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Double annulation of *ortho*- and *peri*-C–H bonds of fused (hetero)arenes to unusual oxepino-pyridines†

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Direct difunctionalization of chemically distinct *ortho*- and *peri*-C–H bonds of fused hetero(arenes) is illustrated through an unusual one-pot domino $\{[4 + 2] \& [5 + 2]\}$ double annulation with alkynes for the first time. This process is viable under Ru(II)-catalysis using a sulfoximine directing group and builds four bonds $[(C-C)-(C-N)]$ and $[(C-C)-(C-O)]$ in a single operation. Such synthetic manifestation offers access to uncommon $[6,7]$ -fused oxepino-pyridine skeletons. DFT calculations provide mechanistic insight into this double annulation of naphthoic acid derivatives with alkynes and corroborate the participation of a ruthena-oxabicyclooctene intermediate, which is responsible for the rare 7-membered ring formation.

Introduction

Diversity oriented synthesis provides efficient access to complex molecular architectures that are present in natural products, pharmaceuticals, agrochemicals, and advanced-materials.¹ This approach has sustained the development of novel therapeutic agents or probes for molecular biology, based on the resilient interaction of heterocycles with biological systems.^{2,3} Continuous efforts have therefore been directed towards the conception of straightforward synthetic methods for the construction of complex heteroarenes.³ In this regard, transition-metal (TM) catalyzed annulations of C–H bonds of (hetero)arenes with alkynes have proven invaluable.^{4,5} In particular, the TM-catalyzed direct functionalization or annulation of the *ortho*-C(2)–H bond of fused (hetero)arenes with alkynes are successful with acid/amide directing groups (DGs) *via* 5/7-membered metallacycle (Fig. 1A-I).⁵ With –OH, –NHR', and –SR'' DGs, the reactivity is shifted towards the *peri*-C(8)–H bond through 5/7-membered metallacycle (Fig. 1A-II).⁶ On the other hand, the activation of the *peri*-C(8)–H bond of fused (hetero)arene carboxylic acid derivatives [e.g. 1-naphthoic acid] is much more challenging and underdeveloped, due probably to the

involvement of a strained $[6,6,6]$ -fused metallacycle (Fig. 2A).⁷ Insertion of an alkyne would not even funnel such C–H activation step, as it would lead to an even more strained $[6,6,8]$ -fused metallacycle (Fig. 2A). Thus, the molecular rigidity and conformational strain have hampered the development of such annulations at the *peri*-C(8)–H bond to form 7-membered fused compounds (Fig. 2A).^{8,9}

Recent domino one-pot double annulation of *o/o'*-C–H bonds of (hetero)arenes with alkynes have led to $[6,6]$ -fused heteroaryls.^{10,11} Although important issues of regio- and chemoselectivity, cumbersome mixtures due to incomplete conversion, catalytic viability, *etc.*, could be addressed,¹² such domino double C–H annulations were not extended to the formation of $[6,7]$ -fused heteroarenes. To make such synthetic

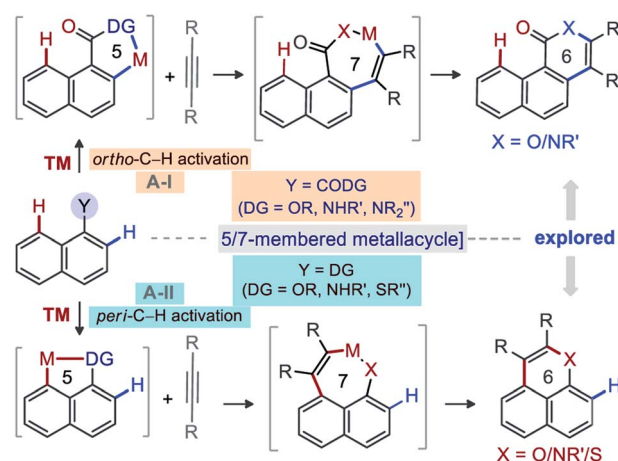


Fig. 1 Background: Annulation of *ortho*-C(2)–H & *peri*-C(8)–H bond of 1-naphthalene derivatives with alkynes.

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Fig. 2 Multiple annulation of (hetero)arenes.

plan feasible, we hypothesized a Ru-catalyzed double annulation of 1-naphthoic acid derivatives with alkynes.

