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Palladium-Catalyzed Cross-Coupling, Divergent Allene Generation, and Cycloadditions toward Cyclobuta[*b*]naphthalen-3(1*H*)-ones and 11H-Benzo[*b*]fluoren-11-ones

Shugao Zhu,* Dan Wang,[⊥] Shihan Liu,[⊥] Yufeng Ma,[⊥] Hong Wang, Yu Lan,* Ruopeng Bai, and Ruwei Shen*

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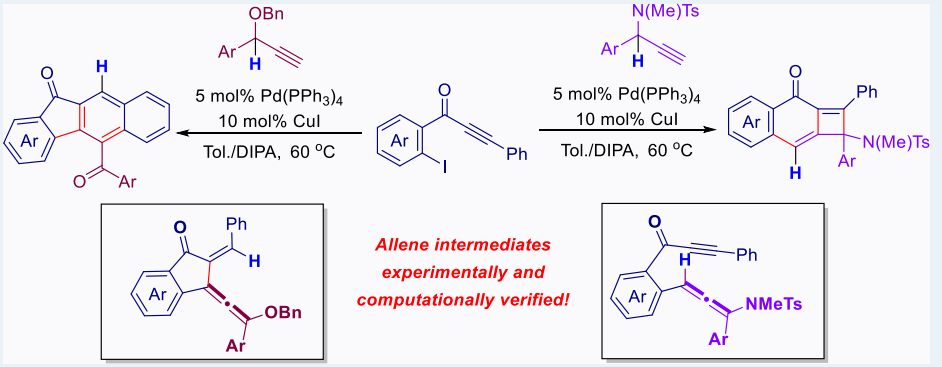

ABSTRACT: The Pd-catalyzed reaction of 1-(2-iodophenyl)-3-arylprop-2-yn-1-ones with propargyl sulfonamide produces cyclobuta[*b*]naphthalen-3(1*H*)-ones, while the reaction of 1-(2-iodophenyl)-3-arylprop-2-yn-1-ones with propargyl ethers under the similar palladium catalysis affords 11H-benzo[*b*]fluoren-11-ones as products. Combined experimental and theoretical studies on the reaction mechanism reveal that the former reaction proceeds through the Pd-catalyzed cross-coupling, propargyl-allenyl isomerization (1,3-H transfer) and [2 + 2] cycloaddition, whereas the latter involves a process of Pd-catalyzed cross-coupling, a propargylic Alder-ene-type reaction (1,8-H transfer) and 6π-electrocyclization leading to the formation of the formal [4 + 2] cycloadducts. The divergent formation of two types of allenic intermediates depending on propargylic substrates is confirmed and elucidated.

KEYWORDS: *tandem reaction, propargyl-allenyl isomerization, Alder-ene reaction, allene, cycloaddition*

INTRODUCTION

Allenes have attracted numerous attention in synthetic organic chemistry in recent years due to their rich properties and versatile reactivities.[1−7] In particular, the relatively high-energy profile and unique geometry of allenes arising from the cumulated diene structural moieties render them valuable and versatile synthetic intermediates for the synthesis of complex carbo- and heterocyclic backbones via diversified cyclization reactions.[8−17] Moreover, allenes are also frequently engaged as reactive intermediates in reaction design for rapid construction of cyclic frameworks that usually cannot be easily obtained from traditional methods.[18−23] Based on a facile and convenient palladium-catalyzed cross-coupling and base-promoted propargyl-allenyl isomerization reactions (CIRs, Scheme 1a), for example, Müller and we have developed a series of tandem transformations of the in situ generated vinyl-allene intermediates **I**, such as Diels-Alder reaction,[24−28] Alder-ene reaction,[29] Claisen rearrangement,[30−32] [3 + 2] azide−olefin cycloaddition,[33] and Schmittel cyclization,[34] to afford a diversity of useful skeletons.[35−39] As our further endeavor, we recently postulated (1) the possible formation of an aryl-tethered heteroatom-substituted allene-ynone intermediate **II** from the CIR of an *ortho*-iodophenyl-ynone and a propargylic substrate and questioned (2) the reactivity of such a functionalized allenic intermediate for cyclization reactions (initial design, Scheme 1b). It is worth noting that previous studies on cyclization reactions of relevant yne-allenes have proven extreme success in the synthesis of a variety of cyclic skeletons via cycloadditions,[40−42] cycloisomerizations,[43] and other annulations[44] upon thermal or photochemical initiation

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Scheme 1. Reaction Design Based on the Generation of the Heteroatom-Substituted Allene Intermediates

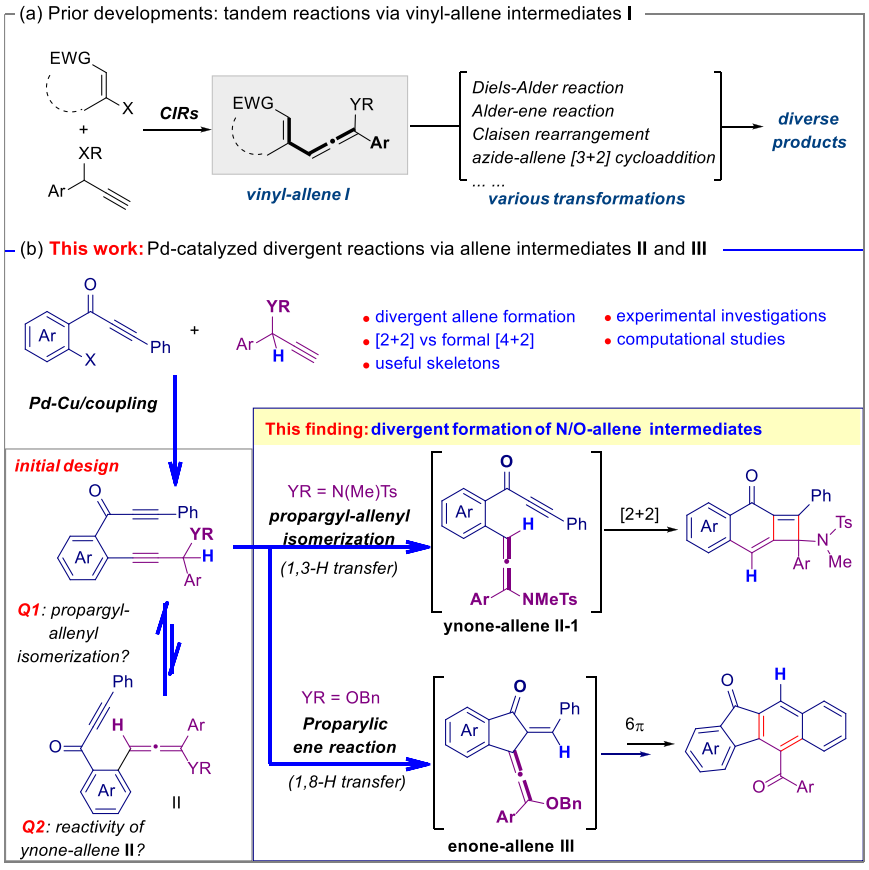
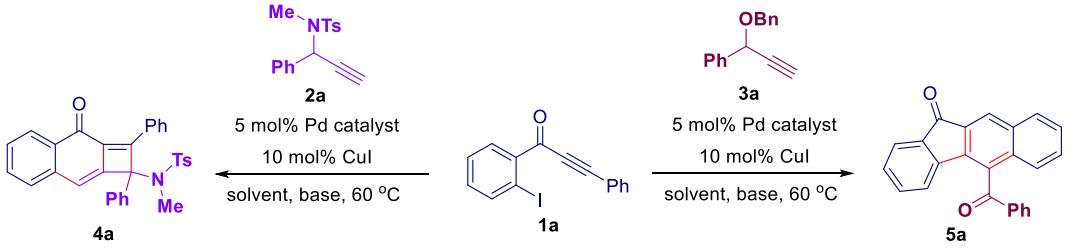


