Cycloaddition

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Thrilling Strain! Donor–Acceptor-Substituted Cyclobutanes for the Synthesis of (Hetero)Cyclic Compounds

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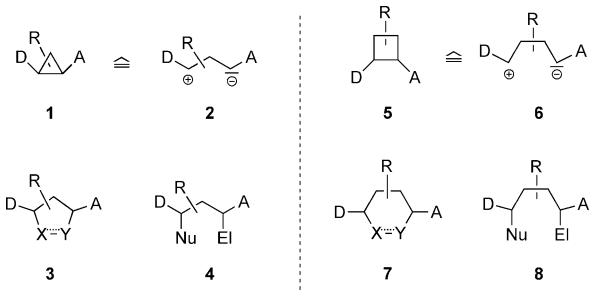
Dedicated to Professor Helmut Vorbrüggen on the occasion of his 85th birthday

cycloaddition · cyclobutanes · homogeneous catalysis · photochemistry · pyrans

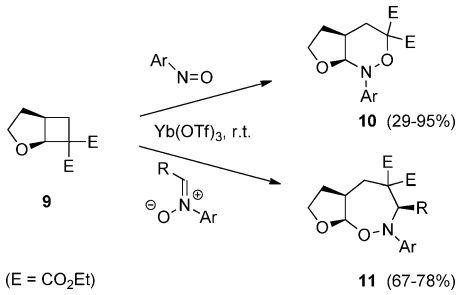
Among the ring-strain-driven reactions of cyclopropane and cyclobutane derivatives[1] those of donor–acceptor-substituted cyclopropanes **1** (D-A cyclopropanes) are most often used in organic synthesis (Scheme 1).[2,3] The high ring strain and



Scheme 1. Reactivity pattern of D-A cyclopropanes **1** and D-A cyclobutanes **5** (Nu = nucleophile, El = electrophile).

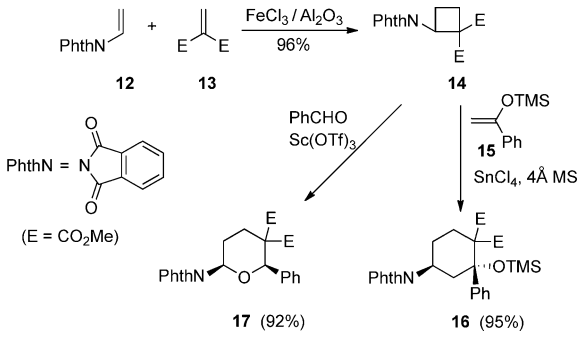
the polarization of the C–C bond by the vicinal substituents causes their equivalence to 1,3-zwitterionic synthons **2**, which undergo cycloadditions to afford **3** or other transformations to give products of type **4**. The homologous vicinal donor–acceptor-substituted cyclobutanes (D-A cyclobutanes) **5** should analogously behave as 1,4-zwitterionic synthons **6** and lead to six-membered cycloadducts **7** or to compounds **8**. The strain of cyclobutane is in the same range as that of cyclopropane (ca. 120 kJ mol^{-1}), but it is distributed over four centers. After the remarkable renaissance of D-A cyclopropanes,[3] a similar breakthrough has been observed with the corresponding cyclobutanes.[4]

Pagenkopf and co-workers reported on the Yb(OTf)$_3$-catalyzed [4+2] and [4+3] cycloadditions of the readily available D-A cyclobutane **9**[5,6] to afford 1,2-tetrahydrooxazines **10** with arylnitroso compounds and oxazepines **11** with *N*-arylnitrones (Scheme 2). The thermodynamically controlled [4+3] cycloadditions provided the *cis* diastereomers exclusively.



Scheme 2. [4+2] and [4+3] cycloadditions of D-A cyclobutane **9** with nitroso compounds or nitrones leading to **10** and **11**. OTf$^-$ = triflate, r.t. = room temperature.

Dialkylamino groups are generally not suitable as substituents of D-A cyclopropanes and cyclobutanes as they are too strong donor groups and lead to over-activation and instability of the compounds. Waser and co-workers recognized that amide groups exert the perfect donor strength in many cases.[7] Compound **14** was prepared starting from alkenes **12** and **13** by a Fe^{III}-catalyzed [2+2] cycloaddition; cyclobutanes with quite a broad range of substitution patterns could be generated (Scheme 3).[8] The $SnCl_4$-catalyzed reaction of **14** with silyl enol ether **15** led to cyclohexane derivative **16** with high selectivity. Carbonyl compounds react with cyclobutanes such as **14** to furnish tetrahydropyrans.[9]



Scheme 3. Cycloaddition of **12** and **13** to D-A cyclobutane **14** and its reactions with **15** or benzaldehyde to give **16** and **17**, respectively. TMS = trimethylsilyl.

