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Photochemistry

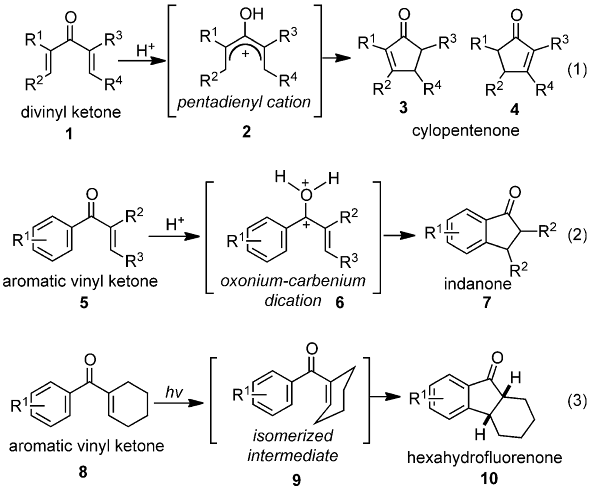
The Photo-Nazarov Reaction: Scope and Application

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

Abstract: The reaction conditions and scope of the photo-Nazarov reaction of aryl vinyl ketones were investigated. In contrast to the conventional acid-catalyzed methods, this photolytic electrocyclization proceeds in the neutral or basic conditions. Irradiating substrates bearing various aromatic rings, acid-sensitive groups, cyclohexenyl, cycloheptenyl, and unsaturated pyran with UV-light (254 nm) smoothly yielded hexahydrofluorenones and related structures. This photo-Nazarov reaction could also be applicable to the substrates carrying β-alkyl groups on the enone, which gave corresponding polycyclic rings containing quaternary centers. These photo-electrocyclized products may prove useful for synthesizing a variety of natural products and their derivatives. Further application of this mild photo-Nazarov reaction in the synthesis of taiwaniaquinol B was achieved.

Introduction

The Nazarov reaction is one of the most effective methods for constructing the cyclopentenone group,[1] a common structural subunit of small molecules. Typically in this method, divinyl ketone **1** is treated with Lewis or Brønsted acids to give a pentadienyl cation **2**, which undergoes 4-π-electron cyclization followed by protonation to yield the cylopentenone **3** or **4** ([Eq. (1)], Scheme 1).[2] This reaction has been extensively studied[3] and applied to natural product synthesis[4] over the years. The electrocyclization of aromatic vinyl ketones proceeds through a different process than the classical Nazarov reaction. In 1997, Ohwada and co-workers reported the superacid-mediated cyclization of 1-phenyl-2-propen-1-ones (**5**) to indanones (**7**) ([Eq. (2)], Scheme 1).[5] They demonstrated that this electrocyclization involves an oxonium–carbenium dication species **6**, consistent with ab initio calculations. This mechanistic work explained why the Nazarov cyclization of aromatic vinyl ketones always requires the use of strong acids and high temperature. Therefore, it is particularly challenging to use the Nazarov cyclization to construct indanones, hexahydrofluorenones, polycyclic heteroaromatic structures, and related skeletons.



Scheme 1. Nazarov reactions.

An important step towards the synthesis of such skeletons came in 1973, when Smith and Agosta reported the photo-Nazarov reaction of aryl vinyl ketones ([Eq. (3)], Scheme 1).[6] Mechanistic studies by the group of Leitich and Schaffner revealed that selective photolytic activation of the enone group leads to formation of the highly active isomerized intermediate **9**, which induces the electrocyclization to hexahydrofluorenone **10**.[7] According to these mechanistic studies, we considered that the cycloalkene ring is required and crucial to this photolysis, which generates the unusual *trans*-olefin in a cyclohexene ring and facilitates the electrocyclization due to a more favorable orbital overlap. For the substrates bearing the acyclic alkenes, this photolytic activation will just lead the isomerization of *Z*/*E* configuration. In contrast to the conventional acid-catalyzed methods, this photolytic electrocyclization proceeds under neutral or basic conditions, and has been successfully used in the substrates with acid-sensitive groups during our syntheses of Nakiterpiosion (**11**) and Nakiterpiosinone (**12**) (Figure 1).[8]

Furthermore, the hydrofluorenone motif frequently exists in bioactive-containing natural products, including *abeo*-abietane

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[a] S. Cai, Z. Xiao, Y. Shi, Prof. Dr. S. Gao
Shanghai Key Laboratory of Green Chemistry and Chemical Processes
Department of Chemistry, East China Normal University
3663N Zhongshan Road, Shanghai 200062 (P.R. China)
Fax: (+86) 21-62604784
E-mail: shgao@chem.ecnu.edu.cn

