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Authors: Jialin Xie, Zhonglin Guo, Yuanqiong Huang, yi qu, Hongjian Song, Haibin Song, Yuxiu Liu, and Qing-Min Wang

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COMMUNICATION

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One-Pot Copper-Catalyzed Cascade Bicyclization Strategy for Synthesis of 2-(1*H*-Indol-1-yl)-4,5-dihydrothiazoles and 2-(1*H*-Indol-1-yl)thiazol-5-yl Aryl Ketones with Molecular Oxygen as an Oxygen Source

Jialin Xie,[a] Zhonglin Guo,[a] Yuanqiong Huang,[a] Yi Qu,[a] Hongjian Song,[a,*] Haibin Song,[a] Yuxiu Liu[a] and Qingmin Wang[a,b,*]

[a] State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, People's Republic of China
[b] Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, People's Republic of China
E-mail: songhongjian@nankai.edu.cn; wangqm@nankai.edu.cn

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Abstract. An atom-economical method for synthesizing *N*-heterocyclic indoles from readily available *o*-alkynylphenyl isothiocyanates and propargylamine derivatives is reported. This method involves a copper-catalyzed cascade bicyclization process consisting of an intramolecular 5-*exo*-*dig* hydrothiolation reaction and an intramolecular hydroamination reaction and, depending on whether or not molecular oxygen is present, selectively affords *Z*-isomers of 2-(1*H*-indol-1-yl)-4,5-dihydrothiazoles or 2-(1*H*-indol-1-yl)thiazol-5-yl aryl ketones in satisfactory yields. Mechanistic studies indicate that molecular oxygen acts as the oxygen source for the ketone moiety in the products.

Keywords: Biologically Active; Copper; Cyclization; Heterocyclic Indoles; Oxygen

The majority (59%) of small-molecule drugs have nitrogen-containing heterocyclic scaffolds.[1] Indoles in particular are commonly found in biologically active molecules (Figure 1) and advanced materials and have thus attracted considerable research attention.[2] Since the classical Fischer indole synthesis was reported,[3] the number of methods for synthesizing functionalized indoles has burgeoned,[4] and the most common methods include metal-catalyzed cyclization reactions[5] and transition-metal-catalyzed C–H bond activation reactions.[6] However, despite these advances, there are only a few methods for the construction of *N*-heterocyclic indoles; the most commonly used methods involve coupling reactions, such as the Buchwald–Hartwig amination and Ullman-type coupling reactions, between indoles and prefunctionalized heterocycles.[7] Except for the coupling reaction, there are few practical methods for building compounds with 2-(1*H*-indol-1-yl)-4,5-dihydrothiazole and 2-(1*H*-indol-1-yl)thiazol-5-yl aryl ketone skeletons from readily available precursors.[8]

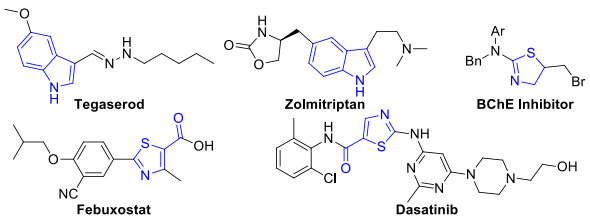

Figure 1. Biologically active compounds with indole and thiazoline caffolds.

Various nitrogen- and sulfur-containing heterocycles have been synthesized from isothiocyanate substrates.[9] In particular, *o*-alkynylphenyl isothiocyanates have been used to construct fused-ring compounds via cascade reactions,[10] which show higher overall efficiency than traditional stepwise syntheses because multiple C–C and C–X bonds can be formed in one pot.[11] For example, in 2014, Cai et al. reported the formation of 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines by means of copper-catalyzed [3+2] cascade cycloaddition reactions between *o*-alkynylphenyl isothiocyanates and isocyanides (Scheme 1a).[10c] Copper, which is abundant in nature, has a wide range of valence states and shows good affinity for molecular oxygen,[12] an environmentally friendly oxygen source for organic synthesis, although its activation remains a challenge. Therefore, copper-promoted syntheses of organic compounds under aerobic conditions have been the subject of extensive research.[13] In particular, much effort has been devoted to aerobic copper-promoted bifunctionalization of alkynes to form carbonyl compounds.[14] To our knowledge, all the reported examples of such reactions have involved aminooxygenation[14a–14e] and bioxygenation[14f–14h]

