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Ru-Catalyzed One-Pot Diannulation of Heteroaryls: Direct Access to π-Conjugated Polycyclic Amides

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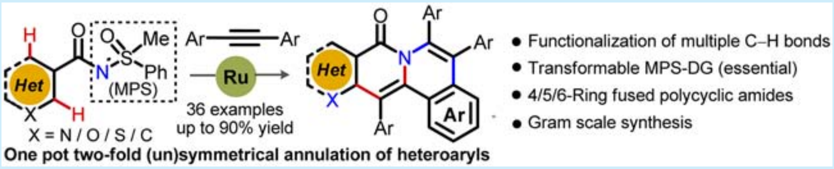
S Supporting Information



ABSTRACT: A novel Ru-catalyzed oxidative double annulation of heteroarenes with symmetrical and unsymmetrical alkynes is reported. A general method for the unsymmetrical annulation of heteroarenes with two distinct alkynes is showcased for the first time. Methylphenyl sulfoximine (MPS) plays an important role in the annulations of heteroarenes and allows the construction of structurally complex π-conjugated heteroarene-fused polycyclic amide skeletons via the formation of multiple C−C and C−N bonds in a single operation. The reaction exhibits excellent substrate scope and tolerates a wide range of functional groups.

Heteroaryls demonstrate unequivocal importance in chemistry as these moieties are widespread in natural products, as well as in pharmaceuticals, agrochemicals and organic materials.[1] Notably, π-conjugated polycyclic heteroaryl scaffolds are invariably found in biologically active molecules;[2] on the other hand, polycyclic heteroarenes significantly contribute to aggregation-induced emission (AIE) phenomenon, a feature essential for optoelectronic materials. Hence, the discovery of novel heteroarene skeletons clearly attracts considerable attention.[3] The π-extended heteroarenes are efficiently formed by the transition metal (TM)-catalyzed directing group (DG)-promoted regioselective oxidative annulation of heteroarenes with alkynes, where ubiquitous C−H bonds systematically participate in the rapid introduction of complexity and diversity in a molecule.[4−7] Notably, the monoannulation of amide-aided arenes with alkynes easily fabricates quinolones, while double annulation efficiently affords unusual π-conjugated polycyclic fused heteroarenes.[3b,8]

The double annulation of DG-enabled heteroaryl carboxylic acid derivatives with unactivated alkynes has rarely been examined using Rh catalysts.[9] It is possible that the "*heteroatom poisoning effect to TM*" arguably renders the reaction ineffective.[10] Clearly, the use of a Ru catalyst for the direct double annulation of DG-molded heteroaryl amides with either symmetrical or unsymmetrical alkynes has not been explored (Figure 1a). In addition, the twofold annulation of *ortho*-substituted DG-molded arenes with alkynes has been particularly unsatisfactory.[11]

Despite these inherent challenges, we became interested in viable synthetic routes and report herein the use of a cost-effective, air-stable Ru-catalyst for a one-pot double annulation of MPS-enabled heteroarenes and *ortho*-substituted arenes with unactivated alkynes; this process affords complex polyfused π-extended heterocyclic amides via the formation of four (two C−C and two C−N) bonds (Figure 1b). Hence, a novel double annulation of heteroarenes with two different alkynes is reported. The MPS-DG plays a vital role in the Ru-catalyzed one-pot diannulations of heteroaryls.

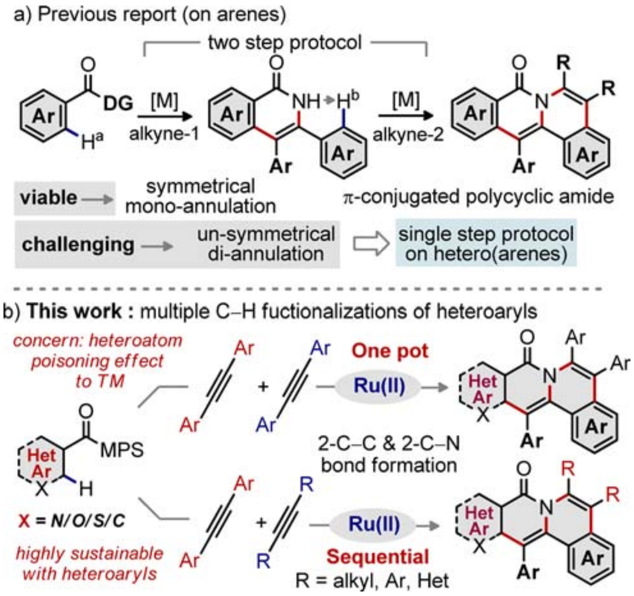


Figure 1. Multiple annulations of (hetero)aryls.

