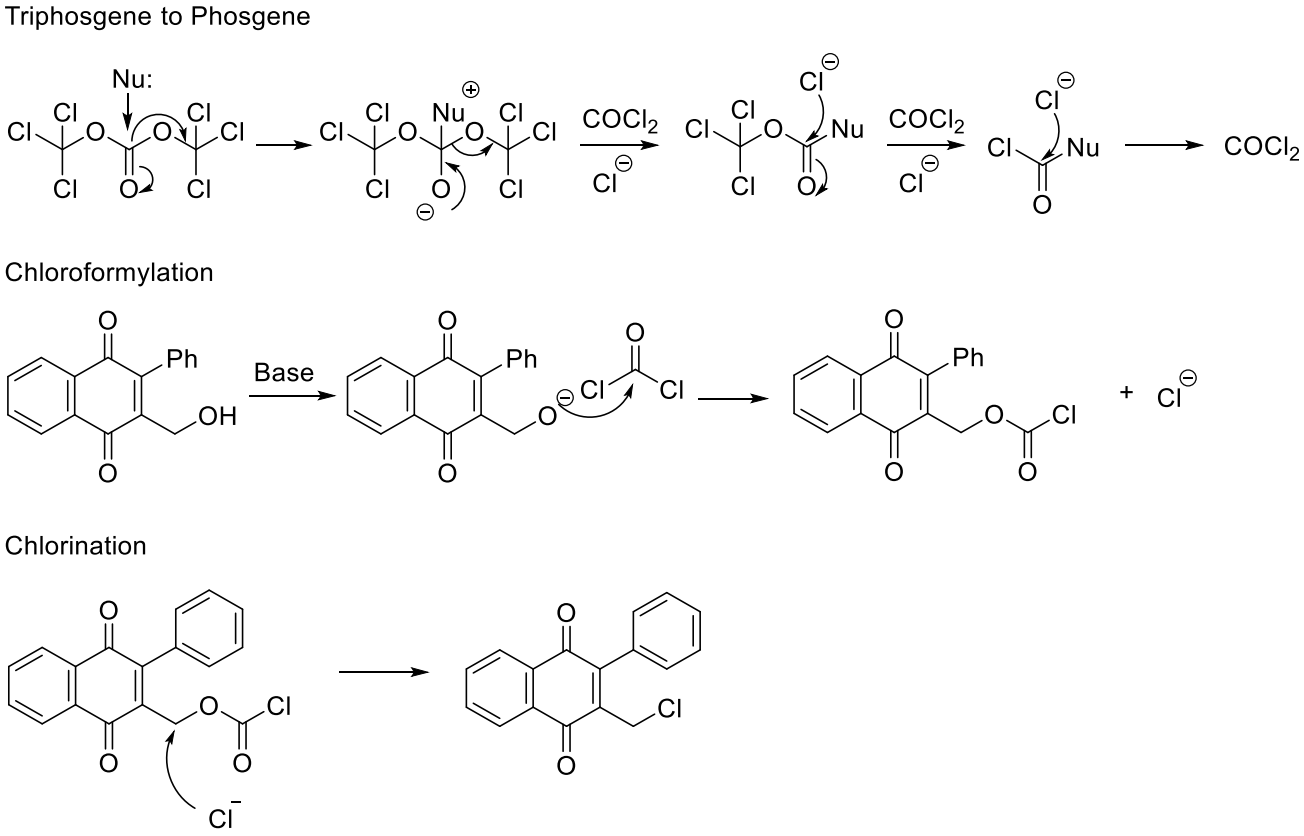
It is well-known that a wide variety of building blocks such as isocyanate, urea, chloroformate, *N*-carboxyanhydride, and carbamoyl chloride can be easily synthesized using phosgene.[18] The most widely used method for the synthesis of chloroformates is the reaction of phosgene with various alcohols. However, phosgene is a highly toxic gas and inconvenient to transport and store. Therefore, phosgene is disadvantageous for the preparation of chloroformates in the laboratory. Bis(trichloromethyl) carbonate (BTC), generally called triphosgene, is solid under standard conditions.[19, 20] It has been reported as a safer replacement for phosgene and trichloromethyl chloroformate. BTC allows *in situ* generations of phosgene in solution upon mixing with an organic base, and its subsequent rapid reaction with alcohol gives the chloroformate. In this work, the cholorformylation reaction was carried out by using the NQ-Ph-OH and triphosgene in the presence of the base. (Scheme 2.5)



Scheme 2.5 Reaction for synthesis of NQ-Ph-chloroformate.

As shown in Table 2.1, entries 1−3, activation of NQ-Ph-OH (**3**) with triphosgene in the presence of 1.2 equiv. of pyridine at different temperatures. As shown in entry 1, the use of 1.2 equiv. of pyridine predominantly produced NQ-Ph-Cl in 100% yield. It means the chlorination reaction instead of the cholorfomylation reaction. The results obviously support the reaction pathway outlined in Scheme 2.6, and importance of the nucleophilic role of the chloride ion.[21] The chloride ion, under these reaction conditions, is a strong nucleophile that attacks the carbonyl carbon of triphosgene giving diphosgene and phosgene. In turn, diphosgene reacts with chloride ions to give two molecules of phosgene. The chloride ion is needed in catalytic amount since it is not consumed in the overall process. Activation of the NQ-Ph-OH with the base and phosgene initially generates

chloroformate (NQ-Ph-chloroformate). In the absence of *α*-branching, the *in situ* generated chloride ion then rapidly attacks the C1 carbon to provide alkyl chloride (NQ-Ph-Cl) by extruding CO_2 and another equivalent of chloride ion.[22]



Scheme 2.6 Reaction pathway of chloroformylation and chlorination.

I considered that decreasing the temperature and short reaction time would inhibit the formation of the undesired NQ-Ph-Cl functionality. According to our expectation, the decrease of temperature to -40 °C and -60 °C resulted in minimal NQ-Ph-Cl along with a

large amount of starting materials. (Entries 2-3) In entry 4, an increase of pyridine from 1.2 to 2.0 equiv. resulted in a similar result with entry 3. As a result of these experiments, I concluded that pyridine alone, as a base/activator, would not avoid chlorination. Then, discussion is shifted for exploring a mixture of amine bases, such as pyridine and triethylamine.[23] As shown in entries 5 and 6, activation of NQ-Ph-OH with triphosgene in the presence of 1.2 equiv. of pyridine with 0.25 equiv. of triethylamine unfavored offered the chlorination product (NQ-Ph-Cl) in 96%. It indicated that the TEA activation system prefers the chlorination reaction, probably due to the difference in the pKa values of their conjugate acids. Then, I considered that low temperature and short reaction time under the activation of TEA would improve the formation of the desired chloroformylation reaction.[24] However, the low temperature and short reaction time show the undesired NQ-Ph-Cl along with unactivated starting material (NQ-Ph-OH).

Table 2.1 Synthesis of NQ-Ph-chloroformate

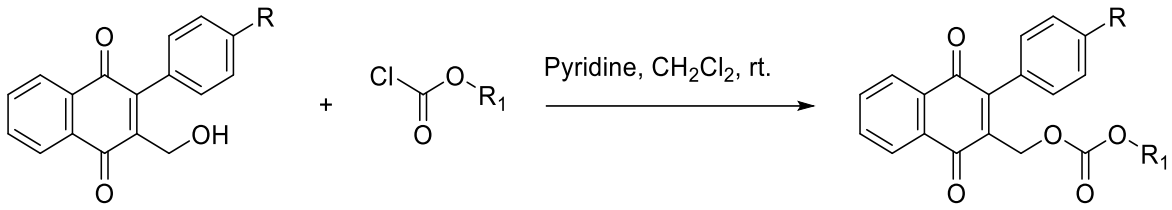
Entry	Base	Temp. (°C)	T. (h)	NQ-Ph-Cl
1	Pyridine 1.2 eq	rt.	12	100
2	Pyridine 1.2 eq	0	12	95
3	Pyridine 1.2 eq	-20	6	trace
4	Pyridine 2 eq	-60	6	trace
5	Pyridine 1.2 eq Et_3N 0.25 eq	0	6	96%
6	Pyridine 1.2 eq Et_3N 0.25 eq	-20	6	96%
7	Et_3N 1.2 eq	-20	6	96%
8	Et_3N 1.2 eq	-40	3	trace
9	Et_3N 2 eq	-60	3	trace

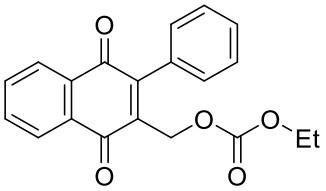
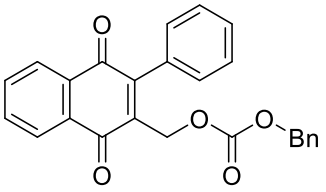
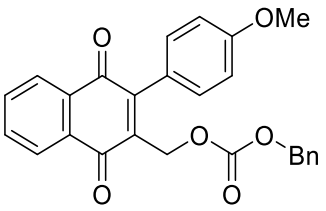
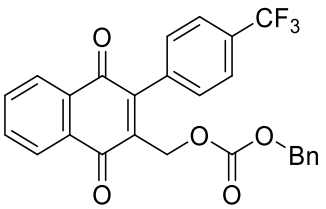
Then, I changed the reaction strategy to the condensation of compound **3** and corresponding chloroformates, carbamoyl, isocyanate and various carboxylic acids. The masking of alcohol, amine, and carboxylic acid with compound **3** were carried out.

Then, I started the synthesis of the compound **4** by using NQ-Ph-OH with ethyl chloroformate. I wanted to use the protected ethanol **4** to test the synthetic reactivity of NQ-photoreactive core **3** with general chloroformate, and evaluated the photoreactivity using the simple protected compound **4**. The protected ethanol **4** was synthesized by the reaction of **3a** with ethyl chloroformate in the presence of pyridine in dichloromethane at room temperature. (Table 2.2) The reaction proceeded smoothly to give compound **4** in 95% yield. Under similar conditions for the synthesis of **4**, benzyl alcohol derivatives **5**–

7 were prepared from benzyl chloroformate with **3a**–**c**, respectively.

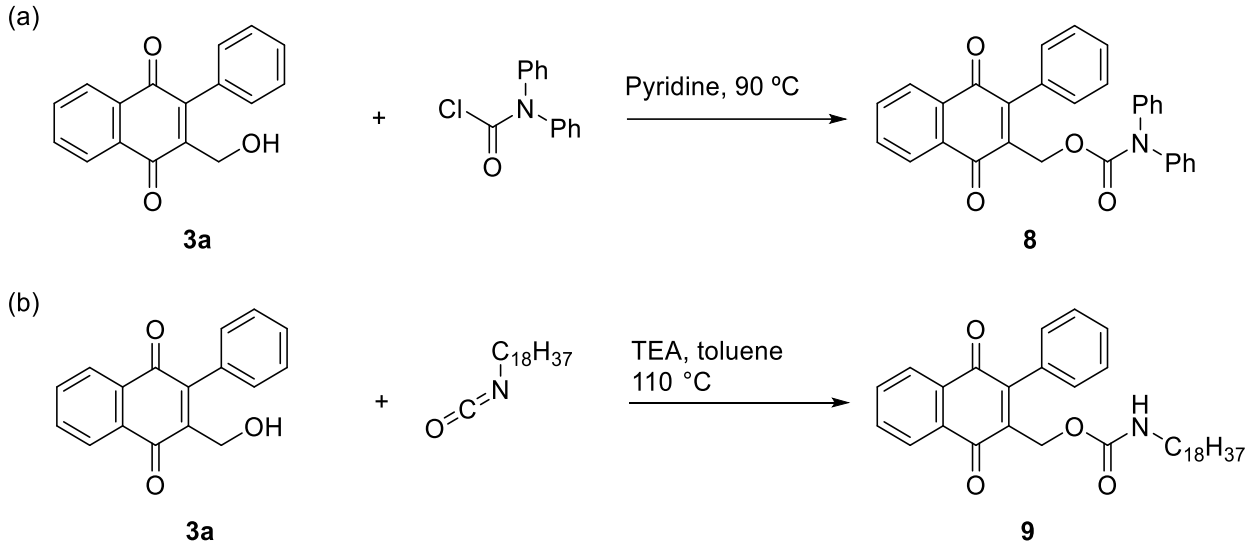
Table 2.2 Conjugation of NQ-core with various alcohols.



Entry	Photoremovable Compound	R	R_1	Time (h)	Product	Yield (%)
1	4	H	Et	5		95
2	5	H	Bn	12		80
3	6	OMe	Bn	12		48
4	7	CF_3	Bn	20		20

The protected amine **8** was also obtained from the reaction of **3a** with *N,N*-

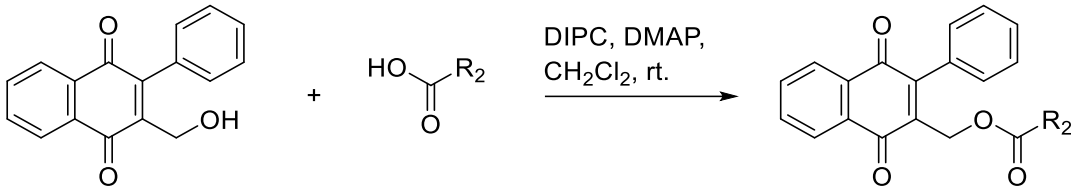
diphenylcarbamoyl chloride, and it result in the compound **8** in 12% yield. (Scheme 2.7 (a)) In the case of the synthesis of the protected octadecylamine **9**, the addition reaction of **3a** to octadecyl isocyanate in the presence of triethylamine was employed, resulting in compound **9** in 21% yield. (Scheme 2.7 (b))

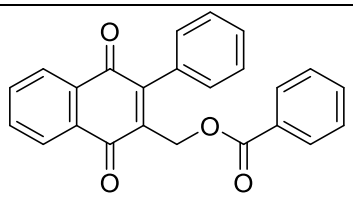
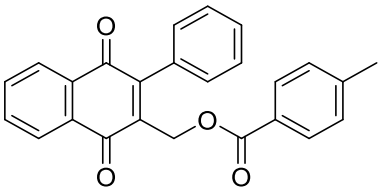
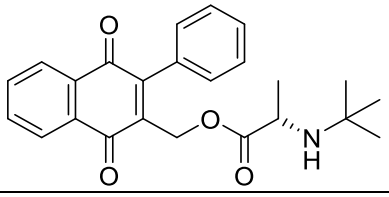


Scheme 2.7 Conjugation of NQ-core with various amines.

The synthesis of protected carboxylic acids was conducted by the condensation of **3a** with benzoic acid, 4-methylbenzoic acid, and N-Boc-L-alanine in the presence of 4-dimethylaminopyridine (DMAP) and *N,N′*-diisopropylcarbodiimide (DIPC) in dichloromethane at room temperature, to afford the desired compounds **10**, **11**, and **12** in 76%, 53%, and 75% yields, respectively. (Table 2.3)

Table 2.3 Conjugation of various carboxylic acids with compound **3a**.

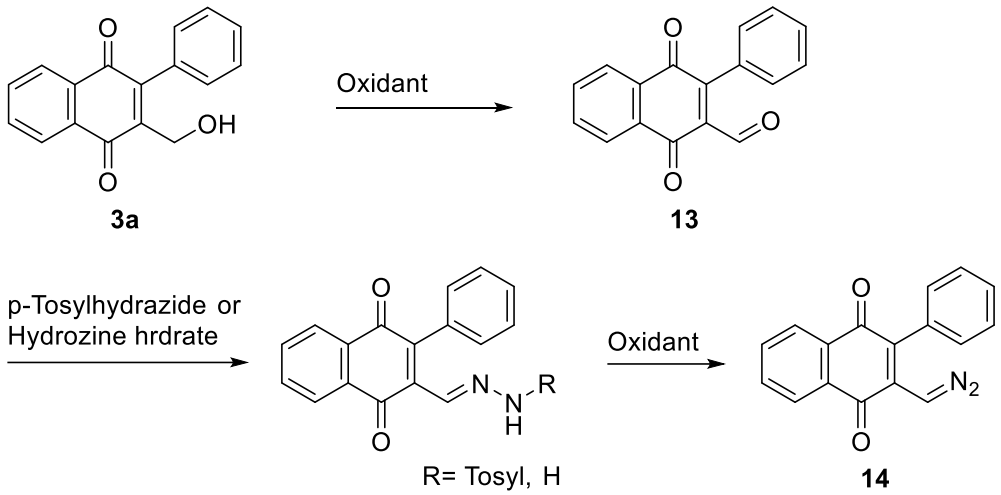


Entry	Photoremovable Compound	R_2	Time (h)	Product	Yield (%)
1	10	Ph	15		76
2	11	*p*-tolyl	15		53
3	12	Boc-L-NHCH$(CH_3)_3$-	15		75

2.3 Synthesis of NQ-Ph-N_2 for Various Acid

Since phosphoric and sulfonic acids were not protected by the direct condensation with **3a**. As previous reported, diazo compounds are versatile substrates in organic synthesis, which have been used as precursors to carbenes.[25] Thus, the 1,4-NQ-based photoreactive framework **3a** was converted into the diazo derivative **14**. The synthetic

plan of the diazo compound **14** was shown in Scheme 2.8.

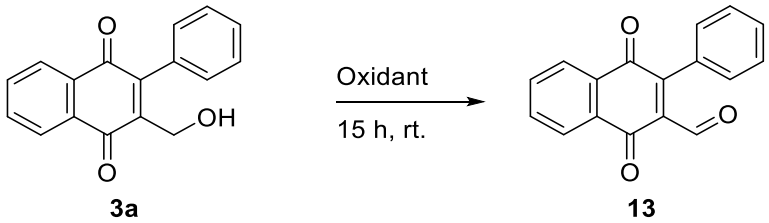


Scheme 2.8 Synthetic plan of compound **14**.

The oxidation of **3a** was evaluated by using different oxidants. The iodine(V) reagents, DMP (Dess-Martin-Periodinane) and IBX (2-Iodoxybenzoic acid), are the optimized reagents for this functional group transformation in complex molecules.[26] At first, the oxidation reaction was carried out by using 1.3 equiv. oxidant DMP at room temperature.[27] Excess $NaHCO_3$ was used during the DMP-oxidation of **3a** to trap the acetic acid byproduct. The oxidation reaction by using DMP offered the desired aldehyde **13** in 86% yield. (Table 2.4: Entry 1) Next, oxidant IBX was used in this reaction. IBX is not soluble in many organic solvents and typical oxidation takes place in DMSO at room temperature.[28] The oxidation of **3a** with 1.3 equiv. IBX in DMSO at room temperature

gave the desired aldehyde **13** in 95% yield. (Table 2.4: Entry 2) I selected the IBX as the optimized oxidant in the oxidation of compound **3a**.

Table 2.4 Oxidation of compound **3a**.

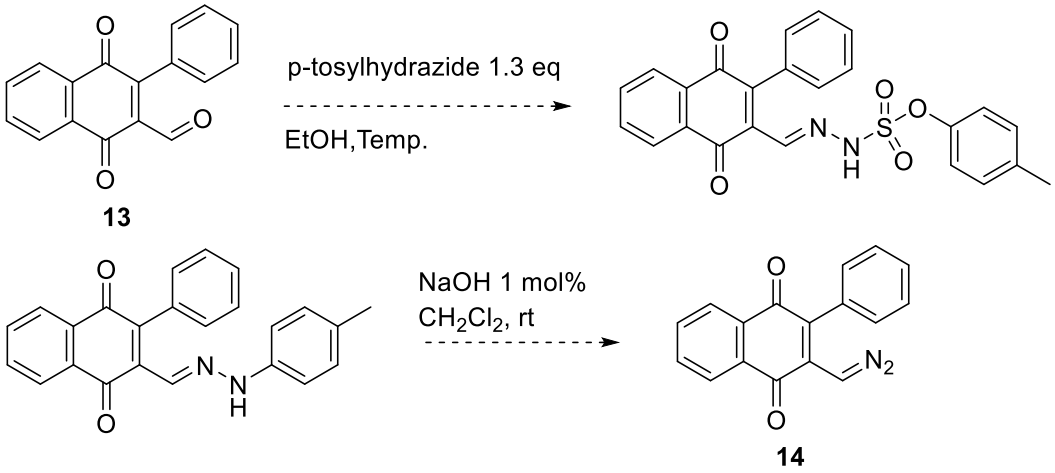


3a **13**

Entry	Oxidant	Yield (%)
1	DMP 1.5 eq	86
2	IBX 1.5 eq	95

Then, I synthesized diazo compound **14** by using the aldehyde **13**. There are lots of reports on the synthesis of diazo compounds by the oxidation of hydrazone or tosyl hydrazone intermediate, which can be obtained from the condensation of the corresponding aldehyde with hydrazine hydrate or tosylhydrazine.[29, 30] Initially, the condensation reaction of aldehyde **13** was carried out by using the *p*-tosylhydrazine as the tosyl group is a good leaving group. (Scheme 2.9) 1.3 equiv. *p*-$TsNHNH_2$ in ethanol was added to aldehyde **13** at 0 °C and was stirred at room temperature. However, there is

not desired hydrazone intermediate generate. I continued to do this reaction by adding 3 mol% acetic acid.[31] Unfortunately, I did not obtain the hydrazone intermediate by using *p*-tosylhydrazine.



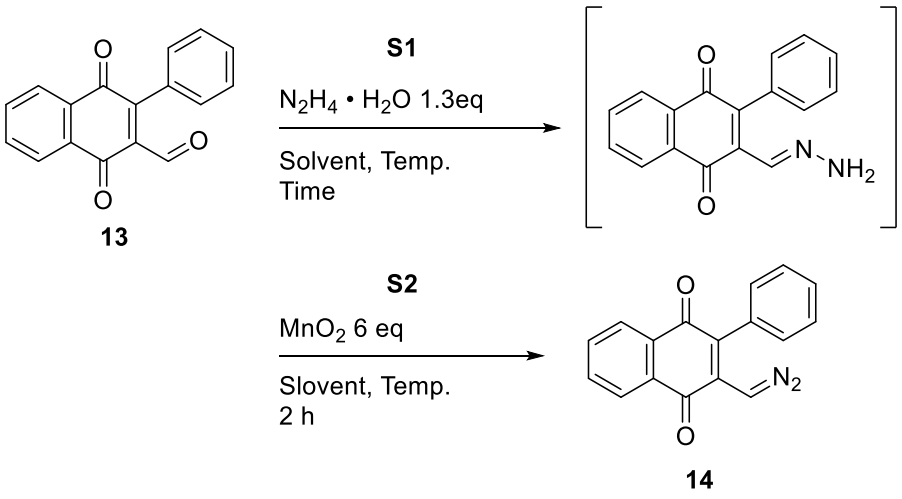
Scheme 2.9 Synthesis of photoreactive diazo compound **14** by two-step method.

Table 2.5 Synthesis of NQ-Ph-tosylhydrazone.

Entry	Catalyst	Temp. (°C)	Yield (%)
1	-	0	0
2	acetic acid 3 mol%	rt	0

I thought it may be due to the steric hindrance. Thus, I used the hydrazine hydrate to condense with aldehyde **13**. (Scheme 2.10) The condensation of aldehyde **13** with 1.1

equiv. hydrazine monohydrate was carried out in ethanol at room temperature.[32] The desired hydrazone intermediate was obtained in 7% isolation yield. The oxidation reaction using 6 equiv. MnO_2 in diethyl ether at 0 °C offered 10% of the desired diazo compound **14**.[33] I found that the hydrazone intermediate decomposed under room temperature, and probably this is the reason for the low yield. Due to the decomposition of hydrazone intermediate, I thought low temperature is better for the condensation step. Thus, I reduced the condensation temperature to -20 °C. After the condensation reaction finished, without any operation, the oxidation was subsequently carried out using the 6 equiv MnO_2. In contrast to expectation, the result showed a decrease of 5%.



Scheme 2.10 Synthesis of photoreactive diazo compound **14** by one-pot method.

To improve the yield of diazo **14**, the optimization was conducted using different

solvents, temperatures, and reaction times. In the optimization reaction, the condensation reaction mixture was concentrated by an evaporator to remove the solvent and excessive hydrazine monohydrate. Next, the continuous oxidation reaction was carried out using the condensation mixture. The condensation conditions of aldehyde **13** and hydrazine hydrate and subsequent oxidation using manganese oxide (MnO_2) were evaluated in Table 2.6. In entries 1-2 of Table 2.6, the condensation solvent was changed to diethyl ether, and I evaluated the reaction under different temperatures. The result showed a small difference of 1%, the condensation reaction at 0 °C and the oxidation at room temperature give a higher yield. The reaction temperature seems not to be the main influence factor. In entry 3 of Table 2.6, I found that a shortage of the condensation reaction time offered the 22% yield of desired diazo **14**. Thus, it suggested that the longer time of condensation reaction result in the decomposition of the hydrazine intermediate. The diethyl ether is not suitable for a large amount of oxidation reaction, due to its explosive. In entries 4-8 of Table 2.6, the same solvent was used in condensation and oxidation for each entry. Tetrahydrofuran, ethyl acetate and ethanol as the solvent was tested for the synthesis of diazo, respectively. The result indicated that tetrahydrofuran is not suitable for this reaction. When the condensation reaction time is 0.2 h, entries 5 and 6 obtained the desired compound in 5% yield. In entries 6-8 of Table 2.6, the yield of diazo **14** increased

with the expansion of the condensation time. Then, the best result was obtained in entry 10 of Table 2.6 with a yield of 35%. The condensation is in ethanol at 0 °C for 2 h and oxidation is in dichloromethane at room temperature for 2 h.

