Phototriggered Dehydration Condensation Using an Aminocyclopropenone

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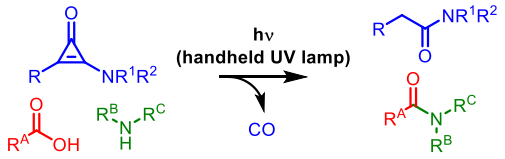
Supporting Information Placeholder



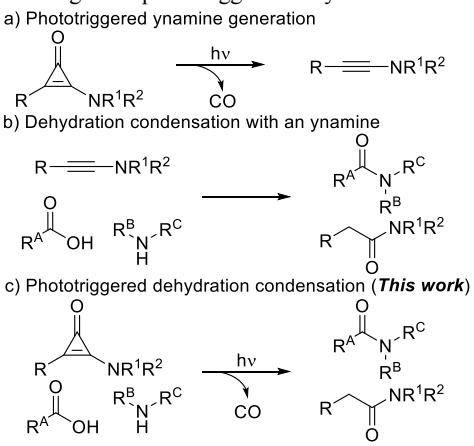
ABSTRACT: A phototriggered dehydration condensation using an aminocyclopropenone has been developed. The UV irradiation of an aminocyclopropenone generated a highly reactive ynamine *in situ*, and the dehydration condensation of a carboxylic acid and an amine coexisting in the reaction solution smoothly proceeded to afford an amide. This reaction is completely controllable by the ON/OFF states of a UV lamp.

Phototriggered chemical reactions have attracted considerable attention because of the following unique features: i) the reaction can be initiated and terminated whenever required, ii) the location of the reaction can be controlled by regulating the irradiation site, iii) the activation of a specific chromophore is possible by selecting an appropriate wavelength, and iv) highly reactive species can be generated *in situ* under mild conditions. These features are particularly useful for the fine control of the polymer synthesis[1] and the chemical modification of biomolecules.[2] In phototriggered chemical reactions, photoexcited species could form reversible active intermediates[3] or photolytically generate active species, such as radicals,[4] carbenes,[5] nitrenes[6] and nitrile imines.[7] These species have mostly been used for the insertion, addition, and abstraction reactions. To the best of our knowledge, there has been no report focusing on phototriggered dehydration condensation. Because dehydration condensation is abundantly observed in multiple situations, such as polymer synthesis, biomolecule synthesis, and biological processes, phototriggered dehydration condensation would be useful for the local control of these reactions with light.

Herein, we report the first phototriggered dehydration condensation using an aminocyclopropenone as a photolabile "caged" dehydrating agent. Cyclopropenone is a highly strained cyclic enone with 2π aromaticity, which was first reported by Breslow.[8] Because of the strain, the ring-opening reaction occurs in the presence of an appropriate nucleophile.[9] The ring strain is also released by thermal[8,10] or photochemical[11] decarbonylation to afford the corresponding alkyne. Cyclopropenones are normally stable under ambient conditions, and the thermal decarbonylation occurs at a high temperature.[8] In contrast, photochemical decarbonylation efficiently occurs at ambient temperature with a quantum yield of 0.2–0.8.[11b] Popik demonstrated a broad range of applications of the phototriggered alkyne formation, such as phototriggered alkyne-azide click reaction [12] and phototriggered en-diyne formation. [13] Kresge reported photoexcitation of an aminocyclopropenone generates carbon monoxide and an aminoalkyne (ynamine).[14] An ynamine acts as a potent dehydrating agent, which converts a carboxylic acid to an acid anhydride, and a carboxylic acid and an amine to an amide.[15] Despite the high reactivity, ynamines are rarely used in synthesis because of their low stability and complicated preparation procedure. Recently an ynamide was reported as a stable and racemization-free condensing agent.[16] However, an ynamide is generally less reactive than an electron-rich ynamine as a compensation for its high stability.

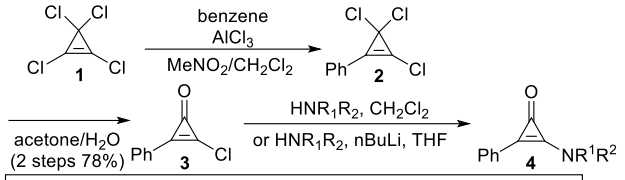
We envisioned that if a highly reactive ynamine is photolytically generated from an aminocyclopropenone and used for the following reaction *in situ*, the high reactivity of the ynamine can be exploited without complicated handling and the generation of the ynamine would be controllable by the ON/OFF states of light irradiation (**Scheme 1**).