Table 1. Selected Results on Optimization for the Diverged Cyclization Reactions[a,j]



entry	1a/2a	catalyst	base	solvent	4a, yield (%)[b]	entry	1a/3a	catalyst	base	solvent	5a, yield (%)[b]
1	1/1.2	$Pd(PPh_3)_2Cl_2$	DIPA	toluene	40	15	1.2/1	$Pd(PPh_3)_2Cl_2$	DIPA	toluene	50
2	1/1.2	$Pd_2(dba)_3$	DIPA	toluene	39	16	1.2/1	$Pd_2(dba)_3$	DIPA	toluene	45
3	1/1.2	$Pd(PPh_3)_4$	DIPA	toluene	58	17	1.2/1	$Pd(PPh_3)_4$	DIPA	toluene	60
4	1/1.2	$Pd(OAc)_2$	DIPA	toluene	35	18	1.2/1	$Pd(OAc)_2$	DIPA	toluene	48
5	1/1.2	$Pd(PPh_3)_4$	Et_3N	toluene	39	19	1.2/1	$Pd(PPh_3)_4$	Et_3N	toluene	20
6	1/1.2	$Pd(PPh_3)_4$	pyridine	toluene	0	20	1.2/1	$Pd(PPh_3)_4$	pyridine	toluene	0
7	1/1.2	$Pd(PPh_3)_4$	K_2CO_3[c]	toluene	0	21	1.2/1	$Pd(PPh_3)_4$	DIPA	THF	17
8	1.2/1	$Pd(PPh_3)_4$	DIPA	toluene	50	22	1.2/1	$Pd(PPh_3)_4$	DIPA	MeCN	37
9	1.5/1	$Pd(PPh_3)_4$	DIPA	toluene	53	23	1.2/1	$Pd(PPh_3)_4$	DIPA	DMF	14
10	2/1	$Pd(PPh_3)_4$	DIPA[d]	toluene	60	24	1.2/1	$Pd(PPh_3)_4$	DIPA	DCM	28
11	**2/1**	**$Pd(PPh_3)_4$**	**DIPA**[e]	**toluene**	**71**	25	1/1	$Pd(PPh_3)_4$	DIPA	toluene	58
12	4/1	$Pd(PPh_3)_4$	DIPA	toluene	68	**26**	**1/1.2**	**$Pd(PPh_3)_4$**	**DIPA**	**toluene**	**73**
13	2/1	$Pd(PPh_3)_4$	DIPA[f]	toluene	65	27	1/1.2	$Pd(PPh_3)_4$	DIPA	toluene	68[h]
14	2/1	$Pd(PPh_3)_4$	DIPA[g]	toluene	67	28	1/1.2	$Pd(PPh_3)_4$	DIPA	toluene	70[i]

[a]Mixture of **1a** (0.25−0.5 mmol), **2a** or **3a** (0.25−0.30 mmol), the Pd catalyst (5% mol), CuI (10% mol), toluene (2 mL), and the base was charged to a Schlenk tube under N_2 and heated at 60 °C. [b]Isolated yield. [c]3 equiv of K_2CO_3 was used. [d]1.5 mL. [e]0.1 mL. [f]0.5 mL. [g]1 mL. [h]80 °C. [i]100 °C. [j]The boldface values for entries 11 and 26 highlight the best reaction conditions.