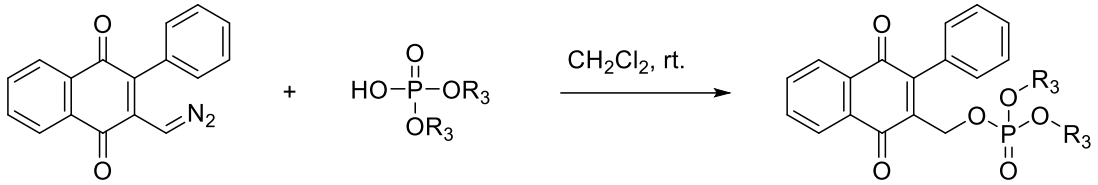
Table 2.6 Synthesis of NQ-Ph-diazo **14**.

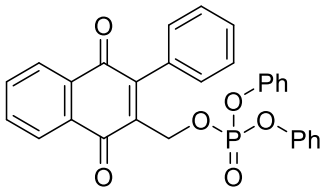
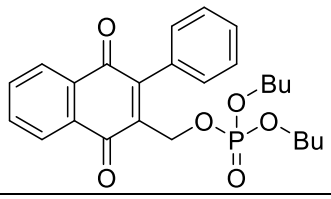
Entry	Solvent		Temp. (°C)		T.	Yield
	S1	S2	S1	S2	(h)	(%)
1	Et_2O	Et_2O	-20	-20	12	18
2	Et_2O	Et_2O	0	rt.	12	19
3	Et_2O	Et_2O	-20	rt.	3	22
4	THF	THF	0	0	2	6
5	EA	EA	0	0	0.2	5
6	EtOH	EtOH	0	0	0.2	5
7	EtOH	EtOH	0	rt.	0.5	13
8	EtOH	EtOH	0	rt.	2	28
9	DCM	DCM	0	rt.	2	27
10	EtOH	DCM	0	rt.	2	35

2.4 Condensation Reaction between NQ-based Framework and Various Acids

When **14** was reacted with diphenyl- and dibutylphosphoric acids in dichloromethane without any additional reagents, the corresponding protected phosphoric and sulfonic acids **15**–**16** were produced in moderate yields (Table 2.7).

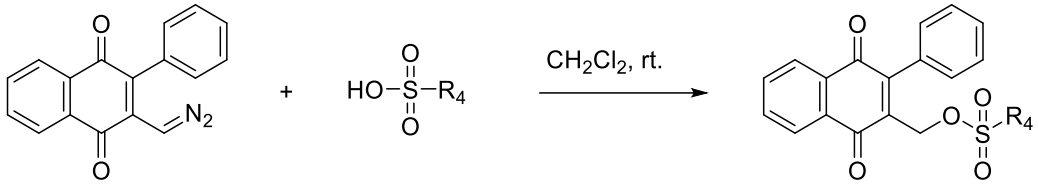
Table 2.7 Masking of various phosphoric acids by using compound **14**.

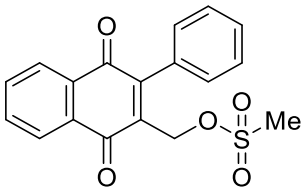
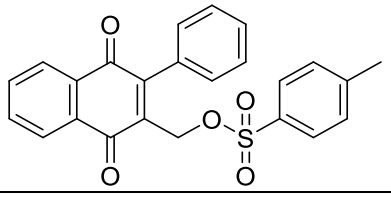


Entry	Photoremovable Compound	R_3	T. (h)	Product	Yield (%)
1	15	Ph	15		65
2	16	*n*-Bu	15		48

Compound **14** was treated with methyl- and *p*-toluenesufonic acids in dichloromethane without any additional reagents, the corresponding protected phosphoric and sulfonic acids **17**–**18** were obtained in nearly quantitative yields (Table 2.8).

Table 2.8 Masking of various phosphoric acids by using compound **14**.

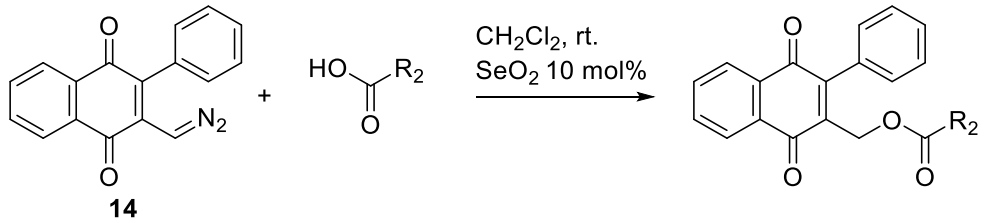


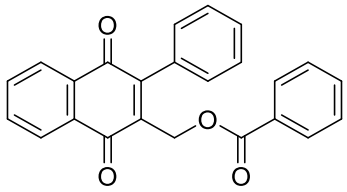
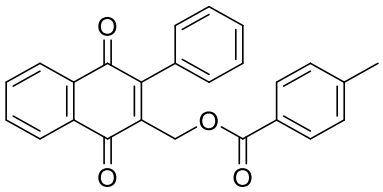
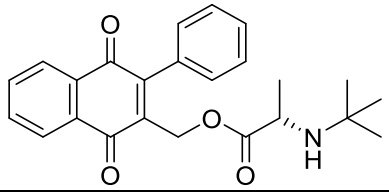
Entry	Photoremovable Compound	R_4	Time (h)	Product	Yield (%)
1	17	Me	2		95
2	18	*p*-toluene	15		97

Diazo compounds have another well-known model of reactivity: esterification of carboxylic acids. Thus, I tested the condensation efficiency of compound **14** with various carboxylic acids, which are used in the above carboxylic acids masking reaction by using compound **3a**. (Table 2.9) At first, the condensation of compound **14** with benzoic acid was carried out in dichloromethane without any catalyst. However, there is no reaction proceed, starting material **14** was found in 100%. Then, I thought it is due to the acidity of the carboxylic acid being lower than phosphoric acid and sulfonic acid. It also can explain the reason why the condensation of sulfonic acids with compound **14** showed a higher yield than phosphoric acid. Thus, 10% selenium dioxide was added as a

catalyst.[34] When the solvent is dichloromethane, various carboxylic acids condensed with compound **14** in the presence of 10 mol% selenium dioxide. Unfortunately, it resulted in a lower yield protected carboxylic acid **10**, **11** and **12** than the condensation reaction using compound **3a**. It suggested that compound **3a** is more suitable for the protection of various carboxylic acids.

Table 2.9 Masking of various alcohols by using compound **14**.

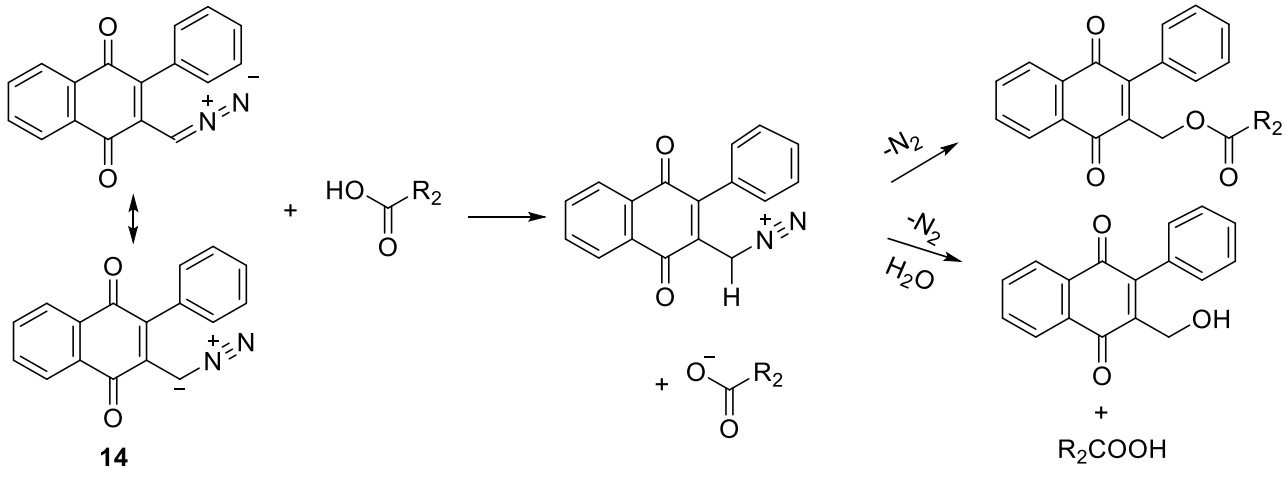


Entry	Photoremovable Compound	R_2	T. (h)	Product	Yield (%)
1	10	Ph	15		52
2	11	*p*-tolyl	15		15
3	12	Boc-L-NHCH$(CH_3)_3$-	15		20

Furthermore, I found that compound **3a** is the reaction byproduct in each entry. I

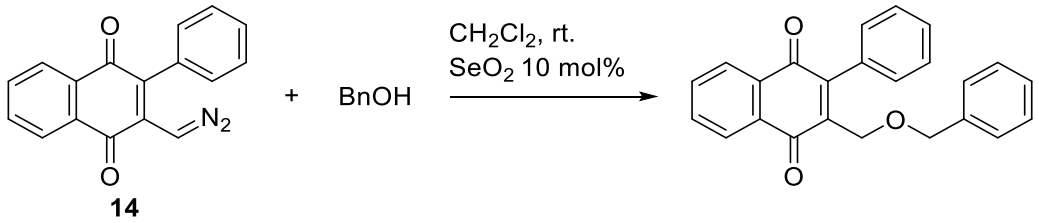
hypothesized that the generation of compound **3a** was derived from water in the solvent. The possible mechanism of the reaction is competing for direct displacement on the alkyl diazonium ion by solvent and unimolecular fission of the diazonium ion to a carbonium ion which subsequently may react with the water in solvent to form the byproduct **3a**. (Scheme 2.11)

The esterification of carboxyl groups is difficult to effect, as solvent water competes effectively with alcohols for electrophilic acyl groups. In contrast, esterification reactions mediated by diazo groups rely on the carboxyl group serving as a nucleophile. The NQ-Ph-OH may be generated from the technical error, which water was included in solvents or reagents.



Scheme 2.11 Reaction pathway of condensation and side reaction.

Compounds **14** can react with various alcohols basic on the above mechanism. To prove the inference, compound **14** was treated with benzyl alcohol in dichloromethane in the presence of 10 mol% selenium dioxide. (Scheme 2.12)



Scheme 2.12 Etherification of diazo **14** and benzyl alcohol.

2.5 Summary

In summary, this chapter introduced the condensation of the NQ-based framework and various functionalities, such as alcohols, amines, carboxylic acids, phosphoric acids and sulfonic acids. The condensation of compound **3a** with various alcohol, amine and carboxylic acid derivatives was carried out smoothly. Due to compound **3a** could not easily mask phosphoric acids and sulfonic acids, I successfully synthesized the diazo compound **14** for various phosphoric and sulfonic acids, and the condensation reactions were carried out in high yield without any reagent.

I also found an interesting new esterification pathway of compound **14** with alcohol

basic on the side reaction.

2.6 Reference

1. Denning, D. M.; Pedowitz, N. J.; Thum, M. D.; Falvey, D. E. *Org. Lett.* **2015,** *17*, 5986-5989.

2. Zhou, L.; Yang, H.; Wang, P. *J. Org. Chem.* **2011,** *76*, 5873-81.

3. Kulikov, A.; Arumugam, S.; Popik, V. V. *J. Org. Chem.* **2008,** *73*, 7611–7615.

4. Furuta, T. Hirayama, Y.; Iwamura, M. *Org. Lett.* **2001,** *3*, 1909-1812.

5. Hennig, A. K.; Deodato, D.; Asad, N.; Herbivo, C.; Dore, T. M. *J. Org. Chem.* **2020,** *85*, 726-744.

6. Atemnkeng, W. N.; Louisiana II, L. D.; Yong, P. K.; Vottero, B.; Banerjee, A. *Org. Lett.* **2003,** *5*, 4460-4471.

7. Atta, S.; Jana, A.; Ananthakirshnan, R.; Narayana Dhuleep, P. S. *J. Agric. Food. Chem.* **2010,** *58*, 11844-51.

8. Bownik, I.; Sebej, P.; Literak, J.; Heger, D.; Simek, Z.; Givens, R. S.; Klan, P. *J. Org. Chem.* **2015,** *80*, 9713-21.

9. Kammari, L.; Plistil, L.; Wirz, J.; Klan, P. *Photochem. Photobiol. Sci.* **2007,** *6*, 50-6.

10. Li, Z.; Mayer, R. J.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2020,** *142*, 8383-8402.

11. Rubinstein, N.; Liu, P.; Miller, E. W.; Weinstain, R. *Chem. Commun.* **2015,** *51*, 6369-72.

12. Givens, R. S.; Kueper, L. W. *Chem. Rev.* **1993,** *93*, 55-66.

13. Engels, J.; Schlaeger, E. J. *J. Med. Chem.* **1977,** *20*, 907–911.

14. Park, C. H.; Givens, R. S. *J. Am. Chem. Soc.* **1997,** *119*, 2453-2463.

15. Senadheera, S. N.; Yousef, A. L.; Givens, R. S. *Beilstein J. Org. Chem.* **2014,** *10*, 2038-2054.

16. Schade, B. H., V.; Schmidt, R.; Herbrich, R.; Krause, E.; Eckardt, T.; Bendig, J. *J. Org. Chem.* **1999,** *64*, 9109-9117.

17. Remes, M.; Roithova, J.; Schroder, D.; Cope, E. D.; Perera, C.; Senadheera, S. N.; Stensrud, K.; Ma, C. C.; Givens, R. S. *J. Org. Chem.* **2011,** *76*, 2180-6.

18. Schneider, W.; Diller, W. In *Ullmann's Encyclopedia of Industrial Chemistry*, **2000**, *26*, 623-632.

19. Liang, F.; Yanai, M.; Suzuki, Y.; Tsuda, A. *Org. Lett.* **2020,** *22*, 3566-3569.

20. Heiner Eckert, H. A., J. *Org. Process Res. Dev.* **2010,** *14*, 1501–1505.

21. Pasquato, L.; Modena, G.; Cotarca, L.; Delogu, P.; Mantovani, S. *J. Org. Chem.* **2000,** *65,* 8224-8228.

22. Ayala, C. E.; Villalpando, A.; Nguyen, A. L.; McCandless, G. T.; Kartika, R. *Org. Lett.* **2012,** *14,* 3676-3679.

23. Yasukouchi, H.; Nishiyama, A.; Mitsuda, M. *Org. Process Res. Dev.* **2018,** *22,* 247-251.

24. Wang, J.; Gong, Y.; Sun, D.; Gong, H. *Organic Chemistry Frontiers,* **2021,** *8,* 2944-2948.

25. Mix, K. A.; Raines, R. T. *Org. Lett.* **2015,** *17,* 2358-2361.

26. Silva, L. F. J.; Olofsson, B. *Nat. Prod. Rep.* **2011,** *28,* 1722-54.

27. Basak, S.; Mal, D. *J. Org. Chem.* **2017,** *82,* 11035-11051.

28. Kumar, K.; Kumar, P.; Joshi, P.; Rawat, D. S. *Tetrahedron Lett.* **2020,** *61,* 151749.

29. Nie, X.; Wang, Y.; Yang, L.; Yang, Z.; Kang, T. *Tetrahedron Lett.* **2017,** *58,* 3003-3007.

30. Xia, Y.; Liu, Z.; Xiao, Q.; Qu, P.; Ge, R.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2012,** *51,* 5714-7.

31. Maheswari, C. S.; Sivaguru, P.; Grzegorz Malecki, J.; Lalitha, A. *Polycycl. Aromat. Compd.* **2018,** *40,* 1045-1058.

32. Lv, L.; Zhu, D.; Li, C. J. *Nat. Commun.* **2019,** *10*, 715.

33. Friscourt, F.; Fahrni, C. J.; Boons, G. J. *Chem. Eur. J.* **2015,** *21*, 13996-4001.

34. Zhang, Y.; Zhang, H.; Ma, C.; Li, J.; Nishiyama, Y.; Tanimoto, H.; Morimoto, T.; Kakiuchi, K. *Tetrahedron Lett.* **2016,** *57*, 5179-5184.

CHAPTER 3 Verification of Photoreleasing of Various Functionalities

3.1 Introduction

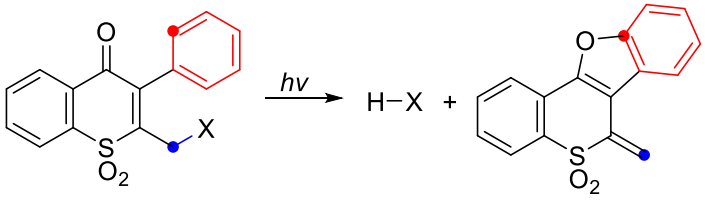
Numbers of photoremovable compounds have been developed since Kaplan introduced a non-active form of ATP that could be released and rendered active by UV irradiation in 1978.[1] It continues to be described as a system in which light triggers the breaking of photolabile bonds and the release of functional molecules.[2] To date, several protecting groups for carboxylic acid, alcohol, amine, ketone, or phosphate residues have been employed in recent years in synthetic chemical procedures, where deblocking of the functional group has been achieved by photolytic irradiation. Furthermore, the application of photoremovable protecting groups to control the activity of biological molecules has been widely used and extensively studied.[3]

For applications in living organisms, phototriggers should have large extinction coefficients above 350 nm and high photolysis efficiency.[4] Thus, it is necessary for the development of new long-wavelength absorbing caging groups with removable with high photoreleasing efficiency.

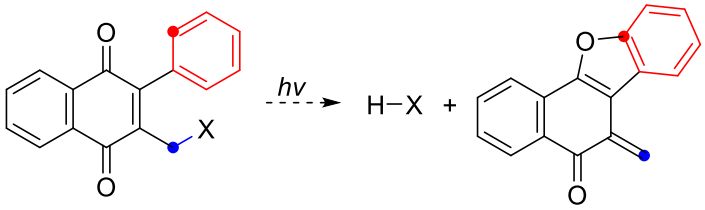
In this work, I developed a novel NQ-based photoremovable protecting group for various groups in chapter 1. In chapter 2, lots of photoremovable compounds were obtained by the condensation of the photoremovable protecting group and various alcohols, amines, and acids.

This chapter focuses mainly on the photoirradiation reaction of the NQ-based photoremovable compounds, which were synthesized in chapter 2. In the previous work of our group, the high photoreleasing efficiency of the thiochromone-based photoremovable group was confirmed, and the photoreleasing pathway was shown in Scheme 3.1(a).[5] Basic on the thiochromone-based framework, I hypothesized photoreleasing pathway of NQ-based framework. (Scheme 3.1(a)) The photoreaction will be evaluated.

(a) Previous report: Thiochromone-based photoremovable group



(b) This wrok: 1,4-Naphthoquinone (NQ)-based photoremovable group



Scheme 3.1 The hypothesis of photoreaction pathway.

3.2 The Evaluation of the Standard Photoreleasing Conditions

The UV/VIS spectra of the photoremovable protecting group **3a** and photoremovable compound **4** showed no major differences (Fig. 3.1, indicating that the functionalities' place did not visibly change the electronic transitions of the chromophore). The UV-absorption spectra of 0.1 mM compound **4** shows absorption at 280-500 nm (λ_{max}= 318 nm) in methanol.

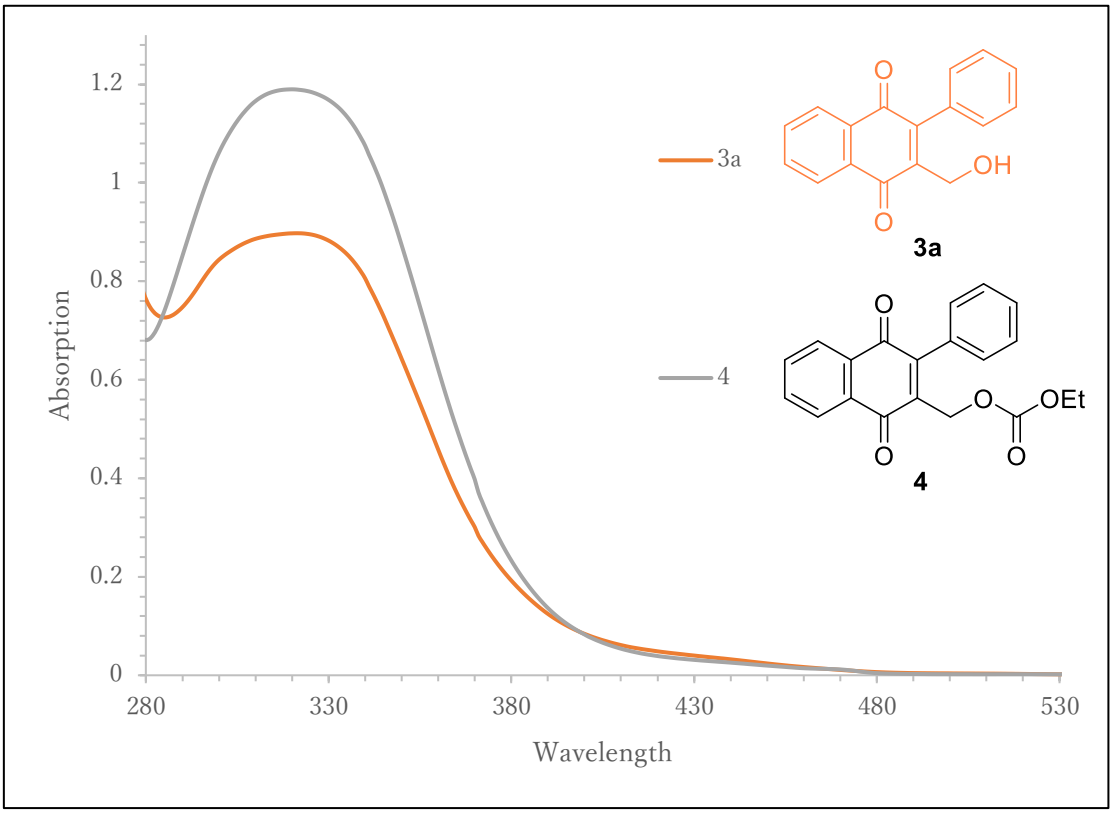


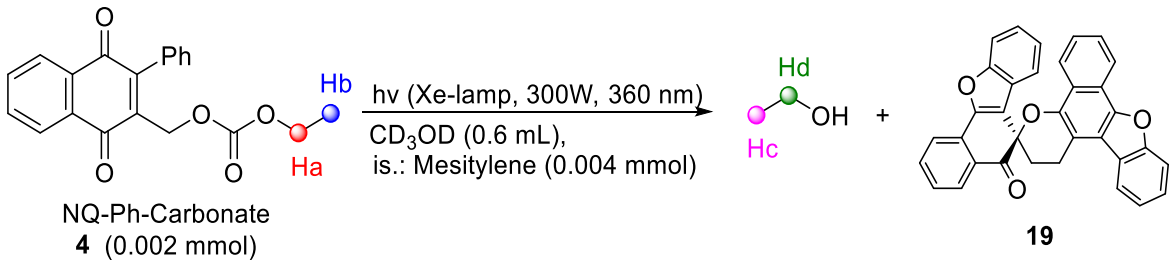
Fig. 3.1 UV-vis absorption spectrum of protecting group **3a** and compound **4**.

Basic on this result, the photoreaction was carried out in CD_3OD with irradiation by 360 nm light (300W Xe lamp) at room temperature and monitored by ^1H NMR spectroscopy.

Compound **4** (2×10^{-3} mmol) and mesitylene (4×10^{-3} mmol, internal standard reference) were dissolved in deuterium solvents (0.6 mL) and transferred into a pyrex NMR tube. The progress of the photoirradiation reactions was monitored by ^1H NMR. At room temperature, the NMR tube was fixed at 1.0 cm in front of a Xe lamp that is set up to give 360 nm of light. During the photoreaction, the sample tube was controlled at room

temperature. In this article, the filter wheel was used for getting the wavelength at 360 nm. The NMR yields were calculated by comparing the ^{1}H integration of a compound with that of the internal standard. All released compounds were confirmed by the comparison with the corresponding commercially available compounds.

The photoirradiation to **4** resulted in the complete consumption of **4** after 20 minutes to yield EtOH in 92% yield. (Scheme 3.2). Another fact was that **4** was stable in methanol even after 7 days under dark conditions. In addition, the findings shown in Scheme 3.2 confirms that the releasing of ethanol and byproduct. The result means that NQ-based photoreactive core **3a** works efficiently as a photoresponsive core due to the structure analysis of photobyproduct.



Scheme 3.2 Photoirradiation reaction of compound **4**.

The reaction was monitored by ^{1}H NMR. The depletion of the selected peaks H_a and H_b (the aliphatic H_a and H_b from the deprotected compound) and the accumulation of the

selected peaks H_c and H_d (the aliphatic H_c and H_d from releasing compound) were measured relative to the internal standard peak, mesitylene. (Fig. 3.2) The depletion of the selected peaks in compound **4** determined the photoreleasing time. With an increase in irradiation time from 0 to 20 min, the intensity of the characteristic peaks at 4.03 ppm (H_a) and 1.08 ppm (H_b) of **4** decreased, and two new CH_2 and CH_3 peaks at (H_c) 3.51 ppm and (H_d) 1.15 ppm of releasing EtOH appeared. Relative photolysis yield of deprotected was calculated. The yield can be obtained by the ratio between actual integral values and the theoretical value of the selected peaks in releasing EtOH.

