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ROYAL SOCIETY
OF CHEMISTRY

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2025, **16**, 3124

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 19th November 2024
Accepted 23rd December 2024

DOI: 10.1039/d4sc07823c

rsc.li/chemical-science

Palladium-catalysed asymmetric cascade transformations of 4-alken-2-ynyl carbonates to construct complex frameworks†

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As a class of readily available and multifunctional building blocks, the chemistry of 4-alken-2-ynyl carbonates remains to be explored. Presented herein is a palladium-catalysed cascade transformative reaction between 4-alken-2-ynyl carbonates and *ortho*-functionalised activated alkenes. Achiral 1,1-bisalkyl-4-alken-2-ynyl carbonates undergo highly regioselective propargylic substitution with *ortho*-hydroxyphenyl-tethered activated alkenes, and an auto-tandem vinylogous addition, unusual central-carbon Tsuji–Trost alkylation, protonation and β-H elimination process is followed to furnish fused and spirocyclic frameworks with high structural complexity. Even kinetic transformations with racemic 1-monoalkylated 4-alken-2-ynyl carbonates can be accomplished in the assemblies with *ortho*-aminophenyl-tethered activated alkenes to afford the analogous alkaloid architectures. This palladium-catalysed auto-tandem protocol exhibits excellent chemo-, regio-, stereoselectivity and reaction efficacy, and substantial functionality compatibility is also observed.

Introduction

Owing to their ready availability and versatile reactivity, propargylic substrates have emerged as valuable reagents in organic synthesis.[1] Upon the oxidative addition of propargylic alcohol derivatives with transition metals, the formed allenyl or propargyl metal species can undergo a variety of transformations, such as allenylation,[2] 1,3-dienylation,[3] propargylation[4] and others,[5] to afford structurally diverse products, even enantioselectively. In addition, pre-installation of a pendent alkene moiety into propargylic skeleton, as in 4-alken-2-ynyl carbonates **1**, would further enrich the transformative potential, since more reactive sites might be envisaged upon activation by transition metals. In this regard, Ma recently revealed that vinylidene-π-allyl palladium intermediates **I**, which were generated *in situ* from 1,1-bisalkyl-substituted 4-alken-2-ynyl carbonates **1** and Pd^0, could undergo Tsuji–Trost-type reaction with stabilized carbon-centred nucleophiles to furnish achiral 1,2,3-butatrienes with exclusive linear selectivity.[6] Unfortunately, the reactivity of racemic propargylic substrates ($R^1 \neq R^2$) was not well investigated in this work, and poor *E*/*Z* selectivity was observed for the sole example. In addition, switching the regioselectivity of nucleophilic substitution to the more sterically hindered C1 position *via* potential species **II** is a formidable challenge, but would provide valuable opportunities in latent reaction design owing to the versatile features of the enyne products (Scheme 1a).[7] Taking advantage of the multiple catalytic roles of palladium,[8] here, we would like to present an unprecedented cascade transformative reaction between 4-alken-2-ynyl carbonates **1** and *ortho*-functionalised activated alkenes, such as 3-olefinic oxindoles **2**. As outlined in Scheme 1b, the oxidative addition of Pd^0 to carbonates **1** would generate propargylic palladium complexes **II**. In sharp contrast to Ma's work, exclusive C1-regioselective substitution with *O*-centered nucleophiles was observed to deliver multifunctional propargylated intermediates **III**. By employing our recently developed π-Lewis base catalysis,[9] Pd^0 further enhanced the nucleophilicity of the alkyne moiety by forming η^2-complexes with increased highest occupied molecular orbital (HOMO) energy levels, thus facilitating intramolecular vinylogous addition to the 3-olefinic oxindole motif to produce ene-π-allyl-Pd intermediates **IV**. Intriguingly, an unusual nucleophilic attack on the central carbon of π-allylpalladium-type species occurred to afford palladacyclobutanes **V**.[10] Subsequent protonation and β-H elimination delivered fused and spirocyclic architectures **3** with high molecular complexity.[3,11] It is noteworthy that highly regio-, chemo- and enantioselective assemblies were achieved in this palladium-based auto-tandem catalysis.[12]