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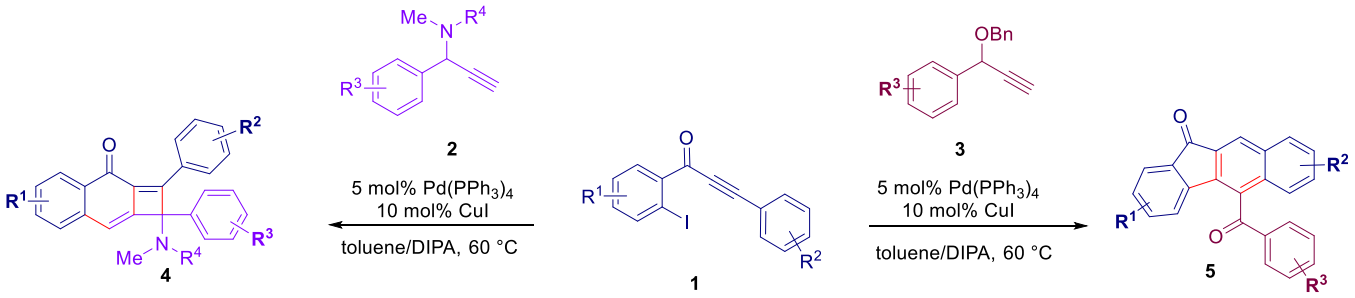
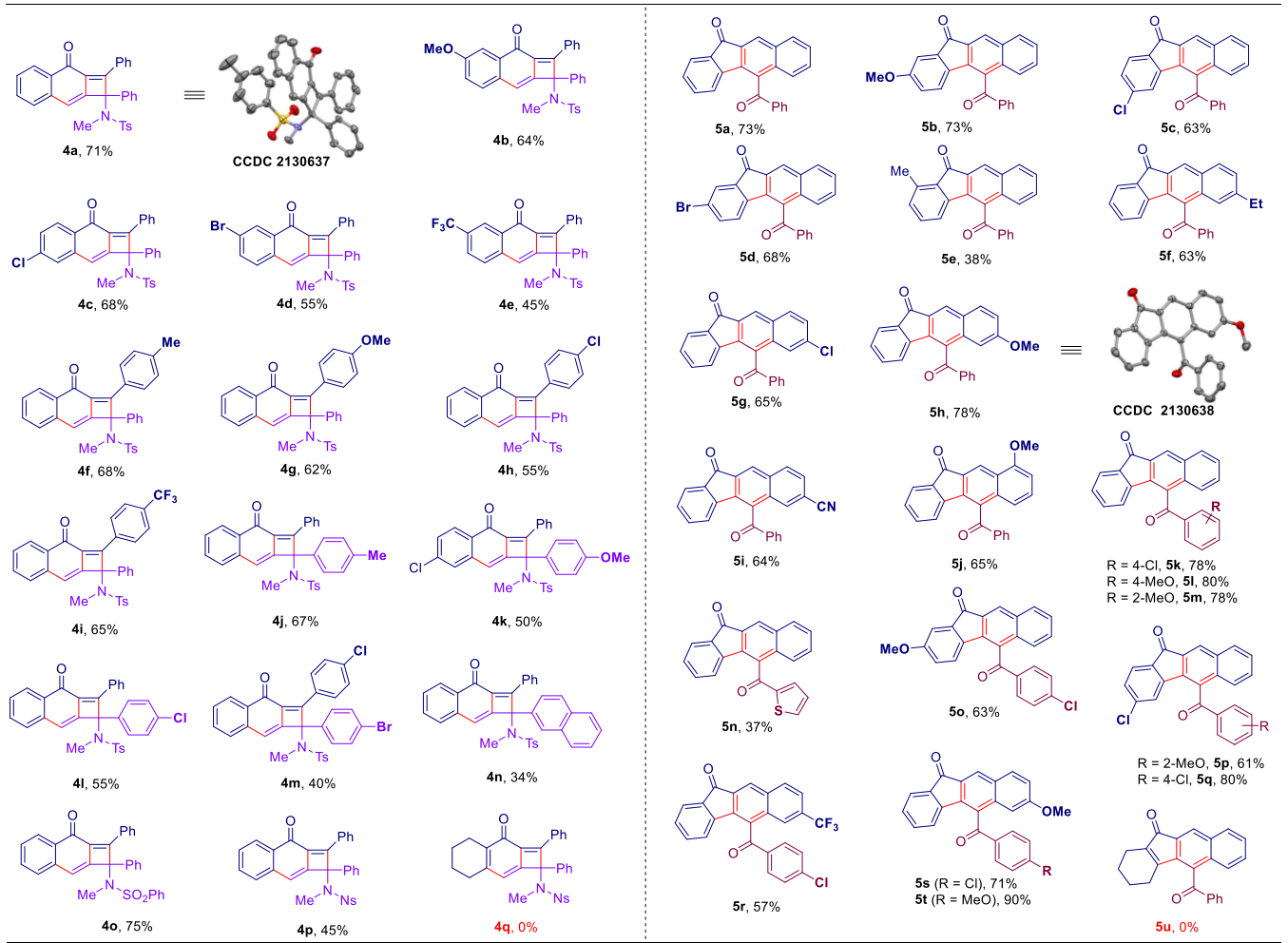
Table 2. Reaction Scope of the Coupling-Isomerization [2 + 2] Cycloaddition and Formal [4 + 2] Cycloaddition Sequence[a]





[a]Reactions were performed on a 0.25 mmol scale. Isolated yields are given. For experimental details, see the SI.

and Lewis acid or transition metal catalysis.[45−59] However, the reactivity on aryl-tethered ynone-allenes has been less explored, and their synthetic utilities remain to be exploited.[60]

During the course of this project, we discovered that the cross-coupling intermediates from *ortho*-iodophenyl-ynones and propargylic substrates undergo divergent isomerizations to generate two types of allene species, i.e., ynone-allene **II**−**1** via propargyl-allenyl isomerization (involving 1,3-hydrogen transfer) and enone-allene **III** via propargylic Alder ene-type[61−63] (involving 1,8-hydrogen transfer), depending on heteroatoms at the propargyl carbon (Scheme 1b). The two different types of allenic intermediates then fulfill formal [2 + 2] and [4 + 2] cycloadditions with high selectivity to provide polycyclic compounds of cyclobuta[*b*]naphthalen-3(1*H*)-one and 11H-benzo[*b*]fluoren-11-one backbones, respectively (this finding, Scheme 1b). Here, we report the details on the development of these types of palladium-catalyzed tandem reactions involving divergent formation of allene intermediates with consecutive cyclizations, as well as a combined experimental and theoretical study to illustrate the reaction mechanism and the origin of the observed selectivity.

