Letter

Visible-Light-Driven Synthesis of 4-Alkyl/Aryl-2-Aminothiazoles Promoted by In Situ Generated Copper Photocatalyst

wenlong lei, Tao Wang, Kai-Wen Feng, Li-Zhu Wu, and Qiang Liu

ACS Catal., **Just Accepted Manuscript** • Publication Date (Web): 20 Oct 2017

Visible-Light-Driven Synthesis of 4-Alkyl/Aryl-2-Aminothiazoles Promoted by In Situ Generated Copper Photocatalyst

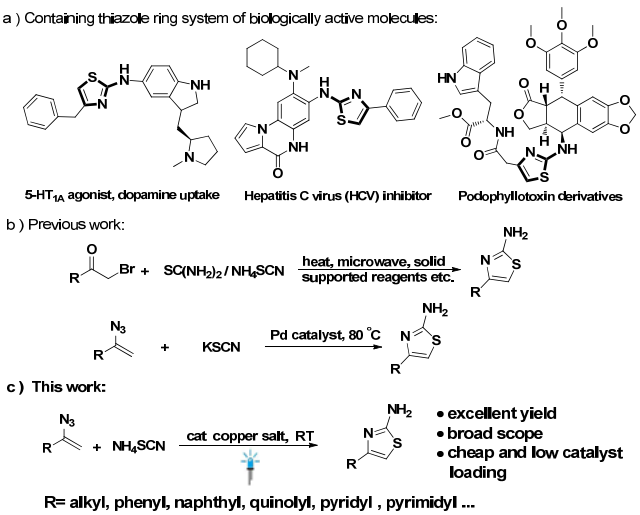
Wen-Long Lei,[†] Tao Wang,[†] Kai-Wen Feng,[†] Li-Zhu Wu,[‡] Qiang Liu*[†]

†State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China.

‡Key Laboratory of Photochemical Conversion and Optoelectronic Materials, Technical Institute of Physics and Chemistry & University of Chinese Academy of Sciences, the Chinese Academy of Sciences, Beijing 100190, P. R. China.

ABSTRACT: Room-temperature synthesis of 4-alkyl/aryl-2-aminothiazoles from vinyl azides and ammonium thiocyanate was accomplished with the aid of copper salts and blue LED irradiation. Mechanism investigation indicates that in situ formed $Cu(NCS)_2^-$ plays dual important roles in the reaction: 1) as the photocatalyst to activate vinyl azides, 2) as the Lewis acid catalyst to promote ring opening of 2*H*-azirines with thiocyanide. This process is distinguished by high yields, mild conditions, low catalyst loadings and tolerating numerous alkyl- and aryl vinyl azides with an array of functional groups.
KEYWORDS: visible light, in situ generated photocatalyst, intermolecular cyclization, copper salt, 2-aminothiazole.

Copper is an inexpensive metal that is earth-abundant and readily available. The use of copper catalysts to effect traditional thermal reaction has seen unprecedented growth in recent decades.[1] On the other hand, the copper salts catalyzed photoreactions are far from reaching enjoyed the same level of success as thermal reactions.[2,7,8] The root cause is a suitable photocatalyst should be robust, absorb light efficiently, and have a long-lived excited state.[3] Exactly, the relatively unstable and short-lived excited states of copper complexes retarded the exploration of copper based photoreaction.[4, 2d] To improve the efficiency of copper complexes as the photocatalysts in the visible-light driven transformations, complicated ligand designs are always necessary for such reactions.[5] More attractively, in situ generated photocatalysts (a combination of simple transition metal salts with substrates) is an ingenious design, which is not only to achieve an important transformation but also to avoid the multi-step synthesis of the catalyst.[6] Recently, Jonas C. Peters and Gregory C. Fu have reported a combination of simple CuCl with substrates to achieve asymmetric C-N cross-couplings induced by visible light.[7] Moreover, Hwang and coworkers have reported a series of C–C/C–N cross-coupling and C–H annulation reactions by in situ generated photocatalysts with simple copper salts with substrates.[8] More recently, We disclosed that simple Cu(II) salts can associate with 2-arylaminoacetates to form Cu(I)-based intermediates which could be excited by visible light.[9] Subsequent energy transfer from the excited Cu(I)-based intermediate to molecular oxygen triggered construction of a range of C-C bonds in air. Despite these contributions, the area of visible-light driven reactions catalyzed by in situ generated Cu(I) complexes remained relatively underappreciated.



