Green Chemistry

Accepted Manuscript

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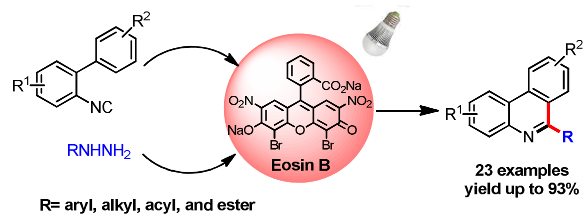

Irradiation of hydrazines and 2-isocyanobiphenyls with visible-light in the presence of organic dye eosin B generates various 6-substituted phenanthridines in good yields.

Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Synthesis of 6-Substituted Phenanthridines by Metal-free, Visible-light Induced Aerobic Oxidative Cyclization of 2‑Isocyanobiphenyls with Hydrazines

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Irradiation of hydrazines with visible-light in the presence of organic dye eosin B generates various types of functional radicals, which are trapped by 2-isocyanobiphenyls to give 6-substituted phenanthridines.

A practical synthesis of phenanthridines is of considerable interest in the fields of organic and pharmaceutical chemistry,[1] since this basic skeleton is widespread in naturally occurring alkaloids and exhibits interesting biological activities.[2] Recently, a cascade radical pathway involving C-radical addition to 2-isocyanobiphenyls and subsequently intramolecular homolytic aromatic substitution has been developed, which allows the rapid assembly of phenanthridine framework with high efficiency.[3] For example, Chatani and co-workers demonstrated a Mn(III)-mediated annulation of 2-isocyanobiphenyls with boronic acid under heating conditions.[3a] We[3b] and Studer[3c] independently reported the synthesis of 6-trifluruomethyl phenanthridines through a CF_3 radical. Very recently, the reaction of 2-isocyanobiphenyls with aromatic aldehydes using ^{t}BuOOH as an oxidant was also developed by Studer.[3d] Each of these methods has its own specific applications, but remains associated with certain disadvantages such as harsh reaction conditions, use of environmentally unfriendly oxidants and limited reaction scope.

As a result of its natural abundance, the use of visible-light as a driving force for green organic synthesis has received much scientific and technological interest in recent years.[4] Although tris(bipyridine) ruthenium and iridium complexes have been proved as powerful photosensitizers in a wide range of organic transformations, organic dyes, which are cheap and easy to modify, would be attractive alternatives compared to metal-based photoredox catalysts.[5] Recently, organic dye has gained considerable attention as an initiator for the generation of aryl radicals from aryl diazonium salts under visible-light condition (scheme 1).[4g] Our group also reported an eosin Y-catalyzed, visible light-induced [4 + 2] benzannulation of biaryl diazonium

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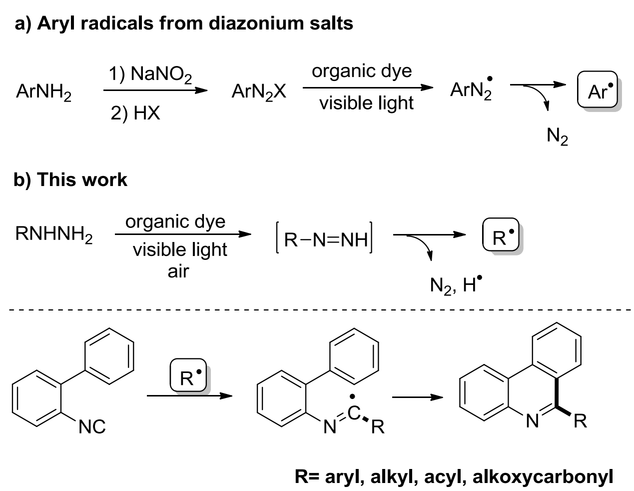
†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/



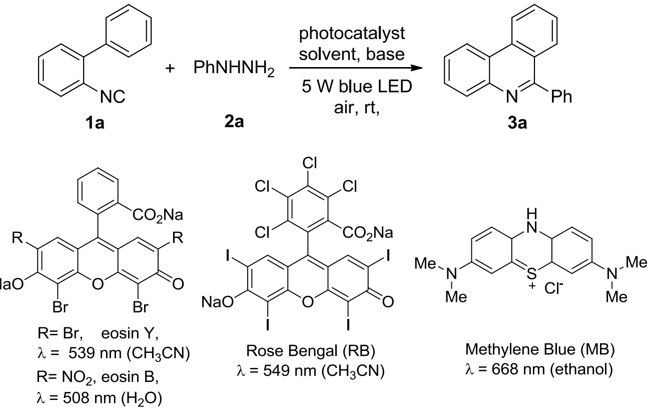
Scheme 1 Radical generation upon visible-light irradiation using organic dye as the photoredox catalyst and our design.

