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Letter

Photoredox Catalysis toward 2-Sulfenylindole Synthesis through a Radical Cascade Process

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01297

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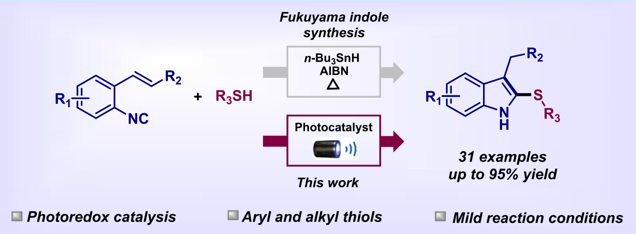
ABSTRACT: A radical cascade process initiated through visible-light induced thiyl radical coupling with *ortho*-substituted arylisocianides followed by an intramolecular cyclization and subsequent aromatization to access 2-sulfenylindoles is described. The key thiyl radicals are promptly generated via a hydrogen atom transfer event. The redox-neutral protocol features broad substrate scope, excellent functional group tolerance, and mild reaction conditions. Furthermore, the implementation of a continuous flow variant allows smooth scalability with a short residence time through process intensification.



The indole motif has been recognized as a privileged framework frequently found in biologically active natural products, agrochemicals, and pharmaceuticals.[1] In particular, this chemical architecture is present in almost 7% of the US FDA approved drugs, consequently standing as one of the most prevalent five-membered nitrogen-based heterocycles.[2] Moreover, a structural analysis reveals that the majority of these indole-based drugs predominantly possess functionalization at the C3 and C5 positions, followed by the C2 position. Recently, sulfenylindoles and derivatives have attracted more attention due to their pronounced biological and pharmaceutical activities, e.g. anti-inflammatory, antitumoral and antiviral (Figure 1).[3]

Therefore, methods that enable selective functionalization or efficient synthesis of sulfur-containing indole derivatives have been pursued.[4]

Among the vast array of described methods for assembling functionalized indoles[5] the initial report disclosed by Fukuyama and co-workers[6] encompassing radical isocyanide insertion followed by an intramolecular cyclization is still attractive. Although the efficiency of this cascade strategy is recognized, the radical generation often requires stoichiometric amounts of a radical initiator (e.g., AIBN and SnBu$_4$ among others), which denotes that the approach was neither environmentally friendly nor broad-functional group compatible, justifying the search for alternative methods for radical generation.[7]

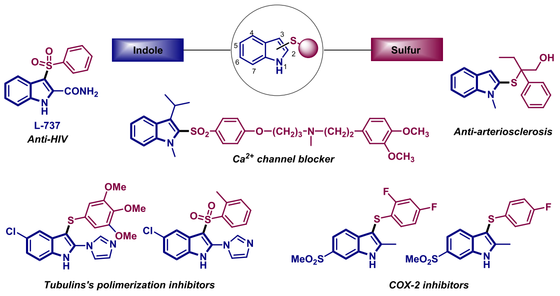


Figure 1. Selected examples of biologically active compounds containing the sulfenylindole scaffold and derivatives.

Over the past decade, visible-light-induced photoredox catalysis has emerged as a greener strategy to generate radicals under mild reaction conditions.[8] Accordingly, progress in understanding reaction mechanisms and the properties of photogenerated reactive intermediates has enabled photocatalytic construction of heterocycles and late-stage functionalization.[9] As a result, highly functionalized *N*-heterocycles including indole-based scaffolds have been synthesized via visible-light-mediated radical isocyanide insertion.[10]

Recently, an interesting visible-light promoted radical cascade addition/cyclization protocol was reported toward the construction of 2-thioarylated indole-3-glyoxylate derivatives using of the iridium complex as photocatalyst and diaryl disulfides.[11] Additionally, photoredox catalysis has also been applied in the synthesis of sulphenylated indoles under mild reaction conditions.[12] Although several methodologies have

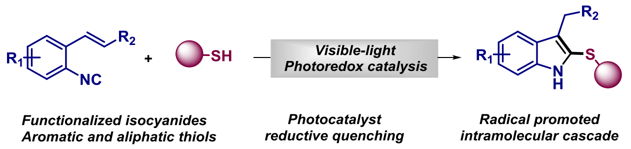
Received: April 13, 2020

demonstrated success in obtaining *S*-aryl indoles,[13] scarce reports for the assembly of *S*-alkyl indols has been unveiled.

In considering complementary strategies to promote the construction of sulfur-containing indole framework, an alternative photoredox catalytic reaction to promote its construction was envisioned.

