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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

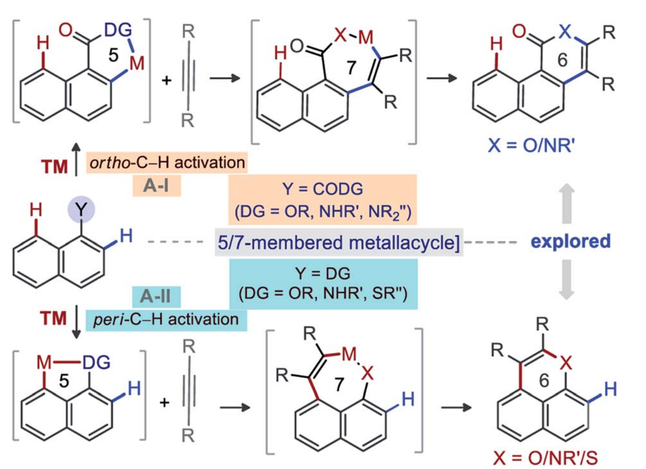

Fig. 1 *Background*: Annulation of *ortho*-C(2)–H & *peri*-C(8)–H bond of 1-naphthalene derivatives with alkynes.

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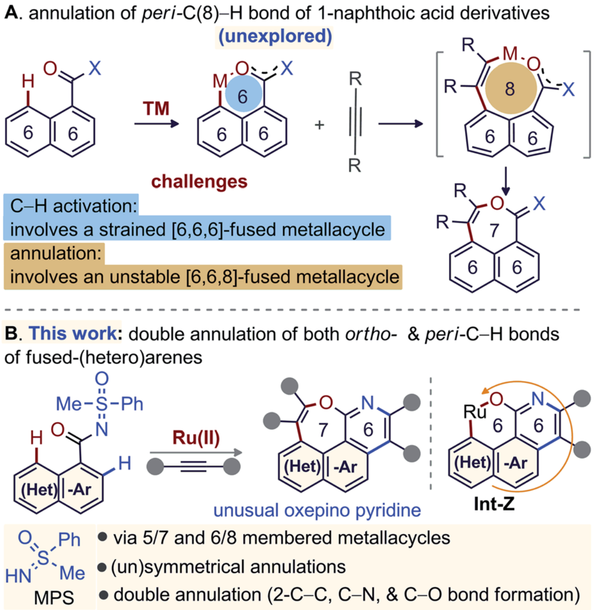


Fig. 2 Multiple annulation of (hetero)arenes.

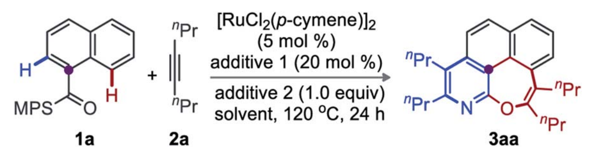
plan feasible, we hypothesized a Ru-catalyzed double annulation of 1-naphthoic acid derivatives with alkynes.

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).

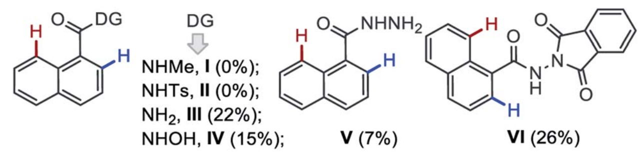
Results and discussion

This one-pot [4 + 2] & [5 + 2] annulation was developed under Ru-catalysis using *N*-[1-naphthoyl]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 {[$RuCl_2$(*p*-cymene)]$_2$ (5.0 mol%), $AgSbF_6$ (20 mol%), NaOAc (1.0 equiv.)} as catalytic system, in $ClCH_2CH_2Cl$ (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 $Zn(OAc)_2 \cdot 2H_2O$ (entries 2–4), while $Cu(OAc)_2 \cdot H_2O$ 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	″	$Zn(OAc)_2 \cdot 2H_2O$	DCE	11
5	″	$Cu(OAc)_2 \cdot H_2O$	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]	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	1,4-Dioxane	68
14[e]	**$AgSbF_6$**	**$Cu(OAc)_2 \cdot H_2O$**	**1,4-Dioxane**	**77**
15	$AgSbF_6$	—	1,4-Dioxane	<5[c]
16	—	$Cu(OAc)_2 \cdot H_2O$	1,4-Dioxane	<5[c]