[b] Prof. Dr. S. Gao
State Key Laboratory of Bioorganic and Natural Products Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (P.R. China)

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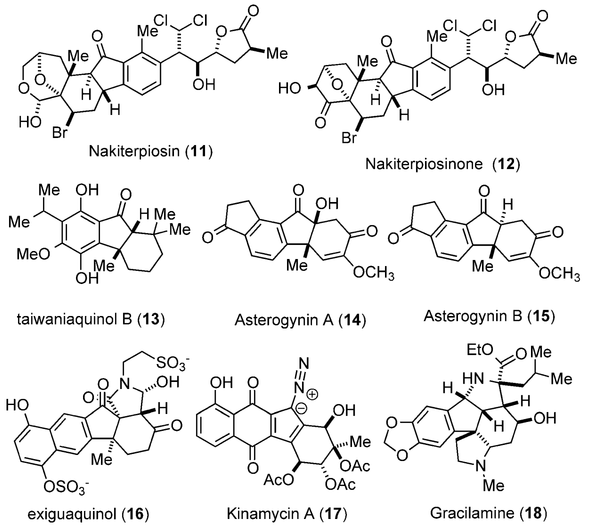


Figure 1. Hydrofluorenone-containing natural products.

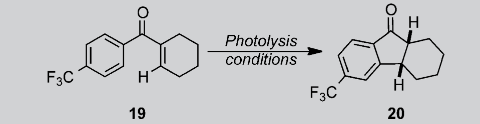
diterpenoids (taiwaniaquinoid B (**13**)),[9] Asterogynin A (**14**),[10] B (**15**),[10] and exiguaquinol (**16**).[11] Structurally related alkaloids, kanamycin A (**17**)[12] and gracilamine (**18**),[13] could also be easily derived from corresponding hydrofluorenone cores.

We believe that the photo-Nazarov reaction is a beneficial supplement of the conventional Nazarov reaction. We systematically investigated the reaction conditions and scope of the photo-Nazarov reaction of aryl vinyl ketones, and show here that the photo-Nazarov cyclization reaction is generally applicable to the synthesis of hydrofluorenones and polycyclic heteroaromatic structures that are not easily accessible by the traditional methods. We further demonstrate its utility and synthetic potential with the synthesis of taiwaniaquinol B (**13**).[4a, 9]

Results and Discussion

We began our studies by evaluating the photo-Nazarov reaction of 1-cyclohexenyl *p*-trifluoromethylphenyl ketone (**19**) and found that solvent and light source strongly affected the efficiency of photo-electrocyclization (Table 1). Irradiating a solution of **19** (2.0 mg mL^{-1}) in degassed acetonitrile with UV-light at 254 nm for 3 h gave **20** in 23 % yield as a single diastereomer (Table 1, entry 1). This photo-Nazarov reaction occurred in neutral solution, albeit in low yield. Although we observed no improvement with using methanol, acetone, or ether as the solvent (Table 1, entries 2–4), performing this reaction in dichloromethane, chloroform, or 1,2-dichloroethane (entries 5–7) dramatically improved the yield of **20** with a shortened reaction time. Encouraged by this result, we explored photolysis under basic conditions by adding stoichiometric amount of *i*Pr$_2$NH, Et$_3$N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) to the system (Table 1, entries 8–11). Yields were similar to those obtained under neutral conditions. The reaction can also be done by irradiating with longer wavelength (300 or 366 nm) UV-light (Table 1, entries 12 and 13) at the expense of reaction time. The reaction yield was improved slightly by using anhydrous solvent (Table 1, entry 15); increasing the concentration to 16 mg mL^{-1} gave a reasonable yield (entry 16) and allowed the solvent to be recovered without any contamination.

Table 1. Optimization of the reaction conditions for the photo-Nazarov reaction of aryl vinyl ketone **19**.