Scheme 1. Design of a phototriggered dehydration condensation



Aminocyclopropenones with various substituents **4a–f** were readily prepared according to the procedures reported in the literature[14] (**Scheme 2**). All of **4a–f** was isolable using SiO_2 column chromatography. These compounds are colorless or slightly yellow, and stable under household fluorescent light. The UV spectra were recorded for synthesized **4a–f** in MeCN (**Figure 1**). All the aminocyclopropenones showed similar spectra pattern having absorption around the 200–350 nm region. The decomposition of the aminocyclopropenones during the UV measurement was negligibly small.

Scheme 2. Synthesis of aminocyclopropenones **4a–f**.



NR^1R^2	NEt_2 (**4a**)	$NiPr_2$ (**4b**)	NBn_2 (**4c**)	NMePh (**4d**)	NPh_2 (**4e**)	NiPrAc (**4f**)
yield of **4** (%)	96	88	97	91	86	34

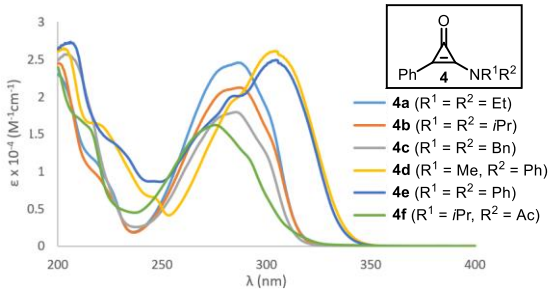


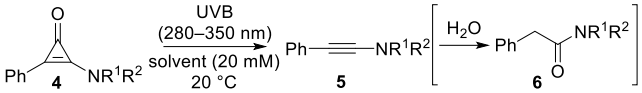
Figure 1. The UV spectra of **4a–f** in MeCN.

First, the phototriggered ynamine generation from **4** was examined (**Table 1**). Unexpectedly, a weak handheld UV lamp, which is generally used for TLC analysis, was sufficient for the photolysis reaction. The MeCN solutions of **4** in a quartz tube were irradiated with a 6 W UVB lamp (280–350 nm) that was placed 4 cm from the reaction vessel until complete consumption of **4**. Aryl- or acyl-substituted aminocyclopropenones **4d–f** produced the corresponding ynamines **5d–f** in 63%–92% yield (entries 7–9), while alkyl-substituted aminocyclopropenones **4a–c** resulted in unidentified complex mixtures (entries 1, 3, and 5). In general, electron-rich ynamines are more reactive than electron-poor ynamines.[17] Thus, the decompositions observed for **4a–c** were possibly related to the high reactivity of the produced ynamines. Consequently, for **4a–c**, corresponding ynamines were indirectly detected as stable amides **6a–c** that are formed by the hydration of the ynamines under the MeCN/H_2O (1/1) condition (entries 2, 4, and 6).

Subsequently, the phototriggered dehydration condensation was examined (**Table 2**). A solution of **4**, carboxylic acid **7a**, and amine **8a** in MeCN was irradiated under the condition same as that of the ynamine formation experiment until **4** disappeared. After the irradiation was stopped, the reaction was rapidly quenched by the acid/base workup and the yield of amide **9aa** was determined via NMR analysis. The condensation of **7a** and **8a** satisfactorily proceeded to afford **9aa** for most of **4**. Ethyl- and isopropyl-substituted aminocyclopropenones resulted in a relatively high **9aa** yield (entries 1–2) while benzyl-substituted one resulted in a low **9aa** yield and a considerable number of byproducts were observed (entry 3). Aryl- substituted ones resulted in low **9aa** yield probably because of the low reactivity of the generated ynamines (entry 4–5). For **4f**, **9aa** was not obtained and ynamine **5f** was recovered in 70% yield (entry 6).

A plausible mechanism of the phototriggered reaction is shown in **Scheme 3**. The photoexcitation of an aminocyclopropenone **4** produces an ynamine **5**. Subsequently, **5** reacts with a carboxylic acid **7** to form a carboxylic acid-ynamine adduct **10**. Finally, **10** reacts with an amine **8** to afford a condensed product **9** and a hydrated ynamine **6**.