As envisioned, the feasibility of the Ru-catalyzed double annulation of MPS-coupled 5-methyl-thiophene-2-carboxylate **2a** with diphenylacetylene (**3a**) under the catalytic conditions, $\{[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), and

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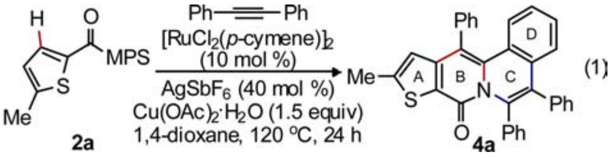
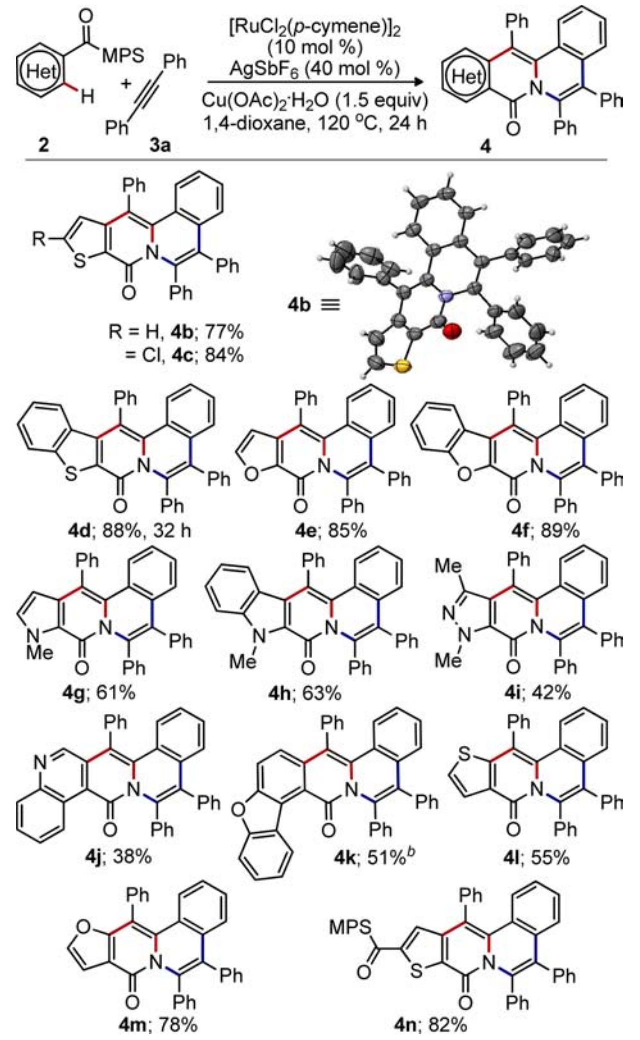
$Cu(OAc)_2 \cdot H_2O$ (1.5 equiv) in 1,4-dioxane at 120 °C for 24 h} was found to be viable, affording **4a** (81%; *four-ring-fused heteroaryl scaffold*) [eq 1].[12,13] $AgSbF_6$ (40 mol %) is adequate generating the active catalyst.



(1)

The generality of this Ru-catalyzed double annulation of MPS-tethered heteroaryls with **3a** is detailed in Scheme 1. Thiophene and benzothiophene derivatives **2b–d** were reacted efficiently, accessing **4b–d** in good to excellent yields. X-ray analysis unambiguously elucidated the structure of **4b**.[14] Likewise, the oxygen bearing heteroarenes, furan (**4e**, 85%) and benzofuran (**4f**, 89%), were readily synthesized. To our delight, the annulations were successfully exhibited with N-heteroarenes, reliably building pyrrole, indole, pyrazole, and quinoline fused polycyclic (four/five-ring-fused) amides **4g–j**; thus, the strong coordination ability of "nitrogen" in N-heteroarenes to TM did not obstruct the reaction. A complex dibenzo[*b*,*d*]furan bearing **4k** (51%; six-ring fused) was also synthesized. Annulation of 3-carboxyl thiophene (**2l**) or furan (**2m**) derivatives with **3a** selectively occurred at the C2-position, yielding **4l** (55%) and **4m** (78%), respectively. To note, annulation of 2,5-bis-MPS tethered thiophene derivative **2n** occurred on only one side; probably the steric encumbrance of **4n** did not ensue further activation.

