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Modular esterification of unstrained carbonyls through palladium-catalyzed alkyne bridging C-C bond activation

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Mingruo Ding[1,6], Mengmeng Niu[1,6], Lingfei Hu[2,6], Qifan Guan[1,6], Shan Yuan[1], Yinghua Yu[3], Maojun Xiao[1], Shenlin Huang[4], Gang Lu[2] ✉ & Xueliang Huang[1,5] ✉

The insertion of an oxygen atom into carbon-carbon (C-C) σ-bonds of readily available ketones to form esters represents a fundamental transformation known as Baeyer-Villiger (BV) oxidation. While this classical reaction serves as a cornerstone in organic synthesis, its scope remains limited to single oxygen-atom insertion into ketone substrates. We herein report a versatile catalytic protocol that enables the insertion of alkynyl phenol analogues into unstrained C-C σ-bonds of diverse carbonyl compounds, including ketones, esters, and amides. This method provides modular access to an array of structurally varied products ranging from linear esters to medium- and macrocyclic lactones. This methodology displays broad substrate scope, excellent functional group tolerance, direct applicability to bioactive molecule modification with effective transfer of axial chirality. An in-depth computational study provides insights into the reaction mechanism.

The creation of structurally diverse molecular libraries that explore expansive chemical space is fundamental to advances in chemical biology and drug discovery[1–4]. Among classical transformations for skeletal editing, the Baeyer–Villiger (BV) oxidation stands as a textbook example of C–C σ-bond cleavage, providing straightforward access to esters from linear ketones and lactones from cyclic ketones[5,6]. Despite its operational simplicity and intermolecular nature, conventional BV oxidation suffers from inherent limitations in product diversity, as the structural complexity remains constrained by the parent ketone framework (Fig. 1A). Given the privileged status of ester motifs in bioactive natural products and pharmaceuticals[7,8], the development of efficient methods capable of generating structurally diverse ester libraries from readily available feedstocks represents an important synthetic objective.

Building upon our success in C–H bond activation[9–16], we envisioned an alkyne-bridging C–C bond activation strategy for ester synthesis using readily available feedstock chemicals. This approach capitalizes on easily accessible reactants derived from abundant starting materials through simple transformations. Guided by this designed principle, we anticipated access to diverse, value-added products with structural complexity (Fig. 1B). Our previous work established a modular route to dibenzo-fused 7- to 8-membered lactones via palladium-catalyzed reactions of *ortho*-halobenzaldehydes with salicylaldehyde-derived carbene precursors[10]. Extending this strategy, we hypothesized that condensation of **1** with abundant ketones **2** would provide modular access to α,β-unsaturated carbonyl intermediates **5**. Subsequent palladium-catalyzed reaction with unsymmetrical internal alkynes

[1]Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research, Ministry of Education of China, Key Laboratory of the Assembly and Application of Organic Functional Molecules of Hunan Province, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha, Hunan, China. [2]Key Laboratory of Colloid and Interface Chemistry, School of Chemistry and Chemical Engineering, Ministry of Education, Shandong University, Jinan, China. [3]State Key Laboratory of Structure Chemistry, Center for Excellence in Molecular Synthesis, Fujian Institute of Research on the Structure of Matter, Fujian College, Chinese Academy of Sciences, Fuzhou, Fujian, China. [4]National Key Laboratory for the Development and Utilization of Forest Food Resources, Nanjing Forestry University, Nanjing, China. [5]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, China. [6]These authors contributed equally: Mingruo Ding, Mengmeng Niu, Lingfei Hu, Qifan Guan. ✉e-mail: ganglu@sdu.edu.cn; huangxl@hunnu.edu.cn

