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Rh(III)-Catalyzed Cascade Annulations To Access Isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones via C−H Activation: Synthesis of Rosettacin

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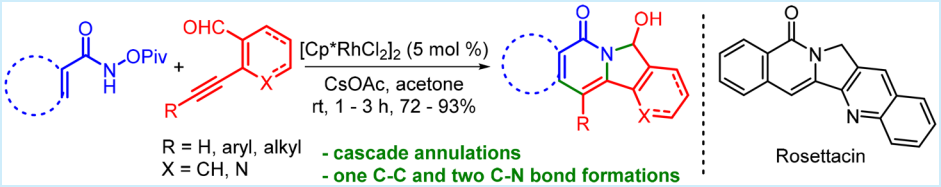
Supporting Information



ABSTRACT: An efficient protocol for the synthesis of diversely substituted 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones from the reaction of *N*-(pivaloyloxy)benzamides with 2-alkynyl aldehydes has been developed, which proceeds through sequential alkyne insertion followed by addition of the amide nitrogen on to the aldehyde. This method provided the products with aminal functionality as a handle for further diversification. The synthetic utility of this strategy was successfully illustrated by the concise, two-step synthesis of an alkaloid, rosettacin, and a topoisomerase I inhibitor.

Indolizin-5(3*H*)-ones fused with aromatic or heteroaromatic units are key structural frameworks embedded in various natural products (Figure 1) such as camptothecin, rosettacin,

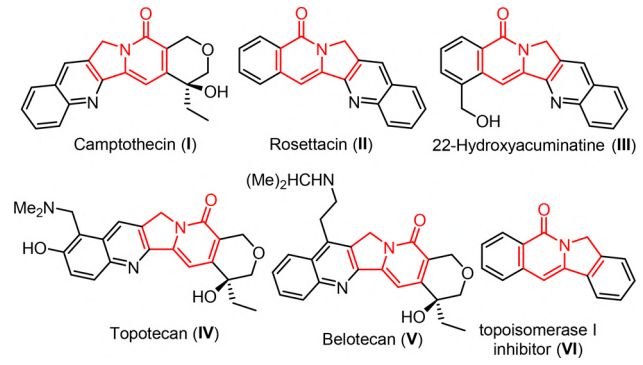


Figure 1. Representative compounds with an indolizin-5(3*H*)-one structural motif.

22-hydroxyacuminatine, and synthetic compounds (camptothecin analogues, e.g., topotecan, belotecan) that exhibit a wide range of interesting biological and medicinal properties.[1−3] Consequently, several strategies have been developed to synthesize these important scaffolds[4,5] including a recently developed flexible strategy to various natural products by Gao and co-workers.[4a] Nonetheless, conceptually different synthetic approaches that provide an access to diversification are still of great interest.

Transition-metal-catalyzed annulation reactions via C−H activation have gained importance as a powerful step- and atom-economical method for the construction of complex molecules.[6] In particular, [Cp*Rh^{III}]-catalyzed direct aryl C−H functionalization toward the insertion of alkyne into aromatic substances holding different directing groups is one of the widely explored reactions, leading to diverse heterocyclic compounds.[7] Fagnou and co-workers discovered that the *N*-pivaloyloxy group can act as a directing group as well as an internal oxidant through N−O bond cleavage during the synthesis of isoquinolones (Figure 2a).[8] Later, this directing group was extensively used in [Cp*Rh^{III}]-catalyzed coupling reactions with alkynes to access isoquinolone derivatives.[9] In 2014, Lin and co-workers identified a novel cascade reaction of O-substituted *N*-hydroxybenzamides with cyclohexadienone-

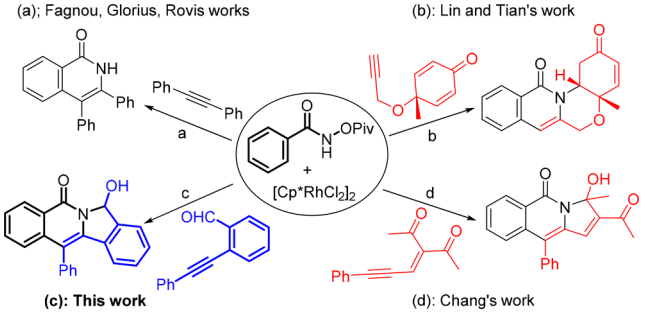


Figure 2. Rh(III)-catalyzed annulations of *N*-(pivaloyloxy)benzamide with alkynes.

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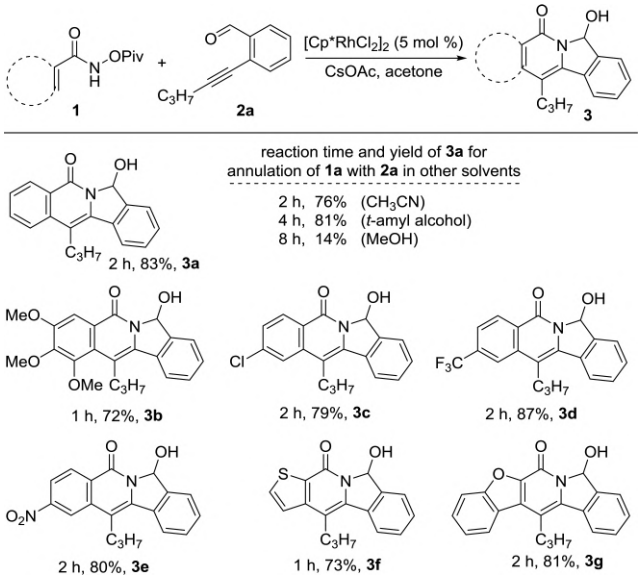
containing 1,6-enynes to obtain *N*-substituted isoquinolones through alkyne insertion followed by aza-Michael addition reaction (Figure 2b).[10] Encouraged by these findings, we envisioned a new cascade annulation of *N*-(pivaloyloxy)-benzamides with 2-alkynyl aldehydes involving sequential isoquinolone formation/addition of NH on to aldehyde (to give the aminal). The successful development of this annulation would lead to an unprecedented facile synthesis of 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones (Figure 2c), which could be readily transformed into polycyclic indolizin-5(3*H*)-ones and their analogues. In continuation of our work on alkyne-assisted annulations,[11] herein we report the results of the above proposed reaction and the total synthesis of rosettacin via rhodium(III)-catalyzed C−H activation cascade annulations. As far as we are aware, such a strategy comprising alkyne insertion followed by the addition of NH on to aldehyde (aminal formation) had not been reported. Very recently, however, while our work was in progress, Chang's research group reported the annulation of *N*-pivaloyloxy benzamide with conjugated enynones to access the tricyclic isoquinolinones (Figure 2d).[12] Nevertheless, there are sufficient differences between the two methods to warrant a further communique on the new work undertaken.

We commenced our studies with the reaction between *N*-(pivaloyloxy)benzamide (**1a**) and 2-(pent-1-yn-1-yl)-benzaldehyde (**2a**). It was observed that the reaction proceeded smoothly in the presence of [$(Cp^*RhCl_2)_2$] (5 mol %) and CsOAc (2 equiv) in acetone at room temperature to give 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-one **3a** in 83% yield in 2 h (Scheme 1). A similar result was observed in other solvents like CH_3CN (2 h, 76%) as well as in *tert*-amyl alcohol (4 h, 81%), while in MeOH a low yield (14%) of the product **3a** was isolated along with starting materials. Having identified the optimized conditions, the scope of this cascade annulation approach was investigated, through the coupling of various *N*-(pivaloyloxy)amides with alkynyl aldehyde **2a** (Scheme 1). Hydroxamic acids containing both electron-donating (3,4,5-trimethoxy, **1b**) as well as electron-withdrawing groups such as 4-chloro (**1c**), 4-trifluoromethyl (**1d**) and 4-nitro (**1e**) smoothly participated in the double annulation without any substantial effect on the outcome of the reaction to furnish the corresponding 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones **3b−e** in 72−87% yield. It is noteworthy that the present cascade process was not limited to *N*-(pivaloyloxy)benzamides, but it could also be extended to *N*-(pivaloyloxy)heteroaryl carboxamides. This was successfully tested by the reactions of *N*-(pivaloyloxy)thiophene-2-carboxamide (**1f**) and benzofuran-2-carboxamide (**1g**) with **2a** to obtain the annulated products **3f** (73%) and **3g** (81%), respectively.