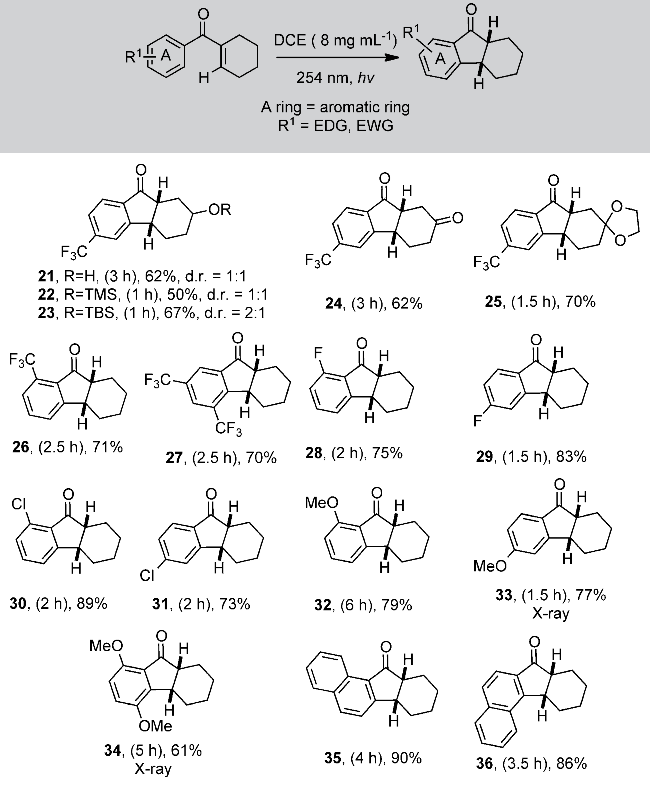
Entry	λ [nm]	Solvent[a]	Base	*c* [mg mL^{-1}]	*t*	Conv.[b] [%]	Yield [%][b]
1	254	CH_3CN	–	2	3 h	100	23
2	254	CH_3OH	–	2	1.5 h	–	0
3	254	CH_3COCH_3	–	2	1 h	97	24
4	254	Et_2O	–	2	1 h	89	0
5	254	CH_2Cl_2	–	2	30 min	100	68
6	254	CH_2Cl_2	–	2	15 min	100	59
7	254	$ClCH_2CH_2Cl$	–	2	20 min	93	74
8	254	$ClCH_2CH_2Cl$	*i*Pr$_2$NH	2	1 h 40 min	100	37
9	254	$ClCH_2CH_2Cl$	Et$_3$N	2	1 h 40 min	100	69
10	254	$ClCH_2CH_2Cl$	DBU	2	1 h 40 min	91	60
11	254	$ClCH_2CH_2Cl$	TMEDA	2	1 h 40 min	100	44
12	300	$ClCH_2CH_2Cl$	–	2	40 min	100	65
13	366	$ClCH_2CH_2Cl$	–	2	3 h	100	65
14	254	$ClCH_2CH_2Cl$	–	2	20 min	100	87
15	254	$ClCH_2CH_2Cl$	–	8	1 h	100	92
16	254	$ClCH_2CH_2Cl$	–	16	1.5 h	100	88

[a] All the photo reactions were run under degassed solvent. [b] Conversion and yields were determined by ^1H NMR spectroscopic crude analysis using CH_2Br_2 as an internal standard, unless noted.

As a comparison, the Nazarov cyclization of **19** under various Lewis or Brønsted acid-promoted conditions was also explored (see details in the Supporting Information). Unsurprisingly, we found that the reaction requires a large excess of strong acid (e.g., 20 equiv concentrated H_2SO_4 or *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)) at high temperature (> 100 °C) and that even under these conditions, the process gives **20** in low yields (up to 48 %). Such harsh conditions are incompatible in preparation of hexahydrofluorenones, especially those with acid-sensitive groups. The photo-Nazarov reaction provides effective solutions under milder conditions at neutral or basic pH.

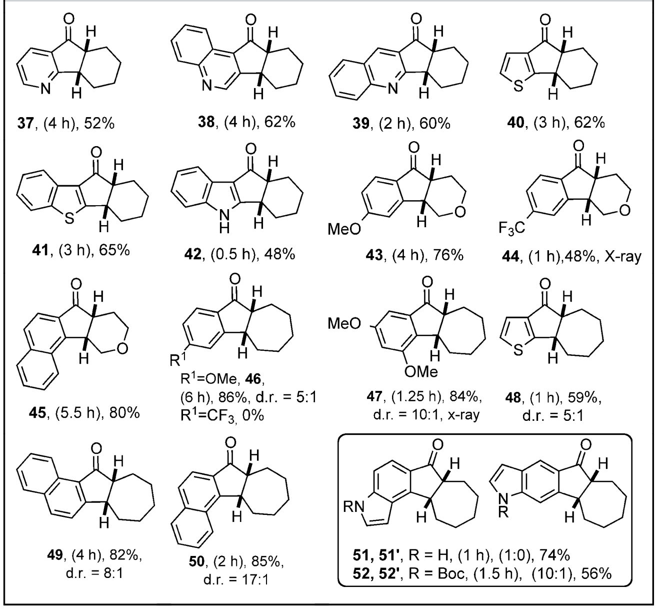
We then investigated the scope of the photo-Nazarov reaction with respect to: 1) functional-group tolerance, 2) aromatic ring compatibility, 3) cycloalkene ring size, and 4) β-substituted groups on the enone. Under the optimized photolytic conditions, we found that the photolysis tolerated substrates with hydroxyl- (**21**, Table 2) and ketone (**24**) functional groups and acid-sensitive protecting groups such as ketal (**25**), *tert*-butyldimethylsilyl ether (OTBS) (**23**), and even the highly acid-sensitive tert- trimethylsilyl ether (OTMS) groups (**22**), producing the corresponding hexahydrofluorenones in good yields. These results provide further evidence that the photo-Nazarov reaction allows effective electrocyclization of substrates containing acid-sensitive groups. With respect to the electron density of aromatic rings, we observed that both electron-withdrawing (CF_3–, F–, Cl–) and -donating (–OMe) substituents on the phenyl rings (**26**–**34**) did not affect the reaction. The desired electrocyclized products were obtained in acceptable yield.

