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A comparison of the benzylic and the allylic group as a donor in the formal [4+2] cycloaddition to tetrahydropyrans using donor-acceptor cyclobutanes

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ABSTRACT

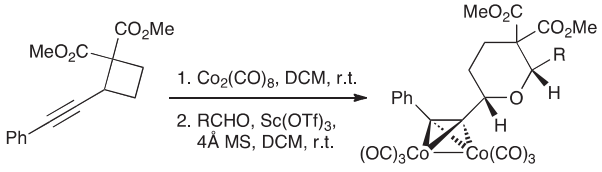
The allyl group was shown to be preferred over the benzyl group as a donor in the formal [4+2]-cycloaddition reaction between a donor-acceptor cyclobutane and various aldehydes to give tetrahydropyrans.

Introduction

Heterocyclic motifs play a key role in organic chemistry, embracing pharmaceutical drugs, natural products and material chemistry. The development of new routes towards heterocyclic compounds is a key challenge for synthetic chemists. We have added to this field a number of methodologies, including stoichiometric organometallic;[1,2] palladium mediated reactions;[3] biomimetic methods;[4] condensation of reactive electrophilic systems;[5] and Lewis acid mediated reactions.[6] As part of our studies, we have previously reported the formal [4+2]-cycloaddition reaction between donor-acceptor cyclobutanes and aldehydes to give tetrahydropyrans, under Lewis acid conditions (Scheme 1).[2]

The use of donor-acceptor cyclobutanes in synthesis has expanded since its initial report.[7] Of note amongst those reports are: Johnson and co-workers simultaneous report of chemistry closely related to ours;[8] the use of an oxygen atom as the donor has been established by Pagenkopf and others;[9] the use of cyclobutanones as shown by Matsuo;[10] and the construction of heteroaromatic systems using cyclobutanes as reported by Rao.[11]

Herein, we report a recent study where we have added extra complexity to the donor-acceptor cyclobutane [4+2]-cycloaddition reaction. Johnson and co-workers have previously shown that both an aromatic or allylic group can act as the donor in the cyclobutane starting material,[8] but there was no discussion as to which was preferred. We have therefore devised an experiment to compare the reactivity of these donor groups. If there are two donor groups on the cyclobutane, one phenyl and one allyl group, it would be interesting to observe which bond will cleave to allow the formal [4+2]-cycloaddition to occur under Lewis acid conditions (Scheme 2). This would provide more insight into the mechanism of the [4+2]-cycloaddition reaction, as well as the introduction of extra substitution to the tetrahydropyran product, resulting in new compounds difficult to access by other means.



Scheme 1. Formal [4+2]-cycloaddition reaction between donor-acceptor cyclobutane and aldehydes.

Results and discussion

We based our route to compound **1** on the elegant chemistry developed by Boeckman and co-workers, who used an anionic ring closure reaction to prepare enantiomerically pure vinylcyclobu-

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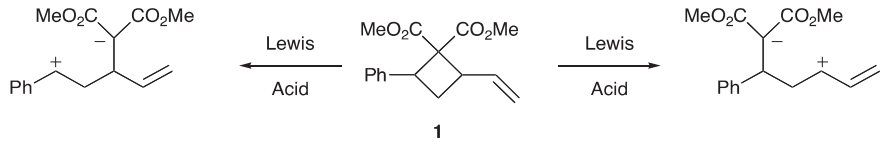
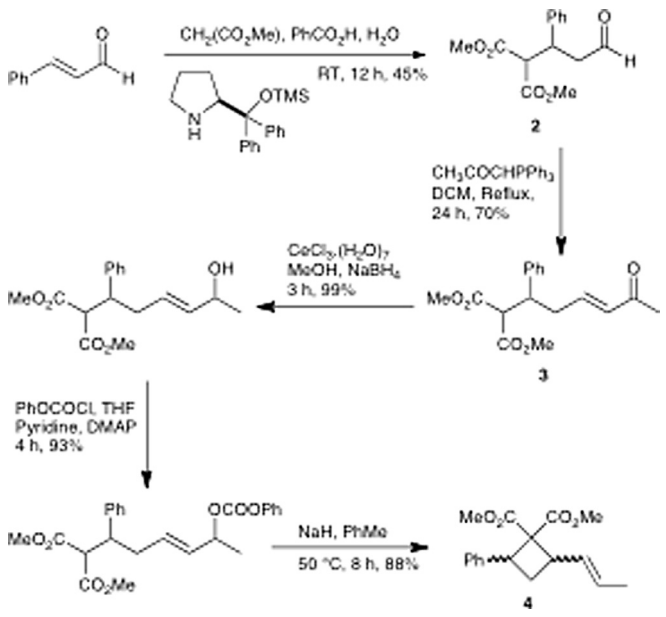


