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An Orchestrated Unsymmetrical Annulation Episode of C(sp^2)−H Bonds with Alkynes and Quinones: Access to Spiro-isoquinolones

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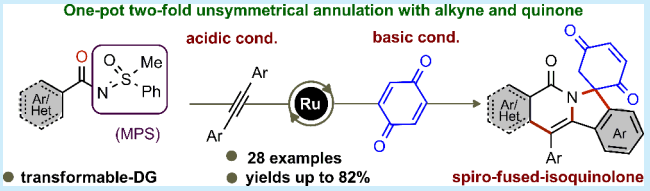
Supporting Information

ABSTRACT: A nontrivial Ru-catalyzed one-pot sequential oxidative coupling of a (hetero)arene/vinylic/chromene system with alkyne and quinone is presented; the methyl phenyl sulfoximine (MPS) directing group is vital. This cyclization forms four (two C−C and two C−N) bonds in a single operation and produces unusual spiro-fused-isoquinolones with a broad scope. The release of phenyl methyl sulfoxide makes the MPS group transformable. A deuterium scrambling study sheds light on the reaction path.



The synthetically validated annulation tool has had a profound impact in chemistry, because this method reliably transforms the readily accessible less-functionalized compounds to structurally complex molecules.[1] In this regard, the transition-metal (TM)-catalyzed and directing group (DG)-supported activation, functionalization, and annulation of inert C−H bonds are incomparable.[2−5] Obviously, the functionalization of environmentally different C−H bonds with distinct coupling partners results in structurally diverse molecular scaffolds.[6] A viable synthetic example of this is the directed double functionalization of proximal C−H bonds with identical functional groups.[7] By contrast, the chelation-assisted unsymmetrical functionalization of C−H bonds is often nonselective, uncontrolled, and unproductive;[8] however, a sequential two-step synthetic process under divergent DGs and/or different catalytic conditions is implemented for the construction of novel molecular scaffolds.[9] A one-pot, single DG-enabled unsymmetrical tandem *o*-C−H difunctionalization of arenes has recently been presented via the intramolecular *o*-C−H hydroarylation and intermolecular *o*′-C−C/C−N bond formations,[10a] and also, the *o*-C−H alkylation and *o*′-C−H amidation of *N*-phenoxyacetamide.[10b]

Usually, two synthetic steps are essential to realize a cascade 2-fold annulation of arenes with different coupling partners; hence, the stitching of distinct functional groups (FG^1/FG^2) requires different catalytic conditions (Figure 1A).[9b,c] We have recently demonstrated the direct double annulation of transformable methylphenyl sulfoximine (MPS)-DG-aided C(sp^2)−H bonds with different alkynes.[11] Thus, the one-pot, 2-fold unsymmetrical C−H diannulation of (hetero)arenes with distinct coupling partners (alkyne and olefin) in the presence of a single DG under single catalytic conditions is a worthwhile endeavor, which has, so far, not been reported. We propose that alkyne over olefin can undergo multiple annulation with C(sp^2)−H bonds and generate **AB** (monoannulation) and **ABB** (diannulation) products,[11a] which eventually obstructs the formation of the projected unsymmetrical diannulation compound **ABC**′/**ABC** (Figure 1B). Moreover, the quinone moiety

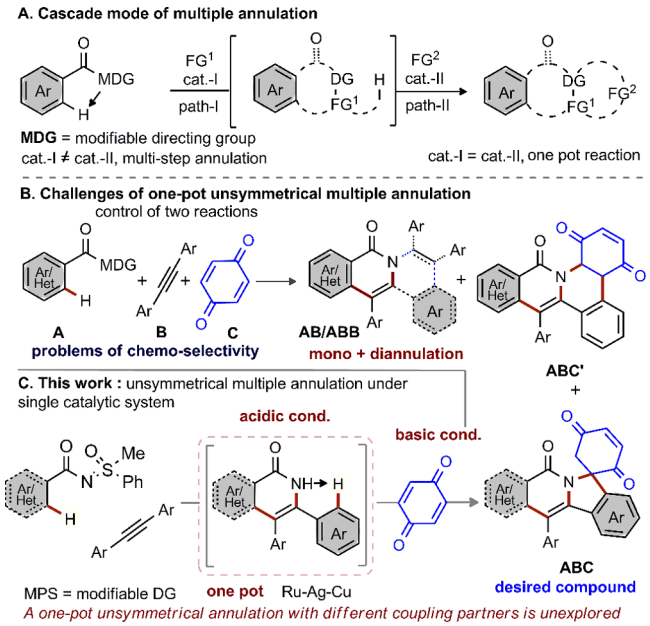


Figure 1. Unsymmetrical annulation of C(sp^2)−H bonds.