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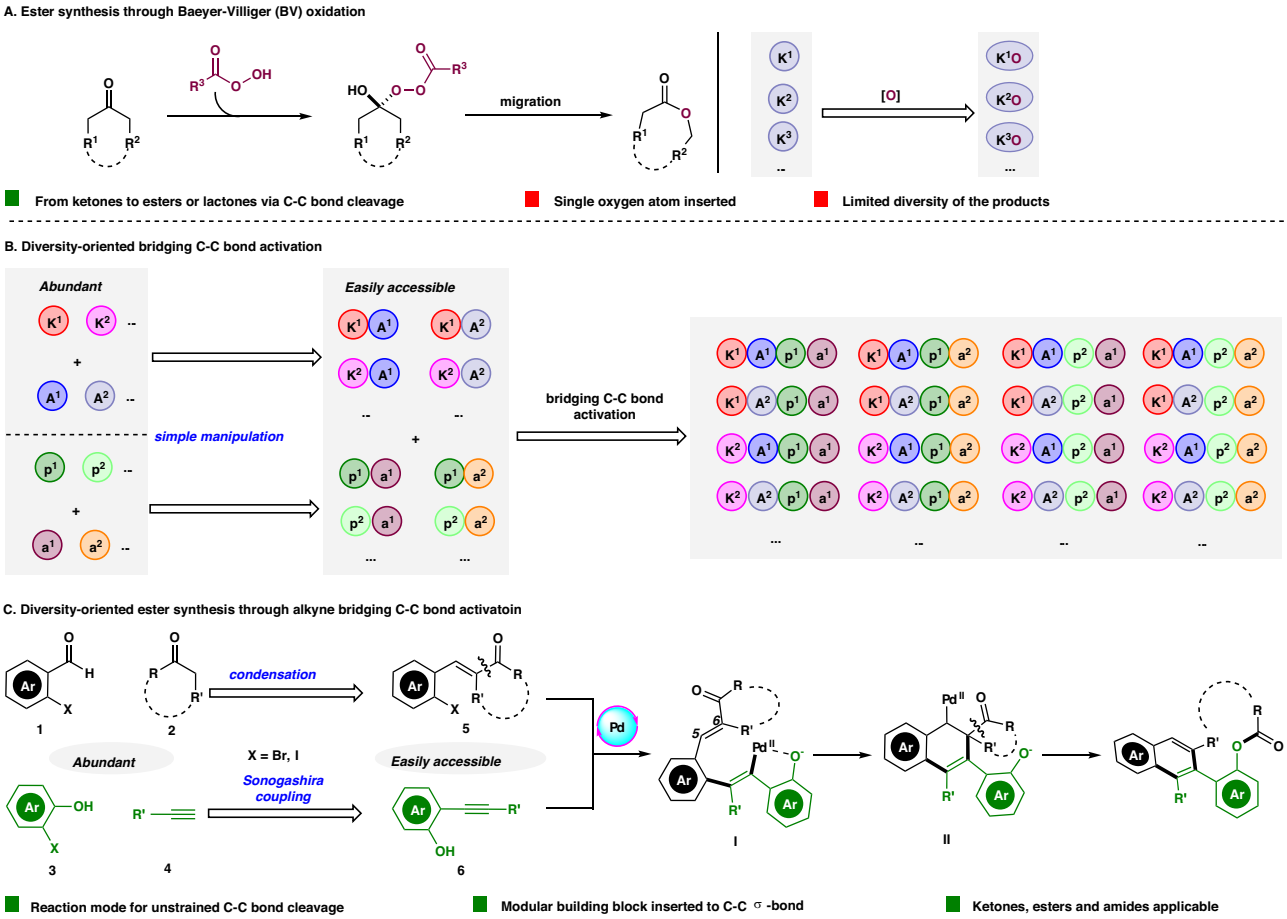

Fig. 1 | Unstrained C–C bond cleavage. A Baeyer–Villiger oxidation. **B** Concept on diversity-oriented bridging C–C bond activation. **C** Diversity-oriented ester synthesis through alkyne-bridging C–C bond activation.

6, which were readily prepared via Sonogashira coupling of **3** and **4**, could enable the envisioned transformation. Key challenges in this design include: (i) Achieving regioselective intermolecular insertion of unsymmetrical alkyne **6** to form intermediate **I**, (ii) controlling 6-*endo-trig* cyclization (**I**→**II**) over the typically favored 5-*exo-trig* pathway, and iii selective cleavage of the unstrained C(acyl)-C σ-bond despite its high dissociation energy[17–22]. The *ortho*-phenol moiety in **6** was designed to serve multiple functions: directing regioselective alkyne insertion, facilitating subsequent C–C bond cleavage, and participating in ester bond formation. We anticipated that careful ligand selection could promote six-membered ring formation, while aromaticity restoration, driving β-carbon elimination[23–28], would enable selective C–C cleavage[29–31]. Unlike conventional approaches such as BV oxidation or diazo-based ketone homologation[32], multi-atom insertions into unstrained carbonyls remain challenging[33–39], typically requiring reactive intermediates like arynes[40] or strained alkenes[41,42] as coupling partners. While Dong's elegant work demonstrated two-carbon insertion into 1-indanones using ethylene/alkynes[43,44], broader substrate scope with more unstrained carbonyl compounds remains unexplored. In 2015, Wu and co-workers developed an innovative method for synthesizing 8-membered lactones via palladium-catalyzed C–C bond cleavage of strained cyclobutanone derivatives[37]. Being aware of the thermodynamic driving force to form an aromatic ring, we expect that a variety of readily available unstrained carbonyl compounds[45–50], including linear or cyclic ketones, esters, and amides[51,52] might be fragmented through our conceived strategy. The feedstock abundance of all starting materials makes this alkyne-bridging C–C activation particularly attractive for rapid diversity generation (Fig. 1C). Notably, BV oxidation cannot cleave C–C bonds in esters and amides. Moreover, while BV reactions insert single oxygen atoms, our approach introduces modular building blocks at the original C(acyl)–C bond. We believe this bridging C–C bond activation principle may inspire new methodological developments.