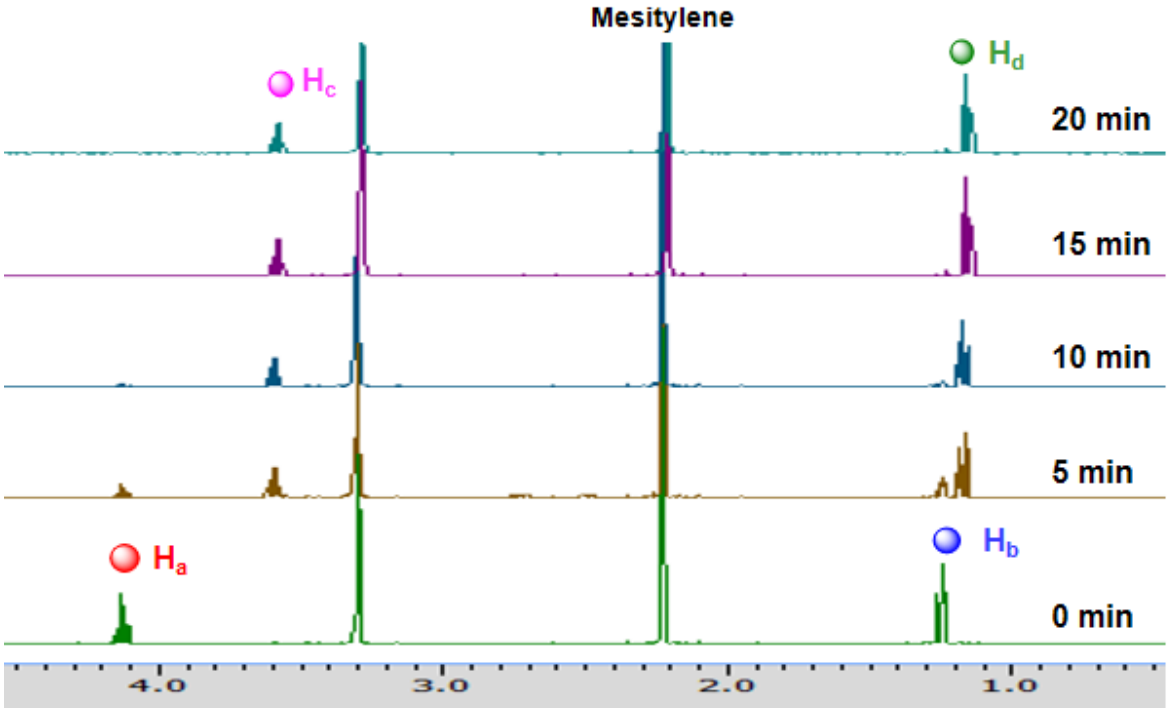


Fig. 3.2 ^{1}H NMR monitoring of photoirradiation reaction.

In these standard photoreaction conditions, we get the photoreleasing yield of all compounds. The photobyproduct **19** was obtained and purified by column chromatography. In this case, the NQ framework was recovered in the form of compound **19** in 82% yield based on the NQ-mother ring.

Photoreactions in various solvents were also examined (Table 2.1). The reaction conditions are the same conditions as the above-mentioned. (Compound **4** (6.7 mM) was irradiated with 360 nm light (300W Xe lamp with a filter wheel) in different solvents at room temperature.)

The photoreaction in polar solvents, such as DMSO, MeCN, acetone, and 1,4-dioxane as well as methanol, proceeded relatively smoothly. On the other hand, no reaction took place in less-polar solvents ($CDCl_3$ and toluene) (Table 2.1: Entries 2 and 3).

In Table 2.1, I found that there were varying degrees of photoreleasing when the polarity Index was higher than 4.1. However, when the polarity Index was lower than 4.1, there is no photoreleasing was found.

Table 2.1 Photoreleasing reactions of **4** in various solvents.

Entry	Solvent	Dielectric constant	Polarity Index (P)	Yield after 5 min *hv* EtOH	Irradiation time	Yield	
						EtOH	**19**
1	CD_3OD	32.6	5.1	39%	20 min	92%	82%
2	$CDCl_3$	4.8	4.1	0%	6 h	0%	0%
3	Toluene-d_8	2.4	2.4	0%	6 h	0%	0%
4	DMSO-d_6	45.0	7.2	20%	2 h	79%	64%
5	CD_3CN	37.5	5.8	0%	6 h	44%	22%
6	Acetone-d_6	20.7	5.1	5%	2 h	58%	30%
7	1,4-Dioxane-d_8	2.2	5.27	0%	6 h	69%	42%

As a result, methanol was determined to be the solvent of choice for the present photoreleasing reaction. Therefore, we selected the standard condition for the photoirradiation reaction. It is a photoremovable compound (6.7 mM) in deuterium methanol using a 360 nm light (300W Xe lamp with a filter wheel) as an irradiation resource at room temperature.

The formation of **19** suggests that the photoreaction pathway proceeds as shown in Scheme 3.3 and 3.4. I postulated three photoreaction pathways. As shown in Scheme 3.3, the carbonyl group is first excited by the absorption of light energy to give a carbonyl biradical **Int1** via the triplet state,[6-9] in which the *C*-radical can be delocalized to produce stabilization. The electrophilic *O*-radical in **Int1** then adds to the neighboring C=C double

bond of the aromatic ring in the manner of the radical addition to C=C accompanied by dearomatization, with the formation of a new biradical intermediate **Int2**. In pathway (a), the C-O bond of this biradical species **Int2** is homolytically cleaved to form **Int3** together with a carboxyl radical. The formation of the carboxyl radical, stabilized by the delocalization of an unpaired electron, would promote the cleavage of the C-O bond. Subsequently, this carboxyl radical immediately releases CO2 to form an ethoxyl radical. Finally, the abstraction of a hydrogen atom by the ethoxy radical reconstructs the aromaticity of six-member ring to release the alcohol and the NQ framework is converted into a four-ring-fused compound **Int4**. I observed that there is only a single product **Int3** after the hydrogen abstraction. However, in pathway (a), the ethoxyl radical is also possible to abstract the hydrogen in other places to give other byproducts.

Therefore, I postulated the possible pathway (b) as follows: from **Int2**, the abstraction of H by the oxygen of the carbonate carbonyl and the cleavage of the C-O bond occur concertedly in an intramolecular manner to generate directly **Int4** accompanied with ethyl bicarbonate. The last step of pathways (a) and (b) is that compound **Int4** dimerizes via a formal *hetero*-Diels-Alder reaction due to its exo-methylene,[10-12] giving **19**. The photoreaction was conducted under room temperature without other operations to give byproduct **19**.

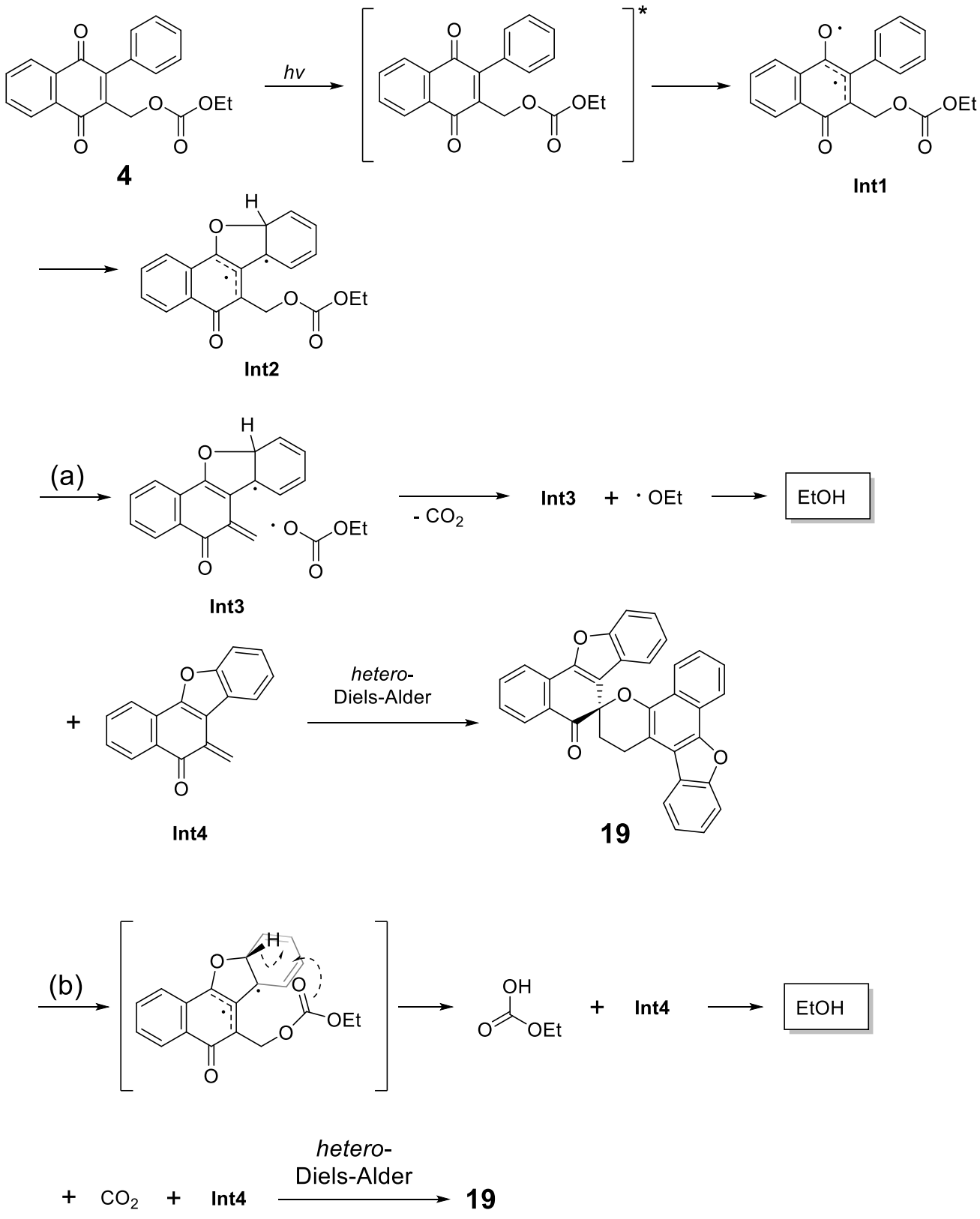
In solvent evaluation, pathways (a) and (b) do not fully explain the phenomenon of selectivity of polar solvents in photoreaction. Thus, I postulated the third pathway (c) of photoreaction. I believe that the ionic intermediate should be involved such as Int7 in Scheme 3.4. The charge-separated state seems to be formed by the intramolecular transfer of the photoexcited state. However, I found that the photoexcited state of naphthoquinone derivatives is possible electron transfer with solvent, such as methanol.[13] It may offer a semiquinone radical specie **Int5** or a radical anion (**Int6**). Then, the intramolecular electron transfer of the radical anion (**Int6**) offers the **Int7**. The new five-member ring intermediate (**Int8**) was obtained by the stabilization of **Int7**. Then, the rearomatization of **Int8** formed the four-ring fused **Int4**, ethoxy anion and a hydrogen cation. Finally, the ethoxy anion capture the hydrogen cation to release ethanol, and byproduct **19** was formed by the *hetero*-Diels-Alder reaction of two molecular **Int4**.

All proposed pathways (a), (b) and (c) can be rationalized as a smooth progression of photoreleasing alcohol, amine, carboxylic acids, phosphoric acids, and sulfonic acids, which are expected to involve a similar effect, proceeded smoothly (vide infra). These pathways are also possible to occur in parallel.

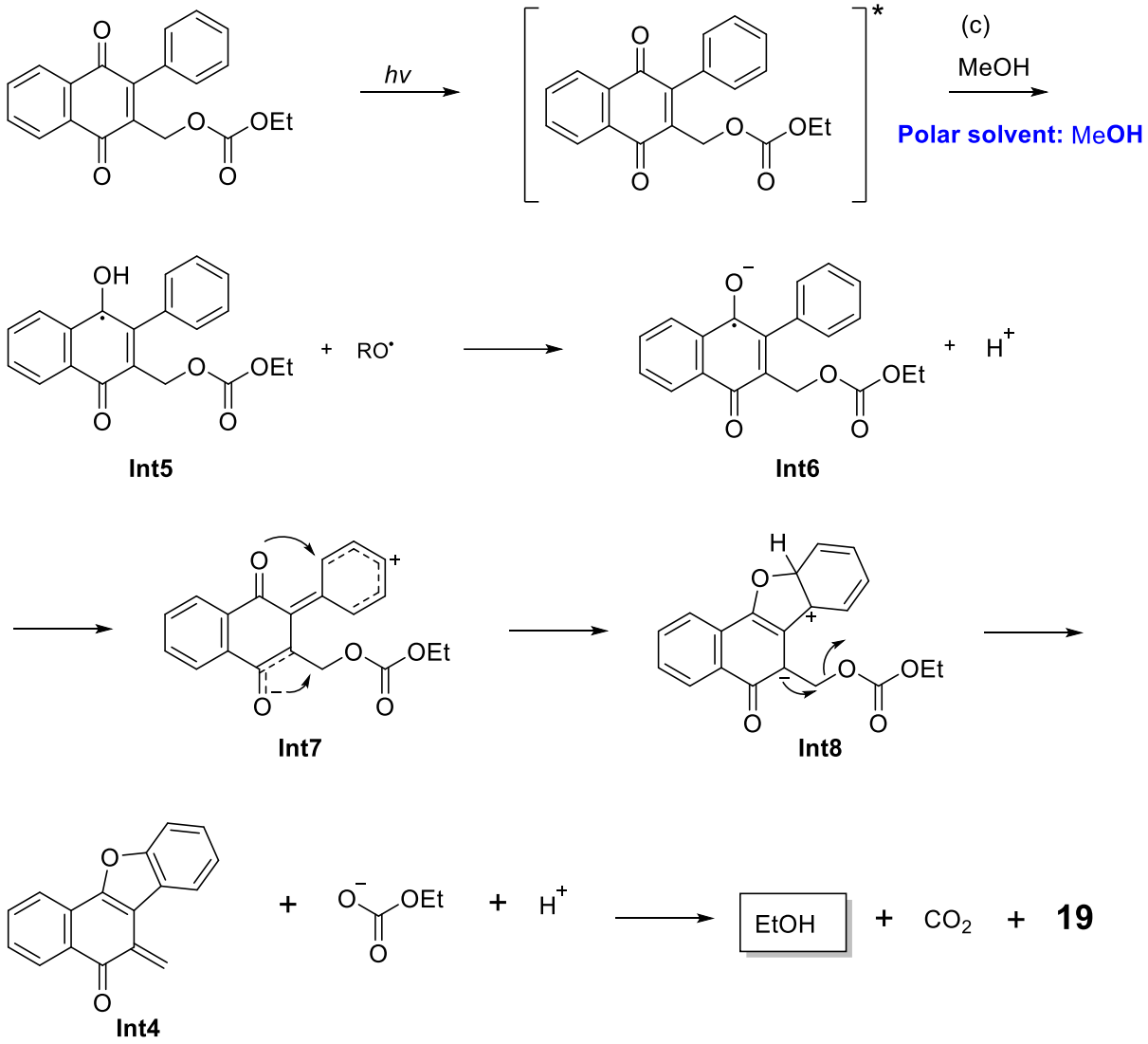
Since the photoreaction proceeded not only in methanol but also in DMSO and acetone at a lower photoreaction speed, the radical intermediate process seems reasonable

to explain the result. I also considered that the reaction in the different solvents may proceed in different reaction pathways. That is, the radical ion pathway (c) may be dominant in methanol, which seems to be a good solvent for photoreleasing.

In contrast, the reaction rate in DMSO and acetone solvents is suppressed. I would like to keep the discussion open for future work, which should involve ultrafast spectroscopy to characterize intermediate species, as well as precise quantum chemical calculations.



Scheme 3.3 Possible photoreaction pathways (a) and (b) of **4**.



Scheme 3.4 Possible photoreaction pathway (c) of **4**.

3.3 Photoreleasing Efficiency of Various Functionalities

We then examined the photoreactions of NQ-based compounds containing

electronically different aromatic rings at the C2-position of NQ. The UV-vis absorption spectra of **5**–**7,** BnOH masked with **3a**–**c** is shown in Fig. 3.3. The absorption spectra of photoremovable compounds **5**–**7** showed different absorbances at 360 nm. The introduction of electronically different substituents (**6**: MeO; **7**: CF_3) have a similar maxima absorption in the area of 322-331 nm.(**5**: 322 nm, **6**: 331 nm, **7**: 331 nm), while **6** with a MeO group on the aromatic ring that is introduced into the 2-position of NQ showed another large absorption at 400 nm, probably due to charge transfer from the aromatic ring that was introduced on the 1,4-dienone unit of NQ. The DFT calculations of compound **6** were proceeded to confirm the result using Gaussian'16.

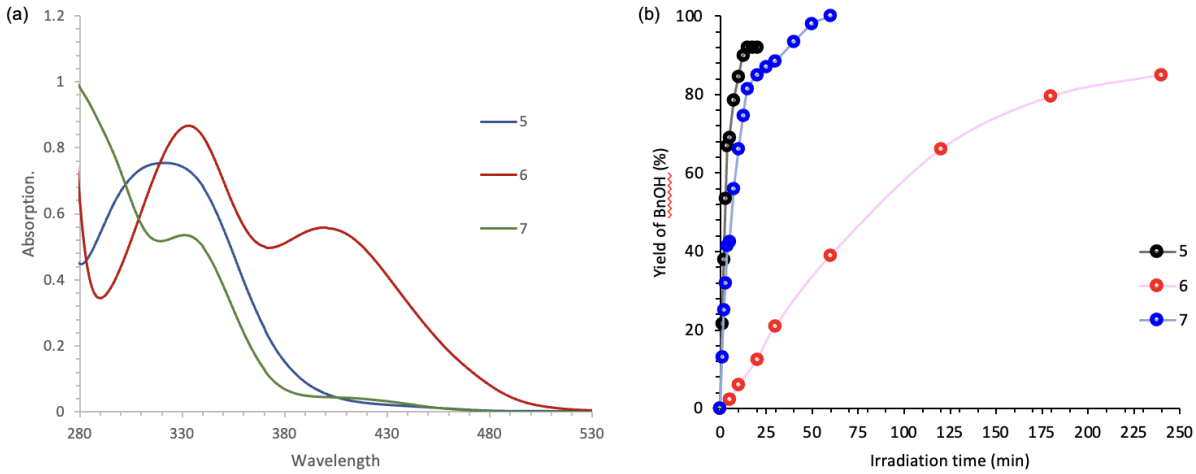


Fig. 3.3 (a) UV-vis absorption spectrum of photoremovable compound **5**–**7**. (b) photoirradiation results of photoremovable compound **5**–**7**.

The DFT calculations of compound **3b** were performed with "TD-DFT: CAM-B3LYP/6-31 + G (3d2f, 2p)/Solvent=Methanol".[14] The blue-colored absorption spectra in Fig. 3.4 is the estimated curve from the calculation, and it matches well with the absorption curve actually measured (orange-coloured curve). Based on these facts, we investigated what molecular orbital between excitations each absorption at around 330 and 410 nm corresponded to. The DFT calculations estimate that the absorption at 330 and 416 nm is assigned to the excitation from HOMO-1 to LUMO and from HOMO to LUMO, respectively. (Fig. 3.5) As clear from the calculation results, the former excitation is the π-π* transition within the bicyclic system derived from 1,4-naphthoquinone (NQ) (HOMO-1 → LUMO), and the latter one the charge transfer transition from the aromatic ring introduced to the C-2 position of NQ to the bicycle (HOMO → LUMO).

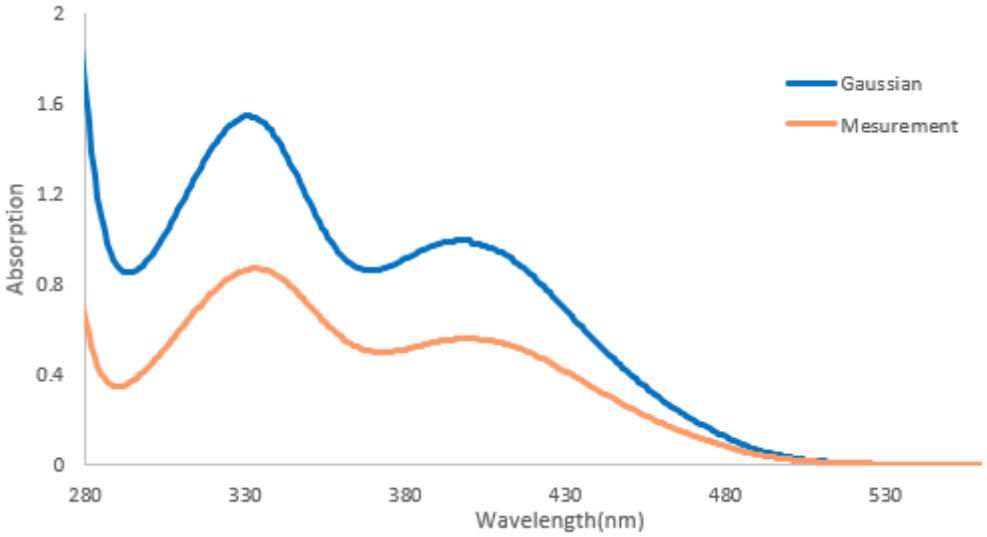


Fig. 3.4. Absorption spectra of **3b**: orange-coloured curve is the spectra measured; the blue-coloured curve is that calculated.

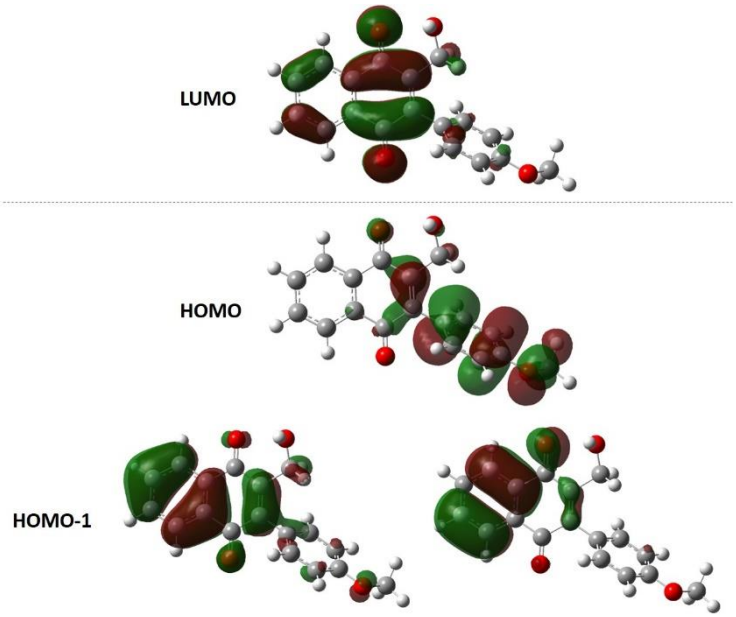


Fig. 3.5. Molecular orbitals, LUMO, HOMO, and HOMO-1, of **3b**.

We carried out the photoreaction of **5**–**7** under the standard conditions that were established above: photoremovable compounds (6.7 mM) in CD_3OD, irradiation with a 360 nm wavelength from a 300W Xe lamp. Compounds **5** and **7** released BnOH

quantitatively after 20 and 50 minutes, respectively. The reactivity of **7** was nearly the same as that for **5**. However, compound **6** with an electron-donating group required 240 minutes for 85% of **6** to consume. At present, we postulate that this low reactivity of **6** can be attributed to charge transfer. Thus, a considerable part of the photoexcitation would be diminished with the charge transfer process but not to **Int1** via the triplet state.

Lastly, various protected functional compounds **8**–**12** and **15**–**18** had maximum absorption at 330 nm, and a similar absorbance at 360 nm. The UV-spectrum of compounds **8**–**12** and **15**–**18** was shown in Fig. 3.6.