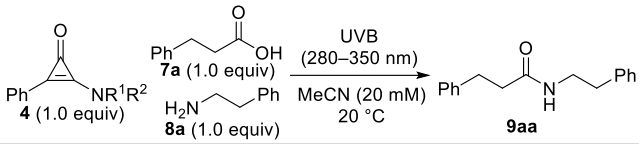
Table 1. Ynamine generation from aminocyclopropenones.



entry	NR^1R^2	solvent	time (h)	major product	yield (%)[a]
1	NEt_2 (**4a**)	MeCN	3	-	decomp.
2		MeCN/water (1/1)	3	**6a**	54
3	$NiPr_2$ (**4b**)	MeCN	2	-	decomp.
4		MeCN/water (1/1)	3	**6b**	65
5	NBn_2 (**4c**)	MeCN	5	-	decomp.
6		MeCN/water (1/1)	5	**6c**	70
7	NMePh (**4d**)	MeCN	5	**5d**	85
8	NPh_2 (**4e**)	MeCN	5	**5e**	92
9	NiPrAc (**4f**)	MeCN	2	**5f**	63

[a] NMR yield.

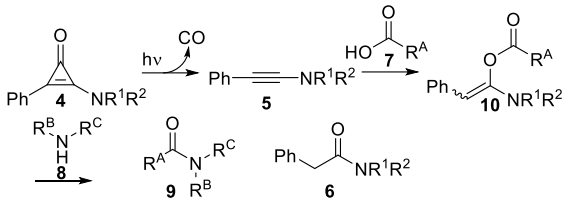
Table 2. Phototriggered dehydration condensation using aminocyclopropenones.



entry	NR^1R^2	time (h)	**9aa** yield (%)[a]	dark condition yield (%)[a]
1	NEt_2 (**4a**)	3	57	1
2	$NiPr_2$ (**4b**)	2	55	0
3	NBn_2 (**4c**)	5	15	2
4	NMePh (**4d**)	5	30	0
5	NPh_2 (**4e**)	5	14	0
6	NiPrAc (**4f**)	2	0	0

[a] NMR yield.

Scheme 3. Plausible mechanism of the phototriggered dehydration condensation.

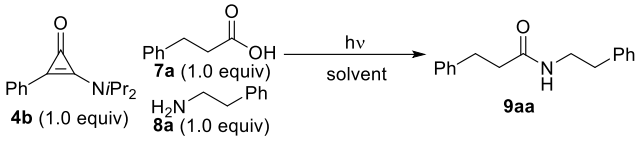


For **4a** and **4c**, a small amount of **9aa** was formed even under dark conditions (**Table 2**, entries 1 and 3). The background reaction in these conditions did not yield the hydrated ynamine **6**, which should be observed if the ynamine **5** would be involved in **9aa** formation. Therefore, the background reaction would occur with a mechanism different from that of the phototriggered dehydration condensation.[18]

Because **4b** resulted in a good condensation yield without the background reactions, the reaction condition was further optimized with **4b** (**Table 3**). For all the conditions, UV irradiation was performed until **4b** disappeared. Solvent screening showed that chlorinated solvents were the best candidates for this reaction (entries 1–9). In the presence of water, the condensation yield was very low probably because the photogenerated ynamine was rapidly hydrated (entry 2). Higher concentration and longer irradiation distance resulted in higher **9aa** yield but decreased the photodecarbonylation rate. The slower rate was probably due to a lower irradiation efficiency (entries 10–12). The UVC (240–260 nm) also initiated the reaction and resulted in a good yield (entry 13). The temperature difference did not affect the photodecarbonylation rate. However, low temperature conditions resulted in a slightly lower condensation yield (entries 14–15). Consistently, for low yielding conditions, multiple byproducts were observed. Although the byproducts have not been identified yet, they could have been formed by thermal

rearrangements or photoexcitation of the reaction intermediates competing with the dehydration condensation to afford **9aa**. In general, photochemical reactions efficiently occur under intense light and low concentration conditions. However, for the phototriggered dehydration condensation using aminocyclopropenones, the light should not be too intense and the concentration should not be too low to avoid the undesired side reactions.