Table 2. Photo-Nazarov reaction of substrates with various of functional groups and aromatic rings.



21, R=H, (3 h), 62%, d.r. = 1:1
22, R=TMS, (1 h), 50%, d.r. = 1:1
23, R=TBS, (1 h), 67%, d.r. = 2:1
24, (3 h), 62%
25, (1.5 h), 70%
26, (2.5 h), 71%
27, (2.5 h), 70%
28, (2 h), 75%
29, (1.5 h), 83%
30, (2 h), 89%
31, (2 h), 73%
32, (6 h), 79%
33, (1.5 h), 77% X-ray
34, (5 h), 61% X-ray
35, (4 h), 90%
36, (3.5 h), 86%

Table 3. Photo-Nazarov reaction of substrates with various heteroaromatic and cycloalkene rings.



37, (4 h), 52%
38, (4 h), 62%
39, (2 h), 60%
40, (3 h), 62%
41, (3 h), 65%
42, (0.5 h), 48%
43, (4 h), 76%
44, (1 h),48%, X-ray
45, (5.5 h), 80%
47, (1.25 h), 84%, d.r. = 10:1, x-ray
48, (1 h), 59%, d.r. = 5:1
49, (4 h), 82%, d.r. = 8:1
50, (2 h), 85%, d.r. = 17:1
51, 51', R = H, (1 h), (1:0), 74%
52, 52', R = Boc, (1.5 h), (10:1), 56%

Naphthyl vinyl ketones also reacted smoothly to give the desired products in excellent yield (**35** and **36**).

To further explore the scope of the reaction, various heteroaromatic vinyl ketones were tested (Table 3). We were pleased to find that substrates containing pyridine (**37**), quinoline (**38** and **39**), thiophene (**40**), benzothiophene (**41**), and indole (**42**) reacted efficiently in the photolysis, yielding the corresponding fused heteroaromatic cycles in good yields as single regioisomers. Based on the obtained products, we concluded that the regioselectivity of this photolytic electrocyclization always occurs on the electron-rich carbons of the aromatic rings. Changing the cyclohexenyl ring to the corresponding unsaturated pyran was also applicable, and the related polycyclic rings (**43**–**45**) were obtained in acceptable yields. The relative stereochemistries of the hexahydrofluorenones obtained were determined unambiguously by using X-ray crystallographic analysis of **33**, **34**, and **44** (Figure 2).

Next we investigated the potential influence of different ring size by using cyclopentenyl, cycloheptenyl, and cyclooctenyl phenyl ketones. We found that irradiating cyclopentenyl and cyclooctenyl phenyl ketones under the optimized photolytic conditions failed to give the electrocyclization products under either neutral or basic conditions. We speculate that photolytic isomerization of the enone in the cyclopentenyl ring may be forbidden due to ring strain, and that a medium-sized cyclooctenyl ring may allow a rapid photo-isomerization equilibrium but low reactivity. Interestingly, we found that photolysis of cycloheptenyl phenyl ketones gave the desired products in a mixture of two diastereomers, and the reaction was highly dependent on the electron density of the aromatic rings. Aromatic rings with electron-donating groups like –OMe (**46** and **47**), naphthyl (**49** and **50**), and electron-rich heteroaromatic rings (**48**, **51**, and **52**) facilitated electrocyclization and gave the desired cyclized products in good yields. Conversely, no reaction occurred in the presence of an electron-withdrawing group, for example, trifluoromethyl. The major diastereomer of the photolysis has a *cis* configuration, which was confirmed by the corresponding X-ray structure of **47** (Figure 2).

