

Regioselective Activation of Benzocyclobutenones and Dienamides Leads To Anti-Bredt Bridged-Ring Systems by a [4+4] Cycloaddition

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Bridged-ring systems are common structural motifs in many functional molecules, including bioactive natural compounds. The anti-Bredt rule has been used to qualitatively define bridged-ring systems with olefins at the bridgehead position. “Bridged skeletons are characterized by their size (e.g. we focus on bicyclo[m.n.1]) and ring strain (hybridization form of the bridgehead carbon, BC),” said Professor Tao Xu, from the Ocean University of China (Qingdao, P. R. of China), who added: “While the sp^2 -hybridized BC underpins certain limitations on both the ring size ($m + n \geq 7$) as well as ring strain, examples can still be found in a number of natural products. However, benzo-fused BC-bearing [m.n.1] systems are unusual ($m + n$

> 8) and, to the best of our knowledge, unknown to chemists when confined in a small ring ($m + n \leq 8$) framework.” The research group of Professor Xu wanted to address this challenge and try to expand the anti-Bredt rule (Figure 1a).

Professor Xu went on to explain that there are two state-of-the-art cycloaddition methods for accessing anti-Bredt bicyclo[5.3.1] scaffolds: “The first is the type II intramolecular Diels–Alder (IMDA) reaction developed by Shea; and the second is the Ni-catalyzed type II [4+4] intramolecular cycloaddition by Wender (Figure 1b)” (for references see the original article). However, according to Professor Xu, a general, catalytic and diversifiable cycloaddition strategy remained