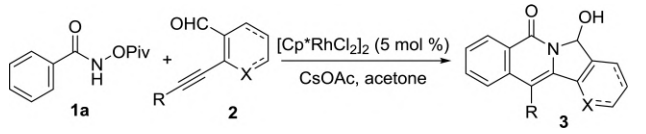
We also evaluated the scope of the reaction with respect to 2-alkynyl aldehyde substrates (Table 1). The annulation reactions of (2-alkynyl) benzaldehydes bearing *n*-butyl (**2b**), cyclopropyl (**2c**), cyclohexyl (**2d**), 2-hydroxyethyl (**2e**), and phenyl (**2f**) with **1a** afforded the corresponding 12-substituted 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones **3h−l** in good yields, indicating that neither the alkyl nor aryl group on the alkyne functionality influenced the reaction outcome. Note in

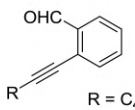
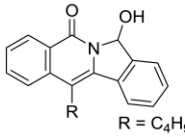
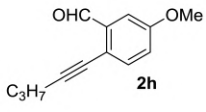
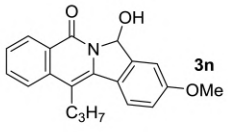
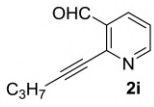
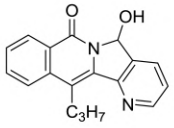
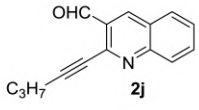
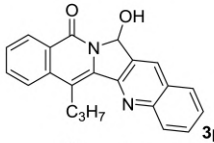
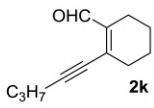
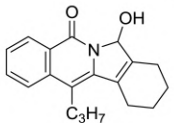
Scheme 1. Optimization and Sope of *N*-(Pivaloyloxy)amides[a,b]



[a]Unless otherwise specified, **1** (1.5 equiv), **2a** (0.29 mmol), [Cp^*RhCl_2]$_2$ (5 mol %), and CsOAc (0.58 mmol) in acetone (2 mL) was stirred for the given time at rt. [b]Isolated yields.

Table 1. Reaction of 1a with Various 2-Alkynyl Aldehydes[a]



entry	alkynyl aldehyde	time (h)	product	yield (%)[b]
1	 R = C_4H_9, **2b**	1	 R = C_4H_9, **3h**	85
2	R = cyclopropyl, **2c**	2	R = cyclopropyl, **3i**	93
3	R = cyclohexyl, **2d**	2	R = cyclohexyl, **3j**	91
4	R = CH_2CH_2OH, **2e**	1.5	R = CH_2CH_2OH, **3k**	90
5	R = Ph, **2f**	1	R = Ph, **3l**	81
6	R = H, **2g**	1	R = H, **3m**	72
7	 **2h**	3	 **3n**	93
8	 **2i**	2.5	 **3o**	82
9	 **2j**	2	 **3p**	85
10	 **2k**	2	 **3q**	78

[a]Unless otherwise specified, **1a** (0.3 mmol), **2** (0.2 mmol), [Cp^*RhCl_2]$_2$ (5 mol %), and CsOAc (0.4 mmol) in acetone (2 mL) was stirred for the given time at rt. [b]Isolated yield.

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particular that 2-ethynylbenzaldehyde (**2g**) participated in this rhodium-catalyzed C−H activation and cascade annulation reaction with **1a** under the optimal conditions to afford **3m** in 72% yield, which suggests that a terminal alkyne group is well tolerated. 2-(Pent-1-yn-1-yl)benzaldehyde containing OMe substitution on the phenyl ring **2h** successfully underwent the reaction to give **3n** in 93% yield. Additionally, when the phenyl group was replaced by a heteroaromatic ring, the corresponding products were still obtained in high yield. For instance, 2-(pent-1-yn-1-yl)nicotinaldehyde (**2i**) and 2-(pent-1-yn-1-yl)-quinoline-3-carbaldehyde (**2j**) furnished the corresponding annulated products **3o** (82%) and **3p** (85%), respectively. To our delight, a cyclohexene ring (**2k**) could be used instead of the benzene ring in the alkynyl aldehyde, leading to the corresponding isoquinolin-5(7*H*)-one **3q** in 78% yield. Based on the results obtained, we believe that the reaction proceeds (Figure 3) via alkyne insertion into the five-membered

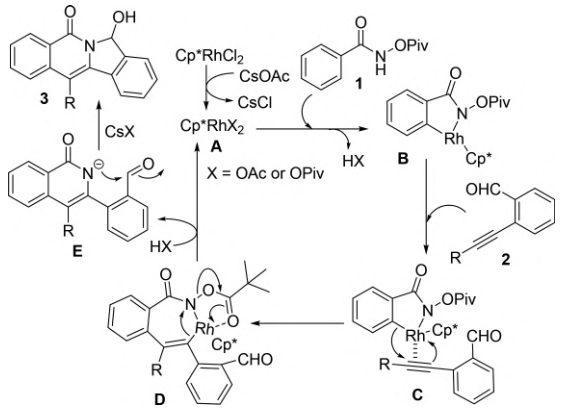
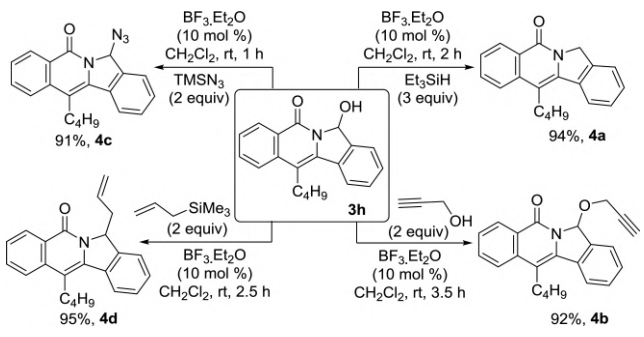


Figure 3. Plausible reaction pathway.

rhodacycle **B**, C−N bond reductive elimination with N−O bond cleavage (**C** and **D**) and base-mediated addition of amide NH on to aldehyde (**E**), similar to the cascade reactions reported by Lin et al. and Chang et al.[10,12] They have extensively studied various experiments to understand and support their proposed reaction pathway.

To exemplify the practical applicability of this protocol, a gram-scale reaction under the standard conditions was conducted to obtain **3h** in 85% yield. Various transformations of this 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-one were also explored (Scheme 2). For example, the reaction of **3h** with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ (10 mol %) in CH_2Cl_2 underwent the reduction of hemiaminal to give isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one (a commonly found structural motif

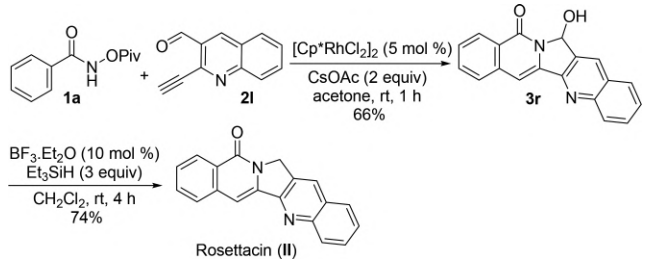
Scheme 2. Diversification of Aminal 3h[a]



in several bioactive natural products) **4a** in 94% yield. Likewise, the treatment of **3h** with other nucleophiles such as propargylic alcohol, TMS-N_3 and allyltrimethyl silane under $BF_3.Et_2O$ (10 mol %)/CH_2Cl_2 conditions offered the functionalized isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones **4b** (92%), **4c** (91%), and **4d** (95%) via C−O, C−N, and C−C bond formations, respectively.