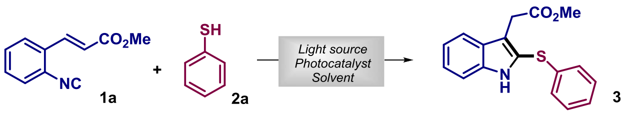
As part of our research program on visible-light-promoted radical cascade reaction in the synthesis of nitrogen-containing heterocycles[14] we herein report a general photocatalytic approach to highly substituted 2-sulfenylindoles through radical thiyl insertion to isocyanides where the thiyl radical generation occurs from thiols under the already described photoredox condition (Scheme 1).

Scheme 1. Photoredox Approach for the Synthesis of 2-Sulfenylindole via Photoredox Catalysis



Our optimization study began with the reaction using 1-isocyano-2-styryl acetate (**1a**) and benzenethiol (**2**) as model substrates (Table 1). We first examined some conditions for thiyl radical generation.[12,14−18] Such approaches have been previously applied in the visible-light photocatalytic thiol−ene reaction, and they are distinguishable mainly by the photocatalyst and solvent of choice (Table 1, entries 1−5).

Table 1. Optimization of the Reaction Conditions



entry[a]	photocatalyst	additive	solvent	yield[b] (%)
1	$[Ru(bpy)_3](PF_6)_2$		DMSO	43
2[c]	eosin Y		CH_3CN	traces
3[d]	rose bengal		DCM	18
4[e]	pyrylium salt		CH_3CN	traces
5[d]	acetophenone		THF	22
Deviation from the Optimal Conditions (Entry 1)				
6[f]	$[Ru(bpy)_3](PF_6)_2$	*p*-toluidine	DMSO	40
7[f,g]	$[Ru(bpy)_3](PF_6)_2$	*p*-toluidine	DMSO	60
8[f,h]	$[Ru(bpy)_3](PF_6)_2$	*p*-toluidine	DMSO	70
9[i]	$[Ru(bpy)_3](PF_6)_2$	*p*-toluidine	DMSO	26
10[j]	$[Ru(bpy)_3](PF_6)_2$	*p*-toluidine	DMSO	0
11	$[Ru(bpy)_3](PF_6)_2$	-	DMSO	18
12		*p*-toluidine	DMSO	0
13[k]	$[Ru(bpy)_3](PF_6)_2$	*p*-toluidine	DMSO	0

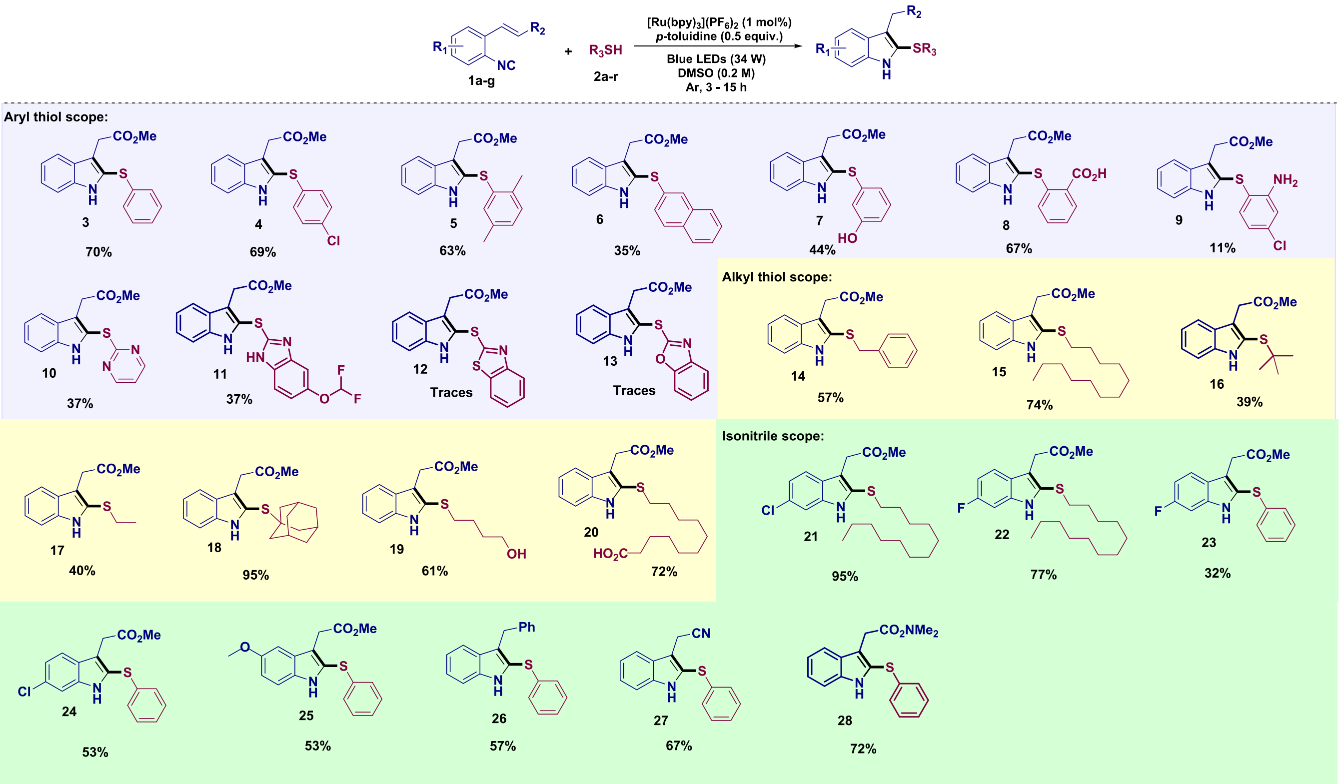
[a] Unless otherwise mentioned, reactions were performed in a 0.1 mmol scale; using 1 equiv of **1a**, 1 equiv of **2a**, 5 mol % of photocatalyst, and 0.5 equiv of *p*-toluidine in 0.5 mL of solvent under blue LED irradiation (see the SI for details). [b] Yields were determined by ^1H NMR analysis of the crude mixture relative to an internal standard. [c] Green LEDs were used as radiation source (7 W). [d] Reaction was performed with two household bulbs (2 × 24 W). [e] Reaction was conducted using 2,4,6-tri(p-tolyl)pyrylium tetrafluoroborate salt as photocatalyst. [f] Reaction was conducted using 1 mol % of $[Ru(bpy)_3](PF_6)_2$ as photocatalyst. [g] Degassed solvent and argon atmosphere. [h] 1.2 equiv of **2a**. [i] Reaction was performed using 1.2 equiv of phenyl disulfide as thiyl radical precursor. [j] Reaction was performed in the presence of TEMPO. [k] Reaction was performed in the absence of light.

