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Photocyclization synthesis of phenanthridine and its derivatives under direct dehydrogenation conditions

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ABSTRACT

A new method for synthesizing phenanthridines by photocyclization has been established. This method does not require inert gas protection, does not require transition metal catalysts and is environmentally friendly, efficient and convenient. It is proposed to use (*E*)-N,1-diphenylformimines as substrates to synthesize phenanthridine and its derivatives by ultraviolet light, which provides a new synthesis route for further research on the synthesis of phenanthridines by photocyclization. Eight new phenanthridine compounds were synthesized. The confirmation of their structures provides a material basis for further study of their properties and tapping of their potential for applications. The establishment of this method further broadens the synthetic pathways of phenanthridine compounds.

Introduction

Phenanthridines are an important group of natural alkaloids [1] typified by trispheridine [2] decarine [3] and chelerythrine [4] (Fig. 1). Many of them show a wide range of pharmacological properties, including antitumor, antileukemic, antifungal, and antiviral activities [5]. Therefore, it is important to develop new methods for the synthesis of these compounds [6]. Recent achievements include palladium-catalyzed cascade reactions [7] annulations employing arynes [8] aza-Wittig reactions [9] oxidative cyclization of 2-isocyanobiphenyls [10] reactions of biaryl-2-carbonitriles with organometallic reagents [11] transition-metal-catalyzed cyclization of imines [12] anionic ring closure reactions [13] UV-promoted phenanthridine syntheses from iminyl radicals [14] photochemical processes [15] and microwave-mediated cyclizations [16]. Although great achievements have been made, further exploration of convenient, efficient, and milder protocols is still significant due to the broad application of phenanthridine derivatives.

Many useful molecular structures can be easily obtained through photochemical organic conversion. Numerous approaches to natural product synthesis have been reported in which a photochemical transformation represents a key step [17]. In 1988, Charles reported an example of photo-promoted imine cyclization reaction to synthesize phenanthridine. The author used Lewis acid as the catalyst. However, the product yield in this work was not very satisfactory [18]. Herein, we report novel metal-free method using (*E*)-N,1-diphenylformimines as substrates to synthesize phenanthridine and its derivatives by ultraviolet light (Scheme 1, d). To the best of our knowledge, this is one of the few

Methods to synthesize phenanthridine by photocatalytic direct dehydrogenation coupling, and the reaction does not require a base. It is an environmentally friendly and atom-economical reaction.

We selected (*E*)-N,1-diphenylmethanimine **1a** (1.0 mmol) as the substrate and reacted it in *t*-BuOH (250 mL) for 1 h under illumination by a high-pressure mercury lamp (UHP). The reaction temperature was 45 °C. The target compound was obtained with an isolated yield of 8% (Table 1, entry 1). Although this yield is very low, it at least proves that this conversion can be achieved under direct light conditions. Here, we carefully optimized the reaction conditions. First, we investigated light sources with different powers, such as 300 W, 500 W, 1000 W, 2000 W, and 2500 W. We found that the yield was the best at 2000 W, reaching 55%. When the light source power was further increased, the yield decreased (Table 1, entries 2–5); we think that a side reaction may have occurred. Next, we conducted screening of many solvents for the reaction, including MeOH, EtOH, DMF, CH_3CN, 1.4-dioxane, etc. Surprisingly, these solvents are not very suitable for this process (Table 1, entries 6–11). We suspect that *tert*-butanol is involved in the chemical reaction here. Therefore, *t*-BuOH is the best solvent for the reaction. Next, we also investigated the reaction time, such as 2 h and 4 h. We found that when the reaction time was more