[a] Conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), [$RuCl_2$(*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] [$RuCl_2$(*p*-cymene)]$_2$ (10 mol%), $AgSbF_6$ (40 mol%) was used. [e] **2a** (1.2 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (10 mol%), $AgSbF_6$ (40 mol%), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.) was used. DCE = $ClCH_2CH_2Cl$, TCE = 1,1,2,2-tetrachloroethane.

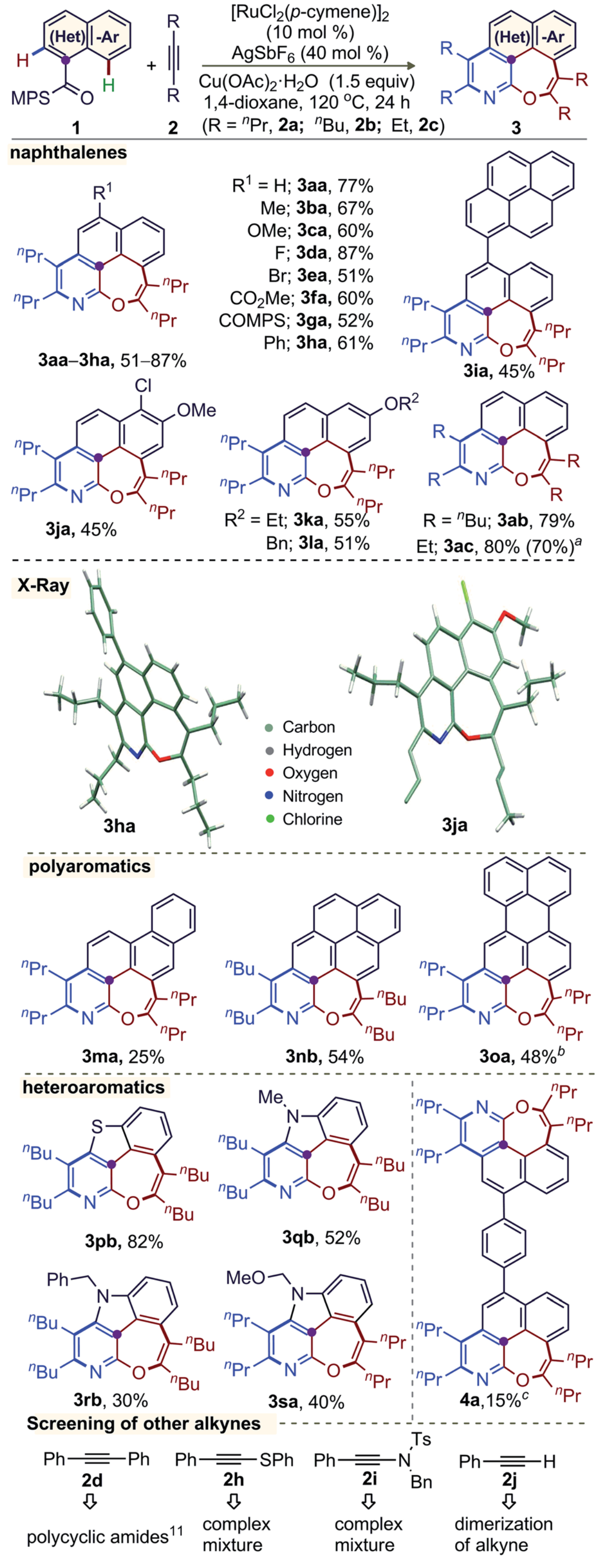
(entry 5). Additives such as KPF_6, $NaPF_6$, or $AgBF_4$ instead of $AgSbF_6$ were not beneficial (entries 6–8). The reaction efficiency was low when conducted in MeCN, toluene or TCE (entries 9–11). The domino diannulation in 1,4-dioxane provided **3aa** in 41% yield (entry 12). The yield of **3aa** was significantly improved to 68% when 10 mol% of Ru-catalyst and 40 mol% of $AgSbF_6$ were used (entry 13). Finally, the catalytic conditions comprising [Ru(*p*-cymene)Cl_2]$_2$ (10 mol%), $AgSbF_6$ (40 mol%), and $Cu(OAc)_2 \cdot H_2O$ (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).[4d]