salts with alkynes.[6] However, diazonium salts usually need to be freshly prepared from anilines using stoichiometric amounts of nitrite salts or other oxidants. In addition, radicals other than aryl radicals are less explored because of the limited availability of the corresponding diazonium salts.

On the other hand, the oxidative degradation of hydrazines that leads to radical species has been essentially known for a long time.[7] Various types of radicals including alkyl,[8] aryl,[9] acyl,[10] alkoxycarbonyl,[11] and sulfonyl radicals[12] could be generated from their hydrazine precursors. However, many of these radical reactions were carried in the presence of toxic transition metals. Despite the use of oxygen as an oxidant has been developed, usually with a catalytic amount of copper or iron as the promoter,[9f-g,11,12] there is still no report on the employment of photoredox catalysts to initiate the formation of radical species from hydrazines. Herein we wish to report the use of organic dye eosin B as an efficient initiator for generation of radical species from hydrazines upon visible-light irradiation in the open air, which were trapped by 2-isocyanobiphenyls to give a series of 6-substituted phenanthridines in good yields (scheme 1).[13]

At the outset, a solution of 2-isocyanobiphenyl (**1a**) and phenyl hydrazine (**2a**) in DMSO was irradiated with a 5 W blue LED in

Table 1 Optimization of reaction conditions.[a]

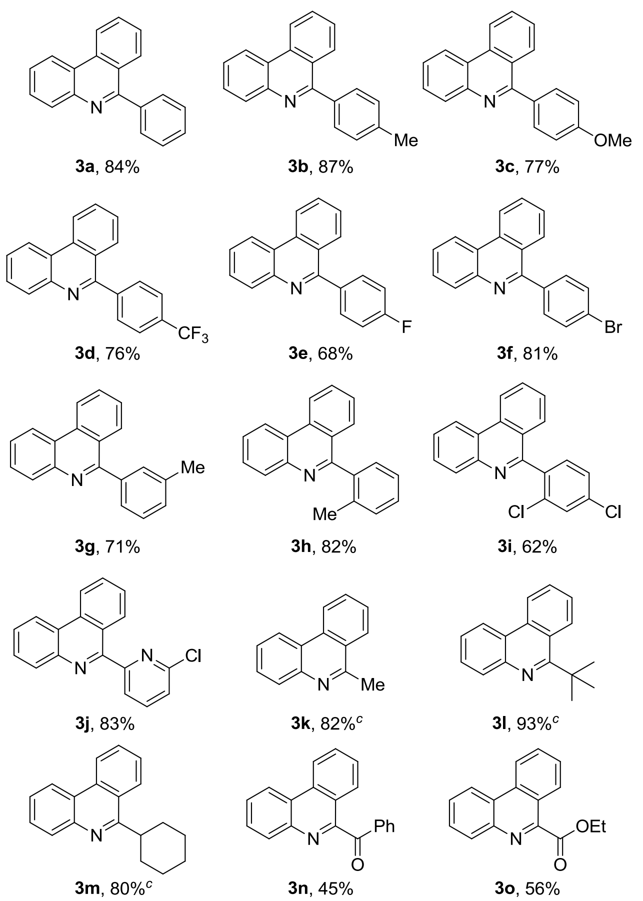


Entry	Catalyst	Solvent	Base	Yield(%)[b].
1	eosin Y	DMSO	none	25
2	eosin B	DMSO	none	64
3	RB	DMSO	none	55
4	MB	DMSO	none	13
5	eosin B	DMF	none	61
6	eosin B	MeCN	none	45
7	eosin B	CH_2Cl_2	none	30
8	eosin B	1,4-dioxane	none	28
9	eosin B	THF	none	33
10	**eosin B**	**DMSO**	**K_2CO_3**	**89**
11	eosin B	DMSO	Na_2CO_3	62
12	eosin B	DMSO	K_2HPO_4	74
13	none	DMSO	K_2CO_3	<10
14	CuI	DMSO	K_2CO_3	11
15	$FeBr_3$	DMSO	K_2CO_3	trace
16[c]	eosin B	DMSO	K_2CO_3	<10
17[d]	eosin B	DMSO	K_2CO_3	0

