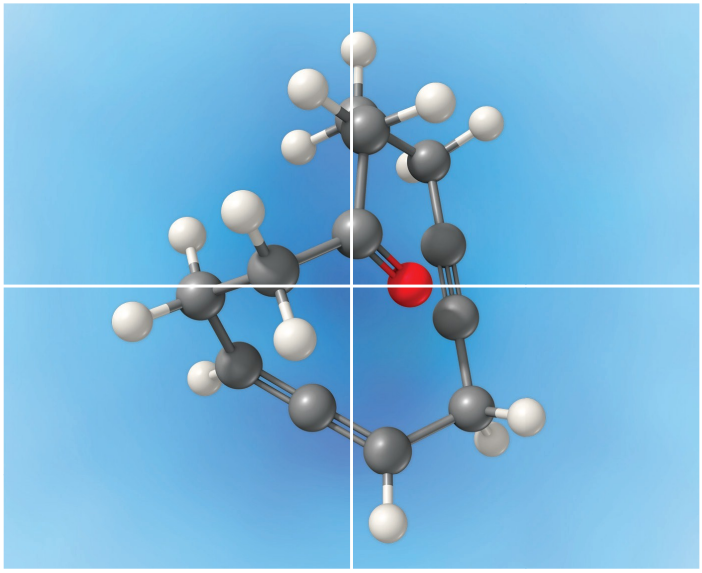
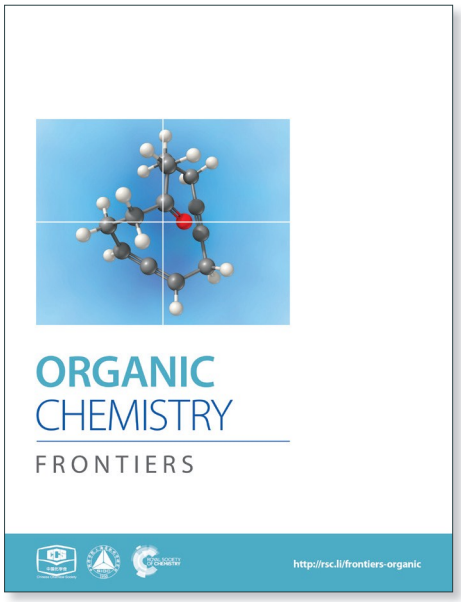
ORGANIC CHEMISTRY

FRONTIERS



Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Journal Name

COMMUNICATION

A Photo-induced C-C Bond Formation Methodology to Construct Tetrahydrofluorenones and Related Structures

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Shujun Cai, [a] Zheming Xiao, [a] Jinjie Ou, [a] Yingbo Shi [a] and Shuanhu Gao [a,*]

A metal-free, photo-induced C-C bond formation methodology was developed to construct tetrahydrofluorenones and related structures. This mild and efficient method proceeds either through an electrocyclization or a radical cyclization from β-Cl or β-Br aryl vinyl ketone. We believe this method is particularly useful for synthesizing of related tetrahydrofluorenones containing natural products.

The naturally occurring fluorenones were discovered from various natural sources including plants, fungus and bacteria. This family of natural products contain the similar core units of fluorenone,[1] azafluorenone[2] or hydrofluorenone. Regarding to the core structures of hydrofluorenone, this group of natural molecules could be furtherly divided into subgroups of tetrahydro-, hexahydro- and decahydro-fluorenones. As shown in the figure 1, the representatives of fluorenone, azafluorenone or hydrofluorenone containing natural products demonstrate diverse and challenging chemical structures. Together with potential bioactivities, this family of natural products aroused considerable attention from synthetic chemists. For instance, the core skeleton of kinamycins[3] and lomaiviticins[4] could be considered as the derivatives of tetrahydrofluorenones. The chemical synthesis and biological studies of these bacterial metabolites involved several research groups in the past decades.[5] Selective and efficient constructions of the core hydrofluorenone rings is the key to synthesizing these molecules. The frequently used strategies to install these hydrofluorenone units may be the cyclopentanone ring formation, wherein a series of Friedel-Crafts reaction,[3i, 3j, 6] metal-catalyzed coupling reactions[3k, 3l] were applied to execute the intramolecular cyclization. However, these reactions require harsh conditions that cannot tolerate the sensitive functional groups in most cases. Therefore, it's still necessary to develop new methodologies to achieve the same goal in mild reaction conditions.

