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# Redox-Neutral [4 + 2] Annulation of *N*-Methoxybenzamides with Alkynes Enabled by an Osmium(II)/HOAc Catalytic System

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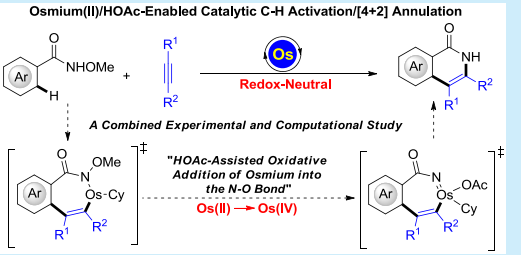
Supporting Information

**ABSTRACT:** By making use of a direct C−H activation strategy, an efficient osmium(II)-catalyzed redox-neutral [4 + 2] annulation of *N*-methoxybenzamides with alkynes has been accomplished. Computational and experimental studies revealed that such transformation leading to the synthesis of the isoquinolone core might follow an Os(II)−Os(IV)−Os(II) catalytic pathway, in which an unusual HOAc-assisted oxidative addition of osmium(II) into the N−O bond to generate the osmium(IV) species was involved as one of the key transition states. Further exploration of divergent C−H activation reaction modes enabled by the osmium(II) catalyst has also been exemplified for one-pot assembly of other either linear or cyclic products.

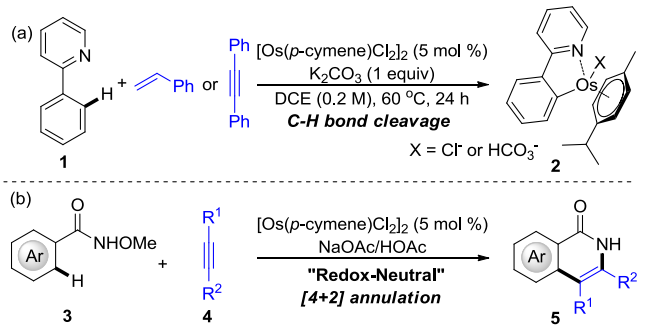





Over the past decades, a transition-metal-catalyzed direct C−H activation/annulation cascade has received considerable attention since it can enable the site-/region-selective synthesis of a broad range of heterocyclic frameworks from simple starting materials in a step- and atom-economical fashion via the directing-group-assisted controllable cleavage of the inert C−H bonds.[1] Since the groundbreaking work by the research groups of Murai,[2a] Lewis,[2b] and Fujiwara,[2c] compelling progress has been made in this hot area of research. Accordingly, most of the first- and second-row transition metals, particularly ruthenium,[3] rhodium,[4] and palladium complexes,[5] have been developed as the catalysts of choice thus far. In sharp contrast, the third-row transition metals have been investigated much less than the first- and second-row transition metals in this field.[6,7] Especially, to the best of our knowledge, there are no examples involving osmium complexes as the catalysts to address the issue of direct C−H functionalization, mainly because they are considered less active on account of their slower ligand exchange kinetics.[8a] Indeed, our preliminary investigation also showed that the reaction of the classical 2-phenylpyridine with either styrene or diphenylacetylene under osmium(II) catalysis was stopped completely at the step of the cleavage of the *ortho*-C−H bond to deliver the almost equivalent five-membered osmacycle species as the dominant product (Scheme 1a).

However, in basic research, the most interesting findings are often obtained in less explored areas. In this vein, recent studies have demonstrated that the osmium species are a class of versatile catalysts. For instance, several newly synthesized osmium complexes have shown to possess relevant catalytic performance in transfer hydrogenation (TH), hydrogenation (HY), as well as dehydrogenation (DHY) processes with activities comparable to or even higher than those of the ruthenium analogues.[8,9] Driven by these elegant works and the successful history of the development of their ruthenium counterparts in C−H activation chemistry, we envisioned that the careful switching of the ligand, the DG, and/or related reaction parameters might control the polarized nature of the Os−C bond through changing the coordination environment between the osmium metal and the substrate, which then tuned the reactivity and the selectivity of the Os−C species to ensure sufficient interactions of the Os−C bond with a proper coupling reagent, thus leading eventually to facile construction of ideal complex products via osmium-catalyzed C−H activation reactions. As part of our ongoing efforts, herein, we would like to disclose the first osmium(II)-catalyzed and HOAc-assisted redox-neutral C−H activation/[4 + 2] annulation example for the synthesis of isoquinolones (Scheme

