Additive-Controlled Divergent Synthesis of Tetrasubstituted 1,3-Enynes and Alkynylated 3*H*-pyrrolo[1,2-*a*]indol-3-ones *via* Rhodium Catalysis

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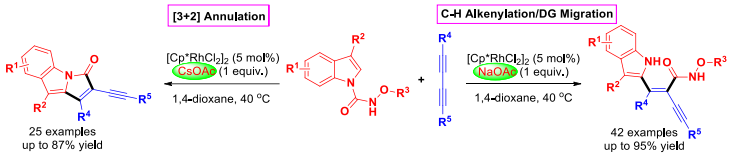
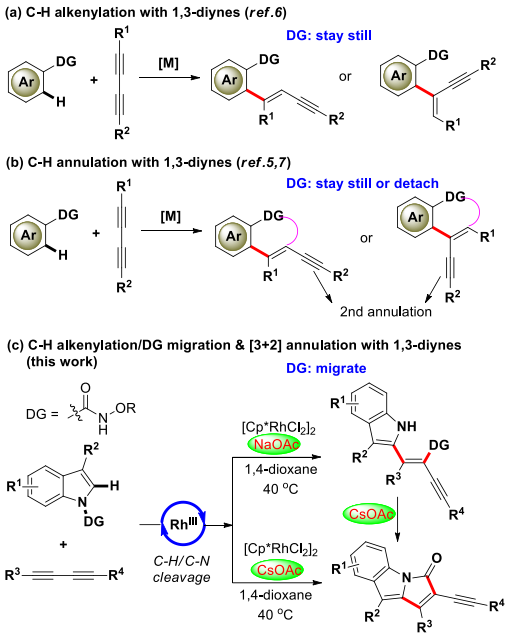
Supporting Information Placeholder



ABSTRACT: Herein we report the additive-controlled divergent synthesis of tetrasubstituted 1,3-enynes and alkynylated 3*H*-pyrrolo[1,2-*a*]indol-3-ones through rhodium-catalyzed C–H alkenylation/DG migration and [3+2] annulation, respectively. This protocol features rare directing group migration in 1,3-diyne-involved C–H activation, excellent regio- and stereoselectivity, excellent monofunctionalization over difunctionalization, broad substrate scope, moderate to high yields, good functional group compatibility and mild redox-neutral conditions.

Transition-metal-catalyzed C–H functionalization with various coupling partners assisted by directing groups (DGs) has contributed significantly to the synthesis of numerous valuable molecules in recent decades.[1] Among them, alkynes, as a versatile coupling partner, have been broadly used in C–H activation such as C–H alkenylation and C–H annulation for preparing alkenes and hetero-/carbocyclic compounds, respectively.[2-4] By contrast, 1,3-diynes which contain two adjacent alkyne moieties were less explored in the field of C–H functionalization, mainly because of the encompassing challenges of achieving high chemo-, regio- and stereoselectivity in the step of the migratory insertion of the organometallic species into 1,3-diynes, as well as the selectivity between mono- and difunctionalization of the two carbon–carbon triple bonds.[5] Nevertheless, several research groups have made their efforts in C–H functionalization with 1,3-diynes, and the reported reactions could be mainly divided into two categories. (a) C–H alkenylation for synthesizing 1,3-enynes: only few examples employing a pyridyl, pyrimidyl or amide substituent as the DG were reported, however, only trisubstituted rather than tetrasubstituted 1,3-enynes were obtained (Scheme 1a).[6] (b) C–H annulation for the assembly of alkynylated heterocycles which could undergo a second annulation at the alkyne moiety: only a handful of examples using an amide, 8-aminoquinoline, oxime, thiocarbamate, hydrazide, 1,2,4-oxadiazolone, 2*H*-imidazole or 2-aminopyridine group as the DG were disclosed (Scheme 1b).[5,7] Despite the remarkable achievements made, however, it should be noted the DGs only display as auxiliary groups which help to improve site selectivity and reactivity in the abovementioned two types of reactions, and stay still at the original position (or detach in individual cases) when the

Scheme 1. C–H functionalization with 1,3-diynes.