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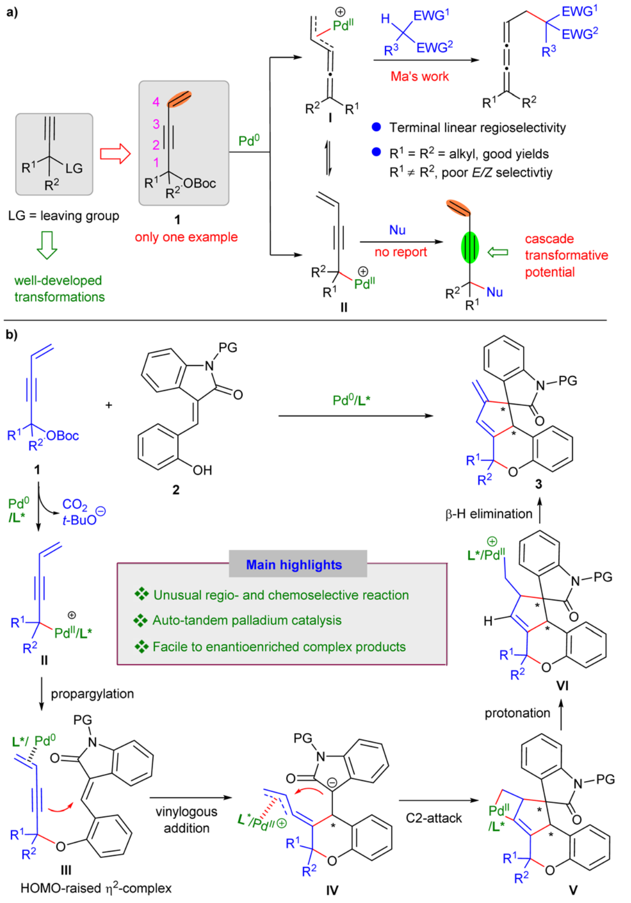
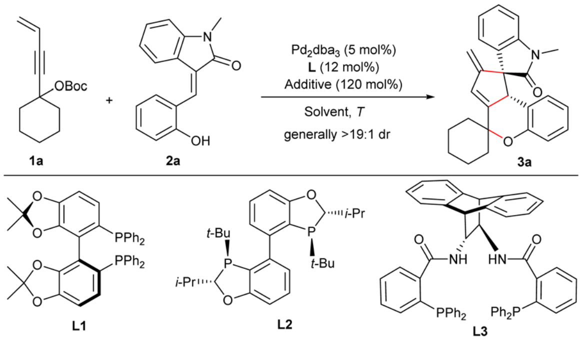
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for new compounds, NMR and HRMS spectra, and HPLC chromatograms, CIF files of enantiopure **3o**, **12g** and racemic **17**, **18**, **20** (CIF). CCDC 2381131–2381135. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4sc07823c



Scheme 1 Typical reaction pathways of propargylic derivatives and our design for palladium-catalysed cascade transformations of 4-alken-2-ynyl carbonates. (a) Transformations from propargylic substrates to 4-alken-2-ynyl carbonates. (b) This work: Pd^0-catalysed cascade transformations of 4-alken-2-ynyl carbonates.

Table 1 Screening conditions for the asymmetric auto-tandem reaction[a]



Entry	L	Solvent	T (°C)	t (h)	Additive	Yield[b] (%)	ee[c] (%)
1[d]	—	MeCN	80	36	—	78	—
2	**L1**	MeCN	80	24	—	56	29
3	**L2**	MeCN	80	24	—	33	58
4	**L3**	MeCN	80	24	—	63	74
5	**L3**	MeCN	50	48	—	63	85
6	**L3**	NMP	50	48	—	58	87
7	**L3**	DMF	50	48	—	62	85
8	**L3**	DMA	50	48	—	57	88
9[e]	**L3**	DMA	50	48	—	60	88
10[e]	**L3**	DMA	50	48	$KHCO_3$	73	89
11[e,f]	**L3**	DMA	45	60	$KHCO_3$	72	91
12[e,f,g]	**L3**	DMA	45	60	$KHCO_3$	48	91

[a] Unless noted otherwise, reactions were performed with carbonate **1a** (0.1 mmol), alkene **2a** (0.12 mmol), Pd_2dba_3 (5 mol%), ligand **L** (12 mol%) and additive (1.2 equiv.) in degassed solvent (1.0 mL) under Ar. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase, and >19 : 1 dr was generally obtained through ^1H NMR analysis. [d] With $Pd(PPh_3)_4$ (5 mol%). [e] In DMA (2.0 mL). [f] With **1a** (0.15 mmol) and **2a** (0.1 mmol). [g] With Pd_2dba_3 (2.5 mol%) and **L3** (6 mol%).