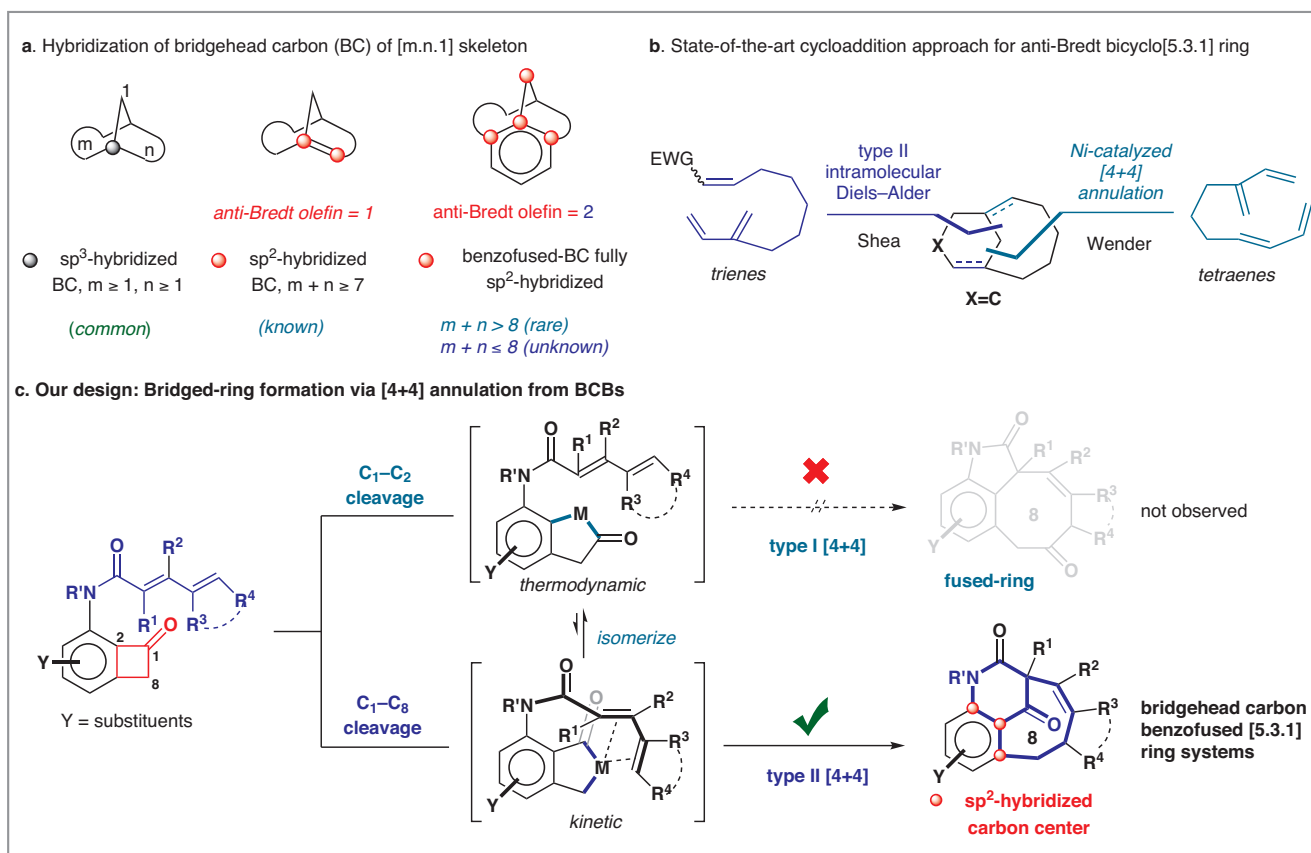


Figure 1 Design of a [4+4] annulation approach to access double anti-Bredt skeleton. a. Hybridization of bridgehead carbon of [m.n.1] systems. b. State-of-the-art cycloaddition approaches. c. Our design.