In order to showcase the synthetic value of this Rh(III)-catalyzed cascade reaction, we decided to carry out the total synthesis of rosettacin (**II**). Rosettacin, one of the aromathecin alkaloids, is used as camptothecin/luotonin A hybrid for binding to the topo-I/DNA covalent binary complex.[2e,f] To date, the total synthesis of rosettacin has been accomplished by nine research groups.[4,13] For instance, the groups of Glorius[13a] and Park[13b] have independently reported the synthesis of **II** in more than five steps employing an intramolecular annulation as the key reaction. We have accomplished the synthesis of rosettacin via the present intermolecular annulation between *N*-(pivaloyloxy)benzamide (**1a**) and 2-ethynylquinoline-3-carbaldehyde (**2l**) in two steps (Scheme 3). The reaction of **1a** with

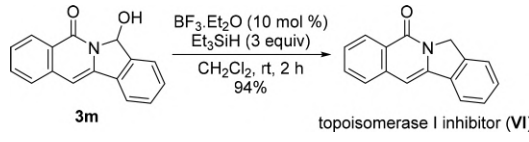
Scheme 3. Total Synthesis of Rosettacin



2l, under the developed conditions, provided the corresponding diannulated product **3r** in 66% yield. The reduction of aminal of **3r** in the presence of $BF_3{\cdot}Et_2O$ (10 mol %)/Et_3SiH in CH_2Cl_2 afforded the rosettacin (**II**) in 74% yield (Scheme 3). This approach was amenable to the synthesis of various analogues of rosettacin through the acid-catalyzed substitution reactions of the annulated product **3r** with different nucleophiles.

Additionally, the isoquinolin-5(7*H*)-one **3m** was transformed into the topoisomerase I inhibitor, isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one **VI**, in 94% yield (Scheme 4). It is important to mention that there are four synthetic approaches known for the synthesis of **VI** to date, each involving harsh conditions or multistep reaction sequence.[2c,4b,14]

Scheme 4. Synthesis of Topoisomerase I Inhibitor



In conclusion, we have developed a one-pot efficient method for the synthesis of 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones from *N*-(pivaloyloxy)amides and 2-alkynyl aldehydes by Rh(III)-catalyzed C−H functionalization. Both aryl and heteroaryl substrates having different substituents were found to be effective coupling partners. Moreover, the present reactions are first examples of cascade Rh(III)-catalyzed alkyne insertion/intramolecular amide nitrogen addition to aldehydes.

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The significance of the products having aminal functionality was shown by further diversification through substitutions in the five-membered ring. Additionally, the application of this method in a short synthesis of rosettacin and topoisomerase I inhibitor was also demonstrated. The flexibility and the extensive scope of this cascade annulation approach should find applications in the synthesis bioactive natural product-like molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03509.

Experimental procedures, characterization details, and ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For representative references, see: (a) Du, W. *Tetrahedron* **2003**, *59*, 8649. (b) Thomas, C. J.; Rahier, N. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 1585. (c) Marco-Contelles, J.; Mayoral, E. P.; Samadi, A.; Carreiras, M. C.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652. (d) Venditto, V. J.; Simanek, E. E. *Mol. Pharmaceutics* **2010**, *7*, 307. (e) Pommier, Y. *Nat. Rev. Cancer* **2006**, *6*, 789. (f) Pommier, Y. *Chem. Rev.* **2009**, *109*, 2894.

(2) For selected references, see: (a) Rodriguez-Berna, G.; Cabañas, M. J. D.; Mangas-Sanjuán, V.; Gonzalez-Alvarez, M.; Gonzalez-Alvarez, I.; Abasolo, I.; Schwartz, S., Jr.; Bermejo, M.; Corma, A. *ACS Med. Chem. Lett.* **2013**, *4*, 651. (b) Fox, B. M.; Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Staker, B. L.; Stewart, L.; Cushman, M. *J. Med. Chem.* **2003**, *46*, 3275. (c) Van, H. T. M.; Cho, W.-J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2551. (d) Xiao, X.; Antony, S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2006**, *49*, 1408. (e) Cheng, K.; Rahier, N. J.; Eisenhauer, B. M.; Gao, R.; Thomas, S. J.; Hecht, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 838. (f) Fox, B. M.; Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Staker, B. L.; Stewart, L.; Cushman, M. *J. Med. Chem.* **2003**, *46*, 3275. (g) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.

(3) (a) Kingsbury, W. D.; Boehm, J. C.; Jakas, D. R.; Holden, K. G.; Hecht, S. M.; Gallagher, G.; Caranfa, M. J.; Mccabe, F. L.; Faucette, L. F.; Johnson, R. K.; Hertzberg, R. P. *J. Med. Chem.* **1991**, *34*, 98. (b) Ban, H.-J.; Oh, I.-J.; Kim, K.-S.; Ju, J.-Y.; Kwon, Y.-S.; Kim, Y.-I.; Lim, S.-C.; Kim, Y.-C. *Tuberc. Respir. Dis.* **2009**, *66*, 93.

(4) (a) Li, K.; Ou, J.; Gao, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 14778. (b) El Blidi, L. E.; Namoune, A.; Bridoux, A.; Nimbarte, V. D.; Lawson, A. M.; Comesse, S.; Daïch, A. *Synthesis* **2015**, *47*, 3583. (c) Pin, F.; Comesse, S.; Sanselme, M.; Daïch, A. *J. Org. Chem.* **2008**, *73*, 1975. (d) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *J. Org. Chem.* **2007**, *72*, 6270.

(5) (a) Wang, F.; Song, G.; Du, Z.; Li, X. *J. Org. Chem.* **2011**, *76*, 2926. (b) Chouhan, G.; Alper, H. *Org. Lett.* **2008**, *10*, 4987. (c) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *Org. Lett.* **2007**, *9*, 2003. (d) Dai, W.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2006**, *8*, 4665. (e) Babjak, M.; Kanazawa, A.; Anderson, R. J.; Greene, A. E. *Org. Biomol. Chem.* **2006**, *4*, 407.

(6) For representative reviews, see: (a) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908. (b) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247. (c) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. *Chem. Rev.* **2015**, *115*, 5301. (d) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.

(7) For selected refs, see: (a) Upadhyay, N. S.; Thorat, V. H.; Sato, R.; Annamalai, P.; Chuang, S.-C.; Cheng, C.-H. *Green Chem.* **2017**, *19*, 3219. (b) Reddy Chidipudi, S.; Burns, D. J.; Khan, I.; Lam, H. W. *Angew. Chem., Int. Ed.* **2015**, *54*, 13975. (c) Zhang, X.; Si, W.; Bao, M.; Asao, N.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2014**, *16*, 4830. (d) Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2013**, *15*, 5750. (e) Pham, M. V.; Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 10610. (f) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (g) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487.

(8) (a) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (b) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449.

(9) For selected references, see: (a) Semakul, N.; Jackson, K. E.; Paton, R. S.; Rovis, T. *Chem. Sci.* **2017**, *8*, 1015. (b) Yu, D.-G.; de Azambuja, F.; Gensch, T.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 9650. (c) Webb, N. J.; Marsden, S. P.; Raw, S. A. *Org. Lett.* **2014**, *16*, 4718. (d) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. (e) Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318. (f) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592.

(10) Fukui, Y.; Liu, P.; Liu, Q.; He, Z.-T.; Wu, N.-Y.; Tian, P.; Lin, G.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 15607.

(11) (a) Raji Reddy, C.; Dilipkumar, U.; Shravya, R. *Chem. Commun.* **2017**, *53*, 1904. (b) Raji Reddy, C.; Rani Valleti, R.; Dilipkumar, U. *Chem. - Eur. J.* **2016**, *22*, 2501. (c) Raji Reddy, C.; Panda, S. A.; Reddy, M. D. *Org. Lett.* **2015**, *17*, 896. (d) Raji Reddy, C.; Dilipkumar, U.; Damoder Reddy, M. *Org. Lett.* **2014**, *16*, 3792.

(12) Hong, S. Y.; Jeong, J.; Chang, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 2408.