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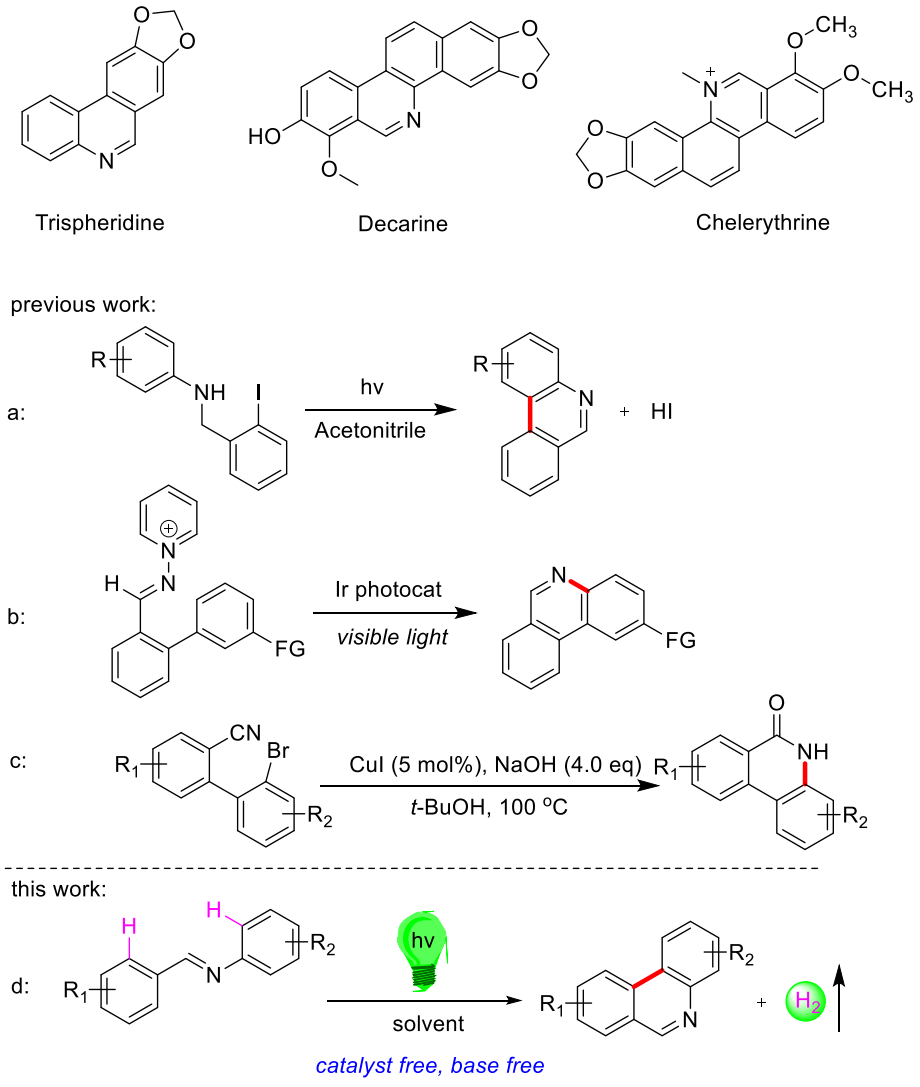
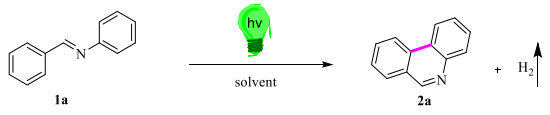


Scheme 1. Examples of natural products and alkaloids containing a phenanthridine core and general photochemical synthesis routes.

