CJC Chinese Journal of Chemistry 中国化学 · An International Journal

Concise Report

Cite this paper: *Chin. J. Chem.* **2026**, *44*, 840—848. **DOI: 10.1002/cjoc.70436**

6-Methoxypyridine-Benzoxazole Ligand-Directed Palladium-Catalyzed Hydroacetoxylative Cyclization of Alkyne-Tethered Cyclohexadienones

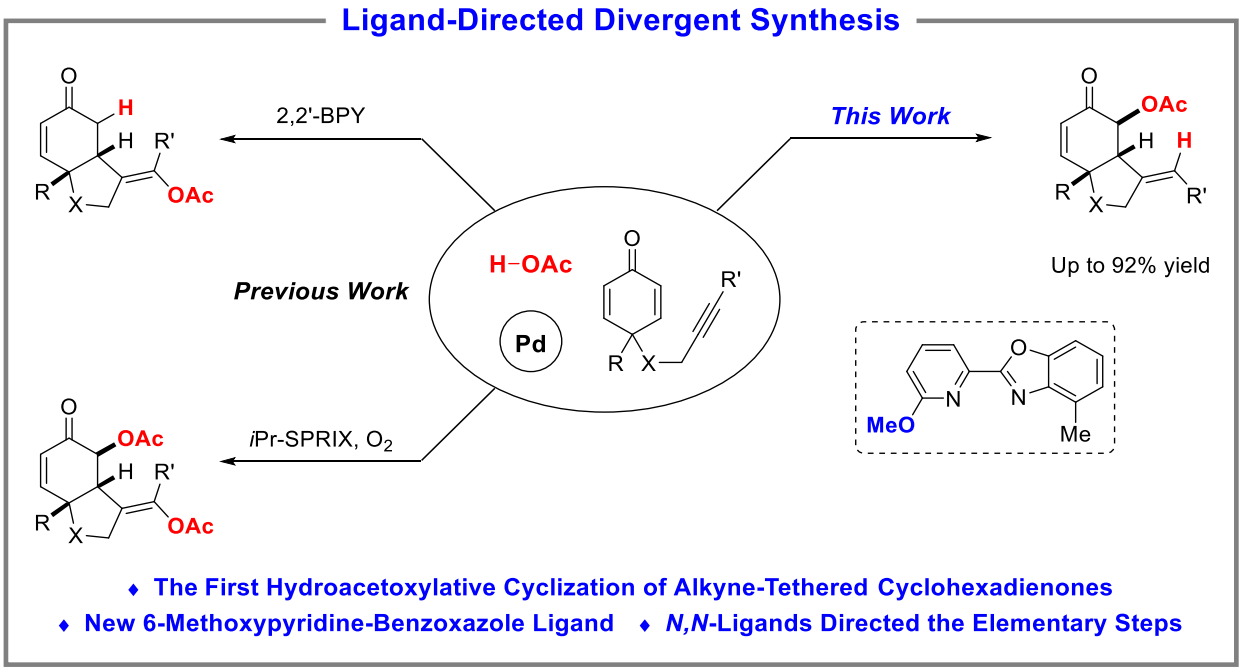
Yu-Qing Bai,[a,b] Li-Xia Liu,[a] Tong Niu,[a] Bo Wu,*[,a] Man Li,*[,c] Rong-Zhen Liao,[c] and Yong-Gui Zhou*[,a]

[a] *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, Liaoning 116023, China*
[b] *University of Chinese Academy of Sciences, Beijing 100049, China*
[c] *School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan, Hubei 430074, China*

Keywords

6-Methoxypyridine-benzoxazole ligand | Low σ-donor ability | Ligand-directed divergent synthesis | Hydroacetoxylative cyclization | *cis*-Hydrobenzofurans | Alkyne-tethered cyclohexadienones | Carboxylic acids | Palladium catalysis

Comprehensive Summary



Ligand-directed divergent synthesis (LDS) has emerged as a powerful chemical tool for the formation of miscellaneous molecular frameworks from common reactants. Consequently, the rational development of ligands is of great concern. Previously, *N*,*N*-ligands were shown to direct the reaction pathways of palladium(II)-catalyzed cascade cyclization of alkyne-tethered cyclohexadienones with acetic acid, thus forming two types of *cis*-hydrobenzofuran products. In this work, we have reported 6-methoxypyridine-benzoxazole ligand-directed palladium(0)-catalyzed hydroacetoxylative cyclization of alkyne-tethered cyclohexadienones with carboxylic acids, providing the structurally novel *cis*-hydrobenzofurans with high yields and broad substrate scope. In this process, carboxylic acids not only serve as hydrogen sources but also act as nucleophiles. Mechanistic investigations and DFT calculations revealed that this reaction was a palladium(0)-catalyzed hydroacetoxylative cyclization, the hydrogen source was from the proton of the carboxylic acid and the low σ-donor ability of 6-methoxypyridine-benzoxazole ligand proved to be crucial for palladium-catalyzed hydrogen transfer from carboxylic acids to alkynes and nucleophilic acetoxylation of the palladium enolate.

*E-mail: bowu@dicp.ac.cn; manlixl@hotmail.com; ygzhou@dicp.ac.cn

For submission: https://wiley.atyponrex.com/journal/CJOC
For published articles: https://onlinelibrary.wiley.com/journal/16147065