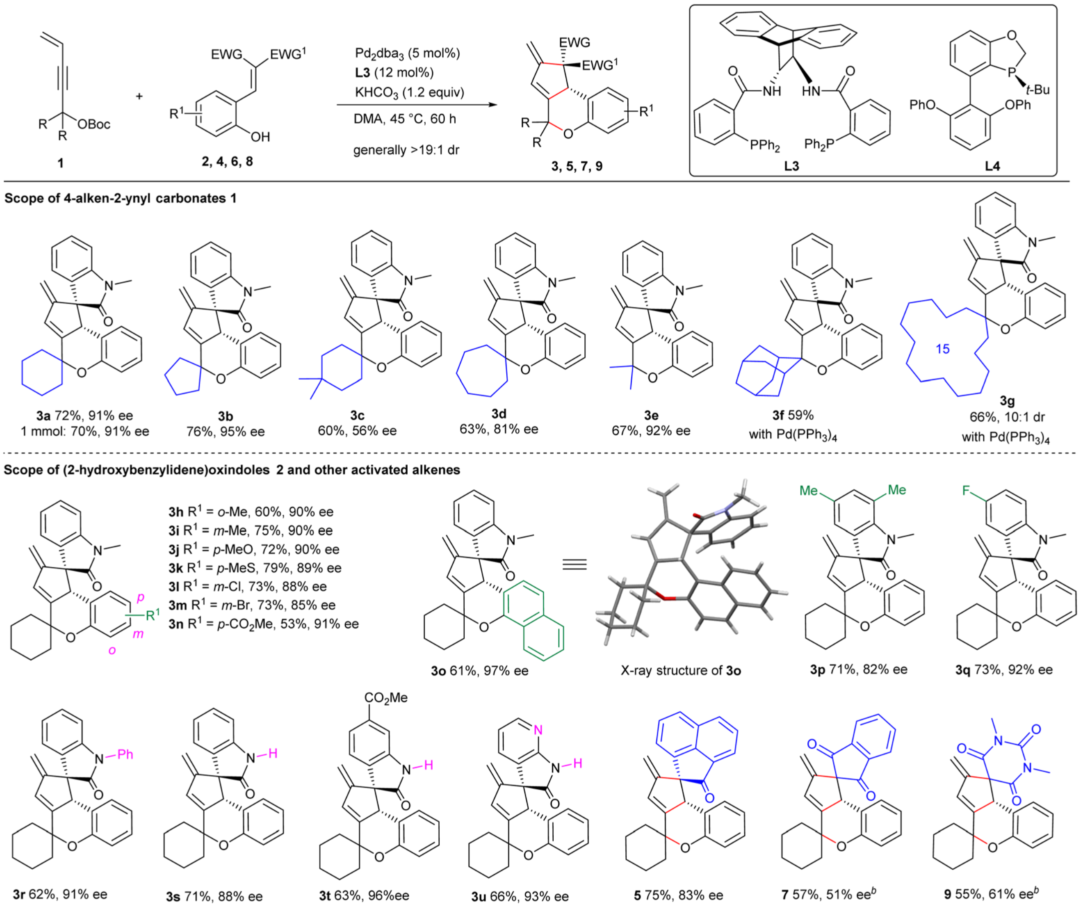
Results and discussion

Reaction optimisation

The reaction of 4-alken-2-ynyl carbonate **1a** and (*E*)-3-(2-hydroxybenzylidene)oxindole **2a** was initially examined in MeCN at 80 °C. The reaction proceeded smoothly in the presence of $Pd(PPh_3)_4$, and product **3a** was obtained straightforwardly in a good yield through the proposed pathway as virtually a single diastereomer (Table 1, entry 1). Next, we turned our attention to the enantioselective synthesis of **3a**. After a brief survey of various chiral ligands, we quickly found that bisphosphine ligands exhibited good catalytic performance for the current transformations.[13] Fair enantioselectivity was observed for ligands **L1** and **L2** in combination with Pd_2dba_3 (entries 2 and 3), and ligand **L3** having an anthracene diamine backbone substantially boosted both the efficiency and enantiocontrol (entry 4). Lowering the temperature enhanced the enantioselectivity, although a longer time was required to achieve better conversions (entry 5). A solvent survey suggested enantiocontrol was slightly improved in polar solvents (entries 6–8), and a higher yield was obtained in diluted DMA (entry 9). Then, several additives were screened,[13] and $KHCO_3$ was found to be beneficial to the yield (entry 10). A satisfactory yield with an excellent ee value was finally obtained by employing 1.5 equivalents of carbonate **1a** at 45 °C (entry 11), whereas the yield was reduced significantly when using 2.5 mol% of Pd_2dba_3 (entry 12).

