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Palladium-catalyzed hydrofunctionalization cyclization of 1,3-enynes to access cyclopenta[*b*]indoles

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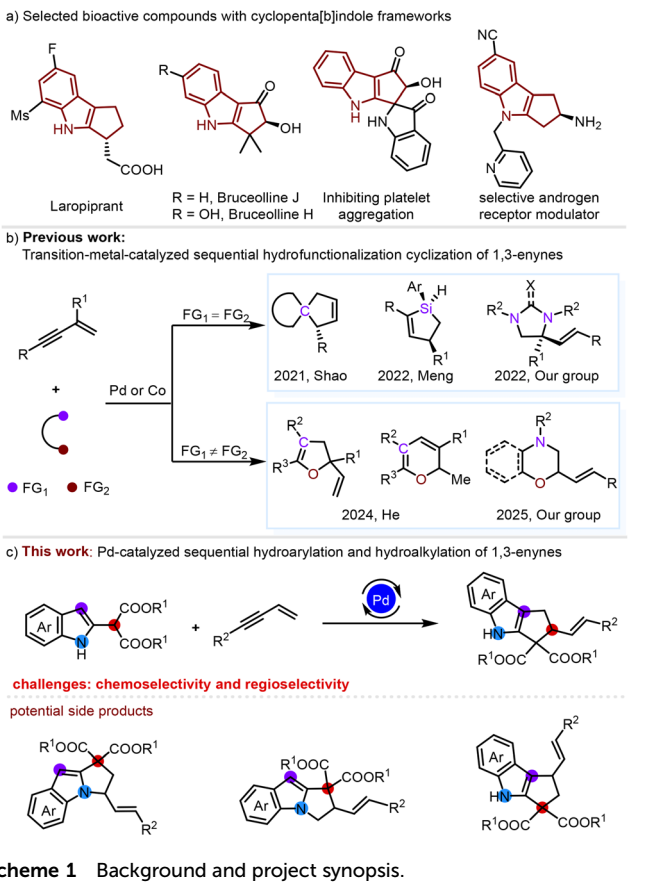
We herein present a palladium-catalyzed sequential hydroarylation and hydroalkylation of readily available 1,3-enynes with indole-2-malonates. This redox-neutral strategy provides a facile, atom and step-economical route for the synthesis of cyclopenta[*b*]indoles under mild conditions, featuring good yields, excellent chemo- and regioselectivities and broad substrate tolerance as well. The synthetic utility of this method is further highlighted by the gram-scale preparation and rapid access to diverse value-added indole derivatives.

Introduction

The cyclopenta[*b*]indole scaffold, an important 6,5,5-tricyclic framework, is frequently encountered in a diverse array of natural products and biologically active compounds,[1] exhibiting wide-ranging biological activities.[2] For instance, laropiprant, as a DP receptor antagonist, is believed to have a cholesterol lowering effect,[3] while bruceollines are used for the treatment of malaria diseases (Scheme 1a).[4] Given their significance, these architectures have garnered considerable interest from the synthetic community.[5] Diverse synthetic strategies have been developed for the construction of cyclopenta[*b*]indoles,[6] as represented by Fischer indole synthesis,[7] dipolar cycloaddition,[8] radical cycloaddition,[9] gold(I)-catalyzed Rautenstrauch rearrangement[10] and the tandem Heck–Suzuki reaction.[11] Despite these elegant approaches, the development of direct, atom- and step-economical protocols using readily available starting materials remains highly desirable.

Over the past decades, transition-metal-catalyzed hydrofunctionalization of unsaturated hydrocarbons has emerged as a powerful and straightforward tool for the rapid access to structurally diverse, value-added compounds.[12–14] Within this field, the sequential hydrofunctionalization is particularly attractive. This strategy exploits the inherent potential of unsaturated hydrocarbons to incorporate multiple functional groups in a single operation, offering an atom-economical and redox-neutral route to versatile cyclic scaffolds.[15] However, to the best of our knowledge, only a few versions of such reactions have been reported to date. Recently, independent studies by Shao,[16] Meng,[17] and our group[18] have demonstrated Pd- or Co-catalyzed sequential hydrofunctionalizations of enynes with two identical functional groups to construct cyclic compounds in good yields with excel-



Scheme 1 Background and project synopsis.