Table 3. Optimization of the conditions.



entry	solvent	concn (mM)	temp (°C)	UV condition (lamp, distance[a])	time (h)	yield (%)[b]
1	MeCN	20	20	UVB, 4 cm	2	55
2	MeCN/H_2O (1/1)	20	20	UVB, 4 cm	3	1
3	THF	20	20	UVB, 4 cm	2	39
4	1,4-dioxane	20	20	UVB, 4 cm	2	39
5	AcOEt	20	20	UVB, 4 cm	2	60
6	CH_2Cl_2	20	20	UVB, 4 cm	2	80
7	$CHCl_3$	20	20	UVB, 4 cm	2	80
8	1,2-dichloroethane	20	20	UVB, 4 cm	2	80
9	toluene	20	20	UVB, 4 cm	2	66
10	CH_2Cl_2	40	20	UVB, 4 cm	2	85
11	CH_2Cl_2	20	20	UVB, 8 cm	3	88
12	CH_2Cl_2	40	20	UVB, 8 cm	5	85
13	CH_2Cl_2	20	20	UVC, 4 cm	4	84
14	1,2-dichloroethane	20	40	UVB, 8 cm	3	87
15	CH_2Cl_2	20	0	UVB, 8 cm	3	77

[a] Distance between the lamp and the reaction vessel. [b] NMR yield.

To investigate the details of the phototriggered dehydration condensation, the reaction progress was monitored by ^{1}H NMR (**Figure 2**). A solution of **4b**, **7a**, **8a**, and 1,3,5-trimethoxybenzene (as an internal standard) in $CDCl_3$ was irradiated with the UVB in a glass NMR tube. The NMR spectrum was observed within 20 min after the irradiation was stopped.

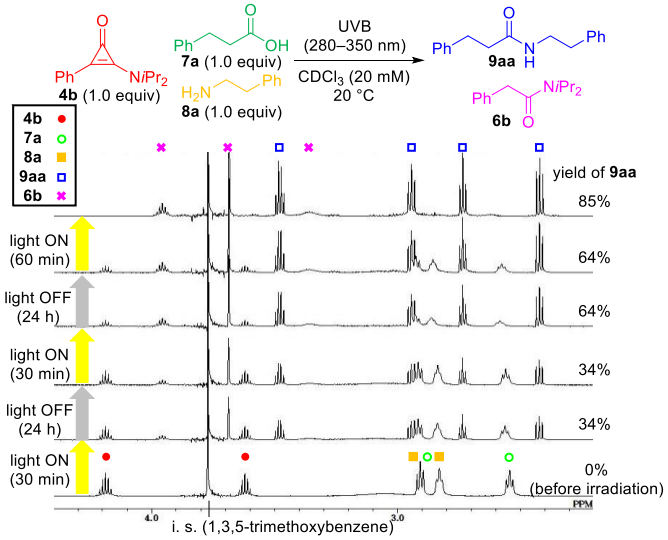


Figure 2. Monitoring of the phototriggered reaction by NMR.

In the NMR study, intermediates such as an ynamine and an active ester were not observed, and the reaction did not progress under dark conditions. The results indicated that the condensation rapidly completed after the ynamine generation and that the reaction is completely controllable by ON/OFF states of the UV irradiation.

The phototriggered condensation with various substrates proceeded with approximately 70%–90% yield (**Figure 3**). For the secondary and tertiary carboxylic acids, 2.0 equiv of carboxylic acid was used to improve the yield. In general, less reactive balky starting materials tended to afford multiple byproducts, which were probably generated by thermally or photochemically induced sidereactions of the intermediates.

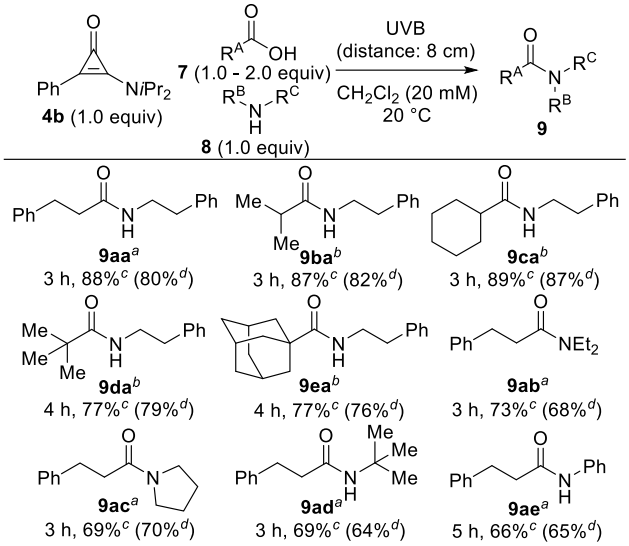


Figure 3. Phototriggered dehydration condensation of various substrates. [a] 1.0 equiv carboxylic acid was used. [b] 2.0 equiv carboxylic acid was used. [c] NMR yield. [d] Isolated yield.