**Scheme 1. Exploration and Development of Direct C−H Activation Enabled by the Osmium(II) Catalysis**

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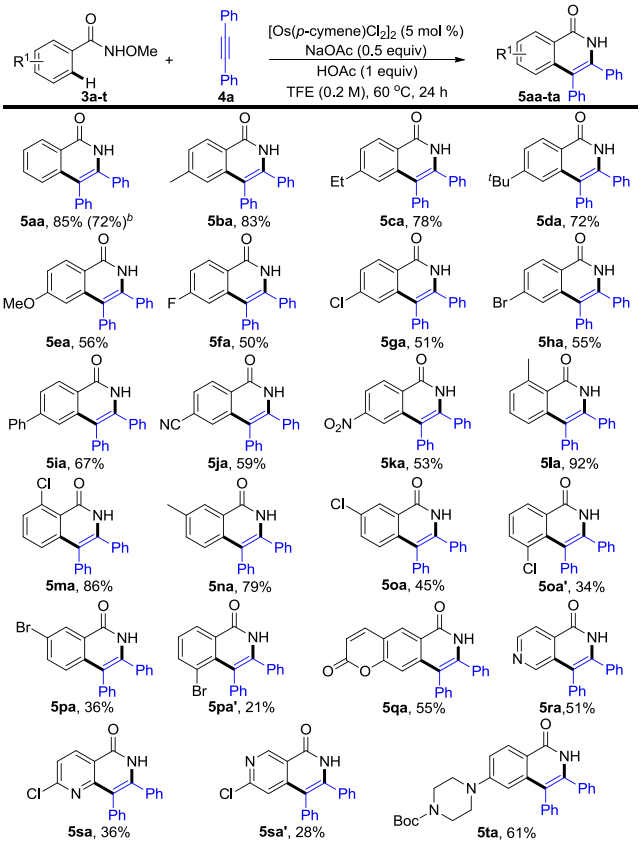
1b). Combined computational and experimental studies clarified the Os(II)−Os(IV)−Os(II) catalytic reaction pathway for the above proof-of-principle demonstration. In addition, the applicability and versatility of the osmium(II)-catalyzed system have been examined as exemplified by the synthesis of 2-alkynylbenzamide, five-membered indole, six-membered isoquinoline, and seven-membered 1*H*-benzo[*c*]-azepine-1,3(2*H*)-dione skeletons through divergent C−H activation reaction modes.

Preliminarily, in a search for appropriate DGs that enable osmium(II)-catalyzed diversified C−H functionalization, we turned our attention to N−OR-substituted benzamides, which represent a type of versatile ODG for the construction of various heterocycles via transition-metal-catalyzed transformations.[4d,10−12] To our delight, the treatment of the simple *N*-methoxybenzamide **3a** with diphenylacetylene **4a** in the presence of $[Os(p\text{-cymene})Cl_2]_2$ (5 mol %) and NaOAc (0.5 equiv) in methanol led to the formation of isoquinolone product **5aa** in 21% isolated yield along with the disappearance of most of the starting materials, which confirmed our aforementioned inference. Encouraged by this result, we next screened the experimental parameters systematically to figure out the optimal conditions for the catalytic C−H functionalization (see Table S1 in the Supporting Information for a detailed optimization). After a number of trials, we were pleased to identify the following optimized conditions: **3a** (1.2 equiv), **4a** (1.0 equiv), $[Os(p\text{-cymene})Cl_2]_2$ (5 mol %), NaOAc (0.5 equiv), and HOAc (1.0 equiv) in TFE at 60 °C for 24 h under an atmosphere of air, delivering the desired isoquinolone product in 85% yield.