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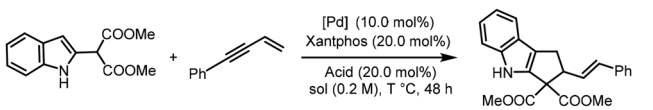
lent enantioselectivity (Scheme 1b, top panel). In contrast, the simultaneous incorporation of two distinct functional groups presents significant synthetic challenges, primarily due to the difficulty in controlling chemo- and regioselectivity, and thus remains in its infancy. In 2024, He and coworkers reported a Pd-catalyzed chemodivergent sequential hydroalkylation and hydroalkenoxylation of enynes with ketoesters, producing multisubstituted dihydrofurans and hydropyrans with excellent regioselectivities.[19] In 2025, our group developed a Pd-catalyzed sequential hydroamination and hydroxylation of 1,3-enynes with 2-aminophenol derivatives, generating 3,4-dihydro-2*H*-1,4-benzoxazines with excellent chemoselectivity (Scheme 1b, bottom panel).[20] As a continuation of our interest in the catalytic hydrofunctionalization of unsaturated hydrocarbons and heterocycle construction,[18,20,21] we herein describe a palladium-catalyzed sequential hydroarylation and hydroalkylation of conjugated enynes with indole-2-malonates (Scheme 1c). This transformation poses a distinct challenge owing to the multiple reactive centers present in both coupling partners, demanding precise control over both chemoselectivity and regioselectivity.

Results and discussion

Our investigation commenced with dimethyl 2-(1*H*-indol-2-yl) malonate **1a** and readily available but-3-en-1-yn-1-ylbenzene **2a** as the model substrates. Utilizing $Pd_2(dba)_3$ as the catalyst, Xantphos as the ligand, PhCOOH as the acid additive and DCM as the solvent, product **3aa** was isolated in 30% yield with good regioselectivity (Table 1, entry 1). Subsequent catalysis optimization revealed that Pd(II) catalysts gave superior results than Pd(0) catalysts, and $Pd(OAc)_2$ proved to be the optimal catalyst, providing **3aa** in 63% yield (Table 1, entries 2–4). Screening of alternative acid additives did not lead to further improvement (Table 1, entries 5–7). Similarly, the evaluation of different solvents did not produce better outcomes, with **3aa** formed in 40–53% yields (Table 1, entries 8–11). Lowering the reaction temperature efficiently suppressed side reactions and improved the yield (Table 1, entries 12 and 13). When the reaction was carried out at 30 °C, **3aa** was produced in 70% yield, with the hydroalkylation byproduct formed in 15% yield (see the SI for more details). Further reduction in temperature proved unbeneficial. In addition, decreasing the catalyst loading led to **3aa** in a comparably lower yield (Table 1, entry 14). A control experiment confirmed that the acid additive is essential, as its omission drastically reduced the formation of **3aa** (Table 1, entry 15).

Adopting the optimized conditions, we then investigated the substrate scope of 1,3-enynes for this reaction (Table 2).

Table 1 Optimization of the reaction conditions[a,b]