Table 1
Selected results for the optimal reaction conditions.[a]



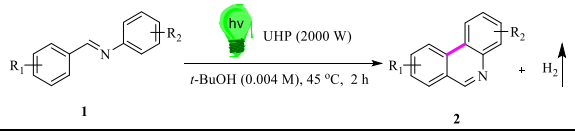
Entry	Light Source	Temperature (°C)	Solvent	Yield (%)[b]
1	UHP (300 W)	45	*t*-BuOH	8
2	UHP (500 W)	45	*t*-BuOH	15
3	UHP (1000 W)	45	*t*-BuOH	53
4	UHP (2000 W)	45	*t*-BuOH	55
5	UHP (2500 W)	45	*t*-BuOH	51
6	UHP (300 W)	45	MeOH	<5
7	UHP (2000 W)	45	EtOH	<5
8	UHP (2000 W)	45	DMF	<5
9	UHP (2000 W)	45	CH_3CN	<5
10	UHP (2000 W)	45	DMSO	<5
11	UHP (2000 W)	45	dioxane	<5
12[c]	UHP (2000 W)	45	*t*-BuOH	75
13[d]	UHP (2000 W)	45	*t*-BuOH	68
14[e]	UHP (2000 W)	45	*t*-BuOH	55

[a]Reaction conditions: **1a** (1.0 mmol), light source (UHP), solvent (250.0 mL), 45 °C for 1 h, under air in pressure tubes; [b] Yields of isolated products after chromatography; [c] 2 h; [d] 4 h; [e] *t*-BuOH (25.0 mL).

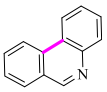
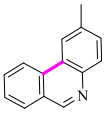
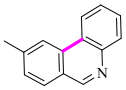
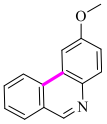
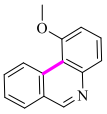
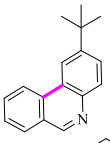
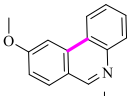
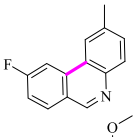
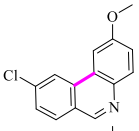
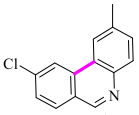
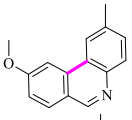
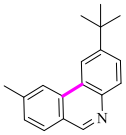
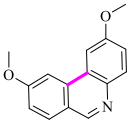
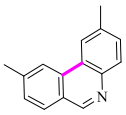
than 2 h, the yield began to decrease, and some by-products with uncertain structure have increased a lot (Table 1, entries 12–13). Here, we choose 2 h as the best reaction time. Finally, we also investigated the amount of solvent, and we observed that the initially used low concentration is suitable for the reaction. When the amount was reduced, the reaction yield decreased by 20% (Table 1, entry 14), and there was no significant increase in the yield when the reaction concentration was increased. Thus far, we have determined the best conditions for the reaction to be as follows: substrate (1.0 mmol), UHP (2000 W), *t*-BuOH (250 mL), reaction temperature of 45 °C, and reaction time of 2 h.

After obtaining the optimal reaction conditions, we investigated the suitability of the reaction substrate. Here, we employed a variety of different substituents, including electron-deficient and electron-rich substituents. First, we tried to use imine substrates with a single electron-rich substituent, and we saw that they could all be converted into corresponding phenanthridines (Table 2, entries 2–7). In the second step, we made many attempts to use disubstituted imines. It can be seen that when the electron-deficient and electron-rich substituents are located on different benzene rings, this conversion can also proceed smoothly, but the separation yields are medium (Table 2, entries 8–10). When the double substituents are all electron-rich substituents, such as methyl-methyl,

Table 2
Substrates scope.[a].



