Applications of Intramolecular (4+3) Cycloadditions of Furans and Pyrroles to the Synthesis of Natural Products

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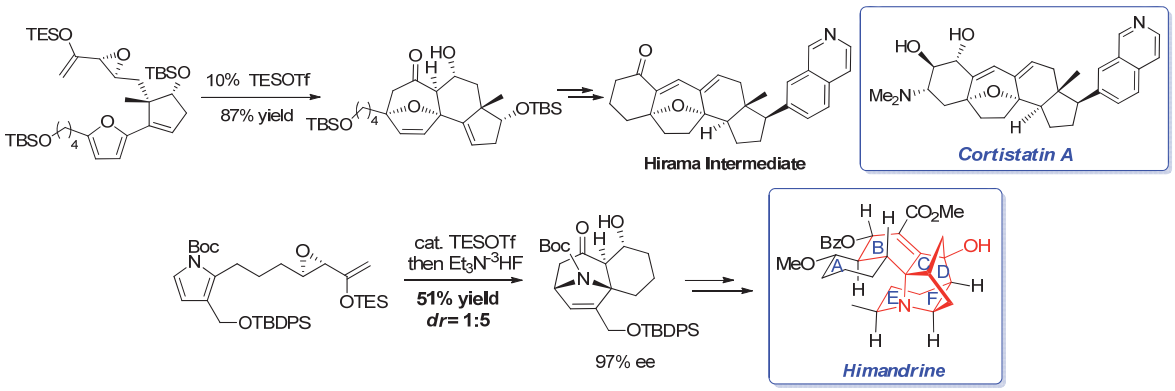
Intramolecular cycloadditions are efficient reactions for the construction of polycyclic frameworks that are found in many bioactive compounds and complex natural products. However, heterocycles undergo cycloaddition reactions with different propensities.

We have developed an intramolecular (4+3) cycloaddition of epoxy enolsilanes and furan that afford products containing an oxabicyclic nucleus in good to excellent yields. The use of optically enriched epoxy enolsilanes affords cycloadducts as single enantiomers bearing multiple stereocenters.[1] We have applied this (4+3) cycloaddition as the key step in the asymmetric formal total synthesis of cortistatin A, which has been found to exhibit potent anti-angiogenetic, anti-HIV and anti-leukemic activity.[2]

Generally, (4+3) cycloadditions with pyrroles acting as dienes are far less common. This is because pyrroles tend to undergo Friedel-Crafts type of reactions, resulting in the restoration of aromaticity instead of cycloadditions. However, our studies have found that pyrroles also engage readily in intramolecular (4+3) cycloadditions with epoxy enolsilanes, resulting in optically active polycyclic structures harboring a tropane nucleus. Based on these results, we have applied this reaction as the key step for the construction of the BCDEF core common to the Type II galbulimima alkaloids.[3]



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[2] (a) Liu, L. L.; Chiu, P. *Chem. Commun*. **2011**, 3416-3417. (b) Kuang, L.; Liu, L. L.; Chiu, P. *Chem.-Eur. J.* **2015**, *21*, 14287.
[3] He, J.; Chen, Z.; Li, W.; Chiu, P. manuscsript in preparation.