[a] 2-isocyanobiphenyl **1a** (0.2 mmol), phenyl hydrazine **2a** (0.6 mmol), base (3 equiv), solvent (1 mL), catalyst (5 mol%), rt in the open air for 18 h. [b] Yields were determined by ^{1}HNMR analysis using CH_3NO_2 as internal standard. [c] The reaction was carried out in the absence of light. [d] Under the protection of nitrogen.

the presence of eosin Y at room temperature. We are delight to find that the desired phenanthridine **3a** was obtained in 25% yield (Table 1, entry 1). An survey of organic dyes demonstrated that eosin B is the best choice of photoredox catalysts, which may attribute to its stronger absorption ability in the range of blue light (Table 1, entries 1-4).[14] The reactions irradiated with household light bulbs or green LED strips provided somewhat diminshed yields and slower rates (see Table S1 in the supporting information). Varying the solvents proved DMSO to be optimal (Table 1, entries 5-9). Further optimizations revealed that this reaction proceeded more efficiently in the presence of inorganic base, and the use of K_2CO_3 gave the best result (Table 1, entries 10-12). Although the slow generation of radical species from hydrazines with only O_2 was reported,[9f-g] less than 10% yield of product was detected in the absence of eosin B, and 85% of phenyl hydrazine remained unreacted after the reaction mixture was stirred at room temperature for 72 h (Table 1, entry 13). This result indicates that eosin B significantly accelerates this reaction as a promoter.[15] However, when CuI or $FeBr_3$ was employed as a

Table 2 Reaction scope of hydrazines.[a,b]

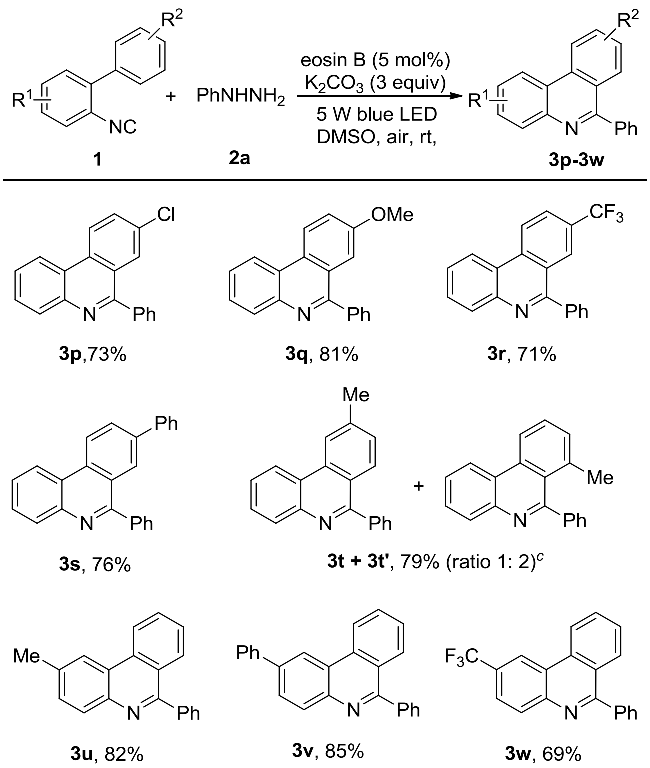


[a] All the reactions were carried out by using 2-isocyanobiphenyl **1a** (0.2 mmol), hydrazines **2** (0.6 mmol), K_2CO_3 (3 equiv), DMSO (1 mL), eosin B (5 mol%) at room temperature in the open air with the irradiation of a 5 W blue LED for 18 h. [b] Isolated yield. [c] Hydrazine hydrochlorides were directly used as the substrates.

catalyst, the reaction resulted in complex mixtures and only trace amount of phenanthridine **3a** was obtained (Table 1, entries 14 and 15). In the control experiments, the reaction was found to be completely shut down without the irradiation of the light or under nitrogen atmosphere (Table 1, entries 16 and 17).