(13) (a) Lerchen, A.; Knecht, T.; Koy, M.; Daniliuc, C. G.; Glorius, F. *Chem. - Eur. J.* **2017**, *23*, 12149. (b) Xu, X.; Liu, Y.; Park, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9372. (c) Walraven, H. G. M.; Pandit, U. K. *Tetrahedron* **1980**, *36*, 321. (d) Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140. (e) Warneke, J.; Winterfeldt, E. *Chem. Ber.* **1972**, *105*, 2120.

(14) (a) Luo, W.-K.; Shi, X.; Zhou, W.; Yang, L. *Org. Lett.* **2016**, *18*, 2036. (b) Godfry, J. C. *J. Org. Chem.* **1959**, *24*, 581.

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Domino Reaction of 2,4-Diyn-1-ols with 1,3-Dicarbonyl Compounds: Direct Access to Aryl/Heteroaryl-Fused Benzofurans and Indoles

Chada Raji Reddy,* Mounika Aila, Muppidi Subbarao, Kamalkishor Warudikar, and René Grée

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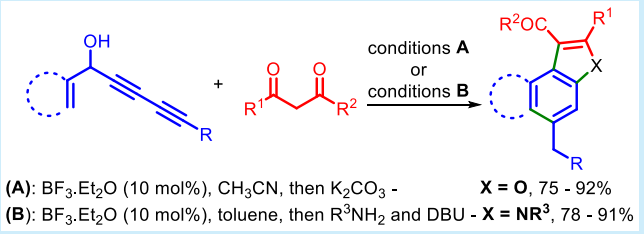
ABSTRACT: A domino propargylation/furanylation (intramolecular *exo-dig*-cyclization)/benzannulation reaction of 2,4-diyn-1-ols with 1,3-dicarbonyl compounds has been developed for the first time. This provides a novel and effective method for the preparation of aryl/heteroaryl-fused benzofurans from easily accessible starting materials in a single step. The methodology was extended to pyrrolyl-benzannulation to obtain aryl/heteroaryl-fused indoles. Further, application of this approach in the synthesis of eustifoline D and dictyodendrin structural frameworks has been demonstrated.



Fused polycyclic heteroaromatics are privileged molecular scaffolds present in a range of bioactive molecules,[1] pharmaceuticals,[2] and bioimaging probes,[3] as well as in optoelectronic materials.[4] Particularly, aryl/heteroaryl annulated-benzofurans are frequently used in organic light-emitting diodes (OLEDs) owing to their charge-transport properties and thermal stability.[5] Further, π-expanded naphthalimides with a fused furan ring were used as novel fluorescent probes and naphthofurans (R7000, **1A**) as mutagenic agents.[6] Moreover, these scaffolds are found to be the core structure of natural products. For instance, the alkaloid eustifoline D (Figure 1, **1B**), isolated by Furukawa from the root bark of *Murraya euchrestifolia*, which has a unique furo[2,3-*c*]carbazole framework, is used as an active constituent in some folk medicines in China.[7] Likewise, aryl/heteroaryl annulated indoles are the key motifs of various molecules and have drawn the attention of the pharmaceutical and material science communities. For example, dictyodendrin A and B, pyrrolo-[2,3-*c*]carbazoles (Figure 1, **1C** and **1D**), are unusual natural alkaloids isolated from the Japanese marine sponge *Dictyodendrilla verongiformis* and known to possess telomerase inhibitory activity.[8] Additionally, the 3*H*-benzo[*e*]indole skeleton has potential applications in molecular probes useful for optical imaging and photochromic materials.[9] This tricyclic framework is also found in enzymes like indoleamine 2,3-dioxygenase (IDO, **1E**), fructose-2,6-biphosphatase 3 (PFKFB3) inhibitors, and drugs for treating Alzheimer's disease and other related conditions.[10]

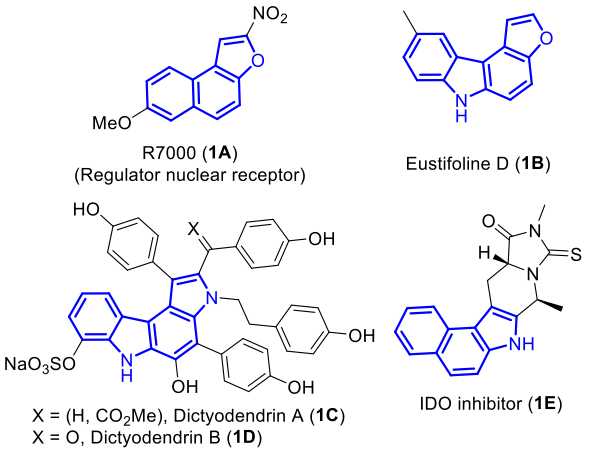


Figure 1. Selected molecules having aryl/heteroaryl-fused benzofurans and indoles.

Due to their pharmacological importance and unique electronic properties, the development of synthetic methods for the construction of aryl/heteroaryl-fused benzofurans and indoles has attracted substantial attention in medicinal, as well as in material chemistry.[11−13] Typically, these methods proceed either through the construction of furan or pyrrole rings on aryl/heteroaryl-annulated benzenes (Scheme 1a)[11] or via the formation of benzene rings on substituted furans or pyrroles (Scheme 1b).[12] However, one-pot assembly of aryl/heteroaryl-annulated benzofuran or indoles from acyclic precursors is uncommon[13] and still remains a challenge. Hence, development of such new methods enabling the direct

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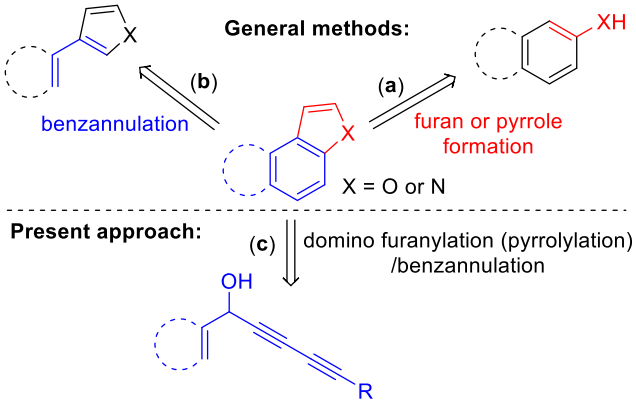
Scheme 1. Approaches to the Synthesis of Aryl/Heteroaryl-Fused Benzofurans and Indoles



access to diversely functionalized (hetero)aryl-fused benzofurans and indoles from readily accessible acyclic compounds is highly desirable. In this direction, a domino reaction is one of the effective strategies for the construction of functionalized heterocycles with molecular diversity and atom as well as pot economy by avoiding separation of the intermediates.[14]

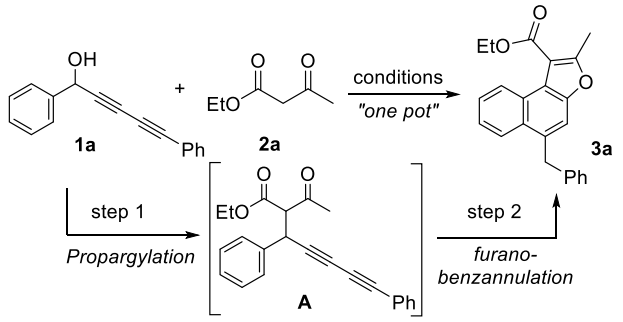
On the other hand, 1-aryl/heteroaryl propargyl alcohols have emerged as adaptable precursors to yield various hetero/carbocycles through nucleophilic substitution followed by alkyne-assisted annulation.[15] However, their analogues with extended alkyne conjugation, 1-aryl-2,4-diyn-1-ols, are underexplored.[16] These 2,4-diyn-1-ols offer an important avenue to undergo additional cyclization in a cascade manner. Our research interests in exploring 2,4-diyn-1-ols[17] led us to examine the possibility of cycloisomerizations for the synthesis of aryl/heteroaryl-annulated benzofurans and indoles. Herein, we describe a novel domino propargylation/furanylation (pyrrolylation)/benzannulation reaction of 2,4-diyn-1-ols with 1,3-dicarbonyl compounds to access the corresponding aryl/heteroaryl-fused benzofurans/indoles in one pot (Scheme 1c). To our knowledge, an approach to benzofuran or indole by the sequential construction of the furan or pyrrole and benzene ring from the annulation of diynols has not been described to date.