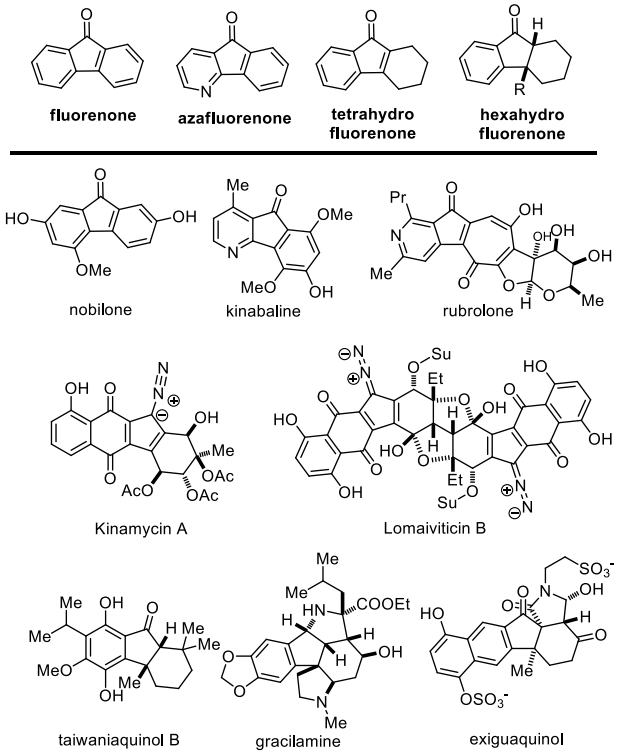


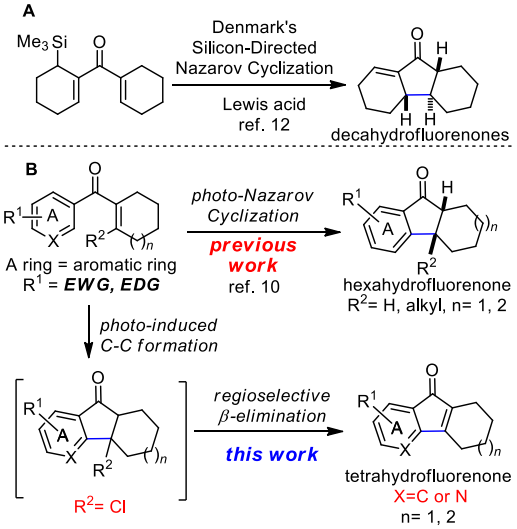
Figure 1. Representatives of fluorenone, azafluorenone or hydrofluorenone containing natural products.

The Nazarov reaction is one of the most effective methods for building the cyclopentenone rings through a 4-π-electron cyclization followed by protonation.[7] However, the acid promoted electrocyclization of aromatic vinyl ketones to construct indanones, hexahydrofluorenones and related skeletons always requires the use of strong acids and high

[a] Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, 3663N Zhongshan Road, Shanghai 200062, China,
Email: shgao@chem.ecnu.edu.cn

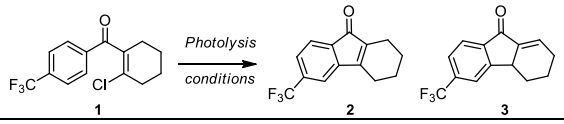
Electronic Supplementary Information (ESI) available: [experimental procedures, Characterization data]. See DOI: 10.1039/x0xx00000x