We believed the reaction would be initiated by N-aided C(2)-H activation and annulation with the alkyne to first form an angularly [6,6,6]-fused benzo[*h*]isoquinolinol. As *peri*-C-H bonds of fused-arenes are susceptible to electrophilic substitution, we anticipated an O-directed ruthenation of the proximal *peri*-C(8)-H bond to provide **Int-Z** (Fig. 2B). Finally, second alkyne incorporation to **Int-Z** and reductive elimination would build the unusual [6,7]-fused oxepino-pyridine motif (Fig. 2B). This one-pot domino double annulation uses the methylphenyl sulfoximine (MPS)-DG.^{12b} Thus, the sequential activation of *ortho*- and *peri*-C-H bonds and annulation results in the formation of N- and O-enabled 6- and 7-membered rings on fused (hetero)arenes by generating four bonds (C-C & C-N and C-C & C-O) in a single operation (Fig. 2B).

Results and discussion

This one-pot [4 + 2] & [5 + 2] annulation was developed under Ru-catalysis using *N*-[1-naphtho-1-yl]methylphenyl sulfoximine (**1a**) and 4-octyne (**2a**). The optimization studies are detailed in Table 1.¹³ The oxepino-pyridine **3aa** was detected in 8% yield using {[RuCl₂(*p*-cymene)]₂ (5.0 mol%), AgSbF₆ (20 mol%), NaOAc (1.0 equiv.)} as catalytic system, in ClCH₂CH₂Cl (DCE) at 120 °C for 24 h (entry 1). The cleavage of the sulfoximine motif presumably helps the formation of **3aa**.^{11d} In general, metal acetates facilitate Ru-mediated C-H activation through CMD (concerted metalation deprotonation), and also act as oxidant in the regeneration of the active catalyst.⁴ Accordingly, the double annulation was slightly improved when the reaction was conducted in the presence of the redox active bases Mn(OAc)₂, AgOAc, and Zn(OAc)₂·2H₂O (entries 2–4), while Cu(OAc)₂·H₂O was found more promising as it delivered **3aa** in 35% yield

Table 1 Optimization of reaction conditions^a

Entry	Additive 1 (20 mol%)	Additive 2 (1.0 equiv.)	Solvent	Yield 3aa ^b (%)
1	AgSbF ₆	NaOAc	DCE	8
2	"	Mn(OAc) ₂	DCE	12
3	"	AgOAc	DCE	15
4	"	Zn(OAc) ₂ ·2H ₂ O	DCE	11
5	"	Cu(OAc) ₂ ·H ₂ O	DCE	35
6	KPF ₆	"	DCE	<5 ^c
7	NaPF ₆	"	DCE	6
8	AgBF ₄	"	DCE	30
9	AgSbF ₆	"	MeCN	<5 ^c
10	"	"	Toluene	7
11	"	"	TCE	22
12	"	"	1,4-Dioxane	41
13 ^d	AgSbF ₆	Cu(OAc) ₂ ·H ₂ O	1,4-Dioxane	68
14 ^e	AgSbF ₆	Cu(OAc) ₂ ·H ₂ O	1,4-Dioxane	77
15	AgSbF ₆	—	1,4-Dioxane	<5 ^c
16	—	Cu(OAc) ₂ ·H ₂ O	1,4-Dioxane	<5 ^c



^a Conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), [RuCl₂(*p*-cymene)]₂ (5.0 mol%), additive-1 (20 mol%), additive-2 (0.3 mmol), solvent (2.0 mL) at 120 °C. ^b Isolated yield. ^c ¹H NMR conversion. ^d [RuCl₂(*p*-cymene)]₂ (10 mol%), AgSbF₆ (40 mol%) was used. ^e **2a** (1.2 mmol), [RuCl₂(*p*-cymene)]₂ (10 mol%), AgSbF₆ (40 mol%), Cu(OAc)₂·H₂O (1.5 equiv.) was used. DCE = ClCH₂CH₂Cl, TCE = 1,1,2,2-tetrachloroethane.

(entry 5). Additives such as KPF₆, NaPF₆, or AgBF₄ instead of AgSbF₆ were not beneficial (entries 6–8). The reaction efficiency was low when conducted in MeCN, toluene or TCE (entries 9–11). The domino diannulation in 1,4-dioxane provided **3aa** in 41% yield (entry 12). The yield of **3aa** was significantly improved to 68% when 10 mol% of Ru-catalyst and 40 mol% of AgSbF₆ were used (entry 13). Finally, the catalytic conditions comprising [Ru(*p*-cymene)Cl₂]₂ (10 mol%), AgSbF₆ (40 mol%), and Cu(OAc)₂·H₂O (1.5 equiv.) in 1,4-dioxane at 120 °C for 24 h were found optimum (entry 14), producing **3aa** in 77% yield. Control experiments revealed that the silver salt and the acetate base were crucial (entries 15 and 16).^{14d}