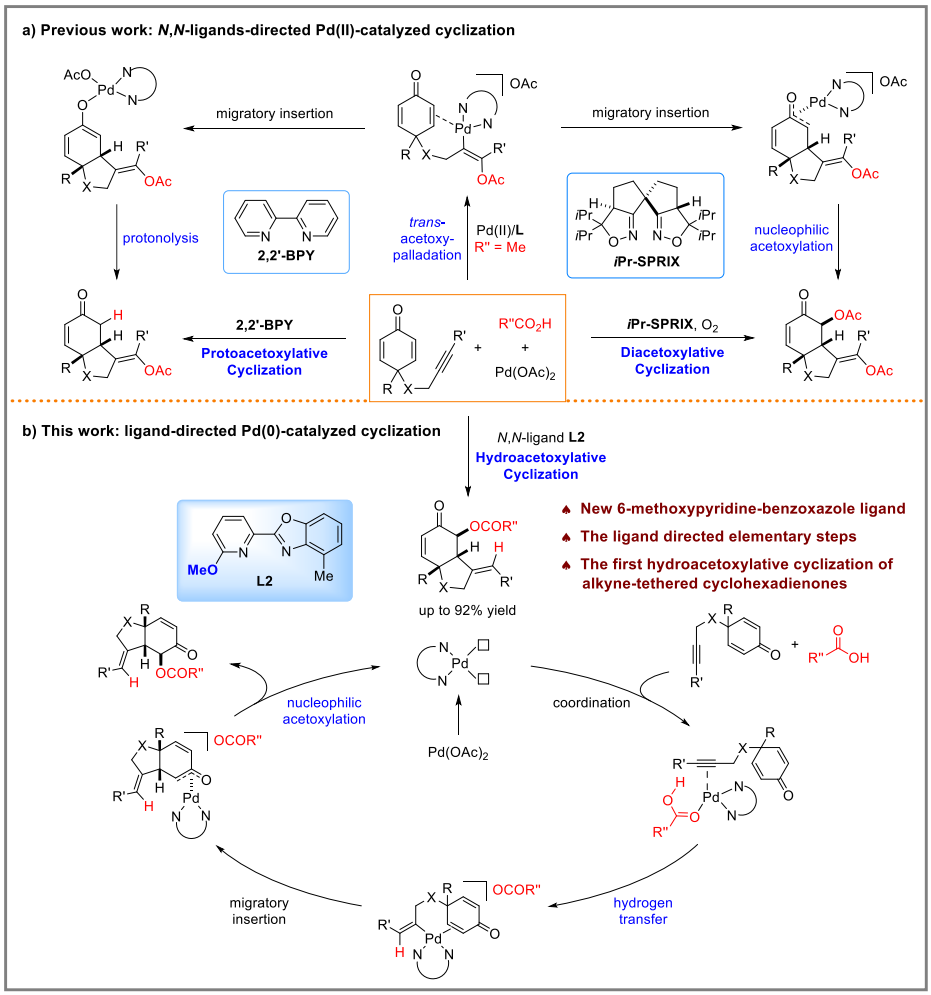
Background and Originality Content

Divergent synthesis has been an influential toolbox for the construction of molecular scaffolds with structural diversity and distinction, providing compound libraries with different biological activities.[1] As an effective and attractive branch of divergent synthesis, ligand-directed divergent synthesis (LDS) enables the efficient preparation of structurally diverse molecular scaffolds from the same starting materials by varying ligands around the common metal centers.[2] This strategy has the potential to widen the chemical space and to develop novel modes of metal catalysis. Thus, it has been highly sought after in the fields of methodology development and organic synthesis. Proverbially, ligands can modulate the steric and electronic properties of metal complexes and may create a vast difference in the mechanistic pathways of reactions, including regioselectivity, chemoselectivity, and product-selectivity.[2] Therefore, the design and synthesis of exquisite and competent ligands would be of significant importance for the development of original LDS applications.

cis-Hydrobenzofurans are broadly present in bioactive molecules, natural products, and pharmaceuticals.[3] Palladium-catalyzed cascade cyclization of alkyne-tethered cyclohexadienones with acetic acid represents one of the prominent approaches for the assembly of *cis*-hydrobenzofurans.[4] Noteworthily, guided by the nature of *N*,*N*-ligands within the palladium complexes, interesting divergent transformations of alkyne-tethered cyclohexadienones with acetic acid were realized, giving two types of *cis*-hydrobenzofuran products (Scheme 1a). The palladium catalyst with 2,2′-bipyridine ligand led to protoacetoxylative cyclization, including nucleophilic *trans*-acetoxypalladation of the alkyne under activating of the Pd(II) catalyst, subsequent migratory insertion of the intramolecular double bond and protonolysis of the resulting palladium enolate.[4a] In contrast, the palladium catalyst embellished with the low σ-donor ligand spiro-bis(isoxazoline) (SPRIX) preferred to undergo diacetoxylative cyclization involving an unusual nucleophilic attack on the palladium enolate as the termination step instead of protonolysis of the palladium enolate.[4c] Both of the pathways featured the identical nucleophilic acetoxypalladation of the alkyne as the initial step. In fact, carboxylic acids can not only act as nucleophiles[4-5] but also serve as hydrogen sources, and have been successfully introduced in transfer hydrogenation of alkenes[6] and hydrometallation of alkynes.[5i,7] In light of our interest in the palladium-catalyzed cascade cyclization, we previously disclosed palladium-catalyzed highly enantioselective protoacetoxylative cyclization of alkyne-tethered cyclohexadienones with carboxylic acids enabled by the newly synthesized planar-chiral oxazole-pyridine *N*,*N*-ligand.[4d] Considering the versatile properties of carboxylic acids, we envisaged the development of a novel pyridine-benzoxazole ligand to facilitate the unprecedented Pd(0)-catalyzed hydroacetoxylative cyclization of alkyne-tethered cyclohexadienones, initiated by Pd(0)-catalyzed hydrogen transfer from carboxylic acids to alkynes and terminated by nucleophilic attack on the palladium enolate (Scheme 1b).

For the proposed Pd(0)-catalyzed hydroacetoxylative cyclization of alkyne-tethered cyclohexadienones, the rational modification of pyridine-benzoxazole ligand should be indispensable to make the interaction between the ligand and the palladium center

Scheme 1 *N*,*N*-Ligands-directed divergent synthesis of *cis*-hydrobenzofurans *via* palladium-catalyzed cascade cyclization of alkyne-tethered cyclohexadienones with carboxylic acids



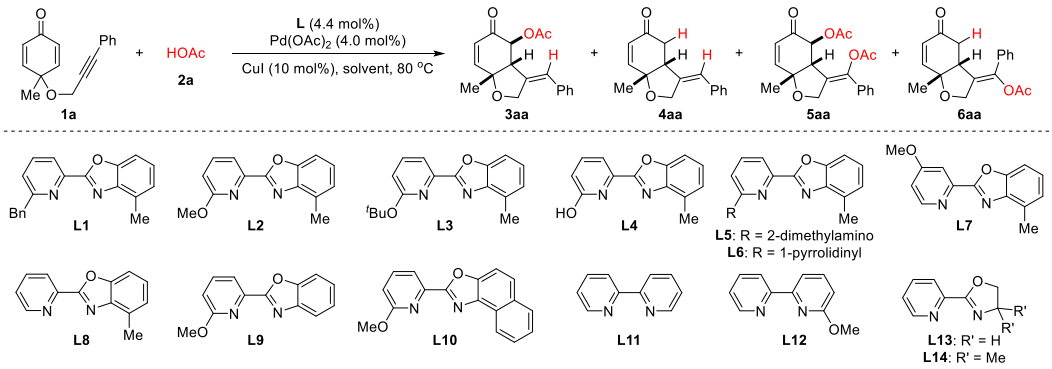
appropriate. As far as we know, Liu's group has demonstrated that the introduction of a sterically hindered substituent into the C6-position of the pyridine ring in pyridine-oxazoline (Pyox) *N*,*N*-ligand is able to weaken the ^{Py}N-Pd bond.[5e-h,8] Therefore, we envisioned decorating the relatively electron-poor pyridine-benzoxazole ligand with a suitable substituent at the C6-position of the pyridine moiety, which would promote the formation of the Pd(0)-alkyne-carboxylic acid complex for hydrogen transfer and the final nucleophilic acetoxylation *via* reducing the electronic density of the corresponding Pd center. Herein, we demonstrate 6-methoxypyridine-benzoxazole ligand-directed unprecedented palladium-catalyzed hydroacetoxylative cyclization of alkyne-tethered cyclohexadienones with carboxylic acids. Mechanistic investigations and DFT calculations provided detailed insights into the origin of fine-tuning in this Pd(0)-catalyzed hydroacetoxylative cyclization reaction pathway.

Results and Discussion

Following the above-mentioned strategy, we first sought to identify the optimal pyridine-benzoxazole ligand *via* the reaction of alkyne-tethered cyclohexadienone **1a** and acetic acid **2a** at 80 °C in toluene using $Pd(OAc)_2$ as the metal precursor and CuI as the additive. To our delight, **L1** with benzyl group at the C6-position of the pyridine moiety resulted in the hydroacetoxylative cyclization, giving the desired product **3aa** in 26% yield (Table 1, entry 1). The *α*-oxy benzofuranone in **3aa** represents a privileged structural motif present in natural products.[9] In accordance with our prediction, pyridine-benzoxazole ligand with a substituent at the C6-position of the pyridine moiety played a vital role in fine-tuning of the reaction pathway.

To further improve the yield, a series of 6-substituted pyridine-benzoxazole ligands were evaluated. 6-Methoxypyridine-benzoxazole ligand (**L2**) dramatically improved the yield of **3aa** to 78% (entry 2). When methoxy group at the C6-position of the pyridine ring was replaced by *tert*-butoxy group, comparable results were obtained (entry 3). As for **L4** bearing hydroxyl group, it caused erosion of the yield of **3aa**. Besides, both the reductive cyclization product **4aa** and the diacetoxylative cyclization product **5aa** increased slightly (entry 4). It was noteworthy that not only alkoxy groups but also amino groups exhibited good performances (entries 5–6). However, no desired product was detected as methoxy group was changed to the C4-position of the pyridine moiety (entry 7), and **L8** with unsubstituted pyridine gave product **3aa** in only 7% yield (entry 8). These results indicated that a substituent at the C6-position was essential for the hydroacetoxylative cyclization. With regard to substituents on the benzoxazole moiety, there was no significant effect on the yield (entries 9–10).

