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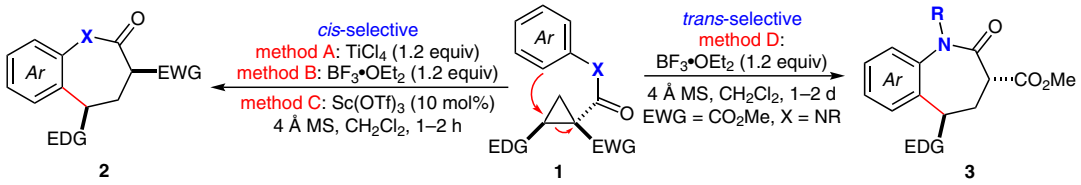
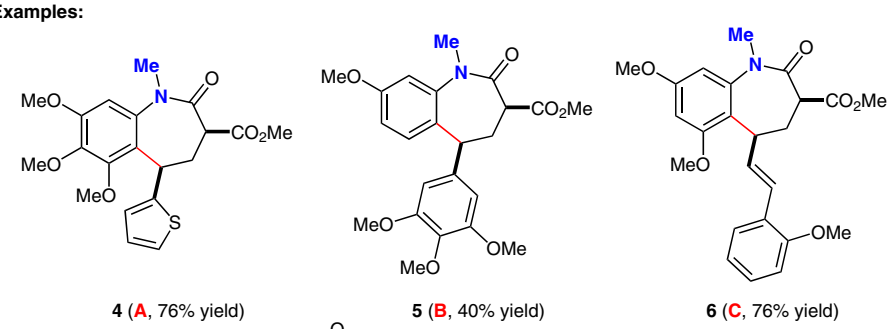
Expanding Stereoelectronic Limits of *endo-tet* Cyclizations: Synthesis of Benz[*b*]azepines from Donor–Acceptor Cyclopropanes
J. Am. Chem. Soc. **2021**, *143*, 13952–13961, DOI: 10.1021/jacs.1c07088.

Demonstrated 6-*endo-tet* Cyclizations!

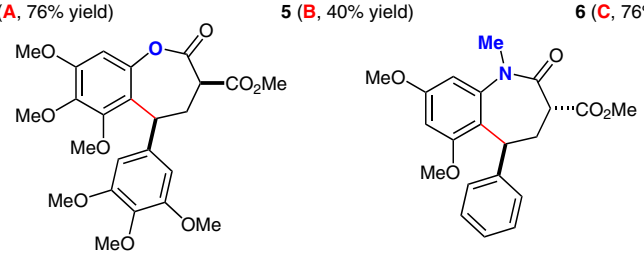
Transformation of cyclopropanes to benzazepinones:



Examples:



4 (**A**, 76% yield) **5** (**B**, 40% yield) **6** (**C**, 76% yield)



7 (**C**, 30% yield, dr = 59:41) **8** (**D**, 73% yield)

Significance: Baldwin's rules represent established dogma when considering the chances of a specific cyclization reaction occurring, and are based on the geometric restraints within the cyclic transition states (TSs) associated with the ideal trajectories for engagement of the reacting centers. These constraints are particularly strong when the attack of a nucleophile at an electrophilic sp^3-carbon atom takes place to break a bond inside a cyclic TS (an *endo-tet* cyclization) that has fewer than eight atoms, and although there is some debate regarding 7-*endo-tet* reactions, the 5-*endo-tet* and 6-*endo-tet* TSs are clearly disfavored. The current report describes a genuine 6-*endo-tet* process to form a seven-membered ring through intramolecular ring opening of donor–acceptor cyclopropanes to form biologically significant tetrahydrobenz[*b*]azepin-2-ones.

Comment: Optimization experiments focused on the screening of Lewis acids, a number of which were identified as capable of promoting the reaction, leading to several general methods being developed, the best of which, in terms of yield and diastereoselectivity, depended on the nature of the substrate. These experiments also showed that under otherwise constant conditions, increasing the reaction time led to the formation of the *trans* isomers through isomerization of the kinetically controlled *cis* products. The S_N2 nature of the process was confirmed through the observed inversion of stereochemistry at the electrophilic carbon atom in the formation of **8**, thereby proving that the reaction constituted a genuine *endo-tet* cyclization, while DFT calculations supported this hypothesis in demonstrating that the proposed mechanism does not involve carbocationic intermediates.

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Category
Synthesis of Heterocycles

Key words
Lewis acids
Baldwin's rules
endo-tet cyclization
benzazepines

Synfact of the Month