Having the optimized conditions in hand, the exploration of the generality and substrate scope with respect to *N*-methoxybenzamides was first conducted. As shown in Scheme 2, a variety of substituted *N*-methoxybenzamides were employed to react with **4a**, and the corresponding isoquinolones were constructed effectively. Various commonly encountered functional groups including alkyl (**5ba−da**), methoxyl (**5ea**), halogens (**5fa−ha**), phenyl (**5ia**), cyano (**5ja**), and nitro group (**5ka**) were fully tolerated in this transformation, furnishing the desired products in moderate to good yields. In addition, the reaction efficiency was not influenced by the position of the substituent; *N*-methoxybenzamides with substituents at either *para*-, *ortho*-, or *meta*-position were all good reactants to afford the desired isoquinolones in good yields. Of note, when *meta*-methyl-substituted *N*-methoxybenzamide was subjected to the standard conditions, the C−H bond cleavage occurred at the less hindered site with exclusive regioselectivity (**5na**), whereas the *meta*-chloro- and bromo-substituted substrates resulted in the generation of a mixture of regioisomers (**5oa−pa** and **5oa′−pa′**), revealing that the nature of the substituent had a clear effect on determining the reaction outcome. Having disclosed the good functional group tolerance for various functionalized phenyl amides, we were next intrigued to further extend the scope to heterocyclic scaffolds, which represent a class of challenging substrates for the application in the field of transition-metal-catalyzed C−H functionalization. Delightfully, several O- or N-containing skeletons including coumarin, pyridine, and piperazine derivatives readily participated in this reaction to yield the corresponding isoquinolones (**5qa−ta**), which further enhanced the versatility of the developed osmium(II)-catalyzed protocol.

**Scheme 2. Scope of *N*-Methoxybenzamides for the Synthesis of Isoquinolones**[a]




[a]Reaction conditions: **3** (0.24 mmol), **4a** (0.2 mmol), $[Os(p\text{-cymene})Cl_2]_2$ (5 mol %), NaOAc (0.5 equiv), and HOAc (1 equiv) in TFE (0.2 M) at 60 °C for 24 h without exclusion of air or moisture; isolated yields were reported. [b]Performed on a 5.0 mmol scale with 2.5 mol % of $[Os(p\text{-cymene})Cl_2]_2$.

Subsequently, a diverse array of alkynes were examined to further probe the robustness of this protocol for the efficient synthesis of isoquinolones. As shown in Scheme 3, the enumerated alkynes including symmetrical diaryl acetylenes bearing various substituents were all compatible with the standard conditions, delivering the corresponding isoquinolones (**5ab−ah**) in moderate to good yields. It was noteworthy that the unsymmetrically substituted aryl/alkyl, alkyl/ester, or alkyl/amido alkynes, including but-1-yn-1-yl benzene, but-2-ynoic acid ester, as well as 1-morpholinobut-2-yn-1-one, all resulted in the formation of the corresponding products (**5ai−al**) with exclusive regioselectivity, thus affording a good complement to previously reported transition-metal-catalyzed examples[11,13] for specific construction of isoquinolones bearing different substituents. To better define the substrate scope, we further explored the other alkynes such as those bearing the bulky dialkyl group as the substituent as well as terminal and liner alkynes (e.g., 1-hexyne, ethyl propiolate, and 4-octyne). However, no expected annulation products were observed, indicating that the size, type, and nature of the alkyne substrate played a vital role in determining the outcome of the reaction.

Having established the osmium(II)-catalyzed [4 + 2] annulation of *N*-methoxybenzamides with alkynes for the construction of diverse isoquinolones, we next made an effort to disclose other reaction modes for further evaluating the