temperature. In contrast to the conventional acid mediated Nazarov reaction, the photo-Nazarov reaction of vinyl aryl ketones provides a mild and reliable method to prepare hydrofluorenones. The pioneer studies of the photo-Nazarov reaction was reported by Smith and Agosta in 1973.[8] Mechanistic studies of this reaction were investigated by the group of Leitich and Schaffner.[9] During our synthesis of hydrofluorenone containing natural products, we systematically studied the photo-Nazarov reaction of various aryl vinyl ketones (Scheme 1B).[10] We found that this mild photolytic electrocyclization proceeds in the neutral or basic conditions to give hexahydrofluorenones and corresponding polycyclic rings efficiently. The photo-Nazarov reaction is particularly useful for preparing the core hexahydrofluorenone that are not easily accessible by the traditional acid-promoted methods. We have successfully applied this mild photo-Nazarov reaction in the synthesis of taiwaniaquinol B[10] and gracilamine.[11a] Further investigation of the synthesis of this family of natural molecules, we hope to construct the tetrahydrofluorenones and related structures through the same electrocyclization process by adding a leaving group (R^2=Cl) at the β position of the aryl vinyl ketones (Scheme 1B). We assumed that photolysis of these substrates may undergo the electrocyclization followed by a rapid regioselective β elimination to form the desired tetrahydrofluorenones. This rational design is inspired by the elegant work developed by Denmark and co-workers to efficiently construct the decahydrofluorenones through the silicon-directed Nazarov reaction (Scheme 1A).[12]



Scheme 1. Photo-Nazarov reaction and proposed photo-induced C-C formation reaction.

To test this synthetic hypothesis, we prepared substrate **1** with a β–Cl group on the aryl vinyl ketone as a leaving group, which is compatible to the model substrate used in the condition screening of the photo-Nazarov reaction. Irradiating a solution of **1** (2.0 mg/mL) in degassed 1,2-dichloroethane with UV-light at 254 nm for 2 h gave the desired product **2** in 45% yield and its regioisomer **3** in 29% yield (Table 1, entry 1). We postulated that the photo-induced electrocyclization of **1** lead the formation of an unstable intermediate which underwent a fast elimination to give **2** and release volatile HCl. This tetrahydrofluorenone **2** may be photoactive and further activated by UV light to undergo the isomerization and yield **3** under the acid condition. In order to restrain the photo-isomerization of **2**, we explored the photolysis under basic conditions by adding stoichiometric amount (2 μL/mL) of Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) diisopropylamine ($^iPr_2NH$) and 2,2,6,6-tetramethylpiperidine (TMP) to neutralize the *in situ* formed HCl (Table 1, entries 2–6). We observed that the only desired products **2** was detected under these basic photolysis conditions except the condition with TMP as base. Notably, photolysis of **1** in presence of $^iPr_2NH$ gave 64% isolated yield at room temperature. We envisioned that a hydrogen bonding between the $^iPr_2NH$ and carbonyl group of **2** may stabilize the enone group and effectively restrain the photo-isomerization. Encouraged by this result, we explored photolysis of **1** with $^iPr_2NH$ in various solvent including acetonitrile, methanol, acetone, ether, dichloromethane and chloroform (Table 1, entries 8–13). It was found that performing this reaction in dichloromethane and chloroform gave similar result with 1,2-dichloroethane, and other solvent system either lead the decomposition of substrate **1** or formed the product in very low yield. The reaction can also be done by irradiating with longer wavelength (300 or 366 nm) UV-light (Table 1, entries 14-17) at the expense of reaction time. The reaction yield was improved slightly by using degassed solvent; increasing the concentration to 4 mg/mL gave **2** in 79% yield (entry 18).