Table 1 Conditions optimization[a]



entry	L	solvent	Yield[b]/%			
			3aa	4aa	5aa	6aa
1	**L1**	Toluene	26	<5	<5	—
2	**L2**	Toluene	78	<5	<5	—
3	**L3**	Toluene	78	5	5	—
4	**L4**	Toluene	49	11	7	—
5	**L5**	Toluene	73	<5	<5	—
6	**L6**	Toluene	77	<5	<5	—
7	**L7**	Toluene	—	—	—	—
8	**L8**	Toluene	7	<5	<5	—
9	**L9**	Toluene	73	5	5	—
10	**L10**	Toluene	79	<5	5	—
11	**L11**	Toluene	—	7	—	53
12	**L12**	Toluene	7	7	—	5
13	**L13**	Toluene	—	<5	—	9
14	**L14**	Toluene	—	—	—	<5
15[c]	**L2**	Toluene	57	10	8	—
16	**L2**	EA	71	6	6	—
17	**L2**	DCE	48	<5	<5	—
18	**L2**	MTBE	64	8	7	—
19[d]	**L2**	Toluene	80 (80)[e]	5	5	—

[a] Reaction conditions: **1a** (0.10 mmol), acetic acid **2a** (0.10 mL, 1.7 mmol), $Pd(OAc)_2$ (4.0 mol%), **L** (4.4 mol%), CuI (10 mol%), solvent (0.90 mL), 80 °C, 1-21 h. [b] Yield was measured by analysis of ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as the internal standard. [c] without CuI. [d] The reaction was conducted on a 0.20 mmol scale. [e] Isolated yield.

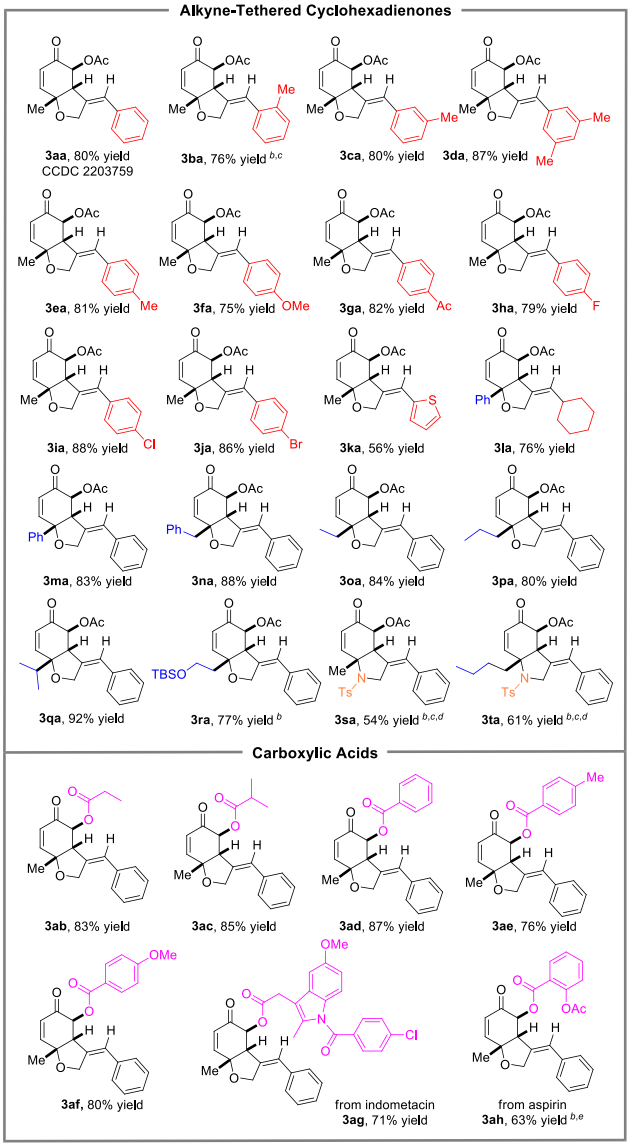
2,2′-Bipyridine ligand (**L11**) was ineffective in promoting the hydroacetoxylative cyclization, affording the protoacetoxylative cyclization product **6aa** as the major product instead (entry 11). While employing **L12** as the ligand enabled the hydroacetoxylative cyclization, the yield of **3aa** was only 7% (entry 12). Pyridine-oxazoline ligands were also not applicable (entries 13–14). Notably, the use of an additive CuI, which might activate the alkynyl and the carbonyl group, proved to be positive for the protocol (see Table S1 in the Supporting Information for screening of additives). In the absence of additive, the hydroacetoxylative cyclization showed the diminished selectivity, giving the desirable product **3aa** in 57% yield (entry 15). Eventually, the examination of solvents disclosed that toluene was obviously better than other solvents. Using ethyl acetate (EA) or methyl *tert*-butyl ether (MTBE) as the solvent, yields of side products **4aa** and **5aa** rose slightly (entries 16 and 18). After the careful optimization of reaction parameters, the reaction with $Pd(OAc)_2$ (4.0 mol%), **L2** (4.4 mol%), and CuI (10 mol%) in toluene at 80 °C furnished the best result, providing *cis*-hydrobenzofuran **3aa** in 80% isolated yield (entry 19).

With the establishment of the optimized conditions, we next explored the generality of the hydroacetoxylative cyclization with regard to alkyne-tethered cyclohexadieneones **1** using acetic acid **2a**. As summarized in Scheme 2, the methyl substituent at different positions of the phenyl ring on the alkyne moiety was well tolerated. However, alkyne-tethered cyclohexadienone **1b** bearing the *ortho*-methyl substituent showed no reactivity under the standard conditions. Delightedly, by changing the additive and increasing the catalyst loading, the desired product **3ba** was obtained in 76% yield. Satisfactory efficiencies were obtained when alkyne-tethered cyclohexadienones **1** containing various electron-donating or electron-withdrawing functional groups at the *para*-position of the phenyl ring were tested (**1f**–**1j**). Moreover, the reaction could be applicable for the substrate with 2-thienyl (**1k**) or cyclohexyl (**1l**) substituent at the terminal of the alkyne, albeit in moderate yield for product **3ka**. When 4-(but-2-yn-1-yloxy)-4-methylcyclohexa-2,5-dien-1-one with a methyl substituent at the terminal of the alkyne was employed as the substrate, the reaction was disordered and no target product was detected. This Pd-catalyzed hydroacetoxylative cyclization also exhibited remarkable compatibility with a wide range of substituents on the prochiral quaternary carbon center of alkyne-tethered cyclohexadienones, including phenyl (**1m**), benzyl (**1n**), ethyl (**1o**), *n*-propyl (**1p**), *iso*-propyl (**1q**) and an alkyl chain with TBSO group (**1r**). Significantly, the reaction could be extended to substrates **1s** and **1t** with a NTs linkage, delivering the corresponding products **3sa** and **3ta** in 54% and 61% yields, respectively. The relative configuration of **3aa** was assigned by X-ray diffraction analysis (see the Supporting Information for details).[10]

Encouraged by the broad substrate scope and promising functional group compatibility of this strategy, we further examined the reaction of alkyne-tethered cyclohexadienone **1a** with other carboxylic acids. It was found that a variety of aliphatic and aromatic carboxylic acids proved to be feasible, and the desired products were afforded in modest to excellent yields even at a lower loading of carboxylic acids. Additionally, carboxylic acids derived from pharmaceuticals such as indometacin and aspirin underwent the hydroacetoxylative cyclization with **1a** smoothly, furnishing the target products **3ag** and **3ah** in 71% and 63% yields, respectively.