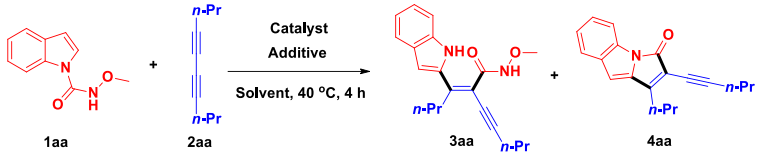


reactions finish. Apparently, it is quite appealing but also challenging to realize the further use of the DGs like intramolecular transfer in 1,3-diyne-involved C–H activation, making DGs as functional reagents and the construction of an extra carbon–carbon/heteroatom bond possible. Recently, C–H functionalization involving DG migration *via* Co,[8] Rh,[9] Mn[10], Ru[11] and Ir[12] catalysis provides a unique strategy to generate multiple

C–X (X = C, N, O) bonds, while this type of reactions still remain limited over the past decade. To the best of our knowledge, there is no precedent involving DG migration in the reported C–H functionalization with 1,3-diynes to date. Based on our experience in functional group migration[13] and rhodium(III)-catalyzed C–H activation,[9i,14] and inspired by the recent DG transfer strategy,[8-12] we herein disclose a C–H alkenylation/DG migration cascade between indoles and 1,3-diynes for the synthesis of more challenging tetrasubstituted 1,3-enynes with the catalytic system of $[Cp^*RhCl_2]_2$/NaOAc (Scheme 1c). Unexpectedly, when CsOAc is used instead of NaOAc as the additive, the initial C–H alkenylation/DG migration products undergo an intramolecular cyclization *in situ* to give the [3+2] annulation products, namely C2-alkynylated 3*H*-pyrrolo[1,2-*a*]indol-3-ones. Despite the elegant synthesis of 3*H*-pyrrolo[1,2-*a*]indol-3-ones *via* Co[15] and Ru[14b] catalysis, this work presents an unprecedented example of rhodium-catalyzed synthesis of C2-alkynylated 3*H*-pyrrolo[1,2-*a*]indol-3-ones. In this paper, the carbamoyl directing group[16] works as an internal acylation reagent that migrates onto the alkene unit of the products after the step of C–H alkenylation. In view of the large occurrence of the 1,3-enyne and 3*H*-pyrrolo[1,2-*a*]indol-3-one motifs in bioactive compounds (Figure S1),[17] our method is quite attractive as it presents an additive-controlled divergent synthesis of the challenging tetrasubstituted 1,3-enynes and alkynylated 3*H*-pyrrolo[1,2-*a*]indol-3-ones *via* rhodium catalysis.

Model substrates indole **1aa** and deca-4,6-diyne **2aa** were used to optimize the reaction parameters including catalysts, additives and solvents (Table 1). Initially, substrates **1aa** and **2aa** were treated with a series of metal catalysts in 1,4-dioxane at 40 °C for 4 h employing NaOAc as the additive (entries 1-7). Pleasingly, $[Cp^*RhCl_2]_2$ was found to be able to catalyze the C–H alkenylation/DG migration cascade highly regio- and stereoselectively (entry 7), delivering the *cis*-adduct **3aa** with the indole moiety exclusively located at the less hindered position as the only isomer in a high yield (85%). Subsequent solvent screening showed that 1,4-dioxane is the optimal (entries 8-13). But interestingly, a trace amount of [3+2] annulation product **4aa** was observed in THF, acetone, CH_3CN and EtOH. Next, various additives were investigated (entries 14-18). KOAc, $Zn(OAc)_2$, Na_2CO_3 and K_2CO_3 could also display as the additive (entries 15-18), with which the desired C–H alkenylation/DG migration product **3aa** was obtained in 30-84% yields. Surprisingly, when CsOAc was employed as the additive (entry 14), the [3+2] annulation product **4aa** instead of the C–H alkenylation/DG migration product **3aa** was selectively afforded as the only product in a highly regioselective manner with 78% yield. Acid additives, such as CH_3CO_2H, CF_3CO_2H and pivalic acid, were proved to be ineffective but with the recovery of the starting materials (entries 1-3, Table S1). Besides, a further reduction in the amount of the catalyst or additive resulted in incomplete consumption of the starting materials, thus leading to lower yields of products **3aa** or **4aa**

Table 1. Optimization of the reaction conditions[a]

