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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.<sup>1</sup> 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.<sup>2,3</sup> Continuous efforts have therefore been directed towards the conception of straightforward synthetic methods for the construction of complex heteroarenes.<sup>3</sup> In this regard, transition-metal (TM) catalyzed annulations of C–H bonds of (hetero)arenes with alkynes have proven invaluable.<sup>4,5</sup> 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).<sup>5</sup> 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).<sup>6</sup> 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).<sup>7</sup> 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).<sup>8,9</sup>

Recent domino one-pot double annulation of *o/o'*-C–H bonds of (hetero)arenes with alkynes have led to [6,6]-fused heteroaryls.<sup>10,11</sup> Although important issues of regio- and chemoselectivity, cumbersome mixtures due to incomplete conversion, catalytic viability, *etc.*, could be addressed,<sup>12</sup> 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.<sup>12b</sup> 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-naphthoyl]methylphenyl sulfoximine (**1a**) and 4-octyne (**2a**). The optimization studies are detailed in Table 1.<sup>13</sup> The oxepino-pyridine **3aa** was detected in 8% yield using {[RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5.0 mol%), AgSbF<sub>6</sub> (20 mol%), NaOAc (1.0 equiv.)} as catalytic system, in ClCH<sub>2</sub>CH<sub>2</sub>Cl (DCE) at 120 °C for 24 h (entry 1). The cleavage of the sulfoximine motif presumably helps the formation of **3aa**.<sup>14d</sup> 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.<sup>4</sup> Accordingly, the double annulation was slightly improved when the reaction was conducted in the presence of the redox active bases Mn(OAc)<sub>2</sub>, AgOAc, and Zn(OAc)<sub>2</sub>·2H<sub>2</sub>O (entries 2–4), while Cu(OAc)<sub>2</sub>·H<sub>2</sub>O was found more promising as it delivered **3aa** in 35% yield

Table 1 Optimization of reaction conditions<sup>a</sup>

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



<sup>a</sup> Conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5.0 mol%), additive-1 (20 mol%), additive-2 (0.3 mmol), solvent (2.0 mL) at 120 °C. <sup>b</sup> Isolated yield. <sup>c</sup> <sup>1</sup>H NMR conversion. <sup>d</sup> [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (10 mol%), AgSbF<sub>6</sub> (40 mol%) was used. <sup>e</sup> **2a** (1.2 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (10 mol%), AgSbF<sub>6</sub> (40 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1.5 equiv.) was used. DCE = ClCH<sub>2</sub>CH<sub>2</sub>Cl, TCE = 1,1,2,2-tetrachloroethane.

(entry 5). Additives such as KPF<sub>6</sub>, NaPF<sub>6</sub>, or AgBF<sub>4</sub> instead of AgSbF<sub>6</sub> 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 AgSbF<sub>6</sub> were used (entry 13). Finally, the catalytic conditions comprising [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (10 mol%), AgSbF<sub>6</sub> (40 mol%), and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (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).<sup>14d</sup>

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.<sup>6</sup> 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.<sup>13</sup>

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 (CO<sub>2</sub>Me, 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, CO<sub>2</sub>Me, COMPS) offers the possibility of further functionalization. The core structure of **3ha** and **3ja** were elucidated by X-ray crystallographic analysis.<sup>14,15</sup> 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.<sup>5g</sup> 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  $\pi$ -conjugated system **4a** with two oxepino-pyridine motifs was made. The reaction of **1a** with diphenylacetylene provided polycyclic amides through linear diannulation.<sup>11,14</sup> 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).<sup>16</sup> 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**- $\beta$ -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.<sup>14</sup> 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). <sup>a</sup>Gram scale: **1a** (1.54 g, 5.0 mmol); PhS(O)Me (63%) was isolated. <sup>b</sup>Reactions were carried out in DCE. <sup>c</sup>**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%),  $\text{AgSbF}_6$  (40 mol%), 1,4-dioxane (2.0 mL) at 120 °C for 24 h. <sup>a</sup>Isolation 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.<sup>12</sup> 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.<sup>11</sup> 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.<sup>14,15</sup> 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  $\pi$ -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 ( $1 \times 10^{-5}$ ).<sup>14</sup> Of note, compounds **3nb** and **3ob** show emission maxima at 436–512 nm with broad bandwidths and weak intensities.<sup>14</sup>