We next examined this photo-Nazarov reaction using vinyl ketones, which carry a β-substituted group on the enone. After a systematic study of properties of the substituted groups and electronic effect of the aromatic rings (Table 4), we conclude that irradiation of substrates with β-alkyl groups on the enone, such as methyl group, led to their corresponding products in good to excellent yields, whereas substrates with alkenyl or phenyl groups showed no reactivity. We also found that the stereo-effect of substituted groups was related to the yield of the electrocyclization. When a β-methyl group on the enone (**54**) was replaced with isopropyl (**55**) or cyclohexyl (**56**), the yields of the photo-Nazarov decreased from 70 to 30%. Substrates with a β-*tert*-butyl group showed no reactivity. Substrates with electron-rich aromatic rings of cyclohexenyl, unsaturated pyran, and cycloheptenyl ketones facilitated the photolysis, whereas strong electron-withdrawing groups like trifluoromethyl were inert. As a result, photolysis proceeded much faster for substrates with electron-rich aromatic rings (–OCH$_2$O–, **53**, $t=0.5$ h; –OMe, **54**, $t=1.5$ h) than for those with electron-deficient aromatic rings (**59**, $t=5$ h) under identical conditions. Photolysis of naphthyl vinyl ketones yielded tetracyclic rings (**57**, **58**, **65**, **66**, and **68**). These photolytic products containing quaternary centers were obtained as single diastereomers, in which the relative stereochemistry of **64** was confirmed by using X-ray crystallographic analysis (Figure 2). Nota-

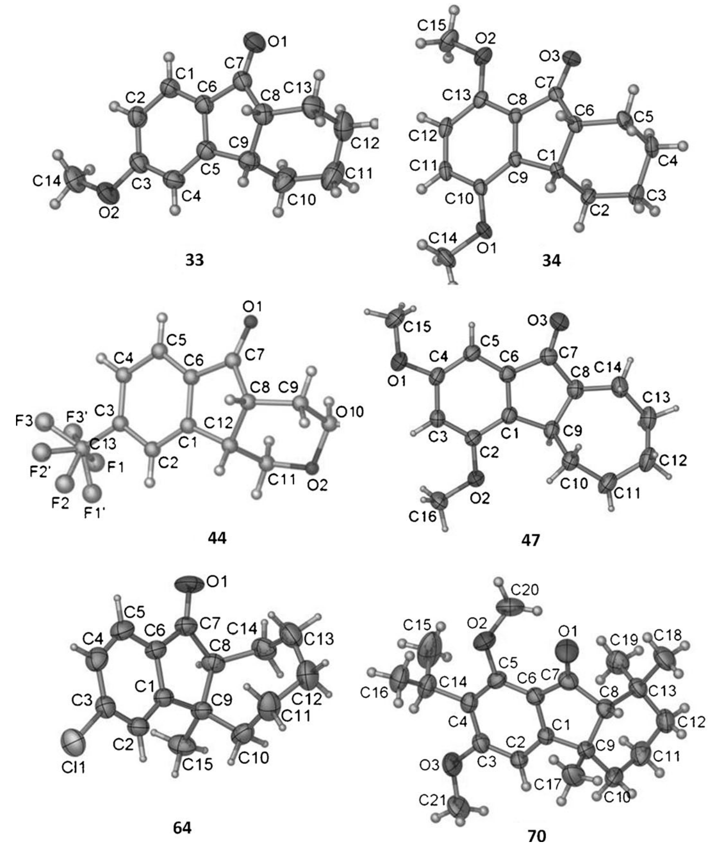
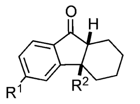
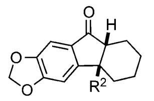


Figure 2. X-ray structures of **33**, **34**, **44**, **47**, **64**, and **70**.

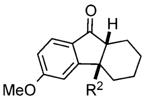
Table 4. Photo-Nazarov reaction of β-alkyl-substituted vinyl substrates.



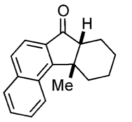
R^1=CF_3, R^2= Me, 0%
R^1=OMe, R^2=phenyl, 0%



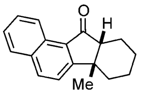
R^2=Me, **53**, (0.5 h), 91%
R^2=ethenyl, 0%



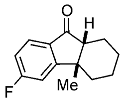
R^2= Me, **54**, (1.5 h), 70%
R^2= *i*Pr, **55**, (3.5 h), 37%
R^2= C_6H_{11}, **56**, (3.5 h), 32%
R^2= *t*Bu, 0%,



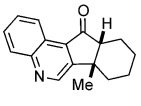
57, (1.5 h), 61%



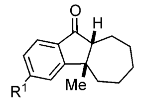
58, (2 h), 80%



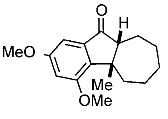
59, (5 h), 64%



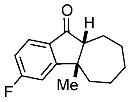
60, (4 h), 52%



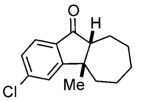
R^1=OMe, **61**, (1.5 h), 91%
R^1=CF_3, 0%



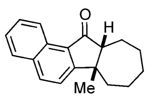
62, (1 h), 94%



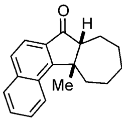
63, (1 h), 92%



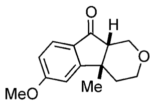
64, (1.5 h), 87% X-ray



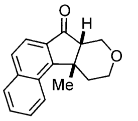
65, (3 h), 94%



66, (3 h), 91%



67, (4 h), 50%



68, (4 h), 58%

bly, the structural features of these photo products are identical to the basic skeleton of taiwaniaquinols, asterogynins, and C-nor-D-homo-steroids. Thus, these photo-electrocyclized products may prove useful for synthesizing a variety of natural products and their derivatives.