Delightfully, when the photocatalytic condition previously described by Yoon[15] and co-workers for thiyl radical generation were applied, the expected cascade product **3** was obtained in 43% yield (entry 1). The described condition employs $[Ru(bpy)_3](PF_6)_2$ as the photocatalyst and *p*-toluidine as electron-transfer mediator in DMSO under blue LED radiation. Moreover, the compatibility of distinctive photochemical protocols, for the thiyl radical generation, has been further evaluated for this cascade annulation strategy (Table 1, entries 2−5). Nonetheless, neither of these strategies delivered the desired 2-sulfenylindole as efficiently as the previous methodology (entry 1 vs entries 2−5, see the Supporting Information for procedure details). After a set of experiments, we focused on fine tuning the reaction conditions presented in entry 1; first, by decreasing the photocatalyst loading to 1 mol %, only a slight erosion in efficiency was observed, with the desired product being obtained in 40% yield (Table 1, entry 6). Furthermore, the solvent system was completely degassed, and the photocatalytic radical cascade reaction gave the indole-derivative in 60% yield (Table 1, entry 7). Fortunately, when the amount of benzenethiol was increased to 1.2 equiv, the compound **3** could be obtained in 70% yield (Table 1, entry 8). Next, a series of solvents were screened (see the Supporting Information), and DMSO gave the optimal result. We further consider whether the photocatalytic cascade triggered by thiyl radical could be accessed using phenyl disulfide as the radical precursor. However, the product was obtained in low yields under our conditions. This result corroborates with the proposed reductive quenching cycle of the photocatalyst, which precludes the reduction of the disulfide for generation of thiyl radical (entry 9).

Aiming to gain insights into the reaction mechanism of the photocatalytic-induced cascade reaction, we performed some additional experiments. When a radical trap such as TEMPO was added to the system, a complete inhibition of the reaction was observed, strongly suggesting a radical pathway for this transformation (entry 10). Accordingly, control experiments reveal that there was no conversion either in the absence of visible-light irradiation or photocatalyst (entries 12 and 13). Finally, low conversion was observed in the absence of *p*-toluidine, a Brønsted base co-catalyst (entry 11).

