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Preparation of Highly Substituted Tetrahydropyrans *via* a Metal Assisted Dipolar Cycloaddition Reaction

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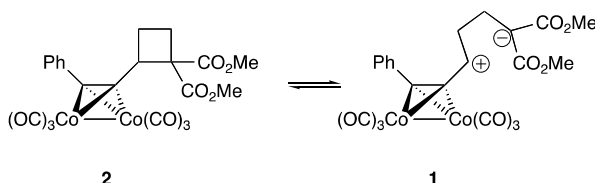
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A range of highly substituted tetrahydropyrans have been prepared by reaction of a donor-acceptor cyclobutane, where the donor is a metal-alkyne complex, with an aldehyde under Lewis acid conditions.

We have recently reported the use of dicobalt complexes in the formation of new carbon-heteroatom bonds through [3+2] cycloaddition reactions *via* a stabilized dipole intermediate.¹ The initial work carried out made use of substituted cyclopropanes with a metal-alkyne complex to stabilize the Nicholas carbocation.² The formation of a Nicholas carbocation through cleavage of a carbon-carbon σ bond allowed the synthesis of highly substituted tetrahydrofurans and pyrrolidines in good yields.³ More recently, we have also reported the use of an iron-dienyl template to facilitate a similar reaction.⁴ Cycloaddition reactions involving three-membered rings have been the subject of recent interest e.g. for the synthesis of tetrahydro-1,2-oxazines, pyridines, and tetrahydrofurans.⁵ Ghorai *et al.* recently reported related reactions for the synthesis of substituted imidazoline starting from aziridines and the synthesis of tetrahydropyrimidines using azetidines.⁶ More recently, they also report a S_N2 type nucleophilic ring opening followed by a [4+2] cycloaddition of the same azetidines with aldehydes and ketones.⁷ However the equivalent strategy using a cyclobutane ring has never been reported. We believe that the use of donor-acceptor cyclobutanes in cycloadditions would both be a novel and useful addition to synthetic organic chemistry.

We now report that a novel and efficient [4+2] cycloaddition reaction has been developed using cyclobutane as a masked dipole. We envisaged treating a substituted cyclobutane **2** with a Lewis acid in order to open the four-membered ring and reveal a stabilized dipole **1** (Scheme 2). The malonate motif stabilizes the carbanion and the cobalt-alkyne complex stabilizes the cation as a Nicholas cation. The dipole could then be trapped with a suitable dipolarophile to effect a cycloaddition reaction.

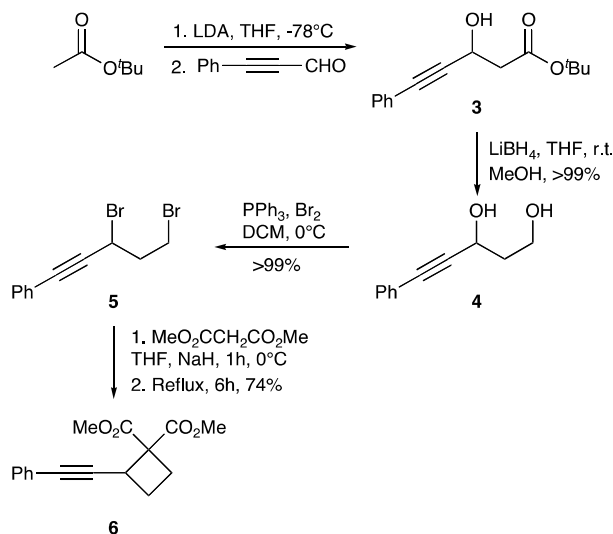
Scheme 1 Cyclobutane-dipole equilibrium.



The substituted propargylic cyclobutane was prepared *via* a four-step methodology in 74% overall yield. The hydroxyester **3** was prepared by simple Aldol chemistry, then reduced to the corresponding alcohol **4** using LiBH₄. The diol **4** was converted into the dibromide **5** using bromine and triphenylphosphine at 0°C (Scheme 2).

This sequence was “chromatography-free” and achieved in excellent yield. After complete conversion of the alcohols into the corresponding bromides, the triphenylphosphine oxide side product was recrystallised thrice from cold petrol affording the dibromide **5** in a quantitative yield. Displacement of the two bromines with dimethyl malonate and sodium hydride afforded the desired cyclobutane **6** in 74% yield.

Scheme 2 Preparation of the required donor-acceptor cyclobutane.



The cyclobutane **6** was then complexed with dicobalt octacarbonyl before adding successively the aldehyde and the Lewis acid (Scheme 3).

Scheme 3 [4+2] Cycloaddition reaction.

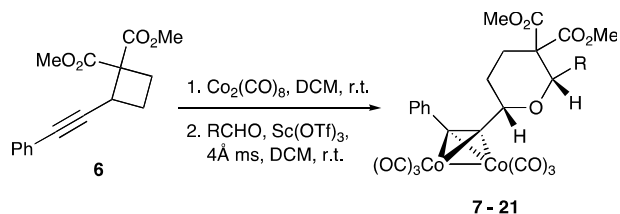


Table 1 Conditions and yields of cycloaddition reaction.