Results

Reaction development

We began our investigation with the use of *α*, *β*-unsaturated ketone **5a** and 2-alkynylphenol **6a** as the initial substrates. After systematic survey of the reaction parameters (for details, see Supplementary Information Tables S1–S5), ester **7a** was obtained in 97% GC yield using $Pd(TFA)_2$ (5 mol%) as the precatalyst, Ad_2P^nBu (10 mol%) as the ligand and Na_2CO_3 (2.0 equiv.) as the base in DCE (0.1 M) at 120 °C for 10 h (Table 1, entry 1). A number of control experiments were subsequently carried out. Firstly, the reactions cannot proceed without the addition of Pd salt or Ad_2^nBuP. Other Pd(II) precatalysts or phosphine-based ligands were less efficient, and the yields of **7a** decreased significantly (Table 1, entries 4–7). Lower the reaction temperature to 100 °C led to a lower yield of **7a**. If the reaction was carried out in the open air, a more complex reaction mixture was obtained, and **7a** was produced in 47% GC yield (Table 1, entry 9).

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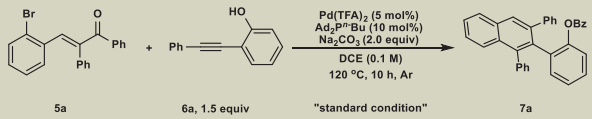
Table 1 | Evaluation of reaction conditions[a]



Entry	Variation from standard conditions	Yield/%[b]
1	None	97
2	Without $Pd(TFA)_2$	-
3	Without $Ad_2{}^{n}BuP$	-
4	$Pd(OAc)_2$ instead of $Pd(TFA)_2$	24
5	$PdCl_2$ instead of $Pd(TFA)_2$	30
6	PPh_3 instead of $Ad_2{}^{n}BuP$	8
7	PCy_3 instead of $Ad_2{}^{n}BuP$	35
8	100 °C instead of 120 °C	48
9	Under atmosphere of air	47

[a]Reaction conditions: **5a** (0.2 mmol), **6a** (0.3 mmol), $Pd(TFA)_2$ (5 mol %), ligand (10 mol%), Na_2CO_3 (2.0 equiv) in anhydrous DCE (2.0 mL), stirred under an atmosphere of argon at 120 °C.
[b]The yields were determined by GC with dodecane as internal standard.

With optimized conditions established, we evaluated the generality and limitations of this palladium-catalyzed alkyne-bridging C–C activation using linear ketones (Fig. 2A). The reaction demonstrated remarkable tolerance toward diverse 2-alkynylphenols, accommodating substrates with varying electronic and steric properties, affording the desired products **7b**–**7j** in moderate to high yields (41–98%). The efficiency seems to be not affected by slight variation of the electron property of the substituents. While the introducing of electron-withdrawing groups, such as *p*-CF_3, *p*-CO_2Me, and *p*-CN, the products (**7g, 7h**, and **7i**) were obtained in diminished yields. Notably, sterically demanding substrates (1-naphthyl, o-tolyl) proved compatible, delivering **7k** and **7l** in 85% and 98% yields, respectively. Similarly, substituents ranging from 4-F to 4-Me and 5-Cl on the phenol ring were tolerated as well, giving the corresponding products **7m**–**7o** in 50–90% yields upon isolation. Particularly encouraging was the compatibility of aliphatic alkynes bearing functional groups like chloro, labile THP-ether, silyl ether, cyclopropyl groups, the reactions furnishing the desired products **7p**–**7t** in high yields. Encouraged by the above results, we thought such an alkyne-bridging C–C bond activation strategy might not be limited to ketones, and the carbon-acyl bonds in esters or amides might be cleavable under current conditions. As illustrated in Fig. 2B, esters **5b** and **5e** were indeed viable substrates to react with 2-alkynylphenol **6a**, and the product **8a** with a free hydroxyl group on the phenyl ring was obtained in high yields after hydrolysis under basic conditions. It is of note to mention that a one-pot procedure for the bridging C–C bond activation of ketone **5a** with **6a** with subsequent hydrolysis, could also give **8a** in high efficiency. Amide **5c** and Weinreb amide **5d** could react with **6a**, albeit in lower overall yields. Given the higher efficiency when α,β-unsaturated ketones and esters were employed as the reactants, we decided to test the reactivity of other analogs. As depicted in Fig. 2C, the reaction accommodated diverse aryl substituents (**7v**–**7z**), with electronic perturbations showing minimal impact on efficiency. Similarly, **5** deriving from ketones with different substituents on the phenyl ring (R^1) could react with internal alkyne **6a** smoothly, giving the corresponding benzoyl esters in good yields (**7aa**–**7ae**). Ketone or ester bearing naphthyl and thiophenyl rings were viable reactants. α,β-Unsaturated ester bearing Isoxepac (an anti-inflammatory agent) motif was a good substrate, giving the corresponding pharmaceutically relevant product **8ah** in 68% yield. Our protocol was also applicable for ketones bearing aliphatic groups (R^1 = Me, ^{n}Bu or Bn, R^2 = Me), and the corresponding products (**7ai**–**7ak, 7am**) were obtained up to 90% isolated yields. The embedding of a benzyloxy group in the reactant is noteworthy, as a product of binol derivatives **7al** could be prepared facilely.