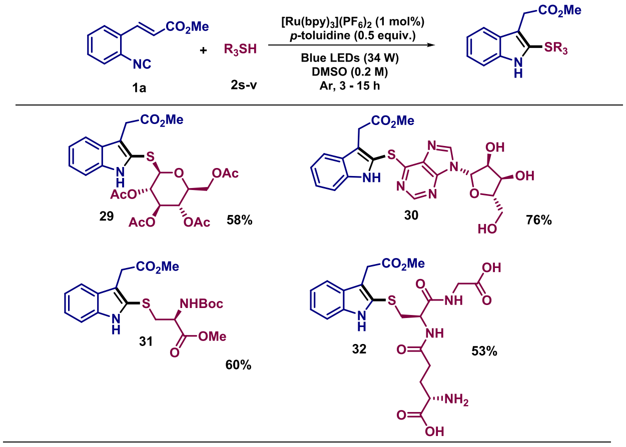
With the optimized reaction conditions in hand, we turned our attention to evaluating the scope and limitation of our cascade protocol toward a range of thiols and isocyanides. To our satisfaction, the optimized reaction conditions were found to be generally applicable for aromatic thiols bearing diverse electronic properties (Scheme 2, compounds **3**−**11**). The reaction tolerated halogen, carboxylic acid and hydroxyl groups in the aromatic rings. The electronic effect of these substituents was not initially found to be problematic. However, the methodology has demonstrated limitations regarding aniline derivatives containing thiols affording the corresponding products in poor yields (Scheme 2, compound **9**). In addition, the redox-neutral photocatalytic protocol was shown to be compatible with 2-mercaptopyrimidine—*a heteroaryl framework present in biorelevant molecules*—yielding the corresponding indole scaffold **10** in 43% yield. Moreover, 5-(difluoromethoxy)-2-mercapto-1*H*-benzimidazole did not interfere with the cascade reaction, although the desired indole was obtained in low yield (Scheme 2, compound **11**,

Scheme 2. Substrate Scope with Varied Thiols and Isocyanides[a]



[a] Unless otherwise stated, reactions were conducted in a 0.10 mmol scale under argon atmosphere. Isolated yields are shown below the structure of products (Supporting Information gives the experimental details: 0.1 mmol of **1a−g**, 0.12 mmol of **2a−r**, 1 mol % of photocatalyst, 0.05 mmol of *p*-toluidine, 0.5 mL of degassed DMSO under blue LEDs radiation).

Scheme 3. Reaction Scope: Synthesis of 2-sulfenylindoles from biomolecules[a]



[a] Unless otherwise stated, reactions were conducted in a 0.10 mmol scale under argon atmosphere. Isolated yields are shown below the structure of products (Supporting Information gives the experimental details: 0.1 mmol of **1**, 0.12 mmol of **2s−v**, 1 mol % of photocatalyst, 0.05 mmol of *p*-toluidine, 0.5 mL of degassed DMSO under blue LEDs radiation).

37% yield). However, under the optimized reaction conditions, the radical annulation employing mercaptobenzothiazole and mercaptobenzoxazole occurred in a small extent or did not proceed. Thus, these substrates currently represent a limitation of the described methodology (compounds **12** and **13**).

We also tested the effectiveness of the protocol for a variety of alkyl thiols, and some examples worked better than aryl thiols. To our delight, aliphatic thiols, including benzylic, cyclic, acyclic, and short and long chain, could be used (compounds **14**−**20**).

We next sought to explore the generality of this methodology with respect to the isocyanide partner (Scheme 2, compounds **21**−**28**). To this end, a variety of 2-alkenylarylisocyanides were synthesized to explore the efficiency of this method. Both electron-donating and -withdrawing groups attached at altered positions of the aromatic ring in the isocyanide **1a** were tolerated, affording the corresponding indole in good yields (compounds **24** and **25**). Furthermore, isocyanide partners bearing other substituents such as phenyl, nitrile, and amide, performed well (compounds **26**−**28**).

Given the broad generality and operational simplicity of this photocatalytic cascade protocol triggered by the thiyl radical, we intended to explore the application of the methodology to late-stage diversification of highly functionalized biomolecules (Scheme 3). At first, the photoinitiated cascade protocol was then extended to glycosyl thiol for the synthesis of a hybrid molecule containing both the indole and saccharide rings (compound **29**, 58% yield). Nonetheless, arabinosyl-6-mercaptopurine was shown to be an excellent thiyl radical precursor under the optimized reaction conditions, furnishing the corresponding indole-derivative in high efficiency (compound **30**, 76% yield). Moreover, the redox-neutral photocatalytic method exhibits good tolerance to *S*-containing amino acids. The reaction between *N*-Boc-cysteine-OMe and the ortho-substituted arylisocyanide **1a** readily underwent radical addition/cyclization to provide a new amino acid **31** in 60% yield.