To demonstrate the practicability and reliability of this photo-Nazarov reaction, we irradiated **19** on the gram scale (1.5 g, 5.9 mmol) under the optimized condition and a comparable yield (1.3 g, isolated in 88% yield) of **20** was obtained. Compound **63** could also be prepared on a large scale (0.9 g, 0.4 mmol) with an acceptable yield (75%) under the standard photolytic conditions. Notably, irradiation of substrates on a large scale always requires a longer reaction time in a concentrated solution (see details in the Supporting Information).

We further demonstrated the synthetic utility of this photo-Nazarov reaction with the formal synthesis of taiwaniaquinoids. In 2006, the group of Liang and Trauner reported that treating **69** with a Lewis acid (TMSOTf) at 105 °C followed by desilylation gave **70** in 70% yield.[4a] We found that irradiating **69** with light at 254 nm under neutral condition gave **70** directly in 79% yield. The NMR spectrum of **70** was fully consistent with reported data, and it was confirmed by using X-ray crystallography. The formal synthesis of taiwaniaquinol B (**13**) was completed following the procedures reported by the group of Liang and Trauner (Scheme 2).[4a]

Conclusion

The photo-Nazarov cyclization of vinyl aryl ketones proceeds under neutral or basic conditions. In contrast, the traditional Brønsted- or Lewis acid-promoted Nazarov cyclization reactions require much harsher conditions. Irradiating substrates bearing various aromatic rings, acid-sensitive groups, cyclohexenyl, unsaturated pyran, and cycloheptenyl with UV-light (254 nm) smoothly yielded hexahydrofluorenones and related structures. This photo-Nazarov reaction could also be applicable to the substrates carrying β-alkyl groups on the enone, which gave corresponding polycyclic rings containing quaternary centers. The photo-Nazarov reaction is particularly useful for preparing hexahydrofluorenones and related structures. We are currently studying the asymmetric photo-Nazarov reaction and further applications in the related natural products synthesis.

Acknowledgements

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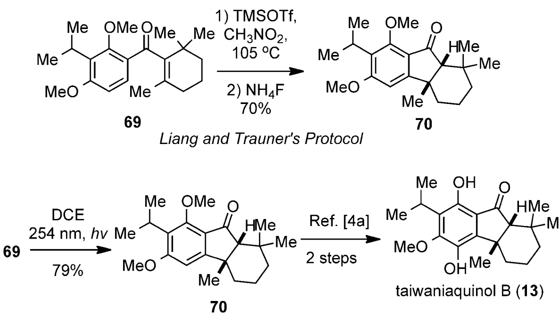

Scheme 2. Synthesis of taiwaniaquinol B using the photo-Nazarov reaction.

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Keywords: cyclization · electrocyclic reactions · ketones · natural products · photochemistry · synthetic methods

[1] I. N. Nazarov, I. I. Zaretskaya, *Izv. Akad. Nauk. SSSR Ser. Khim.* **1941**, 211–224.

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

[3] For the chemoselectivity of Nazarov reactions, see: a) T. K. Jones, S. E. Denmark, *Helv. Chim. Acta* **1983**, *66*, 2377–2396; b) S. E. Denmark, R. C. Klix, *Tetrahedron* **1988**, *44*, 4043–4060; c) S. E. Denmark, M. A. Wallace, C. B. Walker, *J. Org. Chem.* **1990**, *55*, 5543–5545; d) W. He, I. R. Herrick, T. A. Atesin, P. A. Caruana, C. A. Kellenberger, A. J. Frontier, *J. Am. Chem. Soc.* **2008**, *130*, 1003–1011; For the enantioselectivity of Nazarov reactions, see: e) S. E. Denmark, M. A. Wallace, C. B. Walker, *J. Org. Chem.* **1990**, *55*, 5543–5545; f) H. Hu, D. Smith, R. E. Cramer, M. A. Tius, *J. Am. Chem. Soc.* **1999**, *121*, 9895–9896; g) P. E. Harrington, M. A. Tius, *Org. Lett.* **2000**, *2*, 2447–2450; h) P. E. Harrington, M. A. Tius, *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514; i) P. E. Harrington, T. Murai, C. Chu, M. A. Tius, *J. Am. Chem. Soc.* **2002**, *124*, 10091–10100; j) V. K. Aggarwal, A. J. Belfield, *Org. Lett.* **2003**, *5*, 5075–5078; k) G. Liang, D. Trauner, *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545; For selective examples of Lewis acid-promoted Nazarov reactions, see: l) G. Liang, S. N. Gradl, D. Trauner, *Org. Lett.* **2003**, *5*, 4931–4934; m) W. He, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2003**, *125*, 14278–14279; n) M. Janka, W. He, A. J. Frontier, R. Eisenberg, *J. Am. Chem. Soc.* **2004**, *126*, 6864–6865.