Entry	λ [nm]	solvent	degassed[a]	base (2 μL/mL)	Con. (mg/mL)	Time	Yield of **2**[b]	Yield of **3**[b]
1	254	$ClCH_2CH_2Cl$	Yes	--	2	2 h	45%	29%
2	254	$ClCH_2CH_2Cl$	Yes	Et_3N	2	1.5 h	38%	–
3	254	$ClCH_2CH_2Cl$	Yes	DBU	2	1.5 h	38%	–
4	254	$ClCH_2CH_2Cl$	Yes	TMEDA	2	1.5 h	13%	–
5	254	$ClCH_2CH_2Cl$	Yes	$^iPr_2NH$	2	1.5 h	67% (64%)[c]	–
6	254	$ClCH_2CH_2Cl$	Yes	TMP	2	1.5 h	48%	10%
7	254	$ClCH_2CH_2Cl$	No	$^iPr_2NH$	2	1 h	61% (62%)[c]	–
8	254	CH_3CN	No	$^iPr_2NH$	2	1 h	6%	–
9	254	CH_3OH	No	$^iPr_2NH$	2	1 h	N.D.[d]	
10	254	CH_3COCH_3	No	$^iPr_2NH$	2	1 h	decomposed	
11	254	Et_2O	No	$^iPr_2NH$	2	1 h	decomposed	
12	254	CH_2Cl_2	No	$^iPr_2NH$	2	1 h	56%	–
13	254	$CHCl_3$	No	$^iPr_2NH$	2	1 h	51%	–
14	300	$ClCH_2CH_2Cl$	Yes	–	2	2.5 h	13%	35%
15	300	$ClCH_2CH_2Cl$	Yes	$^iPr_2NH$	2	2.5 h	45%	–
16	366	$ClCH_2CH_2Cl$	Yes	–	2	3.0 h	44%	21%
17	366	$ClCH_2CH_2Cl$	Yes	$^iPr_2NH$	2	3.0 h	82% (72%)[c]	–
18	254	$ClCH_2CH_2Cl$	Yes	$^iPr_2NH$[e]	4	2.0 h	79%	–

Table 1. Condition screening of photo-induced C–C bond formation [a] The solvents was degassed by bubbling nitrogen through the solution for 0.5 h. [b] All were determined by 1H NMR crude analysis using CH_2Br_2 as an internal standard, unless noted. [c] All were purified by silica gel column chromatography to give product. [d] Not detected. [e] The concentration is 4 μl/mL.