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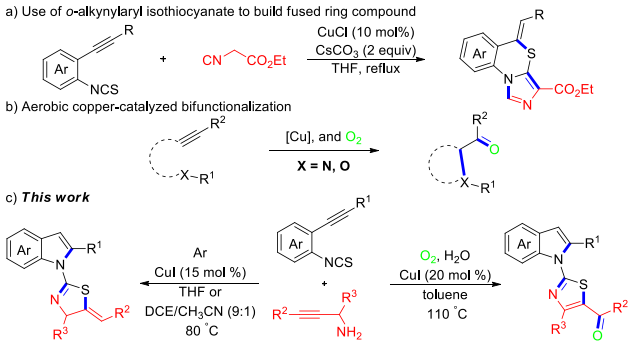
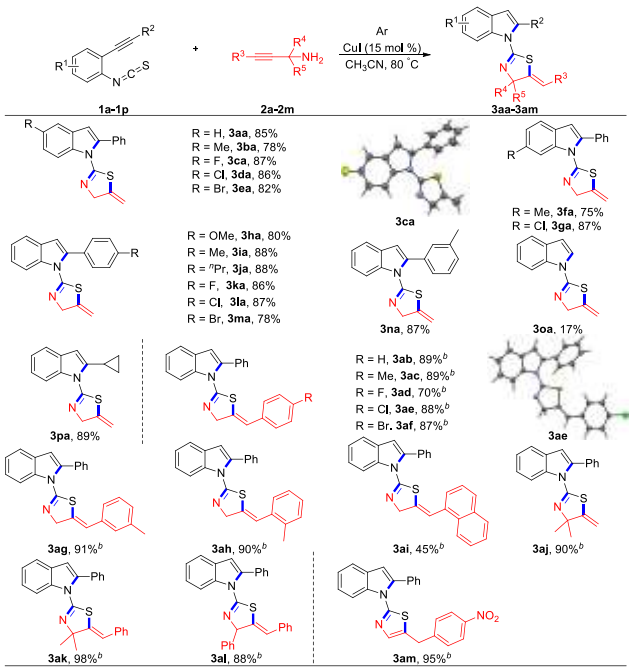
processes (Scheme 1b), and there are no examples of alkyne bifunctionalization by means of aerobic copper-catalyzed thiooxygenation.[15] One of the limiting factors may be catalyst poisoning by sulfur species.[16]



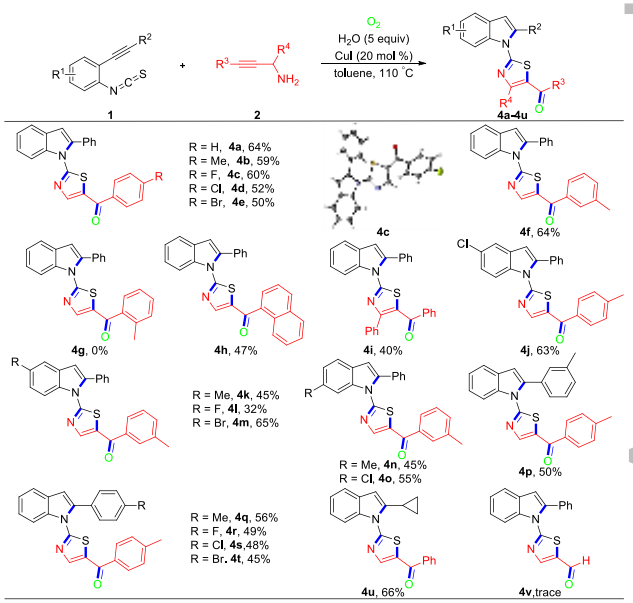
Scheme 1. One-pot, de novo synthesis of 2-(1*H*-indol-1-yl)-4,5-dihydrothiazoles and 2-(1*H*-indol-1-yl)thiazol-5-yl aryl ketones.