1 2

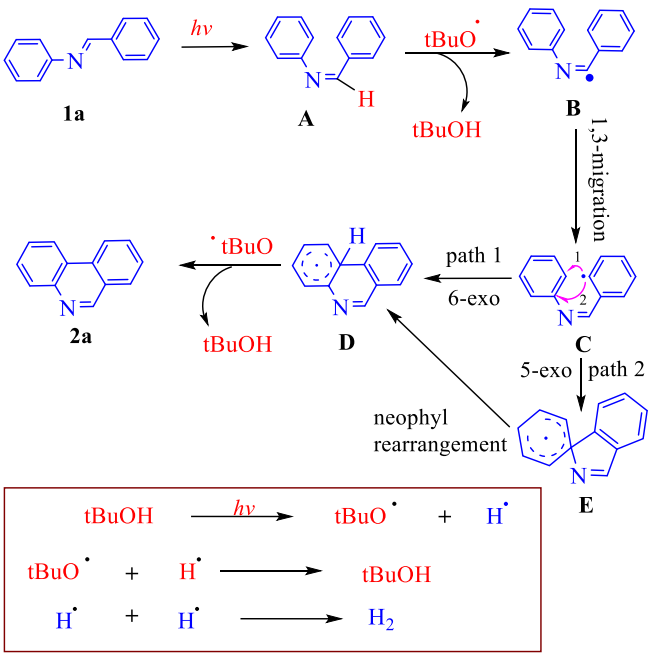
Entry	Product	Yield (%)[b]
1		75
2		79
3		71
4		81
5		78
6		72
7		69
8		45
9		62
10		56
11		85
12		74
13		62
14		80

[a]Reaction conditions: **1** (0.4 mmol), light source (UHP), *t*-BuOH (0.004 M), 45 °C for 2 h, under air in pressure tubes; [b] Yields of isolated products after chromatography.

methyl-methoxy, and methoxy-methoxy, the target product can be obtained in a higher yield (Table 2, entries 11–14). This result once again confirmed that electron-rich substrates show good applicability for the reaction.

According to the experimental results, combined with related literature [19,20], the following possible mechanism is proposed for this reaction (Scheme 2, taking the **1a** reaction to produce **2a** as an example): First, imine compound **1a** undergoes cis–trans isomerization under the action of light. It is isomerized to compound **A**. At the same time, *tert*-butanol decomposes under light to produce *tert*-butoxy radicals and hydrogen radicals. *Tert*-butoxy radicals abstract the benzylic hydrogen atom of compound **A** to form free radical intermediate **B** and *tert*-butanol. Free radical intermediate **B** undergoes 1,3-migration to generate intermediate **C**, and **C** undergoes two possible processes to produce cyclohexadiene radical **D**. One is the process of 6-exo cyclization (path 1) to directly generate **D**; the other (path 2) is that the radical attack on the aromatic ring directly connects *N* to the ipso position of the benzene ring to induce 5-exo cyclization to form spiro ring free radical **E**, and subsequently, the spirocyclic radical **E** rearranges to produce cyclohexadiene radical **D**. Cyclohexadienyl radicals lose hydrogen atoms under the action of *tert*-butoxy to generate *tert*-butanol and the final product phenanthridine **2a**.

We have established a new method to synthesize phenanthridine and its derivatives via a photocyclization reaction. First, using substituted benzaldehyde and substituted aniline as raw materials, (*E*)-N,1-diphenylformimine compound intermediates are obtained through dehydration, and then, phenanthridine compounds are synthesized by photocyclization reaction under mercury lamp irradiation. This method was used to synthesize around 20 kinds of phenanthridine compounds, and their possible reaction mechanism was proposed. Compared with traditional methods for synthesizing phenanthridine and its derivatives, this method has the following advantages: (1) No metal catalyst is required, and the substrate does not need to be prefunctionalized. (2) The reaction conditions are mild, and the reaction time is short. (3) The method exhibits functional group tolerance, good performance and high atom economy. (4) *t*-BuOH as a solvent is green and environmentally friendly. The synthesis method provides a



Scheme 2. A plausible mechanism.

simple and efficient synthesis route for phenanthridine compounds and lays a material foundation for the application of such compounds in the fields of medicines and materials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152734.