Substrate scope and limitations

Under the optimised conditions, the scope of the 3-vinyl propargylic carbonates **1** was first explored in the reactions with (*E*)-3-(2-hydroxybenzylidene) oxindole **2a** under the catalysis of Pd_2dba_3/**L3** with $KHCO_3$ as an additive. As summarised in Scheme 2, an array of carbonates **1** derived from different cyclic ketones reacted smoothly with **2a**, generally affording the corresponding products **3a–3d** in moderate yields with remarkable diastereo- and enantioselectivity, even in a 1.0 mmol scale reaction (product 3a), whereas a moderate ee value was observed for product **3c** bearing a 4,4-dimethylcyclohexane moiety. Pleasingly, product **3e** having *gem*-dimethyl groups was furnished with comparably good results. Unfortunately, no



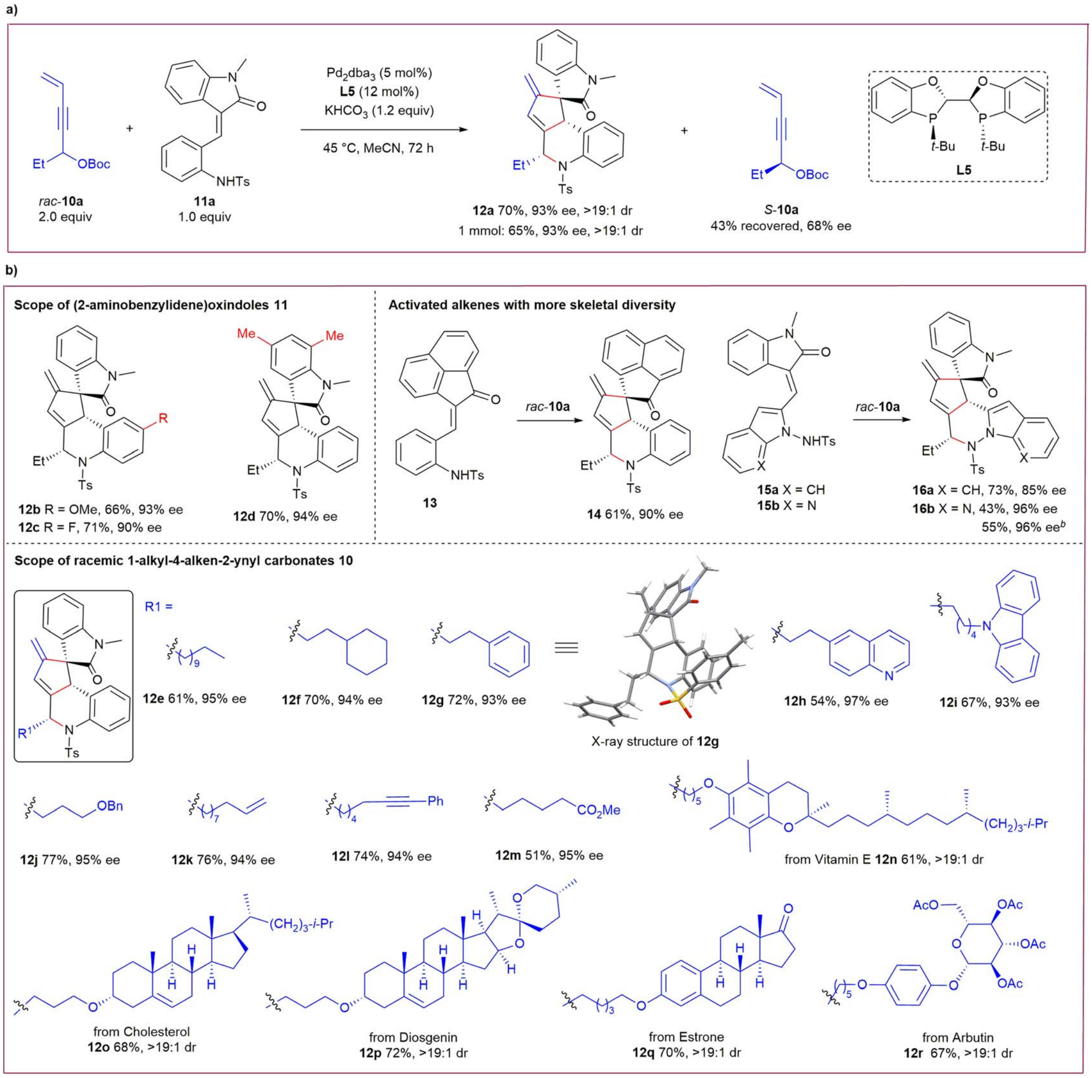
Scheme 2 Substrate scope of asymmetric auto-tandem reaction of achiral 4-alken-2-ynyl carbonates **1** and diverse activated alkenes.^{a}Unless noted otherwise, reactions were performed with carbonate **1** (0.15 mmol), activated alkene (0.1 mmol), Pd$_2$dba$_3$ (5 mol%), **L3** (12 mol%) and KHCO$_3$ (1.2 equiv.) in degassed dry DMA (2.0 mL) at 45 °C for 60 h under Ar; yields refer to the isolated product; dr was determined by ^{1}H NMR analysis of the crude product; ee was determined by HPLC analysis on a chiral stationary phase. ^{b}With **L4** (20 mol%) in toluene (1.0 mL) at 80 °C for 24 h.

