# 11-Step and Scalable Total Synthesis of Hamigeran M Enabled by Five C–H Functionalizations

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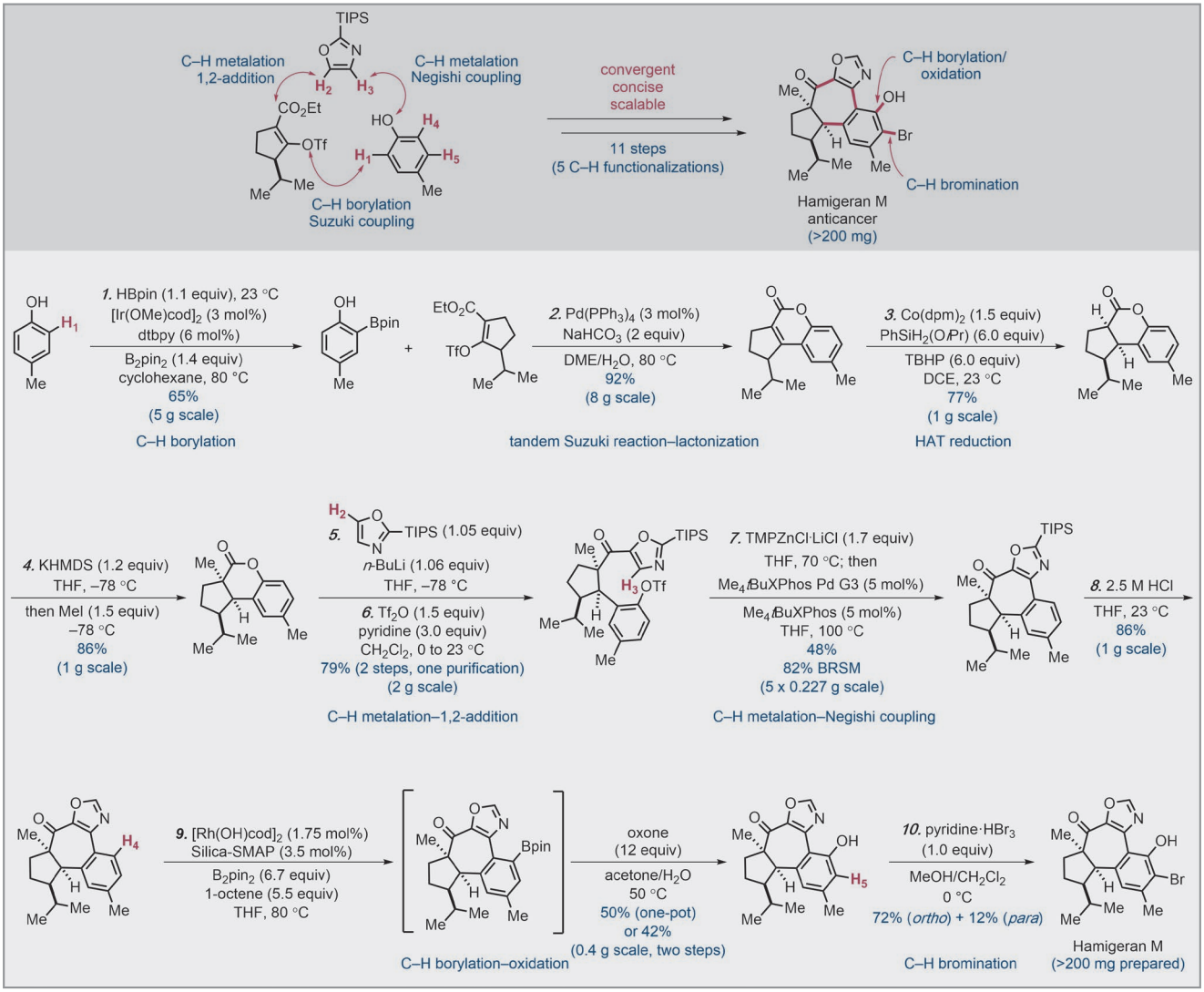
Advances in the field of C–H functionalization have brought revolutionary changes in the total synthesis of natural products. Direct functionalizations of C–H bonds in complex structural settings can significantly enhance synthetic efficiency and economy by avoiding preliminary functional group installations and subsequent manipulations. The group of Professor Mingji Dai, from Purdue University (West Lafayette, Indiana, USA), has been developing innovative strategies and methodologies to facilitate the total synthesis and biological profiling of complex bioactive natural products (for recent examples of contributions from the Dai group: *Angew. Chem. Int. Ed.* **2021**, *61*, e202115633); *J. Am. Chem. Soc.* **2021**, *143*, 16383–16387;