Inspired by the research described above, we herein report that we have achieved the first copper-catalyzed cascade bicyclization reactions between *o*-alkynylphenyl isothiocyanates and propargylamine derivatives (Scheme 1c), despite the fact that amines are unstable to oxidants.[17] Unlike previously reported reactions of similar substrates, these reactions afforded 2-(1*H*-indol-1-yl)-4,5-dihydrothiazoles rather than fused-ring compounds.[10] Furthermore, the reactions could also generate 2-(1*H*-indol-1-yl)thiazol-5-yl aryl ketones when molecular oxygen was present.



Scheme 2. Synthesis of 2-(1*H*-indol-1-yl)-4,5-dihydrothiazoles. [a]Isolated yields are reported. [b]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), CuI (15 mol %), DCE:CH_3CN (9:1, 2 mL), under Ar, 80 °C, 10 h.

We began by investigating the reactions of *o*-alkynylphenyl isothiocyanates **1** and propargyl amines **2** (Scheme 2). Treatment of *o*-**1a** (0.3 mmol) with **2a** (0.45 mmol) in the presence of CuI (15 mol %) in CH_3CN (3 mL) at 80 °C for 6 h under Ar afforded the desired product, 2-(1*H*-indol-1-yl)-4,5-dihydrothiazole **3aa**, in 85% yield (for detailed optimization studies, see Supporting Information [SI], Table S1). Subsequently, we investigated the substrate scope of the reaction to afford various 2-(1*H*-indol-1-yl)-4,5-dihydrothiazoles **3**. First, we explored the effect of substituents R^1 and R^2 on **1** and found that substrates **1a–1n**, and **1p** reacted with **2a** to afford the target products in good to excellent yields. Neither the electronic properties of R^1 nor its position (*para* or *meta*) markedly affected the yields of products **3aa–3ga**.[18] The structure of **3ca** was confirmed by single-crystal X-ray analysis (see SI, Table S3).[19] In addition, when R^1 was H and R^2 was an aryl group, the target products (**3ha–3na**) were obtained in satisfactory yields regardless of the electronic properties of the substituent on the aryl group. In addition, R^2 could be H or cyclopropyl, but the yield of **3oa** obtained from the former substrate was relatively low (17%). The reason for the low yield of the product may be that Glaser coupling happened to the terminal alkyne substrate in the presence of amine.[20] We also investigated other aliphatic R groups, such as *t*-Bu and trimethylsilyl, but the desired products were obtained in only trace amounts.



Scheme 3. Synthesis of 2-(1*H*-indol-1-yl)thiazol-5-yl aryl ketones. [a]Isolated yields are reported.

We also evaluated the reactions of various propargylamine derivatives **2** with **1a**. To our delight, internal propargylamine derivatives (**2b–2i**)

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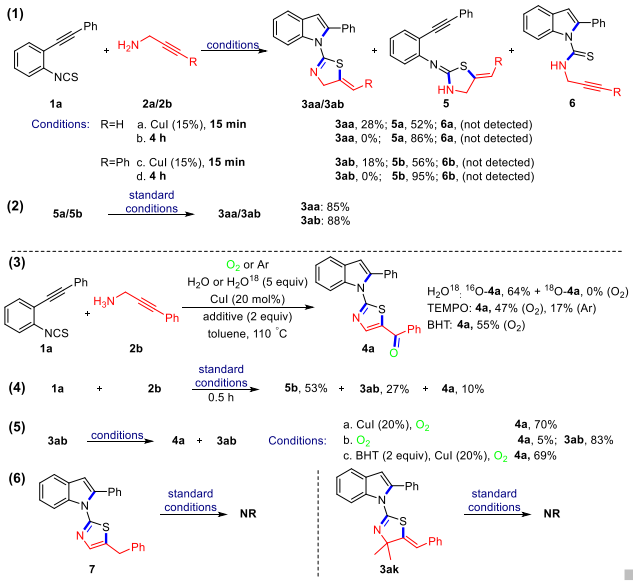
containing various aryl groups were compatible with the reaction conditions, and the yields generally were ≥70%. Even the sterically hindered substrate 3-(*o*-methylphenyl) propargylamine (**2h**) could be converted to desired product **3ah** in high yield (90%). It is noteworthy that only *Z*-isomers were formed, as determined by single-crystal X-ray analysis of **3ae** (see SI, Table S4);[19] this result may be due to kinetic effects, as outlined in Baldwin's rules.[21] When the propargylamine had an *α*-substituent (**2j**–**2l**), the reaction proceeded smoothly to furnish the desired products (**3aj**–**3al**). Surprisingly, when a nitro group was present on the phenyl ring, only aromatization product **3am** was obtained.