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]

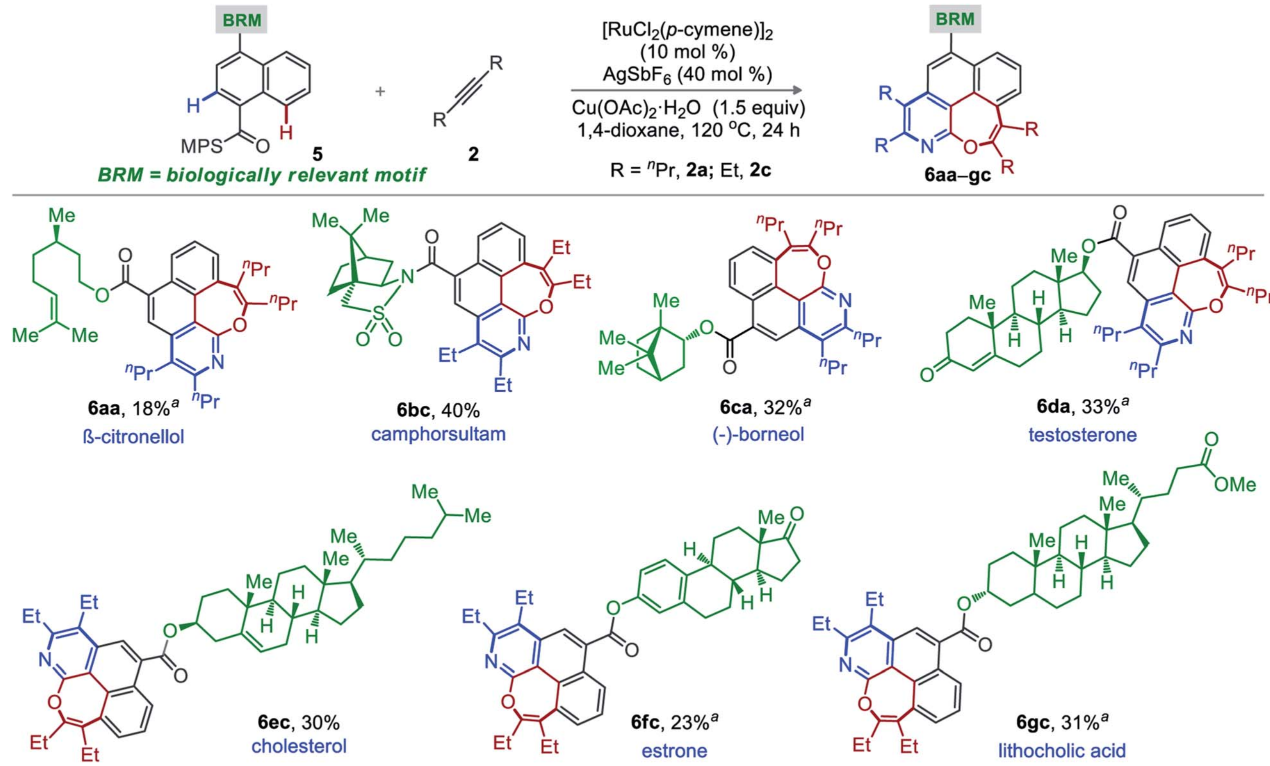
The generality of this annulation among fused (hetero)arenes exhibiting *peri*-C–H bonds and unactivated alkynes was explored under the optimized catalytic conditions (Scheme 1). The annulation of naphthalene derivatives **1a–l**, bearing either electron-donating (Me, OMe, OEt), labile halo (F, Cl, Br), electron-withdrawing (CO_2Me, 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_2Me, 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 diannulation.[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, **6ec**-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). [a]Gram scale: **1a** (1.54 g, 5.0 mmol); PhS(O)Me (63%) was isolated. [b]Reactions were carried out in DCE. [c]**2a** (1.8 mmol).