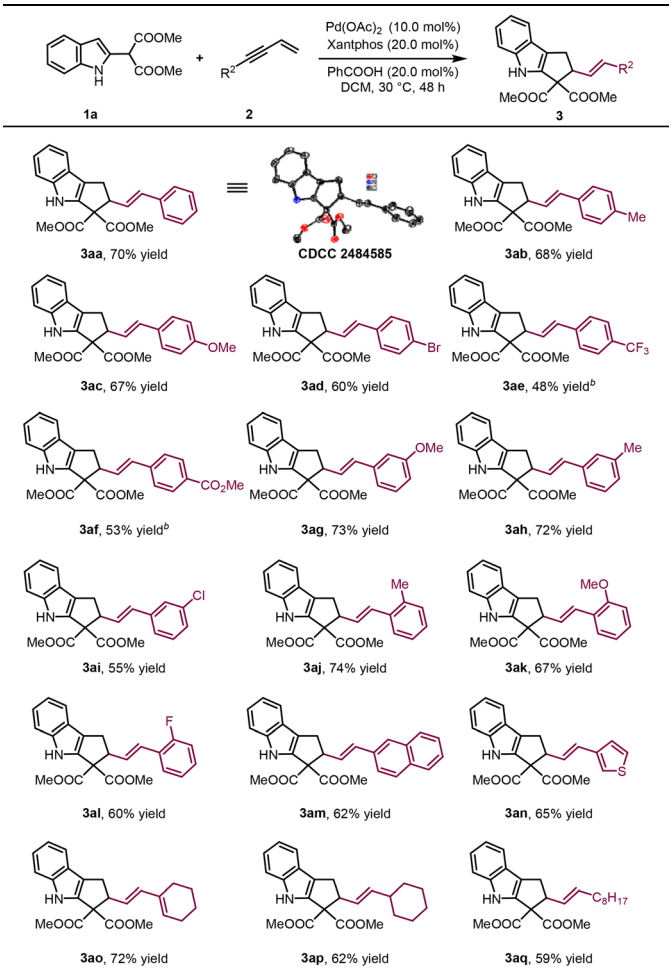


1a 2a 3aa

Entry	[Pd] source	Acid	Solvent	T/°C	Yield %
1	$Pd_2(dba)_3$	PhCOOH	DCM	80	30
2	$Pd(PPh_3)_4$	PhCOOH	DCM	80	20
3	$[Pd(allyl)Cl]_2$	PhCOOH	DCM	80	60
4	$Pd(OAc)_2$	PhCOOH	DCM	80	63
5	$Pd(OAc)_2$	$PhCH_2COOH$	DCM	80	59
6	$Pd(OAc)_2$	Ph_3CCOOH	DCM	80	59
7	$Pd(OAc)_2$	$(PhO)_2POOH$	DCM	80	31
8	$Pd(OAc)_2$	PhCOOH	Tol	80	52
9	$Pd(OAc)_2$	PhCOOH	DME	80	43
10	$Pd(OAc)_2$	PhCOOH	DCE	80	53
11	$Pd(OAc)_2$	PhCOOH	DMF	80	40
12	$Pd(OAc)_2$	PhCOOH	DCM	50	65
13	$Pd(OAc)_2$	PhCOOH	DCM	30	70
14[c]	$Pd(OAc)_2$	PhCOOH	DCM	30	54
15	$Pd(OAc)_2$	—	DCM	30	34

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Pd] (10.0 mol%), ligand (20.0 mol%), acid (20.0 mol%), solvent (0.2 M), T °C (oil bath temperature), 48 h. [b] Isolated yields. [c] $Pd(OAc)_2$ (5.0 mol%) and Xantphos (10.0 mol%).

Table 2 Substrate scope of 1,3-enynes[a]



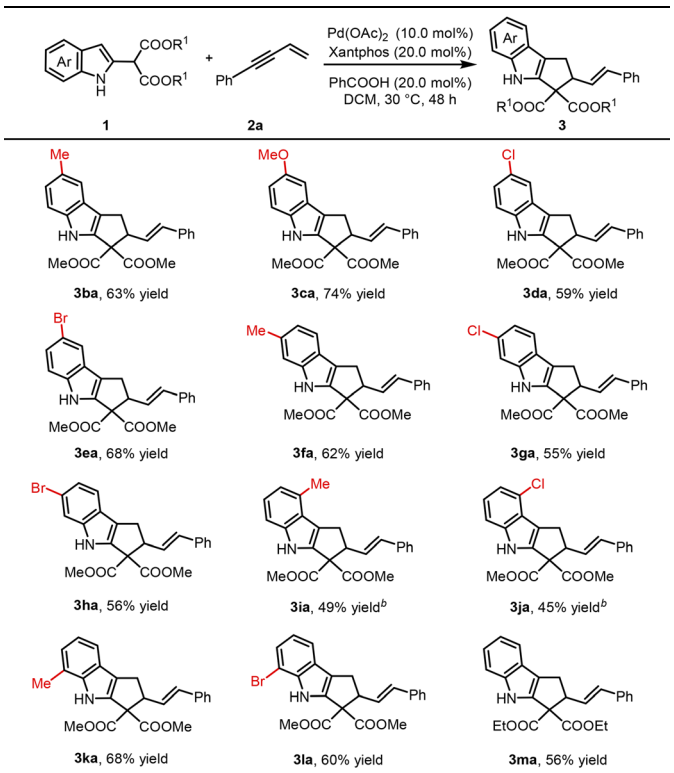
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (10.0 mol%), Xantphos (20.0 mol%), PhCOOH (20.0 mol%), DCM (0.2 M), at 30 °C (oil bath temperature) under argon for 48 h; isolated yields. [b] 80 °C (oil bath temperature).