To examine the proposed plan, the reaction between 1-phenyl-2,4-diyn-1-ol (**1a**) and ethyl acetoacetate (**2a**) was employed as a model reaction. First, the propargylation reaction was tested in the presence of different acid catalysts to form the intermediate **A** and found that $BF_3{\cdot}Et_2O$ (10 mol % in acetonitrile) was the best choice among the tested acid catalysts such as *p*TSA, $Sc(OTf)_3$, $Cu(OTf)_2$, $In(OTf)_3$, and $FeCl_3$ (entries 1 to 6, Table 1). Then, the conversion of **A** to the benzofuran **3a** was verified in the presence of a base through furan formation, followed by a benzannulation reaction. To our delight, treatment of **A** with K_2CO_3 in acetonitrile at 80 °C provided the target **3a** in 97% yield (entry 7, Table 1). Other bases, such as DBU or $NaHCO_3$, were found to be less effective in yielding **3a** (entries 8 and 9, Table 1) even after a prolonged reaction time. With these conditions, next we performed both the reactions in a one-pot manner eluding the isolation of intermediate **A** to obtain **3a** in 92% yield (entry 10, Table 1).

Having established the optimal reaction conditions, the scope with respect to 2,4-diyn-1-ols, as well as 1,3-dicarbonyl compounds, was next examined (Scheme 2). A variety of 1-aryl/heteroaryl 2,4-diyn-1-ols **1** (see the Supporting Information for the structure of 2,4-diyn-1-ols) were well tolerated in this domino furanylation/benzannulation with ethyl acetoacetate (**2a**) to give the corresponding aryl/heteroaryl-fused benzofurans **3** in good to high yields. 1,5-Diphenylpenta-2,4-diyn-1-ol (**1a**) having substitutions such as 4-OMe and 4-Ph groups on the 1-phenyl ring reacted easily, affording the desired naphtho[2,1-*b*]furans **3b** (91%) and **3c** (83%), respectively. In addition, 2,4-diyn-1-ol bearing a 1-naphthyl group at the C1 position was also a viable substrate, furnishing the corresponding phenanthro[3,4-*b*]furan **3d** in 86% yield. Remarkably, the present domino annulation exhibits good tolerance for 1-heteroaryl groups such as 3-carbazolyl and 2-thiophenyl on diynols, providing the 7*H*-benzofuro[5,4-*b*]carbazole **3e** and thieno[2,3-*e*]benzofuran **3f** in good yields. Further study revealed that the tested diynols, with either the 4-CF_3-phenyl group or trimethylsilyl (TMS) at the C5 position (alkyne carbon), underwent furanyl-benzannulation to furnish the expected naphtho[2,1-*b*]furans **3g** (85%) and **3h** (86%), respectively. Subsequently, diverse 1,3-dicarbonyl compounds were investigated in their reactions with **1a** under the optimal conditions. The alkyl acetoacetate possessing either a methyl or an allyl group endured this reaction to afford naphtho-furans **3i** (82%) and **3j** (81%). The reaction of ethyl 3-oxo-3-(*p*-tolyl)propanoate (**2d**) with **1a** worked well to afford **3k** in 80% yield. Similarly, a diketo-compound, pentane-2,4-dione (**2e**), was also indicated to be suitable in this domino annulation with different diyn-1-ols to deliver the matching naphtho[2,1-*b*]furans **3l**, **3m** and phenanthro[3,4-*b*]furan **3n** in good yield. Notably, 1,3-cyclohexadione (**2f**, cyclic diketocompound) also smoothly participated to produce 9,10-dihydronaphtho[2,1-*b*]benzofuran-11(8*H*)-ones **3o** (89%) and **3p** (75%).

Next, we endeavored to construct the furo[2,3-*c*]carbazole, a unique framework embedded in the eustifoline D natural

Table 1. Optimization of Reaction Conditions[a]



entry	propargylation [acid (10 mol %)]	furano-benzannulation (base, temp, time)	product	yield (%)[b]
1	*p*TSA, 1 h	–	**A**	72
2	$BF_3{\cdot}Et_2O$, 0.5 h	–	**A**	95
3	$Sc(OTf)_3$, 1.5 h	–	**A**	70
4	$Cu(OTf)_2$, 2 h	–	**A**	76
5	$FeCl_3$, 1 h	–	**A**	65
6	$In(OTf)_3$, 2 h	–	**A**	85
7	–	K_2CO_3, 80 °C, 7 h	**3a**	97
8	–	DBU, 80 °C, 12 h	**3a**	20
9	–	$NaHCO_3$, 80 °C, 12 h	**3a**	10
10[c]	$BF_3{\cdot}Et_2O$, 0.5 h	K_2CO_3, 80 °C, 7 h	**3a**	92

[a]Entries 1 to 6: Reactions were performed using 0.5 mmol of **1a** with 0.35 mmol of **2a** in 3 mL of CH_3CN and acid at 0 °C to rt. Entries 7 to 9: Reaction of **A** with 1.25 mmol of base in CH_3CN at 80 °C. [b]Isolated yield. [c]One-pot reaction.

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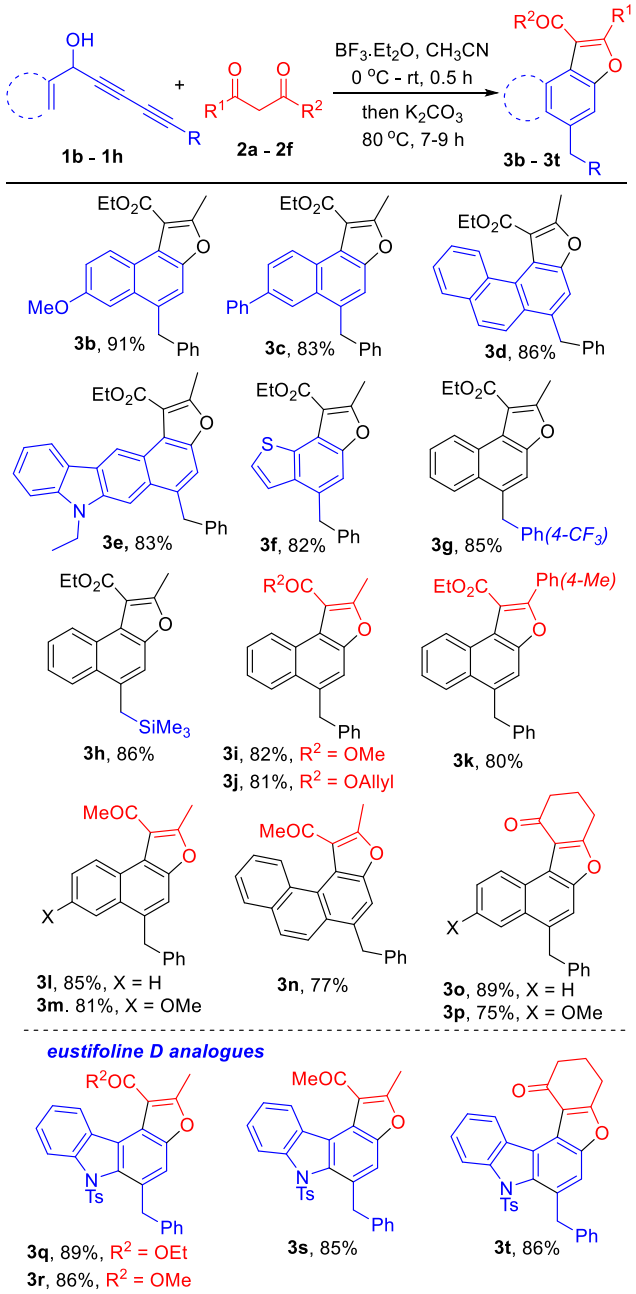
Scheme 2. Investigation of Substrate Scope[a]