is an effective Michael acceptor and is susceptible to Heck coupling; thus, *α*,*α*′-difunctionalization of the quinone motif to install a spiro-skeleton is possible, although challenging.[12] However, the Ir-catalyzed oxidative coupling of isoquinolone with benzoquinone is feasible for constructing novel spiro-fused heteroarenes.[13] Thus far, there have been no reports on the respective one-pot unsymmetrical multiple annulations of heteroarene/vinylic system from a simple carboxylate precursor.

Based on our preliminary understanding of the MPS-DG assisted annulation of hetero(arene)/vinylic systems, we herein invent a tunable one-step synthetic technique for the divergent

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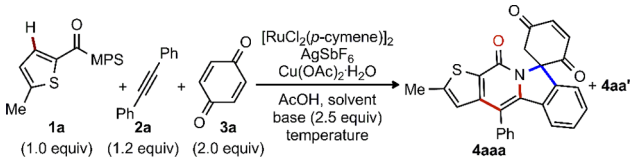
annulation of C(sp^2)−H bonds with alkyne and quinone (Figure 1C). The strategy involves monoannulation of proximal C−H bond of MPS-DG bearing amide and alkyne under cost-effective, air-stable Ru catalyst in the presence of acid source.[14] The in situ formation of isoquinolone/pyridone through proto-demetalation restrict further diannulation with alkyne and the oxidizable MPS-DG helps regeneration of the active catalyst. Next, the base-promoted annulation with quinone delivers the synthetically promising unusual spiro-fused-isoquinolones of pharmaceutical and material importance.[15] The isolation of methylphenyl sulfoxide, which is the sole precursor of MPS, endorses MPS-DG as transformable.[16]

The feasibility of the one-pot three component cascade annulations (envisaged in Figure 1C) is probed by subjecting MPS-coupled 5-methyl-thiophene-2-carboxylate (**1a**) with diphenylacetylene (**2a**) and benzoquinone (**3a**) in the presence of Ru-catalysts (see Table 1). Pleasingly, the predicted product

Table 1. Optimization of Reaction Conditions[a]



entry	additive (2.0 equiv)	base (2.5 equiv)	temperature (°C)	yield of **4aaa** (%)
1			120	20 (35)[b,c]
2			60/120	35 (21)[b,c]
3			60/120	45 (18)
4	AcOH		90/120	26 (11)
5	AcOH	$NaHCO_3$	90/120	62 (07)
6	AcOH	Na_2CO_3	90/120	40 (10)
7	AcOH	K_2CO_3	90/120	39 (10)
8	AcOH	K_3PO_4	90/120	61 (06)
9	AcOH	KH_2PO_4	90/120	66 (05)
10	AcOH	KH_2PO_4	90/120	50 (15)[d]
11	AcOH	KH_2PO_4	90/120	72 (04)[e]
12	AcOH	KH_2PO_4	90/120	35 (40)[f,g]
13	AcOH	KH_2PO_4	90/120	43 (16)[h]
14	AcOH	KH_2PO_4	90/120	39 (0)[i]

[a]Conditions: **1a** (0.18 mmol, 1.0 equiv), **2a** (1.2 equiv), Ru-catalyst (10 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv), additive (2.0 equiv), DCE (1.5 mL) at 90 °C for 10 h; then BQ (2.0 equiv), base (2.5 equiv) and 1,4-dioxane (1.5 mL), at 120 °C for 10 h; yield of **4aa′** (diannulation with alkyne) is shown in parentheses. [b]All of the reactants in one-pot synthesis. [c]**2a** (1.0 equiv). [d]1,4-dioxane instead of DCE. [e]Addition of 1,4-dioxane (1.5 mL) after first cyclization. [f]In the absence of $Cu(OAc)_2{\cdot}H_2O$. [g]Yield of **4aa** (monoannulation with alkyne) is shown in parentheses. [h]O_2 used as oxidant. [i]$CuBr_2$ used as oxidant.