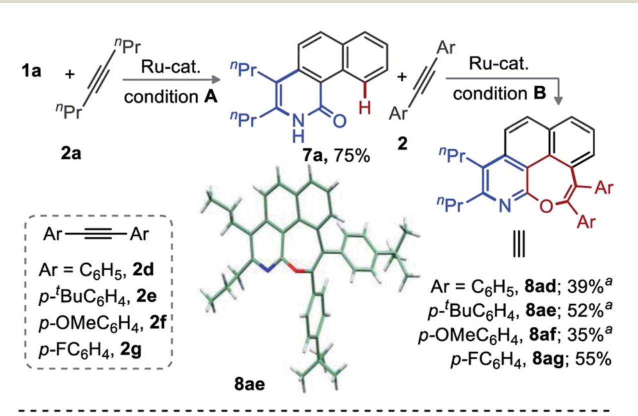
Scheme 2 Double annulation of MPS-bearing naphthalene-1-carboxylic acid moulded in biologically relevant motifs. Reactions were carried out with **5** (0.3 mmol), **2** (1.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%), $AgSbF_6$ (40 mol%), 1,4-dioxane (2.0 mL) at 120 °C for 24 h. [a]Isolation of unreacted 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.[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-demetallation.[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).

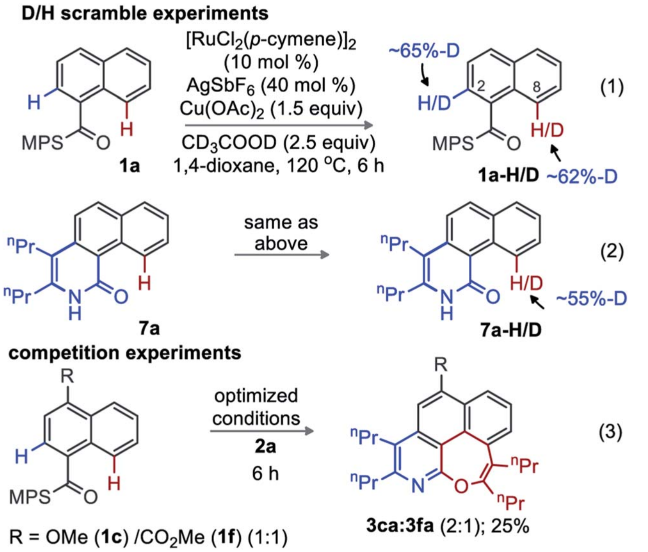
Exposing **1a** to the optimized conditions in presence of CD_3CO_2D (2.5 equiv.) resulted in D-incorporation at C2 (65%) and C8 (62%) positions (eqn (1)). Similarly, 55% of deuterium incorporation occurred at C8 in an identical experiment with **7a** (eqn (2)). Therefore, activation of both the *ortho*- 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), $[RuCl_2(p\text{-cymene})]_2$ (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), $[RuCl_2(p\text{-cymene})]_2$ (7.5 mol%), $AgSbF_6$ (30 mol%), $Cu(OAc)_2\cdot H_2O$ (0.3 mmol), KH_2PO_4 (0.6 mmol), 1,4-dioxane (2.0 mL) at 120 °C for 20 h. [a]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)[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.), $[RuOAcL]^+$ (L = *p*-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 [RuOAc(*p*-cymene)]$^+$ with **1a** at first provides **B** with a release of 20.5 kcal mol^{-1}. Next, C–H metalation occurs through $\mathbf{TS_{BC}}$ 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 metallacyclopropene 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 ($\mathbf{TS_{EF}}$). 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 $[Ru(OAc)L]^+$ 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 $[Ru(OAc)L]^+$ 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