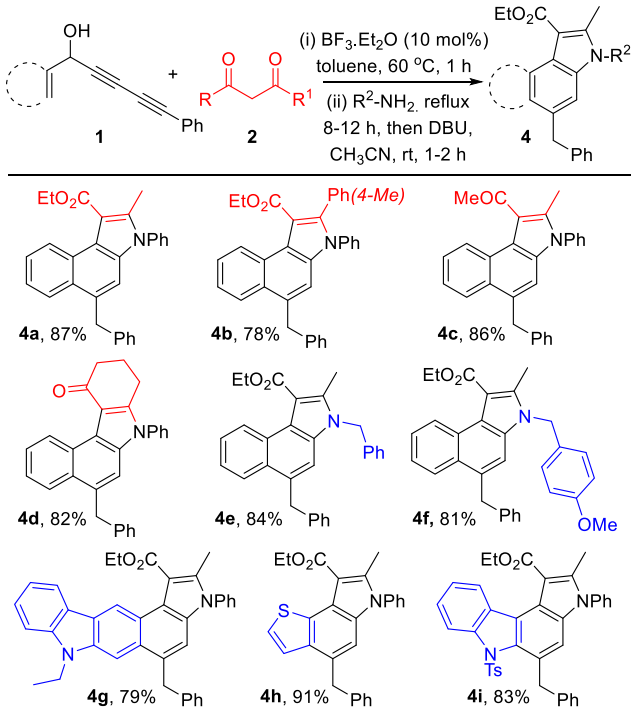


[a]All reactions were performed using 0.5 mmol of **1** with 0.35 mmol of **2** in 3 mL of CH_3CN and $BF_3{\cdot}Et_2O$ (10 mol %). After stirring at rt for 30 min, K_2CO_3 (1.25 mmol) was added and stirred at 80 °C.

product.[7] Pleasingly, the reaction of suitable 2,4-diyn-1-ol **1i**, derived from indole-3-carboxaldehyde, with **2a** under optimal conditions, offered the furo[2,3-*c*]carbazole **3q** in 89% yield (Scheme 2). Additionally, a few more 1,3-dicarbonyls including 1,3-cyclohexanedione were examined with 2,4-diyn-1-ol **1i**, to obtain the corresponding furo[2,3-*c*]carbazole products **3r**, **3s**, and **3t** (eustifoline D analogues) in good yields (Scheme 2).

Next, we wondered if the annulated-indole products **4** could be formed also in the presence of an amine using the present approach via domino pyrrolylation/benzannulation reactions. The reaction of **1a** with **2a** in the presence of aniline was carried out under the conditions used for furano-benzannulation. As predicted, the construction of **4a** is challenged by the catalytic activity of acid in the presence of aniline (base) and only a low yield of the product formation was observed, which forced us to further optimize the reaction conditions (for details, see Supporting Information Table S1). Gratifyingly, the desired benzo[*e*]indole **4a** was isolated in 87% yield by heating in toluene at 60 °C in the presence of $BF_3{\cdot}Et_2O$ (10 mol %) for 1 h followed by addition of amine and reflux for 8 h, then removal of toluene, addition of DBU in CH_3CN, and stirring at room temperature for 1 h. These optimized conditions were subsequently employed to examine the generality of this method (Scheme 3). Initially, diverse 1,3-dicarbonyl com-

Scheme 3. Generality of Domino Pyrrolo-benzannulation[a,b]



[a]Reactions performed using 0.5 mmol of **1** and 0.6 mmol of **2** and $BF_3{\cdot}Et_2O$ (10 mol %) in toluene (3 mL) at 60 °C for 1 h, then addition of $R^2{-}NH_2$ (0.6 mmol) and reflux for 8−12 h. Removal of toluene and addition of DBU in CH_3CN (0.5 mmol) stirred at rt. [b]Isolated yields.

pounds **2d** to **2f** were treated with **1a** in the presence of aniline and the reaction proceeded smoothly, affording the desired benzo[e]indoles **4b** to **4d** in 78−86% yields. Different amines such as benzyl amine and 4-methoxy benzylamine were also studied in the reaction of **1a** with **2a** to obtain the expected *N*-benzyl products **4e** (84%) and **4f** (81%), respectively. To our delight, annulation of 1-heteroaryl 2,4-diyn-1-ols **1e** and **1f** with **2a** in the presence of aniline led to the formation of 3,7-dihydroindolo[5,4-*b*]carbazole **4g** (79%) and 6*H*-thieno[3,2-*e*]indole **4h** (91%), respectively. Notably, the developed method was found to be suitable for the synthesis of pyrrolo[2,3-*c*]carbazole **4i**, from the reaction of 1-(3-indoloyl)-2,4-diyn-1-ol **1i** with **2a** in 83% yield (Scheme 3). This molecule has the structural motif of dictyodendrin A and B.[8]

On the basis of our experimental results and the literature reports,[17,18] a plausible reaction mechanism is depicted in Scheme 4. Initially, the propargylation (involving nucleophilic

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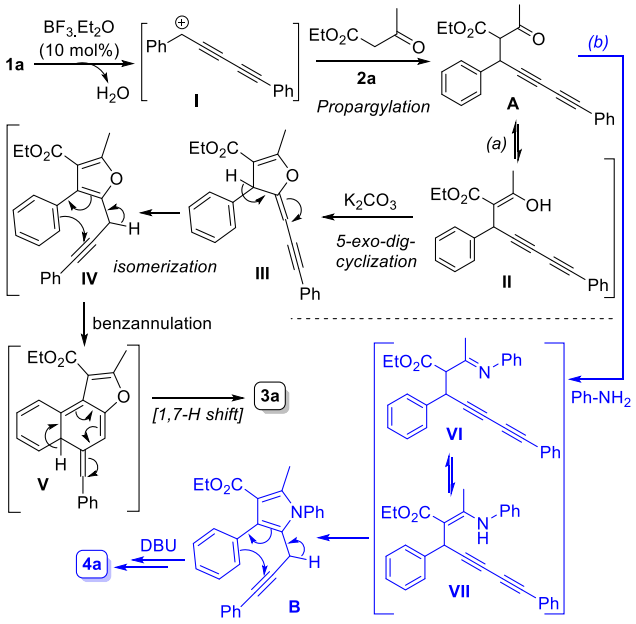
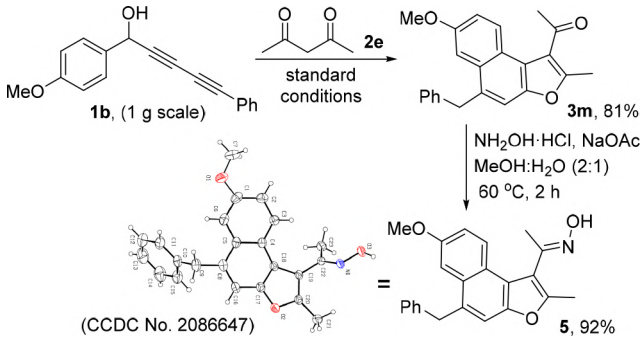
Scheme 4. Proposed Mechanism



substitution via a carbocation **I**) occurred to generate the intermediate **A** (isolated and fully characterized) from **1a** and propargylic alcohol **2a** in the presence of $BF_3{\cdot}Et_2O$. Next, base-mediated intramolecular 5-*exo*-*dig*-cyclization of enol **II** and subsequent isomerization of **III** would provide the propargylfuran **IV**. Later, the intermediate undergoes further cycloisomerization through **V** (1,7-hydrogen shift driven aromatization) to result in the benzannulated product, fused-benzofuran **3a**. For the formation of benzo-annulated indole (Scheme 4, route b), it is considered that the intermediate **A** reacts with aniline to give the corresponding imines **VI** which tautomerize to the corresponding conjugated enamines **VII**. From these derivatives, a similar sequence of cyclization−isomerization−benzannulation−aromatization should occur to afford the target **4a** via pyrrole **B** (isolated and fully characterized).

To establish the reaction scalability of this method, a gram scale preparation of **3m** (81%) was attained by the reaction of **1b** with **2e**. Additionally, the practicality of functional groups on the furan ring is shown through further derivatization toward expanding the structural diversity. To our delight, the treatment of **3m** with $NH_2OH{\cdot}HCl$/NaOAc in $MeOH/H_2O$ (2:1) provided the ketoxime **5** in 92% yield (Scheme 5). The structure of **5** was confirmed by a single crystal X-ray method.