RESULTS AND DISCUSSION

Reaction Discovery and Optimization. We initially explored the reactions of 1-(2-iodophenyl)-3-phenylprop-2-yn-1-one (**1a**), with propargyl tosylamide **2a** and propargyl benzyl ether **3a** under the palladium catalysis in the presence of an excessive base, which was expected to facilitate the cross-

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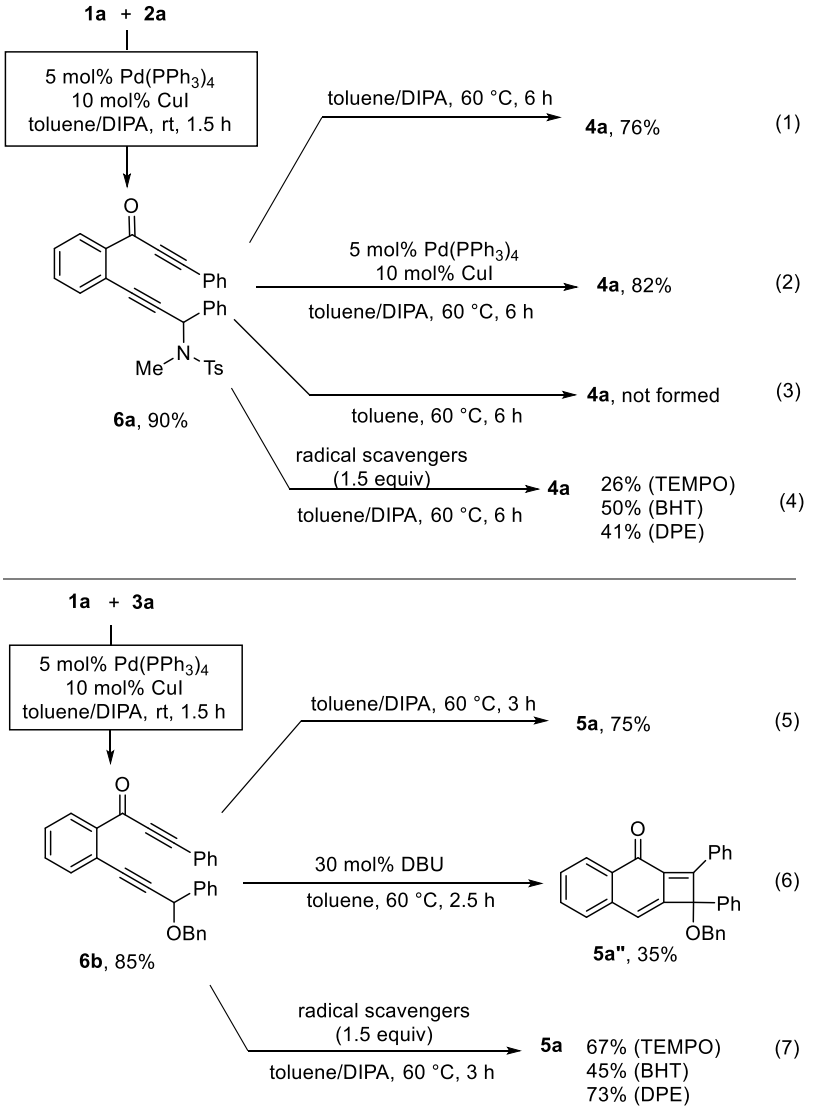
Scheme 2. Control Experiments



coupling reaction and promote the propargyl-allenyl isomerization. The preliminary experiments showed that **1a** coupled with **2a** in the presence of 5 mol % $Pd(PPh_3)_2Cl_2$, 10 mol % CuI and diisopropylamine (DIPA) to form the alkynylation intermediate, which was finally converted to a cyclobuta[*b*]-naphthalen-3(1*H*)-one product **4a** in 40% yield as the product (Table 1, entry 1). In contrast, the reaction of **1a** and **3a** under similar reaction conditions gave rise to a skeletally different product, i.e., 5-benzoyl-11H-benzo[*b*]fluoren-11-one (**5a**) in 50% yield (Table 1, entry 15). Encouraged by these intriguing results, we next performed a series of optimization experiments by varying reaction parameters including the palladium catalyst, base, solvent, reaction temperature, and molar ratios of the substrates to improve the product yields (for detailed results, see Tables S1 and S2 in the Supporting Information). It was found that the combination of a catalytic amount of $Pd(PPh_3)_4$ and CuI with an excess DIPA as the base in toluene was the best system for both reactions. The optimal conditions were obtained as follows: the reaction of **1a** and **2a** (2/1 molar ratio) with 5 mol % $Pd(PPh_3)_4$ and 10 mol % CuI in toluene/DIPA at 60 °C for 6 h gave **4a** in 71% yield (Table 1, entry 11); and the reaction of **1a** and **3a** (1/1.2 molar ratio) with 5 mol % $Pd(PPh_3)_4$ and 10 mol % CuI in toluene/DIPA at 60 °C for 3 h produced **5a** in 73% yield (Table 1, entry 26).

Reaction Scope. With the optimal conditions in hand, the scopes of the two reactions were investigated (Table 2). Thus, 1-(2-iodophenyl)-3-phenylprop-2-yn-1-ones bearing R^1 substituents as MeO, Cl, Br, and CF_3 were all competent substrates to yield the corresponding products (**4a**−**4i**). The incorporation of an electron-withdrawing group R^1 (CF_3) leads to a decreased product yield as indicated from the results of **4e**. In contrast, electronic nature of the R^2 group has little impact on the reaction, and the products **4f**−**4i** were all obtained in moderate to good yields (55−68%). Regarding propargyl tosylamides **2**, R^3 substituents including p-Me, p-MeO, p-Cl, and p-Br were tolerated to furnish products **4j**−**4m** in moderate to good yields. The reaction of a naphthanenyl-derived substrate was also applicable, albeit producing **4n** in a low yield. In addition, the performance of propargyl benzenesulfonamide and propargyl o-nitrobenzenesulfonamide were checked, and the reactions gave the products **4o** and **4p** in 75% and 45% yields, respectively. Noted that the reaction of 1-(2-iodocyclohex-1-en-1-yl)-3-phenylprop-2-yn-1-one failed