Scheme 2. Alternate donors on the cyclobutane ring.

tane derivatives.[12] Staring with the Michael addition reaction between dimethyl malonate and cinnamaldehyde under the reaction conditions developed by Ma and co-workers,[13] the Michael product **2** was formed in 45% yield. We did not attempt to optimize the reaction or control the enantioselectivity of the reaction at this stage. Subsequent Wittig reaction with acetylmethylene triphenylphosphorane gave ketone **3** in 70% yield. Following the steps developed by Boeckman and co-workers, Luche reduction of the ketone and conversion into the phenyl carbonate gave an inseparable mixture of diastereoisomers (1:1). Cyclisation to the required cyclobutane **4** was carried out using sodium hydride in toluene at 50 °C. An inseparable 3:1 mixture of diastereoisomers was isolated in 88% yield. Replacing the leaving group with methyl carbonate did not change the ratio of the diastereoisomers but also lowered the yield. The change in the diastereomeric ratio suggests that one isomer is more readily able to cyclise (Scheme 3).

With a suitably substituted cyclobutane **4** in hand, we were able to carry out the key formal [4+2]-cycloaddition. Using previously developed reaction conditions, cyclobutane **4** was treated with varying equivalents of benzaldehyde in the presence of $Sc(OTf)_3$ (10 mol%) in DCM. Gratifyingly the desired formal [4+2]-cycloaddition tetrahydropyran product was obtained along with various by-products, which were all isolated and identified (Scheme 4,



Scheme 3. Synthetic route to donor-acceptor cyclobutane **4**.

Table 1
Comparison of different amounts of benzaldehyde.

PhCHO (equiv.)	Yield 5 (%)	Yield 6 (%)	Yield 7 (%)
1.2	18	20	0
2.2	18	25	2
5.0	47	17	0

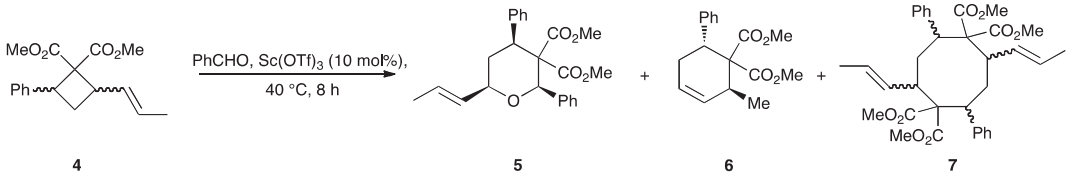
Table 1). It was immediately apparent that cyclobutane **4** was less reactive than analogous literature compounds, since larger equivalents of the aldehyde was required to achieve workable yields. This could possibly be explained by the increased steric demand of the cyclobutane starting material which is known to hinder cycloaddition reactions.

The target pyran product **5** was purified and spectroscopic analysis, including nOe experiments, showed it to be the single diastereoisomer **5**, arising from breaking of the cyclobutane bond that would give rise to an allyl cation. The best yield (47%) was obtained when a large excess of aldehyde (5 equiv.) was used. We did not observe, or isolate, any tetrahydropyran products that would arise from ring opening to give the benzyl cation. The major by-product of the reaction was the rearranged cyclohexene product **6**, the stereochemistry of this product was also established by nOe experiments. A small amount of dimer **7** was also isolated from the complex reaction mixture on one occasion. We were able to determine the regiochemistry of the dimer product but not its stereochemistry. Both the cyclohexene **6** and dimer **7** are also the result of the bond cleavage that leads to the allyl cation, in accordance to the formation of tetrahydropyran **5**.

We next tried to optimize the reaction conditions in order to improve the ratio of the target tetrahydropyran product to side-products by experimenting with different solvents and catalysts (Table 2). Despite our best efforts, the initial reaction conditions appeared to be best suited to this formal [4+2]-cycloaddition reaction. Changing the solvent had a detrimental effect on the reaction outcome and other Lewis acids did not provide any advantage over $Sc(OTf)_3$, similar to the findings of Johnson and co-workers.[8]

With the encouraging result of successful tetrahydropyran formation, we repeated the [4+2]-cycloaddition reaction with a limited range of aromatic and unsaturated aldehydes using the optimized conditions (Scheme 5, Table 3).

Introducing either electron-donating or electron-withdrawing groups to the aromatic ring had detrimental effects on the reaction, shutting down formation of the desired tetrahydropyran product; the major product being the rearrangement to give cyclohexene **10** (Table 3). More investigation is needed to account for this unusual observation. However, the unsaturated aldehydes acrolein and



Scheme 4. Initial attempt of formal [4+2]-cycloaddition reaction using cyclobutane **4**.