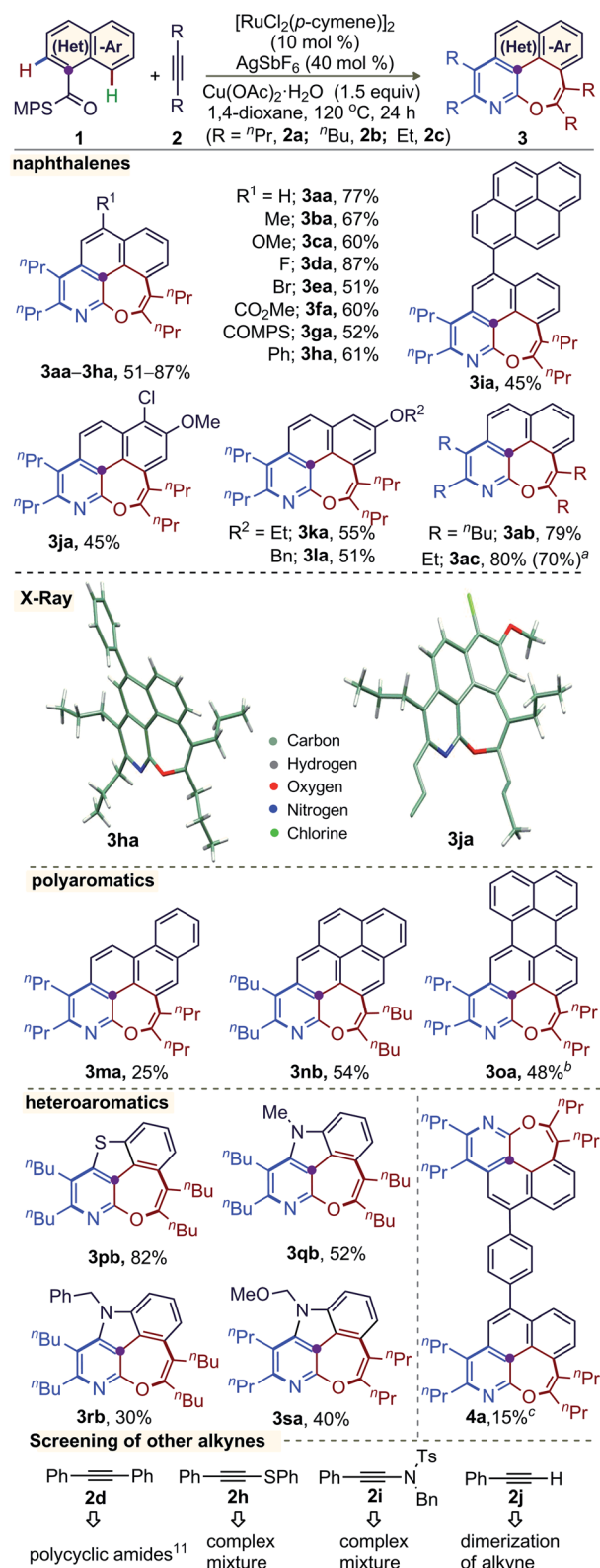
To validate the role of DGs in this one-pot domino {[4 + 2] & [5 + 2]} double annulation strategy, various DG-enabled 1-naphthyl bearing amides (**I–VI**) were subjected to the annulation with **2a** under the optimized conditions (bottom of Table 1). The substrates having NH-Me (**I**) and NH-tosyl (**II**) DGs proved unreactive, whereas, simple 1-naphthylamide (**III**) underwent this domino annulations with **2a** producing **3aa** in poor yield.⁶ The N-oxidizable group protected amides [**IV** (with N-O bond), **V**, and **VI** (with N-N bond)] provided **3aa** in 15%,

7%, and 26% yield, respectively. Thus, the MPS-DG was found most effective for the construction of the [6,7]-fused oxepino-pyridine skeleton.¹³