apparent conversion was observed when using propargylic carbonates bearing an admantyl or cyclopentadecyl group, while racemic **3f** and **3g** could be obtained in moderate yields catalysed by Pd(PPh$_3$)$_4$. Next, the scope of functionalized alkenes **2** was evaluated (Scheme 2). Substrates with a broad range of electron-donating and -withdrawing groups at various positions of the phenyl or oxindole unit were well tolerated, generally affording the desired products **3h–3q** in moderate yields with high levels of enantioselectivity. Notably, similarly good data were obtained for (7-aza)oxindoles **2** having an *N*-phenyl or even a free NH group (products **3r–3u**).

In addition to 3-olefinic oxindoles **2**, activated alkenes derived from other skeletons were also applicable. As outlined in Scheme 2, benzylideneacenaphthenone **4** was successfully assembled with carbonate **1a** to deliver **5** in good yield and enantioselectivity under the standard conditions. Moreover, both activated alkenes **6** and **8** condensed from 1,3-indandione and barbituric acid with salicylaldehyde, respectively, proved to be reliable counterparts in the reactions with **1a** under the catalysis of Pd$_2$dba$_3$/**L4**, albeit with moderate enantiocontrol (products **7** and **9**). These results not only showcased the robustness of the current catalytic strategy, but also enriched the structural diversity of the frameworks constructed.

The successful cascade transformations of achiral 1,1-bisalkyl-substituted 4-alken-2-ynyl carbonates **1** inspired us to investigate the potential application of more challenging racemic propargylic carbonates. As illustrated in Scheme 3a, gratifyingly, 1-ethyl carbonate *rac*-**10a** (2 equiv.) could be efficiently utilised in similar asymmetric cascade transformations with (2-aminobenzylidene) oxindole **11a** catalysed by Pd$_2$dba$_3$ and ligand **L5**, furnishing an analogous alkaloid architecture **12a** in a moderate yield with excellent stereoselectivity, even on a larger scale. In addition, simultaneous kinetic resolution for recovered *rac*-**10a** was observed, albeit with moderate enantioselectivity.[14]