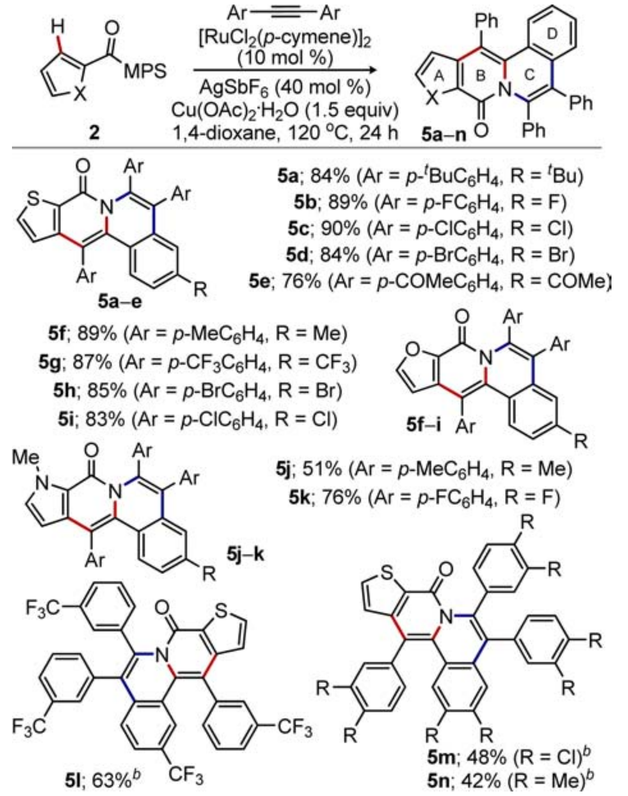
Scheme 1. Double Annulation of Heteroaryls with 1,2-Diphenylacetylene[a]



[a]Conditions: **2** (0.5 mmol), **3a** (1.5 mmol), Ru-catalyst (10 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.75 mmol), 1,4-dioxane (3.0 mL) at 120 °C for 24 h. [b]**2k** (0.3 mmol) was used.

We next examined the reactivity of various 1,2-diaryl acetylenes in this direct double annulation (Scheme 2).

Scheme 2. Double Annulation of Heteroaryls with 1,2-Diarylacetylenes[a]



[a]Conditions: **2** (0.5 mmol), **3** (1.5 mmol), Ru-catalyst (10 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.75 mmol), 1,4-dioxane (3.0 mL) at 120 °C for 24 h. [b]**2b** (0.3 mmol) was used.

Gratifyingly, a wide range of alkynes with the substituents in the arenes [*p*-electron-donating (^{t}Bu), *p*-halo (F, Cl, or Br), or *p*-electron-withdrawing (COMe)] smoothly underwent annulation with **2b** to produce **5a–e** in excellent yields. Likewise, furan **5f–i** and *N*-methyl pyrrole **5j–k** bearing polycyclic amides were fruitfully prepared. As expected, annulation of **2b** with a *meta* or *meta,para*-disubstituted arene bearing alkynes exclusively delivered **5l–n** with the functionalization of the sterically less crowded C–H bond of arene, albeit in moderate yield.

The manufacture of a large variation of novel π-extended four/five/six-ring-fused heteroaryl scaffolds from MPS-tether heteroaryl carboxylic acid derivatives (Scheme 1 and 2), which is otherwise difficult to access, truly validates the synthetic versatility of the challenging direct double-annulation of the heteroarene core under the Ru-catalysis. This result significantly encouraged envisaging a double unsymmetrical annulation of **2**