The generality of this annulation among fused (hetero)arenes exhibiting *peri*-C–H bonds and unactivated alkynes was explored under the optimized catalytic conditions (Scheme 1). The annulation of naphthalene derivatives **1a–l**, bearing either electron-donating (Me, OMe, OEt), labile halo (F, Cl, Br), electron-withdrawing (CO₂Me, COMPS), arene (Ph, pyrene), and OBN substituents at position 4, 5, or 6, with **2a**, was successful in producing the respective 6,7-fused oxepino-pyridine **3aa–la** in 45–87% yield. The tolerance of modifiable functionalities (*i.e.* F, Cl, Br, CO₂Me, COMPS) offers the possibility of further functionalization. The core structure of **3ha** and **3ja** were elucidated by X-ray crystallographic analysis.^{14,15} Likewise, this double-annulation of **1a** with the other internal alkynes **5-decyne (2b)** and **3-hexyne (2c)** delivered **3ab** (79%) and **3ac** (80%), respectively. Moreover, the gram scale synthesis of **3ac** (1.15 g) with recovery of PhSOMe (0.44 g) showed the robustness of the catalytic system and the transformable nature of the MPS group.^{5g} Polyarene bearing scaffolds, for example: phenanthrene (**1m**), pyrene (**1n**), and perylene (**1o**), delivered **3ma**, **3nb** and **3oa**, albeit in moderate yield.

Importantly, benzothiophene derivative **1p** smoothly reacted with **2b** to afford **3pb** in 82% yield. Indole-3-carboxylic acid derivatives **1q–s** were used in this double annulation with **2b** and **2a**. The respective complex heteroarenes **3qb**, **3rb**, and **3sa** were reliably accessed. The common N-protecting groups benzyl and MOM did not prevent the reaction. The yields are moderate in these cases, but the construction of these molecular scaffolds with three heteroatoms (*i.e.* S–N–O, N–N–O) in a 5,6,7-fused system is remarkable. Notably, the current synthetic plan was successful in making 8 bonds (4 C–C, 2 C–N, and 2 C–O) in a single operation; thus, an extended π -conjugated system **4a** with two oxepino-pyridine motifs was made. The reaction of **1a** with diphenylacetylene provided polycyclic amides through linear dia-annulation.^{11,14} On the other hand, the reaction of a thioalkyne or an ynamide with **1a** produced complex mixtures (Scheme 1). Lastly, the terminal alkyne phenylacetylene underwent dimerization under the optimized oxidative condition.

The site-specific introduction of a novel functionality on an unreactive site of a complex motif has tremendous significance to the field of complex molecule synthesis and is often termed as late stage functionalization (LSF).¹⁶ In particular, LSF through C–H functionalization is very useful in drug discovery and draws significant attention from the scientific community. Accordingly, a range of biologically relevant motifs moulded with MPS-bearing naphthalene-1-carboxylic acid (**5a–g**) were synthesized and were independently subjected to the optimized reaction conditions with **2a** and **2c** (Scheme 2). Thus, the desired oxepino-pyridines **6aa**– β -citronellol, **6bc**–camphorsultam, **6ca**–(–)-boreneol, **6cc**–cholesterol, **6fc**–estrone, and **6gc**–lithocholic acid were constructed without any structural (chemical and stereochemical) changes of the complex architecture.¹⁴ The poor-to-moderate synthetic yields are due to low conversions. Isolation of unreacted precursors justifies the mass balance of the transformation.



Scheme 1 Synthesis of 6,7-oxepino[2,3-*b*]pyridine. Reactions were carried out with **1** (0.3 mmol) and **2** (1.2 mmol). ^aGram scale: **1a** (1.54 g, 5.0 mmol); PhS(OMe) (63%) was isolated. ^bReactions were carried out in DCE. ^c**2a** (1.8 mmol).



Scheme 2 Double annulation of MPS-bearing naphthalene-1-carboxylic acid moulded in biologically relevant motifs. Reactions were carried out with **5** (0.3 mmol), **2** (1.2 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (10 mol%), AgSbF_6 (40 mol%), 1,4-dioxane (2.0 mL) at 120 °C for 24 h. ^aIsolation of unreacted precursors (20–55%).