References

[1] (a) F.-R. Stermitz, K.-A. Larson, D.-K. Kim, J. Med. Chem. 16 (1973) 939–940;
(b) Y.-C. Chang, P.-W. Hsieh, F.-R. Chang, R.-R. Wu, C.-C. Liaw, K.-H. Lee, Y.-C. Wu, Planta Med. 69 (2003) 148–152;
(c) J. Fotie, D.-S. Bohle, M. Olivier, M.-A. Gomez, S. Nzimiro, J. N. Prod. 70 (2007) 1650–1653;
(d) S. Pegoraro, M. Lang, T. Dreker, J. Kraus, S. Hamm, C. Meere, J. Feurle, S. Tasler, S. Prütting, Z. Kuras, V. Visan, S. Grissmer, B. Med, Chem. Lett. 19 (2009) 2299–2304;
(e) X.-J. Yang, F. Miao, Y. Yao, F.-J. Cao, R. Yang, Y.-N. Ma, B.-F. Qin, L. Zhou, Molecules. 17 (2012) 13026–13035;
(f) T.-C. Wu, J.-J. Chen, Y.-T. Wu, Org. Lett. 13 (2011) 4794–4797;
(g) C. Krug, J.-F. Hartwig, J. Am. Chem. Soc. 124 (2002) 1674–1679;
(h) M. Pucheault, S. Darses, J.-P. Genet, J. Am. Chem. Soc. 126 (2004) 15356–15357;
(i) S.-U. Son, S.-B. Kim, J.-A. Reingold, G.-B. Carpenter, D.-A. Sweigart, J. Am. Chem. Soc. 127 (2005) 12238–12239;
(k) P.M. Gois, A.-F. Trindade, L.-F. Veiros, V. André, M.-T. Duarte, C.-A.M. Afonso, S. Caddick, F.-G.-N. Cloke, Angew. Chem. Int. Ed. 46 (2007) 5750–5753;
(l) J.-F. Yang, X.-Y. Chen, Z.-Q. Wang, Tetrahedron Lett. 56 (2015) 5673–5675;
(m) T. Yamamoto, T. Ohta, Y. Ito, Org. Lett. 7 (2005) 4153–4155;
(n) K. Suzuki, T. Arao, S. Ishii, Y. Maeda, K. Kondo, T. Aoyama, Tetrahedron 47 (2006) 5789–5792;
(o) P. He, Y. Lu, C.-G. Dong, Q.-S. Hu, Org. Lett. 9 (2007) 343–346;
(k) S. Lin, X. Lu, J. Org. Chem. 72 (2007) 9757–9760;
(p) M. Kuriyama, R. Shimazawa, R. Shirai, J. Org. Chem. 73 (2008) 1597–1600;
(q) Y. Liu, G.-Y. Zhang, H.-M. Huang, Org. Lett. 19 (2017) 6674–6677;
(r) T. Zou, S.-S. Pi, J.-H. Li, Org. Lett. 11 (2009) 453–456.
[2] W. Guo, S. Li, L. Tang, M. Li, L. Wen, C. Chen, Org. Lett. 17 (2015) 1232–1235.
[3] T. Nakanishi, M. Suzuki, J. Nat. Prod. 61 (1998) 1263-1267.
[4] (a) T. Nakanishi, M. Suzuki, A. Saimoto, T. Kabasawa, J. Nat. Prod. 62 (1999) 864–867;
(b) T. Nakanishi, M. Suzuki, Org. Lett. 1 (1999) 985–988;
(c) H. Fuchino, M. Kawano, K.-M. Yasumoto, S. Sekita, Chem. Pharm. Bull. 58 (2010) 1047–1050;
(d) K. Li, K.-J. Frankowski, D.N. Frick, J. Med. Chem. 55 (2012) 3319–3330.
[5] (a) D. Nanni, P. Pareschi, C. Rizzoli, P. Sgarabotto, A. Tundo, Tetrahedron 51 (1995) 9045–9062;