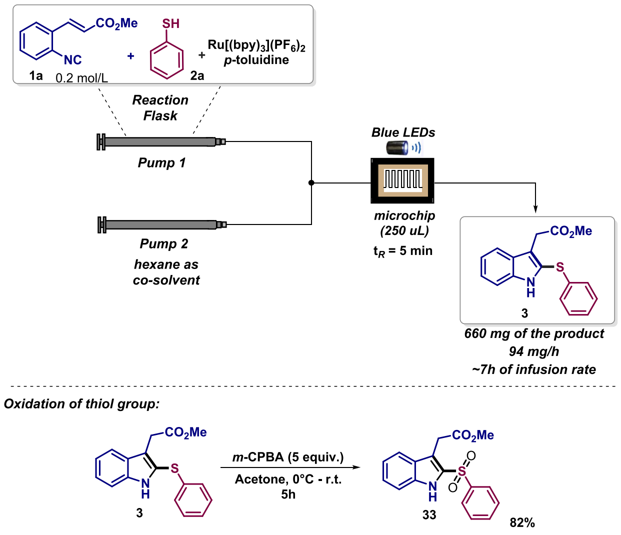
We were pleased to find that the tripeptide glutathione was compatible under the standard photocatalytic condition, affording the desired indole-containing tripeptide **32** in 53% yield. It can be anticipated that the unique features of this photoredox-mediated radical cascade protocol would also enable further exploration in both polypeptide cross-linking and antibody−drug conjugation.[19]

Recognizing the potential value of these thiol-containing indoles to the synthetic and pharmaceutical communities, we envisioned exploring the scale-up potential of this methodology by utilizing microreactor technology. It is noteworthy that besides efficiency of mass, energy, and electron transfer, the continuous flow process offers other benefits, namely safety and precision, therefore allowing process intensification.[20]

To this end, the designed flow setup was assembled employing two syringe pumps, fluorinated ethylene propylene (FEP) as capillary material, T-mixer, and a glass microreactor chip placed between two 36 W blue LEDs light (see the Supporting Information for details).

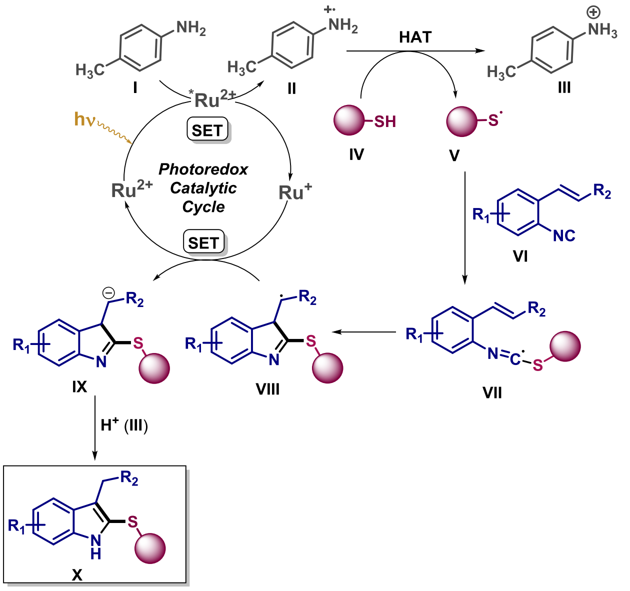
Gratifying, we observed that a residence time (t_R) of 5 min was adequate to achieve complete conversion of the isocyanide intermediate delivering the desired product in 63% yield (for comparison: under batch conditions, 3 h reaction time, 70% yield). Moreover, by employing the continuous-flow setup, 3.5 mmol of starting material could be continuously converted into the indole derivative around 7 h (2.13 mmol; 660 mg), exhibiting the same selectivity compared to the batch process (Scheme 4).

Scheme 4. Continuous Flow Synthesis of the Indole Derivative and Synthetic Transformation



On the basis of literature precedents by Yoon's group and those outlined in our optimization (Table 1), a reaction mechanism was proposed (Scheme 5). Upon excitation with visible light, the ground-state photocatalyst Ru^{2+} is promoted to oxidizing the metal-to-ligand charge transfer (MLCT) excited state ($*E_{1/2}*^{II/I}$ = +0.77 V vs SCE)[21] which undergoes reductive quenching with the Brønsted base *p*-toluidine (E_0 = +0.72 V),[12] affording reduced form of the photocatalyst Ru^+ along with the generation of an aniline radical cation. Then, the aminium radical cation—through a hydrogen atom abstraction (HAT) event—could oxidize the thiol, therefor generating the thiyl radical (Scheme 5). Next, the thiyl radical addition onto the isocyanide **VI** triggers a chemo- and regioselective radical cascade process, producing the imidoyl radical (**VII**). The intermediate radical further undergoes 5-*exo-trig* cyclization to produce the *α*-carbonyl radical (**VIII**), which is then quenched by the reduced photocatalyst to produce the carbanion **IX** and regenerate the catalyst Ru^{2+} to complete the photoredox cycle. Ultimately, **IX** could be easily protonated to generate the final *S*-containing indole product **X**. Regarding the reaction with arylthiols, it is not possible to exclude the potential presence of benzenethiolate in the reaction media; for that case, the mechanism could start after an electron transfer from thiolate to the $*Ru^{2+}$. The quenching of the photoexcited catalyst leads to the generation of thiyl radical which could be intercepted by the isocyanide.[22]