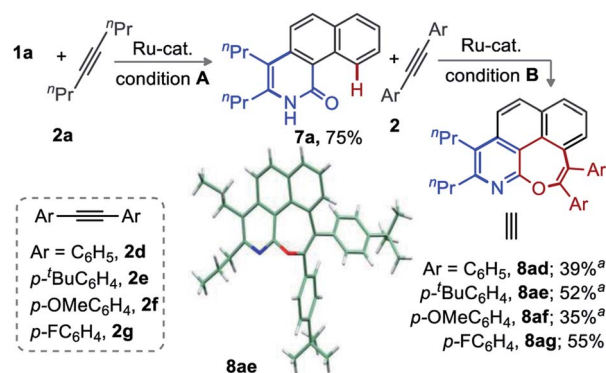
Encouraged by the broad range of oxepino-pyridines derivatives obtained (Schemes 1 and 2), the title reaction was next envisaged with two different alkynes. However, the difference in reactivity, regio- and chemoselectivity with different alkynes led to unexploitable annulation mixtures.¹² To make this challenging unsymmetrical transformation viable, a two-step annulation sequence was tested. Accordingly, benzo[*h*]isoquinolinone **7a** (0.5 mmol, 75%) was accessed from **1a** and **2a** when the reaction was carried out in presence of AcOH under Ru-catalysis (Scheme 3, Conditions A). Presumably the acid suppresses the second annulation through proto-demetalation.¹¹ Next, the annulation of **7a** with 1,2-diaryl alkynes (**2d–g**) led to the respective [6,7]-fused oxepino-pyridines (**8ad–ag**) in moderate yields (Scheme 3). The structure of **8ae** was unambiguously confirmed by X-ray crystallography.^{14,15} A deuterium scrambling study and competition experiments were then performed to gain some mechanistic insight into this annulation (Scheme 4).

Exposing **1a** to the optimized conditions in presence of $\text{CD}_3\text{CO}_2\text{D}$ (2.5 equiv.) resulted in D-incorporation at C2 (65%) and C8 (62%) positions (eqn (1)). Similarly, 55% of deuterium incorporation occurred at C8 in an identical experiment with **7a** (eqn (2)). Therefore, activation of both the *ortho*- and *peri*-C–H bonds of MPS-enabled-1-naphthylamide is reversible. The competitive annulation of an equimolar mixture of **1c** and **1f** with **2a** led to a 2 : 1 ratio of **3ca** and **3fa**; thus, an electron-rich arene reacts faster than an electron-poor one (eqn (3)).

In general, the π -conjugated polyfused heteroarenes show interesting photophysical properties. Thus, the absorption and

emission spectra of oxepino-pyridines **3nb**, **3oa**, **3pb**, **3qb**, **3sa**, **4a**, and **8ae** were measured in dichloromethane (1×10^{-5}).¹⁴ Of note, compounds **3nb** and **3ob** show emission maxima at 436–512 nm with broad bandwidths and weak intensities.¹⁴

The mechanism of the title reaction has been studied computationally, employing the Gaussian 09 software package.¹⁷ Following a recent report, optimizations were carried



Scheme 3 Unsymmetrical double-annulation of arenes with different alkynes. Conditions A: **1** (0.5 mmol), **2a** (1.0 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (5.0 mol%), AgSbF_6 (20 mol%), AcOH (4.0 mmol), DCE (2.5 mL) at 120 °C for 20 h. Conditions B: **7a** (0.3 mmol), **2** (0.45 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (7.5 mol%), AgSbF_6 (30 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.3 mmol), KH_2PO_4 (0.6 mmol), 1,4-dioxane (2.0 mL) at 120 °C for 20 h. ^aIsolation of unreacted mono-annulation product (30–45%).