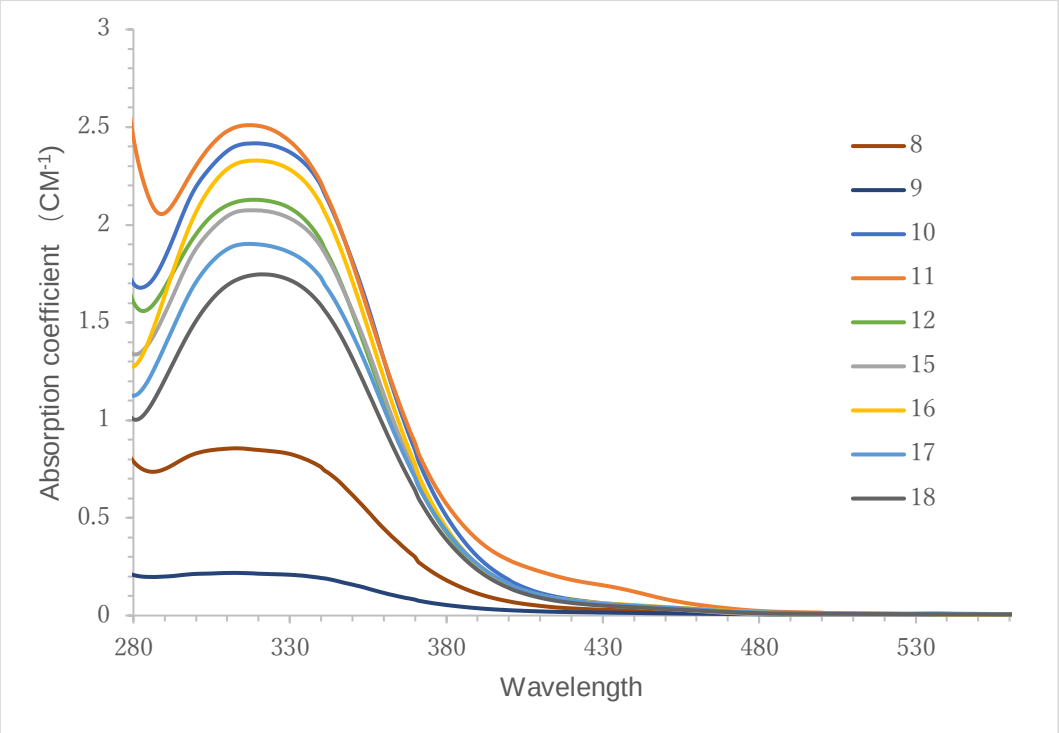
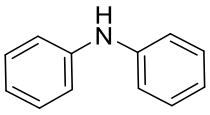
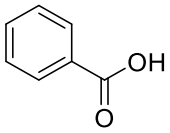
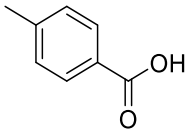
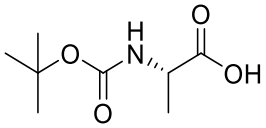
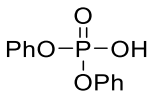
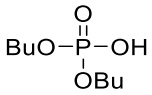
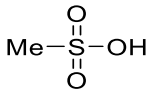
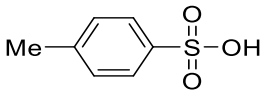


Fig. 3.6 The *UV*-vis absorption spectrum of compounds **8**–**12** and **15**–**18**.

The photoreleasing behaviour of these compounds was studied under the above standard conditions and the results are summarized in Table 3.2. In general, the photoreactions proceeded within 20 min with the corresponding functional compounds being released in high yields. The photorelease of *N*, *N*-diphenylamine from **8** required a much longer reaction time (55 min) than that of *N*-octadecylamine, probably due to the basicity of the released secondary amine. (Table 3.2: Entry 1) The photoreaction of the protected amine **9** was completed within 10 min to yield *n*-octadecylamine quantitatively (Table 3.2: Entry 2). The protected aromatic and aliphatic carboxylic acids **10**–**12** were photodeprotected smoothly to give benzoic, *p*-toluic and *N*-Boc-amino acids in 92%, 99% and 93% yields, respectively (Table 3.2: Entries 3–5). Compounds **15**–**18** also reacted under irradiation by 360 nm light with corresponding phosphoric and sulfonic acids being released, respectively (Table 3.2: Entries 6–9). Although the wavelength of the irradiated light was optimized for each protected compound, the findings presented herein demonstrate that the developed NQ-based framework functions highly efficiently as a photoresponsive core in photodeprotection reactions.

Table 3.2 Photoreactions of the NQ-based photoremovable compounds **8**–**12** and **15**–**18**.

Entry	Photoremovable Compound	Released Compound	Irradiation Time	Yield of Released Compound
1	**8**		55 min	93%
2	**9**	$C_{18}H_{37}NH_2$	10 min	98%
3	**10**		20 min	92%
4	**11**		15 min	99%
5	**12**		10 min	93%
6	**15**		15 min	90%
7	**16**		15 min	99%
8	**17**		15 min	99%
9	**18**		10 min	98%

3.4 Summary

In conclusion, various functionalities, such as alcohols, amines, carboxylic,

phosphoric, and sulfonic acid masked with the NQ-based core **1** could be deprotected by irradiation with 360 nm light in a relatively short time with the original functionalities being released in high yields (in most cases, more than 90%). The present synthetic method for preparing the photoresponsive core is quite simple, and therefore, electronically versatile analogues could be produced by only changing readily available reaction partners, arylboronic acid derivatives and aldehydes. Furthermore, the appropriate selection of the irradiation wavelength for the desired purpose would enable the rapid or gradual release of functional compounds.

3.5 References

1. Kaplan, J. H.; Forbush III, B.; Hoffman, J. F. *Biochemistry* **1978,** *17*, 1925-1935.

2. McKay, L. J.; Carling, C.-J.; Branda, N. R. *J. Photochem. Photobiol. A* **2021,** *421*.

3. Vorob'ev, A. Y.; Dranova, T. Y.; Moskalensky, A. E. *Sci. Rep.* **2019,** *9*, 13421.

4. Furuta, T.; Watanabe, T.; Tanabe, S.; Sakyo, J.; Matsuba, C. *Org. Lett.* **2007,** *9*, 4717-4720.

5. Kitani, S.; Sugawara, K.; Tsutsumi, K.; Morimoto, T.; Kakiuchi, K. *Chem. Commun.* **2008**, 2103-2105.

6. Zhang, Z.; Hao, S.; Zhu, H.; Wang, W. *J. Photochem. Photobiol B*: *Biol*. **2008**, *92*, 77-82.

7. Görner, H. *Photochem. Photobiol. Sci.* **2004**, *3*, 71.

8. Brahmia, O.; Richard, C. *Photochem. Photobiol. Sci*. **2003**, *2*, 1038.

9. Amada, I.; Yamaji, M.; Sase, M.; Shizuka, H. *J. Chem. Soc. Faraday Trans*. **1995**, *91*, 2751-2759.

10. Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2000**, *39*, 3558-3588.

11. Jørgensen, K. A. *Eur. J. Org. Chem*. **2004**, *2004*, 2093-2102.

12. Li, N. K.; Sun, B. B.; Chen, J. B.; Yang, H. D.; Wang, B. L.; Yu, J. Q.; Wang, X. W.; Wang, Z. *Org. Chem. Front.* **2021**, *8*, 2009-2018.

13. Gorner, H. *Photochem. Photobiol. Sci.* **2004**, *3*, 71–78.

14. P. Hatchian, A. F. I., J. Bloino, G. Zheng, J. L.; Sonnenberg, M. Hada, M. Ehara, K. Toyota, R.Fukuda, J. Hasegawa, M. Ishida, I. Nakajima, Y. Honda, O. Kitao, H. Nakai, I. Vreven, J. A. Montgomery, Jr. J. E. Peralta, E. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, I. Keith,R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, I. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, I. W.

Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., *Wallingford CT* **2013** .

Summary

In this dissertation, I focused on the development of a highly effective photoremovable compound in a straightforward and derivatization available synthetic strategy. To date, there are lots of reports on the synthesis and application of photoremovable compounds, due to their promising foreground in the biological field. There are some important requirements for a good photoremovable compound, (such as longer wavelength, fast response and solubility) which can be applied to biological without damage to the organism. Although people modified their mother ring to fulfil the requirements for the application of biological by installing some substituents. However, the synthetic strategy is complicated and has lots of steps. To solve such a problem, I have conducted my doctoral research on the creation of a photoremovable compound in a straightforward and derivatization available synthetic strategy.

In chapter 1, I focused on the synthesis of the photoremovable response core **3**. It was successfully synthesized in three methods from the commercially available 1,4-naphthoquinone. The one-shot synthetic method is a 1,4-addition-aldol reaction, where a rhodium complex catalyzes both of the two carbon-carbon bond-forming reactions, the catalytic cycle consisting of the 1,4-addition of an organorhodium species to an unsaturated ketone and the aldol addition of the resulting rhodium intermediate to an

aldehyde. The stepwise method is the combination of a 1,4-addition reaction - Baylis Hillman Reaction or a 1,4-addition reaction - Aldol Reaction. The two stepwise methods showed the different yields of compound **3**. In three methods, the 1,4-addition reaction - Aldol Reaction shows the highest yield of 82%, the one-shot rhodium catalyst reaction shows the shortest synthetic step with a moderate yield of 42%. In both methods, electronically versatile analogues could be produced by only changing readily available reaction partners, arylboronic acid derivatives and aldehydes.

Chapter 2 focused on the preparation of various photoremovable compounds, which are masked with different functionalities. It introduced the condensation of the NQ-based framework and various functionalities, such as alcohols, amines, carboxylic acids, phosphoric acids and sulfonic acids. The condensation of compound **3a** with various alcohol, amine and carboxylic acid derivatives was carried out smoothly. Due to compound **3a** could not easily mask phosphoric acids and sulfonic acids, I successfully synthesized the diazo compound **14** for various phosphoric and sulfonic acids, and the condensation reactions were carried out in high yield without any reagent.

In chapter 3, I focused on the evaluation of the standard photoirradiation conditions and the photoreleasing efficiency of various photoremovable compounds. Various functionalities, such as alcohols, amines, carboxylic, phosphoric, and sulfonic acid

masked with the NQ-based core **3** could be deprotected by irradiation with 360 nm light in a relatively short time with the original functionalities being released in high yields. The photoreleasing byproduct was isolated and confirmed by X-ray analysis.

In conclusion, I reported herein on the creation of the novel 1,4-naphthoquinone (NQ)-based compound **3** as a photoremovable core, the synthesis of various functionalities protected by the core, and their photoreactivity. The photoremovable core and its derivatives were prepared by a relatively straightforward method based on 1,4-addition and aldol reactions. Various functionalities, such as alcohols, amines, carboxylic, phosphoric, and sulfonic acid masked with the NQ-based core 3 could be deprotected by irradiation with 360 nm light in a relatively short time with the original functionalities being released in high yields (in most cases, more than 90%). The present synthetic method for preparing the photoresponsive core is quite simple, and therefore, electronically versatile analogues could be produced by only changing readily available reaction partners, arylboronic acid derivatives and aldehydes. Furthermore, the appropriate selection of the irradiation wavelength for the desired purpose would enable the rapid or gradual release of functional compounds.

Experimental Section and Supporting Information

1. General Information.

All chemicals and solvents were of analytical grade and were used without further purifications. The progress of the reactions was monitored by silica gel thin layer chromatography (TLC) plates (mesh size 60Å, MERCK). Products were purified by flash column chromatography (FCC) on 40-63 m silica gel 60 (MERCK). ^{1}H NMR and ^{13}C NMR were measured by using JEOL JNM-ECX500 (^{1}H NMR: 500 MHz, ^{13}C NMR: 125 MHz). The NMR chemical shift values were adjusted based on the chloroform ($CDCl_3$) solvent peak (^{1}H NMR: δ7.26, ^{13}C NMR: δ77.16) or the methanol (CD_3OD) (^{1}H NMR δ 3.31). Data are reported as follows: chemical shift, integration, coupling constants (Hz), multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, and m= multiplet). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a JEOL JNM-ECP 500 instrument (125 MHz). Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard (0 ppm in ^{1}H NMR). Infrared absorption spectra (IR) were measured using a JASCO FT. Mass spectra were measured on a JOEL JMS-700 MStation or HP-1100 LC-MS spectrometer. Ultraviolet-visible light spectrum measurements (UV-vis) were performed using JASCO V630iRM. The solvents used for UV-vis measurements are of HPLC grade. NMR monitoring was preformed using Mesitylene as

internal standard. The photoirradiation reactions were performed using Max 303 (360 nm, 60/60HZ, 300W) (ASAGI SPECTRA Co., Ltd). All the glassware used in this work are made of Pyrex glass. X-ray was analyzed by Rigaku SmartLab9kW/IP/HY/N.

2. Materials.

The reagents used in this study were purchased from Sigma-Aldrich, Wako Pure Chemical, Kanto Chemical. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), toluene, methylene chloride (DCM), chloroform and dimethylformamide was purchased from Kanto Chemical and Wako Pure Chemical. Deuterated chloroform (CD_3OD) for NMR tube reactions was used after further dried with 4A, 1/6 activated molecular sieves.

3. An attempt to carry out the Cu(I)-mediated one-pot synthesis of 1a.

A solution of PhMgBr in THF (3.6 mmol, 3.6 mL) was added dropwise to a suspension of 1,4-naphthoquinone (3 mmol, 474.45 mg) and ligand-copper complex in 3 mL THF at -78 °C and the mixture was stirred at the same temperature for 1 h. Then, after elevating the temperature to -40 °C, a suspension of paraformaldehyde (6 mmol, 192 mg) in THF (5 mL) was added slowly, and the whole mixture was stirred at the same temperature for 4 h and 0 °C for 10 h. Water (20 mL) was added to the resulting mixture. and the aqueous layer was separated and then extracted with EtOAc (8 mL× 3). The combined organic layers were dried over $MgSO_4$ and then concentrated in vacuo after

filtration. From the analysis of the ^{1}H NMR of the crude mixture, no formation of **1a** was observed.

4. Representative procedure of the stepwise synthesis of 1

Synthesis of 1a.

To a 100 mL round bottom flask equipped with a drying tube ($CaCl_2$) were placed $Pd(OAc)_2$ (112.4 mg, 0.5 mmol), bipyridyl (93.8 mg, 0.6mmol), and DMF (15 mL), and the mixture was stirred for 30 min at room temperature under air. To the mixture were added naphthoquinone (1.58 g, 10 mmol), phenylboronic acid (2.93 g, 24.0 mmol), and another DMF (35 mL). The whole mixture was stirred at 60 °C under air and monitored with TLC. After 7h, water (50 mL) was added to the resulting mixture, and the aqueous layer was separated and extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The concentrate was purified with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 15/1) to give **1a** in 81%.

Synthesis of 3a.

To a 10 mL two-necked round bottom flask were placed **1a** (468 mg, 2 mmol), 10% Pd/C (21.3 mg, 0.2 mmol), and AcOEt (4 mL). After degassing by three freeze-pump-

thaw cycles and charging N_2, the mixture was stirred at room temperature under an atmospheric H_2. The reaction was monitored by GC. After 18 h, the reaction mixture was filtrated and concentrated with an evaporator and dried under vacuum. Then, the crude mixture and paraformaldehyde (21.8 mg, 1.06 mmol), and THF (6 mL) were placed to a 20 mL two-necked round bottom flask. The mixture was sonicated for 10 min and cooled to -78 °C. LDA (62.5 mg, 0.583 mmol) was added dropwise through a syringe. The temperature was elevated to 0 °C programmatically (-78 °C for 4h, -40 °C for 2h). After 16h at 0 °C, silica was added into the reaction mixture, and the reaction mixture was stirred at room temperature for another 1h. After the insoluble contents were filtered out, the filtrate was concentrated in vacuo. The concentrate was purified with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 5/1) to give **3a** (432.96 mg, 1.64 mmol) in 82% yield.

Representative procedure of the one-shot synthesis of 3.

To a 100 mL three-necked round bottom flask were placed triphenylboroxin (1.87 g, 6 mmol), NaOMe (271 mg, 6 mmol), naphthoquinone (790.75 mg, 5 mmol), and $[RhCl(cod)]_2$ (74 mg, 0.15 mmol) and paraformaldehyde (300.3 mg, 1 mmol), and 1,4-dioxane (30 mL). The mixture was stirred at 60 °C and monitored with TLC analysis. After stirring for 18 h, NH_4Cl (10 mL) was added to the reaction mixture. The organic

layer was extracted with CH_2Cl_2 (15 mL× 3), washed with H_2O (50 mL × 3), and dried over $MgSO_4$. After insoluble materials were filtered out, silica gel for column chromatography was added to the solution, and the mixture was stirred at room temperature under air. The filtrate was concentrated in vacuo, and the concentrate was purified with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 5/1) to give 1a (554.4 mg, 2.1 mmol) in 42% yield.

Representative procedure for the synthesis of protected alcohols (4, 5, 6 and 7).

Compound **3a** (66 mg, 0.25 mmol) and CH_2Cl_2 (3 mL) were placed to a 5 mL two-necked round bottom flask. Then, pyridine (29.66 mg, 0.375 mmol) was added to the mixture at 0 °C. Ethyl chloroformate (81.39 mg, 1.25 mmol) was added dropwise through a syringe at 0 °C, and the whole mixture was stirred at the same temperature with monitoring with TLC. After 3 h, 2M HCl aq. (2.0 mL) was added to the resulting mixture at 0 °C. The separated aqueous layer was extracted with CH_2Cl_2 (8 mL × 3), and the combined organic layers were washed with H_2O (10 mL) and dried over $MgSO_4$. After the insoluble materials were filtered out, the filtrate was concentrated in vacuo. The concentrate was purified with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 5/1) to give **4** (79.8 mg, 0.238 mmol) in 95% yield.

Procedure for the synthesis of protected amines using carbamoyl chloride (8).

3a (66 mg, 0.25 mmol) and pyridine (1 mL) were placed to a 5 mL two-necked round bottom flask. A solution of *N*, *N*-diphenylcarbamoyl chloride (86.9 mg, 0.375 mmol) in pyridine (1 mL) was added dropwise to the mixture through a syringe. The whole mixture was stirred at 80 °C and monitored with TLC. After 20 h, H_2O (20 mL) was added to the reaction mixture cooled to room temperature, and the aqueous layer was separated and extracted with CH_2Cl_2 (8 mL× 3). The combined organic layer was dried over $MgSO_4$. Then, after the insoluble materials were filtered out, the filtrate was concentrated in vacuo. The concentrate was purified with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 5/1) to give **8** (13.77 mg, 0.03 mmol) in 12% yield.

Procedure for the synthesis of protected amines using isocyanate (9).

3a (66 mg, 0.25 mmol) was placed to a 5 mL two-necked round bottom flask. TEA (5.06 mg, 0.05 mmol) and octadecyl isocyanate (81.27 mg, 0.275 mmol) was successively added dropwise through a syringe at room temperature. The mixture was stirred at 80 °C and monitored with TLC. After 20 h, the resulting $NaHCO_3$ (10 mL) was added to the reaction mixture cooled to room temperature, and the aqueous layer was separated. The aqueous layer was extracted with CH_2Cl_2 (8 mL× 3), and the combined organic layers were washed with H_2O (20 mL × 3) and dried over $MgSO_4$. After the insoluble materials were filtered out, the filtrate was concentrated in vacuo. The concentrate was purified

with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 10/1) to give **9** (28.7 mg, 0.053 mmol) in 21% yield.

Representative procedure for the synthesis of protected carboxylic acids (10, 11 and 12).

To a 5 mL two-necked round bottom flask were placed **3a** (19.1 mg, 0.072 mmol), benzoic acid (7.35 mg, 0.06 mmol), DMAP (1.22 mg, 0.01 mmol), and CH_2Cl_2 (2 mL). *N*, *N*-Diisopropylcarbodiimide (DIPC) (12.62 mg, 0.1 mmol) was added portionwise to the mixture at room temperature, and the mixture was stirred at room temperature and monitored with TLC. After 18 h, the reaction mixture was concentrated in vacuo, and the concentrate was purified with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 5/1) to give **10** (16.8 mg, 0.046 mmol) in 76% yield.

Procedure for the transformation of NQ-Ph-OH to the aldehyde (13).

3a (396 mg, 1.5 mmol) and DMSO (8 mL) were placed to a 20 mL two-necked round bottom flask. To the mixture was added slowly a solution of 2-iodoxybenzoic acid (630.05 mg, 2.25 mmol) in DMSO (5 mL) through a syringe. The whole mixture was stirred at room temperature and monitored with TLC. After 10 h, H_2O (20 mL) was added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL× 3). The combined organic layers were dried over $MgSO_4$ and

filtrated. The filtrate was concentrated in vacuo. The concentrate was purified with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 10/1) to give **13** (373.4 mg, 1.43 mmol) in 95% yield.

Procedure for the synthesis of 14.

A mixture of **13** (373.35 mg, 1.43 mmol) and ethanol (5 mL) were cooled to 0 °C, and to the mixture was added slowly hydrazine monohydrate (114.54 mg, 2.29 mmol) through a syringe at the same temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo. To a solution of the concentrate in CH_2Cl_2 (8 mL) was added portionwise MnO_2 (372.97 mg, 4.29 mmol) at room temperature. The whole mixture was stirred at room temperature and monitored with TLC. After 2 h, the resulting mixture was filtrated through celite® (50 mg) and the filtcake was washed with CH_2Cl_2 (30 mL), and the filtrate was concentrated in vacuo. The concentrate was purified with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 10/1) to give **14** (137.1 mg, 0.50 mmol) in 35% yield.

Representative procedure for the synthesis of protected phosphoric and sulfonic acids (15, 16, 17, and 18).

To a 5 mL two-necked round bottom flask were placed **14** (20.1 mg, 0.073 mmol) andCH_2Cl_2 (2 mL). Diphenylphosphoric acid (15.3 mg, 0.061 mmol) was added slowly

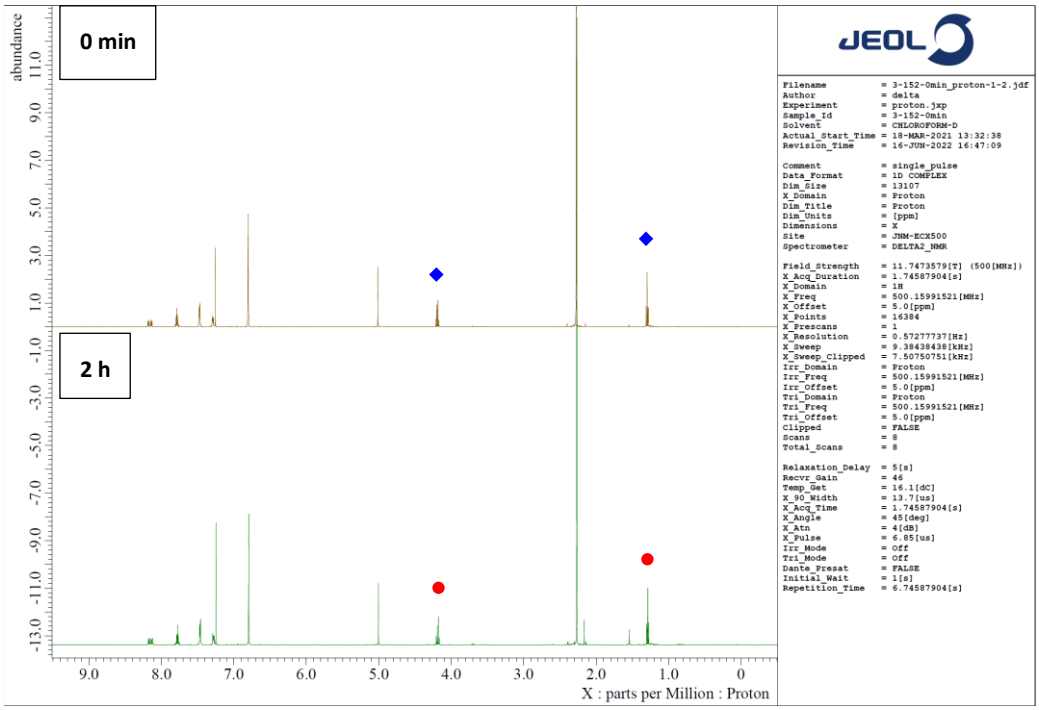
to the solution through a syringe, and the mixture was stirred at room temperature and monitored with TLC. After 3h, the reaction mixture was concentrated in vacuo, and the concentrate was purified with column chromatography on silica-gel (eluent: hexane/ethyl acetate= 3/1) to give **13** (19.7 mg, 0.040 mmol) in 65% yield.

5. Representative procedure for the photoreaction.

4 (2×10^{-3} mmol) and mesitylene (4×10^{-3} mmol, internal standard reference) were dissolved in deuterium solvents (0.6 mL) and transferred into a pyrex NMR tube. The progress of the photoirradiation reactions was monitored with ^{1}H NMR measurement. At room temperature, the NMR tube was fixed at 1.0 cm in front of Xe lamp that is sets up to give 360nm of light. The NMR yields were calculated by comparing the ^{1}H integration of a compound with that of the internal standard. All released compounds were confirmed by the corresponding commercially available compounds.

6. ^{1}H NMR monitoring of photoreaction.

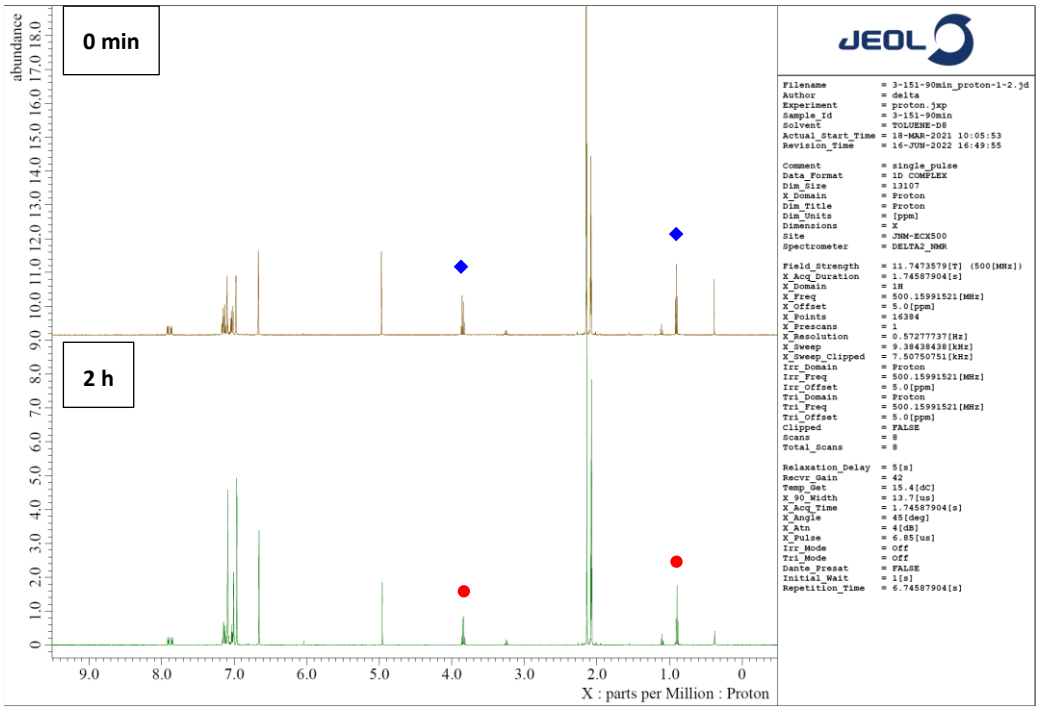
6-1. Monitoring of photoreaction of **4** in $CDCl_3$.