Scheme 1. Synthesis of 4-Alkyl/Aryl-2-Aminothiazoles.

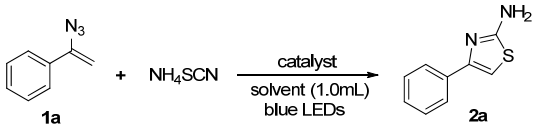
Thiocyanide is a highly affinitive ligand for Cu (I) salts.[10] The linear $Cu(NCS)_2^-$ could be in situ prepared easily by copper salts and excess amount of thiocyanide in room temperature.[11] As a continuing effort to develop sustainable and environmentally benign photoreactions, as well as the shortage of fossil fuels, we report a new methodology in this paper that the in situ formed $Cu(NCS)_2^-$, which plays the dual roles of both photocatalyst and Lewis acid catalyst, promotes synthesis of 4-alkyl/aryl-2-aminothiazoles by directly constructing C-S/C-N bond under visible light irradiation.

Compounds containing 2-aminothiazole ring are a commonly occurring structural motif found in natural

products and pharmaceutical compounds.[12] A diverse range of biological activities exhibited by this structure include anticancer,[13] anti-inflammatory,[14] antiviral,[15] and psychotropic activities.[16] 2-aminothiazoles traditionally are prepared by the intermolecular cyclization of α-halocarbonyl compounds with thioureas or ammonium thiocyanate (Scheme 1).[17]

Vinyl azides, a class of unique functionalized alkenes with high intrinsic reactivity, could be easily prepared from corresponding alkenes or alkynes.[18] They have served as prominent versatile synthons for the synthesis of various nitrogen-containing molecules.[19] Recently, the Pd(OAc)2 catalyzed intermolecular cyclization of vinyl azides with potassium thiocyanate at 80 °C has also been reported.[20] Yoon and co-workers have reported that energy transfer from Ir(Ⅲ) based photocatalysts to vinyl azides produced 2*H*-azirines.[21] We hypothesize that energy transfer from in situ produced $Cu(NCS)_2^-$ to vinyl azides could also take place and generate 2*H*-azirines, which is highly strained and easy to be attacked by thiocyanide at room temperature. The subsequent intramolecular nucleophilic attack of the cyanide with imino anion should obtain the desired 2-aminothiazoles. As this process proceeds at room temperature and no noble metal catalyst is employed, it may be open a new window for pharmaceutical exploitation and the total synthesis of natural products containing 2-minothiazole structural motif.

Table 1. Optimization of the Reaction Conditions. [a]



1a 2a

entry	catalyst	x mol %(cat)	yield(%)[d]
1	$Cu(OAc)_2$	10	95
2[b]	$Cu(OAc)_2$	10	n.r.
3	no catalyst	0	28
4	CuBr	10	86
5	CuCl	10	94
6	CuSCN	10	95
7	$Pd(OAc)_2$	10	12
8[c]	$Cu(OAc)_2$	10	23
9[c,e]	$Cu(OAc)_2$	10	69
10	$Cu(OAc)_2$	5	95
11	$Cu(OAc)_2$	2	95

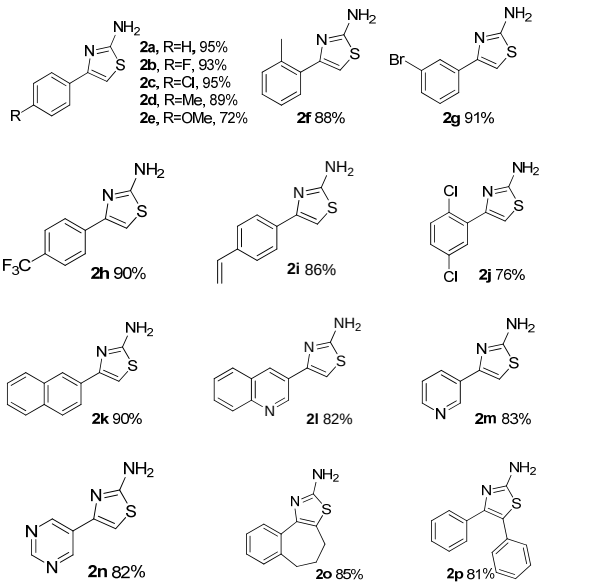
[a] Reaction conditions: vinyl azide (0.1 mmol, 1.0 equiv), NH_4SCN (0.2 mmol, 2.0 equiv) 1.0 mL CH_3CN under an argon atmosphere and irradiation of 5 W blue LEDs for 20 h at room temperature. [b] Reaction performed in the absence of light. [c] 2.0 equiv KSCN instead of NH_4SCN. [d] Isolated yields. [e] 2.0 equiv KH2PO4 was added. n. r. = no reaction.