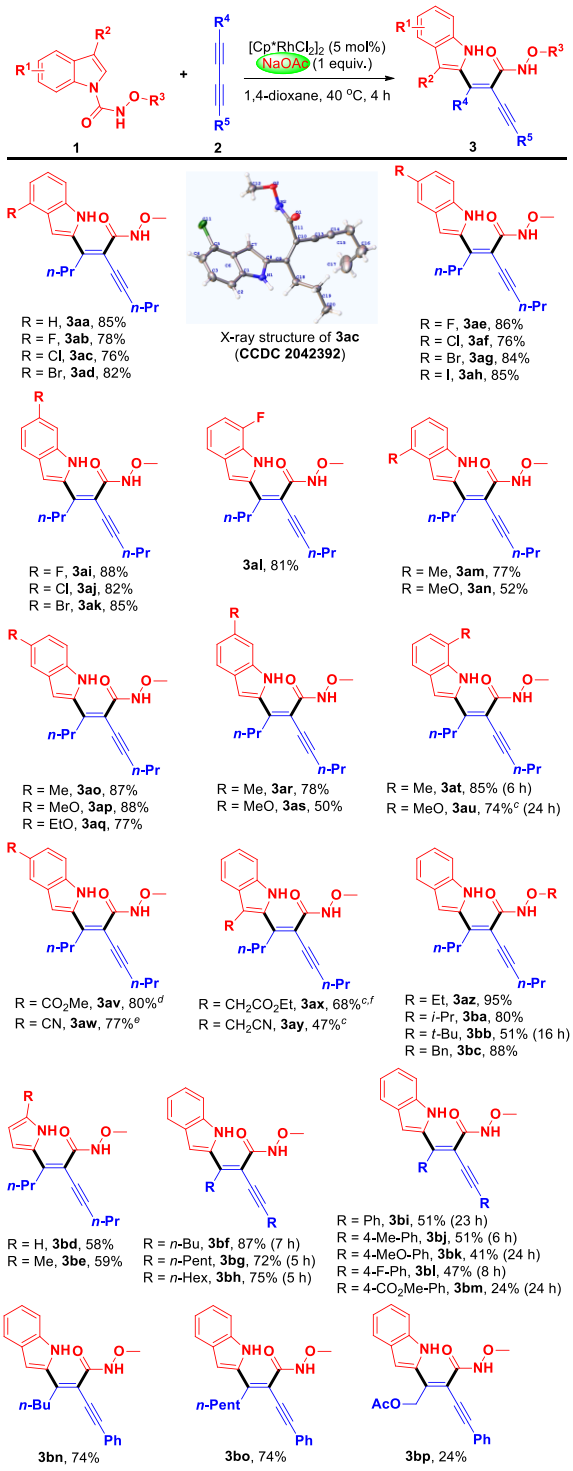


Entry	Catalyst	Additive	Solvent	Yield of **3aa** (%)[b]	Yield of **4aa** (%)[b]
1	$MnBr(CO)_5$	NaOAc	1,4-dioxane	0	0
2	$[Cp^*IrCl_2]_2$	NaOAc	1,4-dioxane	trace	0
3	$[RuCl_2(p\text{-cym})]_2$	NaOAc	1,4-dioxane	<5	0
4	$CoCp_2^*PF_6$	NaOAc	1,4-dioxane	0	0
5	$Pd(OAc)_2$	NaOAc	1,4-dioxane	0	0
6	$Ni(OTf)_2$	NaOAc	1,4-dioxane	0	0
7	**$[Cp^*RhCl_2]_2$**	**NaOAc**	**1,4-dioxane**	**85**	0
8	$[Cp^*RhCl_2]_2$	NaOAc	Toluene	60	0
9	$[Cp^*RhCl_2]_2$	NaOAc	DCE	56	0
10	$[Cp^*RhCl_2]_2$	NaOAc	THF	75	trace
11	$[Cp^*RhCl_2]_2$	NaOAc	Acetone	72	<5
12	$[Cp^*RhCl_2]_2$	NaOAc	CH_3CN	60	<5
13	$[Cp^*RhCl_2]_2$	NaOAc	EtOH	69	trace
14	**$[Cp^*RhCl_2]_2$**	**CsOAc**	**1,4-dioxane**	trace	**78**
15	$[Cp^*RhCl_2]_2$	KOAc	1,4-dioxane	63	8
16	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	1,4-dioxane	84	trace
17	$[Cp^*RhCl_2]_2$	Na_2CO_3	1,4-dioxane	42	trace
18	$[Cp^*RhCl_2]_2$	K_2CO_3	1,4-dioxane	30	6
19	-	NaOAc/CsOAc	1,4-dioxane	0/0	0/0
20	$[Cp^*RhCl_2]_2$	-	1,4-dioxane	0	0

[a]Reaction conditions: **1aa** (0.25 mmol), **2aa** (0.275 mmol), catalyst (5 mol%), additive (0.25 mmol), solvent (4.0 mL), 40 °C, 4 h.
[b]Isolated yields.