Reaction profile:

Time	Yield of EtOH
0 h	0%
2 h	0%

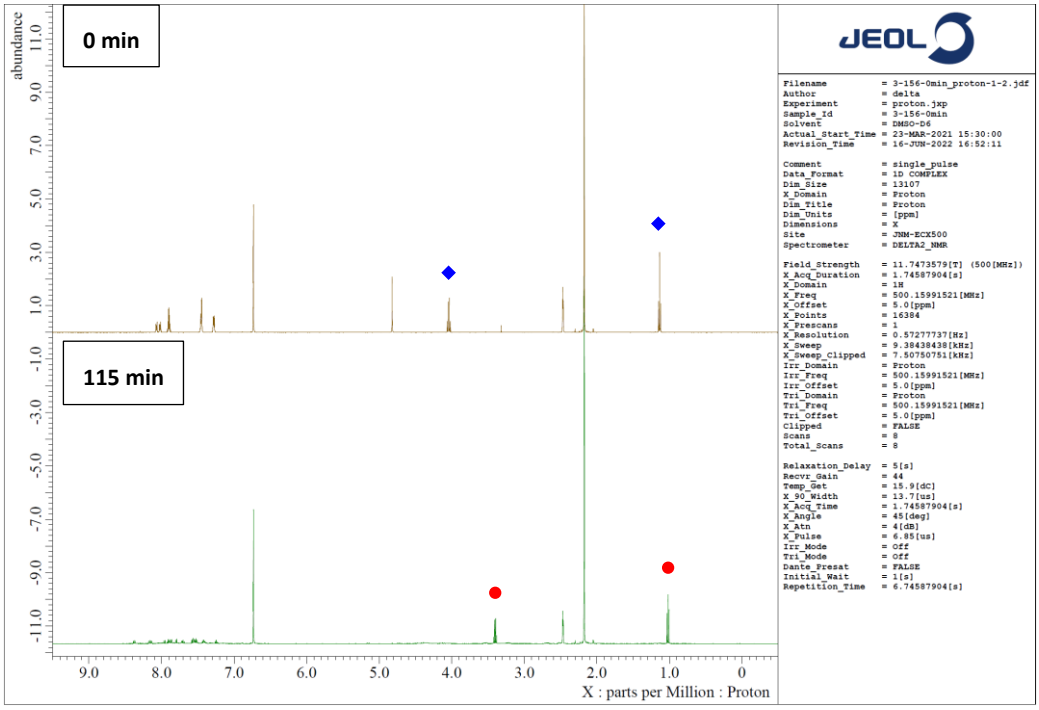
6-2. Monitoring of photoreaction of **4** in Toluene-d_8.



Reaction profile:

Time	Yield of EtOH
0 h	0%
2 h	0%

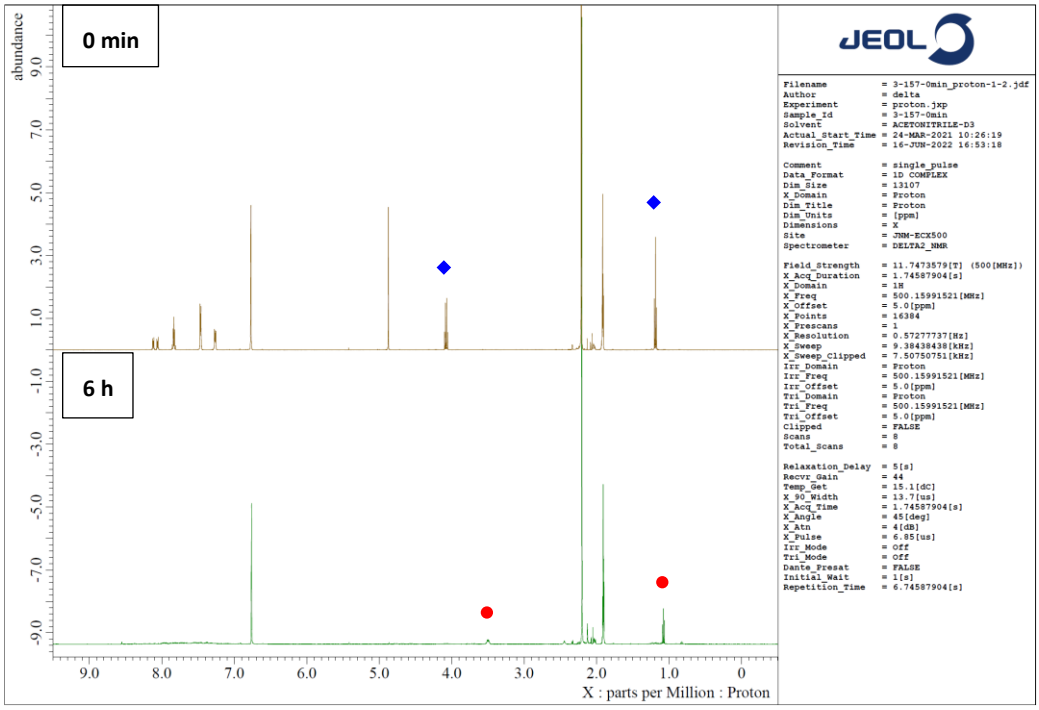
6-3. Monitoring of photoreaction of **4** in DMSO-d_6.



Reaction profile:

Time	Yield of EtOH
0 min	0%
5 min	20%
15 min	41%
25 min	52%
95 min	74%
115 min	79%

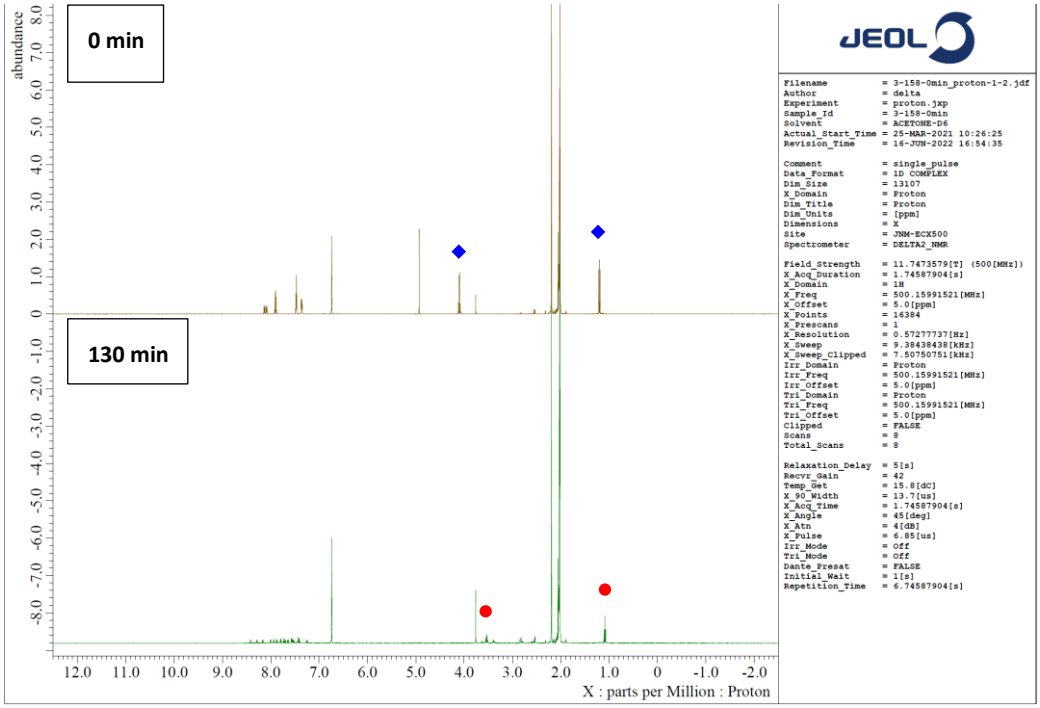
6-4. Monitoring of photoreaction of **4** in MeCN-d_3.



Reaction profile:

Time	Yield of EtOH
0 h	0%
0.5 h	9%
2 h	29%
4 h	40%
6 h	44%

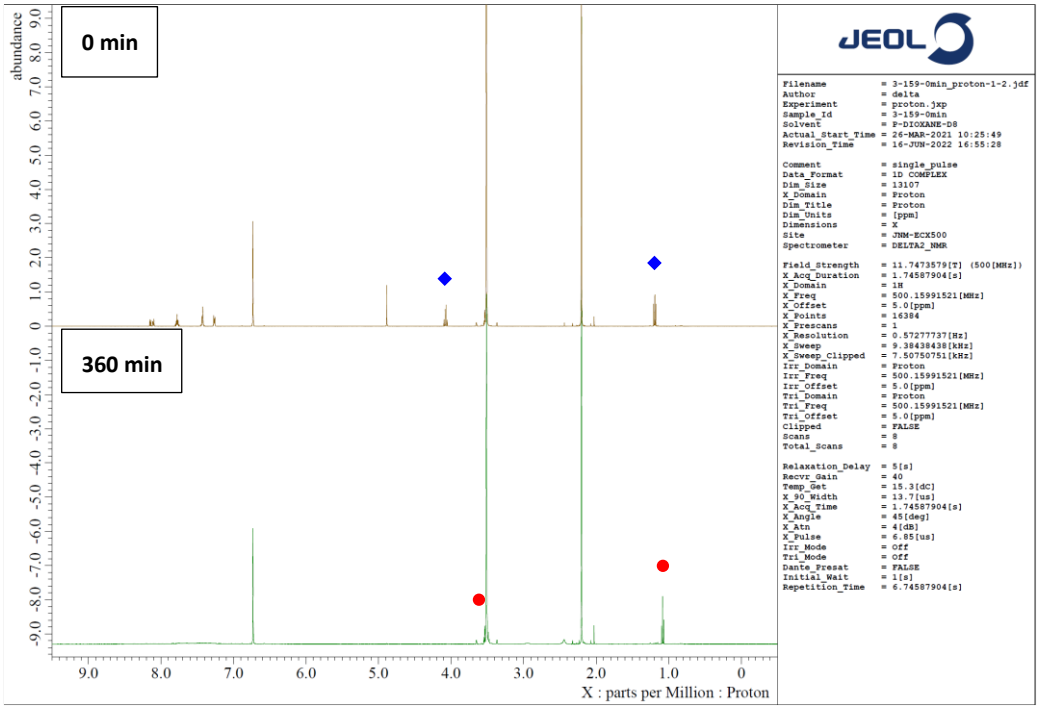
6-5. Monitoring of photoreaction of **4** in Acetone-d_6.



Reaction profile:

Time	Yield of EtOH
0 min	0%
10 min	7%
40 min	43%
90 min	50%
130 min	58%

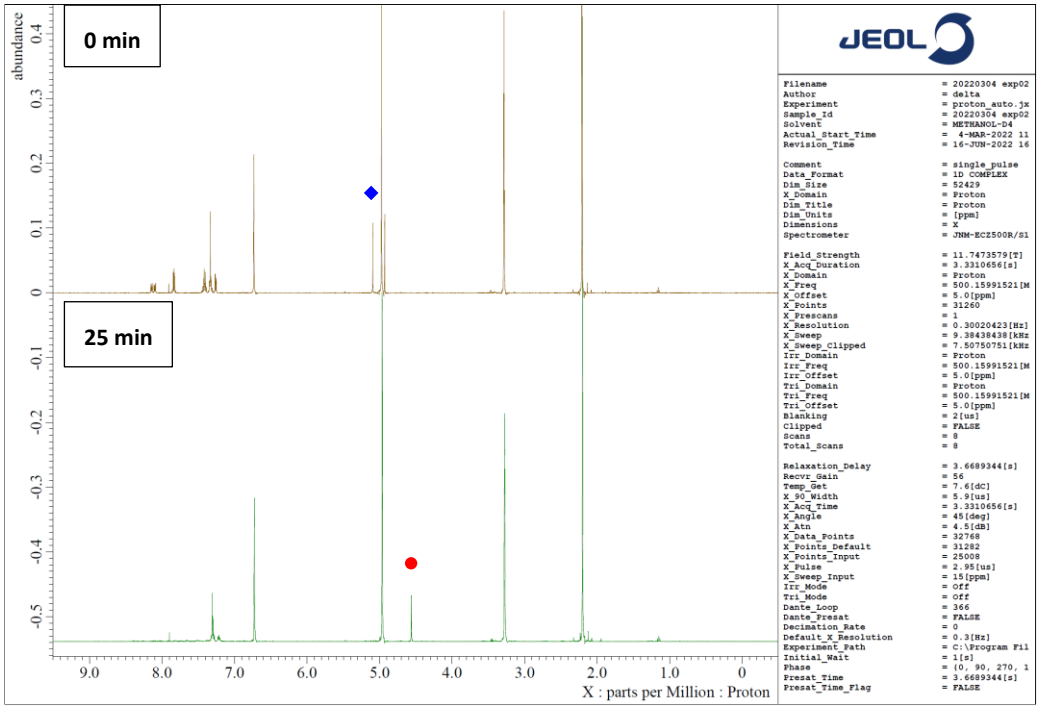
6-6. Monitoring of photoreaction of **4** in 1,4-Dioxane-d_8.



Reaction profile:

Time	Yield of EtOH
0 min	0%
20 min	0%
40 min	14%
80 min	23%
360 min	69%

6-7. Monitoring of photoreaction of **5**.

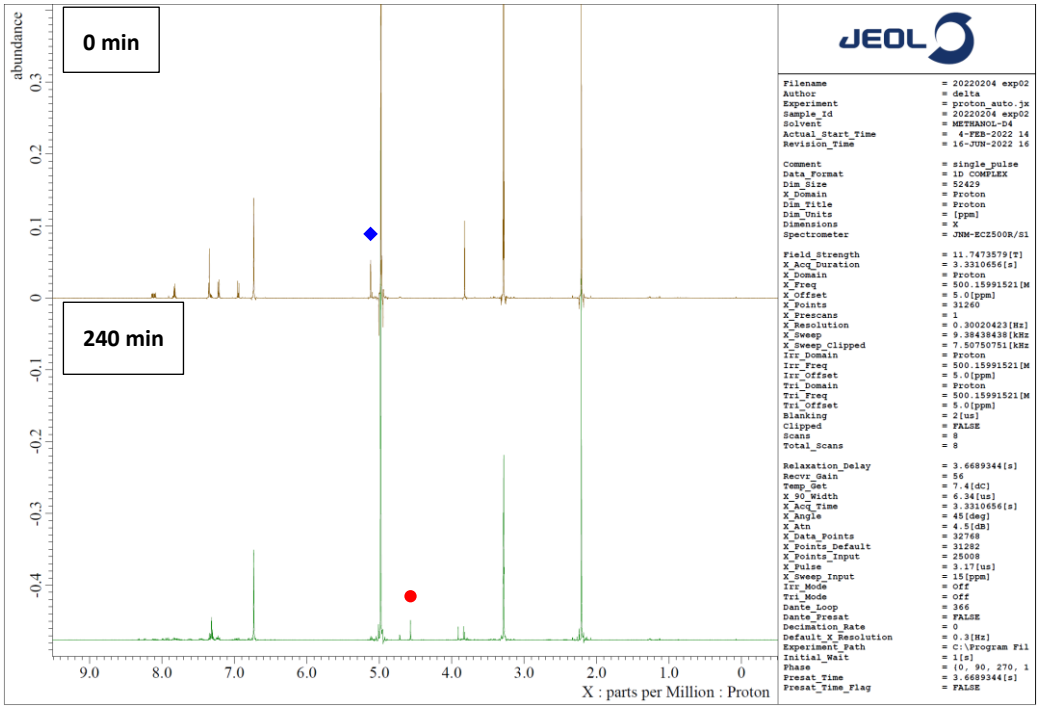


Reaction profile:

Time	Yield of BnOH
0 min	0%
1 min	22%
2 min	32%
3 min	38%
4 min	41%
5 min	48%

Time	Yield of BnOH
7.5 min	61%
10 min	76%
12.5 min	88%
15 min	92%
20 min	97%
25 min	100%

6-8. Monitoring of photoreactions of **6**.

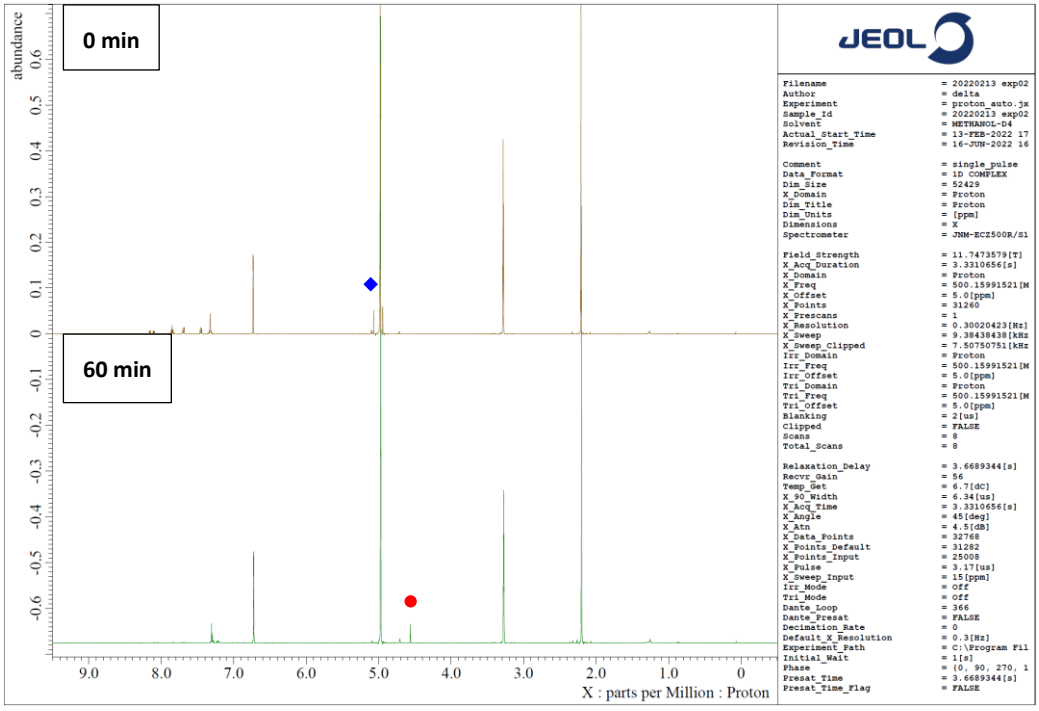


Reaction profile:

Time	Yield of BnOH
0 min	0%
5 min	3%
10 min	6%
20 min	13%
30 min	21%

Time	Yield of BnOH
60 min	39%
120 min	66%
180 min	80%
240 min	85%

6-9. Monitoring of photoreactions of **7**.

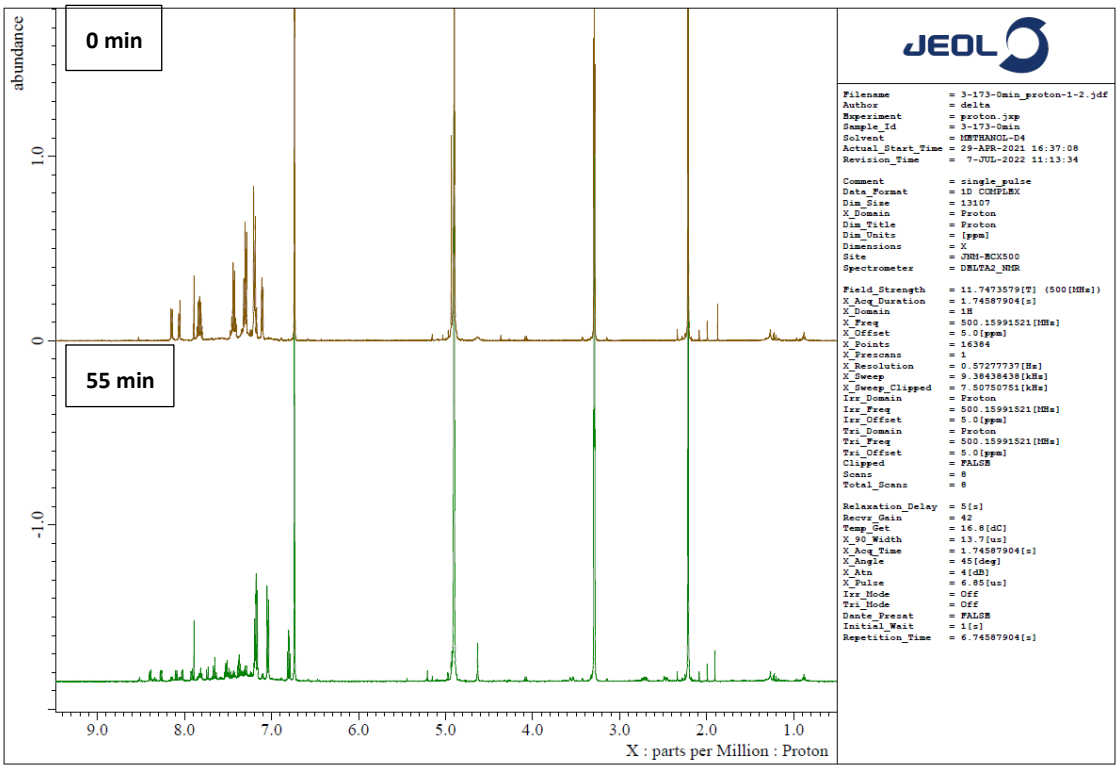


Reaction profile:

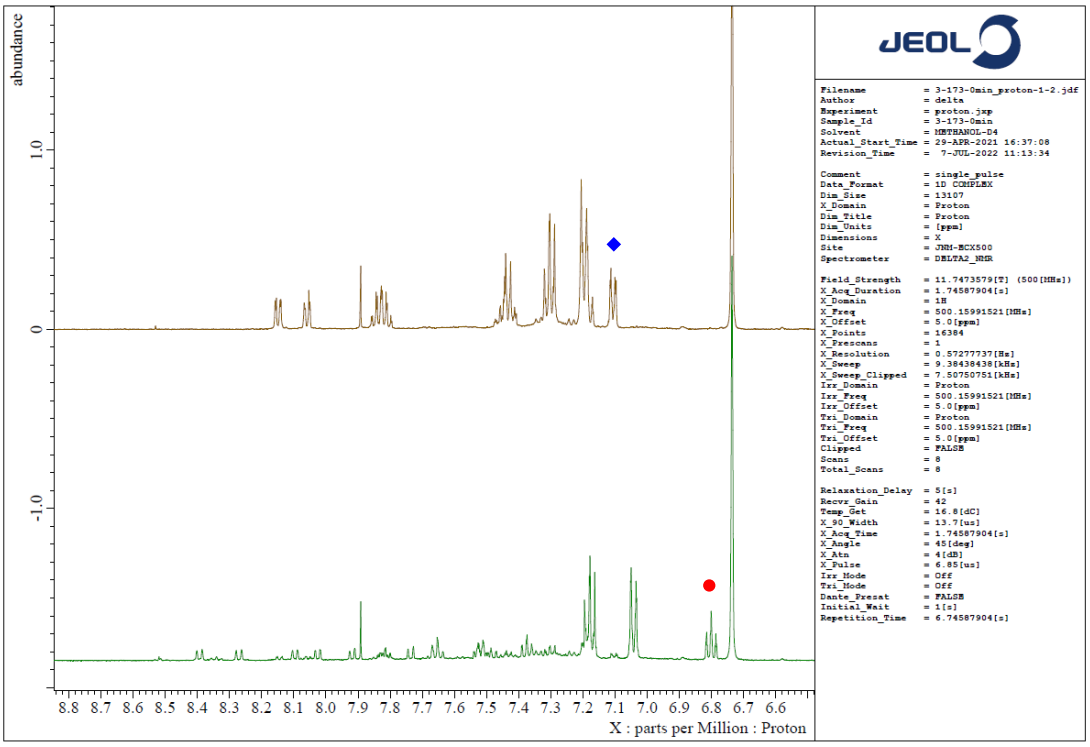
Time	Yield of BnOH
0 min	0%
1 min	13%
2 min	25%
3 min	32%
4 min	42%
5 min	43%
7.5 min	56%
10 min	66%

Time	Yield of BnOH
12.5 min	75%
15 min	82%
20 min	85%
25 min	87%
30 min	89%
40 min	94%
50 min	98%
60 min	100%

6-10. Monitoring of photoreactions of **8**.