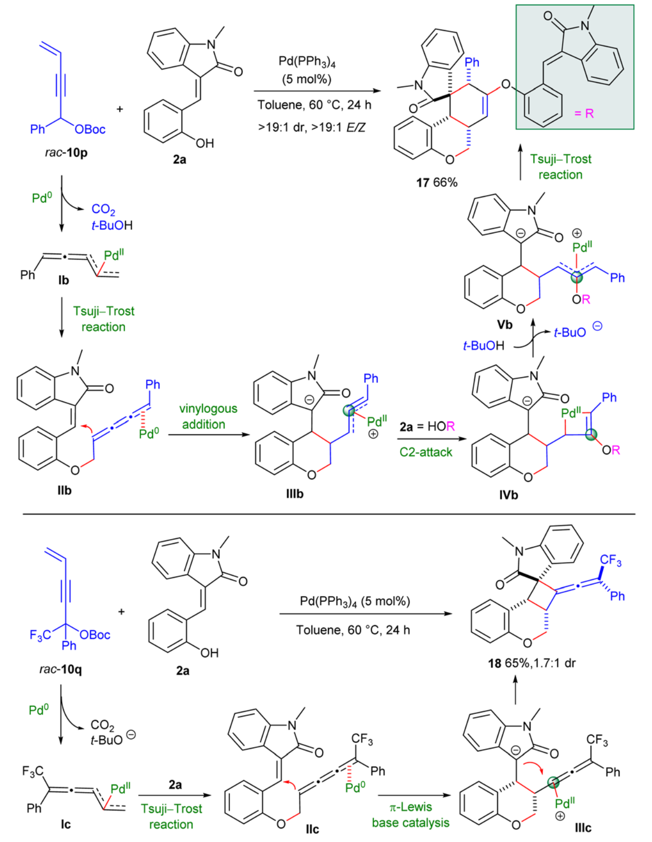
The substrate scope for this type of kinetic transformation is substantial. As summarised in Scheme 3b, good yields and high enantioselectivity were uniformly obtained for activated alkenes **11** with different substituents on the aryl unit under the standard catalytic conditions (products **12b–12d**). Activated alkene **13** and newly designed **15** smoothly participated in the reactions with *rac*-**10a** to produce complex frameworks **14** and **16a–**



Scheme 3 Substrate scope for kinetic transformations of racemic 1-alkyl-substituted 4-alken-2-ynyl carbonates **10**.[a](a) Kinetic transformations of racemic 1-alkyl-4-alken-2-ynyl carbonates *via* auto-tandem catalysis. (b) Substrate scope investigation.[a]Unless noted otherwise, reactions were performed with racemic carbonate **10** (0.2 mmol), activated alkene (0.1 mmol), Pd_2dba_3 (5 mol%), **L5** (12 mol%) and $KHCO_3$ (1.2 equiv.) in degassed MeCN (1.0 mL) at 45 °C for 72 h under Ar; [b]With *rac*-**10a** (0.3 mmol).

16b with high efficiency. Importantly, a spectrum of racemic propargylic carbonates **10** with diverse 1-alkyl substitutions, including those bearing various functionalities, were compatible in the reactions with activated alkene **11a**, yielding products **12e–12m** with high enantiocontrol. This method also provides an efficient tool for the late-stage modification of bioactive molecules. A broad range of chiral drugs (or their fragments) containing a 3-vinyl motif were competent in this process, which led to the complex products **12n–12r** in moderate yields with excellent diastereoselectivity.