To demonstrate the robustness of this synthetic methodology, the hydroacetoxylative cyclization of **1a** with acetic acid **2a** was conducted on a gram-scale under the standard conditions, giving **3aa** in 82% yield comparable to that of the 0.2 mmol scale (Scheme 3a). Subsequently, we investigated the potential utility of *cis*-hydrobenzofurans **3aa** and **3ra**. The hydrolysis of the acetate of **3aa** promoted by potassium carbonate in a mixture of tetrahydrofuran and water produced alcohol **6** in 78% yield. The treatment of alcohol **6** with methanesulfonic anhydride and then

Scheme 2 Substrate scope: alkyne-tethered cyclohexadienones **1** and carboxylic acids **2**

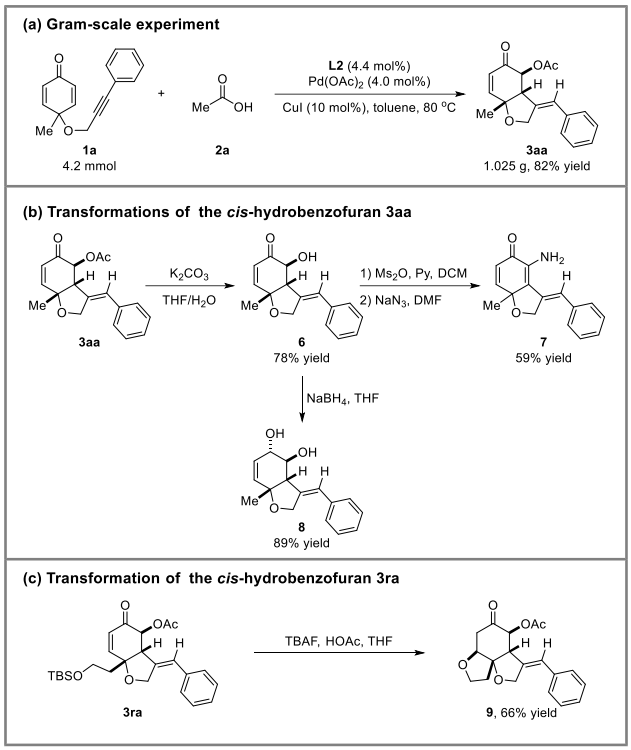


[a] Reaction conditions for *cis*-hydrobenzofurans **3aa**–**3ta**: **1** (0.20 mmol), **2a** (0.20 mL, 3.4 mmol), $Pd(OAc)_2$ (4.0 mol%), **L2** (4.4 mol%), CuI (10 mol%), toluene (1.8 mL), 80 °C, 1–96 h; reaction conditions for *cis*-hydrobenzofurans **3ab**–**3ah**: **1a** (0.20 mmol), **2** (2.0 mmol), $Pd(OAc)_2$ (4.0 mol%), **L2** (4.4 mol%), CuI (10 mol%), toluene (2.0 mL), 80 °C, 1–6 h; all products **3** were obtained in >20 : 1 dr. [b] $Pd(OAc)_2$ (8.0 mol%), **L2** (8.8 mol%). [c] NIS (10 mol%). [d] 100 °C. [e] Aspirin (1.0 mmol).

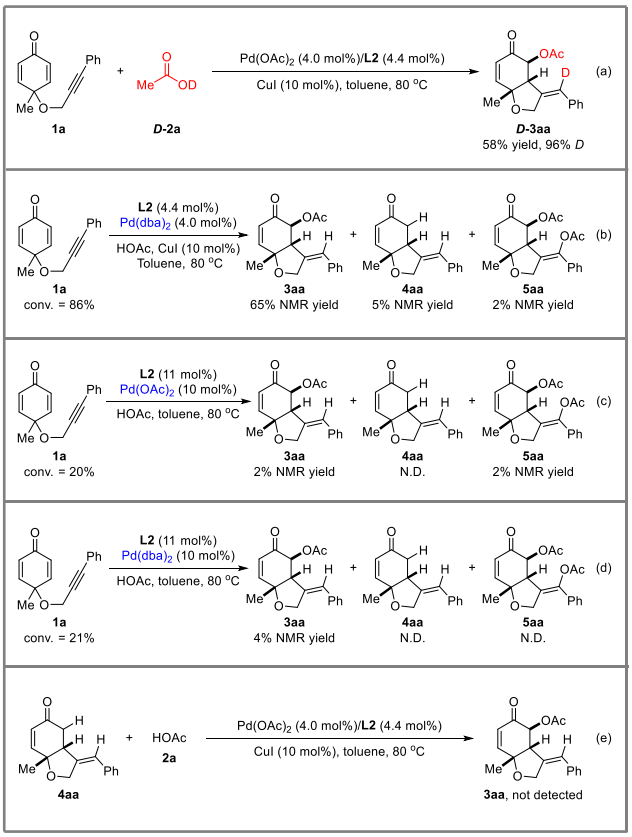
sodium azide accidentally provided enaminone **7** in 59% yield. Diol **8** was obtained in excellent yield *via* 1,2-reduction of the *α*,*β*-unsaturated carbonyl group (Scheme 3b). Finally, the deprotection of the silyl group of **3ra** with tetrabutylammonium fluoride (TBAF) under the acidic conditions followed by an intramolecular *oxa*-Michael addition reaction generated the tricyclic product **9** in 66% yield (Scheme 3c).

To shed light on the detailed mechanism, we designed several experiments, as shown in Scheme 4. First, a deuterium labeling experiment was performed with 100 equivalent of *D*-acetic acid, and product *D*-**3aa** was acquired with 96% *D* incorporation, which implied that the hydrogen source was from the proton of acetic acid (Scheme 4a). Using $Pd(dba)_2$ as the metal precursor under the standard reaction conditions, product **3aa** was generated in 65% NMR yield, demonstrating that this reaction was a Pd(0)-catalyzed hydroacetoxylative cyclization (Scheme 4b). In addition, a small

Scheme 3 Experiment at gram-scale and synthetic transformations



Scheme 4 Experiment evidence of the mechanism



amount of the reductive cyclization product **4aa** and the diacetoxylative cyclization product **5aa** could be monitored by thin layer chromatography and ^{1}H NMR analysis, suggesting Pd(0)-Pd(II) reductive cyclization and Pd(II)-Pd(0) diacetoxylative cyclization promoted each other. To further verify the generation of the active Pd(0) species from the Pd(II) catalyst *via* Pd(II)-Pd(0) diacetoxylative cyclization, the experiments utilizing $Pd(OAc)_2$ and $Pd(dba)_2$ as metal precursors were carried out at low conversion, respectively. When $Pd(OAc)_2$ was used as the metal precursor, cyclization products **3aa** and **5aa** could be detected at 20% conversion of **1a** (Scheme 4c). For $Pd(dba)_2$, only product **3aa** was produced, and no diacetoxylative cyclization product **5aa** was detected at nearly the same conversion (Scheme 4d). Both outcomes evidently identified that the active Pd(0) species was formed by the initial Pd(II)-Pd(0) diacetoxylative cyclization. Moreover, the reaction of **4aa** under the standard conditions failed to give product **3aa**, indicating that **4aa** was not an intermediate in the reaction (Scheme 4e).

Density functional theory (DFT) calculations were performed to elucidate the reaction mechanism and origin of fine-tuning in this Pd(0)-catalyzed hydroacetoxylative cyclization. The reaction of alkyne-tethered cyclohexadienone **1a** and acetic acid **2a** catalyzed by $Pd(OAc)_2$/**L2** in the absence of CuI (Table 1, entry 15) was chosen as the model system for this mechanistic investigation (computational details were given in the Supporting Information). The calculated energy profile and key optimized transition state structures were shown in Figure 1 while alternative reaction pathways were provided in the Supporting Information.