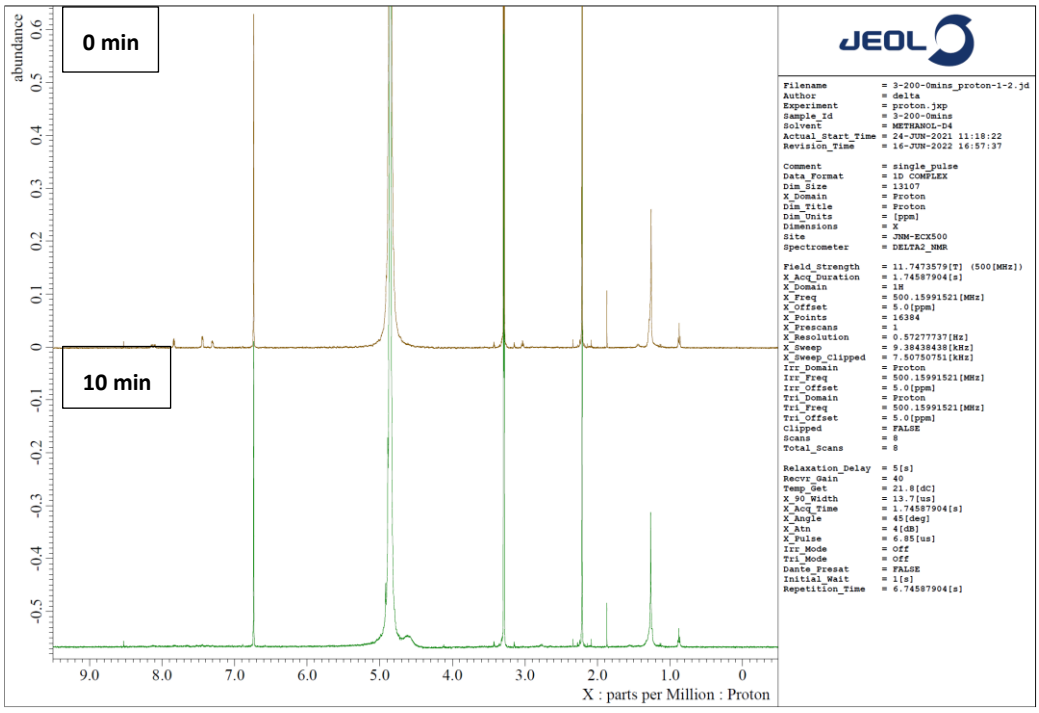
Comparison of ^{1}H NMR charts expanded in the area from 6.5 to 8.8 ppm.



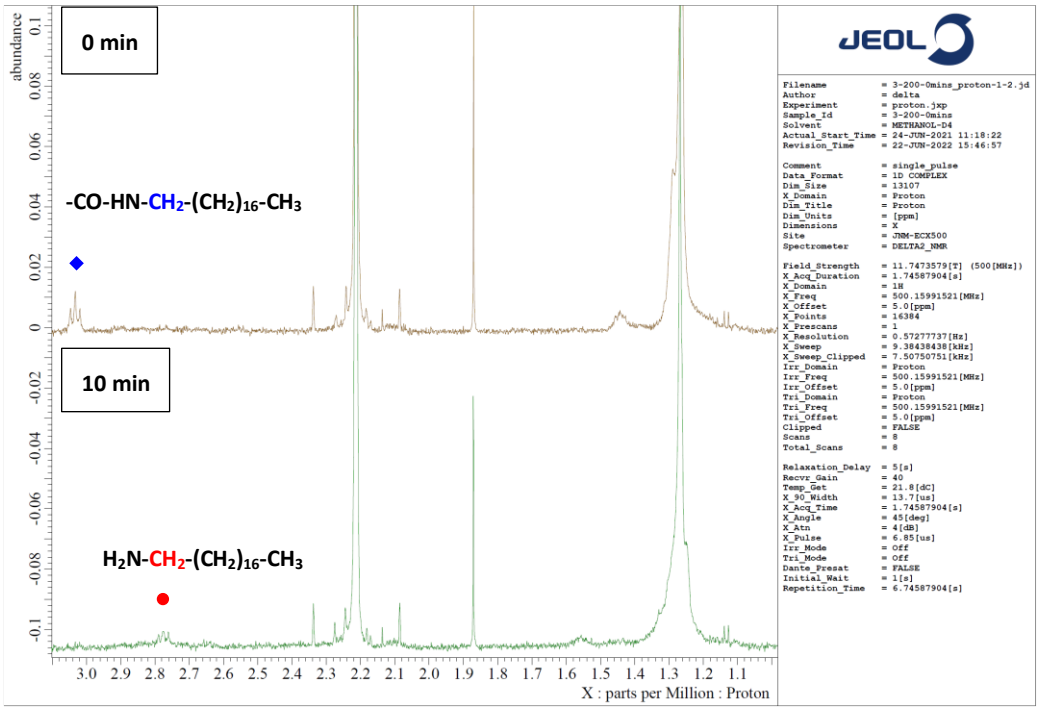
Reaction profile:

Time/min	Yield of released Ph_2 N
0	0%
3	8%
15	45%
25	69%
55	93%

6-11. Monitoring of photoreactions of **9**.



Comparison of ^{1}H NMR charts expanded in the area from 1.0 to 3.1 ppm.

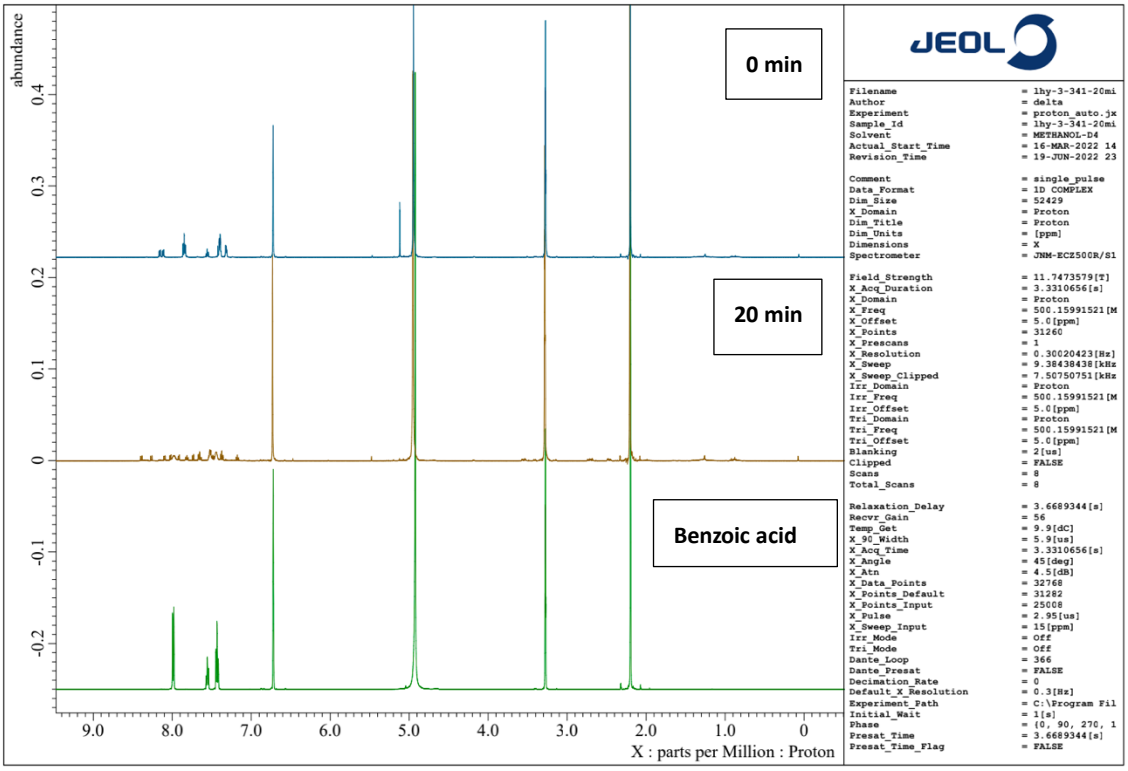


Reaction profile:

Time	Yield of $C_{18}H_{37}NH_2$
0 min	0%
10 min	98%

6-12. Monitoring of photoreactions of **10**.

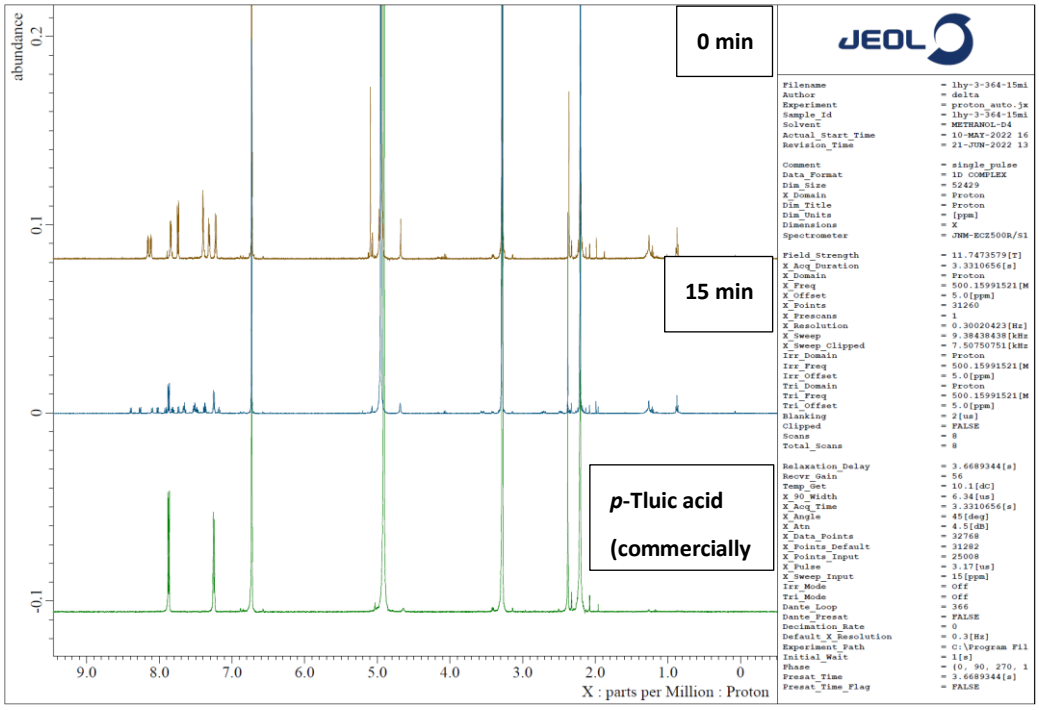
Comparison of whole ^{1}H NMR charts.



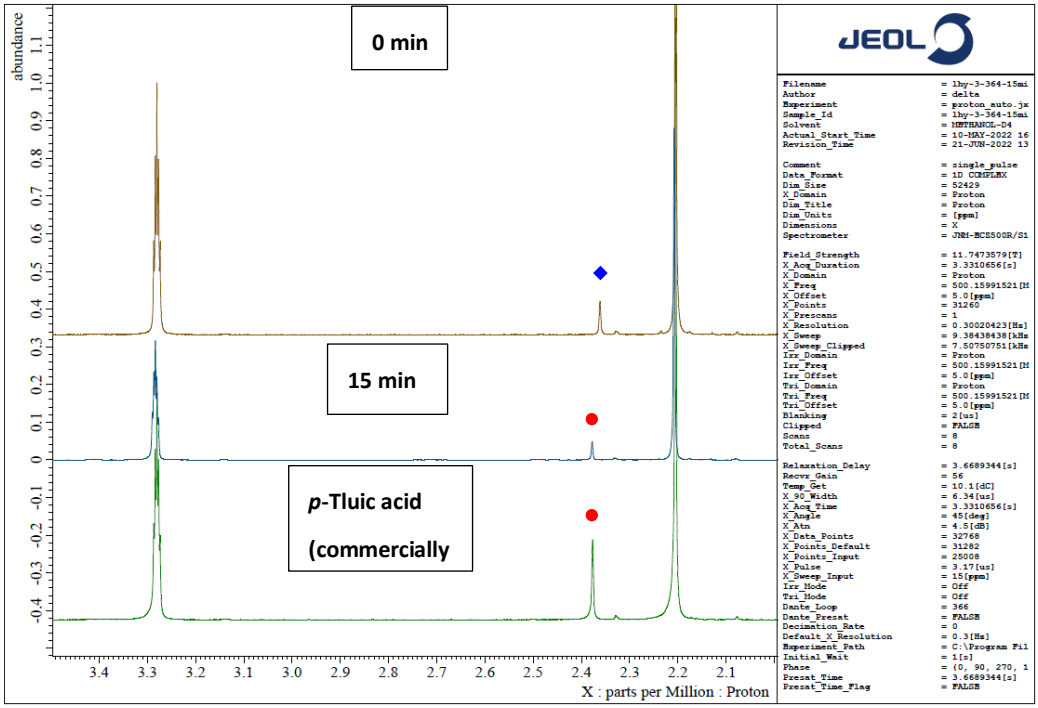
Time/min	Yield of released alcohol
0	0%
1	26%
5	38%
10	43%
20	92%

6-13. Monitoring of photoreactions of **11**.

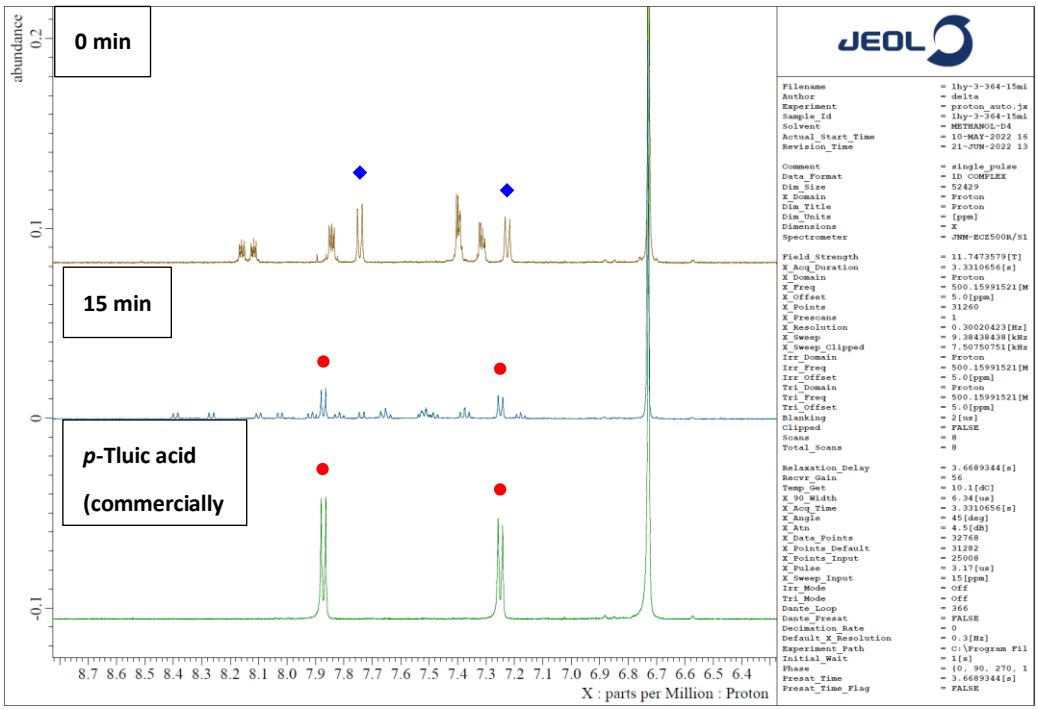
Comparison of whole ^{1}H NMR charts.



Comparison of ^{1}H NMR charts expanded in the area from 2.0 to 3.5 ppm.



Comparison of ^{1}H NMR charts expanded in the area from 6.3 to 8.8 ppm.

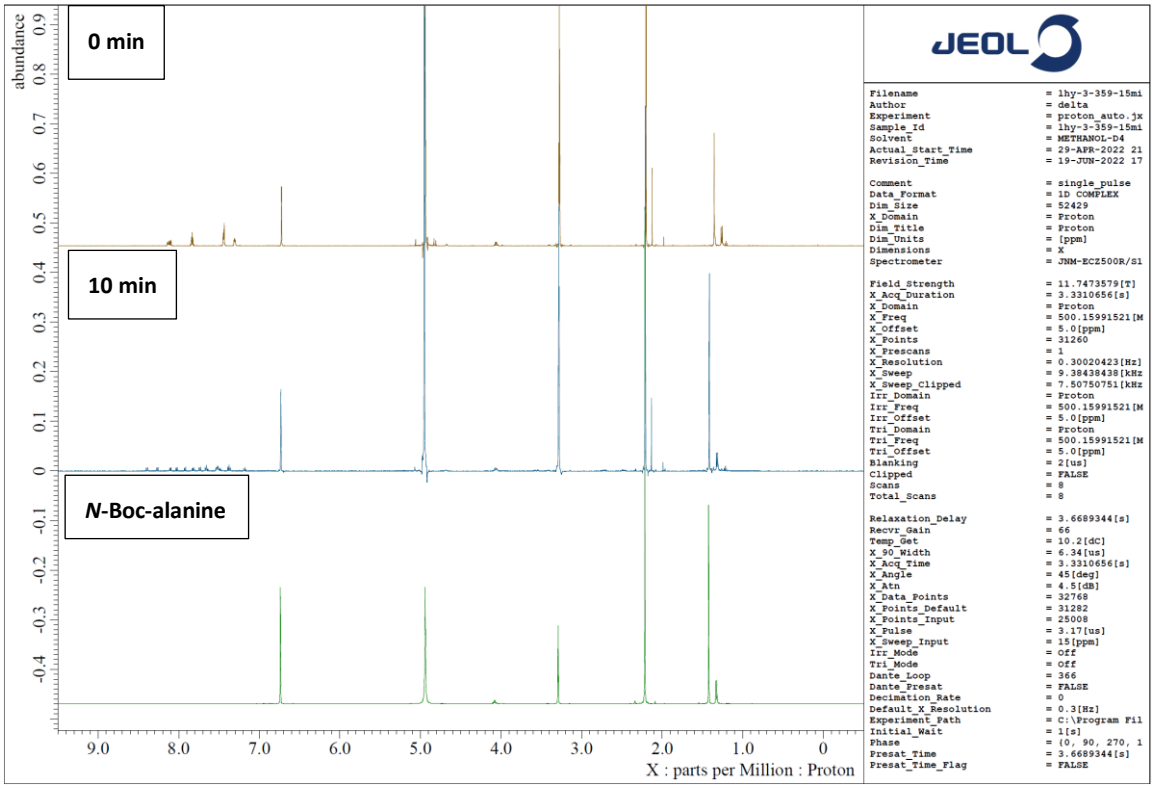


Reaction profile:

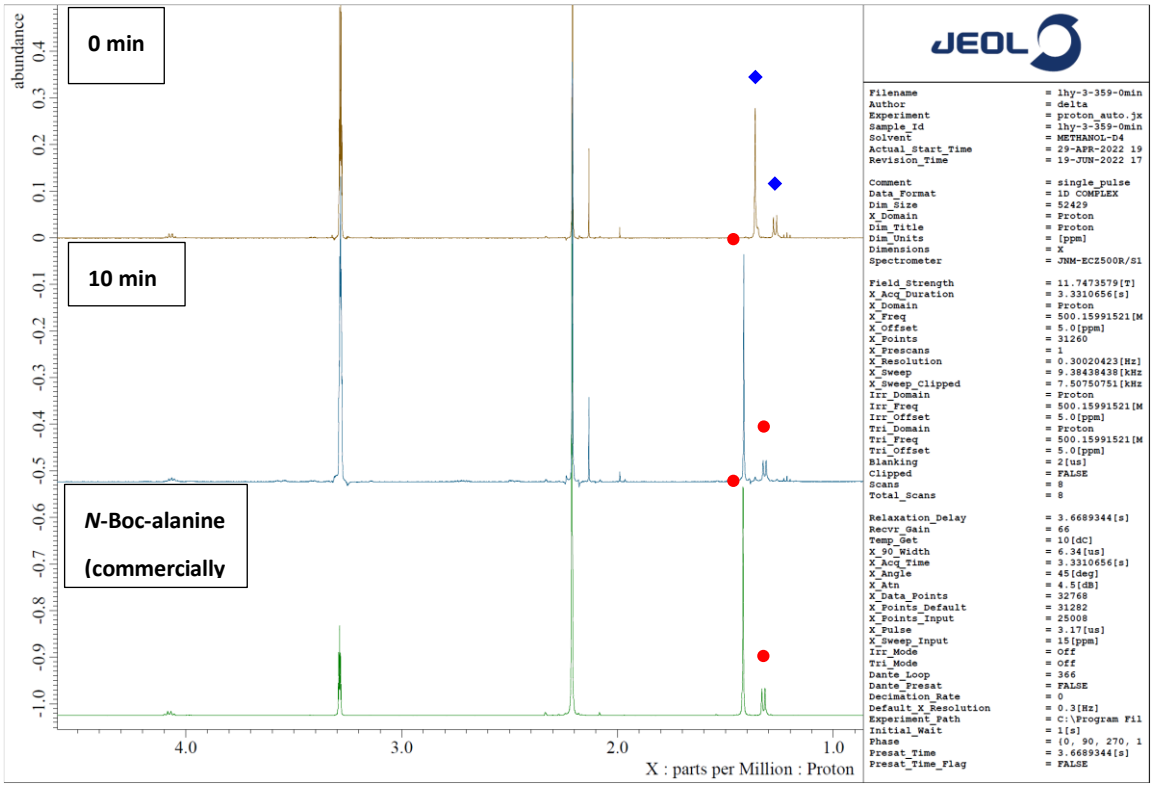
Time	Yield of *p*-Toluic acid
0 min	0%
15 min	99%

6-14. Monitoring of photoreactions of **12**.

Comparison of whole ^{1}H NMR charts.



Comparison of ^{1}H NMR charts expanded in the area from 0.9 to 4.6 ppm.

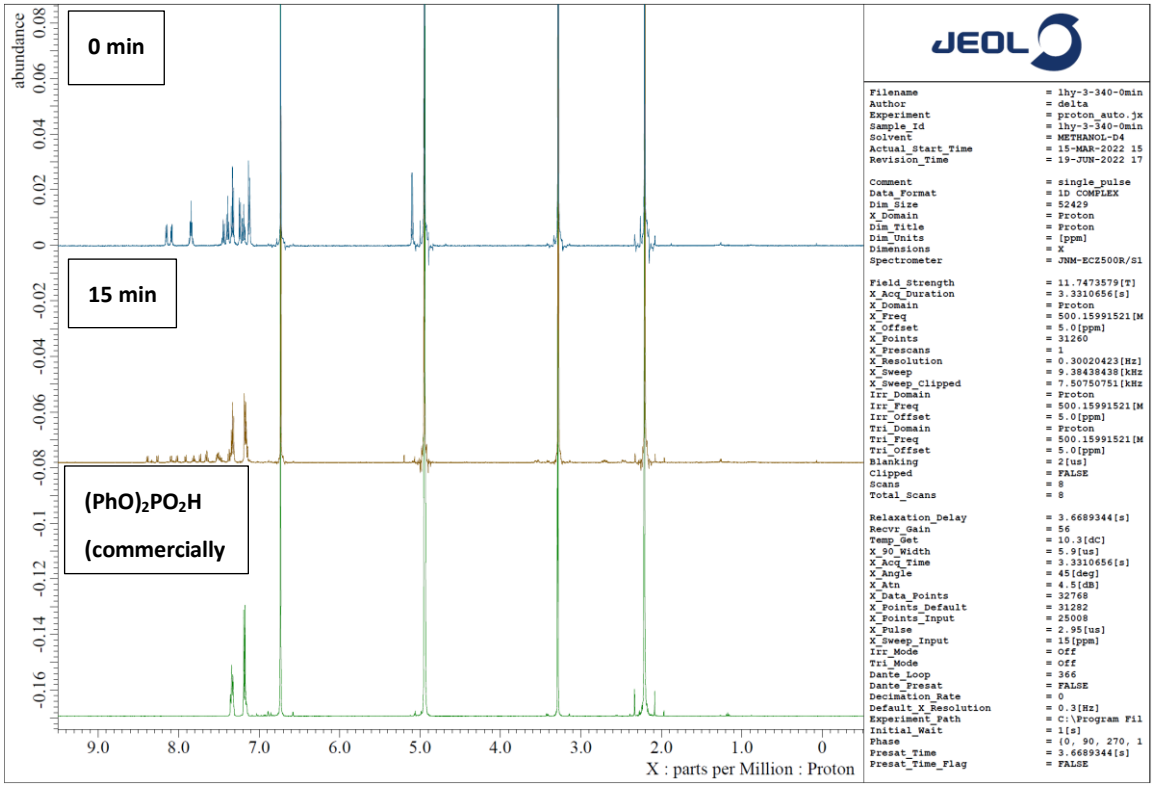


Reaction profile:

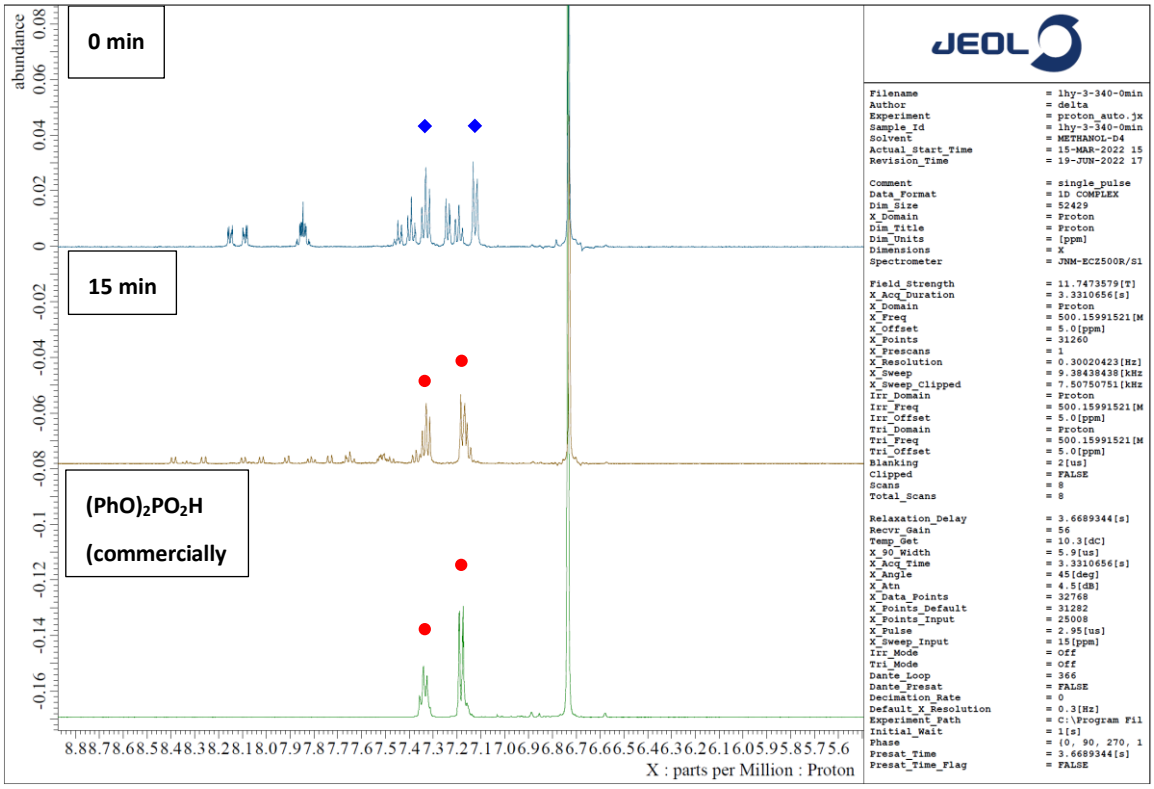
Time	Yield of *N*-Boc-alanine
0 min	0%
15 min	93%

6-15. Monitoring of photoreactions of **15**.