Intriguingly, in the presence of molecular oxygen, carbonylation product 2-(1*H*-indol-1-yl)thiazol-5-yl aryl ketone **4a** was obtained in 64% yield from a one-pot reaction of **1a** and internal propargylamine **2b** (1.5 equiv) in toluene at 110 °C for 15 h in the presence of CuI (20 mol %) and H_2O (5 equiv) (Scheme 3; for details on the optimization of the reaction conditions, see Table S2 in the SI). Our next step was to explore the substrate scope of this aerobic reaction. First, we investigated the effect of the substituent on the aryl moiety (R^3) of the internal propargylamine substrate. When the benzene ring bore a methyl group or a halogen atom or was replaced by a naphthalene ring, the desired products (**4b** or **4f**, **4c**–**4e**, and **4h**, respectively) were obtained in yields of 47–60%. Unfortunately, this reaction was sensitive to steric hindrance: **4g** was not obtained from a substrate with an *o*-methyl group on the benzene ring. The structure of **4c** was ascertained by means of single-crystal X-ray analysis (see SI, Table S5).[19] We were pleased to find that a propargylamine with an *α*-aryl group furnished **4i** in 40% yield.

We next examined a series of *o*-alkynylphenyl isothiocyanates **1**, which provided products **4j**–**4u** in moderate yields. Specifically, when R^1 was an aryl group with an electron-donating group or an electron-withdrawing group, the desired products (**4j**–**4o**) were obtained in yields of 32–65%. Moreover, substrates with various aryl substituents R^2 on the C≡C bond were also compatible with the reaction conditions, giving products **4p**–**4t** regardless of the electronic properties of the substituent on the aryl group. It is noteworthy that a cyclopropane-containing substrate could also be converted to the corresponding product (**4u**) in 66% yield, whereas a terminal alkyne formed only a trace of carbonylation product **4v**.



Scheme 4. Control experiments.

To investigate the reaction mechanism, we carried out some control experiments (Scheme 4). In the absence of a copper catalyst, reaction of **1a** with **2a** (a terminal alkyne) or **2b** (an internal alkyne) at 80 °C for 4 h under argon yielded only **5**; whereas when the reaction was carried out in the presence of the copper catalyst for 15 min, **5** and 2-(1*H*-indol-1-yl)-4,5-dihydrothiazole **3aa** or **3ab** were obtained (eq 1). Compound **6** was not detected under either of these reaction conditions. These results prove that **5** was a reaction intermediate and that it could be formed in the absence of the copper catalyst; and these tests also rule out the possibility that indole ring formation was the first step. Furthermore, we found that subjecting **5** to the optimal reaction conditions led to the formation of the final product (eq 2), confirming that **5** was indeed an intermediate.