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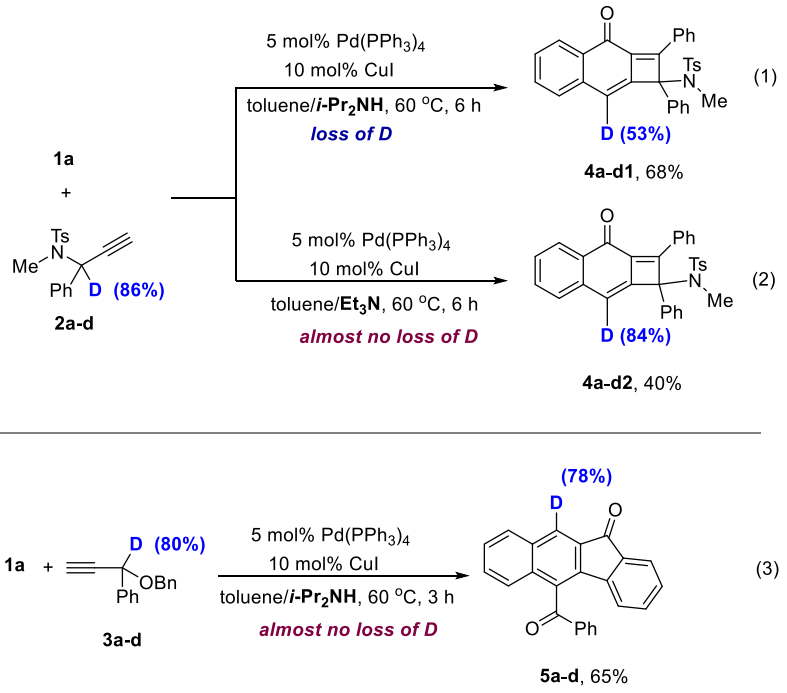
Scheme 3. Deuterium-Labeled Experiments



to generate the expected product **4q**. The structure of **4a** was further characterized by an X-ray diffraction study.

The reactions of various 1-(2-iodophenyl)-3-phenylprop-2-yn-1-ones **1** with propargylic benzyl ethers **2** were also evaluated (Table 2, right column). 1-(2-Iodophenyl)-3-phenylprop-2-yn-1-ones **1** bearing R^1 substituents as Me, MeO, Cl, and even the Br atom all reacted smoothly with **3a**, to afford the corresponding products **5a**−**5e** in 38−73% yields. Varied R^2 substituents like Et, Cl, MeO, CN, and CF_3 were allowed to give the expected products **5f**−**5j, 5r** in 57−78% yields. Several variants on R^3 like *p*-Cl, *p*-MeO, and *o*-MeO groups in propargyl benzyl ethers **3** were examined, and the reactions gave the expected products (**5k**−**5m**, **5o**−**5t**) in good to high yields. It is notable that the incorporation of the electron-donating *p*-MeO group as R^3 gave the products high yields (**5l** and **5t**). However, the reaction of a 2-thiophenyl substrate with **1a** gave the product **5n** in a low yield (37%). Similarly, 1-(2-iodocyclohex-1-en-1-yl)-3-phenylprop-2-yn-1-one was not a suitable substrate to give the desired product **5u**. The structure of **5h** was further determined by an X-ray single crystal diffraction analysis unambiguously.

Mechanism Study. The distinguished chemoselectivity of the above reactions clearly suggests remarkably different reactivities between the oxygen- and nitrogen-substituted alkyne-ynone intermediates engaged in the reactions. Thus, a series of control experiments were conducted to probe the reaction mechanism. As shown in Scheme 2, the Pd/Cu-catalyzed reaction of **1a** and **2a** performed at room temperature for 1.5 h afforded the cross-coupling product **6a** in 90% yield. Treatment of **6a** with DIPA in toluene for 6 h afforded **4a** in 76−82% yield, while the reaction in the absence of DIPA did not give **4a** (Scheme 2, eqs 1−3). In addition, it was observed that the presence of radical scavengers, i.e., 2,2,6,6-tetramethyl-1-piperidinyloxy, butylated hydroxytoluene, and 1,1-diphenylethene, led to a significant loss of product yield of **4a** (Scheme 2, eq 4).

On the other hand, the cross-coupling intermediate **6b** from **1a** and **3a** was also isolated. Heating of **6b** with toluene affords **5a** in 75% yield (Scheme 2, eq 4). We also checked the reactions in the presence of the stronger base, i.e., DBU. It was found that a catalytic amount of DBU promoted the transformation of **6b** into the cyclobuta[*b*]naphthalen-3(1H)-one **5a″** in 35% yield (Scheme 2, eq 6).[64] These results imply that the acidity of propargylic C−H in the alkyne-ynone intermediate (**6a**/**6b**) may play a critical role in the selectivity of the reaction. Moreover, it was found that the presence of radical scavengers did not shut down the transformation, suggesting that a free radical pathway is unlikely for the reaction (Scheme 2, eq 7). In addition, the detection of $PhCH_2OH$ by GC/MS analysis of the reaction mixture indicated the involvement of a hydrolysis step for the formation of the final product **5a**.

The labeling studies using deuterated substrates were performed to further gain insights into the mechanism (Scheme 3). The reaction of **1a** and **2a**−**d** gave **4a**−**d1** in 68% yield, in which only ca. 53% content of D was observed at C(8) (Scheme 3, eq 1). The significant loss of D content supports the notion that H/D exchange takes place in the DIPA-assisted propargyl-allenyl isomerization step (Scheme 5, vide infra). Conducting the reaction using the aprotonic Et_3N as the base afforded **4a**−**d2** in which 84% D was incorporated, further supporting this assumption (Scheme 3, eq 2). On the other hand, the reaction of **1a** and **3a**−**d** under the optimal conditions produced **5a**−**d** in 65% yield. ^{1}H NMR analysis of this product showed that about 78% content of the D atom was incorporated into the C(10) position, almost consistent with the D content of **3a**−**d** at the propargylic carbon (Scheme 3, eq 3). This result led us to postulate that a direct 1,8-H transfer of the cross-coupling intermediate **6b** might take place during the reaction to form a different allenic intermediate (like species **15-Z** in Scheme 5, vide infra) to fulfill the sequence.