[4] For recent examples using Nazarov cyclization in natural products syntheses, see: a) G. Liang, Y. Xu, I. B. Seiple, D. Trauner, *J. Am. Chem. Soc.* **2006**, *128*, 11022–11023; b) W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2007**, *129*, 498–499; c) J. A. Malona, K. Cariou, A. J. Frontier, *J. Am. Chem. Soc.* **2009**, 131, 7560–7561; d) W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2008**, *130*, 300–308; e) A. P. Marcus, A. S. Lee, R. L. Davis, D. J. Tantillo, R. Sarpong, *Angew. Chem.* **2008**, *120*, 6479–6483; *Angew. Chem. Int. Ed.* **2008**, *47*, 6379–6383; f) W.-D. Z. Li, W.-G. Duo, C.-H. Zhuang, *Org. Lett.* **2011**, *13*, 3538–3541; for a review of natural product synthesis using photochemical reactions as key steps, see: g) T. Bach, J. P. Hehn, *Angew. Chem.* **2011**, *123*, 1032–1077; *Angew. Chem. Int. Ed.* **2011**, *50*, 1000–1045.

[5] T. Suzuki, T. Ohwada, K. Shudo, *J. Am. Chem. Soc.* **1997**, *119*, 6774–6780.

[6] a) A. B. Smith III, W. C. Agosta, *J. Am. Chem. Soc.* **1973**, *95*, 1961–1968; For related photo-Nazarov cyclization reactions, see: b) J. K. Crandall, R. P. Haseltine, *J. Am. Chem. Soc.* **1968**, *90*, 6251–6253; c) R. Noyori, M. Katô, *Tetrahedron Lett.* **1968**, *9*, 5075–5077.

[7] a) J. Leitich, I. Heise, S. Werner, C. Krüger, 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.

[8] a) S. Gao, Q. Wang, L. Lum, C. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 371–383; b) S. Gao, Q. Wang, C. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 1410–1412; c) S. Gao, Q. Wang, G. Wang, B. Lomenick, J. Liu, C. Fan, L. Deng, J. Huang, L. Lum, C. Chen, *Synlett* **2012**, *23*, 2298–2310; For another example of application; see d) F. Churruca, M. Fousteris, Y. Ishikawa, M. von Wantoch Rekowski, C. Hounsou, T. Surrey, A. Giannis, *Org. Lett.* **2010**, *12*, 2096–2099.

[9] For the synthesis of taiwaniaquinols, see: a) M. Banerjee, R. Mukhopadhyay, B. Achari, A. K. Banerjee, *Org. Lett.* **2003**, *5*, 3931–3933; b) E. Fillion, D. Fishlock, *J. Am. Chem. Soc.* **2005**, *127*, 13144–13145; c) M. Banerjee, R. Mukhopadhyay, B. Achari, A. K. Banerjee, *J. Org. Chem.* **2006**, *71*, 2787–2796; d) L. Planas, M. Mogi, H. Takita, T. Kajimoto, M. Node, *J. Org. Chem.* **2006**, *71*, 2896–2898; e) R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739; f) S. L. Li, P. Chiu, *Tetrahedron Lett.* **2008**, *49*, 1741–1744; g) S. Tang, Y. Xu, J. He, Y. He, J. Zheng, X. Pan, X. She, *Org. Lett.* **2008**, *10*, 1855–1858; h) G. Majetich, J. M. Shimkus, *Tetrahedron Lett.* **2009**, *50*, 3311–3313; i) E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, R. Alvarez-Manzaneda, R. Meneses, H. Es-Samti, A. Fernandez, *J. Org. Chem.* **2009**, *74*, 3384–3388; j) E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, A. Haidour, J. M. Ramos, R. Alvarez-Manzaneda, Y. Charrah, H. Es-Samti, *Org. Biomol. Chem.* **2009**, *7*, 5146–5155; k) M. Node, M. Ozeki, L. Planas, M. Nakano, H. Takita, D. Mori, S. Tamatani, T. Kajimoto, *J. Org. Chem.* **2010**, *75*, 190–196; l) C. K. Jana, R. Scopelliti, K. Gademann, *Synthesis* **2010**, 2223–2232; m) C. K. Jana, R. Scopelliti, K. Gademann, *Chem. Eur. J.* **2010**, *16*, 7692–7695; n) X. Liao, L. M. Stanley, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 2088–2091; o) E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, A. Haidour, J. M. Ramos, R. Alvarez-Manzaneda, M. Hmamouchi, H. Es-Samti, *Chem. Commun.* **2009**, 592–594; p) E. Alvarez-Manzaneda, R. Chahboun, E. Alvarez, R. Tapia, R. Alvarez-Manzaneda, *Chem. Commun.* **2010**, *46*, 9244–9246; q) R. Tapia, J. J. Guardia, E. Alvarez, A. Haidour, J. M. Ramos, R. Alvarez-Manzaneda, R. Chahboun, E. Alvarez-Manzaneda, *J. Org. Chem.* **2012**, *77*, 573–584; r) J. Deng, R. Li, Y. Luo, J. Li, S. Zhou, Y. Li, J. Hu, A. Li, *Org. Lett.* **2013**, *15*, 2022–2025.

