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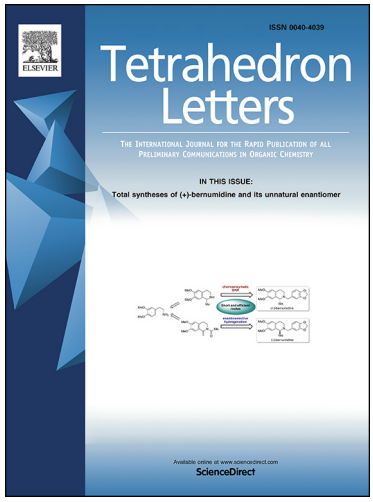

Cu(I)-Catalyzed Cascade Intramolecular Cyclization of 2-Propynol Phenyl Azides and Diarylphosphine Oxides for the Synthesis of Bisphosphorylated Indole Derivatives

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PII: S0040-4039(18)31078-5
DOI: https://doi.org/10.1016/j.tetlet.2018.09.006
Reference: TETL 50245

To appear in: *Tetrahedron Letters*

Received Date: 29 July 2018
Revised Date: 2 September 2018
Accepted Date: 3 September 2018

Please cite this article as: Song, X-R., Li, R., Yang, T., Bai, J., Yang, R., Chen, X., Ding, H., Xiao, Q., Liang, Y-M., Cu(I)-Catalyzed Cascade Intramolecular Cyclization of 2-Propynol Phenyl Azides and Diarylphosphine Oxides for the Synthesis of Bisphosphorylated Indole Derivatives, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.09.006

Tetrahedron Letters
journal homepage: www.elsevier.com

Cu(I)-Catalyzed Cascade Intramolecular Cyclization of 2-Propynol Phenyl Azides and Diarylphosphine Oxides for the Synthesis of Bisphosphorylated Indole Derivatives

Xian-Rong Song,[a] Ren Li,[a] Tao Yang,[a] Jiang Bai,[a] Ruchun Yang,[a] Xi Chen,[a] Haixin Ding,[a] Qiang Xiao*[a] and Yong-Min Liang[b]

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2-Propynol Phenyl Azides
Bisphosphorylated Indoles
Copper-Catalyzed
Cascade Cyclization

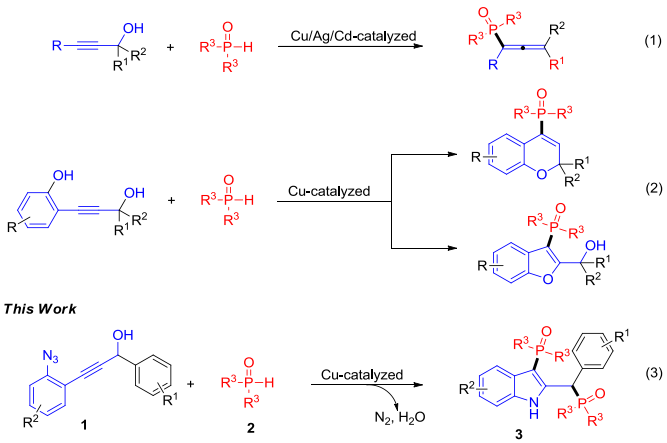
ABSTRACT

The $[Cu(OTf)]_2 \cdot C_6H_6$ catalyzed cascade intermolecular addition–intramolecular cyclization reaction of easily prepared 2-propynol phenyl azides and diarylphosphine oxides was developed. This novel reaction leads to simultaneous formation of one C—N and two C—P bonds in a single step to give bisphosphorylatd indole derivatives under mild conditions in moderate to good yields.

Introduction

Functional indoles are widely spread in natural products and synthetic molecules, which possess numerous pharmaceutical properties.[1] In particular, 3-phosphinoylindole derivatives were screened as nonnucleoside reverse transcriptase inhibitors (NNTRI), among which compound IDX-899 demonstrates high activity against wild-type and NNRTI-resistant HIV-1.[2] In addition, 3-phosphinoylindoles were used as ligands in cross-coupling reactions for the direct arylation of carbonyl compounds.[3] Owing to the significant pharmaceutical activities of these compounds, as well as synthetic relevance, great efforts have been devoted to develop efficient approaches for their preparation.[4] For example, Lu and co-workers developed a novel approach to 3-phosphinoylindoles through metal-free electrophilic phosphination of indoles.[5] Very recently, Kozlowski and Wang group reported Lewis acid-catalyzed phosphorylation of 2-indolylmethanols for the synthesis of 3-phosphinoylindoles.[6] Despite the many advances in this field, further exploration and development of more effective protocol for their preparation are still extremely attractive and desirable.

