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Postponed protonation under competitive conditions in rhodium catalyzed domino reactions

The readily available α,β-unsaturated compound (Michael acceptor) serves as one of the most important building blocks in synthetic chemistry, which is widely used in conjugate addition reaction. The characteristic of conjugate addition reaction is that it is essentially a domino reaction, in which the formation of enol intermediates can provide a platform for subsequent reactions. Numerous efforts have been devoted to the field of transition metal-catalyzed functionalization of C-C bonds in recent decades, which is committed to improving the efficiency of synthesis. It is an interesting idea to connect conjugate addition reaction and C–C bond activation in a single domino reaction, as it could avoid the necessity of additional directing groups in the conventional transition metal-catalyzed C–C bond activation.

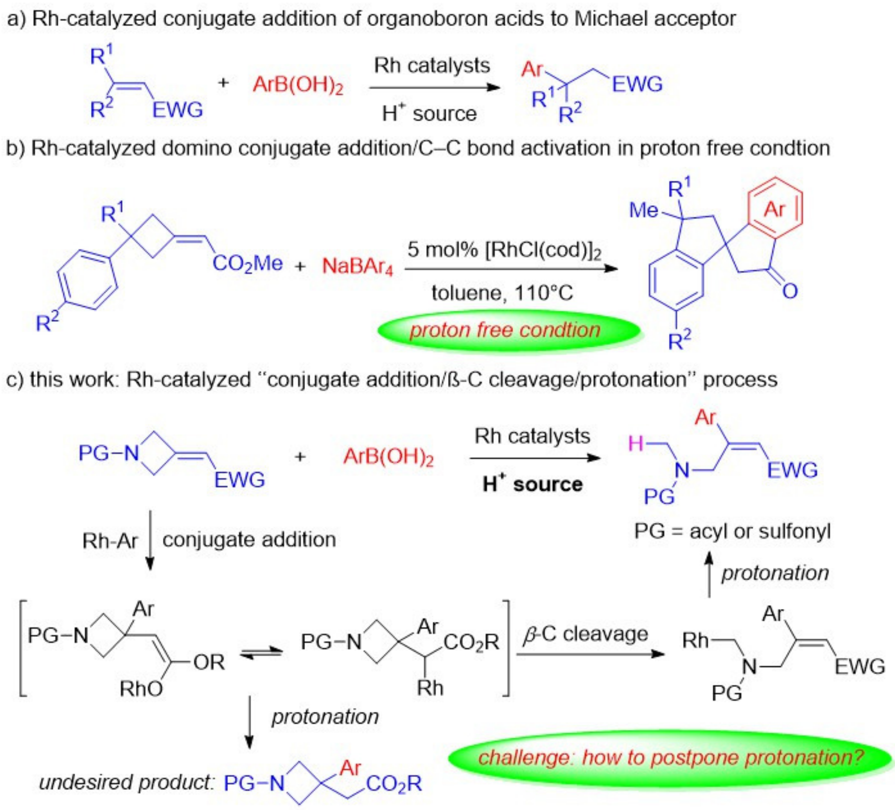

Fig. 1. Rh-catalyzed domino "conjugate addition/β-C cleavage/protonation" strategy and challenge.

The rhodium catalysts have been proven a powerful tool to facilitate the coupling of Michael acceptor with organoboron reagents, which usually undergoes the formation of enol intermediates and the following protonation process (Fig. 1a). The pioneering study on domino conjugate addition/C–C bond activation has been realized with rhodium catalytic system in proton free condition (Fig. 1b). However, the controllable conjugate addition/C–C activation process under competitive protonation circumstances remained challenging. In this study, we described the rhodium-catalyzed ‘‘conjugate addition/β-C cleavage/protonation'' (CCP) strategy with 2-(azetidin-3-ylidene)acetates and arylboronic acids to afford unsaturated γ-aminobutyric acids, which focused on the solution that postponed kinetically more favorable protonation under competitive conditions (Fig. 1c).

We found the electron-deficient ligand and the protic agent with a large p*K*a value were beneficial to postpone the protonation step. The study demonstrated with substrates covering a very wide range. With arylboronic acids containing various functional groups, including: alkyl, alkoxy, amide, ester, halides, alkenyl, heterocycle, etc., the CCP products could be obtained in good to excellent yields. The substrates with various electron-withdrawing groups and N-protecting groups also furnished the CCP products smoothly in good yields. The CCP product contains the unsaturated γ-aminobutyric acids (GABA) unit and could be transformed to various structures based on the functional groups. For example, it could undergo cyclization to form the unsaturated γ-lactam, or hydrolysis to give the unsaturated γ-aminobutyric acid, or asymmetric reduction of the double bond to give the chiral γ-aminobutyric acid ester which could be further transformed to the chiral γ-lactam (Fig. 2).

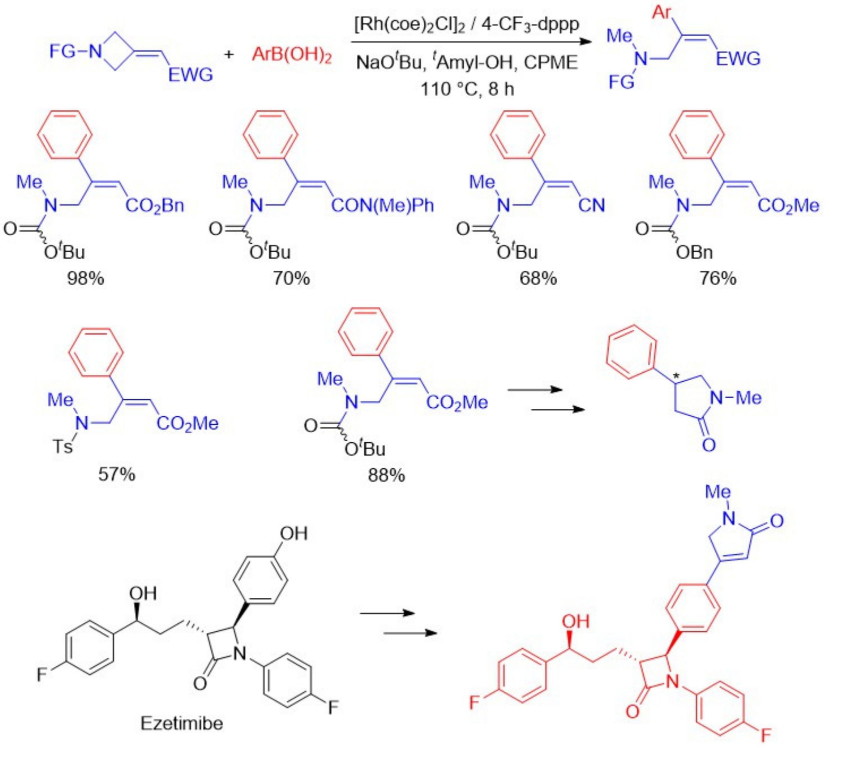

Fig. 2. CCP products and its transformation applications.

The study showed how β-C cleavage, other than the well-known protonation, could occur for an intermediate of conjugate addition in the presence of a protic agent.

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Publication

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