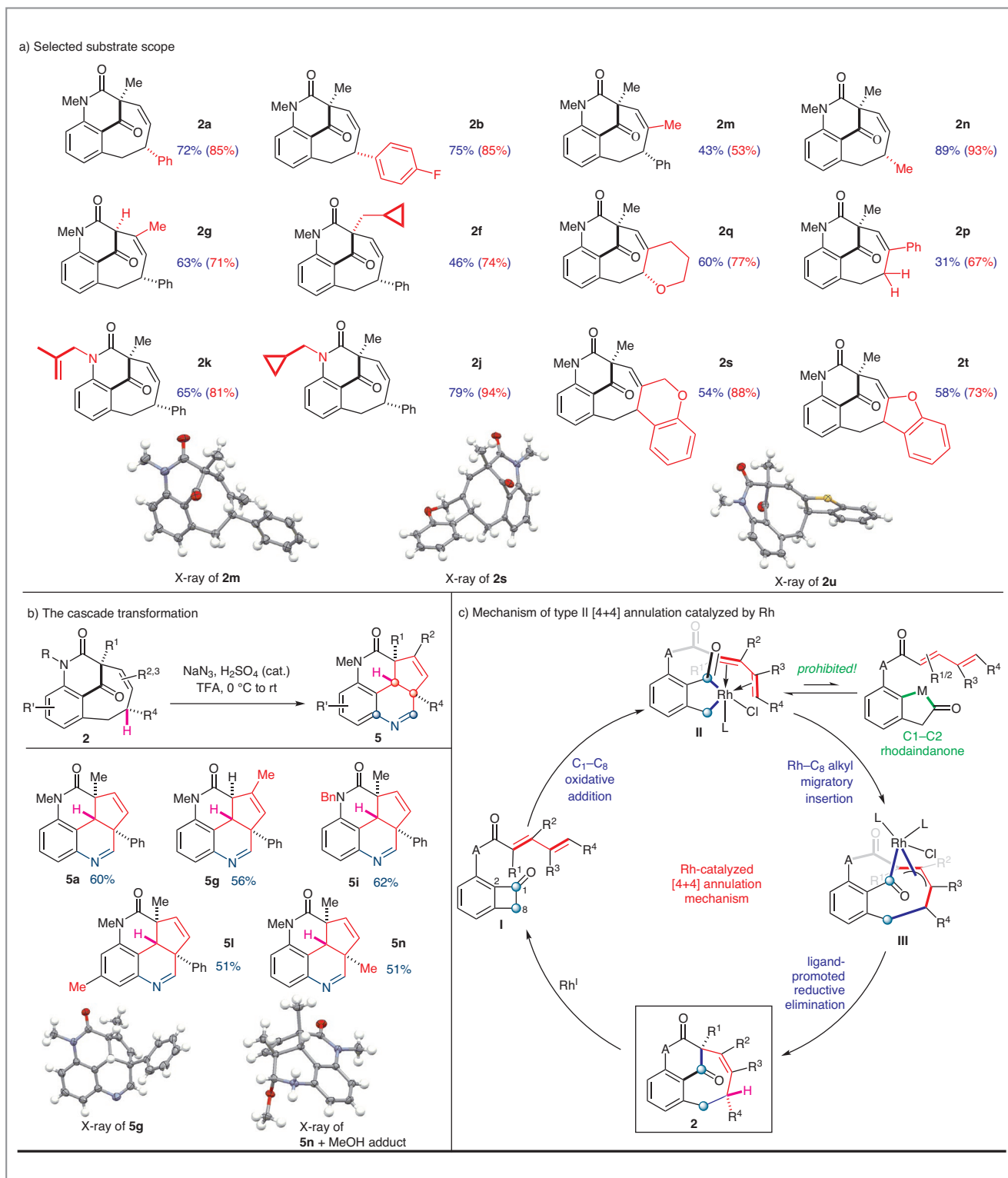


Figure 2 Broad substrate scope: a. Selected examples of the type II [4+4] annulation. b. Examples of the cascade transformation leading to polyfused rings. c. Proposed mechanism.

elusive, especially for the bridged ring systems that bear highly strained, consecutive double bonds surrounding the bridgehead carbon. Professor Xu explained: “We designed a formal [4+4] annulation reaction starting from regioselective C1–C8 activation of a benzocyclobutenone (BCB) using Rh(I) as catalyst. The normal ‘cut and sew’ chemistry coined by Guangbin Dong and co-workers won’t happen here, because the isomerization to its thermodynamic C1–C2-cleaved counterpart is inhibited by the excess amount of phosphine ligands. The former rhodacycle will participate in a migratory insertion and reductive elimination leading to benzo-fused bridgehead bicyclo[5.3.1] ring systems (Figure 1c).”

The chemistry proved to be viable through screening many conditions. “In addition, a very broad substrate scope was examined (Figure 2), demonstrating that the methodology

is robust and that it can be applied in a number of complex settings,” remarked Professor Xu, who continued: “What’s more, a cascade transformation consisting of through-space 1,5-hydride transfer, cation-induced cyclization and Schmidt reaction was serendipitously discovered, which led to the formation of complex fused-ring skeletons. This cascade reaction also fills the gap of converting complex bridged rings into their fused counterparts. During this transformation, one allylic C–H bond and one benzylic C–C bond are chemoselectively disconnected, which leads to recombination of one C–C bond and two C–N bonds.” Professor Xu concluded: “We look forward to its application in functional molecule synthesis in the near future.”

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About the authors



J. Zhang

Jianyu Zhang was born and raised in Shandong, P. R. of China. He earned both his Bachelor’s and Master’s degrees at Liaocheng University (P. R. of China). He joined Professor Xu’s lab in 2016, where he started transition-metal-catalyzed diene and benzocyclobutenone coupling. He has just passed his doctoral defense and will earn his doctoral degree of pharmacy in June 2021. He has decided to pursue an industrial career in the near future.



Prof. T. Xu

Tao Xu was born in Handan, Hebei province, P. R. of China. He obtained a B.Sc. degree from Dalian University of China (P. R. of China) then in 2011, a Ph.D. degree from Peking University (P. R. of China). In the same year, he started postdoctoral training with Guangbin Dong (University of Texas at Austin, now at University of Chicago, USA). In 2015, he joined Ocean University of China (P. R. of China) as a full professor and was promoted to tier III in 2018. His research group is focused on transition-metal-catalyzed reactions involving inert bond activations and their application in marine natural product total synthesis.



X. Wang

Xi Wang was born in Anhui, P. R. of China. She obtained an undergraduate degree from the University of Jinan in Shandong province (P. R. of China) in 2019. Currently, she is a second-year student in Prof. Tao Xu’s group at the Ocean University of China (P. R. of China). Her research interest is photocatalytic free-radical cycloaddition and its application in complex marine natural product synthesis.