As illustrated in Figure 1, the reaction initiates from the Pd(0) species **Int0**, with substrate **1a** coordinating to the palladium center through its alkenyl and alkynyl groups in a bidentate fashion while the pyridine moiety of **L2** remains dissociated. This structural feature aligns with the expectation that the sterically hindered methoxy group weakens the ^{Py}N-Pd bond, decreasing the electronic density of the Pd(0) center. This electron deficiency strengthens the interaction between **1a** and the Pd(0) center, promoting subsequent transformations. Dissociation of **1a** from **Int0** results in a sharp free energy increase of 43.8 kcal/mol (**Int0-1**, Figure S4). The coordination of one toluene molecule to the Pd(0) center lowers the energy to 25.5 kcal/mol, as in intermediate **Int0-1A** (Figure 1a). The addition of a second toluene (**Int0-1B**, Figure S4) raises the energy slightly, by 0.8 kcal/mol relative to **Int0-1A**. These results underscore the highly favorable coordination between **1a** and the Pd(0) center.

From **Int0**, the reaction proceeds with a ligand exchange event, wherein the alkenyl group in **Int0** is replaced by acetic acid **2a**, yielding **Int1**, the precursor for hydrogen transfer. This transformation (**Int0**→**Int1**) is endergonic by 10.6 kcal/mol. Next, ligand-to-ligand hydrogen transfer (LLHT) occurs *via* **TS1** (Figure 1b), transferring a hydrogen atom from the ligated acetic acid to the alkynyl group, furnishing the vinyl palladium species **Int2** (1.1 kcal/mol). This LLHT step was calculated to have an overall energy barrier of 22.2 kcal/mol. Alternative mechanisms involving oxidative addition of **2a** to the Pd(0) center were considered but found to be disfavored due to the higher energy barriers (see Figure S4).

At **Int2**, a structural reorganization enables the alkenyl group to coordinate to the Pd(II) center while the ligated acetate is stabilized by an additional acetic acid molecule *via* hydrogen bond, generating **Int3** (2.4 kcal/mol). **Int3** then undergoes migratory insertion *via* **TS2** with a relatively low total barrier of 8.7 kcal/mol, indicating a facile transformation. Computations reveal that migratory insertion encounters the higher energy barrier without the second acetic acid molecule (see Figure S5), highlighting its crucial stabilizing role. An alternative migratory insertion pathway, in which ligand **L2** remains bidentate, is found to be significantly less favourable, as the corresponding transition state **TS2A** is 13.1 kcal/mol higher in energy than **TS2**. This emphasizes the crucial role of the MeO-substituted ligand (**L2**), whose weak σ-donor ability allows for the necessary ligand dissociation during the transformation. Following **TS2**, **Int4** is delivered, with the transition from **Int3** to **Int4** being exergonic by 20.7 kcal/mol.

Nucleophilic acetoxylation of **Int4** *via* **TS3** requires overcoming a total barrier of 28.6 kcal/mol, and the coordination of the pyridine moiety to the Pd(II) center further increases the barrier to

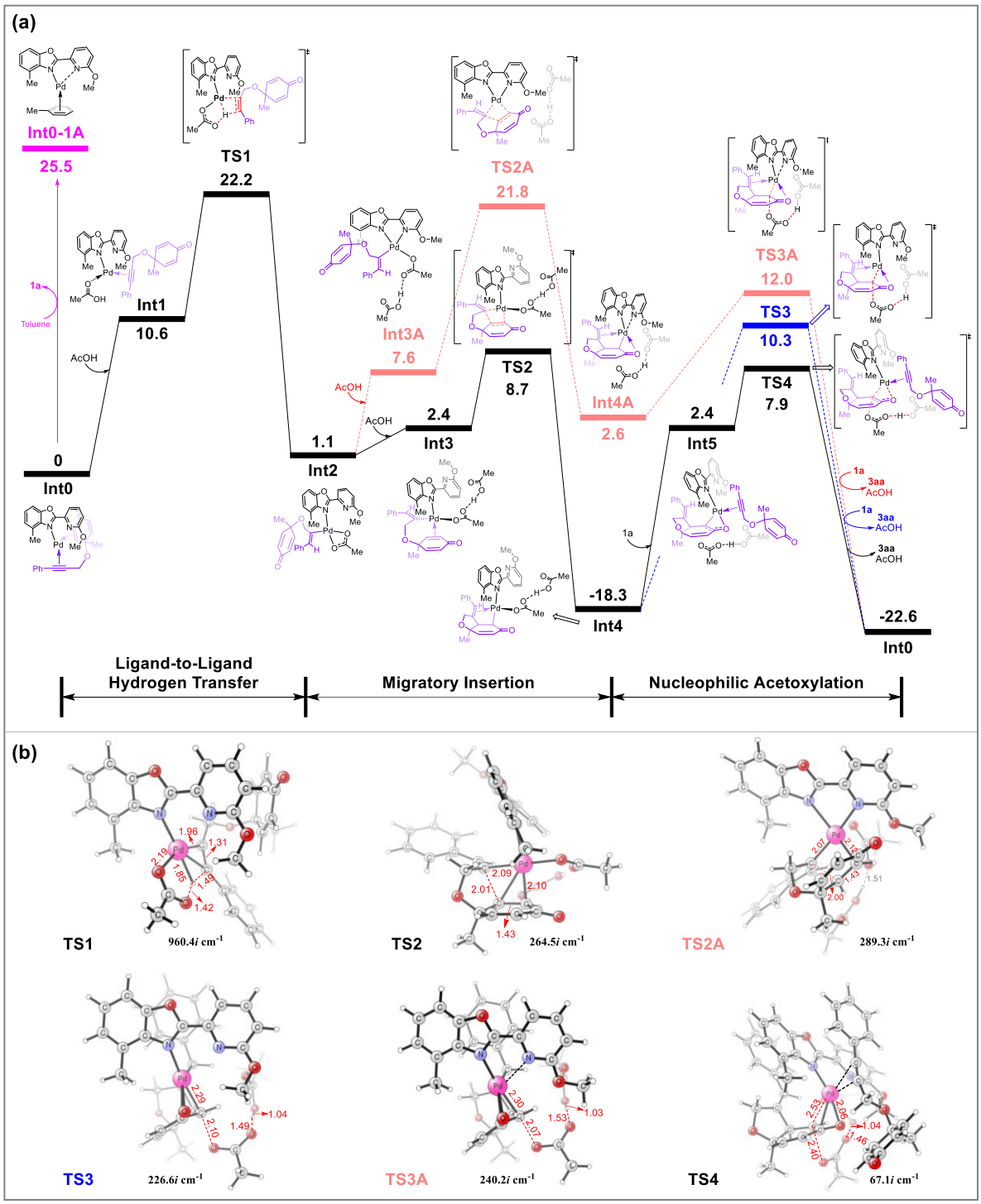


Figure 1 (a) Calculated free energy profile (kcal/mol) for the Pd(0)-catalyzed hydroacetoxylative cyclization of **1a** at the theoretical level of (SMD-toluene)-B3LYP-D3(BJ)/def2-TZVPP//B3LYP-D3(BJ)/6-31g(d,p)-SDD(Pd). (b) Selected optimized transition state structures were shown; the imaginary frequencies were indicated as well. Distances were given in Ångström.

30.3 kcal/mol (**TS3A**). However, the coordination of another **1a** to the Pd(II) center lowers the total barrier to 26.2 kcal/mol (**TS4**), likely due to the stabilization of the electron-deficient Pd center through the interaction with the alkynyl group of the second **1a** molecule. Downhill from **TS4**, product **3aa** is released, and **Int0** is regenerated for the next catalytic cycle. The overall reaction is calculated to be exergonic by 22.6 kcal/mol, confirming its thermodynamic feasibility.

As shown in Figure 1b, the transition state **TS4** adopts an *anti*-displacement mode, with the acetate group positioned *trans* to the vinyl group. A *syn* displacement pathway was investigated but found to have a significantly higher energy barrier than **TS4** (see Figure S6), demonstrating that nucleophilic acetoxylation is stereospecific. This result is consistent with experimental observations, which show the exclusive formation of the *trans* product **3aa**. Protonolysis as an alternative termination step was also considered. Computational results suggest that protonolysis has a barrier of about 11.6 kcal/mol (see Figure S6), corresponding to the energy difference between **Int4** and **Int4C**. However, the formation of the protonolysis product is endergonic by 2.4 kcal/mol and less thermodynamically favourable than the nucleophilic acetoxylation pathway.