Next, we studied the mechanism of the aerobic copper-catalyzed reaction (eqs 3–6). The reaction of **1a** and **2b** in the presence of $H_2{}^{18}O$ under an $^{16}O_2$ atmosphere did not afford [^{18}O]-**4a** (eq 3), as determined by high-resolution mass spectrometry (see SI, Figure S1). This result indicates that the oxygen atom originated from molecular oxygen rather than from water. When TEMPO was added to the reaction mixture under either O_2 or Ar, the radical scavenger did not markedly inhibit the reaction, and it could serve as an oxidant. Moreover, addition of the radical inhibitor BHT also did not substantially inhibit the reaction (eq 4), a result that rules out the involvement of a radical process. If the reaction was quenched after 0.5 h, we could isolate **5b** and **3ab** (eq 4), indicating that **5b** was an intermediate and that **3ab** may also have been an intermediate. To assess this possibility, we studied the reactions of **3ab** under various conditions (eq 5). Surprisingly, **4a** was obtained in 70% yield under the standard conditions (eq 5a), and only a 5% yield of **4a** was obtained in the absence of the copper salt (eq 5b). These results confirm that **3ab** was in fact an intermediate and that

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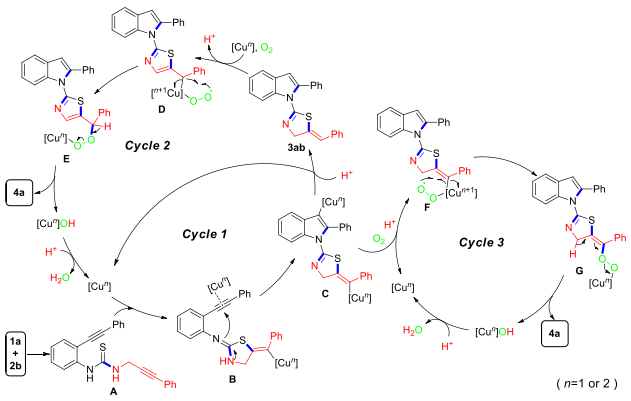
CuI was indispensable for the oxidation process. That **3ab** reacted in the presence of BHT confirms that a radical oxidation process was not involved (eq 5c). Moreover, neither **7** nor **3ak** underwent further oxidation under the standard conditions (eq 6), which indicates that **7** was not involved in this reaction and that the α-H of the thiazoline ring was important during oxidation.

On the basis of the results of the above-described experiments and literature reports,[11, 15, 22] a plausible mechanism for the formation of **3ab** and **4a** is outlined in Scheme 5. First, thiourea **A** is rapidly formed by a reaction of **1a** and **2b**. Then, a copper-catalyzed intramolecular *5-exo-dig* hydrothiolation reaction and a subsequent intramolecular hydroamination reaction give intermediate **C**. Protonation of **C** yields **3ab** and releases the catalyst, thus completing catalytic cycle 1. In the next step, **3ab** undergoes a copper-mediated oxidation by molecular oxygen accompanied by thiazoline–thiazole tautomerization (cycle 2)[22c] to form highly active Cu-peroxo species **D**, which rapidly isomerizes to organoperoxide **E**. Finally, **E** is transformed to oxidation product **4a** and [Cu^n-OH] by removal of the benzyl proton and subsequent O–O bond cleavage. [Cu^n-OH] is converted back to [Cu^n] by anion exchange to complete catalytic cycle 2 and generate 1 equiv of H_2O. An alternative mechanism (cycle 3) has a low probability but has not been ruled out. This alternative mechanism involves a direct oxidative addition reaction between a small amount of vinyl-Cu intermediate **C** and molecular oxygen to afford Cu-peroxo species **F**. Rapid isomerization of **F**, O–O bond cleavage, and isomerization of **G** generate **4a** and [Cu^n-OH].



Scheme 5. Plausible reaction mechanism.

In summary, we have developed a method for building 2-(1*H*-indol-1-yl)-4,5-dihydrothiazoles by means of copper-catalyzed cascade bicyclization reactions between *o*-alkynylphenyl isothiocyanates and propargylamine derivatives. This mild method has a wide substrate scope, shows 100% atom economy, and selectively affords *Z*-isomer products. When carried out in the presence of molecular oxygen, the reaction can also produce 2-(1*H*-indol-1-yl)thiazol-5-yl aryl ketones in moderate yields by successive formation of C–C, C–N, and C=O bonds. It provides an alternative method for introducing molecular oxygen, which serves both as the oxygen source and as the oxidant, into the thiazole skeleton. Studies of the use of this method for the construction of other nitrogen heterocycles are in progress in our laboratory.