While our previously reported carbene-bridging C–H activation provided efficient access to seven- and eight-membered lactones[10], this approach proved ineffective for larger ring systems. Having achieved selective C–C bond cleavage in linear ketones, we envisioned that our alkyne-bridging C–C bond activation strategy could be adapted for functionalizing unstrained cyclic ketones, potentially enabling modular synthesis of medium-to-macrocyclic lactones through simple variation of the ketone ring size. In line with this assumption, reactants deriving from cyclopentanone and cyclohexanone were prepared and subjected to test the reactivity. To our delight, the corresponding 9-membered and 10-membered lactones **9a** and **9b** could be obtained in 56% and 64% yields upon isolation under a set of slightly different conditions by using $Pd(OAc)_2$ as the palladium source and K_2HPO_4 as base (Fig. 3). This success prompted a thorough evaluation of substrate scope, which revealed remarkable generality.

As demonstrated in Fig. 3, indanone and tetralone derivatives could react to give the corresponding 9- and 10-membered lactones **9c** and **9d** in good isolated yields. Acetal moiety, and potentially catalyst poisoning sites containing S and N atoms are tolerated in the reactions (**9e**–**9g**). Compared with the reactions of linear carbonyl compounds, α, β-unsaturated ester containing a δ-lactone moiety reacts well with 2-alkynylphenol. Besides the corresponding 10-membered lactones **9h**, an intriguing decarboxylated **9i** bearing an 8-membered *O*-heterocycle was obtained in 40% isolated yield. Even a bridged bicyclic ketone participated effectively, affording **9j** and demonstrating the method's tolerance for complex architectures. Most significantly, systematic variation of cyclic ketone size, ranging from cycloheptanone to cyclopentadecanone, enabled straightforward access to diverse medium- and macrocyclic lactones **9k**–**9p**.

Recognizing that this alkyne-bridging C–C activation constructs multi-substituted biaryl scaffolds, we investigated the

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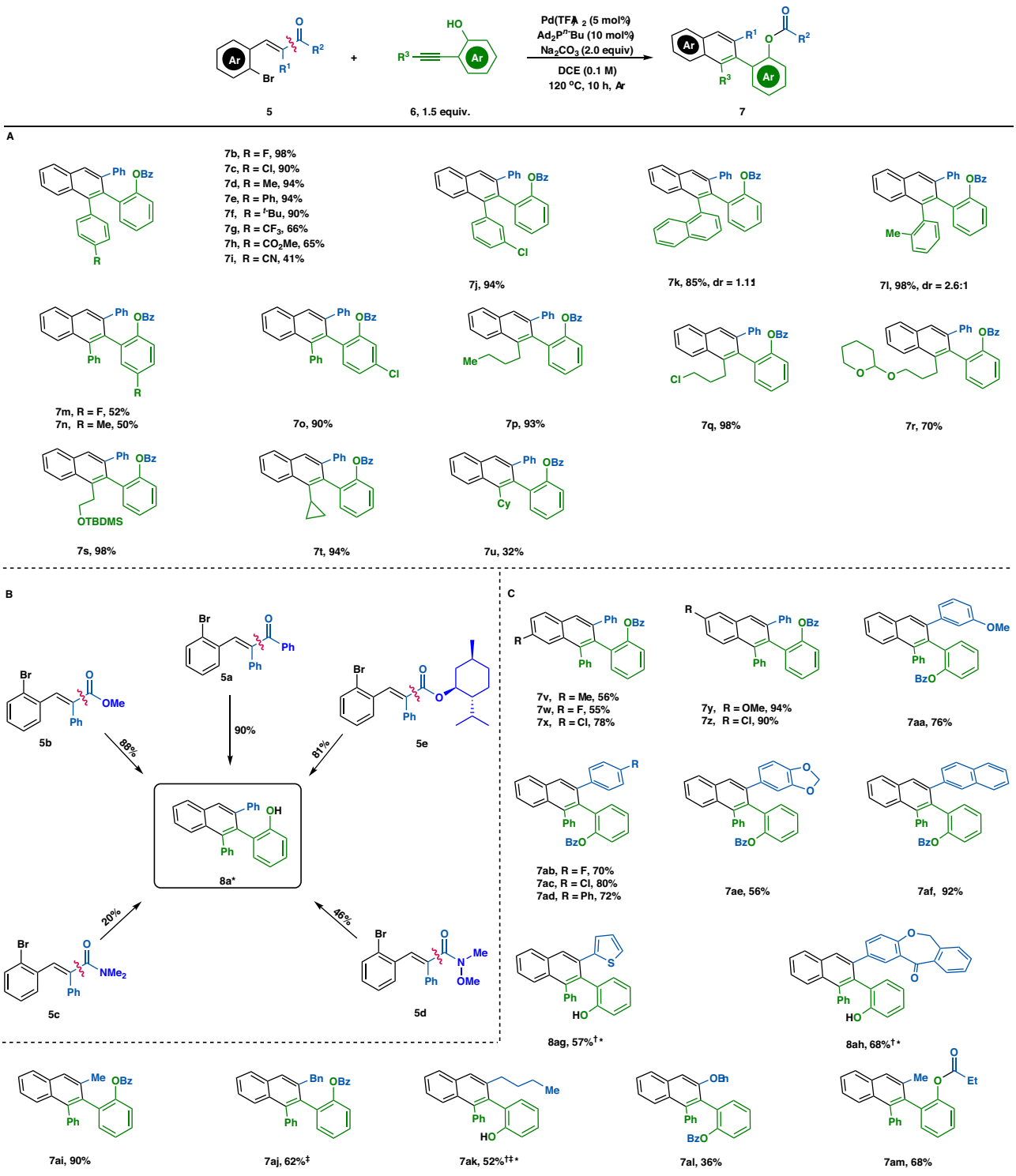