Comparison of whole ^{1}H NMR charts.



Comparison of ^{1}H NMR charts expanded in the area from 5.5 to 8.9 ppm.

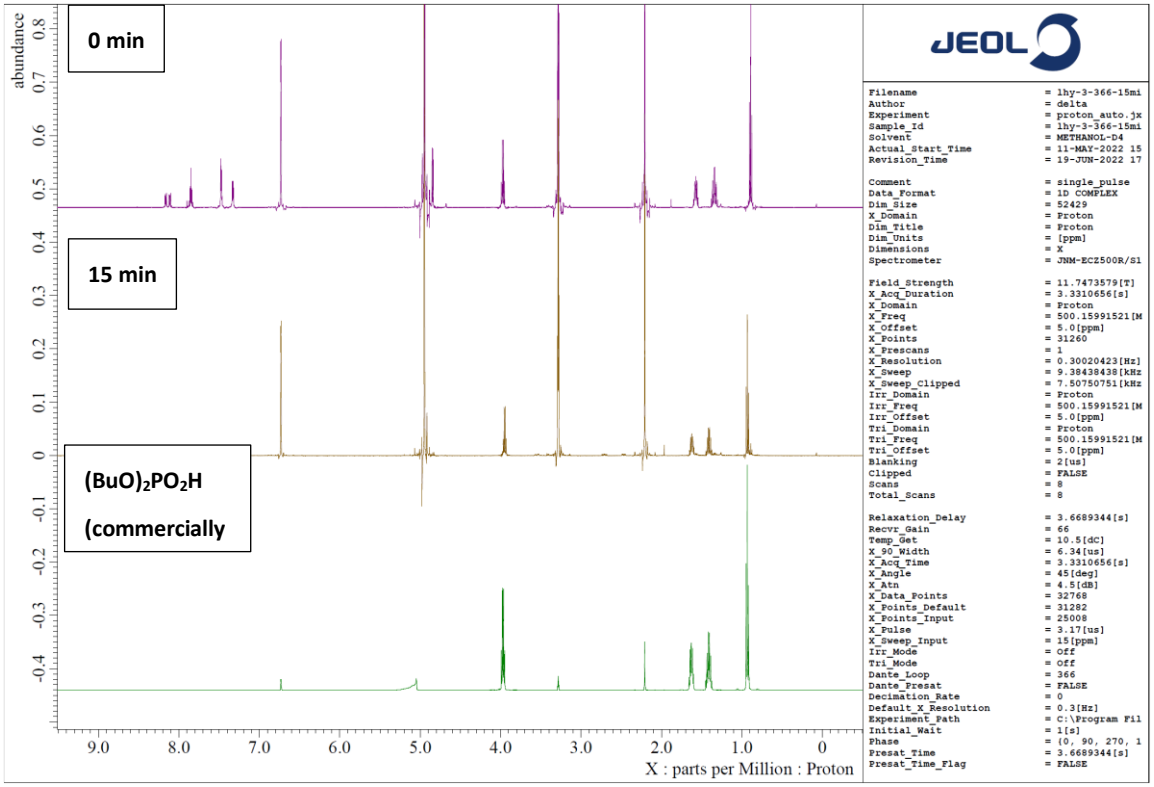


Reaction profile:

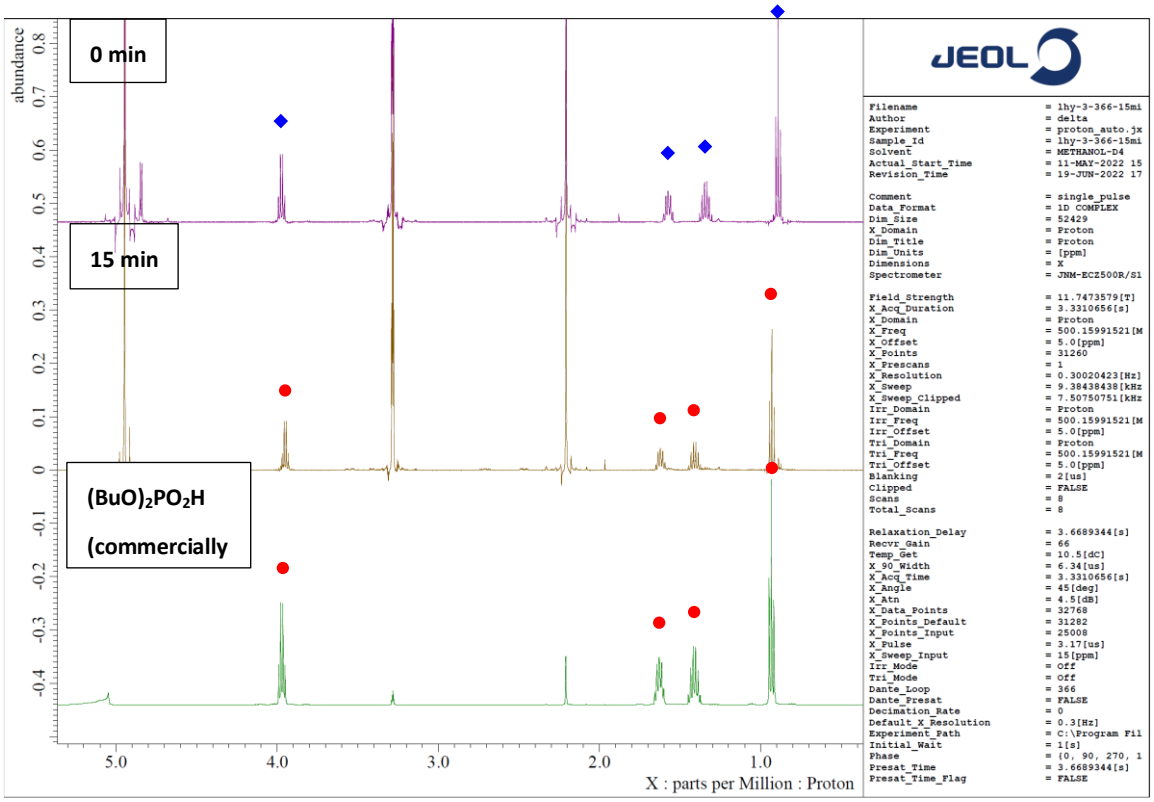
Time	Yield of $(PhO)_2PO_2H$
0 min	0%
15 min	90%

6-16. Monitoring of photoreactions of **16**.

Comparison of whole ^{1}H NMR charts.



Comparison of ^{1}H NMR charts expanded in the area from 0.4 to 5.3 ppm.

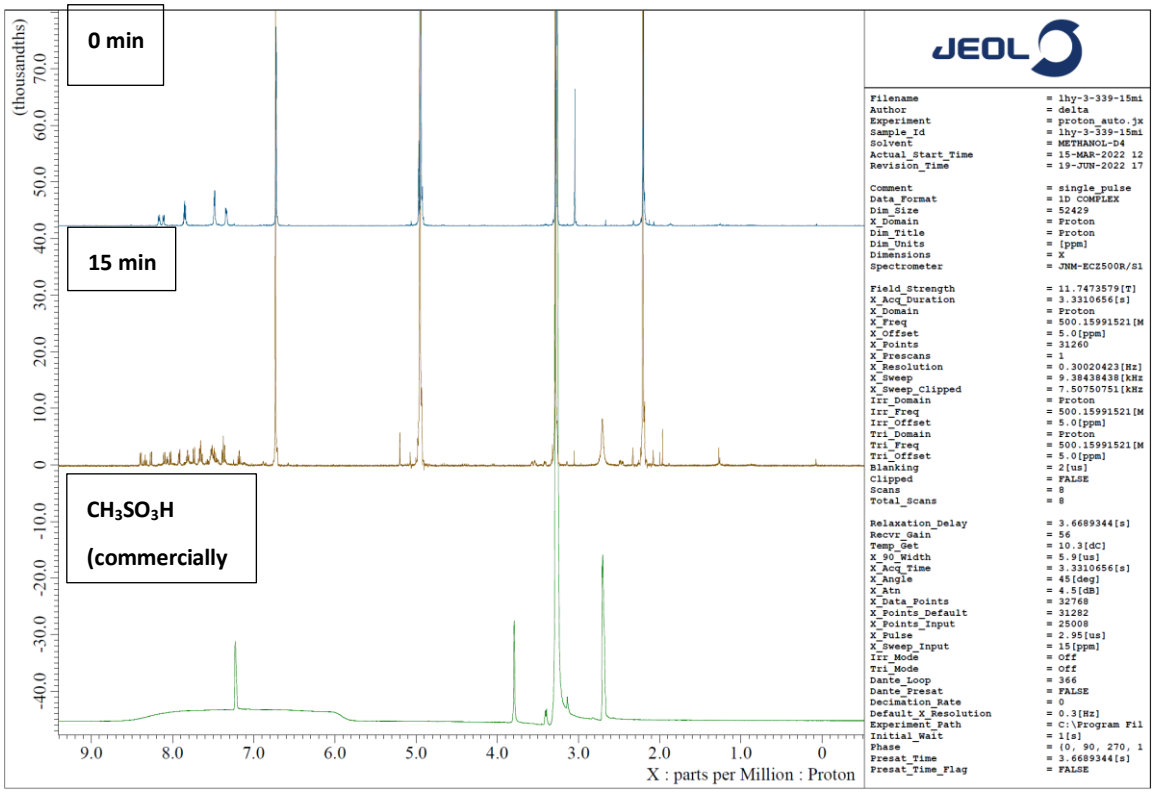


Reaction profile:

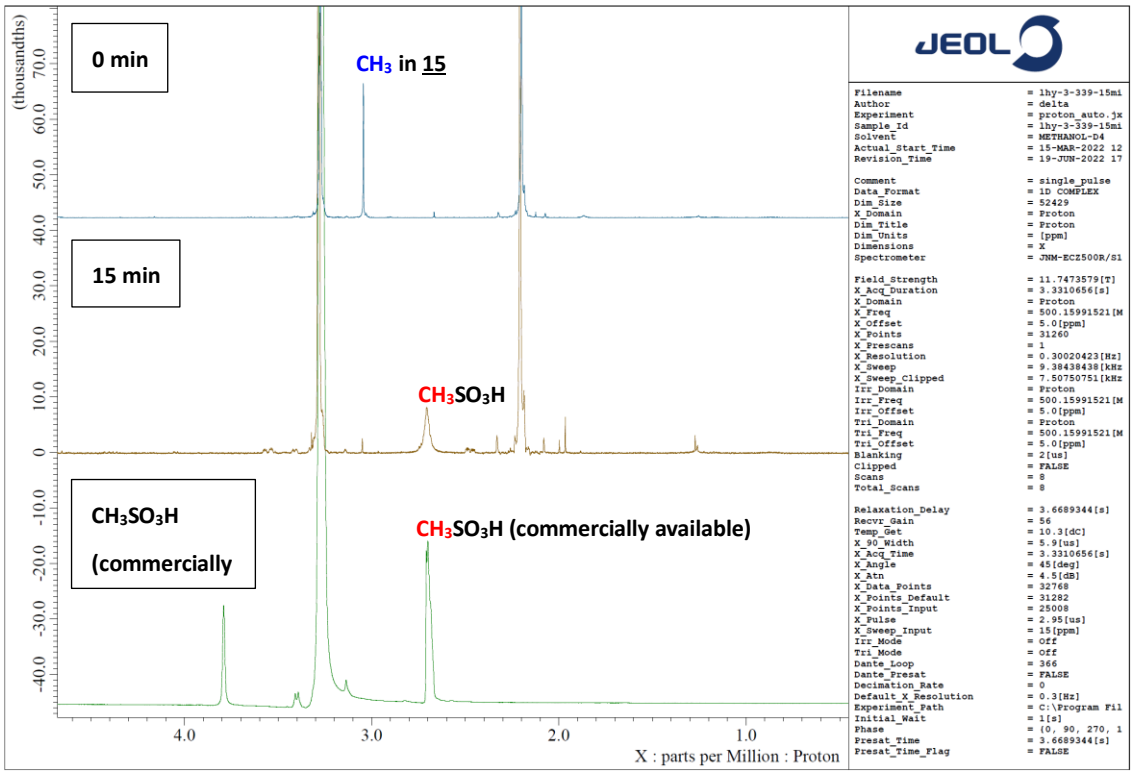
Time	Yield of $(BuO)_2PO_2H$
0 min	0%
15 min	99%

6-17. Monitoring of photoreactions of **17** (Table 2, Entry 6).

Comparison of whole ^{1}H NMR charts.



Comparison of ^{1}H NMR charts expanded in the area from 0.5 to 4.6 ppm.

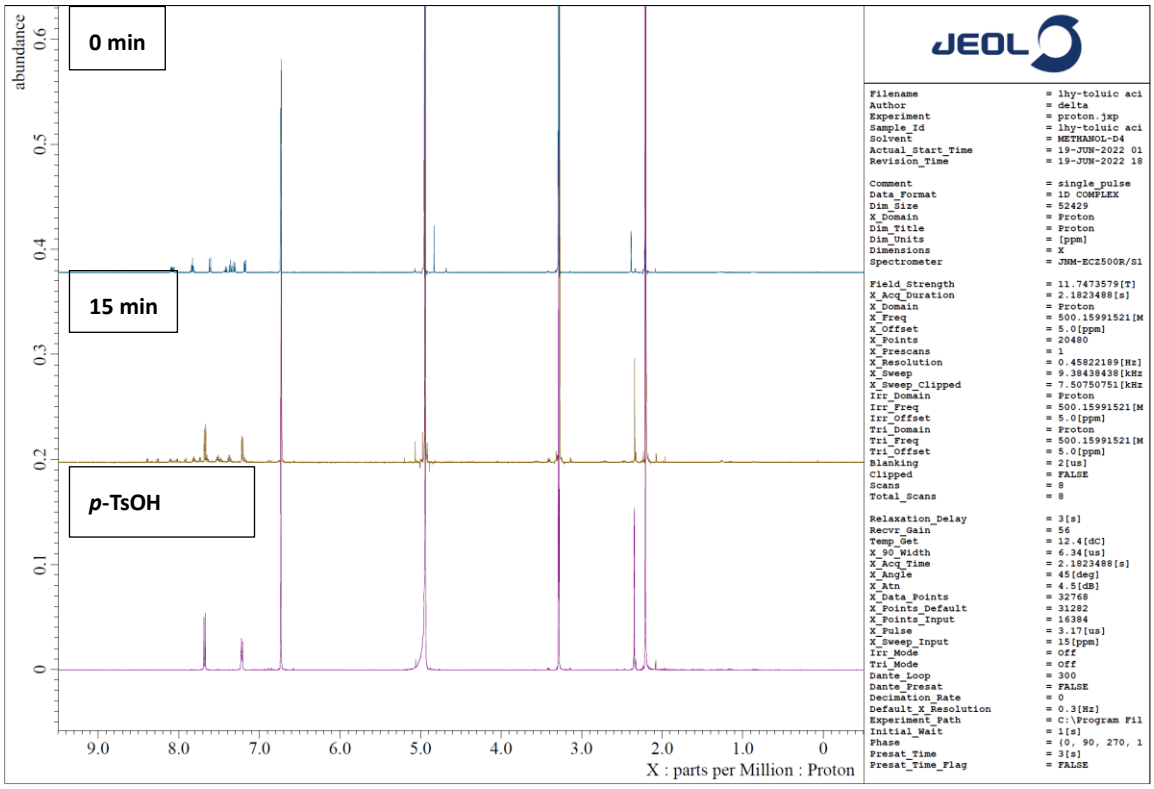


Reaction profile:

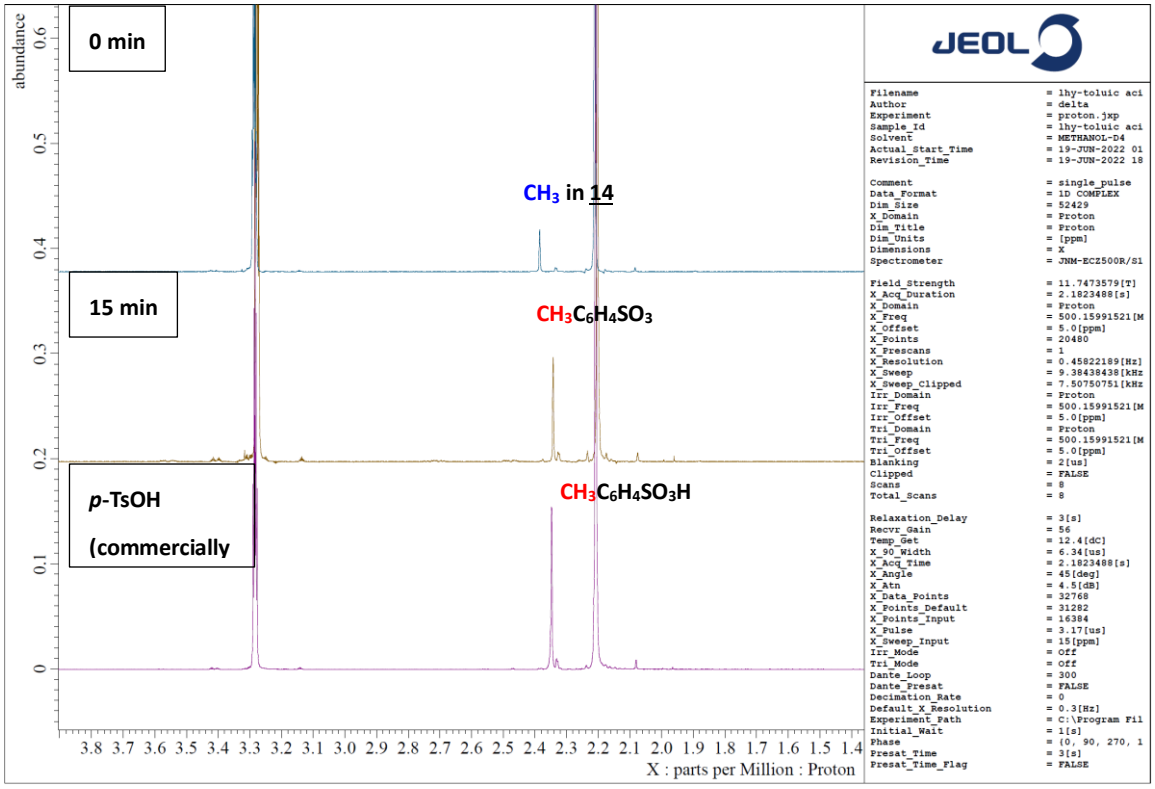
Time	Yield of CH_3SO_2OH
0 min	0%
15 min	99%

6-18. Monitoring of photoreactions of **18**.

Comparison of whole ^{1}H NMR charts.



Comparison of ^{1}H NMR charts expanded in the area from 1.4 to 3.9 ppm.



Reaction profile:

Time	Yield of 4-CH_3-C_6H_4-SO_2OH
0 min	0%
15 min	98%

7. Spectral data

2-Phenylnaphthalene-1,4-dione (1a).

Yield 81%; R_f 0.45 (hexane/AcOEt= 3/1); yellow solid; mp 115.1-115.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17-8.21 (m, 1H), 8.11-8.15 (m, 1H), 7.76-7.81 (m, two overlapping signals, 2H), 7.56-7.60 (m, two overlapping signals, 2H), 7.46-7.50 (m, two overlapping signals, 3H), 7.08 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 184.0, 147.6, 135.0, 133.7, 133.6, 132.1, 133.1, 132.1, 131.7, 129.9, 129.3, 128.3, 126.8, 125.7; IR (KBr, cm^{-1}) 1670, 1650, 1600, 1589, 1570, 1348, 1333, 1308, 1246, 1206, 759; HRMS (EI) calcd for $C_{16}H_{10}O_2$ 234.0681, found 234.0674.

2-(4-Methoxyphenyl)naphthalene-1,4-dione (1b).

Yield 78%; R_f 0.43 (hexane/AcOEt= 3/1); orange solid; mp 122.5-123.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (t, *J*= 4.5 Hz, 1H), 8.08 (t, *J*= 4.0 Hz, 1H), 7.75 (dd, *J*= 4.0, 4.5 Hz, 2H), 7.57 (d, *J*= 8.5 Hz, 2H), 7.02 (s, 1H), 6.98 (d, *J*= 8.5 Hz. 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.0, 184.6, 161.1, 147.0, 133.6, 133.6, 133.5, 132.3, 131.9, 131.0, 126.8, 125.7, 125.4, 113.9, 55.3; IR (KBr, cm^{-1}) 1650, 1599, 1589, 1570, 1333, 1308, 1246, 1230, 759, 696; HRMS (EI) calcd for $C_{17}H_{12}O_3$ 264.0786, found 264.0784.

2-(4-(Trifluoromethyl)phenyl)naphthalene-1,4-dione (1c).

Yield 53%; R_f 0.34 (hexane/AcOEt= 3/1); yellow solid; mp 122.7-123.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19-8.23 (m, 1H), 8.13-8.17 (m, 1H), 7.79-7.84 (m, two

overlapping signals, 2H), 7.75 (d, *J*= 10.0 Hz, 2H), 7.73 (d, *J*= 10.0 Hz, 2H), 7.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7 183.7, 146.6, 136.8, 136.0, 134.1, 134.1 (br, J_{C-F}= 3.3 Hz), 132.0, 131.8, 131.6 (*J*= 32.6 Hz), 129.9, 127.0, 126.0, 125.3 (q, J_{C-F}= 7.5 Hz), 123.9 (q, J_{C-F}= 272.5 Hz); IR (KBr, cm^{-1}) 1659, 1593, 1407, 1352, 1326, 1250, 1166, 1111, 1069, 1049, 783. HRMS (EI) calcd for $C_{17}H_9F_3O_2$ 302.0555, found 302.0546.

2-(Hydroxymethyl)-3-phenylnaphthalene-1,4-dione (3a).

Yield 82%; R_f 0.20 (hexane/AcOEt= 3/1); yellow solid; mp 167.4-167.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.19 (m, two overlapping signals, 2H), 7.78-7.81 (m, two overlapping signals, 2H), 7.45-7.50 (m, two overlapping signals, 3H), 7.29-7.33 (m, two overlapping signals, 2H), 4.51-4.53 (2H, d, *J*= 7.5 Hz), 2.83 (1H, t, *J*= 7.5 Hz); ^{13}C NMR (125MHz, $CDCl_3$) δ 187.1, 184.7, 146.5, 143.1, 134.4, 134.1, 132.1, 132.0, 131.9, 129.9, 129.4, 128.3, 127.0, 126.3, 59.4; IR (KBr, cm^{-1}) 3507, 2956, 2899, 1661, 1603, 1500, 1455, 1386, 1340, 1306, 1226, 1076, 1019, 961, 778, 721; HRMS (EI) calcd for $C_{17}H_{12}O_3$ 264.0786, found: 264.0782.

2-(Hydroxymethyl)-3-(4-methoxyphenyl)naphthalene-1,4-dione (3b).

Yield 7%; R_f 0.23 (hexane/AcOEt= 3/1); yellow solid; mp 152.3-153.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.18 (m, two overlapping signals, 2H), 7.78-7.81 (m, two overlapping signals, 2H), 7.29 (dt, *J*= 2.5, 9.0 Hz, 2H), 7.01 (dt, *J*= 2.5, 9.0 Hz, 2H), 4.56

(s, 2H), 3.88 (s, 3H), 2.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 185.0, 160.5, 146.2, 142.5, 134.3, 134.0, 132.1, 132.0, 131.8, 127.0, 126.2, 123.9, 113.7, 59.6, 55.5; IR (KBr, cm^{-1}) 3409, 2941, 2830, 1648, 1592, 1515, 1447, 1325, 1291, 1236, 1169, 1068, 1012, 934, 801, 723; HRMS (EI) calcd for $C_{18}H_{14}O_4$ 294.0892, found 294.0890.