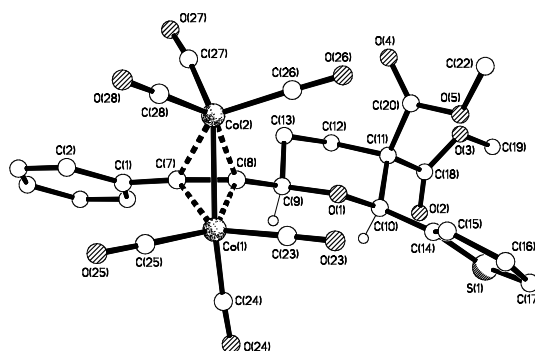
Aldehyde (R)	Product	Time	Yield	d.e.
CO ₂ Et	7	17 h	58%	20%
CH ₃	8	30 min	73%	23%
Ph	9	1 d	34%	<i>cis</i>
4-CH ₃ Ph	10	10 min	64%	<i>cis</i>
2-CH ₃ Ph	11	1 h	47%	<i>cis</i>
PhCH=CH	12	1 h	82%	<i>cis</i>
PhCH=CCH ₃	13	25 min	84%	<i>cis</i>
CH ₃ CH=CH	14	1 h	82%	<i>cis</i>
CH ₃ CH=CHCH=CH	15	1 h	51%	<i>cis</i>
4-CH ₃ OPh	16	15 min	85%	<i>cis</i>
4-PhOPh	17	2 h	65%	<i>cis</i>
2-C ₄ H ₃ O	18	10 min	95%	<i>cis</i>
2-C ₄ H ₃ S	19	15 min	73%	<i>cis</i>
2,4-(CH ₃ O) ₂ Ph	20	10 min	92%	<i>cis</i>
3,4-(CH ₃ O) ₂ Ph	21	10 min	92%	<i>cis</i>

nitrobenzaldehyde gave only the complexed starting material **2**, with no sign of the pyran. Thus there is a marked difference between the three- and four-membered ring dipole precursors: our previous studies found that electron deficient aldehydes gave the best yields with the cyclopropane, but low diastereoselectivities. In contrast the cyclobutane gives significantly better yields with electron rich aldehydes, and for the first time, excellent stereocontrol.

To assess the effect of steric hindrance, a comparison was made between *p*-tolualdehyde and *o*-tolualdehyde. The *p*-substituted aldehyde afforded **10** in 64% yield after only 10 minutes while *o*-tolualdehyde gave **11** in only 47% yield after 1 hour.

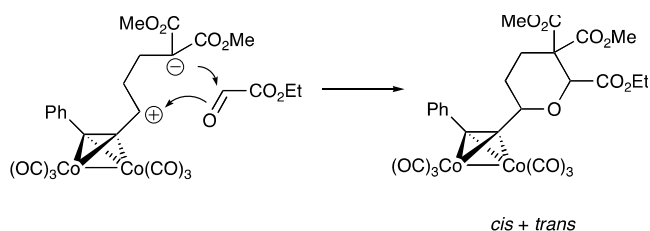
All diastereoselectivities were confirmed by nOe experiments and, in addition, X-ray crystal structures⁸ were determined for **8**, **10**-CH₂Cl₂, **18** and **19** (see Fig. 1 for structure of tetrahydropyran **19** and ESI for those of the others).

Figure 1 X-ray crystal structure of tetrahydropyran **19**.



The mechanism of the reaction is not yet known, but the results described above suggest that two different mechanisms are likely to occur whether the aldehyde is electron rich or poor. If the aldehyde is electron poor the reaction is very slow or does not proceed at all. In this case, we believe the highly electron deficient carbonyl is subject to attack first by the malonate carbanion (Scheme 4).

Scheme 4 Proposed mechanism for the cycloaddition with electron deficient aldehydes.



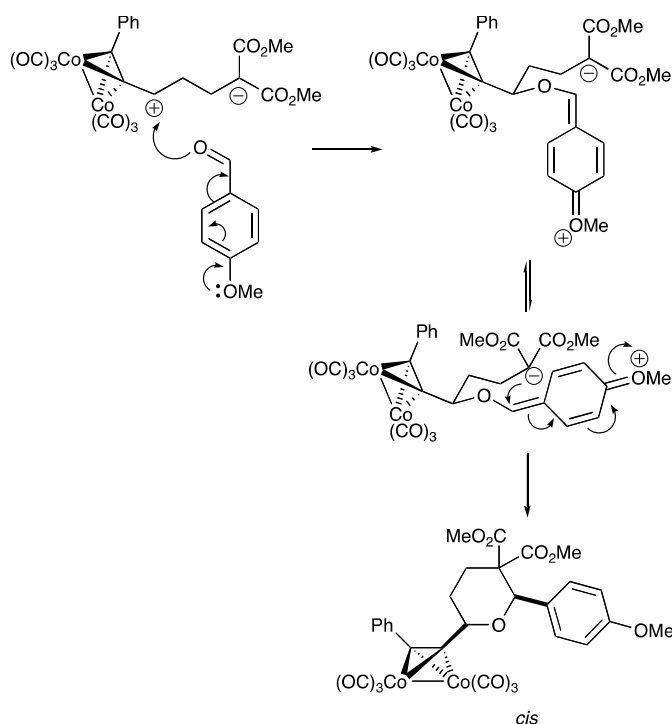
When electron rich or conjugated aldehydes are used, the oxygen of the carbonyl will attack the Nicholas carbocation first, through delocalization of π electrons. In this case the mechanism is not concerted, the carbon-oxygen bond can rotate to obtain the most stable conformation before trapping the carbanion which may explain why only the *cis* isomer is obtained (Scheme 5).