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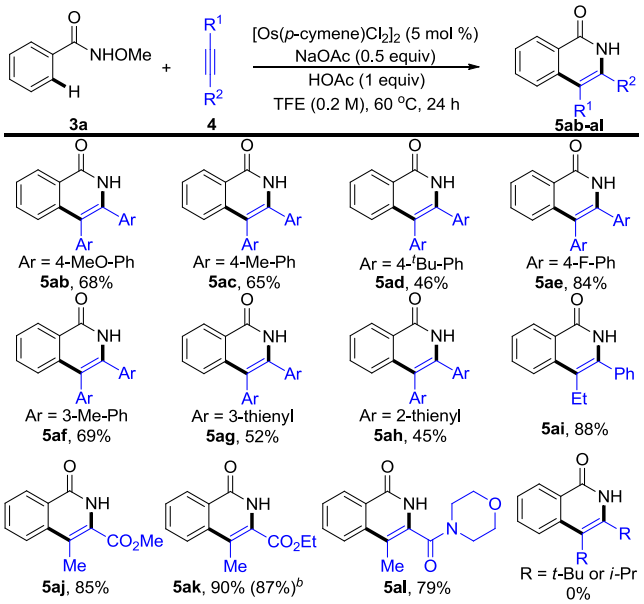
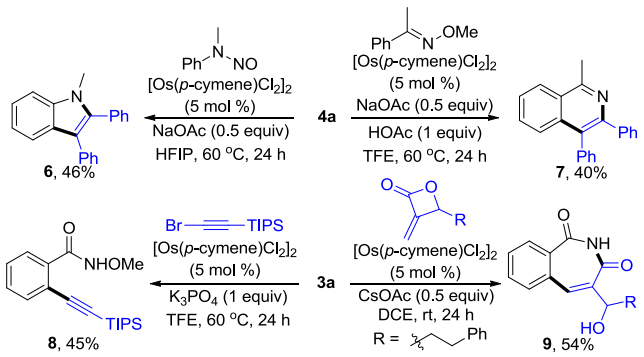
**Scheme 3. Substrate Scope of Alkynes**[a]




[a]Reaction conditions: **3a** (0.24 mmol), **4** (0.2 mmol), [Os(*p*-cymene)$Cl_2$]$_2$ (5 mol %), NaOAc (0.5 equiv), and HOAc (1 equiv) in TFE (0.2 M) at 60 °C for 24 h without exclusion of air or moisture; isolated yields were reported. [b]Performed on a 4.0 mmol scale with 2.5 mol % of [Os(*p*-cymene)$Cl_2$]$_2$.

application potentials of the developed osmium(II) catalytic system (Scheme 4). As predicted, *N*-methyl-*N*-phenylnitrous

**Scheme 4. Divergent C−H Functionalizations under Osmium(II) Catalysis**




amide and oxime readily participated in the coupling with diphenylacetylene **4a** under the osmium(II)-catalyzed conditions, delivering the corresponding indole derivative **6** and isoquinoline product **7**. Besides, the osmium(II)-catalyzed C−H alkynylation or [4 + 3] annulation of *N*-methoxybenzamide **3a** with different coupling partners were also achieved to give the corresponding products **8** and **9** in synthetically useful yields. Taken together, these results further illustrated the remarkable robustness and versatility of the developed osmium(II)-catalyzed system in mediating divergent C−H functionalization reactions.

Given the unique features of the novel osmium(II) catalyst in mediating the classic C−H activation/[4 + 2] annulation, we became intrigued to elucidate the reaction mechanism. As shown in Figure 1, DFT calculations were performed by selecting Os(*p*-cymene)$(OAc)_2$ (**Cat.**) as the starting point. First, the N−H and C−H activations occurred via a concerted metalation−deprotonation (CMD) mechanism,[14] through transition states **TS-1** and **TS-2**, respectively, to yield the five-membered osmacycle complex **INT-4** with an overall energy barrier of 22.0 kcal/mol (from **Cat.** to **TS-2**) (see Figure S1 in the Supporting Information for detailed DFT calculations). It was worth emphasizing that the subsequent alkyne coordination and migratory insertion into the C−Os rather than the N−Os bond were involved ($\Delta G^{\ddagger}$ = 26.0 kcal/mol for **TS-3** vs $\Delta G^{\ddagger}$ = 33.1 kcal for **TS-3′**) to generate **INT-6**. From then on, a relatively high energy barrier of 24.5 kcal/mol (from **INT-6** to **TS-4′**) was involved for the following C−N bond reductive elimination process, which had been proved as the key step in precedent transition-metal-catalyzed C−H/N−H annulation of *N*-methoxybenzamides.[10−12,15] Alternatively, an oxidative addition of osmium into the N−O bond proceeded via **TS-4** ($\Delta G^{\ddagger}$ = 14.0 kcal/mol) with the assistance of HOAc,[16] producing the osmium(IV) species **INT-7** with a free energy of −7.6 kcal/mol. Thereafter, the facile reductive elimination occurred via the transition states **TS-5** and **TS-6** with the free energy of −2.7 kcal/mol and −3.3 kcal/mol, respectively, followed by the protonlysis and the ligand exchange in the presence of HOAc to deliver the final isoquinolone product along with extrusion of the active osmium(II) catalyst. Of note, our DFT calculations also showed that the absence of HOAc resulted in a high energy barrier of 16.8 kcal/mol (from **INT-6** to **TS-4″**) for the oxidative addition process, implying HOAc was crucial for this transformation, which was consistent with our experimental observation that the use of HOAc as an additive obviously improved the reaction efficiency. Besides, following **INT-7**, a sequential HOAc-assisted coordination (via **TS-5′**) and reductive elimination (via **TS-6′**) were also ruled out since the relatively high energy profiles (−1.6 kcal/mol for **TS-5′** vs −2.7 kcal/mol for **TS-5** and 8.2 kcal/mol for **TS-6′** vs −3.3 kcal/mol for **TS-6**) were involved in this reaction pathway for the generation of the isoquinolone product.