Fig. 2 | Reaction scope with respect to the reactions of linear carbonyls with 2-alkynylphenols. A Scope of alkynylphenols. **B** Reaction with different α,β-unsaturated carbonyl compounds. **C** Scope of α,β-unsaturated ketones or esters. *Upon the completion of the reaction, the mixture was treated with NaOH in MeOH. †α,β-unsaturated methyl carboxylate was used as the initial material. ‡Reaction conducted with $Pd(OAc)_2$ (5 mol%), Ad_2P^nBu (10 mol%), K_2HPO_4 (2.0 equiv.), 1,4-dioxane (0.05 M), at 130 °C, 7 h, under an atmosphere of Argon.

potential for controlling axial chirality using commercially available chiral ketones (Fig. 4). We selected (D)-camphor as our initial substrate due to its cost-effectiveness, rigid backbone, and well-defined stereochemistry. Remarkably, the corresponding chiral α,β-unsaturated ketone reacted smoothly with various alkynylphenols under standard conditions, affording products **10a**–**10f** as single diastereomers in moderate to high yields (40–70%). Single-crystal X-ray analysis of **10a** unambiguously confirmed both the structure and absolute configuration. The methodology proved general for bioactive chiral ketones. Epiandrosterone and estrone derivatives reacted efficiently with **6a** under standard conditions. The relatively remote chiral centers in the reactants seem to well

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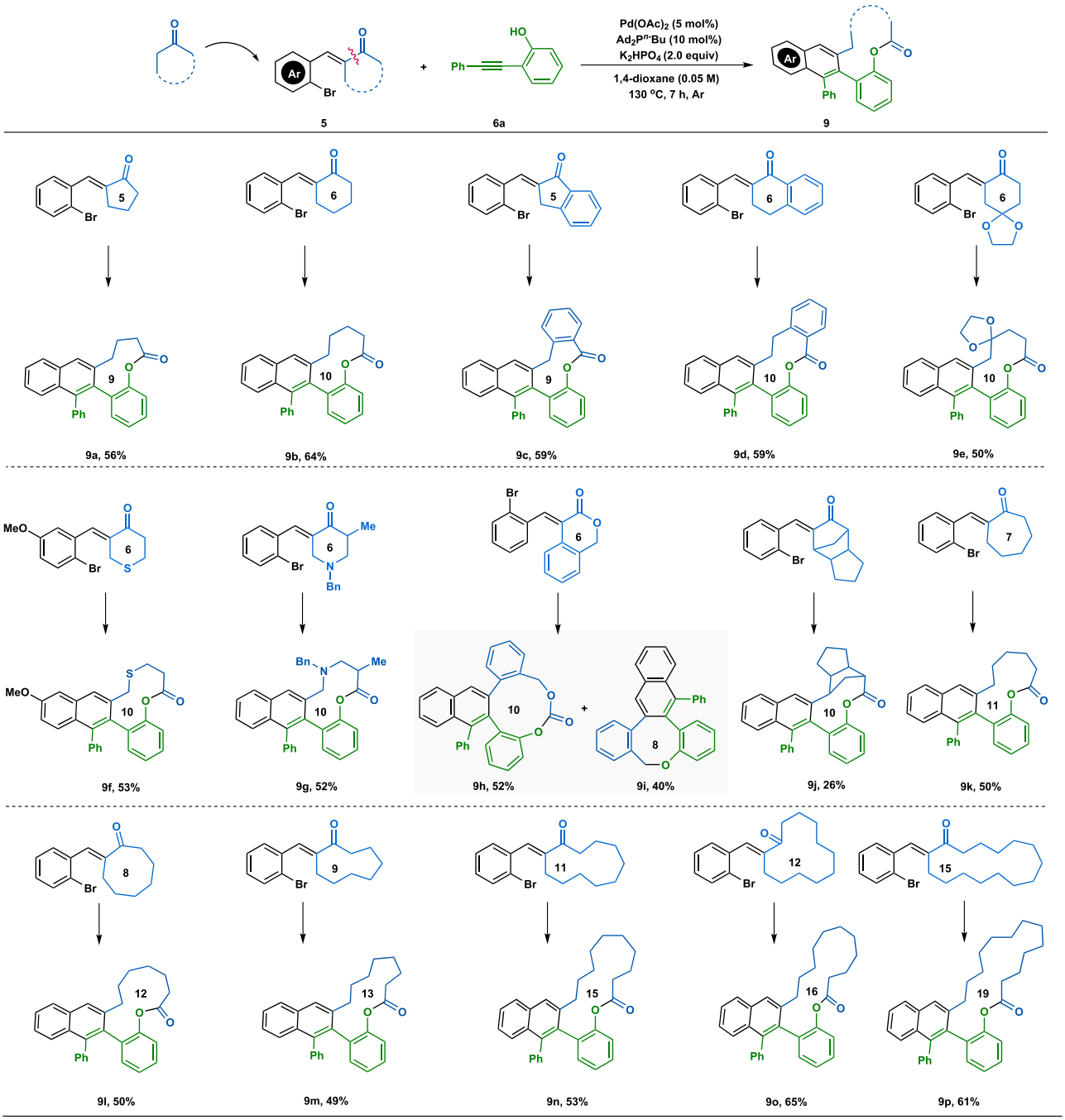