Finally, a naphthalene-conjugated aminocyclopropenone **4g** was synthesized and employed for the phototriggered dehydration condensation. As shown in **Figure 4**, **4g** absorbed longer wavelength than **4b**. For the phototriggered reactions, UVA (330–400 nm), UVB (280–350 nm), or UVC (240–260 nm) were used as light sources (**Table 4**). The reactions with **4g** proceeded with any of the UV sources. In the same manner as the reaction with **4b**, **9aa** and a hydrated ynamine were produced as **4g** was consumed. It is worth noting that UVA which was not highly effective for **4b**, efficiently worked for **4g** (entries 3–4). Excitation with less harmful UVA would be particularly useful for the functionalization of biomolecules.

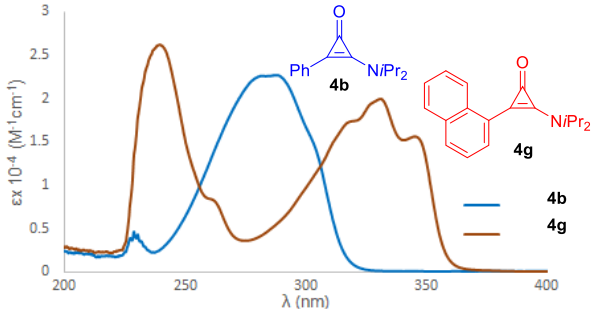
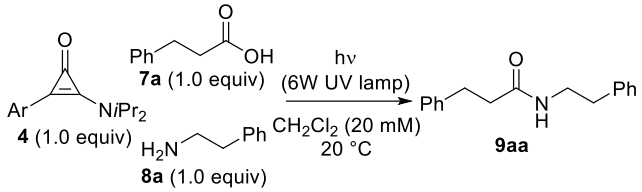


Figure 4. UV spectra of **4b** and **4g** in CH_2Cl_2.

Table 4. Reactions with a naphthalene conjugated aminocyclopropenone.



entry	Ar	UV condition (lamp, distance)	time (h)	yield (%)[a]
1[b]		UVC, 4 cm	4	78
2[b]	1-Naphthyl (**4g**)	UVB, 8 cm	4	76
3[b]		UVA, 4 cm	9	74
4[c]	Ph (**4b**)	UVA, 4 cm	9	25

[a] NMR yield. [b]UV irradiation was performed until **4g** disappeared. [c]70% of **4b** was recovered.

In conclusion, we demonstrated the first phototriggered dehydration condensation that is completely controllable by the ON/OFF states of UV irradiation. This method would be useful for a simple preparation of an extremely reactive ynamine and for the local control of a dehydration reaction. These studies are currently under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Detailed experimental procedures for the synthesis of aminocyclopropenones and photochemical reactions; ^{1}H and ^{13}C NMR spectra of all new compounds. (PDF)

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REFERENCES

[1] (a) Jonkheijm, P.; Weinrich, D.; K hn, M.; Engelkamp, H.; Christianen, P. C. M.; Kuhlmann, J.; Maan, J. C.; N sse, D.; Schroeder, H.; Wacker, R.; Breinbauer, R.; Niemeyer, C. M.; Waldmann, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4421. (b) Yamago, S.; Ukai, Y.; Matsumoto, A.; Nakamura, Y. *J. Am. Chem. Soc.* **2009**, *131*, 2100. (c) Pauloehrl, T.; Delaittre, G.; Winkler, V.; Welle, A.; Bruns, M.; B rner, H. G.; Greiner, A. M.; Bastmeyer, M.; Barner-Kowollik, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1071.

[2] (a) Singh, A.; Thornton, E. R.; Westheimer, F. H. *J. Biol. Chem.* **1962**, *237*, 3006. (b) Knowles, J. R. *Acc. Chem. Res.* **1972**, *5*, 155. (c) Campbell, P.; Gioannini, T. L. *Photochem. Photobiol.* **1979**, *29*, 883. (d) Hashimoto, M.; Hatanaka, Y. *Eur. J. Org. Chem.* **2008**, *15*, 2513.