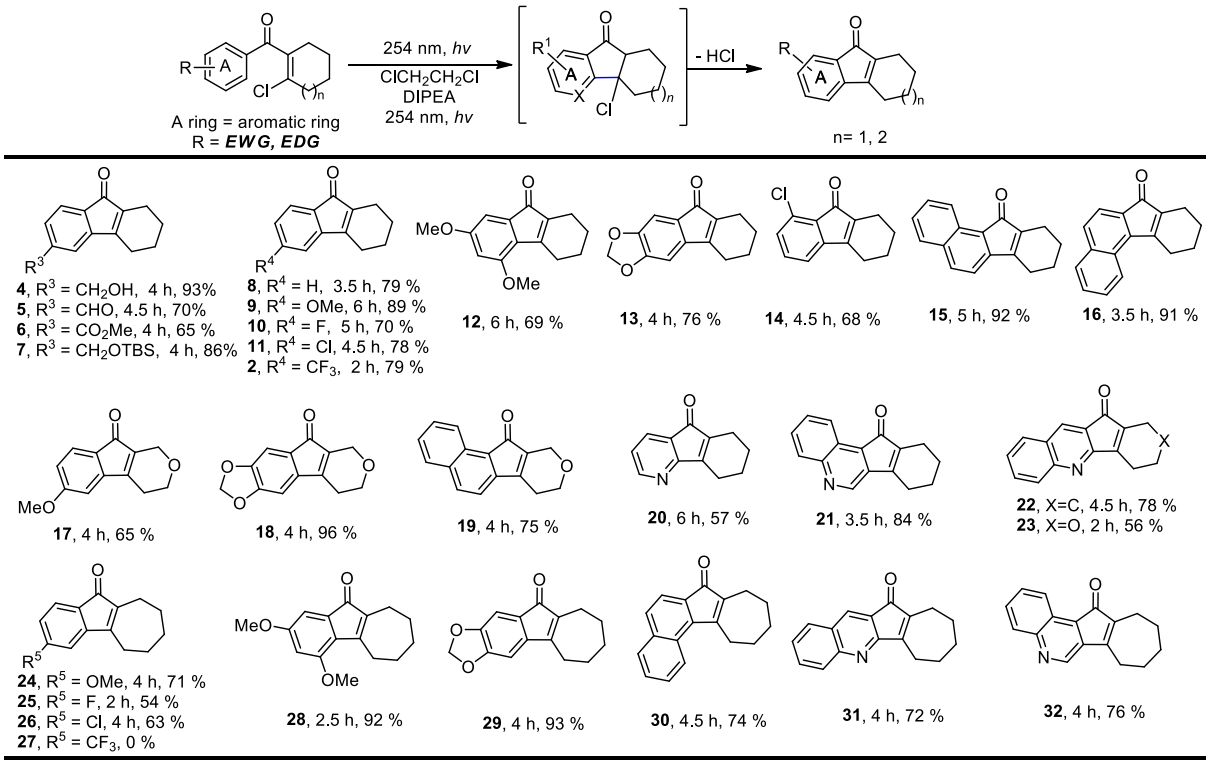


Table 2. Reaction scope of photo-induced C-C bond formation of substrates with a β-Cl group on aryl vinyl ketones

We then investigated the scope of this photo-induced C–C bond formation to construct tetrahydrofluorenone under the optimized conditions with respect to the functional-group tolerance, aromatic ring compatibility, cycloalkene ring size. To our delight, this mild photolysis tolerated substrates with hydroxyl- (**4**, Table 2), aldehyde (**5**) and ester functional groups (**6**) and acid-sensitive protecting groups such as tert-butyldimethylsilyl ether (OTBS) (**7**) producing the corresponding tetrahydrofluorenone in good yields. We then surveyed the electron density of aromatic rings and observed that both electron-donating (OMe-, -CH_2OCH_2-) and -withdrawing substituted groups (F-, Cl-, CF_3-) on the phenyl rings (**9**–**14**) worked well in the photolysis. The desired electrocyclized products were obtained in acceptable yields. Photolysis of substrates with naphthyl groups smoothly yielded the desired cyclized products in excellent yield (**15** and **16**). When changing the cyclohexenyl ring to the unsaturated pyran ring, the electrocyclization was also applicable and the desired polycyclic rings (**17**–**19**) were achieved in acceptable yields. We also investigated substrates containing hetero-aromatic rings including pyridine and quinoline in this photolysis. We were pleased to find that these substrates reacted efficiently and installed tetrahydroazafluorenone (**20**) and the corresponding heteroaromatic cycles (**21**-**23**) in good yields. We also studied the ring size of the cycloalkene ring. In accordance with the photo-Nazarov reaction, the cyclohexene could only be replace by cycloheptene ring and corresponding clopentenyl and cyclooctenyl phenyl ketones failed to give the electrocyclization products under the optimized photolytic condition. Aromatic rings with electron-donating groups such as -OMe (**24** and **28**), -CH_2OCH_2- (**29**), naphthyl (**30**), and electron-rich heteroaromatic rings (**31** and **32**) facilitated electrocyclization and furnished the desired cyclized products in good yields. Substrates with substituted halogens like –F (**25**) and –Cl (**26**) also worked and formed the corresponding products in moderate yield. Notably, the strong electron-withdrawing group trifluoromethyl on phenyl ring (**27**) lead the substrate inert under the photolysis. The structures of the photo reaction products were determined unambiguously by using X-ray crystallographic analysis of **2**, **7**, **13** and **25** (Figure 2). Based on the reaction scope study, we concluded that the reactivity of the substrates with a β-Cl group on aryl vinyl ketones are totally agree with those used in the photo-Nazarov reactions.[10] We considered that these reactions further support our originally proposed reaction process and also provide a platform for preparing related tetrahydrofluorenones.

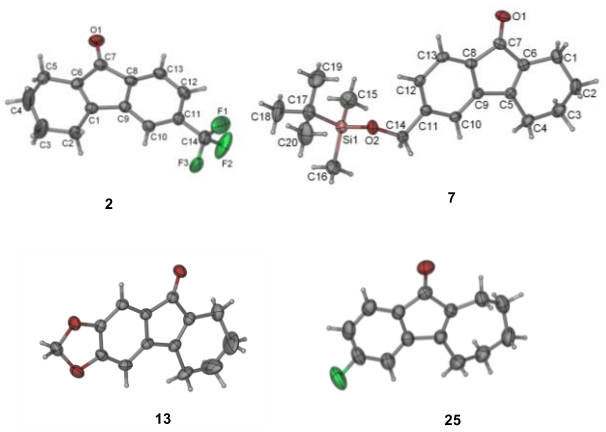


Figure 2. X-ray structures of **2**, **7**, **13** and **25**.