[10] S. Cao, L. Ross, G. Tamayo, J. Clardy, *Org. Lett.* **2010**, *12*, 4661–4663.

[11] For the isolation of exiguaquinol, see: a) P. de Almeida Leone, A. R. Carroll, L. Towerzey, G. King, B. M. McArdle, G. Kern, S. Fisher, N. A. Hooper, R. J. Quinn, *Org. Lett.* **2008**, *10*, 2585–2588; For the synthetic study of exiguaquinol, see: b) G. M. Schwarzwalder, S. E. Steinhardt, H. V. Pham, K. N. Houk, C. D. Vanderwal, *Org. Lett.* **2013**, *15*, 6014–6017.

[12] For the isolation of kinamycins, see: a) S. Itō, 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, S. Itō, T. Matsuya, *J. Antibiot.* **1971**, *24*, 353–359; c) S. Ōmura, A. Nakagawa, H. Yamada, T. Hata, A. Furusake, *Chem. Pharm. Bull.* **1973**, *21*, 931–940; d) A. Furusaki, M. Marsui, T. Watanabe, S. Ōmura, A. Nakagawa, T. Hata, *Isr. J. Chem.* **1972**, *10*, 173–187; e) S. J. Gould, N. Tamayo, C. R. Melville, M. C. Cone, *J. Am. Chem. Soc.* **1994**, *116*, 2207–2208; f) S. Mithani, G. Weeratunga, N. J. Taylor, G. I. Dmitrienko, *J. Am. Chem. Soc.* **1994**, *116*, 2209–2210; For the synthetic studies, see: g) X. Lei, J. A. Porco, *J. Am. Chem. Soc.* **2006**, *128*, 14790–14791; h) T. Kumamoto, Y. Kitani, H. Tsuchiya, K. Yamaguchi, H. Seki, T. Ishikawa, *Tetrahedron* **2007**, *63*, 5189–5199; i) K. C. Nicolaou, H. Li, A. L. Nold, D. Pappo, A. Lenzen, *J. Am. Chem. Soc.* **2007**, *129*, 10356–10357; j) C. M. Woo, L. Lu, S. L. Gholap, D. R. Smith, S. B. Herzon, *J. Am. Chem. Soc.* **2010**, *132*, 2540–2541; k) S. S. Scully, J. A. Porco, *Angew. Chem.* **2011**, *123*, 9896–9900; *Angew. Chem. Int. Ed.* **2011**, *50*, 9722–9726; l) N. Chen, M. B. Carriere, R. S. Laufer, N. J. Taylor, G. I. Dmitrienko, *Org. Lett.* **2008**, *10*, 381–384; m) S. S. Scully, J. A. Porco, *Org. Lett.* **2012**, *14*, 2646–2649; n) C. M. Woo, S. L. Gholap, L. Lu, M. Kaneko, Z. Li, P. C. Ravikumar, S. B. Herzon, *J. Am. Chem. Soc.* **2012**, *134*, 17262–17273.

[13] For the isolation of gracilamine, see: a) N. Ünver, G. İ. Kaya, *Turk. J. Chem.* **2005**, *29*, 547–553; For the total synthesis of gracilamine, see: b) S. Tian, W. Zi, D. Ma, *Angew. Chem.* **2012**, *124*, 10288–10291; *Angew. Chem. Int. Ed.* **2012**, *51*, 10141–10144.

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