2-(Hydroxymethyl)-3-(4-(trifluoromethyl)phenyl)naphthalene-1,4-dione (3c).

Yield 11%; R_f 0.29 (hexane/AcOEt= 3/1); yellow solid; mp 187.7-188.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.19 (m, two overlapping signals, 2H), 7.79-7.83 (m, two overlapping signals, 2H), 7.75 (d, *J*= 8.0 Hz, 2H), 7.46 (d, *J*= 8.0 Hz, 2H), 4.47 (s, 2H), 2.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7, 184.3, 145.2, 143.6, 135.6, 134.6, 134.4, 131.9, 131.4 (q, J_{C-F}= 32.7 Hz), 130.4, 127.1, 126.5, 125.3 (q, J_{C-F}= 3.5 Hz) 124.0 (q, J_{C-F}= 272.2 Hz), 59.2; IR (KBr, cm^{-1}) 3476, 3075,2918, 1659,1581, 1447, 1403, 1347, 1302, 1180, 1113, 1046, 1001, 946, 768, 723; HRMS (EI) calcd for $C_{18}H_{11}F_3O_3$ 332.0660, found 332.0655.

(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl ethyl carbonate (4).

Yield 95%; R_f 0.29 (hexane/AcOEt= 3/1); yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.18-8.20 (m, 1H), 8.13-8.15 (m, 1H), 7.77-7.82 (m, two overlapping signals, 2H), 7.47-7.50 (m, two overlapping signals, 3H), 7.27-7.32 (m, two overlapping signals, 2H), 5.01 (s, 2H), 4.20 (q, *J*= 7.0 Hz, 2H), 1.30 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ184.4,

184.1, 154.6, 149.6, 138.7, 134.3, 134.2, 132.0, 132.0, 131.7, 129.6, 129.6, 128.3, 127.0, 126.6, 64.6, 62.0, 14.1; IR (KBr, cm^{-1}) 3325, 3078, 2987, 2931, 1772, 1649, 1581, 1458, 1379, 1244, 1064, 940, 738; HRMS (EI) calcd for $C_{20}H_{16}O_5$ 336.0998, found 336.0993.

Benzyl ((1,4-dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl) carbonate (5).

Yield 80%; R_f 0.34 (hexane/AcOEt= 3/1); yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.16-8.20 (m, 1H), 8.12-8.15 (m, 1H), 7.77-7.82 (m, two overlapping signals, 2H), 7.42-7.48 (m, two overlapping signals, 3H), 7.34-7.37 (m, three overlapping signals, 5H), 7.26-7.29 (m, two overlapping signals, 2H), 5.16 (s, 2H), 5.04 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4, 184.1, 154.5, 149.7, 138.7, 135.1, 134.3, 134.2, 132.1, 132.0, 131.7, 129.6, 129.5, 128.7, 128.5, 128.3, 127.0, 126.6, 70.1, 62.2; IR (KBr, cm^{-1}) 3432, 3053, 2963, 1748, 1659, 1581, 1447, 1381, 1336, 1236, 1079, 946, 745; HRMS (EI) calcd for $C_{25}H_{18}O_5$ 398.1154, found 398.1159.

Benzyl ((3-(4-methoxyphenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl) carbonate (6).

Yield 48%; R_f 0.31 (hexane/AcOEt= 3/1); orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14-8.17 (m, 1H), 8.11-8.14 (m, 1H), 7.74-7.80 (m, two overlapping signals, 2H), 7.32-7.39 (m, two overlapping signals, 5H), 7.24 (dt, J= 2.3, 9.0 Hz, 2H), 6.96 (dt, J= 5.0, 8.5 Hz, 2H), 5.18 (s, 2H), 5.07 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6,

184.1, 160.7, 154.6, 149.3, 137.9, 135.1, 134.2, 134.1, 132.0, 131.9, 131.4, 128.7, 128.5, 127.0, 126.5, 123.7, 113.8, 70.1, 62.6, 55.4; IR (KBr, cm^{-1}) 3309, 3075, 3031, 2952, 2830, 1748, 1670, 1604, 1503, 1437, 1391, 1336, 1236, 1158, 1024, 980, 945, 756; HRMS (EI) calcd for $C_{26}H_{20}O_6$ 428.1260, found: 428.1263.

Benzyl ((1,4-dioxo-3-(4-(trifluoromethyl)phenyl)-1,4-dihydronaphthalen-2-yl)methyl) carbonate (7).

Yield 20%; R_f 0.37 (hexane/AcOEt= 3/1); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15-8.19 (m, 1H), 8.11-8.15 (m, 1H), 7.76-7.81 (m, two overlapping signals, 2H), 7.40-7.48 (m, two overlapping signals, 3H), 7.33-7.37 (m, two overlapping signals, 4H), 7.25-7.30 (m, two overlapping signals, 2H), 5.16 (s, 2H), 5.04 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9, 183.6, 154.4, 148.2, 139.3, 135.3, 134.9, 134.6, 134.5, 131.8 (br, J_{C-F}= 12 Hz), 131.5 (q, J_{C-F}= 32.0), 123.0, 123.0, 128.9, 128.8, 128.8, 128.6, 128.6, 127.1, 127.1, 126.8, 126.8, 125.4 (br, J_{C-F}= 2.6 Hz), 123.9 (q, J_{C-F}= 273.4 Hz), 70.3, 61.8; IR (KBr, cm^{-1}) 3476, 3075, 2919, 1659, 1581, 1447, 1402, 1347, 1303, 1180, 1113, 1046, 1002, 946, 768, 723; HRMS (ESI) calcd for $C_{26}H_{17}F_3O_5$ 466.1028, found 466.0920.

(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl diphenylcarbamate (8).

Yield 12%; R_f 0.18 (hexane/AcOEt= 3/1); orange solid; mp 170.1-171.3 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (dd, *J*= 7.5, 9.0 Hz, 1H), 8.11 (dd, *J*= 1,5, 7.5 Hz, 1H), 7.75-7.81 (m, two

overlapping signals, 2H), 7.42-7.46 (m, two overlapping signals, 3H), 7.28-7.31 (m, two overlapping signals, 4H), 7.18-7.21 (m, three overlapping signals, 6H), 7.12 (dd, *J*= 1.5, 7.5 Hz, 2H), 5.03 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 184.1, 154.1, 149.4, 142.5, 139.5, 134.2, 134.1, 132.1, 132.0, 131.8, 129.6, 129.4, 129.0, 128.2, 127.0, 126.9, 126.5, 126.3, 60.3; IR (KBr, cm^{-1}) 3442, 3319, 3053, 3020, 2975, 1738, 1679, 1581, 1481, 1303, 1202, 1058, 980, 756; HRMS (EI) calcd for $C_{30}H_{21}NO_4$ 459.1471, found 459.1468.

(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl octadecylcarbamate (9).

Yield 21%; R_f 0.33 (hexane/AcOEt= 3/1); yellow solid; mp 99.5-100.2 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (dd, *J*= 3.0, 6.0 Hz, 1H), 8.13 (dd, *J*= 3.5, 6.5 Hz, 1H), 7.76-7.80 (m, two overlapping signals, 2H), 7.44-7.47 (m, two overlapping signals, 3H), 7.28 (d, *J*= 3.5 Hz, 2H), 4.95 (s, 2H), 4.58 (t, *J*= 5.0 Hz, 1H), 3.13 (dd, *J*= 7.0, 7.0 Hz, 2H), 1.46 (t, *J*= 6.5 Hz, 2H), 1.25 (s, 30H), 0.88 (t, *J*= 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 184.4, 155.7, 148.9, 140.2, 134.1, 134.1, 132.1, 132.1, 129.5, 129.4, 128.2, 126.9, 126.5, 59.4, 41.3, 32.1, 30.0, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 26.9, 22.8, 14.3; IR (KBr, cm^{-1}) 3320, 2919, 2852, 1703, 1648, 1537, 1459, 1313, 1247, 1146, 1079, 1035, 968, 768; HRMS (EI) calcd for $C_{36}H_{49}NO_4$ 559.3662, found 559.3666.

(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl benzoate (10).

Yield 76%; R_f 0.34 (hexane/AcOEt= 3/1); yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.19-8.22

(m, 1H), 8.15-8.19 (m, 1H), 7.95 (dd, *J*= 1.0, 8.0 Hz, 2H), 7.78-7.83 (m, two overlapping signals, 2H), 7.55 (tt, *J*= 1.3, 7.5 Hz, 1H), 7.40-7.44 (m, three overlapping signals, 5H), 7.29-7.32 (m, two overlapping signals, 2H), 5.19 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 184.2, 165.9, 149.5, 139.6, 134.3, 134.2, 133.3, 132.1, 132.0, 131.9, 129.8, 129.7, 129.5, 129.4, 128.5, 128.4, 127.0, 126.7, 59.5; IR (KBr, cm^{-1}) 3410, 2908, 2384, 1715, 1670, 1604, 1437, 1313, 1258, 1091, 701; HRMS (EI) calcd for $C_{24}H_{16}O_4$ 368.1049, found: 368.1050.

(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl 4-methylbenzoate (11).

Yield 53%; R_f 0.35 (hexane/AcOEt= 3/1); brown oil; ^{1}H NMR ($CDCl_3$) δ 8.20-8.22 (m, 1H), 8.15-8.19 (m, 1H), 7.84 (d, *J*= 8.5 Hz, 2H), 7.78-7.82 (m, two overlapping signals, 2H), 7.41-7.45 (m, two overlapping signals, 3H), 7.30-7.32 (m, two overlapping signals, 2H), 7.21 (d, *J*= 8.0 Hz, 2H), 5.17 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 184.2, 166.0, 149.5, 144.0, 139.8, 134.2, 134.2, 132.1, 132.0, 132.0, 129.9, 129.5, 129.5, 129.2, 128.3, 127.0, 127.0, 126.7, 59.4, 21.8; IR (KBr, cm^{-1}) 3053, 2930, 2863, 1715, 1670, 1603, 1295, 1268, 1258, 1104, 1102, 701; HRMS (EI) calcd for $C_{25}H_{18}O_4$ 382.1205, found 382.1212.

(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl (*tert*-butoxycarbonyl)-L-alaninate (12).

Yield 75%; R_f 0.31 (hexane/AcOEt= 3/1); yellow solid; ^{1}H NMR ($CDCl_3$) δ 8.15-8.20 (m, two overlapping signals, 2H), 7.79-7.83 (m, two overlapping signals, 2H), 7.45-7.50 (m, two overlapping signals, 3H), 7.27-7.31 (m, two overlapping signals, 2H), 5.06 (d, *J*= 11.0 Hz, 1H), 5.02 (d, *J*= 8.0 Hz, 1H), 4.94 (d, *J*= 11.0, 1H), 4.30 (m, 1H), 1.43 (s, 9H), 1.36 (d, *J*= 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.3, 184.0, 172.7, 155.1, 149.5, 139.0, 134.2, 134.2, 132.0, 131.9, 131.7, 129.6, 129.5, 128.3, 127.0, 126.5, 79.9, 59.8, 49.2, 28.4, 18.7; IR (KBr, cm^{-1}) 3420, 2351, 2083, 1659, 1492, 1447, 1303, 1158, 1058, 745; HRMS (EI) calcd for $C_{25}H_{25}NO_6$ 435.1682, found: 435.1757.

1,4-Dioxo-3-phenyl-1,4-dihydronaphthalene-2-carbaldehyde (13).

Yield 95%; R_f 0.31 (hexane/AcOEt= 3/1); orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (1H, s), 8.15 (dd, *J*= 2.0, 6.5 Hz, 1H), 8.14 (dd, *J*= 2.0, 6.5 Hz, 1H), 7.82 (dt, *J*= 7.0, 14.0 Hz, 1H), 7.81 (dt, *J*= 7.0, 14.0 Hz, 1H), 7.46-7.54 (m, two overlapping signals, 3H), 7.32 (dd, *J*= 1.5, 9.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 185.0, 182.9, 149.0, 136.1, 134.8, 134.4, 131.8, 131.7, 130.8, 130.7, 129.5, 128.3, 126.9, 126.6; IR (KBr, cm^{-1}) 3063, 3019, 2952, 2918, 2862, 1692, 1648, 1581, 1481, 1436, 1303, 1269, 1213, 1080, 1002, 890, 834, 768, 690; HRMS (EI) calcd for $C_{17}H_{10}O_3$ 262.0630, found 262.0632.

2-(Diazomethyl)-3-phenylnaphthalene-1,4-dione (14).

Yield 35%; R_f 0.43 (hexane/AcOEt= 3/1); red oil; ^{1}H NMR (500 MHz, $CDCl_3$)δ 8.13 (dd, *J*= 1.0, 7.5 Hz, 1H), 8.11 (dd, *J*= 1.5, 8.0 Hz, 1H), 7.76 (dt, *J*= 1.5, 13.5 Hz, 1H), 7.71 (dt, *J*= 1.0, 7.5 Hz, 1H), 7.45-7.49 (m, two overlapping signals, 2H), 7.39-7.43 (m, 1H), 7.27 (dt, *J*= 1.5, 6.5 Hz, 2H), 4.97 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.8, 180.7, 138.3, 134.5, 133.9, 132.9, 132.8, 132.0, 131.8, 129.9, 128.7, 128.6, 126.8, 126.3, 48.9; IR (KBr, cm−1) 3465, 3075, 2919, 2852, 2373, 2083, 1670, 1626, 1579, 1515, 1291, 1225, 1058, 768, 701; HRMS (EI) calcd for $C_{17}H_{10}O_2N_2$ 274.0742, found 274.0736.

Diphenyl ((1,4-dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl) phosphate (15).

Yield 65%; R_f 0.14 (hexane/AcOEt= 3/1); yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.20-8.13 (m, 2H), 7.81 (dd, *J*= 1.5, 4.5 Hz, 1H), 7.79 (dd, *J*= 1.5, 4.5 Hz, 1H), 7.44-7.48 (m, 1H), 7.40 (t, *J*= 8.0 Hz, 2H), 7.33 (t, *J*= 8.0 Hz, 4H), 7.25 (dd, *J*= 1.0, 8.0 Hz, 2H), 7.17-7.21 (m, three overlapping signals, 6H), 5.13 (d, *J*= 4.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 183.6, 150.5, 150.5, 149.7, 138.3, 138.3, 134.3, 134.2, 132.0, 131.9, 131.3, 129.9, 129.7, 129.6, 128.3, 127.0, 126.7, 125.5, 120.3, 120.2, 62.9 ($J_{C\text{-}P}$= 6 Hz); IR (KBr, cm^{-1}) 3465, 2919, 1670, 1592, 1447, 1291, 1202, 1024, 946, 745; HRMS (EI) calcd for $C_{29}H_{21}O_6P$ 496.1076, found 496.1148.

Dibutyl ((1,4-dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl) phosphate (16).

Yield 48%; R_f 0.14 (hexane/AcOEt= 3/1); yellow oil; ^{1}H NMR ($CDCl_3$) δ8.20-8.14

(m, 2H), 7.81 (dd, *J*= 1.5, 3.5 Hz, 1H), 7.80 (dd, *J*= 1.5, 3.5 Hz, 1H), 7.47-7.50 (m, two overlapping signals, 3H), 7.34 (dd, *J*= 2.0, 6.0 Hz, 2H), 4.88 (d, *J*= 5.0 Hz, 2H), 3.99-4.08 (m, 4H), 1.61-1.67 (m, 4H), 1.34-1.41 (m, 4H), 0.92 (t, *J*= 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 183.8, 149.3, 139.1, 139.0, 134.3, 134.2, 132.0, 132.0, 131.6, 129.7, 129.6, 128.3, 127.0, 126.6, 67.8 (J_{C-P}= 5.8 Hz), 61.4(J_{C-P}= 4.8 Hz), 32.3 (J_{C-P}= 6.9 Hz), 18.8, 13.8; IR (KBr, cm^{-1}) 3464, 2950, 2873, 1670, 1593, 1563, 1277, 992, 959, 894, 741; HRMS (EI) calcd for $C_{25}H_{29}O_6P$ 456.1702, found 456.1798.

(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl methanesulfonate (17).

Yield 95%; R_f 0.14 (hexane/AcOEt= 3/1); yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.07-8.13 (m, two overlapping signals, 2H), 7.72-7.78 (m, two overlapping signals, 2H), 7.44 (t, *J*= 3.0 Hz, 3H), 7.25-7.28 (m, two overlapping signals, 2H), 4.97 (s, 2H), 3.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 183.9, 150.6, 136.6, 134.6, 134.5, 132.0, 131.7, 131.1, 130.1, 130.0, 129.6, 129.6, 128.5, 127.2, 126.6, 64.5 (J_{C-S}= 7.5, 8.4 Hz), 37.5 (J_{C-S}= 3.9,12.0 Hz); IR (KBr, cm^{-1}) 3432, 3031, 2930, 2351, 1670, 1591, 1459, 1347, 1291, 1158, 1068, 990, 946, 834, 756; HRMS (EI) calcd for $C_{18}H_{14}O_5S$ 342.0562, found: 342.0635.

(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)methyl 4-methylbenzenesulfonate (18).

Yield 97%; R_f 0.26 (hexane/AcOEt= 3/1); yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.10-8.15 (m, two overlapping signals, 2H), 7.76-7.82 (m, two overlapping signals, 2H), 7.74 (d, *J*= 8.0 Hz, 2H), 7.42-7.49 (m, two overlapping signals, 3H), 7.31 (d, *J*= 8.0 Hz, 2H) 7.25-7.27 (m, two overlapping signals, 2H) 4.90 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 183.3, 150.2, 145.1, 136.9, 134.3, 134.3, 132.4, 131.9, 131.7, 131.1, 129.9, 129.7, 129.5, 128.3, 128.3, 127.0, 126.6, 64.0, 21.8; IR (KBr, cm^{-1}) 3320, 3063, 2918, 1670, 1603, 1458, 1358, 1291, 1190, 1102, 957, 834, 768, 734, 667; HRMS (EI) calcd for $C_{24}H_{18}O_5S$ 418.0875, found 418.0933.

1,2-Dihydro-5'H-spiro[benzo[h]benzofuro[3,2-f]chromene-3,6'-naphtho[1,2-b]benzofuran]-5'-one (19).

Yield 82%; R_f 0.45 (hexane/AcOEt= 3/1); yellow solid; mp 284.4-285.3 °C; ^{1}H NMR ($CDCl_3$) δ 8.43 (d, *J*= 2.0 Hz, 1H), 8.35 (d, *J*= 2.3 Hz, 1H), 8.02 (dd, *J*= 1.9, 4.0 Hz, 2H), 7.88 (d, *J*= 1.9 Hz, 1H), 7.72-7.75 (m, two overlapping signals, 2H), 7.59-7.65 (m, two overlapping signals, 3H), 7.51 (t, *J*= 2.0 Hz, 1H), 7.45 (dd, *J*= 2.0, 4.4 Hz, 2H), 7.35 (dd, *J*= 2.0, 4.4 Hz, 2H), 7.17 (t, *J*= 1.9 Hz, 1H), 3.50-3.55 (1H, c), 3.36-3.55 (c, 1H), 2.70-2.77 (c, 1H), 2.45 (dd, *J*= 1.4, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 156.4, 155.8, 147.9, 146.5, 144.9, 135.1, 130.5, 129.0, 128.9, 128.2, 126.4, 125.9, 125.7, 125.7, 124.7, 123.9, 122.7, 122.6, 121.7, 121.4, 120.9, 120.8, 119.9, 117.6, 112.0, 109.6, 80.2,

29.2, 19.5; IR (KBr, cm^{-1}) 3063, 2908, 2840, 2339, 1692, 1581, 1437, 1359, 1281, 1202, 1046, 934, 756; HRMS (DART) calcd for $C_{34}H_{20}O_4$ 492.1362, found 492.1443; X-ray crystallographic analysis CCDC2179533.

8. X-ray structural characterization of 19.

Compound **19** was crystallized from Methanol.

Empirical Fomula	$C_{34}H_{20}O_4$
Formula Weight	492.14
Crystal Color, Habit	Yellow, bulk
Crystal Dimensions	0.08 × 0.06 × 0.01
Crystal System	Triclinic
Lattice Type	Primitive
Lattice Parameters	a= 9.0375(3) Å b= 9.9759(3) Å c= 14.9438(4) Å V= 1260.62(8) $Å^3$
Space Group	P-1
Z value	1
D_{cal}	1.408 g/cm^3
F_{000}	554
μ (MoKa)	0.095 mm^{-1}
Z value	1
D_{cal}	1.408 g/cm^3
Correction	Reported T Limits: Tmin=0.839 Tmax=1.000
Radiation	MoKα (λ= 0.71075)
Temperature	103 K
No. of Reflections Measured	Total: 17631 Unique: 4598 (R_{int}= 0.0392)
Reflection/Parameter Ratio	11.97
Residues: R1 (I > 2.00s(I))	R_1= 0.0483

Residues: R (All reflections)	R= 0.0658
Residues: wR2 (All reflections)	wR_2= 0.1267
Maximum peak in Final Diff. Map	e•$Å^{-3}$ 0.57

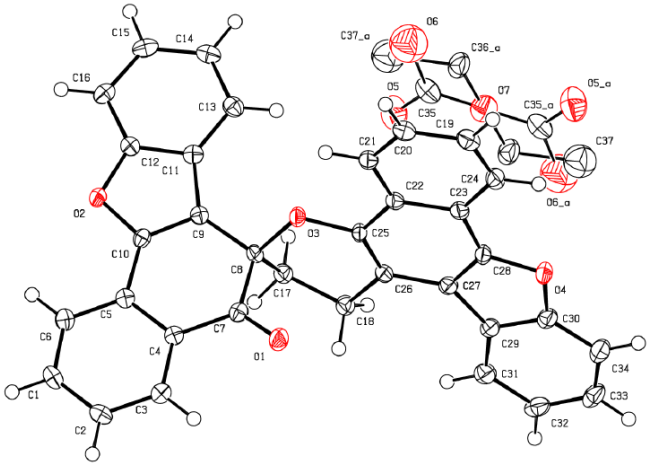
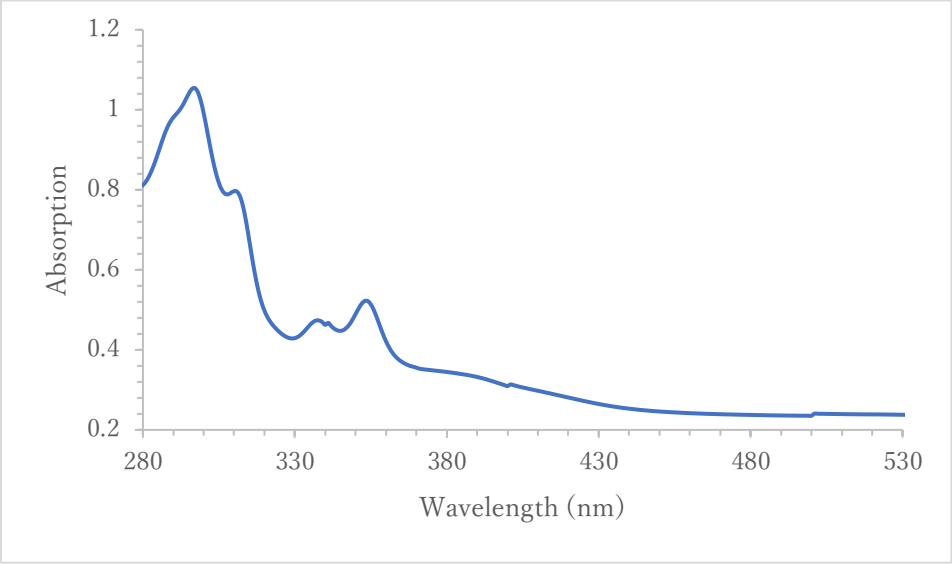


Figure. ORTEP representation of **19**

9. uv spectrum of 19 (50 uM in methanol).



Acknowledgements

Foremost, I would like to express my sincere gratitude to my supervisor Prof. Tsuyoshi for the continuous support of my Ph.D study and research, for his encouragement, motivation and patience.

I would like to express my appreciation and gratitude to my direct supervisor, Assoc. Prof. Tsumoru Morimoto for his continuous guidance, excellent discussion, and technical assistance during my study.

I would like to thank Prof. Hiroko Yamada and Prof. Hiroharu Ajiro as doctoral advisory committee members for their valuable discussion and suggestion. I am very thankful to Assoc. Prof. Hiroki Tanimoto for his great help and valuable advice for my work.

I would like to express my sincere gratitude Prof. Kiyomi Kakiuchi as a former Head of Synthetic Organic Chemistry Laboratory for offering me the opportunity to study in NAIST, giving me guidance and continuous support for this research.

And I would like to express my thankful to all the students and member in the former Synthetic Organic Chemistry Laboratory and the Photonic and Reactive Molecular Science Laboratory.

My sincere also goes to Dr. Marine Louis for giving me encouragement, and suggestions for life and the future.

I also would like to thank Leigh McDowell who give me lots of help and suggestion for the English writing.

My thank also goes to my lovely friend in NAIST, Pablo Reine Diaz, Tan Leeyae, Chan Kok Sim, Kamolchanok Sarisuta, Beta Achromi Nurohmah, Yangyang Zhou, Jinyu Hao, Xin Zhao, Yuanyu Zhang, Menghua Shi. I appreciate their supporting and love.

Finally, I would like to give special thanks to my parents, sisters, friends and all relatives in China for their selfless love and support and for being my solid backing.