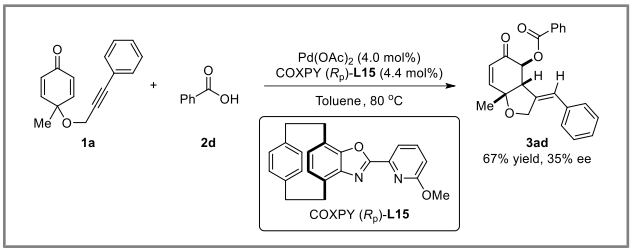
Based on the computational results, the energy barrier of nucleophilic acetoxylation (**TS4**, 26.2 kcal/mol) is 4.0 kcal/mol higher

than that of LLHT (**TS1**, 22.2 kcal/mol), which identifies nucleophilic acetoxylation might be the rate-determining step in the overall transformation. The computed activation barrier for **TS4** (26.2 kcal/mol) agrees well with the reaction conditions (80 °C). Notably, the electron-deficient nature of the Pd center, modulated by the ligand, plays a pivotal role in facilitating the catalytic cycle, enabling the efficient hydroacetoxylative cyclization.

Experimental studies and DFT calculations demonstrated that this Pd(0)-catalyzed hydroacetoxylative cyclization was a ligand-directed reaction, and 6-methoxypyridine-benzoxazole ligand fine-tuned the elementary steps, including Pd(0)-catalyzed hydrogen transfer from carboxylic acids to alkynes as the initial step and nucleophilic attack on the palladium enolate as the termination step. Compared with the widely explored control of regioselectivities and chemoselectivities by ligands,[2] this reaction supplements the existing LDS.

We have also briefly explored the Pd-catalyzed asymmetric version of this hydroacetoxylative cyclization. Using the newly developed [2.2]paracyclophane-based planar-chiral oxazole-6-MeO-pyridine ligand (COXPY (R_p)-**L15**), the reaction of **1a** with benzoic acid **2d** delivered product **3ad** in 67% yield and moderate 35% ee (Scheme 5). Although the enantioselectivity was not satisfying, it demonstrated the potential for the asymmetric hydroacetoxylative cyclization.

Scheme 5 Palladium-catalyzed asymmetric hydroacetoxylative cyclization of alkyne-tethered cyclohexadienone **1a** with benzoic acid **2d**



Conclusions

In summary, we have realized the 6-methoxypyridine-benzoxazole ligand-directed original palladium(0)-catalyzed hydroacetoxylative cyclization of alkyne-tethered cyclohexadienones with carboxylic acids, in which carboxylic acids are used as both hydrogen sources and nucleophiles, furnishing a myriad of the structurally novel *cis*-hydrobenzofurans. Mechanistic investigations and DFT calculations proved that the newly developed 6-methoxypyridine-benzoxazole ligand fine-tuned the reaction pathway *via* the promotion of the initial hydrogen transfer from carboxylic acids to alkynes and the final nucleophilic acetoxylation. We hope that this work will stimulate the development of wider ligand-directed divergent synthesis.

Experimental

General procedure for cyclization with acetic acid. Under a nitrogen atmosphere, a solution of palladium acetate (0.0080 mmol, 1.8 mg, 4.0 mol%), **L2** (0.0088 mmol, 2.1 mg, 4.4 mol%) and acetic acid **2a** (HOAc, 0.20 mL, 3.4 mmol) in toluene (1.8 mL) was stirred at room temperature for 2 h. Thereafter, alkyne-tethered cyclohexadienones **1** (0.20 mmol) and cuprous iodide (0.020 mmol, 3.8 mg, 10 mol%) were added sequentially, and the mixture was stirred at 80 °C (oil bath temperature) until substrates **1** were fully consumed. After the completion of the reaction, the volatiles were removed under the reduced pressure. The crude residue was directly purified by flash column chromatography on silica gel using hexanes/acetone as eluent to give the desirable cyclization products **3**.

General procedure for cyclization with other carboxylic acids. Under a nitrogen atmosphere, a solution of palladium acetate (0.0080 mmol, 1.8 mg, 4.0 mol%), **L2** (0.0088 mmol, 2.1 mg, 4.4 mol%) and carboxylic acids **2** (2.0 mmol) in toluene (2.0 mL) was stirred at room temperature for 2 h. Thereafter, alkyne-tethered cyclohexadienone **1a** (0.20 mmol, 47.7 mg) and cuprous iodide (0.020 mmol, 3.8 mg, 10 mol%) were added sequentially, and the mixture was stirred at 80 °C (oil bath temperature) until substrate **1a** was fully consumed. After the completion of the reaction, the volatiles were removed under the reduced pressure. The residue was dissolved in ethyl acetate and quenched with the saturated aqueous solution of sodium bicarbonate (15 mL). After separation, the aqueous phase was extracted with ethyl acetate (5.0 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under the reduced pressure. The crude residue was purified by flash column chromatography on silica gel using hexanes/acetone as eluent to give the desirable products **3**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.70436.

Acknowledgement

We thank National Key Research and Development Program of China (2023YFA1507500), National Natural Science Foundation of China (22171260) and Dalian Institute of Chemical Physics (DICP I202404, I202442) for financial support.

References

[1] For selected reviews: (a) Miller, L. C.; Sarpong, R. Divergent Reactions on Racemic Mixtures. *Chem. Soc. Rev.* **2011**, *40*, 4550–4562; (b) Anagnostaki, E. E.; Zografos, A. L. "Common Synthetic Scaffolds" in the Synthesis of Structurally Diverse Natural Products. *Chem. Soc. Rev.* **2012**, *41*, 5613–5625; (c) Serba, C.; Winssinger, N. Following the Lead from Nature: Divergent Pathways in Natural Product Synthesis and Diversity-Oriented Synthesis. *Eur. J. Org. Chem.* **2013**, *2013*, 4195–4214; (d) Shimokawa, J. Divergent Strategy in Natural Product Total Synthesis. *Tetrahedron Lett.* **2014**, *55*, 6156–6162; (e) Garcia-Castro, M.; Zimmermann, S.; Sankar, M. G.; Kumar, K. Scaffold Diversity Synthesis and Its Application in Probe and Drug Discovery. *Angew. Chem. Int. Ed.* **2016**, *55*, 7586–7605; (f) Li, L.; Chen, Z.; Zhang, X.; Jia, Y. Divergent Strategy in Natural Product Total Synthesis. *Chem. Rev.* **2018**, *118*, 3752–3832; (g) Kim, T.; Ha, M. W.; Kim, J. Recent Advances in Divergent Synthetic Strategies for Indole-Based Natural Product Libraries. *Molecules* **2022**, *27*, 2171; (h) Hou, S.-H.; Zhou, F.-F.; Sun, Y.-H.; Li, Q.-Z. Deconstructive and Divergent Synthesis of Bioactive Natural Products. *Molecules* **2023**, *28*, 6193. For selected examples: (i) Zhang, Y.; Zhang, Y.; Guo, Y.; Liu, S.; Shen, X. Reductive Quenching-Initiated Catalyst-Controlled Divergent Alkylation of α-CF_3-Olefins. *Chem Catal.* **2022**, *2*, 1380–1393; (j) Zhou, G.; Guo, Z.; Liu, S.; Shen, X. Divergent Synthesis of Fluoroalkyl Ketones through Controlling the Reactivity of Organoboronate Complex. *J. Am. Chem. Soc.* **2024**, *146*, 4026–4035; (k) Meng, R.-F.; Kong, Y.-J.; Wu, X.-Y.; Zhang, H.; Wang, W.; Liang, W.-J.; Zheng, L.; Lin, C.; Su, W.; Xiao, J.-A. Structurally Divergent Synthesis of Azetidines, 5,6-Dihydro-1,3-oxazines and 2,3-Dihydro-1,4-oxazines through Palladium-Catalyzed Tandem Allylic Substitution Reaction. *Chin. J. Chem.* **2024**, *42*, 2773–2778; (l) Li, B.; Xie, M.; Li, J.; Shen, N.; Zhang, X.; Fan, X. Cobalt-Catalyzed Switchable [4+1] and [4+1+1] Spirocyclization of Aromatic Amides with 2-Diazo-1*H*-indene-1,3(2*H*)-dione: Access to Spiro Indene-2,1'-isoindolinones and Spiro Isochroman-3,1'-isoindolinones. *Chin. J. Chem.* **2024**, *42*, 363–369; (m) Chen, S.; Fang, Z.; Liu, S.; He, X.; Lan, Y.; Shen, X. Enantioselective Synthesis of Benzosilacyclohexanes with Racemic Benzosilacyclobutenes and Diastereoselectivity Reversal. *Sci. Bull.* **2025**, *70*, 3733–3737.