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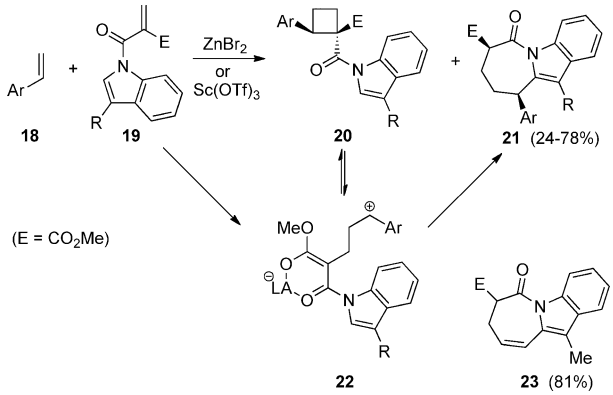
$Sc(OTf)_3$ was identified to be the best catalyst for the [4+2] cycloaddition with benzaldehyde to afford **17**.

An elegant route to azepino[1,2-*a*]indoles **21** with D-A cyclobutanes **20** as intermediates was recently published by France and co-workers[10] (Scheme 4). Alkenes **19** and styrene derivatives **18** were expected to lead to cyclobutanes **20**, and with zinc bromide as a mild Lewis acid the anticipated [2+2] cycloadducts **20** were indeed obtained, but roughly the same quantity of product **21** was also isolated. The tricyclic compounds **21** were formed exclusively by using 10 mol% of scandium triflate as the catalyst. The isolated cyclobutanes

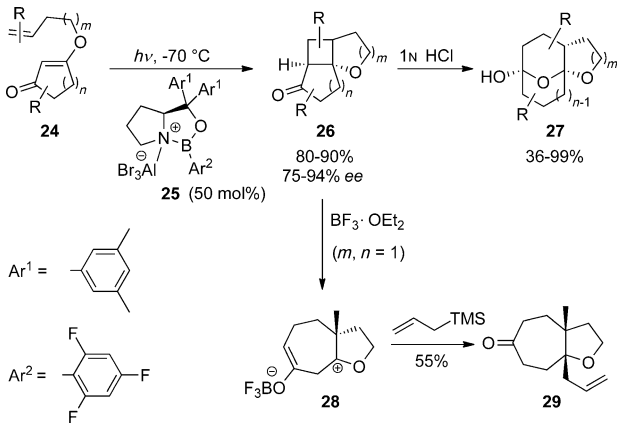


Scheme 4. Lewis acid promoted [2+2] cycloadditions of **18** with **19** to give D-A cyclobutanes **20** and formation of azepino[1,2-*a*]indoles **21**.

20 rearrange with $Sc(OTf)_3$ to give **21** and hence the following interpretation is plausible: D-A cyclobutanes **20** were reversibly formed via zwitterions **22**, which irreversibly led to the final products **21**. The last step corresponds to an intramolecular Friedel–Crafts alkylation at the C-2 position of the indole ring. Zwitterions such as **22** that are formed by the addition of a Lewis acid are very likely intermediates in the cycloadditions of compounds **9** and **14** described above.

The scope of the synthesis of pharmacologically interesting azepino[1,2-*a*]indoles **21** seems to be quite broad. Prerequisite is a sufficiently strong donor at the olefin component. A substituent at C-3 of the indole derivative is apparently required, probably to prevent competing side reactions at this position. Starting from ethyl vinyl ether and **19** (R = Me) the unsaturated azepinoindole derivative **23** was obtained, which results from the primary product by elimination of ethanol. Many other derivatives of this compound class should be available by addition reactions to the double bond of **23**.

Besides the discussed Lewis acid induced [2+2] cycloadditions of electron-deficient alkenes with electron-rich alkenes, photochemical [2+2] cycloadditions of donor–acceptor-substituted alkenes with unactivated alkenes are another option to prepare D-A cyclobutanes. Alkoxy substituents as donor groups allow ring cleavage under acid catalysis—equivalent to a retro-aldol reaction—to afford 1,5-dicarbonyl compounds. This two-step method is known as the de Mayo reaction[11] and a ring enlargement starting from cyclic D-A alkenes is possible. Brimioulle and Bach[12] used this route to D-A cyclobutanes and added 50 mol% of the



Scheme 5. Enantioselective photochemical [2+2] cycloadditions of **24** to afford **26** in the presence of chiral Lewis acid **25** and subsequent reactions to give **27** and **29**.

chiral Lewis acid **25** during intramolecular photocycloadditions of **24**; the products **26** were formed with 75–94% *ee* (Scheme 5). This elegant method allowed the synthesis of a series of tri- and tetracyclic compounds **26**, which are building blocks of considerable value. Reactions with diluted hydrochloric acid lead to tricyclic hemiacetals **27** being formed by ring opening to an intermediate oxocarbenium ion, water addition, and ring reclosure with the carbonyl group. Oxocarbenium ions such as **28** can also be trapped by silylated nucleophiles if Lewis acids are employed for the ring cleavage. The reaction of **26** $(m,n=1)$ in the presence of boron trifluoride with allyltrimethylsilane diastereoselectively furnished bicyclic product **29**.

All the discussed examples demonstrate the enormous potential of D-A cyclobutanes for the (stereoselective) syntheses of carbo- and heterocycles. Enantioselective versions should be further developed to offer new options for the generation of interesting molecular skeletons in enantiopure form. In addition, carbohydrate chemistry, where D-A cyclopropanes have already been employed creatively, could be another field where the corresponding cyclobutane derivatives could be used. Unusual substitution patterns and ring expansions could be feasible. We are curious to learn more about the use of stress and strain![13]

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