Moreover, the alkyne migratory insertion process via **TS-3** was detected in the whole favorable catalytic cycle, suggesting that it should act as the turnover limiting step for this osmium(II)-catalyzed [4 + 2] annulation.

To further gain more insight into the reaction mechanism and validate computational results, a set of experimental investigations were then carried out (Scheme 5). Deuterium-labeling experiments in the presence of $CD_3OD$ resulted in no obvious deuterium incorporation in both recovered *N*-methoxybenzamide **3a** and the desired isoquinolone product **5aa**, revealing an irreversible C−H cleavage process for the developed osmium(II)-catalyzed annulation (Scheme 5a). Moreover, kinetic isotope studies from a competitive experiment and two parallel, side-by-side reactions probed primary KIE values of 1.3 and 1.6, respectively, indicating that the C−H bond cleavage might not be involved in the turnover limiting step,[17] which was in good agreement with the DFT calculation results involving a relatively low energy barrier for the C−H cleavage step compared with the alkyne migratory insertion process (Scheme 5b). When *N*-methyl-substituted **3a** was subjected to the osmium(II)-catalyzed C−H annulation with **4a**, no reaction occurred (Scheme 5c, left), revealing that the N−H bond of NH−OMe was indispensable for this transformation. Meanwhile, the treatment of *N*-acetoxybenzamide with **4a** under the standard conditions resulted in the formation of benzamide rather than the desired isoquinolone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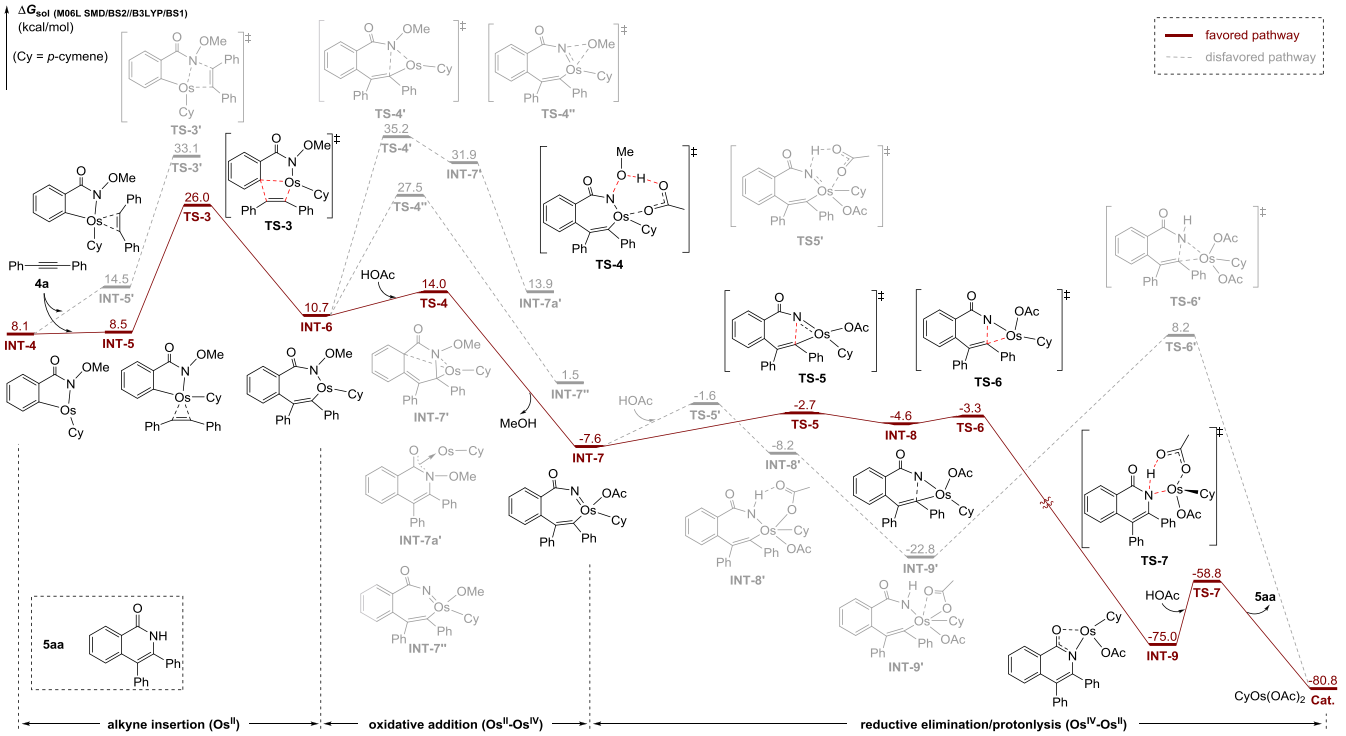
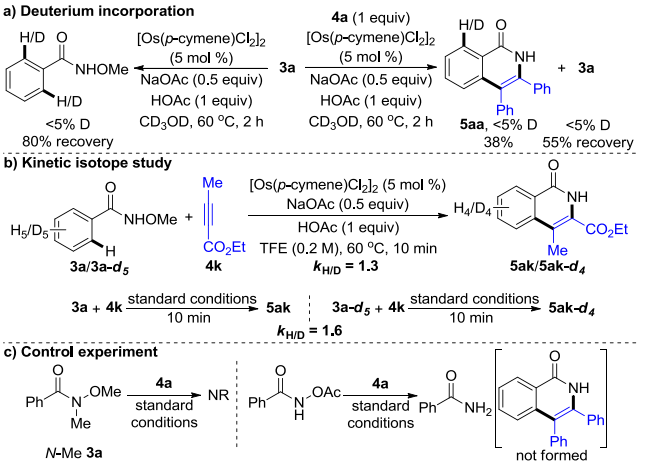