(entries 4-7, Table S1). At last, blank experiments were conducted (entries 19 and 20). The results showed no formation of product **3aa** or **4aa** was observed with single catalyst or additive but with the materials untouched. Notably, no further functionalization of the alkyne moiety in **3aa** or **4aa** was observed during condition optimization, thus an excellent monofunctionalization over difunctionalization was achieved. This may be because the steric hindrance of the tetrasubstituted alkene unit in **3aa** or **4aa** prevents the alkyne moiety from the second functionalization. In this way, Rh(III)-catalyzed additive-controlled divergent synthesis of **3aa** and **4aa** through C–H alkenylation/DG migration and [3+2] annulation, respectively, was realized in excellent regio- and stereoselectivity, and monofunctionalization selectivity.

Scheme 2. Substrate scope of the Rh(III)-catalyzed C–H alkenylation/DG migration. [a,b]

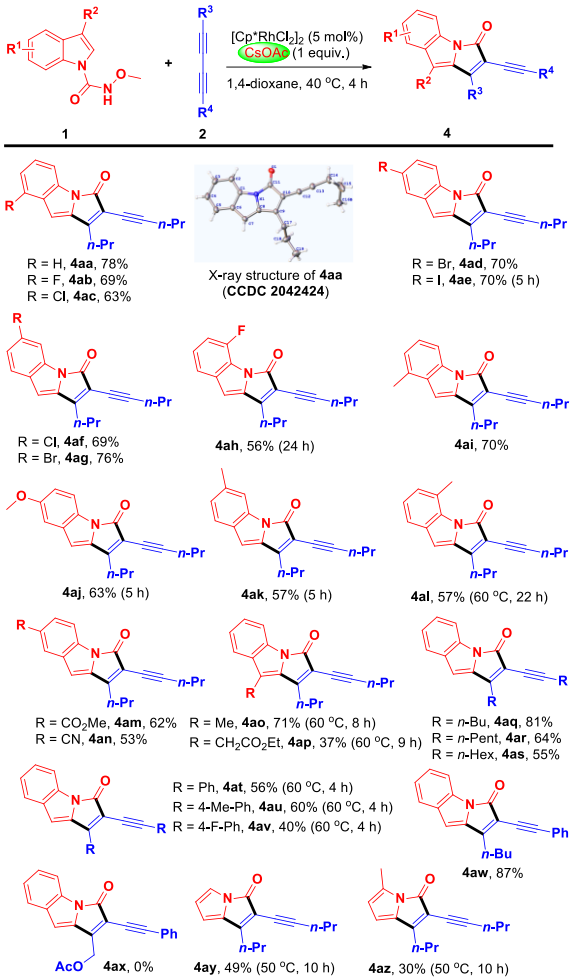


[a]Reaction conditions: **1** (0.25 mmol), **2** (0.275 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), NaOAc (0.25 mmol), 1,4-dioxane (4.0 mL), 40 °C, 4 h. [b]Isolated yields. [c]$[Cp^*RhCl_2]_2$ (10 mol%) and NaOAc (0.5 mmol) were used. [d]The annulation product **4am** was obtained in 15% yield. [e]The annulation product **4an** was obtained in 10% yield. [f]The annulation product **4ap** was obtained in 7% yield.