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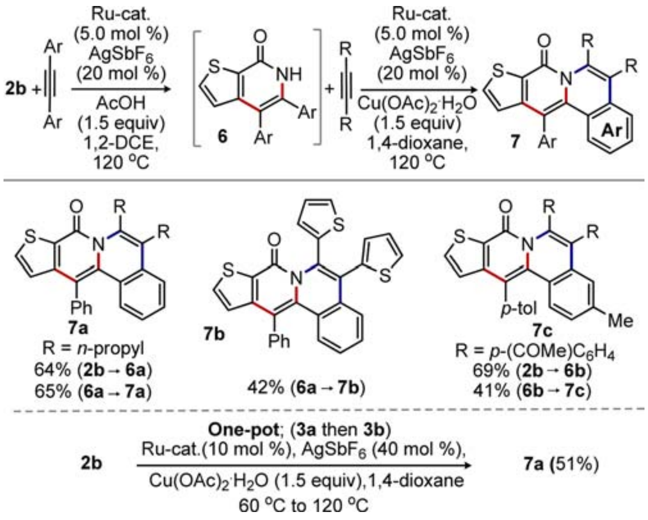
with two distinct unactivated alkynes (Scheme 3). To our satisfaction, the reaction of **2b** with **3a** under the Ru–Ag catalysis in the presence of AcOH led primarily to the monoannulation product **6a** (64%);[7j,k] subsequent annulation with 4-octyne (**3b**) in Ru–Ag catalysts and $Cu(OAc)_2 \cdot H_2O$ in 1,4-dioxane successfully delivered the unsymmetrical double annulation product **7a** (65%) (Scheme 3). Likewise, the products with the fusion of different 1,2-diaryl acetylenes [aryl-heteroaryl (**7b**)] and [aryl(electron-rich)-aryl(electron-poor) (**7c**)] were constructed in appreciable yields.[15] Interestingly, one-pot unsymmetrical double annulations of **2b** with **3a** and 4-octyne (**3b**) provided **7a** in 51% yield. The current unsymmetrical functionalization of multiple C–H bonds, centered on heteroarenes, is a distinct advantage over the complementary methods.[3b,8,12]

Scheme 3. Sequential and One-Pot Double Annulation of Heteroaryls with Different Alkynes[a]

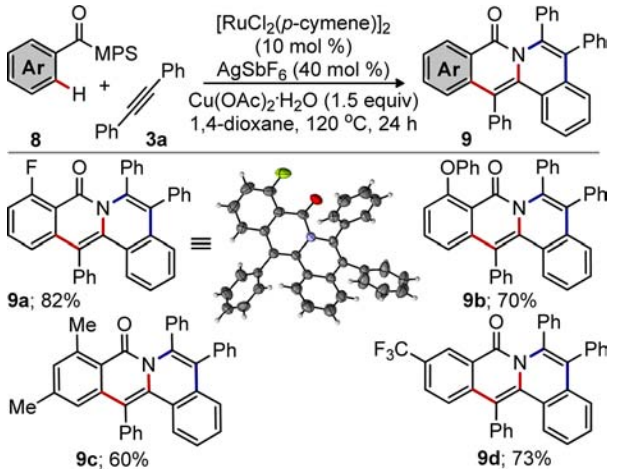


[a]Conditions: **2b** (0.5 mmol), **3** (0.75 mmol), Ru-catalyst (5.0 mol %), $AgSbF_6$ (20 mol %), AcOH (1.5 equiv), 1,2-DCE (2.5 mL) at 120 °C for 20 h. **6** (0.25 mmol), **3** (0.375 mmol), Ru-catalyst (5.0 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv), 1,4-dioxane (2.0 mL) at 120 °C for 20 h. **2b** + **3a** under 1,4-dioxane at 60 °C, 11 h, then **3b** was added and heated at 120 °C for 11 h.[12]

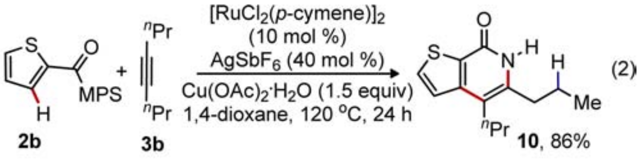
Of note, the DG-assisted direct double annulations of *ortho*-substituted arenes suffer mostly with poor performance.[11] Pleasingly, the direct double annulations of *o*-F/OPh/Me substituted *N*-aroyl sulfoximine derivatives **8** with **3a** under the optimized conditions resulted **9a** (82%), **9b** (70%), and **9c** (60%) (Scheme 4). A regioselective annulation at the sterically less hindered *o*-C–H bond exclusively occurred with *m*-CF_3 bearing an arene to yield **9d**.