Fig. 3 | Scope for C–C cleavage of unstrained cyclic carbonyl compounds. Scope of the cyclic ketones.

induce the generation of axial chirality. Both **10g** and **10h** were obtained as single diastereoisomers in high yields after ring opening with MeOH under basic conditions. Pleasingly, we could obtain the crystal structure of **10g**. Methylated derivative **10h** also provided suitable crystals for X-ray analysis.

Computational studies

Density functional theory (DFT) calculations were performed to understand the mechanism of this C–C bond activation of linear carbonyl substrates, particularly regarding the role of 2-alkynylphenols in promoting unstrained C–C cleavage. The DFT calculations were performed at the B3LYP-D3/SDD-6-311++ G(d,p)/SMD(DCE)//B3LYP-D3/SDD-6-311G(d,p) level of theory[53–55] using α, β-unsaturated ketone **5a** and 2-alkynylphenol **6a** as model substrates. The reaction commences with the oxidative addition of ArBr with Pd(0) species via **TS1**, requiring a barrier of 22.7 kcal/mol (Fig. 5A). Under the basic condition (Na_2CO_3), the 2-alkynylphenol substrate **4a** is assumed to be deprotonated to afford its sodium phenolate, which is thermodynamically favored by 1.8 kcal/mol (see details in Supplementary Information Fig. S1). The formed Pd(II) intermediate (**INT1**) derived from ArBr oxidative addition undergoes ligand exchange with the sodium phenolate to generate the phenoxy Pd(II) species (**INT2**) with alkyne coordination. Subsequently, the O-directed alkyne migratory insertion proceeds via

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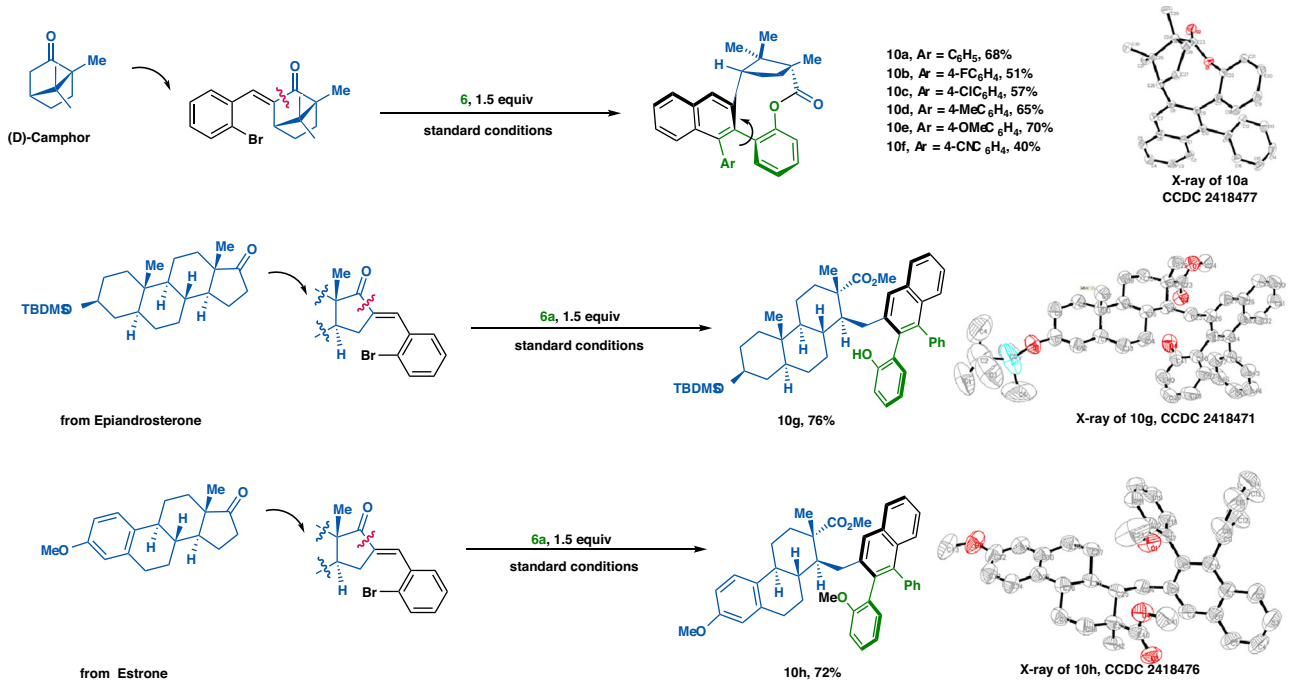

Fig. 4 | Construction of axial chirality through late-stage C–C bond editing of bioactive molecules. Axial chirality transfer by using chiral ketones as starting materials.