Subsequently, the general applicability of Rh(III)-catalyzed C–H alkenylation/DG migration was checked (Scheme 2). Overall, a variety of indoles possessing diverse substituents at R^1, R^2, R^3 and 1,3-diynes carrying various substituents at R^4, R^5 were well tolerated to construct the 1,3-enynes **3** in moderate to high yields and excellent regio- and stereoselectivity. At first, the scope of indoles was explored with **2aa** as the model coupling partner. For example, halogen-substituted indoles reacted well to yield the 1,3-enynes **3ab**-**3al** in 76-88% yields. The addition of electron-donating group substituted indoles to **2aa** happened successfully to deliver products **3am**-**3au** in 50-88% yields. The reactions of indoles substituted with electron-withdrawing groups went smoothly to produce adducts **3av**-**3aw** in 77-80% yields. Indoles having functional groups at C3 position could also add to **2aa** to provide products **3ax**-**3ay**, albeit with lower yields (47-68%). This result is justified by the steric hindrance caused by the C3 substituents. To our delight, the introduction of different alkyl groups at R^3 position of the indole was allowed, and products **3az**-**3bc** were prepared in 51-95% yields. In addition, pyrrole substrates were also tolerated, affording products **3bd**-**3be** in 58-59% yields. Then, the scope of 1,3-diynes was investigated with **1aa** as the reaction partner. For instance, the reactions of symmetrical 1,3-diynes bearing various alkyl groups underwent smoothly to prepare products **3bf**-**3bh** in 72-87% yields. Likewise, this process could also be applicable to symmetrical 1,3-diynes having various aryl groups, which interacted with **1aa** to assemble products **3bi**-**3bm** in 24-51% yields. Representative unsymmetrical 1,3-diynes were also tolerated, affording the desired products **3bn**-**3bp** in 24-74% yields with the indole moiety dominantly located at the less hindered carbon of the alkyne units. Notably, all the indicated products listed in Scheme 2 were obtained as single isomers, confirming the exclusive regio- and stereoselectivity of this Rh(III)-catalyzed C–H alkenylation/DG migration.

Next, the scope of Rh(III)-catalyzed [3+2] annulation was examined (Scheme 3). In general, a diversity of indoles substituted at R^1, R^2 and 1,3-diynes carrying various substituents at R^3, R^4 were suitable substrates, and the desired 3*H*-pyrrolo[1,2-*a*]indol-3-ones **4** were synthesized with moderate to high yields and excellent regioselectivity. For example, halogenated indoles reacted well with **2aa** to furnish products **4ab**-**4ah** in 56-76% yields. The [3+2] annulation reactions of electron-rich or electron-deficient indoles with **2aa** underwent uneventfully to give products **4ai**-**4an** in 53-70% yields. The reactions of indoles bearing substituents at C3 position with **2aa** worked to provide products **4ao**-**4ap** in 37-71% yields, although harsher reaction conditions were required. With respect to the scope of 1,3-diynes, alkyl substituted symmetrical 1,3-diynes were converted into the desired products **4aq**-**4as** in 55-81% yields. Similarly, this annulation process was also compatible with symmetrical 1,3-diynes carrying aryl groups,

Scheme 3. Substrate scope of Rh(III)-catalyzed [3+2] annulation. [a,b]



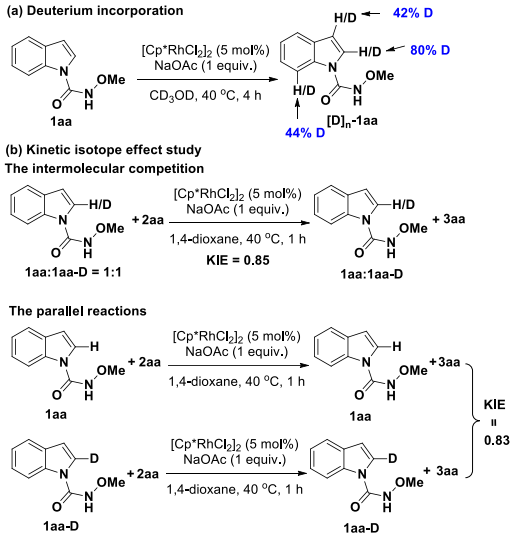
[a]Reaction conditions: **1** (0.25 mmol), **2** (0.275 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), CsOAc (0.25 mmol), 1,4-dioxane (4.0 mL), 40 °C, 4 h. [b]Isolated yields.

which reacted successfully to assemble products **4at**-**4av** in 40-60% yields. Representative unsymmetrical 1,3-diynes such as octa-1,3-diyn-1-ylbenzene could be converted into the desired product **4aw** in 87% yield, while the reaction of 5-phenylpenta-2,4-diyn-1-yl acetate gave a complex mixture. To our delight, pyrrole substrates could also undergo this [3+2] annulation, albeit with moderate yields of the desired products **4ay**-**4az**. Impressively, all the indicated products listed in Scheme 3 were obtained as single regioisomers, demonstrating the excellent regioselectivity of this Rh(III)-catalyzed [3+2] annulation.

To further prove the synthetic utility of the methodology, the Rh(III)-catalyzed C–H alkenylation/DG migration between **1aa** and **2aa** was carried out at gram scale (Scheme S1a). The result shows the reaction could be easily scaled up with a high yield (81%). Additionally, a study on various directing groups disclosed the substituents on the amide nitrogen had a crucial impact on the reaction results, and the free hydrogen and alkoxy groups like MeO are both indispensable (Scheme S1b).