[2] (a) Peng, J.-B.; Wu, X.-F. Ligand- and Solvent-Controlled Regio- and Chemodivergent Carbonylative Reactions. *Angew. Chem. Int. Ed.* **2018**, *57*, 1152–1160; (b) Lee, Y.-C.; Kumar, K.; Waldmann, H. Ligand-Directed Divergent Synthesis of Carbo- and Heterocyclic Ring Systems. *Angew. Chem. Int. Ed.* **2018**, *57*, 5212–5226; (c) Chintawar, C. C.; Yadav, A. K.; Kumar, A.; Sancheti, S. P.; Patil, N. T. Divergent Gold Catalysis: Unlocking Molecular Diversity through Catalyst Control. *Chem. Rev.* **2021**, *121*, 8478–8558; (d) Ke, Y.; Li, W.; Liu, W.; Kong, W. Ni-Catalyzed Ligand-Controlled Divergent and Selective Synthesis. *Sci. China Chem.* **2023**, *66*, 2951–2976; (e) Wang, Y.; Feng, J.; Li, E.-Q.; Jia, Z.; Loh, T.-P. Recent Advances in Ligand-Enabled Palladium-Catalyzed Divergent Synthesis. *Org. Biomol. Chem.* **2024**, *22*, 37–54; (f) Park, S. Recent Advances in Ligand-Controlled Regio- or Stereodivergent Transition-Metal-Catalyzed Hydroelementation (H[E]) (E = H, B, Si, Ge) of C-C Unsaturated Systems. *Synthesis* **2024**, *56*, 3083–3107.

[3] For selected examples: (a) Chen, Y.-Q.; Shen, Y.-H.; Su, Y.-Q.; Kong, L.-Y.; Zhang, W.-D. Incarviditone: A Novel Cytotoxic Benzofuranone Dimer from *Incarvillea delavayi* Bureau et Franchet. *Chem. Biodiversity* **2009**, *6*, 779–783; (b) Franck, G.; Brödner, K.; Helmchen, G. Enantioselective Modular Synthesis of Cyclohexenones: Total Syntheses of (+)-Crypto- and (+)-Infectocaryone. *Org. Lett.* **2010**, *12*, 3886–3889; (c) Wegner, J.; Ley, S. V.; Kirschning, A.; Hansen, A.-L.; Garcia, J. M.; Baxendale, I. R. A Total Synthesis of Millingtonine A. *Org. Lett.* **2012**, *14*, 696–699; (d) Brown, P. D.; Willis, A. C.; Sherburn, M. S.; Lawrence, A. L. Total Synthesis of Incarviditone and Incarvilleatone. *Org. Lett.* **2012**, *14*, 4537–4539; (e) Hexum, J. K.; Tello-Aburto, R.; Struntz, N. B.; Harned, A. M.; Harki, D. A. Bicyclic Cyclohexenones as Inhibitors of NF-κB Signaling. *ACS Med. Chem. Lett.* **2012**, *3*, 459–464; (f) He, C.; Zhu, C.; Dai, Z.; Tseng, C.-C.; Ding, H. Divergent Total Synthesis of Indoxamycins A, C, and F. *Angew. Chem. Int. Ed.* **2013**, *52*, 13256–13260.

[4] (a) Tello-Aburto, R.; Harned, A. M. Palladium-Catalyzed Reactions of Cyclohexadienones: Regioselective Cyclizations Triggered by Alkyne Acetoxylation. *Org. Lett.* **2009**, *11*, 3998–4000; (b) Tello-Aburto, R.; Kalstabakken, K. A.; Harned, A. M. Ligand and Substrate Effects during Pd-Catalyzed Cyclizations of Alkyne-Tethered Cyclohexadienones. *Org. Biomol. Chem.* **2013**, *11*, 5596–5604; (c) Takenaka, K.; Mohanta, S. C.; Sasai, H. Palladium Enolate Umpolung: Cyclative Diacetoxylation of Alkynyl Cyclohexadienones Promoted by a Pd/SPRIX Catalyst. *Angew. Chem. Int. Ed.* **2014**, *53*, 4675–4679; (d) Bai, Y.-Q.; Wang, X.-W.; Wu, B.; Wang, X.-Q.; Liao, R.-Z.; Li, M.; Zhou, Y.-G. Design and Synthesis of Planar-Chiral Oxazole-Pyridine *N*,*N*-Ligands: Application in Palladium-Catalyzed Asymmetric Acetoxylative Cyclization. *ACS Catal.* **2023**, *13*, 9829–9838.

[5] For review: (a) Liu, W.; Chen, P. Palladium-Catalyzed Cyclization of 1,6-Enynes. *Chin. J. Org. Chem.* **2024**, *44*, 2077–2091. For selected examples: (b) Zhang, Q.; Lu, X. Highly Enantioselective Palladium(II)-Catalyzed Cyclization of (*Z*)-4′-Acetoxy-2′-butenyl 2-Alkynoates: An Efficient Synthesis of Optically Active γ-Butyrolactones. *J. Am. Chem. Soc.* **2000**, *122*, 7604–7607; (c) Zhang, Q.; Lu, X.; Han, X. Palladium(II)-Catalyzed Asymmetric Cyclization of (*Z*)-4′-Acetoxy-2′-butenyl 2-Alkynoates. Role of Nitrogen-Containing Ligands in Palladium(II)-Mediated Reactions. *J. Org. Chem.* **2001**, *66*, 7676–7684; (d) Zhao, L.; Lu, X.; Xu, W. Palladium(II)-Catalyzed Enyne Coupling Reaction Initiated by Acetoxypalladation of Alkynes and Quenched by Protonolysis of the Carbon-Palladium Bond. *J. Org. Chem.* **2005**, *70*, 4059–4063; (e) Tian, B.; Chen, P.; Leng, X.; Liu, G. Palladium-Catalysed Enantioselective Diacetoxylation of Terminal Alkenes. *Nat. Catal.* **2021**, *4*, 172–179; (f) Tian, B.; Li, X.; Chen, P.; Liu, G. Asymmetric Palladium-Catalyzed Oxycarbonylation of Terminal Alkenes: Efficient Access to β-Hydroxy Alkylcarboxylic Acids. *Angew. Chem. Int. Ed.* **2021**, *60*, 14881–14886; (g) Yang, X.; Li, X.; Chen, P.; Liu, G. Palladium(II)-Catalyzed Enantioselective Hydrooxygenation of Unactivated Terminal Alkenes. *J. Am. Chem. Soc.* **2022**, *144*, 7972–7977; (h) Li, X.; Yang, T.; Li, J.; Li, X.; Chen, P.; Lin, Z.; Liu, G. Regio- and Enantioselective Remote Dioxygenation of Internal Alkenes. *Nat. Chem.* **2023**, *15*, 862–871; (i) Dong, M.; Qi, L.; Qian, J.; Yu, S.; Tong, X. Pd(0)-Catalyzed Asymmetric 7-*Endo* Hydroacyloxylative Cyclization of 1,6-Enyne Enabled by an Anion Ligand-Directed Strategy. *J. Am. Chem. Soc.* **2023**, *145*, 1973–1981.