In the past decade, the Lewis acid-catalyzed cascade transformation of propargylic alcohols has become an efficient way to access various compounds with rich structural diversity.[7] In this regard, applying propargylic alcohols towards the phosphorus-containing compounds have been developed. For example, the Zhao,[8] Yang[9] and Han[10] groups reported the metal-catalyzed dehydrative C—P coupling of propargylic alcohols with diarylphosphine oxides leading to allenylphosphoryl compounds (Scheme 1-1). Subsequently, Liang and our group have developed a copper-catalyzed cascade cyclization of 2-propynolphenols with diarylphosphine oxides to form 3-



Scheme 1 Previous works and our new attempt

phosphinoylbenzofurans and 4-phosphorylated 2*H*-chromenes *via* the allenylphosphoryl intermediate, respectively (Scheme 1-2).[11] Base on the above results and our continuous interest in the potential application of propargylic alcohols for heterocycle synthesis,[12] it was reasoned that attacking the aromatic allenylphosphoryl intermediate by an *ortho*-azide group would lead to the phosphorylated *N*-containing heterocycle. To the best of our knowledge, the cascade reaction of 2-propynol phenyl azides to functional indoles has not been disclosed yet. Herein, we reported our findings (Scheme 1-3).

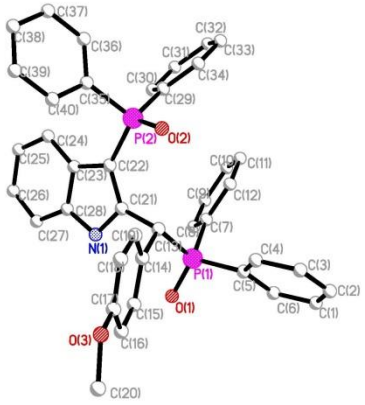
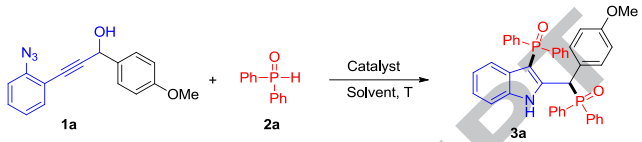


Figure 1 X-ray structure of **3a**

Results and Discussion

Our exploration was initiated by chosing 2-propynol phenyl azides **1a** and diphenylphosphine oxide **2a** as model substrates to study the possible reactivity. In a preliminary experiment, the reaction was performed in CH_3NO_2 at 100 °C using $Cu(OTf)_2$ (20 mol%) as catalyst. To our delight, the reaction proceeded to give a new florescent compound in 50% yield (Table 1, entry 1). Its ^{31}P NMR showed two ^{31}P signals having characteristic P-C chemical shifts. Further X-ray crystallographic analysis unambiguously confirmed the structure as unexpected bisphosphorylated indole **3a** (Figure 1).[13] To the best of our knowledge, this is the first reported bisphosphorylated indole and also the first reported indole synthesis from 2-propynol phenyl azide. Encouraged by this result, different metal catalysts were investigated and $[Cu(OTf)]_2.C_6H_6$ was found to be the most efficient one (Table 1, entries 1−5). Subsequently, a variety of representative solvents including MeCN, CH_3NO_2, DCM, dioxane, were examined carefully, in which DCE gave the highest yield of 70% (Table 1, entries 6−9). The reaction was carried out under lower temperature and gave a decreased yield of **3a**, showing that 100 °C is the most suitable reaction temperature. Changing the substrate ratio to 1:5 could improve the reaction conversion with 83% yield of product **3a** isolated (Table 1, entries 11-12). An additional control experiment demonstrated that an argon atmosphere was beneficial for this transformation. Furthermore, no better result was obtained after increasing or decreasing the catalyst loadings (Table 1, entries 14-15). After extensive screening on other parameters, the optimum reaction conditions for all subsequent transformation were affirmed as the use of $[Cu(OTf)]_2.C_6H_6$ (20 mol%), diphenylphosphine oxide (5.0 equiv) in DCE at 100 °C for 4.0 h under argon.