Scheme 5. Proposed Reaction Mechanism



In summary, we have developed a highly efficient visible-light-mediated radical cascade reaction which provides access to a range of highly *S*-functionalized indoles in a sustainable perspective. Because of the distinct way of generating the thiyl radical, our approach should be seen as an alternative methodology to Reiser's work,[11] which allows the synthesis of 2-thioindoles with different architectures. This operationally simple methodology was shown to be compatible with both aromatic and aliphatic thiols. Furthermore, many sensitive functional groups were tolerated, therefore enabling the application of late stage functionalization of *S*-containing biomolecules. This mild and versatile strategy offers a complementary alternative to the previous reported methodologies. Under the continuous-flow regime, we have demonstrated the scalability of our methodology with a residence time of 5 min through process intensification. Further studies on the applications of this methodology are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01297.

All synthetic procedures for new compounds as well as their analytical data, involving ^{1}H NMR, ^{13}C NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **3−11** and **14−33** (ZIP)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to CNPq (INCT Catálise), FAPESP (14/50249-8, 15/17141-1, 17/03120-8, and 18/12986-1) for financial support. GSK is also acknowledged for the financial support. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

REFERENCES

(1) (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, J. V.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235−2246. (b) Zhang, M. Z.; Chen, Q.; Yang, G. F. *Eur. J. Med. Chem.* **2015**, *89*, 421−441. (c) Pedras, M. S. C.; To, Q. H. *Chem. Commun.* **2016**, *52*, 5880−5883. (d) Tang, K.; Huang, J.; Pan, J.; Zhang, X.; Lua, W. *RSC Adv.* **2015**, *5*, 19620−19623. (e) e Norwood, V. M.; Huigens, R. W. *ChemBioChem* **2019**, *20*, 2273.

(2) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(3) (a) Ragno, R.; Coluccia, A.; La Regina, G.; De Martino, G.; Piscitelli, F.; Lavecchia, A.; Novellino, E.; Bergamini, A.; Ciaprini, C.; Sinistro, A.; Maga, G.; Crespan, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 3172−3184. (b) La Regina, G.; Bai, R.; Rensen, W. M.; Di Cesare, E.; Coluccia, A.; Piscitelli, F.; Famiglini, F.; Reggio, A.; Nalli, M.; Pelliccia, S.; Da Pozzo, E.; Costa, B.; Granata, I.; Porta, A.; Maresca, B.; Soriani, A.; Lannitto, M. L.; Santoni, A.; Li, J.; Cona, M. M.; Chen, F.; Ni, Y.; Brancale, A.; Dondio, G.; Vultaggio, S.; Varasi, M.; Mercurio, C.; Martini, C.; Hamel, E.; Lavia, P.; Novellino, E.; Silvestrini, R. *J. Med. Chem.* **2013**, *56*, 123−149. (c) Ait Mou, Y.; Toth, A.; Cassan, C.; Czuriga, D.; de Tombe, P. P.; Papp, Z.; Lacampagne, A.; Cazorla, O. *Cardiovasc. Res.* **2011**, *91*, 412−419. (d) Campbell, J. A.; Bordunov, V.; Broka, C. A.; Browner, M. F.; Kress, J. M.; Mirzadegan, T.; Ramesha, C.; Sanpablo, B. F.; Stabler, R.; Takahara, P.; Villasenor, A.; Walker, K. A. M.; Wang, J.-H.; Welch, M.; Weller, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4741−4745. (e) Kanbe, K.; Okamura, M.; Hattori, S.; Naganawa, H.; Hamada, M.; Okami, Y.; Takeuchi, T. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 632−635. (f) Sravanthi, T. V.; Manju, S. L. *Eur. J. Pharm. Sci.* **2016**, *91*, 1−10.

