

RESEARCH ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/d6qo00090h

Received 22nd January 2026,
Accepted 6th March 2026

DOI: 10.1039/d6qo00090h

rsc.li/frontiers-organic

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

Zonglin Ma, Xihang Lu, Hequan Yao * and Aijin Lin *

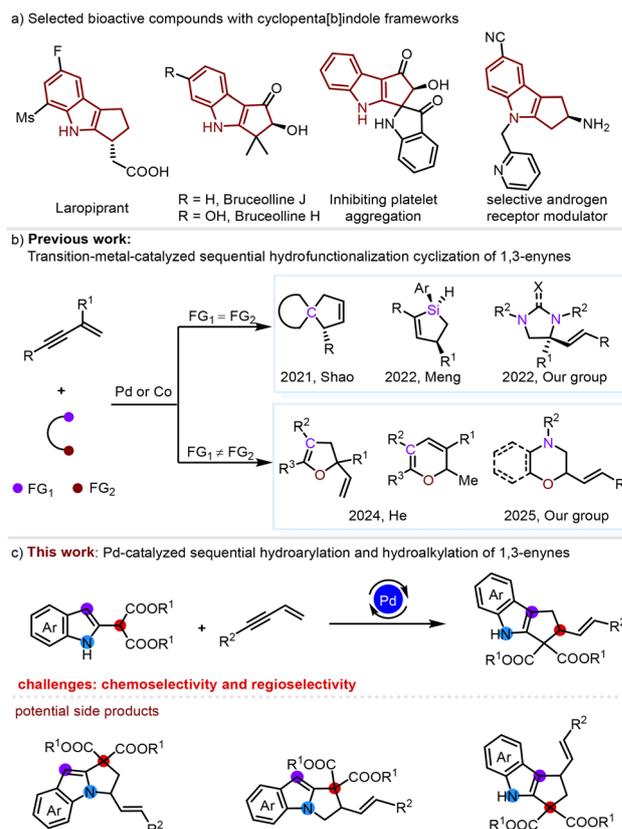
We herein present a palladium-catalyzed sequential hydroarylation and hydroalkylation of readily available 1,3-enynes with indole-2-malonates. This redox-neutral strategy provides a facile, atom and step-economical route for the synthesis of cyclopenta[*b*]indoles under mild conditions, featuring good 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 rearrangement¹⁰ 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

group¹⁸ 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.

State Key Laboratory of Natural Medicines (SKLNM) and Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing 210009, P. R. China. E-mail: hyao@cpu.edu.cn, ajlin@cpu.edu.cn



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, H₂O 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 NaBH₃CN 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}

Acknowledgements

The authors acknowledge the generous financial support from the National Natural Science Foundation of China (NSFC 22371299), the Natural Science Foundation of Jiangsu Province (BK20242068), the Project Program of State Key Laboratory of Natural Medicines (SKLNMZZ202211), and the Open Project of State Key Laboratory of Natural Medicines (SKLNMKF202401).

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