Table 1 Optimization of reaction for synthesis of **3a**[a]



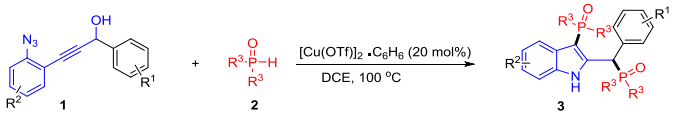
Entry	Catalyst	Solvent	T[°C]	Yield[%][b]
1	$Cu(OTf)_2$	$MeNO_2$	100	50
2	AgOTf	$MeNO_2$	100	15
3	$Cu(OAc)_2$	$MeNO_2$	100	trace
4	$[Cu(OTf)]_2.C_6H_6$	$MeNO_2$	100	60
5	$Cu(acac)_2$	$MeNO_2$	100	<5
6	$[Cu(OTf)]_2.C_6H_6$	DCE	100	70
7	$[Cu(OTf)]_2.C_6H_6$	DCM	40	57
8	$[Cu(OTf)]_2.C_6H_6$	MeCN	100	trace
9	$[Cu(OTf)]_2.C_6H_6$	1,4-dioxane	100	<5
10[c]	$[Cu(OTf)]_2.C_6H_6$	DCE	80	65
11[d]	$[Cu(OTf)]_2.C_6H_6$	DCE	100	78
12[e]	$[Cu(OTf)]_2.C_6H_6$	DCE	100	83
13[e,f]	$[Cu(OTf)]_2.C_6H_6$	DCE	100	73
14[e,g]	$[Cu(OTf)]_2.C_6H_6$	DCE	100	82
15[e,h]	$[Cu(OTf)]_2.C_6H_6$	DCE	100	78

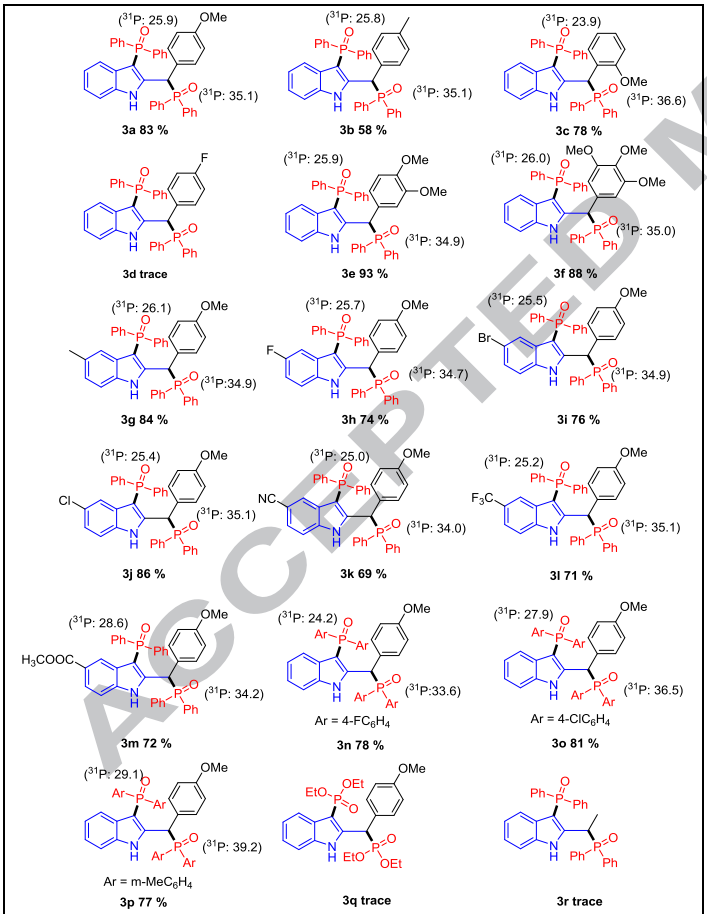
[a]Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), **2a** (0.35 mmol), catalyst (20 mol%), and solvent (2.0 mL) at the indicated temperature for 4.0 h under argon. [b]Isolated yields. [c]At 80 °C . [d]4.0 equiv. of **2a** was used. [e]5.0 equiv. of **2a** was used. [f]Under air. [g]30 mol% of catalyst. [h]Using 15 mol% of catalyst was used.