In order to solve the limitation of this photo-induced electrocyclization and expand the reaction scope, we decided to examine the photolysis using substrates bearing a β-Br group on aryl vinyl ketones. Instead of the photolytic electrocyclization, we realized that a photo-induced homolysis of C-Br bond may occur on these substrates to produce vinyl radicals which may undergo a fast radical cyclization to furnish the desired tetrahydrofluorenones.[13,14] To test this hypothesis, we selectively prepared some substrates related to those shown in table 2 and investigated their photolysis. To our delight, irradiating of these substrates using the optimized condition smoothly gave the same cyclized products in even better yields (Table 3). We observed that these photolysis proceed with a faster reaction rate in most cases which demonstrate the intramolecular radical cyclizations are favourable for the ring closure. We also prepared the β-Br substrate with trifluoromethyl group on phenyl ring. Remarkably, we found photolysis of this substrate efficiently gave the desired product **27** in 69% yield which was not achieved using the related β-Cl substrate. We believe that this photo-induced intramolecular radical cyclization is a beneficial supplement of the photo-induced electrocyclization. An effective combination of these two photolytic strategies may provide a reliable solution for synthesizing a variety of natural products and their derivatives.

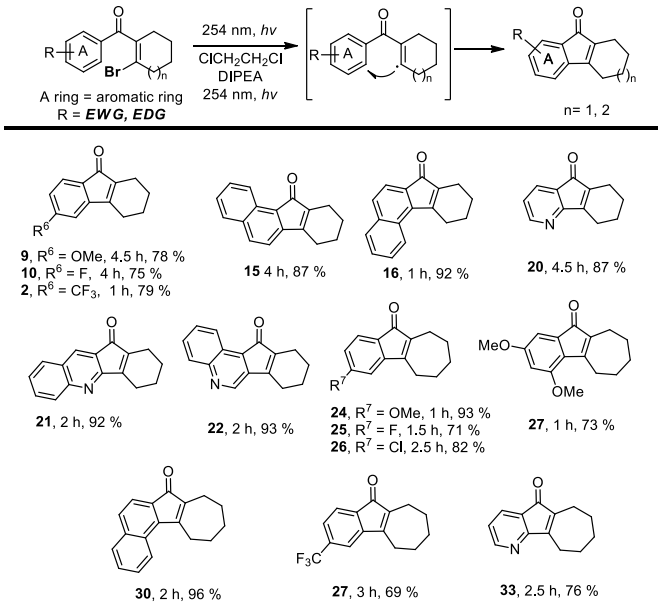


Table 3. Photolysis of various β-bromo aryl vinyl ketones.

In conclusion, we developed a metal-free, photo-induced C-C bond formation methodology to construct tetrahydrofluorenones and related structures based on our previously reported photo-Nazarov reaction. This mild photolysis proceeds either through an electrocyclization or a radical cyclization from a β-Cl or β-Br aryl vinyl ketone. We systematically studied the reaction conditions and scope with respect to the functional groups tolerance and properties of aromatic rings. Based on these results, we believe this method is particularly useful for synthesizing of tetrahydrofluorenones and related structures. We are currently studying the applications of this methodology in natural products synthesis.

Acknowledgment

We thank the National Natural Science Foundation of China (21272076, 21422203), the Qi Ming Xing Foundation of Shanghai Ministry of Science and Technology (14QA1401400), the program for professor of special appointment (Eastern Scholar) at Shanghai institutions of higher learning, Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT) and Program for New Century Excellent Talents in University (NCET-13-0199) for generous financial support.