TS2 ($\Delta G^{\ddagger}$ = 22.9 kcal/mol with respect to **INT1**). Based on the alkenyl Pd(II) intermediate (**INT3**), the straightforward C(alkenyl)-C(acyl) oxidative addition can be excluded due to the extremely high barrier (**TS3**, $\Delta G^{\ddagger}$ = 47.4 kcal/mol). In contrast, the intramolecular alkene migratory insertion into the Pd-C(alkenyl) bond is more favorable. This process includes two competing pathways, i.e., 6-*endo*-trig cyclization versus 5-*exo*-trig cyclization. The computational results show that the 5-*exo*-trig cyclization (**TS4b**) is superior to the 6-*endo*-trig cyclization (**TS4a**). The higher barrier of **TS4a** is mostly due to the greater conformational deformations. Although the unproductive 5-*exo*-trig cyclization (**TS4b**) has a lower barrier, it is a reversible process because the ensuing β-H elimination (**TS5**) requires a much higher barrier. The desired 6-*endo*-trig cyclization (**TS4a**) leads to a seven-membered palladacycle (**INT4a**), which may proceed via β-C elimination to cleave the targeted C–C bond. However, the computed barrier of β-C elimination (**TS6b**) cannot compete with **TS5** along the 5-*exo*-trig pathway. Alternatively, the nucleophilic attack at the carbonyl carbon by the phenolate oxygen shows a much lower barrier (**TS6a**, $\Delta G^{\ddagger}$ = 9.7 kcal/mol), generating a polyfused ring system (**INT5**). More importantly, this nucleophilic attack results in two tertiary carbon centers in **INT5**, leading to the preactivation of the targeted C(sp^3)-C(sp^3) bond. This is supported by the elongated C–C bond length (1.61 Å) in **INT5** compared to that (1.56 Å) in **INT4a** (Fig. 5B). The subsequent retro-oxidative cyclization via **TS7** with a barrier of 20.0 kcal/mol delivers the corresponding product **7a**. In addition, although the C–C bond in **INT5** is relatively preactivated, the lower barrier of **TS7** (retro-oxidative cyclization) compared to **TS6b** (β-C elimination) can also be attributed to the distinct steric environments around the Pd center. Due to the bulky phosphine ligand (Ad_2P^nBu), **TS6b** bearing a four-coordinated Pd(II) suffers from greater steric hindrance between ligand and substrate (Fig. 5B, see NCI plots in Supplementary Information). In contrast, the three-coordinated Pd(II) center in **TS7** is less steric demanding.

Discussion

In summary, we have developed a versatile platform for modular ester synthesis via alkyne-bridging C–C bond activation of unstrained carbonyl compounds. This method enables efficient construction of biaryl-containing esters from readily available starting materials while offering good functional group tolerance and structural diversity. Compared to our previous carbene-bridging C–H activation approach, which was limited to seven- and eight-membered lactones, the current strategy provides access to a broad range of medium-to-macrocyclic lactones through simple variation of cyclic ketone precursors. Notably, the axial chirality in products can be precisely controlled through chiral elements in the reactants. We envision that this general platform will inspire new strategies for activating other challenging inert bond systems.

Methods

General procedure for the synthesis of 7

To an oven-dried Schlenk tube was added Pd $(TFA)_2$ (5 mol%, 3.3 mg), Ad_2P^nBu (10 mol%, 7.2 mg), Na_2CO_3 (2.0 equiv., 42.4 mg), starting materials **5** (0.2 mmol) and **6** (0.3 mmol). The tube was degassed and filled with dry argon, repeated three times. DCE (2.0 mL) was added via syringe. This mixture was stirred at 120 °C for 10 h. When the reaction was complete, the reaction mixture was cooled to RT and filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to give the crude mixture, which was purified by flash column chromatography on silica gel to give the desired product **7**.

General procedure for the synthesis of 9

To an oven-dried Schlenk tube was added Pd $(OAc)_2$ (5 mol%, 2.3 mg), Ad_2P^nBu (10 mol%, 7.2 mg), K_2HPO_4 (2.0 equiv., 69.6 mg), starting materials **5** (0.2 mmol) and **6** (0.3 mmol). The tube was degassed and filled with dry argon, repeated three times. 1,4-Dioxane (4.0 mL) was added via syringe. This mixture was stirred at 130 °C for 7 h. When the reaction was complete, the reaction mixture was cooled to RT and filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to give the crude mixture, which was purified by flash column chromatography on silica gel to give the desired product **9**.