[3] (a) Walling, C.; Gibian, M. J. *J. Am. Chem. Soc.* **1965**, *87*, 3361. (b) Breslow, R.; Winnik, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 3083. (c) P. G. Sammes, *Tetrahedron* **1976**, *32*, 405.

[4] Johnston, L. J. *Chem. Rev.* **1993**. *93*, 251.

[5] (a) Griffin, G. W. *Angew. Chem. Int. Ed.* **1971**, *10*, 537. (b) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981.

[6] (a) Labbe, G. *Chem. Rev.* **1969**, *69*, 345. (b) Morita, H.; Tatami, A.; Maeda, T.; Kim, B. J.; Kawashima, W.; Yoshimura, T.; Abe, H.; Akasaka, T. *J. Org. Chem.* **2008**, *73*, 7159.

[7] (a) Clovis, J. S.; Eckell, A.; Huisgen, R.; Sustmann, R. *Chem. Ber.* **1967**, *100*, 60. (b) Li, Z.; Qian, L.; Li, L.; Bernhammer, J. C.; Huynh, H. V.; Lee, J.; Yao, S. Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 2002. (c) Tian, Y.; Jacinto, M. P.; Zeng, Y.; Yu, Z.; Qu, J.; Liu, W. R.; Lin, Q. *J. Am. Chem. Soc.* **2017**, *139*, 6078.

[8] Breslow, R.; Haynie, R.; Mirra, J. *J. Am. Chem. Soc.* **1959** *81*, 247.

[9] (a) Breslow, R.; Eicher, T.; Krebs, A.; Peterson, R. A.; Posner J. *J. Am. Chem. Soc.*, **1965**, *87*, 1320. (b) Shih, H.-W.; Prescher, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 10036. (c) Row, R. D.; Shih, H.-W.; Alexander, A. T.; Mehl, R. A.; Prescher, J. A. *J. Am. Chem. Soc.* **2017**, *139*, 7370.

[10] Wilcox, C.; Breslow, R. *Tetrahedron Lett.* **1980**, *21*, 3241.

[11] (a) Ciabattoni, J.; Nathan, E. C. III *J. Am. Chem. Soc.* **1969**, *91*, 4766. (b) Poloukhtine, A.; Popik, V. V. *J. Org. Chem.* **2003**, *68*, 7833. (c) Poloukhtine, A.; Popik, V. V. *J. Phys. Chem. A* **2006**, *110*, 1749.

[12] (a) Poloukhtine, A. A.; Mbua, N. E.; Wolfert, M. A.; Boons, G. J.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769. (b) Sutton, D. A.; Popik, V. V. *J. Org. Chem.* **2016**, *81*, 8850.

[13] (a) Poloukhtine, A.; Popik, V. V. *Chem. Commun.* **2005**, 617. (b) Poloukhtine, A.; Popik, V. V., *J. Org. Chem.* **2005**, *70*, 1297. (c) Poloukhtine, A.; Karpov, G.; Popik, V. V. *Curr. Top. Med. Chem.* **2008**, *8*, 460.

[14] (a) Chiang, Y.; Grant, A. S.; Kresge, A. J.; Pruszynski, P.; Schepp, N. P.; Win, J. *Angew. Chem. Int. Ed.* **1991**, *30*, 1356. (b) Chiang, Y.; Kresge, A. J.; Paine, S. W.; Popik, V. V. *J. Phys. Org. Chem.* **1996**, *9*, 361. (c) Chiang, Y.; Grant, A. S.; Kresge, A. J.; Paine, S. W. *J. Am. Chem. Soc.* **1996**, *118*, 4366.

[15] (a) Viehe, H. G. *Angew. Chem. Int. Ed.* **1967**, *6*, 767. (b) Steglich, W.; Höfle, G.; König, W.; Weygand, F. *Chem. Ber.* **1968**, *101*, 308.

[16] Hu, L.; Xu, S.; Zhao, Z.; Yang, Y.; Peng, Z.; Yang, M.; Wang, C.; Zhao, J. *J. Am. Chem. Soc.*, **2016**, *138*, 13135.

[17] DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.

[18] For more detailed information, see Supporting Information.