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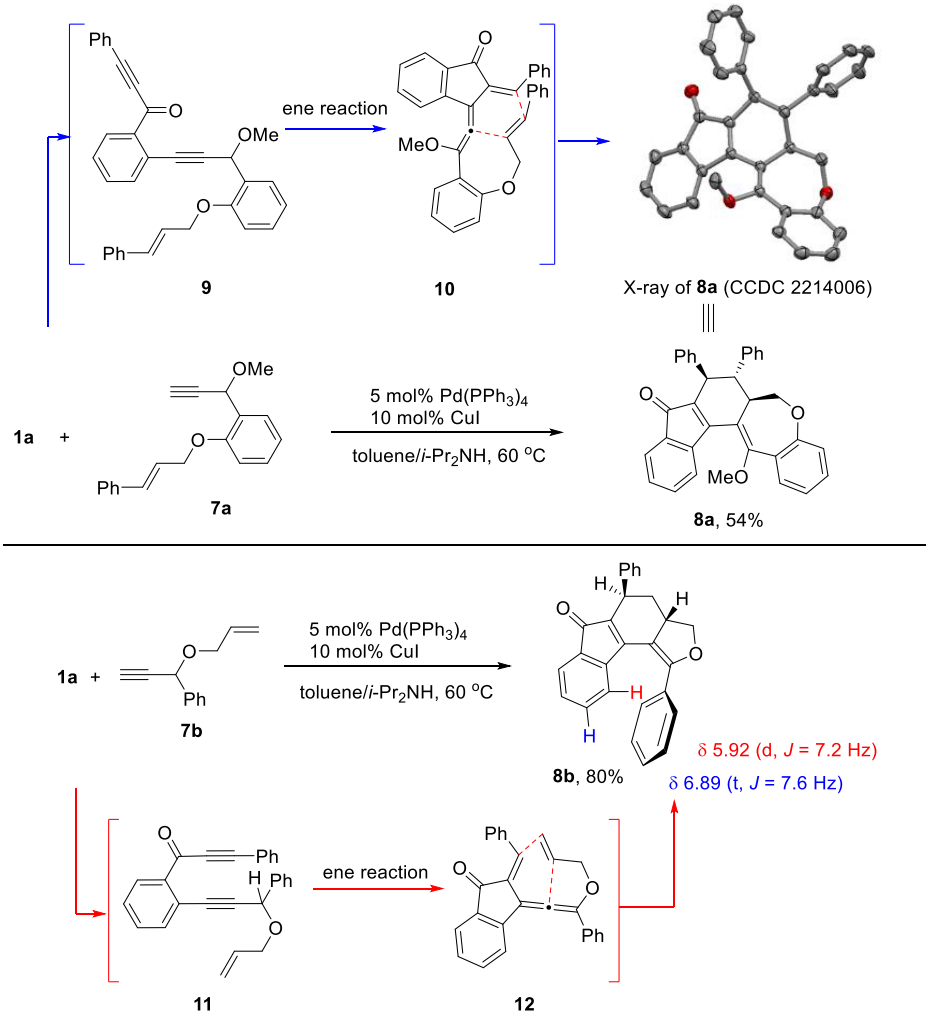
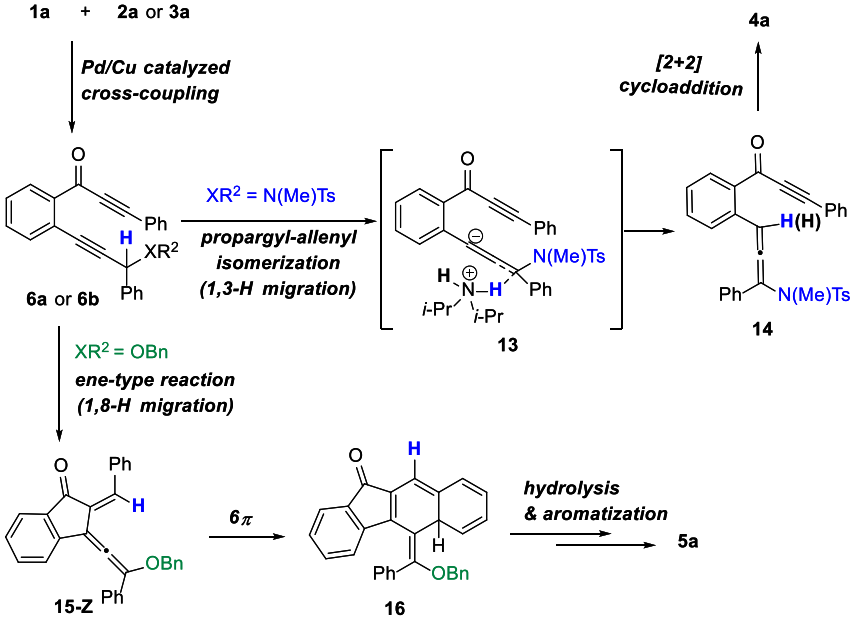
Scheme 4. Intramolecular Trapping of the Enone-Allene Intermediate



Scheme 5. Proposed Mechanisms for the Reactions



To verify the above hypothesis, we performed the reactions of **1a** with allyl-substituted propargyl ethers **7a** and **7b** to capture the possible intermediates. Gratifyingly, both reactions proceeded smoothly under the optimal conditions and gave