(4) For the selective S-functionalization of indoles, see: (a) Nalbandian, C. J.; Miller, E. M.; Toenjes, S. T.; Gustafson, J. L. *Chem. Commun.* **2017**, *53*, 1494−1497. (b) Gensch, T.; Klauck, F. J. R.; Glorius, F. *Angew. Chem., Int. Ed.* **2016**, *55*, 11287−11291. (c) Hostier, T.; Ferey, V.; Ricci, G.; Pardo, D. G.; Cossy, J. *Chem. Commun.* **2015**, *51*, 13898−13901. (d) Pagire, S. K.; Hossain, A.; Reiser, O. *Org. Lett.* **2018**, *20*, 648−651. (e) Ji, Y.-Z.; Li, H.-J.; Zhang, J. Y.; Wu, Y.-C. *Chem. Commun.* **2019**, *55*, 11864−11867.

(5) (a) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263. (b) Batail, N.; Bendjeriou, A.; Lomberget, T.; Barret, R.; Dufaud, V.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 2055−2062. (c) Liu, Y.; Wang, H. *Chem. Commun.* **2019**, *55*, 3544−3547. (d) Velezheva, V. S.; Sokolov, A. I.; Kornienko, A. G.; Lyssenko, K. A.; Nelyubina, Y. V.; Godovikov, I. A.; Peregudov, A. S.; Mironov, A. F. *Tetrahedron Lett.* **2008**, *49*, 7106−7109. (e) Yu, S.; Qi, L.; Hu, K.; Gong, J.; Cheng, T.; Wang, Q.; Chen, J.; Wu, H. *J. Org. Chem.* **2017**, *82*, 3631−3638. (f) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, *134*, 9098−9101. (g) Xia, H. D.; Zhang, Y. D.; Wang, Y. H.; Zhang, C. *Org. Lett.* **2018**, *20*, 4052−4056. (h) Miao, B.; Li, S.; Li, G.; Ma, S. *Org. Lett.* **2016**, *18*, 2556−2559. (i) Feu, K. S.; Deobald, A. M.; Narayanaperumal, S.; Corrêa, A. G.; Paixão, M. W. *Eur. J. Org. Chem.* **2013**, *2013*, 5917−5922. For reviews, see: (j) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29−41. (k) Bartoli, G.; Dalpozzo, R.; Nardi, M. *Chem. Soc. Rev.* **2014**, *43*, 4728−4750. (l) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195−7210. (m) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911.

(6) (a) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (b) Tokuyama, H.; Watanabe, M.; Hayashi, Y.; Kurokawa, T.; Peng, G.; Fukuyama, T. *Synlett* **2001**, 1403−1406.

(7) (a) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080−3082. (b) Yamazaki, O.; Togo, H.; Matsubayashi, S.; Yokoyama, S. *Tetrahedron* **1999**, *55*, 3735−3747.

(8) (a) Blum, T. R.; Miller, Z. D.; Bates, D. M.; Guzei, I. A.; Yoon, T. P. *Science* **2016**, *354*, 1391−1395. (b) Tay, N. E. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2017**, *139*, 16100−16104. (c) Ghosh, I.; Shaikh, R. S.; König, B. *Angew. Chem., Int. Ed.* **2017**, *56*, 8544−8549. (d) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. *Science* **2015**, *349*, 1532−1536. (e) Patel, N. R.; Kelly, C. B.; Siegenfeld, A. P.; Molander, G. A. *ACS Catal.* **2017**, *7*, 1766−1770. For reviews see: (f) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075−10166. (g) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem., Int. Ed.* **2018**, *57*, 10034−10072. (h) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898−6926. (i) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. *Org. Process Res. Dev.* **2016**, *20*, 1156−1163. (j) Lima, C. G. S.; Lima, T. M.; Duarte, M.; Jurberg, I. D.; Paixão, M. W. *ACS Catal.* **2016**, *6*, 1389−1407.

(9) (a) Chen, J. R.; Hu, X. Q.; Lu, L. Q.; Xiao, W. J. *Acc. Chem. Res.* **2016**, *49*, 1911−1923. (b) Pantaine, L. R. E.; Milligan, J. A.; Matsui, J. K.; Kelly, C. B.; Molander, G. A. *Org. Lett.* **2019**, *21*, 2317−2321. (c) Wang, C. H.; Li, Y. H.; Yang, S. D. *Org. Lett.* **2018**, *20*, 2382−2385. (d) Wang, R.; Jiang, H.; Cheng, Y.; Kadi, A. A.; Fun, H. K.;

Zhang, Y.; Yu, S. *Synthesis* **2014**, *46*, 2711−2726. (e) Cavanaugh, C. L.; Nicewicz, D. A. *Org. Lett.* **2015**, *17*, 6082−6085. (f) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, *547*, 79−83.