4aaa (20%) and diannulation compound **4aa′** (35%; from **1a** and **2a**) formed when the reaction was executed under the catalytic conditions [Ru-catalyst (10 mol %), $AgSbF_6$ (40 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv) in 1,2-dichloroethane (DCE) at 120 °C for 10 h] (entry 1 in Table 1). This result is particularly noteworthy, because MPS-bearing heteroarenes and alkynes are amenable to annulation, which occurs even at 60 °C.[11a]

To realize better turnout of **4aaa**, the annulation episode among **1a**, **2a**, and **3a** was conducted at 60 °C (where alkyne undergoes cyclization) and 120 °C (where quinone commences annulation) in a single pot under one catalytic condition; pleasingly, **4aaa** was isolated in 35% yield (entry 2 in Table 1). This information encouraged us to survey the reaction via turnwise addition of **2a** and **3a**. Thus, the entire transformation was performed accordingly [the reaction, at first, was performed at 60 °C in the presence of 1.2 equiv of **2a** for 10 h; subsequently, **3a** was introduced and the mixture was then heated at 120 °C for 10 h]; this process resulted 45% **4aaa**, along with the diannulation product **4aa′** (18%) (entry 3 in Table 1). Interestingly, annulation between **1a** and **2a** in the presence of 2 equiv AcOH restricted the formation of **4aa′** to 11%; meanwhile, the delivery of **4aaa** was affected (entry 4 in Table 1), which is a consequence of ineffective binding of Ru to the NH moiety of monoannulation product in an acid medium. Interestingly, the addition of $NaHCO_3$ base, along with **3a**, helped the production of **4aaa** (62%), endorsing the requirement of base after first cyclization (entry 5 in Table 1).

Encouraged by the observation, various bases (Na_2CO_3, K_2CO_3, K_3PO_4, and KH_2PO_4) were screened (see entries 6−9 in Table 1); KH_2PO_4 was found to produce the optimum yield of **4aaa**: 66% (see entry 9 in Table 1). Although the overall reaction in 1,2-DCE was better over 1,4-dioxane (entries 9 and 10 in Table 1), the use of a mixture of solvents in this 2-fold cyclization strategy [1,2-DCE for the first annulation and subsequent addition of 1,4-dioxane in the second annulation] led to 72% **4aaa** (entry 11 in Table 1). This transformation, in the absence of $Cu(OAc)_2{\cdot}H_2O$, provided **4aaa** in only 35% yield, along with 40% of the monoannulation compound **4aa** (entry 12 in Table 1), which suggests that the oxidant is indispensable, since it helps the regeneration of active catalyst after second annulation. Moreover, the reaction in the presence of oxidant O_2 or $CuBr_2$ was not effective (see entries 13 and 14 in Table 1).[9j] Thus, the one-pot synthetic avenue for the unsymmetrical annulation of **1a** with **2a** and **3a** under the optimized catalytic conditions (entry 11 in Table 1) smoothly provided unusual spiro-fused isoquinolone **4aaa**.

The synthetic generality of this unprecedented two successive unsymmetrical annulation is validated by examining MPS-assisted cyclization of C(sp^2)−H bonds of challenging heteroarene/vinylic/chromene systems with alkynes and quinones (Scheme 1−3). Thus, the MPS-coupled thiophene-2-/benzothiophene-2-carboxylate (**1a**−**1d**) were reacted with **2a** and **3a** to afford the desired spiro-products **4aaa**−**4daa** (72%−82%); the modifiable Br-group survived to provide **4caa**. The thiophene-3-/benzothiophene-3-carboxylates also participated, delivering **4eaa** (62%) and **4faa** (51%). Similarly, the spiro-product from oxygen-bearing heteroarene **4gaa** (72%) was readily isolated from the cyclization cascade of MPS-bearing furan-3-carboxylate (**1g**) with **2a** and **3a**; identical reaction in 1.0 mmol scale resulted in a 66% yield of **4gaa**.

The naphthaquinone (**3b**) also participated in the cascade cyclization episode with **1b**/**1g**/**1h** and **2a** to deliver **4bab** (70%), **4gab** (74%), and **4hab** (57%), respectively (see Scheme 1). Moreover, the N-bearing heterocycles pyrrole and indole skeleton were stitched with **2a** and **3b** accessing the poly fused spiro-skeletons **4iab** and **4jab**, albeit in moderate yield. The product **4gac** was isolated from the annulations of **1g** with **2a** and 2-chloro-benzoquinone (**3c**); X-ray analysis confirms the structure of **4gac**.[17] Annulations of challenging *o*-substituted arene motif with **2a** and **3b** delivered **4kab**.