Having the optimized conditions in hand, we next investigated Cu-catalyzed cascade cyclization of various 2-propynol phenyl azides **1** with diarylphosphine oxides **2** to explore the generality of the method, and the results are summarized in Table 2. Upon repeating the reaction with diphenylphosphine oxide **2a**, substrates **1** with electron-donating groups on the aryl ring of the benzyl alcohol moiety all worked well, efficiently delivering the corresponding functionalized indoles **3a-3c** and **3e-3f** in moderate to excellent yields. Substrates with substituents at *ortho* position could be transformed into the corresponding products, which demonstrated that steric interaction did not significantly affect the reactivity. However, substrates bearing electron-withdrawing group **1d** proved to be ineffective for this transformation, possibly due to its relative instability of the propargyl carbocation intermediate (for details see the scheme 3). Furthermore, several multi-substituted substrates were also compatible with this protocol to generate the corresponding bisphosphorylated indoles in excellent yields (**3e−3f**). Next, we further turned our attention to evaluate substituents (R^2) on another aryl moiety under optimal conditions. Both electron-rich and electron-deficient groups at the *para* position of the substrates worked efficiently to give the desired products in

satisfactory yields (**3g-3m**). Additionally, a series of halogen-containing substrates (**2h-2j**) could be well tolerated in this transformation. It was noteworthy that substrates with strong electron-deficient groups (CN, CF_3, COOMe) also worked to give the corresponding products (**3k**-**3m**) in good yields. Moreover, the scope of diaryl phosphine oxides **2** with **1a** was further investigated under optimal conditions. Diphenylphosphine oxides substituted by F (**2b**), Cl (**2c**) or Me (**2d**) were tolerated as well, and the corresponding products **3n**-**3p** were obtained in moderate to good yields. However, no desired product was isolated when diethyl phosphite (**2e**) was employed under the optimal conditions. Unfortunately, when the alkyl-substituted substrate was performed under the optimal conditions, no corresponding product **3r** was isolated.

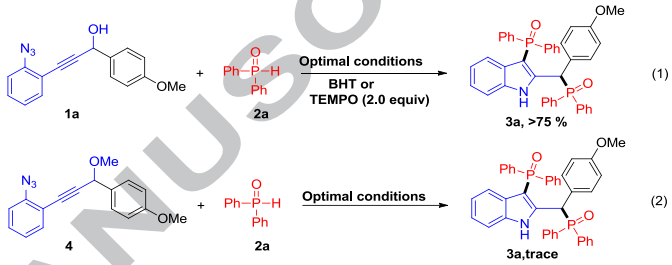
Table 2 Transformation of propargylic alcohols **1** to bisphosphorylated indole derivatives **3**[a]





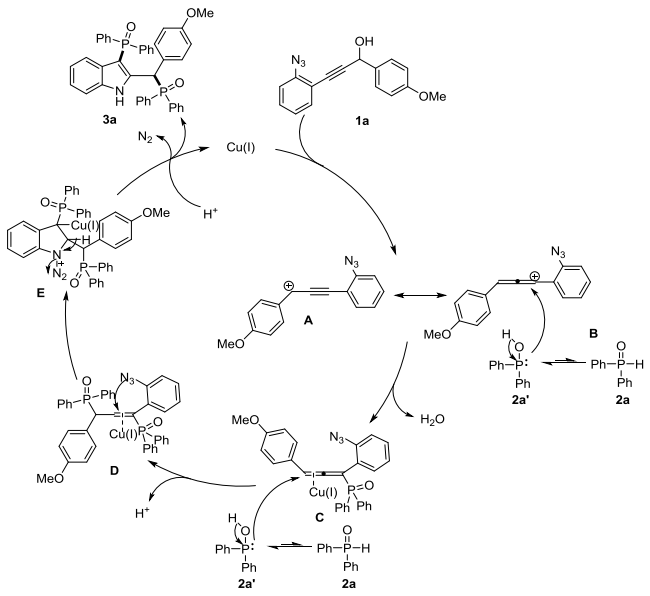
[a] Unless otherwise noted, all reactions were performed with **1** (0.1 mmol) and **2** (0.5 mmol) in DCE (2.0 mL) at 100 °C for 4.0 h. Isolated yields.

To gain further mechanistic insight into the transformation, some control experiments were investigated (Scheme 2). When the reaction was carried out in the presence of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) or BHT (2,6-di-tert-butyl-4-methylphenol), these transformations were found to be almost unaffected, indicating that the reaction might not proceed through a radical pathway (Scheme 2-1). Moreover, we assumed that one possible pathway would be a tandem sequence involving the copper catalyst decomposes the azide to copper nitrene intermediate. To verify this hypothesis, the alcohol protected 2-propynol phenyl azide **4** was prepared and used as starting material to undergo this transformation under the optimal conditions; however, the desired product **3a** was not observed (Scheme 2-2). This result clearly indicates that copper nitrene intermediate is not involved in this novel transformation.