References

1 For isolation of nobilone, see: X. Zhang, J. Xu, J. Wang, N. Wang, H. Kurihara, S. Kitanaka, X. Yao, *J. Nat. Prod.* 2007, **70**, 24–28.
2 For isolation of kinabaline, see: (a) D. Tadić, B. K. Cassels, M. Lcboeuf, A. Cavé, *phytochemistry* 1987, **26,** 537–541. (b) For isolation of Rubrolone, see: W. Schuep, J. F. Blount, T. H. Williams, A. Stempel, *J. Antibiot*. 1978, **31**, 1226.
3 For the isolation of kinamycins, see: (a) S. Ito, T. Matsuya, S. Ōmura, M. Otani, A. Nakagawa, *J. Antibiot.* 1970, **23**, 315–317. (b) T. Hata, S. Ōmura, Y. Iwai, A. Nakagawa, M. Otani, *J.*

Antibiot. 1971, **24**, 353–359. (c) S. Ōmura, A. Nakagawa, H. Yamada, T. Hata, A. Furusaki, T. Watanabe, *Chem. Pharm. Bull.* 1971, **19**, 2428–2430. (d) S. Ōmura, A. Nakagawa, H. Yamada, T. Hata, A. Furusaki, *Chem. Pharm. Bull.* 1973, **21**, 931–940. (e) M. C. Cone, P. J. Seaton, K. A. Halley, S. J. Gould, *J. Antibiot.* 1989, **42**, 179–188. (f) K. Isshiki, T. Sawa, H. Naganawa, N. Matsuda, S. Hattori, M. Hamada, T. Takeuchi, M. Oosono, M. Ishizuka, Z. Yang, B. Zhu, W. Xu, *J. Antibiot.* 1989, **42**, 467–469. (g) P. J. Seaton, S. J. Gould, *J. Antibiot.* 1989, **42**, 189–197. (h) T. A. Smitka, R. Bonjouklian, T. J. Perun, A. H. Hunt, R. S. Foster, J. S. Mynderse, R. C. Yao, *J. Antibiot.* 1992, **45**, 581–583. For synthesis of kinamycins, see: (i) X. Lei, J. A. Porco, *J. Am. Chem. Soc.* 2006, **128**, 14790–14791. (j) S. S. Scully, J. A. Porco, *Angew. Chem. Int. Ed.* 2011, **50**, 1–6. (k) K. C. Nicolaou, H. Li, A. L. Nold, D. Pappo, A. Lenzen, *J. Am. Chem. Soc.* 2007, **129**, 10356–10357. (l) C. M. Woo, L. Lu, S. L. Gholap, D. R. Smith, S. B. Herzon, *J. Am. Chem. Soc.* 2010, **132**, 2540–2541.

4 For isolation of lomivitaicins, see: (a) H. He, W. D. Ding, V. S. Bernan, A. D. Richardson, C. M. Irel, M. Greenstein, G. A. Ellestad, G. T. Carter, *J. Am. Chem. Soc.* 2001, **123**, 5362–5363. (b) C. M. Woo, N. E. Beizer, J. E. Janso, S. B. Herzon, *J. Am. Chem. Soc.* 2012, **134**, 15285–15288. For synthesis of lomivitaicins, see: (c) W. Zhang, A. Baranczak, G. A. Sulikowski, *Org. Lett.*, 2008, **10**, 1939–1941. (d) K. C. Nicolaou, A. L. Nold, H. Li, *Angew. Chem., Int. Ed.*, 2009, **48**, 5860–5863. (e) E. S. Krygowski, K. Murphy-Benenato, M. D. Shair, *Angew. Chem., Int. Ed.* 2008, **47**, 1680–1684. (f) H. G. Lee, J. Y. Ahn, A. S. Lee, M. D. Shair, *Chem.–Eur. J.* 2010, **16**, 13058–13062. (g) S. B. Herzon, L. Lu, C. M. Woo, S. L. Gholap, *J. Am. Chem. Soc.* 2011, **133**, 7260–7263.