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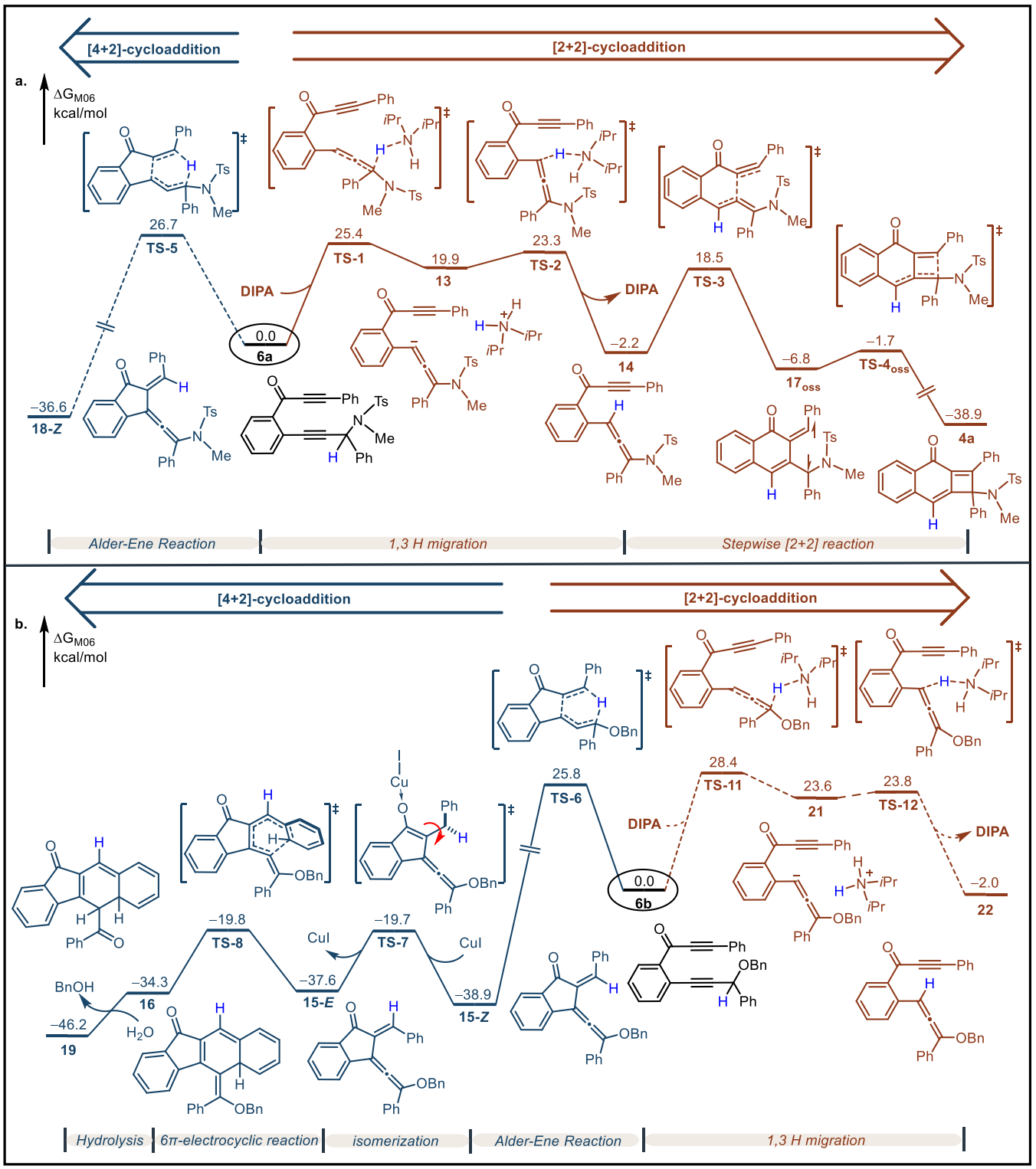

Figure 1. (a) Free energy profile for the formal [2 + 2] or [4 + 2] cycloaddition of 1,6-diynes **6a** with **DIPA**. The energy values are in kcal mol^{-1} and represent the relative free energies calculated at the M06/6-311+G(d,p)-SDD/SMD(toluene)//M06/6-31G(d)-SDD/SMD(toluene) level of theory in toluene solvent. (b) Free energy profile for the formal [2 + 2] or [4 + 2] cycloaddition of 1,6-diynes **6b** with **DIPA**. The energy values are in kcal mol^{-1} and represent the relative free energies calculated at the M06/6-311+G(d,p)-SDD/SMD(toluene)//M06/6-31G(d)-SDD/SMD(toluene) level of theory in toluene solvent.

rise to the fused pentacyclic and tetracyclic products **8a** and **8b** with excellent diastereoselectivity in 54 and 80% yield, respectively (Scheme 4). The structure of **8a** was unambiguously confirmed by an X-ray diffraction study. The product **8b** was fully characterized by NMR spectra including COSY, NOESY, HSQC, and HMBC. It was interestingly observed that $H_{(Ph)}$ atoms of the indanone moiety in compound **8b** show NMR signals at a relatively high field probably because of the shielding effect of the remote phenyl ring incorporated at the 2,3-dihydrofuran moiety. The formation of these products

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thus can be rationalized by a process of intramolecular Diels–Alder reaction of the enone-allene intermediate **10**/**12**, generated from a propargylic Alder-ene-type reaction of **9**/**11**.

At this stage, the plausible mechanism of the reaction was proposed (Scheme 5). The Pd/Cu-catalyzed Sonogashira coupling reaction first generates the coupling intermediate. In the case of propargyl tosylamide **2a** as the coupling partner, the cross-coupling intermediate **6a** undergoes DIPA-assisted propargyl-allenyl isomerization to form an ynone-allene intermediate **14**. The isomerization should proceed through an ion-pair intermediacy **13**, as indicated by the deuterium-labeled experiments (Scheme 5, eqs 1 and 2). Subsequent intramolecular [2 + 2] cycloaddition of **14** furnishes the product **4a**. When propargyl benzyl ether **3a** was employed as the coupling partner, the resulted intermediate **6b** may undergo a propargylic Alder-ene-type reaction to give a cyclized enone-allene intermediate **15-Z**. This step may be influenced by the sterically hindering effect of a substitute *ortho* to the carbonyl group in substrate **1**, which is indicated by a low yield of **5e** (Table 2). Subsequent 6π-electrocyclization forms a fused tetracyclic intermediate **16**. Successive hydrolysis of the vinyl ether motif and aromatization finally form **5a**.