Scheme 2 Control experiments

On the basis of the above detailed observation and literature reports,[11,14] a plausible mechanism for this cascade reaction was proposed in Scheme 3. Initially, the hydroxyl group is activated by copper catalyst and generates propargylic cation intermediate **A**, which followed through a tautomerization to form allenic cation intermediate **B**. The intermediate **B** was attacked by nucleophile **2a** to give intermediate **C**, followed by nucleophilic attack of another **2a** to generate intermediate **D**. Then, intermediate **D** could undergo 5-*endo*-trig cyclization to produce intermediate **E**. Finally, the desired product **3a** was formed with the release of a molecule of nitrogen gas.



Scheme 3 Plausible mechanism

In summary, we have successfully developed a copper-catalyzed bisphosphorylation/cascade cyclization of 2-propynol phenyl azides to construct a series of bisphosphorylated indole derivatives. This transformation proceeds with the formation of two C—P bonds and C—N bond simultaneously in moderate to good yields. This novel transformation applied diarylphosphine oxide as nucleophies and avoided using ligands and oxidants. Although the substituent effect exerts a clear influence on the reaction, this is the first example to synthesize bisphosphorylated indoles using propargylic alcohols,[15] which was identified as acceptable substrate compatibility, especially for electron-donating groups. Further biological activity study of the obtained bisphosphorylated indoles are underway in our laboratory and will be reported in due course.

Acknowledgments

We acknowledge the National Science Foundation of China (No. 21676131 and No. 21462019), the Science Foundation of Jiangxi Province (20181BAB203005, 20161BAB213085, 20143ACB20012), Jiangxi Science & Technology Normal University (2017QNBJRC004 , Doctor Startup Fund) for financial support.

References and notes

1 (a) Atta-ur-Rahman, B. A.; Indole Alkaloids, Harwood Academic, Chichester, 1998; (b) Rizzo, S.; Waldmann, H. *Chem. Rev.* **2014**, *114*, 4621; (c) Chen, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671; (d) Tan, S.-J.; Lim, J.-L.; Low, Y.-Y.; Sim, K.-S.; Lim, S.-H.; Kam, T.-S. *J. Nat. Prod.* **2014**, *77*, 2068.

2 (a) Zhou, X. J.; Garner, R. C.; Nicholson, S.; Kissling, C. J.; Mayers, D. *J. Clin. Pharmacol.*, **2009**, *49*, 1408; (b) Alexandre, F. R.; Amador, A.; Bot, S.; Caillet, C.; Convard, T.; Jakubik, J.; Musiu, C.; Poddesu, B.; Vargiu, L.; Liuzzi, M.; Roland, A.; Seifer, M.; Standring, D.; Storer, R.; Dousson, C. B. *J. Med. Chem.*, **2011**, *54*, 392; (c) Storer, R.; Dousson, C.; Alexandre, F. R.; Roland, A.; Phosphoindoles as HIV inhibitors, WO PCT Int. Appl. 054182, **2006**; (d) Zhou, X.-J.; Pietropaolo, K.; Damphousse, D.; Belanger, B. Chen, J.; Sullivan-Bo'lyai, J.; Mayers, D. *Antimicrob. Agents Chemother.*, **2009**, *53*, 1739; (e) La Regina, G.; Coluccia, A.; Silvestri, R. *Antiviral Chem. Chemother.*, **2010**, *20*, 213.

3 (a) Fu, W. C.; So, C. M.; Chow, W. K.; Yuen, O. Y.; Kwong, F. Y. *Org. Lett.* **2015**, *17*, 4612; (b) Jia, T.; Bellomo, A.; Baina, K. E. L.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 3740; (c) So, C. M.; Kwong, F. Y. *Chem. Soc. Rev.* **2011**, *40*, 4963; (d) Zheng, B.; Jia, T.; Walsh, P. *Org. Lett.* **2013**, *15*, 4190; (e) Benincori, T.; Piccolo, O.; Rizzo, S.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 8340.

4 (a) Kondoh, A.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2010**, *12*, 1476; (b) Zhou, A.-X.; Mao, L.-L.; Wang, G.-W.; Yang, S.-D. *Chem. Commun.*, **2014**, *50*, 8529; (c) Sun, W. B.; Xue, J. F.; Zhang, G. Y.; Zeng, R. S.; An, L. T.; Zhang, P. Z.; Zou, J. P. *Adv. Synth. Catal.* **2016**, *358*, 1753; (d) Hu, G.; Shan, C.; Chen, W.; Xu, P.; Gao, Y.; Zhao, Y. *Org. Lett.*, **2016**, *18*, 6066; (e) Su, F.; Lin, W.; Zhu, P.; He, D.; Lin, J.; Zhang, H.; Wen, T.-B. *Adv. Synth. Catal.* **2017**, *359*, 947.