Aryl enynes bearing electron-donating (–Me, –OMe) or bromine substituents at the *para*-position of the phenyl ring were all compatible with this catalytic system, delivering tricyclic indoles **3ab–3ad** in 60–68% yields. When electron-withdrawing groups, such as trifluoromethyl and ester, were incorporated on the phenyl ring, **3ae** and **3af** were obtained in 48% and 53% yields, respectively, at 80 °C, which might be due to their lower reactivities. The reaction of *meta*-substituted enynes with **1a** proceeded smoothly to generate products **3ag–3ai** in 55–73% yields. Good results were also observed when incorporating functional groups such as methyl, methoxy and fluoride at the *ortho*-position of phenyl rings (**3aj–3al**). In addition to phenyl groups, other fused arenes and heterocycles, such as naphthalene (**2m**) and thiophene (**2n**), were tolerated in this transformation as well, delivering the desired products **3am** and **3an** in 62–65% yields. Moreover, on switching the aromatic rings to the cyclohexene moiety, the reaction proceeded smoothly to provide product **3ao** in 72% yield. Aliphatic enynes also participated to afford **3ap** and **3aq** in 62% and 59% yields, respectively. The relative configuration of **3aa** was determined by X-ray diffraction analysis of a single crystal.[22]

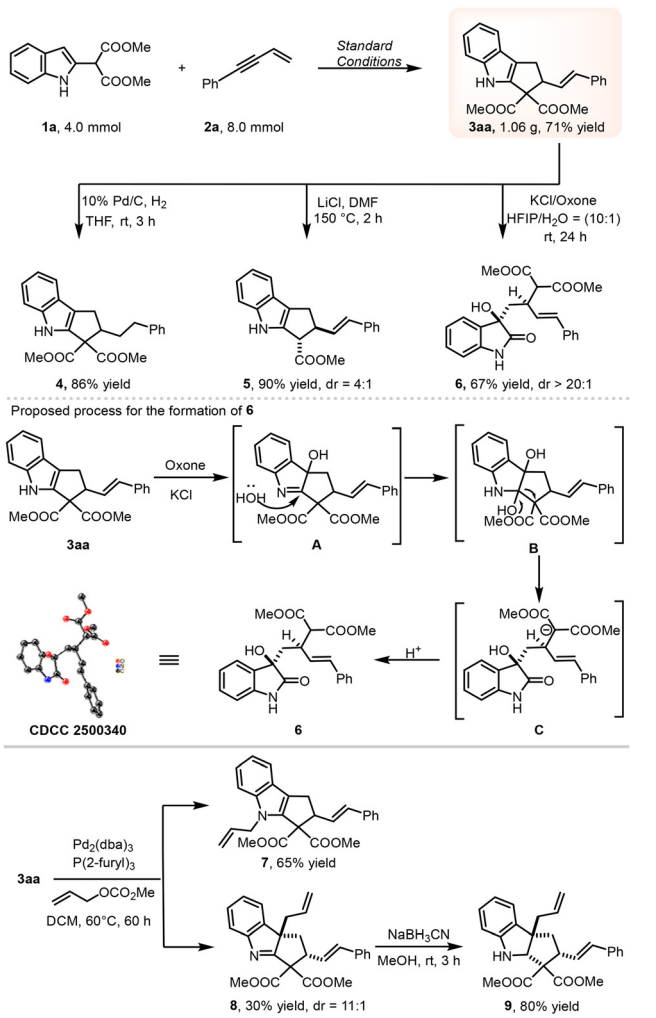
Subsequently, we then surveyed the generality of the reaction with regard to indoles. As shown in Table 3, both electron-donating (–Me, –OMe) and electron-withdrawing (–Cl, –Br) groups at the 5- or 6-positions of the aromatic rings were well tolerated in this reaction, producing compounds **3ba–3ha** in 55–74% yields. However, introducing substituents at the 4-position of the indole skeletons led to products **3ia** and **3ja** in slightly lower yields, which might be due to steric repulsion. The developed protocol also proved compatible with different substituents at the C7-position, as shown by the generation of products **3ka** and **3la** in 68% and 60% yields, respectively. On replacing methyl ester with ethyl ester, **3ma** was formed in 56% yield with excellent regioselectivity. When introducing a methyl group on the indole nitrogen, no product was detected with most of the starting material recovered (see the SI for more details).

