Inside Story
annulation, ketones, amides, enones, Suzuki coupling
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Polycyclic Structure Synthesis via a Three-step “[2+*n*]” Annulation

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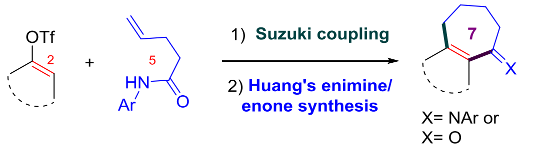
Dong-Huang Chen, Qian He, Dong-Ping Wu, Pei-Qiang Huang and Jian-Liang Ye (from left to right).
In the middle is the statue of Professor Jia-Xi Lu, a very well-known late Chinese chemist.

Mr. Dong-Ping Wu is currently a second-year master's student within Prof. Pei-Qiang Huang’s research group at Xiamen University.
Miss Qian He is currently a third-year master's student within Prof. Pei-Qiang Huang’s research group at Xiamen University.



Carbocycles are ubiquitous in natural organic molecules and medicinal agents. Therefore, developing methodologies for the efficient construction of carbocycles constitutes an important goal in organic synthesis. In this regard, for the construction of six-membered rings, the Diels-Alder [4+2] cycloaddition reaction (Figure 1, eq 1) and Robinson annulation (Figure 2, eq 1) represent two paradigms in terms of efficiency, selectivity, and versatility. Hence development of analogous methods for building other ring systems became the pursuit of many synthetic organic chemists. In this context, very recently, Uyeda’s group reported a catalytic reductive [4+1]-cycloaddition of vinylidenes and dienes that allows access to five-membered rings (Figure 1, eq 2).[1] Recently, under the supervision of Prof. Huang, we, Wu, He, *et al.*, developed a new strategy for the synthesis of fused six and seven-membered cyclic enimines and enones via a three-step “[2+5]” annulation protocol from simple cycloketones and terminal olefinic amides.[2]

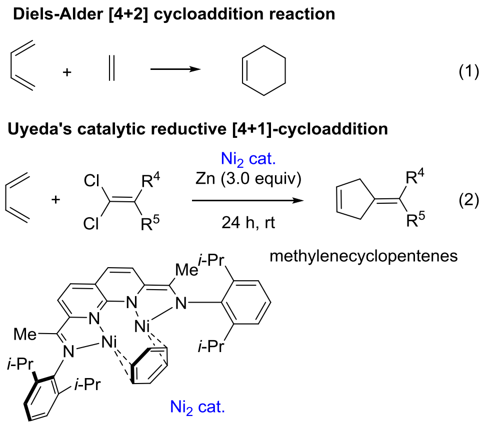


Figure 1 The 1,3-diene-based [4+*n*] cycloaddition reactions.

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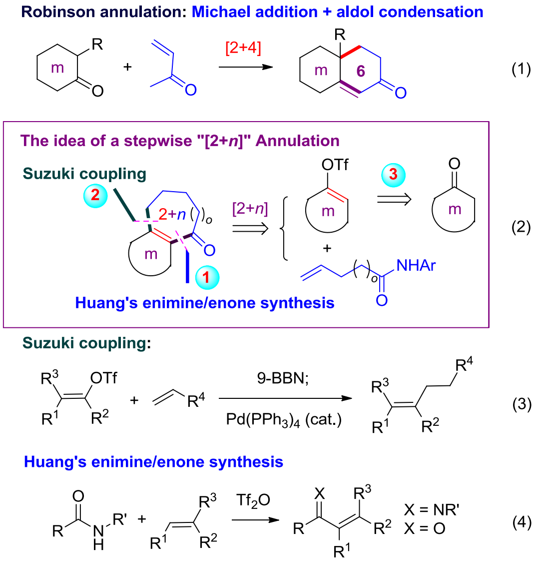

Figure 2 Known knowledge and conceptual advance of this contribution.

Polycyclic structures incorporated a fused seven-membered carbon ring are found in a number of bioactive and structurally complex natural products and medicinal agents. Although many strategies[3] including [5+2][4-6] and [4+3][7] cycloadditions have been developed to construct such ring systems, flexible and versatile methods employing simple starting materials are still in high demand.

Inspired by the Robinson [2+4] annulation, which is based on the tandem Michael addition reaction and intramolecular aldol condensation reaction of cycloketones and α,β-unsaturated ketones (Figure 2, eq 1), we came up with the idea of developing a flexible, yet stepwise [2+*n*] annulation for forming fused carbocyclic ring systems (Figure 2, eq 2). It was envisaged that the [2+*n*] annulation reactions could be achieved by combining the Suzuki coupling methodology[8] (Figure 2, eq 3) with the enimine/enone synthetic methodology developed by the Huang group[9] (Figure 2, eq 4). It was further expected that the excellent chemoselectivity and functional group tolerance afforded by the two latter methodologies would ensue accessing to "[2+*n*]" annulation products covering different fused (poly)cyclic systems and bearing diverse functional groups, and allowing further elaboration into structurally complex natural products.

On one hand, this method relies on the well-established Suzuki coupling methodology, which could convert cycloketone **1** and olefinic secondary amide **3** to special olefinic secondary amide **5**. On the other hand, it also relies on the chemoselective activation of secondary amide with Tf_2O/2-fluoropyridine to generate a highly reactive nitrilium intermediate, which could react efficiently with an alkene to form a fused six- or seven-membered ring system **6**. After a lot of experiments, we successfully prepared the key secondary amides **5** by the Suzuki coupling of the enol triflates **2** and simple olefinic secondary amides **3** (Figure 3). The enol triflates **2** were readily prepared from the corresponding commercially available cyclic ketones **1**, and the boron reagents **4** were generated *in situ* from readily available olefinic amides **3** (Figure 3). Finally, the secondary amides **5** were successfully converted into the fused six- and seven-membered cyclic enimines **6** and enones **7** under the action of Tf_2O/2-fluoropyridine.

Currently, we have only demonstrated the [2+5] annulation reactions and three examples on [2+4] annulation reactions to yield fused 7 and 6-membered bicyclic and tricyclic ring systems, respectively. The expansion of this annulation to the synthesis of other ring systems are under investigation. We believe that the flexibility and versatility of the method, combined with the mild conditions, would render it a valuable tool for the total synthesis of structurally complex natural products containing the related fused ring systems.

As beginners of research, we appreciate the opportunity to engage in this project. During this work, we have experienced both difficulties, frustrations and happiness of success, and began to feel the charm of scientific research.

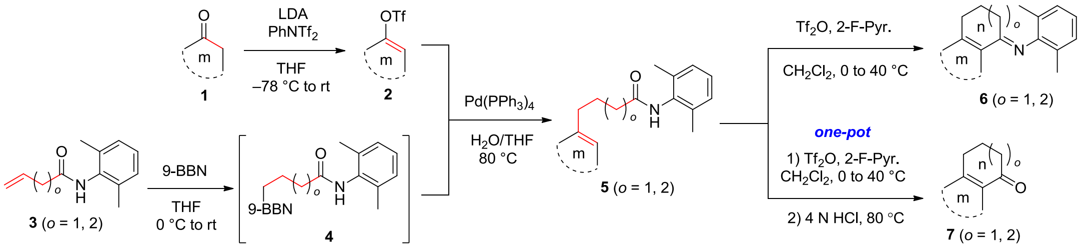

Figure 3 Fused six and seven-membered cyclic enimines and enones synthesis via the three-step "[2+*n*]" annulation.

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