Experimental Section

2-(1*H*-Indol-1-yl)-4,5-dihydrothiazoles: An oven-dried Schlenk tube was charged with *o*-alkynylphenyl isothiocyanate **1a** (0.3 mmol, 1 equiv), propargylamine derivative **2a** (0.45 mmol, 1.5 equiv), CuI (0.045 mmol, 15 mol %), and dry CH_3CN (3.0 mL). The tube was evacuated and backfilled with Ar three times. The reaction mixture was stirred under Ar at room temperature for 15 min and then at 80 °C for 6 h. After concentration of the solution in vacuo, the residue was purified via flash silica gel column chromatography with petroleum ether/ethyl acetate as the eluent to afford desired compound **3**.

2-(1*H*-Indol-1-yl)thiazol-5-yl Aryl Ketones: A oven-dried Schlenk tube was charged with an *o*-alkynylphenyl isothiocyanate **1** (0.2 mmol, 1 equiv), a propargylamine derivative **2** (0.3 mmol, 1.5 equiv), CuI (0.040 mmol, 20 mol %), H_2O (1.0 mmol, 5 equiv), and dry toluene (3.0 mL). The tube was evacuated and backfilled with oxygen three times. The reaction mixture was stirred under oxygen at 30 °C for 20 min and then at 110 °C for 15 h. After concentration of the solution in vacuo, the residue was purified via flash silica gel column chromatography with petroleum ether/ethyl acetate as the eluent to afford desired compound **4**.

Acknowledgements

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References

[1] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.

[2] a) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761. b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489. c) R. A. Irgashev, A. A. Karmatsky, G. L. Rusinov, V. N. Charushin, *Org. Lett.* **2016**, *18*, 804.

[3] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241. b) B. Robinson, *Chem. Rev.* **1969**, *69*, 227.

[4] For some reviews of indole synthesis, see: a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875. b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215. c) M. Shiri, *Chem. Rev.* **2012**, *112*, 3508. d) R. Chinchilla, C. Nájera, *Chem. Rev.* **2014**, *114*, 1783.

[5] For selected examples, see: a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689. b) J. L. Rutherford, M. P. Rainka, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 15168. c) B. M. Trost, A. McClory, *Angew. Chem.* **2007**, *119*, 2120; *Angew. Chem., Int. Ed.* **2007**, *46*,

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2074. d) G. T. Li, X. G. Huang, L. M. Zhang, *Angew. Chem.* **2008**, *120*, 352; *Angew. Chem., Int. Ed*. **2008**, *47*, 346. e) T. Newhouse, C. A. Lewis, P. S. Baran, *J. Am. Chem. Soc.* **2009**, *131*, 6360. f) S. Tong, Z. R. Xu, M. Mamboury, Q. Wang, J. P. Zhu, *Angew. Chem.* **2015**, *127*, 11975; *Angew. Chem., Int. Ed.* **2015**, *54*, 11809.

[6] For selected examples, see: a) R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem*. **2009**, *121*, 8222; *Angew. Chem., Int. Ed.* **2009**, *48*, 8078. b) D. B. Zhao, Z. Z. Shi, F. Glorius, *Angew. Chem*. **2013**, *125*, 12652; *Angew. Chem., Int. Ed.* **2013**, *52*, 12426. c) B. Q. Liu, C. Song, C. Sun, S. G. Zhou, J. P. Zhu, *J. Am. Chem. Soc*. **2013**, *135*, 16625. d) J. Zoller, D. C. Fabry, M. A. Ronge, M. Rueping, *Angew. Chem.* **2014**, *126*, 13480; *Angew. Chem., Int. Ed.* **2014**, *53*, 13264. e) H. Wang, M. Moselage, M. J. Gonzalez, L. Ackermann, *ACS Catal.* **2016**, *6*, 2705.