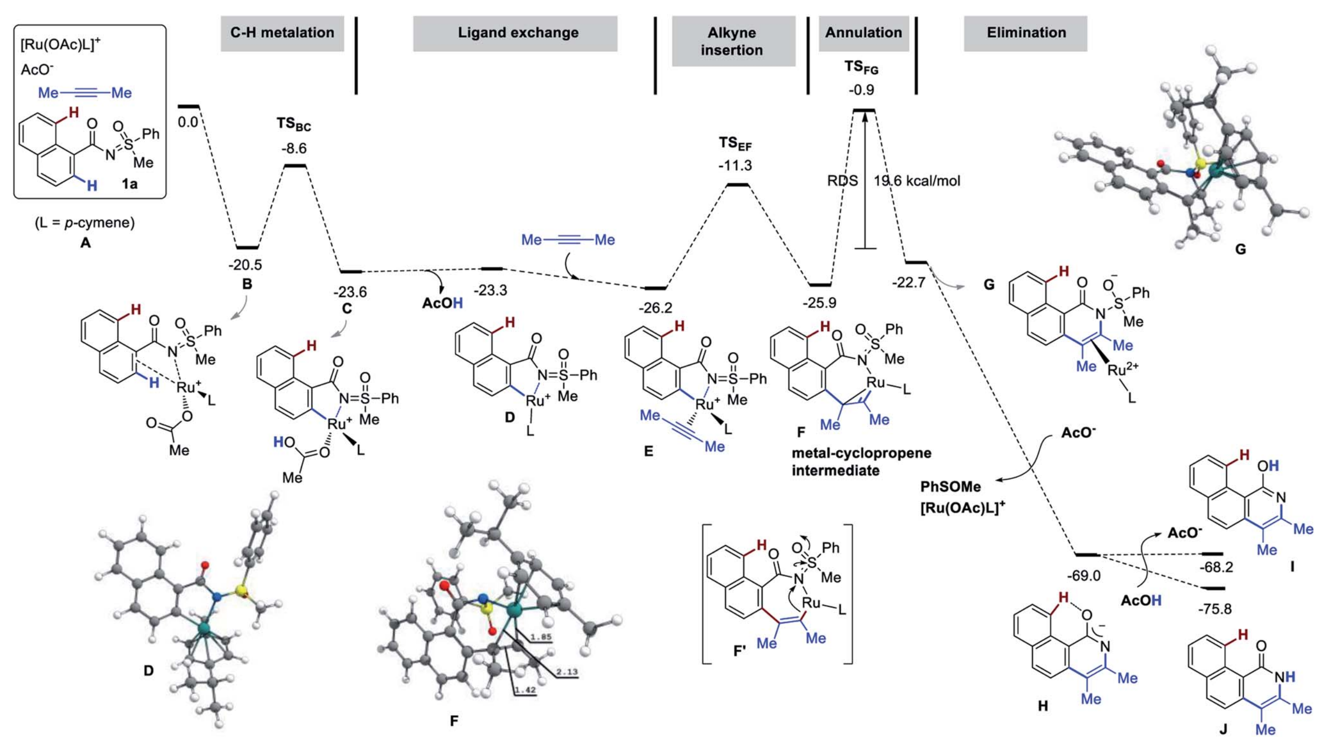


Fig. 3 Free energy profile (ΔG_{393}, kcal mol^{-1}), part 1 (first annulation).