[6] (a) Guo, S.; Wang, X.; Zhou, J. S. Asymmetric Umpolung Hydrogenation and Deuteration of Alkenes Catalyzed by Nickel. *Org. Lett.* **2020**, *22*, 1204–1207; (b) Zhou, J. S.; Guo, S.; Zhao, X.; Chi, Y. R. Nickel-Catalyzed Enantioselective Umpolung Hydrogenation for Stereoselective Synthesis of β-Amido Esters. *Chem. Commun.* **2021**, *57*, 11501–11504.

[7] For reviews: (a) Haydl, A. M.; Breit, B.; Liang, T.; Krische, M. J. Alkynes as Electrophilic or Nucleophilic Allylmetal Precursors in Transition-Metal Catalysis. *Angew. Chem. Int. Ed.* **2017**, *56*, 11312–11325; (b) Cera, G.; Maestri, G. Palladium/Brønsted Acid Catalysis for Hydrofunctionalizations of Alkynes: from Tsuji-Trost Allylations to Stereoselective Methodologies. *ChemCatChem* **2022**, *14*, e202200295; (c) Muzart, J. Pd^0 Catalyst/Carboxylic Acid-Mediated Hydrofunctionalization of Alkynes and Allenes, Two Plausible Hydropalladation Mechanisms of a Versatile Process. *Tetrahedron* **2024**, *167*, 134256. For selected examples: (d) Oh, C. H.; Jung, S. H.; Rhim, C. Y. Chemoselectivities in Palladium- and Rhodium-Catalyzed Allenyne Cyclizations. *Tetrahedron Lett.* **2001**, *42*, 8669–8671; (e) Zhang, Z.; Gevorgyan, V. Palladium Hydride-Enabled Hydroalkenylation of Strained Molecules. *J. Am. Chem. Soc.* **2022**, *144*, 20875–20883; (f) Sarkar, S.; Ghosh, S.; Kurandina, D.; Noffel, Y.; Gevorgyan, V. Enhanced Excited-State Hydricity of Pd-H Allows for Unusual Head-to-Tail Hydroalkenylation of Alkenes. *J. Am. Chem. Soc.* **2023**, *145*, 12224–12232; (g) Li, Q.; Li, J.; Zhang, J.; Wu, S.; Zhang, Y.; Lin, A.; Yao, H. Enantioselective Synthesis of Bicyclo[3.2.1] octadienes *via* Palladium-Catalyzed Intramolecular Alkene-Alkyne Coupling Reaction. *Angew. Chem. Int. Ed.* **2023**, *62*, e202313404; (h) Sun, D.; Zhou, B.; Liu, L.; Chen, X.; Hou, H.; Han, Y.; Yan, C.; Shi, Y.; Zhu, S. Palladium-Catalyzed Borylative Cyclization and Cyclopropanation of Terminal Alkyne-Derived Enynes. *Org. Lett.* **2023**, *25*, 4677–4681; (i) Liang, R.-X.; Ding, C.; Cai, H.-J.; Wang, J.-Y.; Li, Q.-C.; Yu, G.-Y.; Jia, Y.-X. Pd-Catalyzed Enantioselective Desymmetrizing 1,7-Enyne Cycloisomerization of Alkyne-Tethered Cyclopentenes. *Org. Lett.* **2024**, *26*, 4400–4405.

[8] (a) Qi, X.; Chen, C.; Hou, C.; Fu, L.; Chen, P.; Liu, G. Enantioselective Pd(II)-Catalyzed Intramolecular Oxidative 6-*endo* Aminoacetoxylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 7415–7419; (b) Chen, C.; Pflüger, P. M.; Chen, P.; Liu, G. Palladium(II)-Catalyzed Enantioselective Aminotrifluoromethoxylation of Unactivated Alkenes using $CsOCF_3$ as a Trifluoromethoxide Source. *Angew. Chem. Int. Ed.* **2019**, *58*, 2392–2396; (c) Li, X.; Qi, X.; Hou, C.; Chen, P.; Liu, G. Palladium(II)-Catalyzed Enantioselective Azidation of Unactivated Alkenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 17239–17244; (d) Li, X.; Jin, J.; Chen, P.; Liu, G. Catalytic Remote Hydrohalogenation of Internal Alkenes. *Nat. Chem.* **2022**, *14*, 425–432; (e) Li, X.; Yang, X.; Chen, P.; Liu, G. Palladium-Catalyzed Remote Hydro-Oxygenation of Internal Alkenes: An Efficient Access to Primary Alcohols. *J. Am. Chem. Soc.* **2022**, *144*, 22877–22883; (f) Hou, C.; Liu, Z.; Gan, L.; Fan, W.; Huang, L.; Chen, P.; Huang, Z.; Liu, G. Palladium-Catalyzed Remote Hydrosulfonamidation of Alkenes: Access to Primary *N*-Alkyl Sulfamides by the SuFEx Reaction. *J. Am. Chem. Soc.* **2024**, *146*, 13536–13545; (g) Yang, X.; Chen, P.; Liu, G. Asymmetric 1,*n*-Remote Aminoacetoxylation of Unactivated Internal Alkenes Enabled by Palladium Catalysis. *Angew. Chem. Int. Ed.* **2024**, *63*, e202408305.

[9] For selected examples: (a) Lee, S.-C.; Brown, G. D. Tribenzylbutyrolactones and Dibenzyldiphenyl-4,5,6,7-tetrahydrobenzofuranones from *Kyrtuthrix maculans*. *J. Nat. Prod.* **1998**, *61*, 29–33; (b) Loukaci, A.; Kayser, O.; Bindseil, K.-U.; Siems, K.; Frevert, J.; Abreu, P. M. New Trichothecenes Isolated from *Holarrhena floribunda*. *J. Nat. Prod.* **2000**, *63*, 52–56; (c) Al-Yahya, M. A.; El-Feraly, F. S.; Dunbar, D. C.; Muhammad, I. *neo*-Clerodane Diterpenoids from *Teucrium oliverianum* and Structure Revision of Teucrolin E. *Phytochemistry* **2002**, *59*, 409–414; (d) Müller, S.; Murillo, R.; Castro, V.; Brecht, V.; Merfort, I. Sesquiterpene Lactones from *Montanoa hibiscifolia* That Inhibit the Transcription Factor NF-KB⊥. *J. Nat. Prod.* **2004**, *67*, 622–630; (e) Burns, A. R.; McAllister, G. D.; Shanahan, S. E.;

Taylor, R. J. K. Total Synthesis and Structural Reassignment of (+)-Dictyosphaeric Acid A: A Tandem Intramolecular Michael Addition/Alkene Migration Approach. *Angew. Chem. Int. Ed.* **2010**, *122*, 5706–5709; (f) Wang, W.; Liao, Y.; Chen, R.; Hou, Y.; Ke, W.; Zhang, B.; Gao, M.; Shao, Z.; Chen, J.; Li, F. Chlorinated Azaphilone Pigments with Antimicrobial and Cytotoxic Activities Isolated from the Deep Sea Derived Fungus *Chaetomium* sp. NA-S01-R1. *Mar. Drugs* **2018**, *16*, 61.

[10] Deposition number 2203759 (for **3aa**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Manuscript received: November 11, 2025
Manuscript revised: December 4, 2025
Manuscript accepted: December 7, 2025
Version of record online: January 21, 2026

The Authors

Left to Right: Yu-Qing Bai, Li-Xia Liu, Tong Niu, Bo Wu, Man Li, Rong-Zhen Liao, Yong-Gui Zhou