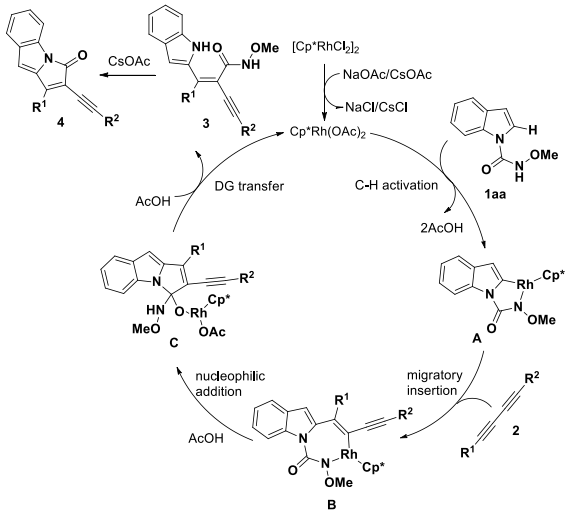
In addition, a deuterium incorporation experiment was performed by treating **1aa** in CD_3OD under standard conditions, and the result shows that 80%, 42% and 44% deuteration was observed at C2, C3, C7 position of **1aa**, respectively (Scheme 4a). This suggests the C–H bond cleavage is reversible. The results of KIE experiments suggested that the step of C–H bond cleavage could not be rate-limiting (Scheme 4b). Besides, we speculated that the stronger alkalinity of CsOAc than that of NaOAc could be responsible for the final cyclization of the C–H alkenylation/DG migration products **3** to give the [3+2] annulation products **4**. Therefore, control experiments were carried out with **3aa** (Table S2). Expectedly, treatment of **3aa** with CsOAc (20 mol%) in 1,4-dioxane at 40 °C for 19 h produced the desired product **4aa** with 94% yield.

Scheme 4. Mechanistic studies.



On the basis of mechanistic study and previous reports,[8b,15] a possible reaction mechanism was proposed (Scheme 5). Initially, directing group assisted C–H activation of **1aa** with the active rhodium complex gives the rhodacycle **A**. Next, intermediate **B** is formed by regioselective coordination and migratory insertion of 1,3-diynes into the Rh–C bond of intermediate **A**. Intermediate **B** then undergoes an intramolecular nucleophilic addition to give intermediate **C**. C–N bond cleavage and following protodemetalation of intermediate **C** afford 1,3-enynes **3** and regenerate the active rhodium catalyst. When CsOAc is used as the additive, compounds **3** undergo a further cyclization to give pyrrolo[1,2-*a*]indoles **4** under the catalysis of CsOAc (Scheme S2).

Scheme 5. Proposed reaction mechanism.



In conclusion, we have developed an additive-controlled divergent synthesis of tetrasubstituted 1,3-enynes and alkynylated 3*H*-pyrrolo[1,2-*a*]indol-3-ones *via* rhodium-catalyzed C–H alkenylation/DG migration and [3+2] annulation, respectively. Our protocol features rare directing group migration in 1,3-diyne-involved C–H functionalization, excellent regio- and stereoselectivity, excellent monofunctionalization over difunctionalization, broad substrate scope, good tolerance of functional groups, moderate to high yields and mild redox-neutral conditions, thus affording an efficient approach for the assembly of the challenging tetrasubstituted 1,3-enyne and alkynylated 3*H*-pyrrolo[1,2-*a*]indol-3-one scaffolds. Bioactivity studies of the indole-containing compounds are undergoing in our laboratory, and we anticipate these molecules embedded with privileged 1,3-enyne or 3*H*-pyrrolo[1,2-*a*]indol-3-one motif will find their pharmaceutical applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data of products, and copies of ^{1}H and ^{13}C spectra (PDF)

X-ray crystal structure of compound **3ac** and **4aa** (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully acknowledge the financial support from the Natural Science Foundation of Zhejiang Province (Grant LY21B020003), National Natural Science Foundation of China (Grant 21602022), Chengdu Talents Program, 1000 Talents Program of Sichuan Province, Longquanyi District Talents Program, Science and Technology Program of Sichuan Province (Grant 2018JY0345), Start-up Funding from Jinhua Branch of Sichuan Industrial Institute of Antibiotics (Grant 1003) and Chengdu University New Faculty Start-up Funding (Grant 2081915037).

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