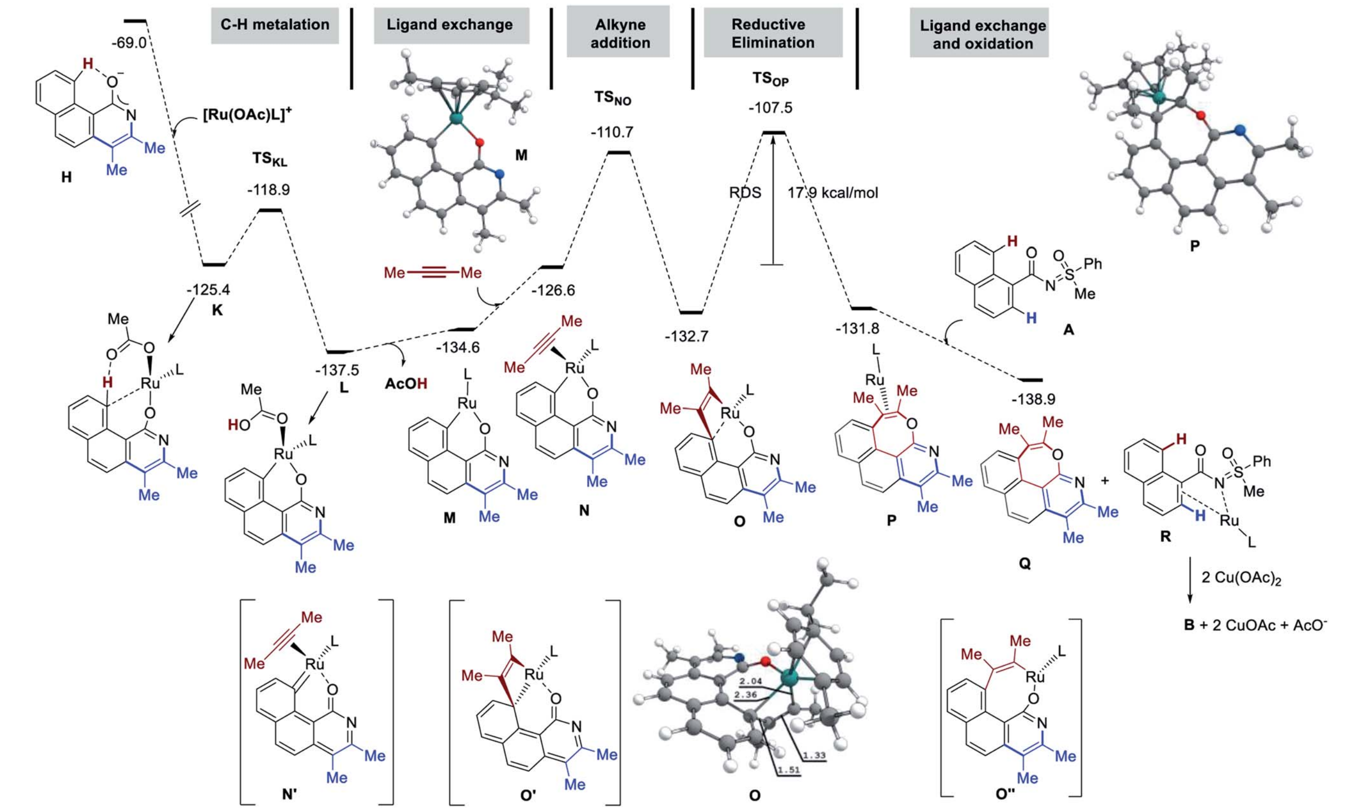


Fig. 4 Free energy profile (ΔG_{393}, kcal mol^{-1}), part 2 (second annulation).

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 ($\mathbf{TS_{KL}}$). 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* $\mathbf{TS_{NO}}$. 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 $[Ru(p\text{-cymene})Cl_2]_2$, $AgSbF_6$, 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).

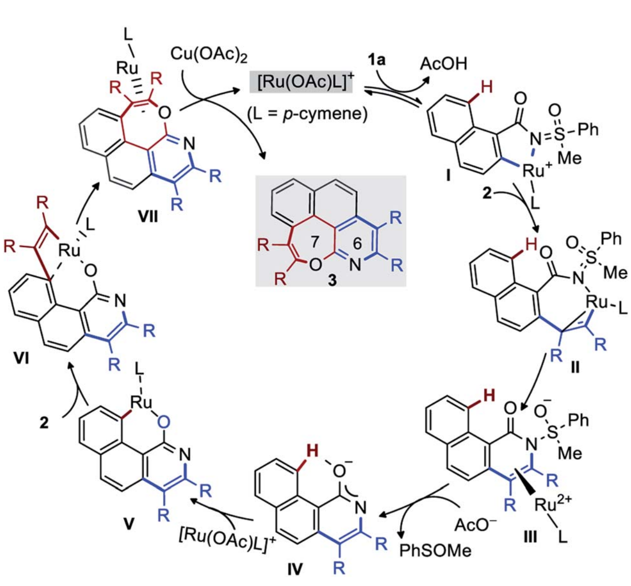


Fig. 5 Plausible catalytic cycle.

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.

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14 See the ESI.†

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