To validate the mechanism of the cycloaddition step to reveal the substituent-controlled chemoselectivity, we conducted density functional theory (DFT) calculations at the M06/6-311 + G(d,p)-SDD/SMD(toluene)//M06/6-31G(d)-SDD/SMD(toluene) level of theory. As shown in Figure 1, 1,6-diynes **6a** and **6b**, in situ generated from Sonogashira coupling, were chosen as the starting species in our theoretical study. In this type of diyne, the acidity of the propargylic hydrogen plays an important role in chemoselectivity. Either base-assisted 1,3-hydrogen transfer or Alder-ene-type hydrogen transfer could occur to achieve different transformations, which would depend on the neighboring substituent group. As shown in Figure 1a, **6a** was chosen as relative zero in calculated free energy profiles. The [2 + 2] cycloaddition could start from a DIPA-assisted intramolecular 1,3-hydrogen transfer. The DIPA-promoted deprotonation of **6a** at the propargyl position could occur to generate an allenyl anion species **13** via transition state **TS-1**. The calculated activation free energy is 25.4 kcal/mol for this process, which would be the rate-determining step. Subsequent re-protonation of the allenyl carbon in **13** could achieve 1,3-hydrogen transfer to generate the ynone-allene intermediate **14**. The following [2 + 2] cycloaddition could take place through a stepwise pathway.[65] The formation of the first C–C bond could occur to generate the diradical intermediate **17** via a close-shell transition state **TS-3** with a free energy barrier of 20.7 kcal/mol. The radical–radical coupling takes place via an open-shell singlet transition state **TS-4** to yield the product **4a** in a highly exergonic step. The competitive intramolecular Alder-ene-type pathway was also considered. As shown in Figure 1a (left part), the Alder-ene-type hydrogen transfer would occur via transition state **TS-5** with a free energy barrier of 26.7 kcal/mol to provide the enone-allene intermediate **18-Z** for further transformations. The calculated activation free energy of this step is 1.3 kcal/mol higher than that of DIPA-assisted 1,3-hydrogen transfer. Therefore, a stepwise process of 1,3-hydrogen transfer followed by [2 + 2] cycloaddition is preferred. On the other hand, DFT calculation revealed that the deprotonation of 1,6-diyne **6b** needs to traverse a free energy barrier of 28.4 kcal/mol via proton transfer transition state **TS-11** (Figure 1b). The free energy barrier of this step is 3.0 kcal/mol higher than the corresponding step using propargyl sulfonamido substituted 1,6-diyne **6a**. It means the deprotonation of **6b** is difficult compared with **6a**. Based on this observation, we considered the alternative intramolecular Alder-ene-type reaction of **6b**. DFT calculation clearly revealed that the free energy barrier of Alder-ene-type reaction via transition state **TS-6** is 25.8 kcal/mol, which is 2.6 kcal/mol lower than that of deprotonation via transition state **TS-11**. Therefore, Alder-ene-type reaction would take precedence over deprotonation, which leads to different chemoselectivity. The Alder-ene reaction gives an enone-allene intermediate **15-Z** with exergonic energy of 38.9 kcal/mol leading to an irreversible process. Subsequently, the copper-promoted *cis-trans* isomerization occurs, eventually resulting in the generation of **15-*E***. This isomerization process is endothermic by 1.3 kcal mol^{-1}, with an overall activation free energy of 19.2 kcal mol^{-1}. The subsequent pericyclic 6π-electrocyclic reaction takes place via transition state **TS-8**, which reversibly provides a dearomatized benzofluorenone intermediate **16**. Then, hydrolysis of vinyl ether moiety results in a ketone intermediate **19**, which could undergo a dehydrogenation to achieve aromatization and yield the product **5a** (see Figure S6 in the Supporting Information). DFT calculation clearly revealed that the chemoselectivity is determined by the acidity of propargyl hydrogen in the 1,6-diyne molecule. We calculated the acidity of intermediate **6a** and **6b** using B3LYP/6-311++G(2df,2p)/IEFPCM(DMSO)//B3LYP/6-31G(d) level of theory.[66−70] We found that the pKa of **6a** is 9.8, which is 0.9 lower than that of **6b**, which could be attributed to the substituent effect. Therefore, **5a** would be the major product when **6b** is used as the reactant. Our DFT calculations are in complete agreement with experimental observation.

CONCLUSIONS

In conclusion, we have reported two sets of palladium-catalyzed tandem reactions involving cross-coupling, allene formation, and formal [2 + 2] or [4 + 2] cycloaddition, thereby providing a rapid synthesis of polycyclic compounds bearing cyclobuta[*b*]naphthalen-3(1H)-one and 5-benzoyl-11H-benzo[*b*]fluoren-11-one skeletons. The method has advantages such as the use of readily available starting materials, operational simplicity, catalytic conditions, and high selectivity. Mechanism studies indicated that the reactions involved the generation of two different types of allenic intermediates, i.e., ynone-allenes via propargyl-allenyl isomerization (1,3-hydrogen transfer) and enone-allenes via the propargylic ene-type reaction (1,8-hydrogen transfer), from the corresponding cross-coupling intermediates. Detailed computational calculations were performed to elucidate the reaction mechanism and provide insights on the origin of the selectivity of the reactions. Ongoing efforts are currently directed to further expanding the scope and applications of the methodology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c00857.

Detailed experimental procedures, compound characterization data, X-ray data, computational details, and copies of NMR spectra for new compounds (PDF)

Crystallographic data for **4a** (cif)

Crystallographic data for **5a** (cif)

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Crystallographic data for **8a** (cif)

AUTHOR INFORMATION

Corresponding Authors

Shugao Zhu − *School of Chemistry and Chemical Engineering, Nanchang University, Nanchang 330031, China;* orcid.org/0000-0001-8814-4161; Email: shugaozhu@ncu.edu.cn

Yu Lan − *School of Chemistry and Chemical Engineering, Chongqing Key Laboratory of Theoretical and Computational Chemistry, Chongqing University, Chongqing 400030, China; College of Chemistry and Institute of Green Catalysis, Zhengzhou University, Zhengzhou 450001, China;* orcid.org/0000-0002-2328-0020; Email: lanyu@cqu.edu.cn

Ruwei Shen − *State Key Laboratory of Materials-Oriented Chemical Engineering, College of Chemical Engineering, Nanjing Tech University, Nanjing 211800, China;* orcid.org/0000-0002-8834-3256; Email: shenrw@njtech.edu.cn

Authors

Dan Wang − *School of Chemistry and Chemical Engineering, Nanchang University, Nanchang 330031, China*

Shihan Liu − *School of Chemistry and Chemical Engineering, Chongqing Key Laboratory of Theoretical and Computational Chemistry, Chongqing University, Chongqing 400030, China*

Yufeng Ma − *School of Chemistry and Chemical Engineering, Nanchang University, Nanchang 330031, China*

Hong Wang − *School of Chemistry and Chemical Engineering, Nanchang University, Nanchang 330031, China*

Ruopeng Bai − *School of Chemistry and Chemical Engineering, Chongqing Key Laboratory of Theoretical and Computational Chemistry, Chongqing University, Chongqing 400030, China;* orcid.org/0000-0002-1097-8526

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.3c00857

Author Contributions

⊥D.W., S.L., and Y.M. contributed equally to this work.

Author Contributions

S.Z. and R.S. contributed to the conception and design of the experiments. D.W., Y.M., and H.W. performed the experiments and analyzed the data. Y.L. and R.B. directed the calculation section, and S.L. completed the DFT calculation. S.Z. directed the whole project. The manuscript was written through the contributions of all authors.

Notes

The authors declare no competing financial interest.

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