Scheme 5. Gram-Scale Synthesis of 3m and Derivatization



In summary, this study presents a handy reaction of 2,4-diyn-1-ols with 1,3-dicarbonyl compounds as a novel method for the synthesis of distinctly functionalized aryl/heteroaryl-annulated benzofurans and indoles. Remarkably, the reaction allows the assembly of two C−C and one C−O (two C−N) bonds by the cleavage of one C−O in a one-pot operation *via* a domino acid-catalyzed propargylation of 1,3-dicarbonyls followed by a base-mediated furanylation or pyrrolylation (intramolecular *exo*-*dig*-cyclization)/benzannulation sequence. This protocol enables accessing eustifoline D analogues as well as the structural framework of dictyodendrins in good to excellent yields. The developed approach is noteworthy for its wide scope, good yields, and a mild, operationally simple strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01615.

Experimental procedures, characterization details, and ^1H and ^{13}C NMR spectra of new compounds (PDF)

Accession Codes

CCDC 2086647 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected papers, see: (a) La Clair, J. J.; Rheingold, A. L.; Burkart, M. D. Ganodone. a Bioactive Benzofuran from the Fruiting Bodies of Ganoderma tsugae. *J. Nat. Prod.* **2011**, *74*, 2045−2051. (b) Le Guevel, Le. R.; Oger, F.; Lecorgne, A.; Dudasova, Z.; Chevance, S.; Bondon, A.; Barath, P.; Simonneaux, G.; Salbert, G. Identification of Small Molecule Regulators of the Nuclear Receptor HNF4α based on Naphthofuran Scaffolds. *Bioorg. Med. Chem.* **2009**, *17*, 7021−7030.

(2) (a) Iitsuka, T.; Hirano, K.; Satoh, T.; Miura, M. Rhodium-Catalyzed Dehydrogenative Coupling of Phenylheteroarenes with Alkynes or Alkenes. *J. Org. Chem.* **2015**, *80*, 2804−2814. (b) Ferri, N.; Beccalli, E. M.; Contini, A.; Corsini, A.; Antonino, M.; Radice, T.; Pratesi, G.; Tinelli, S.; Zunino, F.; Gelmi, M. L. Antiproliferative effects on human tumor cells and rat aortic smooth muscular cells of 2,3-heteroarylmaleimides and heterofused imides. *Bioorg. Med. Chem.* **2008**, *16*, 1691−1701.

(3) (a) Krawczyk, P. Modulation of benzofuran structure as a fluorescent probe to optimize linear and nonlinear optical properties and biological activities. *J. Mol. Model.* **2020**, *26*, 272. (b) Singh, D. K.; Jang, K.; Kim, J.; Lee, J.; Kim, I. Intramolecular electrophilic cyclization approach to 6-substituted naphtho [2,1-b] benzofurans: novel dual-state emissive fluorophores with blue emission. *ACS Comb. Sci.* **2019**, *21*, 408−416. (c) Sameiro, M.; Goncalves, T. Fluorescent Labeling of Bio-molecules with Organic Probes. *Chem. Rev.* **2009**, *109*, 190−212.

(4) For representative papers, see: (a) Im, Y.; Lee, J. Y. Effect of the Position of Nitrogen In Pyridoindole on Photophysical Properties and Device Performances of α-, β-, γ Carboline Based High Triplet Energy Host Materials for Deep Blue Devices. *Chem. Commun.* **2013**, *49*, 5948−5950. (b) Jiao, C.; Huang, K. W.; Luo, J.; Zhang, K.; Chi, C.; Wu, J. Bis-N-annulated Quaterrylenebis(dicarboximide) as a New Soluble and Stable Near-Infrared Dye. *Org. Lett.* **2009**, *11*, 4508−4511.

(5) (a) Kim, S. M.; Yun, J. H.; Han, S. H.; Lee, J. Y. A Design Strategy of Bipolar Host Materials for More Than 30 times Extended Lifetime in Phosphorescent Organic Light-Emitting Diodes using Benzocarbazole and Quinazoline. *J. Mater. Chem. C* **2017**, *5*, 9072−9079. (b) Tao, Y.; Yang, C.; Qin, J. Organic host materials for phosphorescent organic light-emitting diodes. *Chem. Soc. Rev.* **2011**, *40*, 2943−2970.

(6) Arrault, X.; Michel, V.; Quillardet, P.; Hofnung, M.; Touati, E. Comparison of kinetics of induction of DNA adducts and gene mutations by a nitrofuran compound, 7-methoxy-2-nitronaphtho[2,1-*b*]furan (R7000), in the caecum and small intestine of Big Blue mice. *Mutagenesis* **2002**, *17*, 353−359.

(7) (a) Ito, C.; Furukawa, H. New Carbazole Alkaloids from Murraya euchrestifolia Hayata. *Chem. Pharm. Bull.* **1990**, *38*, 1548−1550. (b) Fan, X.; Yu, L. Z.; Wei, Y.; Shi, M. Cascade Amination/Cyclization/Aromatization Process for the Rapid Construction of [2,3-c] Dihydro carbazoles and [2,3-c] Carbazoles. *Org. Lett.* **2017**, *19*, 4476−4479 and references cited therein.

(8) Warabi, K.; Matsunaga, S.; Van Soest, R. W. M.; Fusetani, N. Dictyodendrins A−E, the first telomerase-inhibitory marine natural products from the sponge Dictyodendrilla verongiformis. *J. Org. Chem.* **2003**, *68*, 2765−2770 and references cited therein.

(9) (a) Izumi, S.; Kawabata, Y.; Takeda, Y.; Momoda, J.; Nagoh, H. 2000, EP1184379. (b) Ye, Y.; Bloch, S.; Kao, J.; Achilefu, S. Multivalent Carbocyanine Molecular Probes: Synthesis and Applications. *Bioconjugate Chem.* **2005**, *16*, 51−61.

(10) (a) Tanaka, M.; Li, X.; Hikawa, H.; Suzuki, T.; Tsutsumi, K.; Sato, M.; Takikawa, O.; Suzuki, H.; Yokoyama, Y. *Bioorg. Med. Chem.* **2013**, *21*, 1159−1165. (b) Bruderer, H.; Godel, T.; Imhof, R.; Jakob-Roetne, R. 1994, US5,318,967.

(11) (a) Zhu, C. F.; Gao, C. H.; Hao, W. J.; Zhu, Y. L.; Tu, S. J.; Wang, D. C.; Jiang, B. Synthesis of C3-alkylated benzofurans via palladium-catalyzed regiocontrolled hydrofuranization of unactivated alkenes. *Org. Chem. Front.* **2021**, *8*, 127−132. (b) Liu, S.; Zang, Y.; Huang, H.; Sun, J. In$(OTf)_3$-Catalyzed Synthesis of 2,3-Dihydro-1H-benzo[e]indoles and 2,3-Dihydrobenzofurans via [3 + 2] Annulation. *Org. Lett.* **2020**, *22*, 8219−8223. (c) Aiken, S.; De Azevedo, O. D. C. C.; Chauhan, K.; Driscoll, T.; Elliott, P. I.; Gabbutt, C. D.; Heron, B. M. Base-Mediated Ring Contraction of Pyran Systems Promoted by Palladium and Phase Transfer Catalysis. *J. Org. Chem.* **2020**, *85*, 952−966. (d) Clarke, A. K.; Ho, H. E.; Rossi-Ashton, J. A.; Taylor, R. J. K.; Unsworth, W. P. Indole Synthesis Using Silver Catalysis. *Chem. - Asian J.* **2019**, *14*, 1900−1911. (e) Liu, L.; Ji, X.; Dong, J.; Zhou, Y.; Yin, S. F. Metal-Free Oxidative Annulation of 2-Naphthols with Terminal Alkynes Affording 2-Arylnaphtho [2,1-b] furans. *Org. Lett.* **2016**, *18*, 3138−3141. (f) Kuram, M. R.; Bhanuchandra, M.; Sahoo, A. K. Direct Access to Benzo[b]furans through Palladium-Catalyzed Oxidative Annulation of Phenols and Unactivated Internal Alkynes. *Angew. Chem., Int. Ed.* **2013**, *52*, 4607−4612. (g) Zhang, F. R.; Li, C. M.; Wang, C.; Qi, C. Z. Facile Synthesis of Benzoindoles and Naphthofurans through Carbonaceous Material-Catalyzed Cyclization of Naphthylamines/Naphthols with Nitroolefins in Water. *Org. Biomol. Chem.* **2015**, *13*, 5022−5029.