To demonstrate the synthetic utility of this protocol, we performed a gram-scale reaction and diverse transformations. As shown in Scheme 2, when the reaction of **1a** was scaled up 20-fold under standard conditions, product **3aa** was formed in 71% yield. The alkenyl motif in product **3aa** was easily reduced under the conditions of Pd/C, leading to product **4** in 86%

Table 3 Substrate scope of indole-2-malonates[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (10.0 mol%), Xantphos (20.0 mol%), PhCOOH (20.0 mol%), DCM (0.2 M), at 30 °C (oil bath temperature) under argon for 48 h; isolated yields. [b] 80 °C (oil bath temperature).



Scheme 2 Further studies of the reaction.

yield. With the treatment of LiCl, **3aa** could undergo a Krapcho decarboxylation to afford the corresponding ester **5** in 90% yield with a moderate dr value. Additionally, compound **3aa** underwent an oxidation/ring-opening sequence in the presence of oxone and KCl, delivering oxindole **6** in 67% yield with >20 : 1 dr. Based on previous studies,[23] a plausible mechanism is proposed as shown in the middle panel. In the presence of oxone and KCl, **3aa** undergoes formal hydroxylation at the C3-position of the indole motif, giving intermediate **A**; subsequently, H_2O attacks the iminium to generate intermediate **B**, which undergoes ring opening to give carbon anion **C**. Finally, protonation of **C** produces oxindole **6**. In addition, the relative configuration of **6** was determined by X-ray diffraction analysis of a single crystal.[22] The Pd-catalyzed allylic substitution reaction of **3aa** afforded *N*-allyl tricyclic indole **7** in 65% yield, along with the C3-allylation product **8** in 30% yield with 11 : 1 dr. The reduction of the imine group in compound **8** with $NaBH_3CN$ proceeded smoothly to give the multi-substituted cyclopentane-fused indoline **9** in 80% yield. The configurations of **5** and **9** were determined by nuclear Overhauser effect spectroscopy experiments (see the SI for more details).

Conclusions

In summary, we have developed a Pd-catalyzed sequential hydroarylation and hydroalkylation of 1,3-enynes with indole-2-malonates. This redox-neutral reaction provides an efficient approach for the synthesis of cyclopenta[*b*]indoles, exhibiting good yields, excellent chemo- and regioselectivities and a broad substrate scope. The synthetic utility of this method is demonstrated by a gram-scale reaction and rapid transformations of the products into versatile indole derivatives. Current efforts are focused on expanding this platform through the asymmetric hydroalkylation and hydroarylation of 1,3-enynes.

Author contributions

A. L. and H. Y. directed the project. Z. M. and X. L. performed the experiments, analysed the data and prepared the SI. H. Y. and A. L. jointly wrote the original draft. A. L. reviewed and edited the manuscript and the SI.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: detailed experimental procedures and characterization data for new compounds. See DOI: **https://doi.org/10.1039/d6qo00090h**.

CCDC 2484585 and 2500340 (**3aa** and **6**) contain the supplementary crystallographic data for this paper.[22a,b]

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