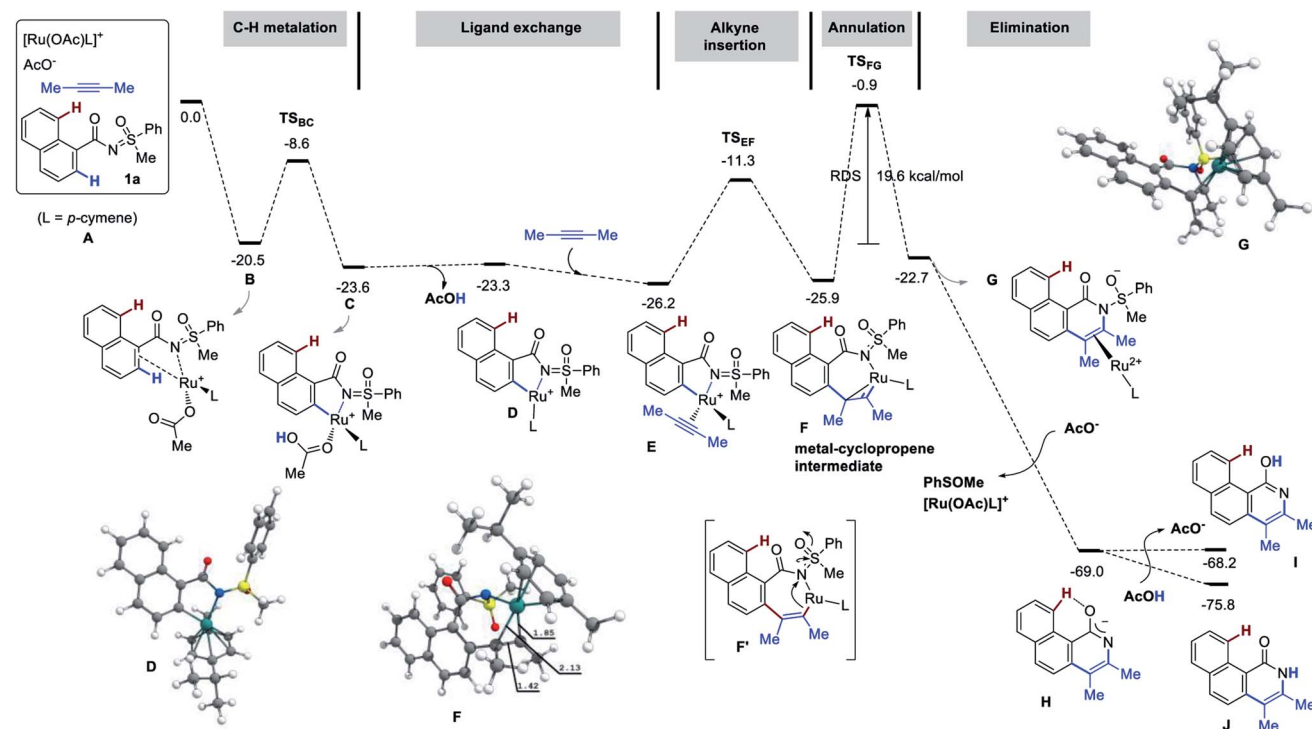


Scheme 4 Deuterium scrambling and competition studies.

out with the M06 functional, the 6-31G(d,p) basis set for all main group elements, and the LANL2DZ+f (ECP)¹⁸ basis set for Ru. Single point calculations were conducted at the M06/6-311++G(d,p)-SDD+f(ECP) level of theory. Solvation energies were obtained at the single point level using SMD approach for 1,4-dioxane. The discussed values are solvent-corrected Gibbs free energies at 393.15 K in kcal mol^{−1} (ΔG_{393}). The molecular system **A** [**1a**, 2-butyne (2.0 equiv.), $[\text{Ru}(\text{OAc})\text{L}]^+$ ($\text{L} = p\text{-cymene}$), AcO^-] was used as a reference for the free energies (Fig. 3). Thus, **A** contains two acetates to ensure two deprotonation of

1a. The complexation of the putative active species $[\text{Ru}(\text{OAc})(p\text{-cymene})]^+$ with **1a** at first provides **B** with a release of 20.5 kcal mol^{−1}. Next, C–H metalation occurs through TS_{BC} lying 11.9 kcal mol^{−1} above **B** to provide metallacycle **C** (−23.6 kcal mol^{−1}). Elimination of acetic acid and insertion of 2-butyne delivers the alkyne-complex **E** (more stable than **C** by 2.6 kcal mol^{−1}). Alkyne insertion does not yield the proposed metal-alkenyl complex **F'**, but rather its valence isomer **F**, which is a metallacyclopentene as witnessed by the distortion of the 7-membered ring and by the short Ru–C distance of 1.85 Å. The formation of **F** is slightly endergonic by 0.3 kcal mol^{−1} that requires 14.9 kcal mol^{−1} of free energy of activation (TS_{EF}). Then, intramolecular nucleophilic addition to the N=S bond gives the annulation intermediate **G** (see arrows in **F'**). The conversion of **F** to **G** is the rate-determining step with a barrier 25.0 kcal mol^{−1} (19.6 kcal mol^{−1} from **B**), which is consistent with the temperature of the reaction (120 °C). Although the resulting complex **G** is less stable than **F** by 3.2 kcal mol^{−1}, the acetate aided dissociation of $[\text{Ru}(\text{OAc})\text{L}]^+$ promotes spontaneous elimination of PhSOMe from the free ligand to give **H**, located as low as −69.0 kcal mol^{−1} on the energy surface. The liberation of PhSOMe, the conjugation of the anion, and the strong H-bond in **H** assist the loss of the sulfur moiety.

Finally, protonation of **H** by AcOH produces pyridine **I** or the pyridone species **J**. In line with the experimental observations, **J** is significantly more stable. The mechanistic insight directed towards the second annulation for the construction of pyridine-fused 7-membered oxepine ring is depicted in Fig. 4. The complexation of **H** (at −69.0 kcal mol^{−1}) with $[\text{Ru}(\text{OAc})\text{L}]^+$ is exergonic by 56.4 kcal mol^{−1} and yields **K** at −125.4 kcal mol^{−1}. Intermediate **K** shows a H-bond between the acetate ligand and

Fig. 3 Free energy profile (ΔG_{393} , kcal mol^{−1}), part 1 (first annulation).