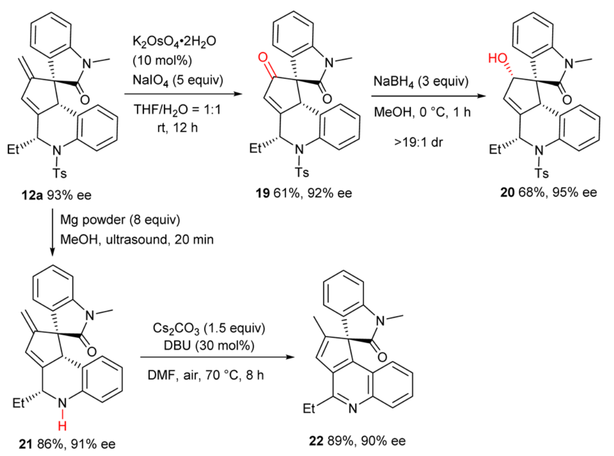
Of particular note, 1-phenyl-substituted carbonate *rac*-**10p** underwent *O*-allylic alkylation with (*E*)-3-(2-hydroxybenzylidene) oxindole **2a** with distinct terminal regioselectivity under the catalysis of $Pd(PPh_3)_4$,[6] probably resulting from the generation of thermally more stable 1-phenyl allenyl-π-allyl species **Ib.** The formed 1,2,3-butatriene intermediate **IIb** could be similarly HOMO-activated by Pd(0) *via* a π-Lewis base pattern, thus facilitating intramolecular vinylogous addition to the 3-olefinic oxindole motif. Interestingly, the resultant η^3-propargylpalladium species **IIIb** was C2-attacked by another molecule of **2a,** delivering palladacyclobutene intermediate **IVb.** Subsequent protonation and intramolecular Tsuji–Trost reaction of **Vb** would furnish spirocyclic product **17** with high diastereo- and *E*/*Z*-selectivity (Scheme 4).[5] Moreover, tertiary propargylic carbonate *rac*-**10q** was found to undergo similar Tsuji–Trost reaction/vinylogous addition with **2a** efficiently through intermediates **Ic** and **IIc**, respectively, whereas the formed η^1-allenylpalladium moiety of **IIIc** was intramolecularly captured by enolate to provide intriguing cyclobutane-fused chromanone **18** having a tetrasubstituted exocyclic allene motif in a moderate yield with fair diastereoselectivity.[2g–i] Although the asymmetric variants were not applicable at the current stage, these explorations clearly demonstrated the versatile reactivity of 4-alken-2-ynyl carbonates and significantly enriched the product diversity.



Scheme 4 Divergent transformations of 1-aryl-4-alken-2-ynyl carbonates.

Synthetic transformations

Further transformations successfully exemplified the synthetic utility of the multifunctional products. As depicted in Scheme 5, osmium-catalysed oxidative cleavage of the terminal olefin moiety of **12a** afforded ketone **19** in a moderate yield, which was further reduced to alcohol **20** with exclusive diastereoselectivity. Additionally, the *N*-Ts group was efficiently removed to deliver amine **21**, and fused quinoline **22** was obtained in high yield *via* a base-promoted isomerization/oxidative aromatization process. It should be noted that the spirooxindole-fused polycycles and their derivatives are core subunits of many bioactive natural products and drug candidates.[15]



Scheme 5 Transformations of product **12a**.

Conclusions

In summary, we successfully developed a cascade transformative reaction between 4-alken-2-ynyl carbonates and *ortho*-functionalized activated alkenes under auto-tandem palladium catalysis. This process showed high regio-, chemo-, and stereoselectivity through integrating classical palladium-mediated nucleophilic substitution with our newly uncovered π-Lewis base catalysis into a one-pot fashion. Both achiral 1,1-bisalkyl- and racemic 1-alkyl-4-alken-2-ynyl carbonates with broad substitution patterns underwent C1-selective propargylation to afford enyne intermediates, and fused and spirocyclic frameworks with high structural complexity were finally furnished enantioselectively upon tandem palladium catalysis, which proceeded *via* a cascade vinylogous addition, unusual central carbon Tsuji–Trost alkylation, protonation and β-H elimination process. In contrast, 1-aryl-substituted 4-alken-2-ynyl carbonates favoured terminal substitution to generate 1,2,3-butatriene intermediates, and regiodivergent transformations gave distinct polycyclic architectures, albeit in a racemic pattern. This work exhibits the versatile reaction potential of multifunctional 4-alken-2-ynyl carbonates, which offer a platform to construct structurally complex compounds *via* auto-tandem catalysis. More results will be reported in due course.

Data availability

The data that support the findings of this study are available in the ESI† or on request from the corresponding author.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from NSFC (21931006 and 21921002). We thank Dr Meng Yang from College of Chemistry, Sichuan University, for X-ray diffraction analysis.

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