Exploration to achieve the double annulation of **2b** with 4-octyne (**3b**) led exclusively to monocyclized product **10**; further annulation by activating the C(sp^3)–H bond turned futile [eq 2]. Interestingly, formation of **11a** (56%) and **11b** (14%) from **2b** and methyl phenylacetylene (**3c**) suggested that the monocyclization product with the methyl group adjacent to the thionyl moiety was attained in situ, which subsequently participated in the second cyclization [eq 3]. A large scale synthesis of **4b** (1.38 g) ascertained the robustness of the catalytic system. The recovery of methylphenyl sulfoxide (**12**), the precursor for MPS, makes this transformation practical [eq 4],[16] advocating the transformable nature of the MPS moiety.

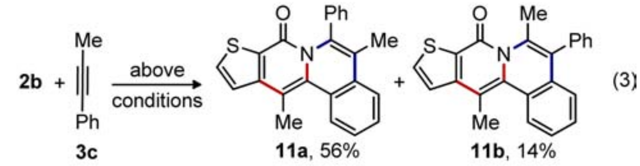
Scheme 4. Double Annulation of *o*/*m*-Substituted Arenes[a]



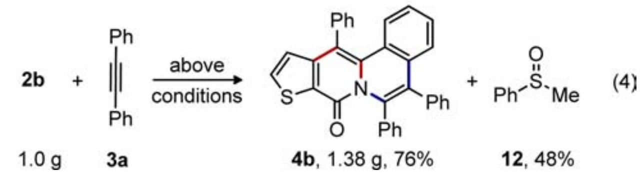
[a]Conditions: **8** (0.5 mmol), **3a** (1.5 mmol), Ru-catalyst (10 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.75 mmol) in 1,4-dioxane (3.0 mL) at 120 °C for 24 h.



(2)



(3)



(4)

Although the mechanistic details are yet to be established, the reaction possibly initiates with the coordination of MPS to the active catalyst, generated from $[\{RuCl_2(p\text{-cymene})\}_2]$, $AgSbF_6$, and $Cu(OAc)_2$, and activates the *ortho* C–H bond of heteroarenes.[12] Next, the interaction of alkyne to the cyclometalated complex followed by the insertion delivers monoannulation product and **12**. Next, the second annulation of the monocyclized product finally provides the desired polycyclic fused heterocycles.[8,12] The exact role of $Cu(OAc)_2$ is not clear; however, the results in Scheme 3 suggest that it helps in the generation of the active catalyst and behaves as an oxidant in the second annulation.

To understand the importance of the novel π-conjugated heteroarene-fused polycyclic amides, the steady state absorption and photoluminescence (PL) measurements were executed for **4j** and **4k** in acetone (Figure 2). Absorbance at 416 and 457 nm with broad PL in the visible range has clearly been observed. The presence of large π-conjugation in these molecules unequivocally tunes the PL band. We believe these compounds, by virtue of their absorbance and fluorescence properties, will find use as fluorescent labels to act as reporter groups in macromolecular studies.[17]

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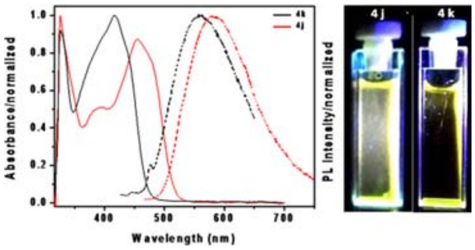

Figure 2. Normalized absorption and PL spectra of derivatives of **4j**, **4k** dispersed in acetone (1×10^{-5} M) and photographs of derivatives of **4j**, **4k** in acetone under the UV lamp.

In summary, a notable Ru(II)-catalyzed oxidative double annulation of MPS-DG-enabled heteroarenes with unactivated alkynes involving one-pot twofold C−H activation is reported. The developed method affords complex heteroarene-fused polycyclic amides via the construction of four bonds (two C−C and two C−N) in a single operation. In addition, excellent substrate scope and functional group tolerance are observed. The unprecedented unsymmetrical double annulation of heteroarenes with two distinct alkynes is successfully demonstrated. The steady state absorption and photoluminescence (PL) measurement of compounds is revealed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03314.

Detailed experimental procedures, NMR spectra (PDF)
HRMS data (PDF)
X-ray crystallographic data (CIF, CIF)

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Notes

The authors declare no competing financial interest.

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(12) See the Supporting Information.

(13) Amide assisted direct double annulations of benzamide with diphenyl acetylene under the optimized conditions provided 24% of the desired product.

(14) CCDC 1506280 [**4b**] and 1506279 [**9a**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) The Ru-catalyzed annulation of quinolone with alkynes is difficult; presumably the MePhS═O has no role in the reaction outcome.

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