The mechanism of the title reaction has been studied computationally, employing the Gaussian 09 software package.<sup>17</sup> 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%),  $\text{AgSbF}_6$  (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%),  $\text{AgSbF}_6$  (30 mol%),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (0.3 mmol),  $\text{KH}_2\text{PO}_4$  (0.6 mmol), 1,4-dioxane (2.0 mL) at 120 °C for 20 h. <sup>a</sup>Isolation 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)<sup>18</sup> 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<sup>-1</sup> ( $\Delta G_{393}$ ). The molecular system **A** [**1a**, 2-butyne (2.0 equiv.), [Ru(OAcL)]<sup>+</sup> (L = *p*-cymene), AcO<sup>-</sup>] 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 [Ru(OAc(*p*-cymene))]<sup>+</sup> with **1a** at first provides **B** with a release of 20.5 kcal mol<sup>-1</sup>. Next, C–H metalation occurs through TS<sub>BC</sub> lying 11.9 kcal mol<sup>-1</sup> above **B** to provide metallacycle **C** (–23.6 kcal mol<sup>-1</sup>). Elimination of acetic acid and insertion of 2-butyne delivers the alkyne-complex **E** (more stable than **C** by 2.6 kcal mol<sup>-1</sup>). Alkyne insertion does not yield the proposed metal-alkenyl complex **F'**, but rather its valence isomer **F**, which is a metallacycloprenene 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<sup>-1</sup> that requires 14.9 kcal mol<sup>-1</sup> of free energy of activation (TS<sub>EF</sub>). 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<sup>-1</sup> (19.6 kcal mol<sup>-1</sup> 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<sup>-1</sup>, the acetate aided dissociation of [Ru(OAcL)]<sup>+</sup> promotes spontaneous elimination of PhSOMe from the free ligand to give **H**, located as low as –69.0 kcal mol<sup>-1</sup> 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<sup>-1</sup>) with [Ru(OAcL)]<sup>+</sup> is exergonic by 56.4 kcal mol<sup>-1</sup> and yields **K** at –125.4 kcal mol<sup>-1</sup>. Intermediate **K** shows a H-bond between the acetate ligand and

Fig. 3 Free energy profile ( $\Delta G_{393}$ , kcal mol<sup>-1</sup>), part 1 (first annulation).

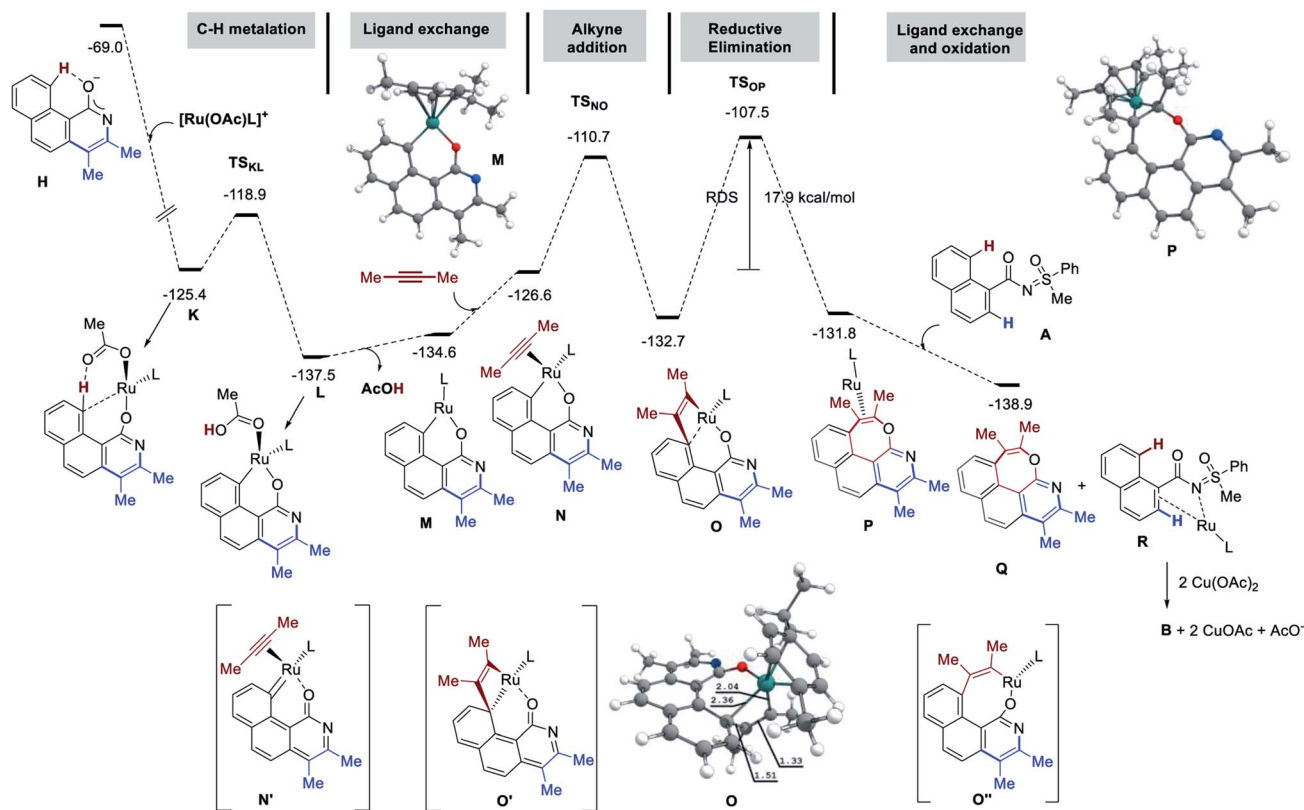


Fig. 4 Free energy profile ( $\Delta G_{393}$ , kcal mol $^{-1}$ ), part 2 (second annulation).

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<sup>*ipso*</sup> 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.<sup>4</sup>

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).



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]<sup>+</sup> 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)<sub>2</sub> 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.

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