With the optimized reaction conditions in hand, we next explored the scope of the reaction with 2-isocyanobiphenyl (**1a**) and a variety of hydrazines. First, different substituted phenyl hydrazines were examined, and they were found to undergo the reactions with **1a** smoothly to give 6-arylated phenanthridine derivatives **3a-i** in good yields. The reaction tolerates various functional groups including methyl, methoxy, trifluoromethyl, and halogen (F, Cl, Br) presented in the aryl hydrazines. As shown in Table 2, *ortho*-, *para*-, and *meta*- substituted toyl hydrazines all worked well in the present system to afford the phenanthridines in good yields. Besides, 2-chloro-6-hydrazinopyridine was also suitable for the reaction, yielding the desired product **3j** in 83%. To further expand the scope of the reaction, alkyl hydrazines were employed as substrates under optimized reaction conditions. We are delight to find that the reactions of 2-isocyanobiphenyl (**1a**) with methylhydrazine, *tert*-butylhydrazine and cyclohexylhydrazine can furnish the corresponding phenanthridines **3k-m** in good to excellent yields. Similarly, a benzoyl group (**3n**) and an ester group (**3o**) were successfully introduced onto the 6-position of phenanthridines, albeit with low efficiency.

Table 3 Reaction scope of isocyanides.[a, b]



[a] All the reactions were carried out under same conditions as described in Table 2. [b] Isolated yield. [c] The ratio was determined by ^{1}H-NMR.

Next, the scope of 2-isocyanobiaryl compounds was examined. As shown in Table 3, the isocyanides bearing either electron-rich or electron-deficient substituent on 4′-position of the aromatic ring all underwent the reactions smoothly to give the corresponding 6- phenyl phenanthridines **3p-s** in similar yields. When the *meta*-methyl derivative was employed, the reaction afforded the two regioisomers **3t** and **3t′** in a ratio of 1: 2. The reaction was not significantly affected by the substitutent on the aromatic ring attached to isocyanides, such as methyl, phenyl, trifluoromethyl groups, leading to the phenanthridines **3u-w** in the yields of 82%, 85% and 69% respectively.

In conclusion, we have described the use of organic dye eosin B as the initiator for the generation of radical species from hydrazines upon visible-light irradiation in the open air. Through the radical cyclization of 2−isocyanobiphenyls with hydrazines under environmentally friendly conditions, the reaction allows the rapid assembly of phenanthridine framework, a common structural unit present in a wide variety of naturally occurring alkaloids. Various functional groups including aryl, alkyl, acyl, and ester were introduced onto the 6-position of phenanthridines in good to excellent yields. Instead of ruthenium and iridium based photosensitizers, the reaction proceeded under metal-free conditions by using inexpensive and easily available organic dye as a photoredox catalyst. These advantages may make this method find potential applications in the synthesis of 6-substituted phenanthridines. Further investigations on the mechanistic details and related radical processes are currently underway in our laboratory.

Acknowledgements

We thank the National Natural Science Foundation of China (Grant Nos. 21202207 and J1103305), the Research Fund for Guangzhou Peal River New Star of Science and Technology (Grant No. 2013J2200017) and the Program for Changjiang Scholars and Innovative Research Team in University of China (Grant No. IRT1298) for the financial support.

Notes and references

1 For recent examples of the synthesis of phenanthridines, see: (*a*) M. L. Read and L.-L. Gundersen, *J. Org. Chem.* 2013, **78**, 1311; (*b*) Y. Wu, S. M. Wong, F. Mao, T. L. Chan and F. Y. Kwong, *Org. Lett.* 2012, **14**, 5306; (*c*) D. Intrieri, M. Mariani, A. Caselli, F. Ragaini and E. Gallo, *Chem. Eur. J.* 2012, **18**, 10487; (*d*) R. T. McBurney, A. M. Z. Slawin, L. A. Smart, Y. Yu and J. C. Walton, *Chem. Commun.* 2011, **47**, 7974; (*e*) J. Peng, T. Chen, C. Chen and B. Li, *J. Org. Chem.* 2011, **76**, 9507; (*f*) A. M. Linsenmeier, C. M. Williams and S. Bräse, *J. Org. Chem.* 2011, **76**, 9127; (*g*) Y. Zhou, J. Dong, F. Zhang and Y. Gong, *J. Org. Chem.* 2011, **76**, 588; (*h*) M. E. Budén, V. B. Dorn, M. Gamba, A. B. Pierini and R. A. Rossi, *J. Org. Chem.* 2010, **75**, 2206; (*h*) N. D. Cá, E. Motti, A. Mega and M. Catellani, *Adv. Synth. Catal.* 2010, **352**, 1451; (*i*) G. Maestri, M. H. Larraufie, E. Derat, C. Ollivier, L. Fensterbank, E. Lacote and M. Malacria, *Org. Lett.* 2010, **12**, 5692.