5 For the reviews of kinamycins , lomivitaicins see: (a) S. J. Gould, *Chem. Rev.* 1997, **97**, 2499–2510. (b) J. Marco-Contelles, M. T. Molina, *Curr. Org. Chem.* 2003, **7**, 1433–1442. (c) C. C. Nawrat, C. J. Moody, *Nat. Prod. Rep.* 2011, **28**, 1426–1444. (d) S. B. Herzon, A. M. Woo, *Nat. Prod. Rep.* 2011, **29**, 87–118.

6 E. Pan, S. Cao, P. J. Brodie, M. W. Callmander, R. Randrianaivo, S. Rakotonandrasana, V. E. Rasamison, K. TenDyke, Y. Shen, E. M. Suh, D. G. I. Kingston *J. Nat. Prod*. 2011, **74**, 1169–1174.

7 (a) I. N. Nazarov, I. I. Zaretskaya, *Izv. Akad. Nauk. SSSR Ser. Khim.* 1941, 211–224. For reviews of Nazarov reaction, see: (b) K. L. Habermas, S. E. Denmark, T. K. Jones, *Org. React.* 1994, **45**, 1 – 158. (c) C. Santelli-Rouvier, M. Santelli, *Synthesis* 1983, 429– 442. (d) *Comprehensive Organic Synthesis*, Vol. 5, (Eds.: S. E. Denmark, B. M. Trost, I. Fleming), Pergamon, Oxford, 1991, pp. 751. (e) A. J. Frontier, C. Christina, *Tetrahedron* 2005, **61**, 7577 –7606. (f) H. Pellissier, *Tetrahedron* 2005, **61**, 6479 – 6517. (g) M. A. Tius, *Eur. J. Org. Chem.* 2005, 2193 – 2206. (h) N. Nakanishi, F. G. West, *Curr. Opin. Drug Discovery Dev.* 2009, **12**, 732. (i) N. Shimada, C. Stewart, M. A. Tius, *Tetrahedron* 2011, **67**, 5851– 5870. (j) T. Vaidya, R. Eisenberg, A. J. Frontier, *ChemCatChem* 2011, **3**, 1531 –1548.

8 A. B. Smith III, W. C. Agosta, *J. Am. Chem. Soc.* 1973, **95**, 1961– 1968.

9 (a) J. Leitich, I. Heise, S. Werner, C. Kr_ger, K. Schaffner, *J. Photochem. Photobiol. A* 1991, **57**, 127 –151. (b) J. Leitich, I. Heise, J. Rust, K. Schaffner, *Eur. J. Org. Chem.* 2001, 2719 – 2726.

10 S. Cai, Z. Xiao, Y. Shi, S. Gao *Chem.-Eur. J.* 2014, **20**, 8677–8681.

11 (a) Y. Shi, B. Yang, S. Cai, S. Gao, *Angew. Chem. Int. Ed.* 2014, **53**, 9539–9543. For others applications; see: (b) S. Gao, Q. Wang, L. Lum, C. Chen, *J. Am. Chem. Soc.* 2010, **132**, 371 – 383. (c) S. Gao, Q. Wang, C. Chen, *J. Am. Chem. Soc.* 2009, **131**, 1410 –1412. (d) F. Churruca, M. Fousteris, Y. Ishikawa, M. von Wantoch Rekowski, C. Hounsou, T. Surrey, A. Giannis, *Org. Lett.* 2010, **12**, 2096 –2099.

12 (a) S. E. Denmark, T. K. Jones, *J. Am. Chem. Soc.* 1982, **104**, 2642-2645. (b) T. K. Jones, S. E. Denmark, *Helv. Chim. Acta* 1983, **66**, 2377– 2396. (c) S. E. Denmark, R. C. Klix, *Tetrahedron* 1988, **44**, 4043 –4060. (d) S. E. Denmark, M. A. Wallace, C. B. Walker, *J. Org. Chem.* 1990, **55**, 5543 –5545.

13 J. N. Moorthy, S. Samanta, *J. Org. Chem.* 2007, **72**, 9786–9789.

14 T. Bach and J. P. Hehn, *Angew. Chem. Int. Ed*. 2011, **50**, 1000 – 1045.