We launched our study by subjecting vinyl azide **1a** and NH_4SCN to various reaction conditions (Table 1). First, various catalysts and solvents were screened under 5W blue LED irradiation (λ_{max}=455 nm) (see supporting information). To our delight, we found that the reaction with 10 mol % $Cu(OAc)_2$ in CH_3CN gave 4-phenyl-2-aminothiazole **2a** in 95% isolated yield (entry 1). Interestingly, similar yields of **2a** were isolated when cuprous salts were used instead of $Cu(OAc)_2$ (entries 4-6), indicating Cu(I) plays an important role in the photoreaction. Further investigation established that both copper salts and blue LED irradiation were required for an efficient reaction (entries 2-3). When $Pd(OAc)_2$ was employed as the catalysts, only few products were detected, indicating the reaction mechanism is different from the reported thermal reaction (entry 7).[20] The replacement of NH_4SCN by KSCN decreased the yield of **3a** sharply (entry 8), and the yield increased significantly when 2.0 equiv of Brønsted acid KH2PO4 was added to the KSCN based system (entry 9). The results demonstrate that NH_4^+ is necessary for the reaction as a proton donor. The copper-based catalytic system was so robust that the yield of **3a** kept no change even though the amount of $Cu(OAc)_2$ was decreased to 2 mol % (entries 10-11).

Having identified the optimal conditions, we next examined the scope of aryl vinyl azides. As shown in Table 2, various substituted aryl vinyl azides worked well with ammonium thiocyanate to provide the desired 4-aryl-2-aminothiazoles in good to excellent yields. Among all the examples presented, it was found that the electronic property slightly affected the product yields. Aryl vinyl

Table 2. Scope of Aryl Vinyl Azides. [a, b]

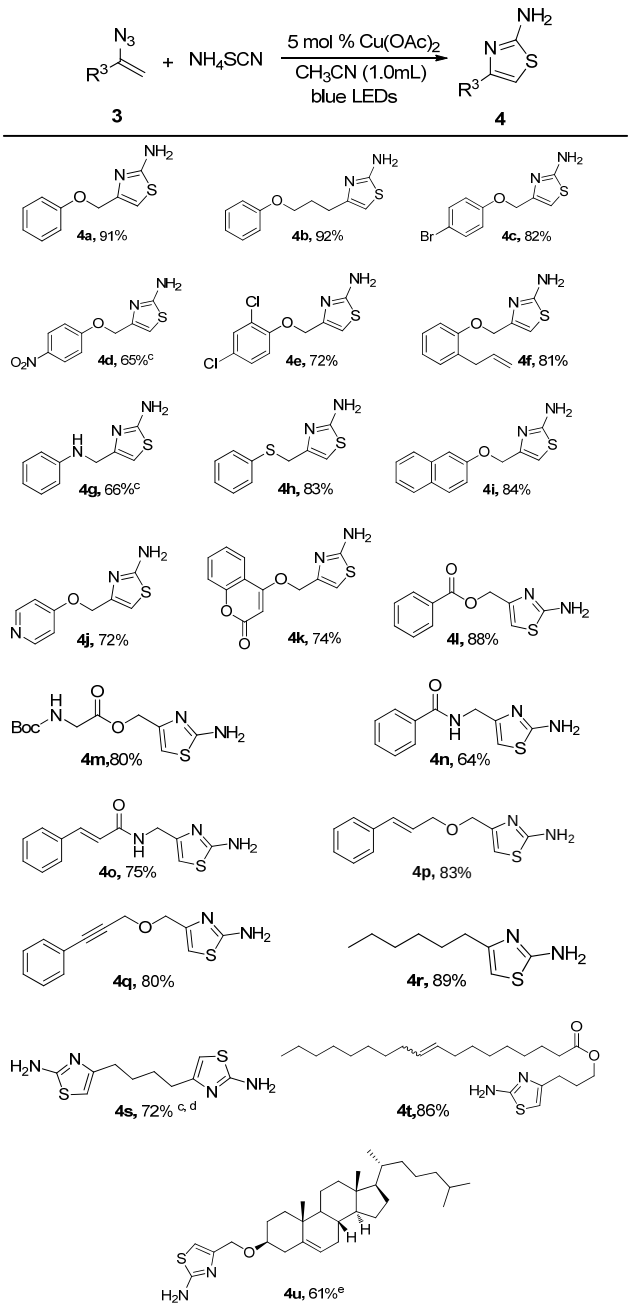
1 2



[a] Reaction conditions: **1** (0.1 mmol, 1.0 equiv), NH4SCN (0.2 mmol, 2.0 equiv), 5 mol % $Cu(OAc)_2$ in 1.0 mL CH3CN under an argon atmosphere and irradiation of 5W blue LEDs for 20 h at room temperature. [b] Isolated yields.