**Figure 1.** Computed Gibbs free energy changes of the reaction pathways for alkyne insertion, oxidative addition, reductive elimination, and protonlysis.

### Scheme 5. Experimental Mechanistic Studies




product (Scheme 5c, right), which not only proved that such a transformation should be via an oxidative addition process of osmium into the N−O bond to result in the cleavage of N−O bond but also revealed that the alkyne coordination and migratory insertion should occur before the oxidative addition of osmium into the N−O bond.

On the basis of both DFT calculations and experimental mechanistic studies, a tandem C−H activation, alkyne migratory insertion, oxidative addition, reductive elimination, and protonolysis process involving the redox-neutral HOAc-assisted Os(II)−Os(IV)−Os(II) pathway is deduced (see Scheme S1 in the Supporting Information for the detailed mechanistic proposal). However, more studies are still needed to unambiguously verify the proposed mechanism.

In summary, we have developed the first osmium(II)-catalyzed redox-neutral C−H activation/[4 + 2] annulation of *N*-methoxybenzamides with alkynes for one-pot assembly of isoquinolones. DFT calculations revealed that an active osmium(IV) intermediate could be facilely formed through HOAc-assisted oxidative addition of osmium(II) into the N−O bond, suggesting an Os(II)−Os(IV)−Os(II) catalytic pathway for such transformation. Further exploration on different C−H activation reaction modes mediated by the osmium(II) catalyst has also been successfully exemplified to deliver either linear or cyclic frameworks including 2-alkynylbenzamide, five-membered indole, six-membered isoquinoline, and seven-membered 1*H*-benzo[*c*]azepine-1,3(2*H*)-dione skeletons, thereby illustrating the remarkable robustness and versatility of the disclosed osmium(II)-catalyzed system. Further studies on the scope, mechanism, and application of this catalytic system to explore the new C−H activation mode are in progress.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03827.

Experimental procedures, characterization of products, computational details, and copies of $^{1}H$ and $^{13}C$ NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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