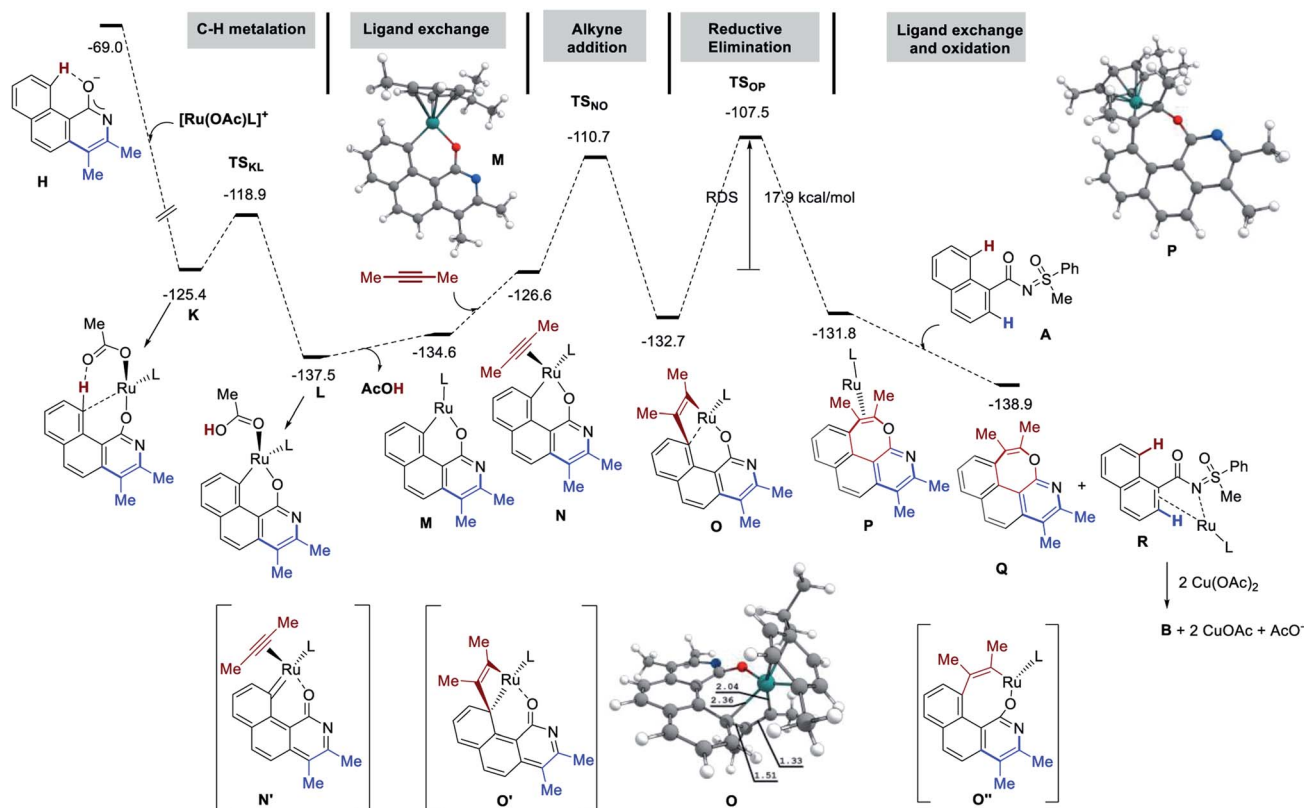


Fig. 4 Free energy profile (ΔG_{393} , kcal mol $^{-1}$), part 2 (second annulation).