azides bearing electron-donating substituent afforded lower yields than those with electron-withdrawing groups in most cases. Many versatile functional groups, such as halides, trifluoromethyl, ethenyl, or others, were all tolerated under the reaction conditions, highlighting the potential of the method in organic synthesis (**2f- 2j**, 76% - 91%). Subsequently, we explored the challenging

Table 3. Scope of Alkyl Vinyl Azides. [a, b]

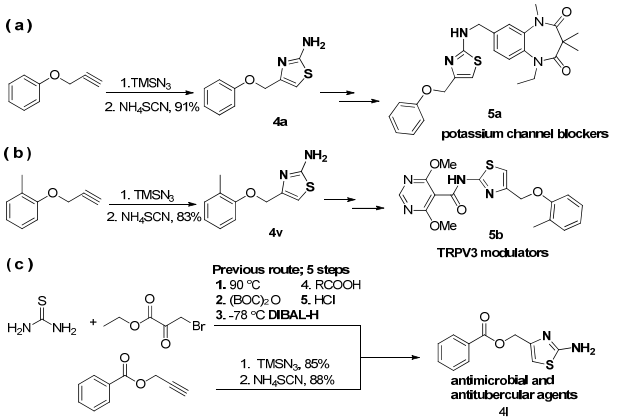


[a] Reaction conditions: **3** (0.1 mmol, 1.0 equiv), NH_4SCN (0.2 mmol, 2.0 equiv), 5 mol % $Cu(OAc)_2$ in 1.0 mL CH_3CN under an argon atmosphere and irradiation of 5W blue LEDs for 20 h at room temperature. [b] Isolated yields. [c] 36 h. [d] NH_4SCN (0. 8 mmol, 4.0 equiv). [e] 2.0 mL CH_3CN.

substrates. Phenyl, naphthyl, quinolyl, pyridyl and pyrimidyl vinyl azides also proceeded smoothly and furnished the 2-aminothiazoles in excellent yields upon isolation (**2k-2n**, 82%-90%). Compound **2k**, obtaining in 42% by Pd catalyst[20], can be prepared in 90% yield by our method. Moreover, the polycyclic and 4, 5-disubstituted aminothiazoles can be also obtained in excellent yield (**2o-2p**, 81%-85%).

We next turned our attention to alkyl vinyl azides which frameworks have been realized as valuable motifs in biological and medical chemistry. To our delight, alkyl vinyl azides containing nitrogen, oxygen, sulfur, ester, acid amide, double bond and triple bond as well as other functional groups were applicable to synthesis of 2-aminothiazoles in good to excellent yields under the standard reaction conditions (Table 3, **4a-4o**). Notably, biologically active moieties such as pyridine (**4j**), coumarin(**4k**), amino acid analogue(**4m**) and α, β-unsaturated carbonyl compounds (**4o**) were also tolerated in the photoreaction. Additionally, the substrates with 2-azidooct-1-ene and 2, 7-diazidoocta-1, 7-diene proceeded smoothly (**4r-4s**, 72%-89%). Finally, vinyl azides containing complex motifs such as cis-9-octadecenoic acid and bioactive Cholesterol can also afford 2-aminothiazoles derivative **4t** and **4u** (61%-86%).

To demonstrate the potential utility of the mild, operationally simple strategy, further transformations were carried out as shown in Scheme 2. We choose phenol as the raw material to synthesize compound **4a** by three steps in excellent yield. Compound **5a**, a potential potassium channel blocker, can be constructed from **4a** (Scheme 2, a)[22]. Compound **4v**, requiring four steps using traditional synthetic approaches in low yield, can be constructed in two steps with the methodology. A potential TRPV3 modulators of **5b** can be synthesized from **4v** (Scheme 2, b)[23]. Further, Compound **4l**, a possible antimicrobial and antitubercular agent, can be easily obtained from **3l** by two steps in our method. Using traditional synthetic protocol would require five steps in harsh conditions and low yield (Scheme 2, c)[12a].