[7] a) Z. J. Liu, J. P. Vors, E. R. F. Gesing, C. Bolm, *Green Chem.* **2011**, *13*, 42. b) Y. C. Teo, F. F. Yong, S. Sim, *Tetrahedron* **2013**, *69*, 7279. c) W. J. Yoo, T. Tsukamoto, S. Kobayashi, *Org. Lett.* **2015**, *17*, 3640. d) S. G. Rull, J. F. Blandez, M. R. Fructos, T. R. Belderrain, M. C. Nicasio, *Adv. Synth. Catal*. **2015**, *357*, 907.

[8] Y. Oda, K. Hirano, T. Satoh, M. Miura, *Org. Lett*. **2012**, *14*, 664.

[9] a) A. Mukerjee, R. Ashare, *Chem. Rev.* **1991**, *91*, 1. b) A. Ranjan, R. Yerande, P. B. Wakchaure, S. G. Yerande, D. H. Dethe, *Org. Lett.* **2014**, *16*, 5788. c) P. Zhao, Y. Liu, C. J. Xi, *Org. Lett.* **2015**, *17*, 4388. d) W. S. Guo, S. L. Li, L. Tang, M. Li, L. R. Wen, C. Chen, *Org. Lett*. **2015**, *17*, 1232. e) X. D. Tang, Z. Z. Zhu, C. R. Qi, W. Q. Wu, H. F. Jiang, *Org. Lett*. **2016**, *18*, 180. f) Z. W. Zhou, F. C. Jia, C. Xu, S. F. Jiang, Y. D. Wu, A. X. Wu, *Chem. Commun.* **2017**, *53*, 1056. g) A. Modi, P. Sau, B. K. Patel, *Org. Lett*. **2017**, *19*, 6128.

[10] a) L. Benati, G. Calestani, R. Leardini, M. Minozzi, D. Nanni, *J. Org. Chem*. **2003**, *68*, 3454. b) T. Saito, H. Nihei, T. Otani, T. Suyama, N. Furukawa, M. Saito, *Chem. Commun*. **2008**, *2*, 172. c) W. Y. Hao, J. B. Zeng, M. Z. Cai, *Chem. Commun.* **2014**, *50*, 11686. d) R. J. Liu, P. F. Wang, W. K. Yuan, L. R. Wen, M. Li, *Adv. Synth. Catal*. **2017**, *359*, 1373.

[11] a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. b) X. Zeng, *Chem. Rev.* **2013**, *113*, 6864.

[12] For some reviews of copper/oxygen systems, see: a) A. E. Lewis, W. B. Tolman, *Chem. Rev.* **2004**, *104*, 1047. b) L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Chem. Rev*. **2004**, *104*, 1013. c) C. Zhang, C. H. Tang, N. Jiao, *Chem. Soc. Rev*. **2012**, *41*, 3464. d) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev*. **2013**, *113*, 6234. e) S. D. McCann, S. S. Stahl, *Acc.Chem. Res*. **2015**, *48*, 1756.

[13] For some recent examples of copper/oxygen systems, see: a) C. P. Frazier, J. R. Engelking, J. R. de Alaniz, *J. Am. Chem. Soc.* **2011**, *133*, 10430. b) H. G. Wang, Y. Wang, D. D. Liang, L. Y. Liu, J. C. Zhang, Q. Zhu, *Angew. Chem.* **2011**, *123*, 5796; *Angew. Chem. Int. Ed.* **2011**, *50*, 5678. c) L. Zhang, X. H. Bi, X. X. Guan, X. Q. Li, Q. Liu, B.-D. Barry, P. Q. Liao, *Angew. Chem.* **2013**, *125*, 11513; *Angew. Chem., Int. Ed.*, **2013**, *52*, 11303. d) J. M. Liu, X. Zhang, H. Yi, C. Liu, R. Liu, H. Zhang, K. L. Zhuo, A. W. Lei, *Angew. Chem.* **2015**, *127*, 1277; *Angew. Chem., Int. Ed.* **2015**, *54*, 1261. e) H. Huang, J. Cai, X. Ji, F. Xiao, Y. Chen, G. J. Deng, *Angew. Chem.* **2016**, *128*, 315; *Angew. Chem. Int. Ed.* **2016**, *55*, 307. f) T. Wdowik, S. R. Chemler, *J. Am. Chem. Soc.* **2017**, *139*, 9515.