2 (*a*) M. Suffness and G. A. Cordell, The Alkaloids, Academic, New York, 1985, vol. 25, pp. 178–189; (*b*) T. Nakanishi and M. Suzuki, *J. Nat. Prod.* 1998, **61**, 1263; (*c*) T. Nakanishi, M. Suzuki, A. Saimoto and T. Kabasawa, *J. Nat. Prod.* 1999, **62**, 864; (*d*) T. Nakanishi and M. Suzuki, *Org. Lett.* 1999, **1**, 985; (*e*) T. Nakanishi, A. Masuda, M. Suwa, Y. Akiyama, N. Hoshino-Abe and M. Suzuki, *Bioorg. Med. Chem. Lett.* 2000, **10**, 2321;

3 (*a*) M. Tobisu, K. Koh, T. Furukawa and N. Chatani, *Angew. Chem. Int. Ed.* 2012, **51**, 11363; (*b*) Q. Wang, X. Dong, T. Xiao and L. Zhou, *Org. Lett.* 2013, **15**, 4846; (*c*) B. Zhang, C. Mck-Lichtenfeld, C. G. Daniliuc and A. Studer, *Angew. Chem. Int. Ed.* 2013, **52**, 10792; (*d*) D. Leifert, C. G. Daniliuc and A. Studer, *Org. Lett.* 2013, **15**, 6286.

4 For reviews on visible-light photoredox catalysis, see: (*a*) J. Xie, H. Jin, P. Xu, C. Zhu, *Tetrahedron Lett*, 2014, **55**, 36; (*b*) M. Reckenthälera and A. G. Griesbeck, *Adv. Synth. Catal.* 2013, **355**, 2727; (*c*) J. Xuan, L.-Q. Lu, J.-R. Chen and W.-J. Xiao, *Eur. J. Org. Chem.* 2013, 6755; (*d*) Y.-Q. Zou, J.-R. Chen and W.-J. Xiao, *Angew. Chem. Int. Ed.* 2013, **52**, 11701; (*e*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.* 2013, **113**, 5322; (*f*) Y. Xi, H. Yi and A. Lei, *Org. Biomol. Chem.* 2013, **11**, 2387; (g) D. P. Hari and B. König, *Angew. Chem. Int. Ed.* 2013, **52**, 4734; (h) L. Shi and W. J. Xia, *Chem. Soc. Rev.* 2012, **41**, 7687; (*i*) J. Xuan and W. J. Xiao, *Angew. Chem. Int. Ed.* 2012, **51**, 6828; (*j*) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.* 2011, **40**, 102; (*k*) T. P. Yoon, M. A. Ischay and J. N. Du, *Nat. Chem.* 2010, **2**, 527; (*l*) K. Zeitler, *Angew. Chem. Int. Ed.* 2009, **48**, 9785.

5 For recent examples using organic dyes as the photoredox catalyst see: (*a*) M. Rueping, C. Vila and T. Bootwicha, *ACS Catal.* 2013, **3**, 1676; (*b*) D. P. Hari, P. Schroll and B. König, *J. Am. Chem. Soc.*

2012, **134**, 2958; (*c*) D. P. Hari, T. Hering and B. König, *Org. Lett.* 2012, **14**, 5334; (*d*) T. Hering, D. P. Hari and B. König, *J. Org. Chem.* 2012, **77**, 10347; (*e*) Q. Liu, Y.-N. Li, H.-H. Zhang, B. Chen, C.-H. Tung and L.- Z. Wu, *Chem. Eur. J.* 2012, **18**, 620; (*f*) K. Fidaly, C. Ceballos, A. Falguières, M. S.-I. Veitia, A. Guy and C. Ferroud, *Green Chem.* 2012, **14**, 1293; (*g*) J. Yu, L. Zhang and G. Yan, *Adv. Synth. Catal.* 2012, **354**, 2625; (*h*) M. Neumann, S. Füldner, B. König and K. Zeitler, *Angew. Chem., Int. Ed.* 2011, **50**, 951; (*i*) D. P. Hari and B. König, *Org. Lett.* 2011, **13**, 3852; (*j*) Y. Pan, C. W. Kee, L. Chen and C.-H. Tan, *Green Chem.* 2011, **13**, 2682; (*k*) Y. Pan, S. Wang, C. W. Kee, E. Dubuisson, Y. Yang, K. P. Loha and C.-H. Tan, *Green Chem*. 2011, **13**, 3341.