(b) M. Tobisu, K. Koh, T. Furukawa, N. Chatani, Angew. Chem. Int. Ed. 51 (2012) 11363–11366;
(c) B. Zhang, C. Mü ck-Lichtenfeld, C.-G. Daniliuc, A. Studer, Angew. Chem. Int. Ed. 52 (2013) 10792–10795;
(d) Q. Wang, X. Dong, T. Xiao, L. Zhou, Org. Lett. 15 (2013) 4846–4849;
(e) D. Leifert, C.-G. Daniliuc, A. Studer, Org. Lett. 15 (2013) 6286–6289;
(f) H. Jiang, Y. Cheng, R. Wang, M. Zheng, Y. Zhang, S. Yu, Angew. Chem. Int. Ed. 52 (2013) 13289–13292.
[6] (a) C. Saluste, R. Whitby, M. Furber, Angew. Chem. Int. Ed. 39 (2000) 4156–4158;
(b) K. Komeyama, D. Sasayama, T. Kawabata, K. Takehira, K. Takaki, Chem. Commun. 7 (2005) 634–636;
(c) M. Tobisu, A. Kitajima, S. Yoshioka, I. Hyodo, M. Oshita, N. Chatani, J. Am. Chem. Soc. 129 (2007) 11431–11437;
(d) H. Kuniyasu, K. Sugoh, M.-S. Su, H. Kurosawa, J. Am. Chem. Soc. 119 (1997) 4669–4677;
(e) Y. Wang, H. Wang, J. Peng, Q. Zhu, Org. Lett. 13 (2011) 4604–4607;
(f) C. Zhu, W. Xie, J. Falck, Chem.-Eur. J. 17 (2011) 12591–12595;
(g) G.-V. Baelen, S. Kuijer, S. Sergeyev, E. Janssen, U.-W. Maes, E. Ruijter, R.-V.-A. Orru, Chem.-Eur. J. 17 (2011) 15039–15044;
(h) T. Vlaar, E. Ruijter, A. Znabet, E. Janssen, B.-U.-W. Maes, R.-V.-A. Orru, Org. Lett. 13 (2011) 6496–6499;
(i) G. Qiu, Y.-H. He, J. Wu, Chem. Commun. 48 (2012) 3836–3838;
(j) T. Vlaar, R.-C. Cioc, P. Mampuys, B.-U.-W. Maes, R.-V.-A. Orru, E. Ruijter, Angew. Chem. Int. Ed. 51 (2012) 13058–13061;
(k) T. Vlaar, E. Ruijter, B.-U.-W. Maes, R.-V.-A. Orru, Angew. Chem., Int. Ed. 52 (2013) 7084–7097;
(l) G. Qiu, G. Liu, S. Pu, J. Wu, Chem. Commun. 48 (2012) 2903–2905;
(m) G. Qiu, C. Chen, L. Yao, J. Wu, Adv. Synth. Catal. 355 (2013) 1579–1584;
(n) I. Ryn, N. Sonoda, D.-P. Curran, Chem. Rev. 96 (1996) 177–194;
(o) G. Qiu, Q. Ding, J. Wu, Chem. Soc. Rev. 42 (2013) 5257–5269;
(p) S. Lang, Chem. Soc. Rev. 42 (2013) 4867–4880.
[7] (a) T. Gerfaud, L. Neuville, J. Zhu, Angew. Chem., Int. Ed. 48 (2009) 572–577;
(b) W.-G. Shou, Y.-Y. Yang, Y.-G. Wang, J. Org. Chem. 71 (2006) 9241–9243.
[8] S.-P. Marsden, A.-E. McGonagle, B. McKeever-Abbas, Org. Lett. 10 (2008) 2589–2591.
[9] (a) M. Tobisu, K. Koh, T. Furukawa, N. Chatani, Angew. Chem., Int. Ed. 51 (2012) 11363–11366;
(b) B. Zhang, C.G. Daniliuc, A. Studer, Org. Lett. 16 (2014) 250–253;
(c) D. Leifert, C.G. Daniliuc, A. Studer, Org. Lett. 15 (2013) 6286–6289;