5 Yuan, T.; Huang, S.; Chun, C.; Lu, G. P. *Org. Biomol. Chem.* **2018**, *16*, 30.

6 Hu, C.; Hong, G.; He, Y.; Zhou, C.; Kozlowski, M. C.; Wang, L. *J. Org. Chem.*, **2018**, *83*, 4739.

7 (a) Zhu, Y.; Sun, L.; Lu, P.; Wang, Y. *ACS Catal.* **2014**, *4*, 1911. (b) Zhang, L.; Fang, G.; Kumar, R. K.; Bi, X. *Synthesis* **2015**, *47*, 2317; (c) Song, X.-R.; Qiu, Y.-F.; Liu, X.-Y.; Liang, Y.-M. *Org. Biomol. Chem.* **2016**, *14*, 11317.

8 Hu, G.; Shan, C.; Chen, W.; Xu, P.; Gao, Y.; Zhao, Y. *Org. Lett.*, **2016**, *18*, 6066.

9 Mao**,** L.-L.; Li, Y.-H.; Yang, S.-D. *Org. Chem. Front.* **2017**, *4*, 608.

10 Yang, J.; Zhang, M.; Qiu, K.; Wang, L.; Yu, J.; Xia, Z.; Shen, R.; Han, L.-B. *Adv. Synth. Catal.* **2017**, *359*, 4417.

11 (a) Li, R.; Chen, X.; Song, X.-R.; Ding, H.; Wang, P.; Xiao, Q.; Liang, Y.-M. *Adv. Synth. Catal.* **2017**, *359*, 3962; (b) Li, X.-S.; Han, Y.-P.; Zhu, X.-Y.; Li, M.; Wei, W.-X.; Liang, Y.-M. *J. Org. Chem.*, **2017,** *82*, 11636.

12 (a) Song, X.-R.; Li, R.; Ding, H.; Yang, R.; Xiao, Q.; Liang, Y.-M. *Tetrahedron Lett*, **2016**, *57*, 4519*;* (b) Li, R.; Song, X.-R.; Chen, X,; Ding, H.; Xiao, Q.; Liang, Y.-M. *Tetrahedron Lett*, **2017**, *58*, 3049; (c) Song, X.-R.; Li, R.; Ding, H.; Chen, X.; Yang, T.; Bai, J.; Xiao, Q.; Liang, Y.-M. *Org. Chem. Front.* **2018**, *5*, 1537.

13 CCDC 1836747 (compound **3a**) contains 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.

14 (a) Georgy, M.; Boucard, V.; Debleds, O.; Zotto, C. D.; Campagne, J.-M. *Tetrahedron* **2009**, *65*, 1758; (b) Xu, C.-F.; Xu, M.; Yang, L.-Q.; Li, C.-Y. *J. Org. Chem.* **2012**, *77*, 3010; (c) Zhang, H.; Tanimoto, H.; Morimoto, T.; Nishiyama, Y.; Kakiuchi, K. *Org. Lett.* **2013**, *15*, 5222.

15 Mahanty, J. S.; Palas Das, M. D., Kundu, N. G. *Tetrahedro*, **1997**, 53, 13397.

Supplementary Material

Supplementary data associated with this article can be found in the online version, at XX.

Graphical Abstract

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Cu(I)-Catalyzed Cascade Intramolecular Cyclization of 2-Propynol Phenyl Azides and Diarylphosphine Oxides for the Synthesis of Bisphosphorylated Indole Derivatives

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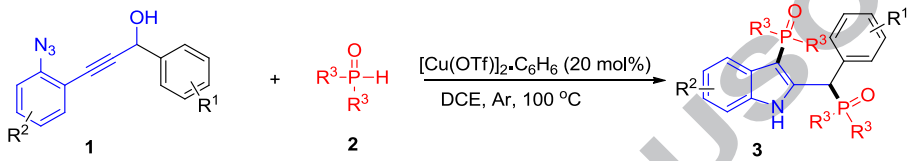

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Highlights

- Cu(I)-catalyzed cascade cyclization of easily prepared 2-propynol phenyl azides to bisphosphorylated indoles .
- This is the first report about the construction of bisphosphorylated indole derivatives.
- This reaction occurred smoothly with formation one C-N bond and two C-P bonds simultaneously.