Scheme 2. Synthetic Applications.[22,23,12a]

Once the scope of our methodology was explored, we turned our attention to the reaction mechanism. As shown in Figure 1, the UV-vis absorption spectra of $Cu(OAc)_2$ or vinyl azide **1a** is not obvious around 455 nm.

While the mixture of $Cu(OAc)_2$ and NH_4SCN exhibits intense absorption in the range of 350-560 nm. We also found that the solution of $Cu(OAc)_2$ in MeCN turned from light blue to claybank when NH_4SCN was added. This straightforward demonstated $Cu(OAc)_2$ and NH_4SCN formed a photocatalyst in situ. To identify the in situ formed copper species, the mixture of $Cu(OAc)_2$ and NH_4SCN in MeCN was studied by HRMS. The peaks at 179.8870 corresponding to $[Cu(NCS)_2^-+H^+]$, which has been in situ prepared by $Cu(OAc)_2$ and NH_4SCN in room temperature[11]. Furthermore, (SCN)2, formed as the by-product of $Cu(NCS)_2^-$ in situ preparation, was also detected by GC-MS(see SI).

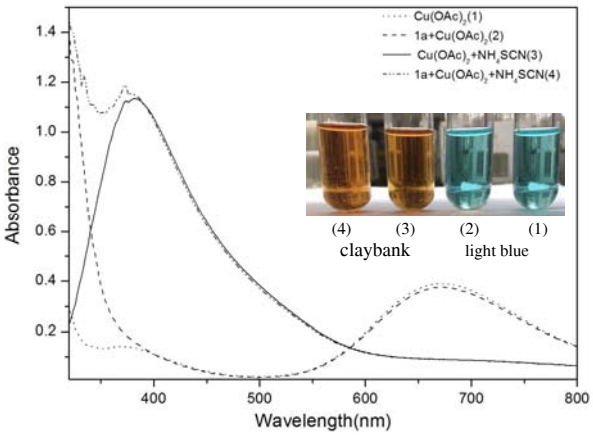
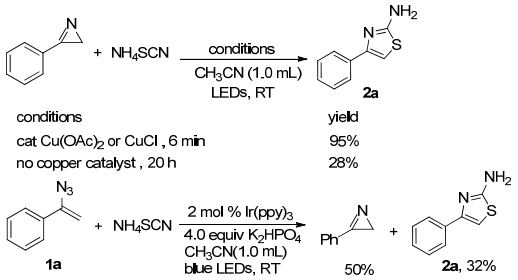


Figure 1. The UV-vis Absorption of Substrates.

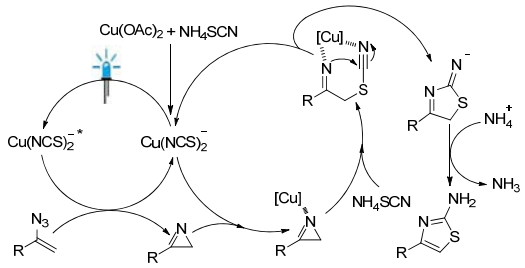
The role of $Cu(NCS)_2^-$ was investigated by the following experiments. Firstly, excitation of the mixture of $Cu(OAc)_2$ and NH_4SCN resulted in a maximal photoluminescence at 551 nm in acetonitrile solution, which was quenched by vinyl azide **1a** with a rate constant of 1.22 x 10^2 $L{\cdot}mol^{-1}$(see SI). Secondly, the photoreaction cannot be fully suppressed even though 3.0 equiv of TEMPO was added(see SI), indicating that radical pathway triggered by the electron transfer between $Cu(NCS)_2^-$ and the substrate is not dominant. In addition, the reaction of 2*H*-azirine with NH_4SCN produced the desired 2-aminothiazole in excellent yield within 6 min with the aid of copper salts such as $Cu(OAc)_2$ and CuCl, while the yield decreased to 28% in the absence of copper salts even though the reaction time was prolonged to 20 h (Scheme 3, A). React-IR monitoring of the consumption of 3-phenyl-2*H*-azirine provided a rate constant of 4.3 x 10^{-3} $mol{\cdot}L^{-1}{\cdot}S^{-1}$ for the copper catalyzed ring-opening process (see SI). Finally, we found that Ir(ppy)3, a photocatalyst which has been employed to produce 2*H*-aziridines from vinyl azides via energy transfer process[24], could also catalyze the 2-aminothiazoles synthesis in the absence of $Cu(OAc)_2$ (Scheme 3, A). Therefore, it is plausible that energy transfer from the excited $Cu(NCS)_2^-$ to vinyl azides generates the intermediate 2*H*-azirines, which quickly transformed to the products.