We next probed the alkyne scope in this one-pot two-successive annulation of MPS-bearing heteroarene and quinone (Scheme 2). Pleasingly, 1,2-diarylacetylenes {having *para*-substituents on the arene moiety, electron-donating

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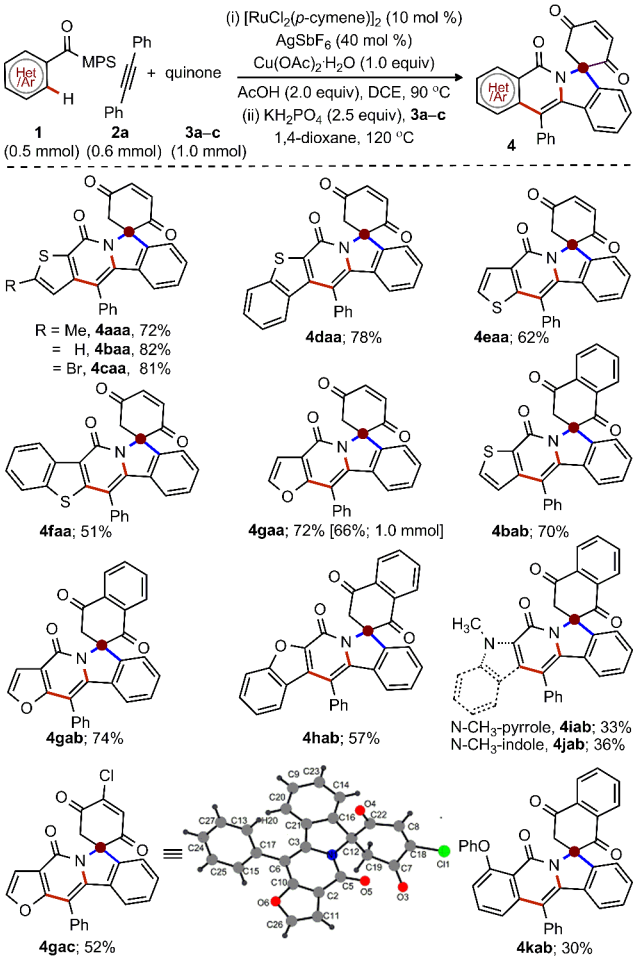
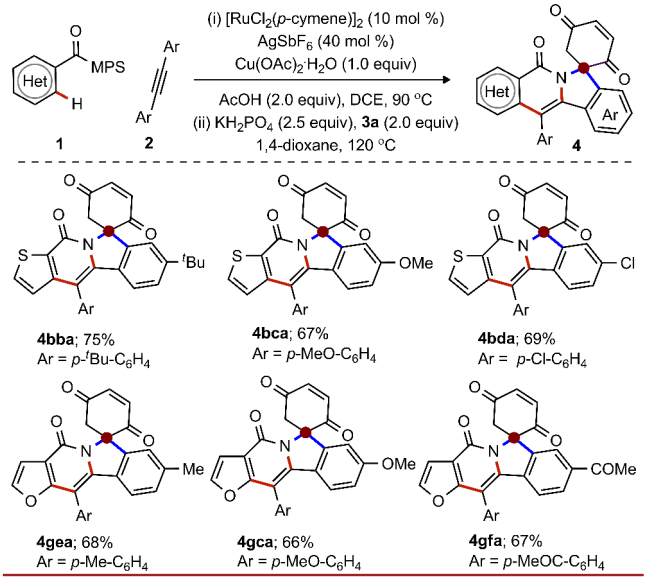
Scheme 1. Cascade Annulation of Heteroaryls 1 with Diphenylacetylene 2a and Quinone 3