6 T. Xiao, X. Dong, Y. Tang, L. Zhou, *Adv. Synth. Catal.* 2012, **354**, 3195.

7 (*a*) F. D. Chattaway, *J. Chem. Soc. Trans.* 1907, **91**, 1323; (*b*) R. L. Hardie and R. H. Thomson, *J. Chem. Soc.* 1957, 2512; (c) F. L. Scott and J. A. Barry, *Tetrahedron Lett.* 1968, **9**, 2461; (*d*) E. S. Huyser and R. H. S. Wang, *J. Org. Chem.* 1968, **33**, 3901.

8 (*a*) E. J. Corey and A. W. Gross, *J. Org. Chem.* 1985, **50**, 5391; (*b*) R. Braslau, L. C. Burrill II, L. K. Mahal and T. Wedeking, *Angew. Chem. Int. Ed.* 1997, **36**, 237; (*c*) R. Braslau, N. Naik and H. Zipse, *J. Am. Chem. Soc.* 2000, **122**, 8421.

9 (*a*) A. S. Demir, Ö. Reis and E. Özgül-Karaaslan, *J. Chem. Soc. Perkin Trans. 1* 2001, 3042; (*b*) A. S. Demir, Ö. Reis and M. Emrullahoğlu, *Tetrahedron* 2002, **58**, 8055; (*c*) Z.-X. Chen and G.-W. Wang, *J. Org. Chem.* 2005, **70**, 2380; (*d*) B. Stefane and S. Polanc, *Synlett* 2008, 1279; (*e*) G.-W. Wang, Y.-M. Lu and Z.-X. Chen, *Org. Lett.* 2009, **11**, 1507; (*f*) T. Taniguchi, H. Zaimoku and H. Ishibashi, *Chem. Eur. J.* 2011, **17**, 4307; (*g*) Y. Su, X. Sun, G. Wu and N. Jiao, *Angew. Chem. Int. Ed.* 2013, **52**, 9808.

10 (*a*) R. Braslau, M. O. Anderson, F. Rivera, A. Jimenez, T. Haddad and J. R. Axon, *Tetrahedron Lett.* 2002, **58**, 5513; (*b*) S. Bath, N. M. Laso, H. Lopwz-Ruiz, B. Quiclet-Sire and S. Z. Zard, *Chem. Commun.* 2003, 204.

11 T. Taniguchi, Y. Sugiura, H. Zaimoku and H. Ishibashi, *Angew. Chem. Int. Ed.* 2010, **49**, 10154.

12 T. Taniguchi, A. Idota and H. Ishibashi, *Org. Biomol. Chem.*, 2011, **9**, 3151.

13 During the present study, the first visible-light promoted synthesis of 6-alkylated phenanthridine derivatives using [*fac*-Ir(ppy)$_3$] as the photoredox catalyst was reported by Yu and coworkers. H. Jiang, Y. Cheng, R.Wang, M. Zheng, Y. Zhang and S. Yu, *Angew. Chem. Int. Ed.* 2013, **52**, 13289. Two reports on the synthesis of 6‑phosphorylated and 6-acyl phenanthridines through a radical pathway aslo appeared: a) B. Zhang, C. G. Daniliuc and A.Studer, *Org. Lett.* 2014, **16**, 250; b) J. Liu, C. Fan, H. Yin, C. Qin, G. Zhang, X. Zhang, H. Yi and A. Lei, *Chem. Commun*. 2014, DOI: 10.1039/C3CC49026B.

14 M. L. Marin, L. Santos-Juanes, A. Arques, A. M. Amat and M. A. Miranda, *Chem. Rev.* 2012, **112**, 1710.

15 See supporting information for a plausible reaction mechanism for this radical cyclization reaction.