On the basis of these results, our mechanistic hypothesis was described as shown in Scheme 3B. Following in situ formation of $Cu(NCS)_2^-$ by the reaction of $Cu(OAc)_2$ with NH_4SCN,[11] the photocatalyst $Cu(NCS)_2^-$ is excited by blue LED irradiation. Then energy transfer from the excited $Cu(NCS)_2^-$ to vinyl azides takes place and produces 2*H*-azirines. Intermediate 2*H*-azirines further transforms into Cu(Ⅰ)-chelated α-thiocyano enamine anion through nucleophilic ring opening aziridines with thiocyanide in the presence of $Cu(NCS)_2^-$. Finally, intramolecular nucleophilic attack of the cyanide with imino anion forms the desired 2-aminothiazoles.

A) Mechanistic Studies.



B) Proposed Mechanism.



Scheme 3. Selected Mechanistic Studies and Proposed Reaction Mechanism for Synthesis of 2-Aminothiazoles.

In summary, we have disclosed a new methodology about synthesizing a broad range of 4-alkyl/aryl-2-aminothiazoles via copper-promoted intermolecular cyclization under visible light irradiation. Moreover, the method is distinguished by a broad scope, high yield, low catalyst loadings and the mild, operationally simple strategy. We anticipate that this new intermolecular cyclization protocol will be particularly used in pharmaceutical exploitation and the total synthesis of natural products containing 2-minothiazole structural motif.

ASSOCIATED CONTENT

Experimental details, characterization data, and copies of NMR spectra of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI:

AUTHOR INFORMATION

Corresponding Author

*E-mail: liuqiang@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful for financial support from NSFC (No. 21572090) and the Fundamental Research Funds for the Central Universities (lzujbky-2017-ko5).

REFERENCES

(1) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed*. **2003**, 42, 5400–5449. (b) Zhu, X.; Chiba, S. *Chem. Soc. Rev*. **2016**, 45, 4504--4523. (c) Bhunia, S.; Pawar, G. G.; Kumar, S.V.; Jiang, Y.W.; Ma, D.W. *Angew. Chem. Int. Ed.* DOI**:** 10.1002/anie.201701690. (d) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev*. **2013**, 113, 6234–6458. (e) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**. 50, 11062-11087. (f) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev*. **2012**, 41, 3464-3484.

(2) (a) Hernandez-Perez, A. C.; Collins, S. K. *Angew. Chem. Int. Ed*. **2013,** 52, 12696-12700. (b) Bagal, D. B.; Kachkovskyi, G.; Knorn, M.; Rawner, T.; Bhanage, B. M.; Reiser, O. Angew. Chem. Int. Ed. **2015**, 54, 6999-7002. (c) Armaroli, N. *Chem. Soc. Rev*. **2001**, 30, 113–124. (d) Wang, B.; Shelar, D. P.; Han, X. Z.; Li, T. T.; Guan, X. G.; Lu,W.; Liu, K.; Chen, Y.; Fu, W. F.; Che, C. M. *Chem. - Eur. J*. **2015**, 21, 1184–1190.

(3) (a) Evans, R. C.; Douglas, P.; Winscom, C. J. *Coord. Chem. Rev*. **2006,** 250, 2093–2126. (b) Yam, V. W.-W. *Acc.Chem. Res.* **2002**, 35, 555–563. (c) Fors, B. P.; Hawker, C. J. *Angew. Chem., Int. Ed*. **2012**, 51, 8850-8853.

(4) (a) McMillin, D. R.; McNett, K. M.; *Chem. Rev.* **1998**, 98, 1201-1220; (b) Scaltrito, D. V.; Thompson, D. W.; O'Callaghan, J. A.; Meyer, G. *J. Coord. Chem. Rev*. **2000**, 208, 243-266; (c) N. Armaroli, *Chem. Soc. Rev*. **2001**, 30, 113-124; (d) Chen, L. X.; Shaw, G. B.; Novozhilova, T. Liu, G. Jennings, K. Attenkofer, G. J. Meyer, P. Coppens, I.; *J. Am. Chem. Soc.* **2003**, 125, 7022-7034; (e) Armaroli, N.; Accorsi, G.; Cardinali, F.; Listorti, A.; *Top. Curr. Chem.* **2007,** 280, 69-115. (f) Iwamura, M.; Takeuchi, S., Tahara, T. *J. Am. Chem. Soc.* **2007**, 129, 5248-5256.