**Scheme 1** Total synthesis of hamigeran M

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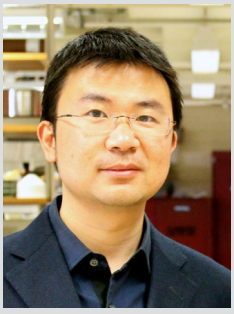
*J. Am. Chem. Soc.* **2021**, *143*, 4379–4386; *Angew. Chem. Int. Ed.* **2021**, *60*, 24828–24832; *J. Am. Chem. Soc.* **2020**, *142*, 13677–13682). They recently reported the first total synthesis of the anticancer natural product hamigeran M. "Our synthetic strategy centers on several enabling C–H functionalizations. The hamigeran molecules are challenging synthetic targets, but with promising therapeutic potential," said Professor Dai. His group and several other groups around the world are particularly interested in the hamigerans with a 6-7-5 tricyclic carbon skeleton. Among them, hamigeran M showed potent activity against leukemia cancer cell proliferation and features a unique oxazole moiety, which is rare in terpene natural products of marine origin. "While the oxazole moiety was formed toward the end of hamigeran M's biosynthesis, we decided to use an oxazole as a key building block and take advantage of its reactivity for two key C–H functionalizations to forge two C–C bonds in the seven-membered ring," said Professor Dai.

Their synthesis is summarized in Scheme 1. Five C–H functionalizations enabled Professor Dai and co-author Baiyang Jiang to complete a concise and modular total synthesis of hamigeran M in 11 steps. "These C–H functionalizations include a C–H borylation to the arylboronate building block for the next tandem Suzuki coupling–lactonization, a C–H metalation–1,2-addition to introduce the oxazole moiety, another oxazole C–H metalation–Negishi coupling to close the seven-membered ring, a late-stage oxazole-directed C–H borylation–oxidation to install the hydroxyl group, and the last electrophilic C–H bromination. In addition to these C–H functionalizations, the HAT reduction of the tetrasubstituted double bond is highly challenging, but essential for the synthesis," said Professor Dai. "Except for the electrophilic C–H bromination, which is a given, we had to treat each of the other four C–H functionalization reactions and the HAT reduction as individual methodology development projects and my co-author Baiyang Jiang deserves all the credit in realizing these transformations and completing the total synthesis," commented Professor Dai. Their synthesis was also scalable and already provided over 200 mg of hamigeran M for them to profile and understand its biological activity, especially anticancer activity. Meanwhile, the concise and modular nature of the synthetic route also opened the gate for the synthesis of more natural and synthetic analogues, in order to improve the corresponding biological function. "We are excited to continue the hamigeran adventure, both synthetically and biologically," concluded Professor Dai.

## About the authors



*Prof. M. Dai*

**Mingji Dai** was born in Pengzhou, Sichuan (P. R. of China). He received his B.S. degree from Peking University (P. R. of China) in 2002. After two years' research with Professors Zhen Yang and Jiahua Chen in the same university, he went to New York City (USA) in 2004 and pursued graduate studies under the guidance of Professor Samuel J. Danishefsky at Columbia University. After earning his Ph.D. in 2009, he took a postdoctoral position in the laboratory of Professor Stuart L. Schreiber at Harvard University (USA) and the Broad Institute (USA). In August 2012, he began his independent career as an assistant professor in the Chemistry Department and Center for Cancer Research of Purdue University (USA). He was promoted to associate professor with tenure in 2018 and full professor in 2020. He is currently a Showalter Faculty Scholar of Purdue University.

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**Baiyang Jiang** was born in Chengdu, Sichuan (P. R. of China). He received his B.S. and M.S. degrees from Peking University (P. R. of China), where he conducted research in the laboratory of Professor Suwei Dong. He joined Professor Mingji Dai's group at Purdue University (USA) in 2017 and is currently pursuing his graduate studies in complex natural product total synthesis.

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