(12) (a) Clarke, A. K.; Lynam, J. M.; Taylor, R. J. K.; Unsworth, W. P. Back-to-Front" Indole Synthesis Using Silver(I) Catalysis: Unexpected C-3 Pyrrole Activation Mode Supported by DFT. *ACS Catal.* **2018**, *8*, 6844−6850. (b) Reddy, C. R.; Valleti, R. R.; Sathish, P. [4 + 2] Benzannulation of 3 Alkenylpyrroles/ Thiophenes with Propargylic Alcohols: Access to Substituted Indoles, Benzothiophenes, and Aza[5]helicenes. *J. Org. Chem.* **2017**, *82*, 2345−2354. (c) Martins, M. G.; Zeni, G.; Back, D. F.; Kaufman, S. T.; Silveira, C. C. Expedient Iodocyclization Approach Toward Polysubstituted 3H-Benzo[e]indoles. *Adv. Synth. Catal.* **2015**, *357*, 3255−3261. (d) Asao, N.; Aikawa, H. Lewis Acid-Catalyzed [4 + 2] Benzannulation between Enynal Units and Enols or Enol Ethers: Novel Synthetic Tools for Polysubstituted Aromatic Compounds Including Indole and Benzofuran Derivatives. *J. Org. Chem.* **2006**, *71*, 5249−5253. (e) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, M. J. Synthesis of Indoles upon Sequential Reaction of 3-Alkynylpyrrole-2-carboxaldehydes with Iodonium Ions and Alkenes. Preparation of Related Benzofuran and Benzothiophene Derivatives. *Adv. Synth. Catal.* **2005**, *347*, 526−530.

(13) (a) Jash, M.; De, S.; Pramanik, S.; Chowdhury, C. Palladium (II)-Catalyzed Cascade Reactions of Ene-Ynes Tethered to Cyano/Aldehyde: Access to Naphtho[1,2-b]furans and Benzo[g]indoles. *J. Org. Chem.* **2019**, *84*, 8959−8975. (b) Zhang, X.; Feng, C.; Jiang, T.; Li, Y.; Pan, L.; Xu, X. Expedient and Divergent Tandem One-Pot Synthesis of Benz[e]indole and Spiro[indene-1,3′-pyrrole] Derivatives from Alkyne-Tethered Chalcones/Cinnamates and TosMIC. *Org. Lett.* **2015**, *17*, 3576−3579. (c) Xia, G.; Han, X.; Lu, X. Efficient Synthesis of Heterocyle-Fused β-Naphthylamines *via* Intramolecular Addition to a Cyano Group Initiated by Nucleopalladation of Alkynes. *Org. Lett.* **2014**, *16*, 6184−6187.

(14) For selected references, see: (a) Tietze, L. F. Domino Reactions in Organic Synthesis. Domino Reactions in Organic Synthesis. *Chem. Rev.* **1996**, *96*, 115−136. (b) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866−880.

(15) For selected reviews, see: (a) Qian, H.; Huang, D.; Bi, Y.; Yan, G. 2-Propargyl Alcohols in Organic Synthesis. *Adv. Synth. Catal.* **2019**, *361*, 3240−3280. (b) Zhang, D. Y.; Hu, X. P. Recent advances in copper-catalyzed propargylic substitution. *Tetrahedron Lett.* **2015**, *56*, 283−295. (c) Reddy, C. R.; Ranjan, R.; Kumaraswamy, P.; Reddy, M. D.; Gree, R. 1-Aryl Propargylic Alcohols as Handy Synthons for the

https://doi.org/10.1021/acs.orglett.1c01615
Org. Lett. 2021, 23, 4882−4887

Construction of Heterocycles and Carbocycles. *Curr. Org. Chem.* **2014**, *18*, 2603−2645.
(16) Representative references, see: (a) Xiao, X.; Hoye, T. R. The domino hexadehydro Diels−Alder reaction transforms polyynes to benzynes to naphthynes to anthracynes to tetracynes (and beyond?). *Nat. Chem.* **2018**, *10*, 838−844. (b) Chinta, B. S.; Baire, B. Total Synthesis of Selaginpulvilins A and C. *Org. Biomol. Chem.* **2018**, *16*, 262−265. (c) Chen, Z.; Jia, X.; Ye, C.; Qiu, G.; Wu, J. AgOTf-catalyzed electrophilic cyclization of triynols with NXS: rapid synthesis of densely trisubstituted naphthalenes and quinolines. *Chem. - Asian J.* **2014**, *9*, 126−130.
(17) (a) Reddy, C. R.; Subbarao, M.; Sathish, P.; Kolgave, D. H.; Donthiri, R. R. One-Pot Assembly of 3-Hydroxycarbazoles via Uninterrupted Propargylation/Hydroxylative Benzannulation Reactions. *Org. Lett.* **2020**, *22*, 689−693. (b) Reddy, C. R.; Dilipkumar, U.; Shravya, R. An Atom- and Pot- Economical Consecutive Multi-Step Reaction Approach to Polycyclic Aromatic Hydrocarbons. *Chem. Commun.* **2017**, *53*, 1904−1907.
(18) (a) Kwon, Y.; Cho, H.; Kim, S. Expedient Synthesis of Phenanthrenes via In(III)-Catalyzed 6-*Exo*-*Dig*-Cycloisomerization. *Org. Lett.* **2013**, *15*, 920−923. (b) Lim, J. W.; Kim, K. H.; Kim, S. H.; Kim, J. N. Copper-catalyzed tandem alkynylation, propargyl−allenyl isomerization, 6π-electrocyclization of Morita−Baylis−Hillman adducts to naphthalenes. *Tetrahedron Lett.* **2012**, *53*, 5449−5454.

https://doi.org/10.1021/acs.orglett.1c01615
Org. Lett. 2021, 23, 4882−4887

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(54) **C5, C6 SUBSTITUTED AND/OR FUSED OXINDOLES AS ANTI-CANCER AGENTS AND PROCESS FOR PREPARATION THEREOF**

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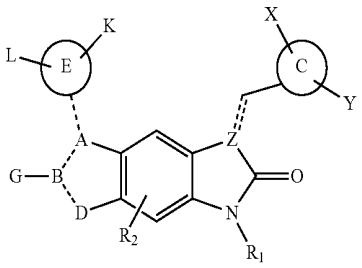
(57) **ABSTRACT**

The present invention describes the C5,C6 Substituted and/or fused oxindole compounds useful as anti-cancer agents and process for preparation thereof. Particularly the present invention relates to C5,C6 Substituted and/or fused oxindole compounds of formula I.

Formula I



wherein,

A=C, CH, CH_2, None

B=C or CH part of open chain and/or cyclic alkyl/aryl/heteroaryl moiety

G=alkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalkyl, alkoxy, aryloxy-all these optionally substituted with one or more substituents

D=O, N, S, OH, SH, NH, None

Z=C, CH_2

Ring E=aryl/heteroaryl/cycloalkyl optionally substituted with one or more substituents

Ring C=aryl/heteroaryl/cycloalkyl optionally substituted with one or more substituents

L=H, alkyl, alkoxy, halogen, CN, OH, amino, NO_2

K=H, alkyl, alkoxy, halogen, CN, OH, amino, NO_2

X=H, alkyl, alkoxy, halogen, CN, OH, amino, NO_2

Y=H, alkyl, alkoxy, halogen, CN, OH, amino, NO_2

R1=H, alkyl

R2=H, alkyl, halogen, CN, NO_2, alkoxy, amino, OH