the *peri*-H of the naphthalene moiety. The Ru–C bond is short (2.36 Å), due to the coordination of Ru to the *ipso*-carbon and makes the *peri*-H acidic. The C–H metalation of the pre-organized complex **K** provides **L** (at –137.5 kcal mol $^{-1}$ on the energy surface). This step requires 6.5 kcal mol $^{-1}$ free energy of activation (TS_{KL}). Next, the substitution of acetic acid with second alkyne equivalent is endergonic by 10.9 kcal mol $^{-1}$ to afford **N** (–126.6 kcal mol $^{-1}$). Of particular interest, the formation of 7-membered ring does not arise from the reductive elimination of a simple 8-membered metallacycle (**O'**). Instead, at the expense of 15.9 kcal mol $^{-1}$ of free energy of activation, the ruthena-oxabicyclooctene complex **O**, located at –132.7 kcal mol $^{-1}$, is achieved from **N** via TS_{NO} . Among the Lewis depiction of **O** and **O'**, the structure **O** is supported by the Ru–C^{*ipso*} distance of 2.35 Å and other geometrical parameters. Its formation can be understood as an intramolecular [2 + 2] cycloaddition between the alkyne and a Ru=C bond as shown in **N'** (a fictive valence isomer of **N**). This process eventually avoids the participation of a highly strained phenanthrene-containing 8-membered ring (**O''**). Then, the reductive elimination of **O** demands 25.2 kcal mol $^{-1}$ free energy of activation to give **P**. This process is slightly endergonic and is the rate-determining step of this second annulation process. The transfer of the RuL moiety from **P** to the precursor **1a** produces the desired [6,7]-fused oxepino-pyridine skeleton **Q** and chelate **R**. This step is exergonic by 7.9 kcal mol $^{-1}$. Finally, as it is generally accepted, one can then propose that complex **R** transforms into **B** by Cu(OAc) $_2$ mediated oxidation. Based on

the experimental observations and insightful computational data, the mechanism of this double annulation is sketched in Fig. 5.⁴

The active Ru-catalyst {generated from [Ru(*p*-cymene)Cl $_2$] $_2$, AgSbF $_6$, and AcO $^-$ } first coordinates to MPS and activates the C(2)–H bond of **1a** to form **I** (**D** in Fig. 3). The coordination of alkyne to **I** and its migratory insertion leads to **II** (**F** in Fig. 3).

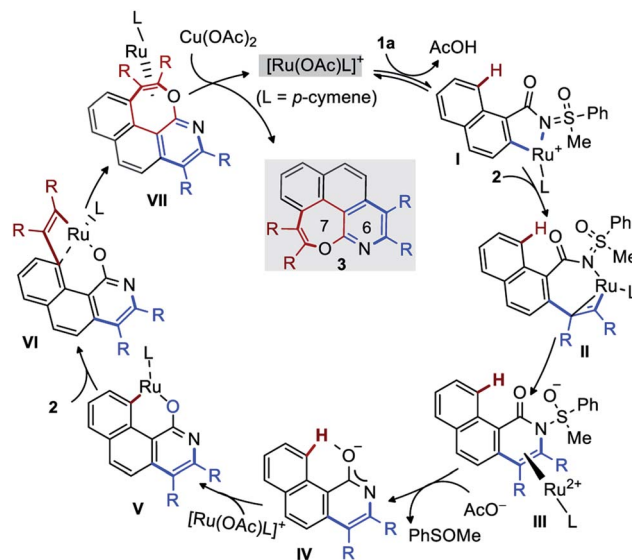


Fig. 5 Plausible catalytic cycle.



Next, the intramolecular nucleophilic addition to the N=S bond provides **III** (**G** in Fig. 3), which is the rate-determining step of the mono-annulation. The acetate-aided expulsion of [Ru(OAc)L]⁺ and elimination of PhSOMe leads to pyridone species **IV** (**H** in Fig. 3). Next, direct C(8)–H ruthenation of **IV** affords **V** (**M** in Fig. 4). Then, alkyne insertion into **V** generates the unusual ruthena-oxabicyclooctene complex **VI** (**O** in Fig. 4). The reductive elimination of **VI** gives **VII** (**P** in Fig. 4) and is the rate-determining step of the second annulation. Finally, Cu(OAc)₂ mediated transfer of RuL moiety to **1a** liberates the desired [6,7]-fused oxepino-pyridine skeleton.

Conclusion

In summary, we have developed an unprecedented Ru-catalyzed sulfoximine-directed one-pot domino $\{[4 + 2] \& [5 + 2]\}$ double annulation of 1-naphthoic acid derivatives with alkynes for the synthesis of unique [6,7]-fused oxepino-pyridine motifs. This transformation functionalizes both chemically distinct *ortho*- and *peri*-C–H bonds of fused-hetero(arenes) through double annulation, making four (C–C & C–N and C–C & C–O) bonds in a single operation. In addition, two-step unsymmetrical annulations with different alkynes are also shown. The detailed DFT calculations endorse the participation of metal-cyclopropene and ruthena-oxabicyclooctene intermediates. The construction of biologically relevant drugs anchored oxepino-pyridine scaffolds, broad scope, and gram scale synthesis make the transformation synthetically viable.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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