(5) (a) Armaroli, N.; Accorsi, G.; Cardinali, F.; Listorti, A. In Photochemistry and Photophysics of Coordination Compounds: Copper; Balzani, V.,Campagna, S., Eds.; Springer: Berlin, Germany, 2007; Topics in Current Chemistry 280, pp 69–116.(b) McMillin, D. R.; Buckner, M. T.; Ahn, B. T. *Inorg. Chem*. **1977**, 16, 943–945 (c) Czerwieniec, R.; Leitl, M. J.; Homeier, H. H. H.; Yersin, H.; *Coord. Chem. Rev*. **2016**, 325, 2-28.

(6) (a) Paria, S.; Reiser, O. *ChemCatChem*. **2014**, 6, 2477–2483. (b) Reiser, O. *Acc. Chem. Res.* **2016**, 49, 1990–1996.

(7) (a) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science*. **2012**, 338, 647-651. (b) Kainz, Q. M.; Matier, C. D. Bartoszewicz, A.; Zultanski, S. L.; Fu, G. C.; Peters, J. C. *Science*. **2016**, 351, 681-684. (c) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J; C. Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, 52, 5129–5133.

(8) Sagadevan, A.; Charpe, V. P.; Ragupathi, A.; Hwang, K. C. *J. Am. Chem. Soc.* **2017**, 139, 2896–2899. (b) Sagadevan, A.; Ragupathi, A.; Hwang, K. C. *Angew. Chem., Int. Ed*. **2015**, 54, 13896-13901. (c) Sagadevan, A.; Ragupathi, A.; Lin, C.-C.; Hwu, J. R.; Hwang, K. C. *Green Chem*. **2015**, 17, 1113- 1119. (d) Sagadevan, A.; Hwang, K. C. *Adv. Synth. Catal.* **2012**, 354, 3421-3427. (e) Sagadevan, A.; Lyu, P. C.; Hwang, K. C. *Green Chem*. **2016**, 18, 4526-4530.

(9) Meng, Q-Y.; Gao, X.-W.; Lei, T.; Liu, Z.; Zhan, F.; Li, Z.-J.; Zhong, J.-J.; Xiao, H.; Feng, K.; Chen, B.; Tao, Y.; Tung, C.-H.; Wu, L.-Z. *Sci. Adv*. **2017**. 3, e1700666.

(10) (a) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, 94, 856–865. (b) Kinoshita, S.; Misumi, S.; Aihara, M.; *B. Chem. Soc. Jpn*. **1974**, 47, 127-130.

(11) (a) Niu, S.Q.; Huang, D. L.; Dau, P. D.; Liu, H.T.; Wang, L. S. Ichiye, T. *J. Chem. Theory Comput*. **2014**, 10, 1283–1291. (b) Watson, W. H.; Kashyap, R. P. Acta Crystallogr. Sect. C 1990, 46, 2312–2316.

((12) (a) Karuvalam, R. P.; Haridas, K. R.; Nayak, S. K.; Guru Rowb, T. N.; Rajeesh, P.; Rishikesan, R.; Suchetha Kumari, N.; *Eur. J. Med. Chem*. **2012**, 49, 172-182. (b) Qian, S.; Wang, H.-K.; Oyama, M.; Vance, J. R.; Chen, M. S. Preparation of podophyllotoxin derivatives as anticancer compounds. WO 2004033423. 22 Apr 2004. U.S.A. (c) Lebel, L. A.; Nowakowski, J. T.; Macor, J. E.; Fox, C. B.; Kenneth Koe, B. *Drug Dev. Res*. **1994**, 33, 413-421.(d) Sagara, Y.; Kimura, T.; Fujikawa, T.; Noguchi, K.; Ohtake, N. *Bioorg. Med. Chem. Lett*. **2003**, 13, 57-60.

(13) Smith, B.; Chang, H.-H.; Medda, F.; Gokhale, V.; Dietrich, J.; Davis, A.; Meuillet, E.; Hulme, C. *Bioorg. Med. Chem. Lett*. **2012**, 22, 3567-3570.