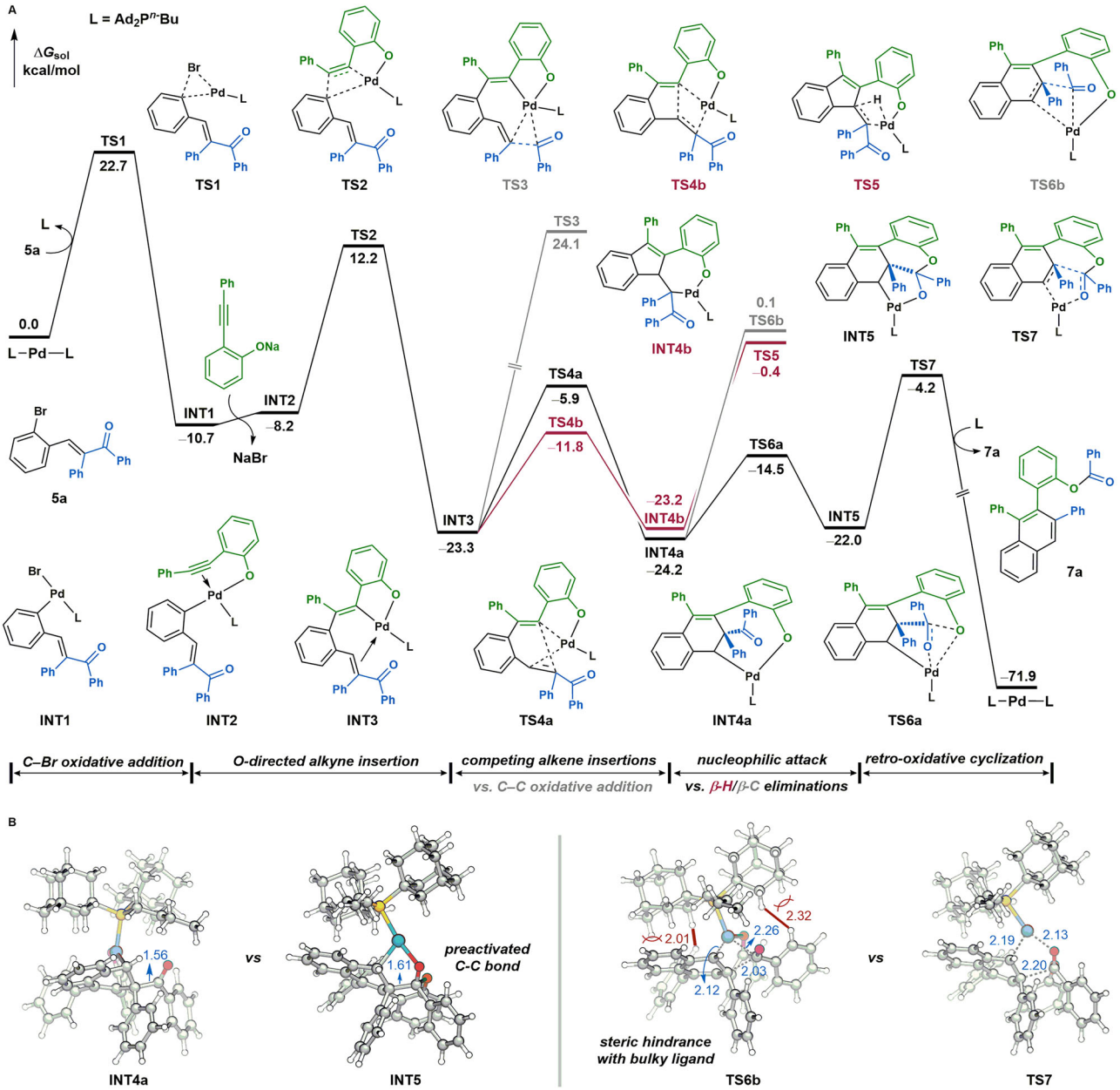

Fig. 5 | Mechanistic studies. A DFT-computed pathways for the reaction of linear carbonyls with 2-alkynylphenols. **B** Optimized structures for key intermediates and transition states. Key bond distances are given in Å.

Data availability

The authors declare that the data supporting the findings of this study, including experimental procedures and compound characterization, are available within the paper and its Supplementary Information files, or from the corresponding author upon request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Center (CCDC), under deposition numbers 2418470 (**9i**), 2418477 (**10a**), 2418491 (**10b**), 2418471 (**10g**), and 2418476 (**10h**). These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. Source data are provided with this paper.

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Author contributions

X.H. conceived and directed the project; X.H. designed the experiments; M.D., M.N., Q.G., S.Y., and M.X. performed the experiments; L.H. and G.L. performed the theoretical studies; Y.Y. performed the single-crystal X-ray analysis; all authors analyzed the experimental results and prepared the manuscript. M.D., M.N., L.H., and Q.G. contributed equally to this work.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Gang Lu or Xueliang Huang.

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