(10) For synthesis of nitrogen heterocycles by isocyanide insertion, see: (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127−2132. (b) Rainier, J. D.; Kennedy, A. R. *J. Org. Chem.* **2000**, *65*, 6213−6216. (c) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215−3218. (d) Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 1216−1219. (e) Zhang, B.; Studer, A. *Chem. Soc. Rev.* **2015**, *44*, 3505−3521. (f) Sadjadi, S.; Heravi, M. M.; Nazari, N. *RSC Adv.* **2016**, *6*, 53203−53272. (g) Vlaar, T.; Cioc, R. C.; Mampuys, P.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 13058−13061. (h) Mitamura, T.; Iwata, K.; Ogawa, A. *J. Org. Chem.* **2011**, *76*, 3880−3887. (i) Heckman, L. M.; He, Z.; Jamison, T. F. *Org. Lett.* **2018**, *20*, 3263−3267. (j) Li, J.; Caiuby, C. A. D.; Paixão, M. W.; Li, C. J. *Eur. J. Org. Chem.* **2018**, *2018*, 2498−2503.

(11) Vidyasagar, A.; Shi, J.; Kreitmeier, P.; Reiser, O. *Org. Lett.* **2018**, *20*, 6984−6989.

(12) (a) Guo, W.; Tan, W.; Zhao, M.; Tao, K.; Zheng, L. Y.; Wu, Y.; Chen, D.; Fan, X. L. *RSC Adv.* **2017**, *7*, 37739−37742. (b) Chen, M.; Huang, Z.-T.; Zheng, Q.-Y. *Chem. Commun.* **2012**, *48*, 11686−11688.

(13) Wimmer, A.; König, B. *Beilstein J. Org. Chem.* **2018**, *14*, 54−83.

(14) (a) da Silva, G. P.; Ali, A.; da Silva, R. C.; Jiang, H.; Paixão, M. W. *Chem. Commun.* **2015**, *51*, 15110−15113. (b) Caiuby, C. A. D.; Ali, A.; Santana, V. T.; Lucas, F. W. de S.; Santos, M. S.; Corrêa, A. G.; Nascimento, O. R.; Jiang, H.; Paixão, M. W. *RSC Adv.* **2018**, *8*, 12879−12886. (c) Correia, J. T. M.; Silva, G. P.; André, E.; Paixão, M. W. *Adv. Synth. Catal.* **2019**, *361*, 5558−5564.

(15) Tyson, E. L.; Niemeyer, Z. L.; Yoon, T. P. *J. Org. Chem.* **2014**, *79*, 1427−1436.

(16) Keshari, T.; Yadav, V. K.; Srivastava, V. P.; Yadav, L.D. S. *Green Chem.* **2014**, *16*, 3986−3992.

(17) Limnios, D.; Kokotos, C. G. *Adv. Synth. Catal.* **2017**, *359*, 323−328.

(18) Zhao, G.; Kaur, S.; Wang, T. *Org. Lett.* **2017**, *19*, 3291−3294.

(19) (a) Bloom, S.; Liu, C.; Kölmel, D. K.; Qiao, J. X.; Zhang, Y.; Poss, M. A.; Ewing, W. R.; MacMillan, D. W. C. *Nat. Chem.* **2018**, *10*, 205−211. (b) Hoyt, E. A.; Cal, P. M. S. D.; Oliveira, B. L.; Bernardes, G. J. L. *Nat. Rev.* **2019**, *3*, 147−171. (c) Preston, G. W.; Wilson, A. *Chem. Soc. Rev.* **2013**, *42*, 3289−3301. (d) Goldflam, M.; Ullman, C. G. *Front. Chem.* **2015**, *3* (69), 1−8.

(20) (a) Grainger, R.; Heightman, T. D.; Ley, S. V.; Lima, F.; Johnson, C. N. *Chem. Sci.* **2019**, *10*, 2264−2271. (b) Zhang, P.; Weeranoppanant, N.; Thomas, D. A.; Tahara, K.; Stelzer, T.; Russell, M. G.; O'Mahony, M.; Myerson, A. S.; Lin, H.; Kelly, L. P.; Jensen, K. F.; Jamison, T. F.; Dai, C.; Cui, Y.; Briggs, N.; Beingessner, R. L.; Adamo, A. *Chem. - Eur. J.* **2018**, *24*, 2776−2784. (c) Lummiss, J. A. M.; Morse, P. D.; Beingessner, R. L.; Jamison, T. F. *Chem. Rec.* **2017**, *17*, 667−680. (d) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 1613−1619. (e) Cambie, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noel, T. *Chem. Rev.* **2016**, *116*, 10276−10341.

(21) Prier, C. K.; Rankic, D. A.; MacMillan, D. W.C. *Chem. Rev.* **2013**, *113*, 5322−5363.

(22) Miyashita, T.; Matsuda, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1740−1742.