(14) (a) Lednicer, D.; Mitscher, L. A.; *The Organic Chemistry of Drug* Synthesis, **1980**, 2, pp. 269. (b) Franklin, P. X.; Pillai, A. D.; Rathod, P. D.; Yerande, S. G.;Nivsarkar, M.; Padh, H.; Sudarsanam, V.; Vasu, K. K. *Eur. J. Med. Chem*. **2008**, 43, 129-134. (c) Inamdar, G. S.; Pandya, A. N.; Thakar, H. M.; Sudarsanam, V.; Kachler, S.; Sabbadin, D.; Moro, S.; Klotz, K.-N.; Vasu, K. K. *Eur. J. Med. Chem*. **2013**, 63, 924-934.

(15) Liu, R.; Huang, Z.; Murray, M. G.; Guo, X.; Liu, G. *J. Med. Chem*. **2011**, 54, 5747-5768.

(16) Zablotskaya, A.; Segal, I.; Germane, S.; Shestakova, I.;Domracheva, I.; Nesterova, A.; Geronikaki, A.; Lukevies, *E. Chem. Heterocycl. Compd.* **2002**, 38, 859-866.

(17) (a) Hantzsch, A. R.; Weber, *J. H. Ber. Dtsch. Chem. Ges.* **1887**, 20, 3118-3132. (b) Meshram, H. M. ; Thakur, Pramod B.; Madhu Babu, B.; Bangade, Vikas M. *Tetrahedron Letters*. **2012**, 53, 5265–5269. (c)Arutyunyan, S.; Nefzi, A. *J. Comb. Chem*. 2010, 12, 315-317. (d) Kumar, D.; Kumar, N. M.; Patel, G.; Gupta, S.; Varma, R. S. *Tetrahedron Lett*. **2011**, 52, 1983-1986.

(18) (a) Hassner, A.; Fowler, F. W.; *Tetrahedron Lett.* **1967**, 8, 1545-1548. (b) Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, 89, 2077-2082. (c) Liu, Z. H.; Liao, P. Q.; Bi, X.H. *Org. Lett*. **2014,** 16, 3668–3671. (d) Zhang, F.-L.; Feng, Yi.; Wang, Chiba, S. *Angew. Chem., Int. Ed*. **2014**, 53, 4390-4394.

(19) (a) Wang, Y. F.; Lonca, G. H.; Chiba, S. *Angew. Chem. Int. Ed.* 2014, 53, 1067-1071. (b) Wang, Y.; Toh, K. K.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, 133, 6411-6421. (c) Jung, N.; Brase, S. *Angew. Chem.Int. Ed*. **2012**, 51, 12169-12171. (d) Hu, B.; Wang, Z.; Ai, N.; Zheng, J.; Liu, X.; Shan, S.; Wang, Z. *Org. Lett*. **2011**, 13, 6362-6365. (e) Wu, S.-W. ; Liu, F. *Org. Lett*. **2016**, 18, 3642–3645. (f) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc*. **2007**, 129, 7500-7501.

(20) Chen, B.H.; Guo, S. S.; Guo, X.; Zhang, G.L.; Yu, Y. P. *Org. Lett*. **2015**, 17, 4698–4701.

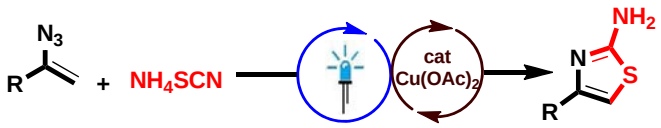
(21) Farney, E. P.; Yoon, T. P. *Angew. Chem. Int. Ed.* **2014**, 53, 793 –797.

(22) Kunio, O.; Shuji, M.; Hokuto, Y.; Naohiro, I.; Noriaki, T.; Kuninori, T.; Motohiro, I, etl. Preparation of nitrogen-containing heterocyclic compounds as potassium channel blockers and their preparation, pharmaceutical compositions and use in the treatment of arrhythmia. JP 2012184225. 27 Sep 2012. Japan

(23) Lawrence, B.; Brian S, B.; Bruce, C.; Cowart, M. D.; Michael J, D.; Ramin, F.; Anurupa, S.; Kevin, S, etl. N-(1,3-Thiazol-2-yl)pyrimidine-5-carboxamides as TRPV3 modulators and their preparation. WO 2016160938. 06 Oct 2016. U.S.A.

(24) Wang, Q. l.; Huang, J.; Zhou, L. *Adv. Synth. Catal.* **2015**, 357, 2479 –2484.

Insert Table of Contents art work here



R= alkyl, phenyl, naphthyl,
quinolyl, pyridyl , pyrimidyl ...

- 37 examples
- up to 95% yield
- broad scope
- cheap and low catalyst loading