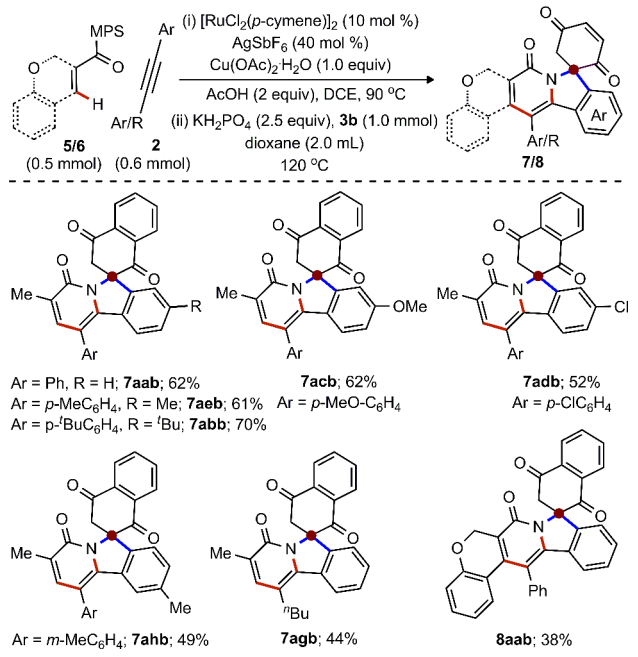
Scheme 2. Cascade Annulation of Heteroaryls 1 with Alkynes (2) and Benzoquinone 3a



[−^{t}Bu (**2b**)/−OMe (**2c**)] or −Cl (**2d**) group} smoothly reacted with **1b** and **3a** under the optimized procedure to afford spiro-fused enlarged isoquinolones **4bba** (75%), **4bca** (67%), and **4bda** (69%). Similarly, the furan-enabled spiro-isoquinolone products **4gea** (68%), **4gca** (66%), and **4gfa** (67%) were undeniably accessed when **1g** coupled with **2e** (*p*-Me−)/**2c**/electron-withdrawing (*p*-COMe) group containing alkyne (**2f**) and **3a**, respectively.

Inspired from the unsymmetrical diannulation of heteroaryls with alkynes and quinones (see Schemes 1 and 2), the identical reaction in the challenging vinylic system was surveyed next (Scheme 3), because vinylic systems have a tendency to

Scheme 3. Cascade Annulation of Vinyl/Chromenes 5/6 with Alkynes (2) and Naphthaquinone 3b



polymerize under the oxidative conditions and also are effective Michael acceptors.[18] Gratifyingly, the reaction of *N*-(methacryloyl)-MPS (**5a**) with **2a** and **3b** under the optimized catalytic conditions in entry 11 in Table 1 delivered **7aab** in 62% yield. To further authenticate the synthetic viability of this 2-fold annulations of acrylamides, the reaction between **5a**, the electron-rich (Me/^{t}Bu/OMe) group containing *para*-substituted 1,2-diarylacetylenes, and **3b** delivered the desired spiro-fused novel heterocycle manifolds **7aeb** (61%), **7abb** (70%), and **7acb** (62%).

The product **7adb** with the labile chloro group in the periphery was also constructed. The *meta*-Me bearing 1,2-diarylalkyne participated in the cascade annulation, accessing **7ahb**. The spiro compound **7agb** was isolated from the annulation of **5a**, unsymmetrical *n*-butyl-phenyl alkyne **2g**, and **3b**; the regioselective monoannulation of **5a** with **2g** makes this process feasible. The 2H-chromene-3-carboxylate derivative **6a** successfully underwent annulations with **2a** and **3b** to deliver the conjugated spiro species **8aab** in 38% yield.

To understand the possible reaction pathway, a few control experiments have been performed (see Scheme 4). The reaction in the absence of oxidant $Cu(OAc)_2$ led to the mono-annulation product (69%); the reductive cleavage of MPS group herein helps oxidation of Ru-catalyst and keeps the catalytic cycle active (see eq 1 in Scheme 4). However, the reaction of **4ba** with benzoquinone under the optimized condition led to 35% of the desired product **4baa** (see eq 1 in Scheme 4). Product **4gaa-D** with 33% deuterium incorporation