[14] a) C. Zhang, N. Jiao, *J. Am. Chem. Soc*. **2010**, *132*, 28. b) W. Wei, X. Y. Hu, X. W. Yan, Q. Zhang, M. Cheng, J. X. Ji, *Chem. Commun*. **2012**, *48*, 305. c) D. C. Mohan, S. N. Rao, S. Adimurthy, *J. Org. Chem*. **2013**, *78*, 1266. d) M. Selvaraju, T. Y. Ye, C. H. Li, P. H. Ho, C. M. Sun, *Chem. Commun.* **2016**, *52*, 6621. e) A. Sagadevan, A. Ragupathi, C. C. Lin, J. R. Hwu, K. C. Hwang, *Green Chem*. **2015**, *17*, 1113. f) A. S. K. Hashmi, M. C. Blanco Jaimes, A. M. Schuster, F. Rominger, *J. Org. Chem*. **2012**, *77*, 6394. g) S. Y. Mai, C. Q. Rao, M. Chen, J. H. Su, J. F. Du, Q. L. Song, *Chem. Commun*. **2017**, *53*, 10366. h) X. X. Peng, D. Wei, W. J. Han, F. Chen, W. Yu, B. Han, *ACS Catal*. **2017**, *7*, 7830.

[15] Q. Q. Lu, J. Zhang, G. L. Zhao, Y. Qi, H. M. Wang, A. W. Lei, *J. Am. Chem. Soc*. **2013**, *135*, 11481.

[16] J. F. Hartwig, *Acc. Chem. Res*. **2008**, *41*, 1534.

[17] B. Xu, E. M. Hartigan, G. Feula, Z. Huang, J. P. Lumb, B. A. Arndtsen, *Angew. Chem.* **2016**, *128*, 16034; *Angew. Chem., Int. Ed.* **2016**, *55*, 15802.

[18] We have tried to synthesize these substrates (**1**) which containing NO_2, CF_3 substitution at R^1, but we have difficult in synthesizing them. When R^1 was changed to OMe, no desired product was obtained.

[19] CCDC 1832456 (**3ca**), 1832420 (**3ae**) and 1837650 (**4c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

[20] C. Glaser, *Annalen der Chemie und Pharmacie*. **1870**, *154*, 137–171.

[21] K. Gilmore, I. V. Alabugin, *Chem. Rev.* **2011**, *111*, 6513.

[22] a) K. K. Toh, Y. F. Wang, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 13942. b) H. H. Peng, N. G. Akhmedov, Y. F. Liang, N. Jiao, X. D. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 8912. c) H. Sterckx, H. De Houwer, C. Mensch, C. Caretti, K. A. Tehrani, W. A. Herrebout, S. Van Doorslaer, B. U. W. Maes, *Chem. Sci.* **2016**, *7*, 346. d) K. Liu, G. Y. Xu, J. T. Sun, *Chem. Sci.* **2018**, *9*, 634. e) S. X. Zhai, S. X. Qiu, X. M. Chen, C. Tao, Y. Li, B. Cheng, H. F. Wan, H. B. Zhai, *ACS Catal.* **2018**, *8*, 6645.

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One-Pot Copper-Catalyzed Cascade Bicyclization Strategy for Synthesis of 2-(1*H*-Indol-1-yl)-4,5-dihydrothiazoles and 2-(1*H*-Indol-1-yl)thiazol-5-yl Aryl Ketones with Molecular Oxygen as an Oxygen Source

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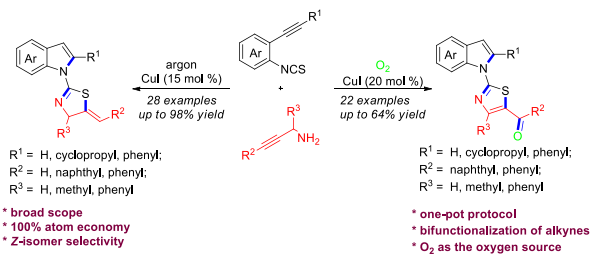

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