(d) I. Deb, N. Yoshikai, Org. Lett. 15 (2013) 4254–4257;
(e) T.-H. Zhu, S.-Y. Wang, Y.-Q. Tao, T.-Q. Wei, S.-J. Ji, Org. Lett. 16 (2014) 1260–1263;
(f) Z. Li, F. Fan, J. Yang, Z.-Q. Liu, Org. Lett. 16 (2014) 3396–3399;
(g) B. Zhang, C. Mueck-Lichtenfeld, C.G. Daniliuc, A. Studer, Angew. Chem., Int. Ed. 52 (2013) 10792–10795;
(h) Z. Xia, J. Huang, Y. He, J. Zhao, J. Lei, Q. Zhu, Org. Lett. 16 (2014) 2546–2549.
[10] (a) L. Zhang, G.Y. Ang, S. Chiba, Org. Lett. 12 (2010) 3682–3685;
(b) M. Lysen, J.L. Kristensen, P. Vedsø, M. Begtrup,-, Org Lett. 4 (2002) 257–259.
[11] (a) M. Blanchot, D.A. Candito, F. Larnaud, M. Lautens, Org. Lett. 13 (2011) 1486–1489;
(b) J. Peng, T. Chen, C. Chen, B. Li, J. Org. Chem. 76 (2011) 9507–9513;
(c) W.-Y. Wang, X. Feng, B.-L. Hu, C.-L. Deng, X.-G. Zhang, J. Org. Chem. 78 (2013) 6025–6030.
[12] (a) J. Pawlas, M.A. Begtrup, Org. Lett. 4 (2002) 2687–2690;
(b) F. Gug, S. Bach, M. Blondel, J.-M. Vierfond, A.-S. Martin, H. Galons, Tetrahedron. 60 (2004) 4705–4708;
(c) F. Gug, M. Blondel, N. Desban, S. Bouaziz, J.-M. Vierfond, H. Galons, Tetrahedron Lett. 46 (2005) 3725–3727.
[13] (a) R.T. McBurney, A.M.Z. Slawin, L.A. Smart, Y. Yu, J.C. Walton, Chem. Commun. 47 (2011) 7974–7976;
(b) F. Portela-Cubillo, E.M. Scanlan, J.S. Scott, J.C. Walton, Chem. Commun. 35 (2008) 4189–4191;
(c) R. Alonso, P.J. Campos, B. García, M.A. Rodríguez, Org. Lett. 8 (2006) 3521–3523;
(d) D.A. Androsov, D.C. Neckers, J. Org. Chem. 72 (2007) 1148–1152;
(e) T. Xiao, L. Li, G. Lin, Q. Wang, P. Zhang, Z.-W. Mao, L. Zhou, Green Chem. 16 (2014) 2418–2421;
(f) X. Sun, S. Yu, Org. Lett. 16 (2014) 2938–2941.
[14] X.-D. An, S. Yu, Org. Lett. 17 (2015) 2692–2695.
[15] (a) M.L. Read, L.-L. Gundersen, J. Org. Chem. 78 (2013) 1311–1316;
(b) F. Portela-Cubillo, J.S. Scott, J.C. Walton, J. Org. Chem. 73 (2008) 5558.
[16] (a) T. Bach, J.P. Hehn, Angew. Chem., Int. Ed. 50 (2011) 1000–1045;
(b) N. Hoffmann, Chem. Rev. 108 (2008) 1052–1103.
[17] C.M. Thompson, S. Docter, Tetrahedron Lett. 29 (1988) 5213–5216.
[18] D. Sanger, C.V. Sonntga, Tetrahedron 26 (1970) 5489–5501.
[19] R.G. Hicks, Org & Biomol Chem. 5 (2007) 1321–1338.
[20] W.R. Bowman, J.E. Lyon, G.J. Pritchard, J. Org. Chem. 7 (2012) 210–227, Arkivoc Online.