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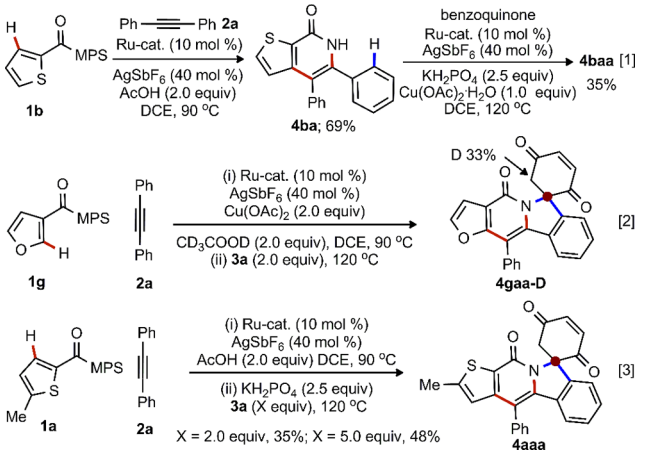
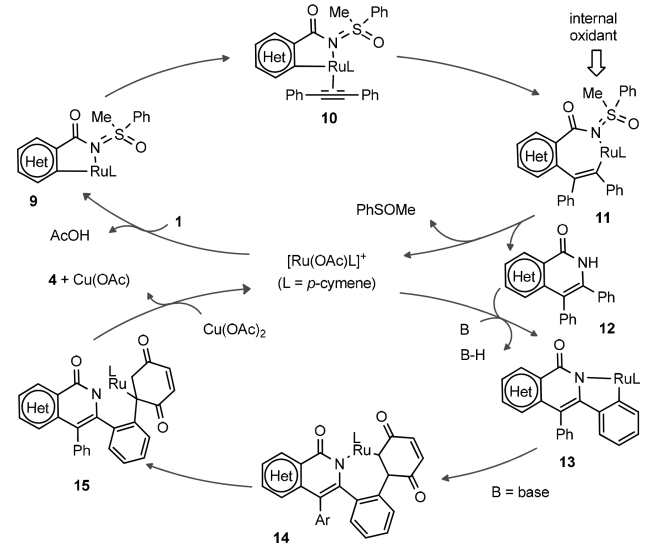
Scheme 4. Control Experiments



in the quinone moiety was detected when the reaction was performed in CD_3CO_2D (eq 2 in Scheme 4), reflecting the occurrence of protodemetalation in the transformation.[19] Hence, formation of the desired spiro-product is possible through the metalation of acidic C(sp^3)−H bond, followed by C−N reductive elimination (see the mechanistic cycle in Scheme 5).

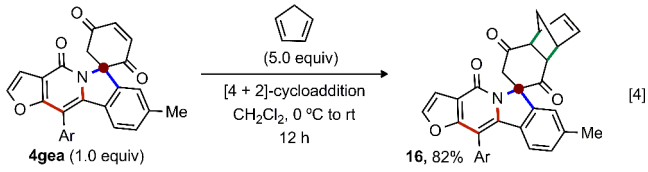
Scheme 5. Proposed Mechanistic Profile



Interestingly, the reaction in the presence of 2 and 5 equiv of BQ produced 35% and 48% of **4aaa**, respectively (see eq 3 in Scheme 4); thus, the weak oxidant BQ is incapable in carrying out the transformation. Consequently, the oxidant $Cu(OAc)_2$ plays a vital role in retaining the catalytic cycle via revival of active Ru(II) species.[5]

Based on the precedence and the current observation, the plausible reaction pathway is outlined in Scheme 5.[3,5] The reaction initiates with the coordination of MPS to the active Ru-species, forming the ruthenacycle **9** via chelation-assisted C−H metalation. Subsequent alkyne coordination−insertion to **9** provides seven-membered ruthenacycle **11** through **10**. Next, synergistic C−N reductive elimination and N−S cleavage affords **12** in situ, which simultaneously undergoes proximal C−H metalation to deliver **13**. Insertion of benzoquinone to **13** gives 7-membered ruthenacycle **14**; protodemetalation of **14** (see eq 2 in Scheme 4), followed by metalation of acidic C(sp^3)−H, generates more-stable 6-membered ruthenacycle **15**.[20] Reductive elimination of **15** finally leads to spiro-fused-isoquinolone **4**. The $Cu(OAc)_2$ helps to regenerate the active Ru-catalyst.[19]

The synthetic manipulation of peripheral olefin moiety in the spiro-isoquinolone scaffold was further elaborated by performing [4 + 2] cycloaddition of **4gea** with cyclopentadiene, resulting in complex molecular entity **16** (eq 4).



In summary, we have revealed, for the first time, the Ru-catalyzed MPS-assisted 2-fold unsymmetrical cyclization of heteroarenes/vinylic systems with different coupling partners (first with the alkynes and then with the quinones); both these annulations are realized via one-pot synthesis, resulting in four bonds (two C−C and two C−N). These highly orchestrated cyclization techniques are largely suitable for the fabrication of unnatural spiro-isoquinolinones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00468.

Detailed experimental procedures and the physical properties of the compounds (NMR data, characterization, and spectra) (PDF)

Accession Codes

CCDC 1819534 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, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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