Cycloaddition reactions were performed in dichloromethane at room temperature using catalytic amounts of Lewis acid under an inert atmosphere.[‡] We had expected the cyclobutane core would have the same reactivity as the cyclopropane we had examined previously,¹ however, the use of boron trifluoride as the activating Lewis acid gave only a complex mixture of products. Instead we found that catalytic quantities of scandium triflate were the preferred additive. A range of aldehydes were then used to trap the dipole formed during the reaction as summarised in Table 1. No reaction was seen without complexation of the alkyne to cobalt hexacarbonyl. Our initial choice of trapping agent was ethyl glyoxylate, as an electron deficient aldehyde, since electron deficient aldehydes gave the best yields in the cyclopropane case. The two separable diastereoisomers of the corresponding tetrahydropyran adduct **7** were isolated in 58% yield with 20% d.e. after 17 hours. Acetaldehyde also afforded its corresponding tetrahydropyran **8** in a 73% yield with 23% d.e. in 30 minutes, however it was the only aliphatic aldehyde that afforded the desired cycloadduct.

On moving to aryl aldehydes, benzaldehyde surprisingly afforded only the *cis*-isomer of **9** in a moderate yield of 34% after 24 hours. Using conjugated and aromatic aldehydes such as cinnamaldehyde and anisaldehyde, only the *cis*-isomers were produced during the reaction (**12** and **16**) in 82% and 85% yield respectively, a trend that continued for other electron rich aldehydes, (e.g. **18**, **20** and **21**). In contrast, *p*-

In summary, we have synthesized an alkynylcyclobutane in 74% yield over 4 steps. We report for the first time a formal [4+2] cycloaddition reaction using a cyclobutane as a dipole precursor, providing a new way for the synthesis of six-membered heterocycles in a diastereoselective fashion. A wide range of aldehydes was used as trapping reagents to form tetrahydropyrans in good yields (up to 95%) and with excellent diastereoselectivities in some cases. Further work is under way to expand the scope of this reaction. The importance of the area has been underlined by the recent report of a related carbocyclic version [4+2] cycloaddition.⁹

Scheme 5 Proposed mechanism for the cycloaddition with electron rich aldehydes.



Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data, crystal structure diagrams for **8**, **10**, and **18**, and copies of NMR spectra are available in the ESI. See DOI: 10.1039/b000000x/

‡ Typical procedure for cycloaddition reactions: Substituted cyclobutane **2** (70 mg) was dissolved in DCM (0.5 M) in a 10 mL oven dried round-bottom flask and activated molecular sieves were added (150 mg). Dicobalt octacarbonyl (1.1 equiv.) was added and the reaction mixture was allowed to stir at room temperature under nitrogen atmosphere for 1.5 hour. Aldehyde (3 equiv.) was added followed by scandium triflate (5 mol%) and the resulting mixture was allowed to stir at room temperature. (Refer to table for reaction times). When the reaction was completed (TLC monitoring), the crude mixture was filtered through a pad of celite and silica and the solvent was evaporated *in vacuo*. The product was purified by flash chromatography on silica gel (5% ethyl acetate/petrol).

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- Crystal data for **8**: C₂₄H₂₀Co₂O₁₁, *M* = 602.26, monoclinic, *C*2/*c*, *a* = 30.4100(16), *b* = 8.0633(4), *c* = 22.1301(12) Å, β = 109.3822(8)°, *U* = 5118.9(5) Å³, *T* = 150(2) K, *Z* = 8, μ(Mo-Kα) = 1.354 mm⁻¹, 25700 reflections measured, 6367 unique (*R*_{int} = 0.0430) which were used in all calculations, *wR*2 = 0.0877 for all data, *R*1 = 0.0360 for 4643 data with *F*² ≥ 2σ(*F*²).
- Crystal data for **10**·CH₂Cl₂: C₃₁H₂₆Cl₂Co₂O₁₁, *M* = 763.28, triclinic, *P*-1, *a* = 9.2516(12), *b* = 13.8248(19), *c* = 14.0220(19) Å, α = 109.6525(19), β = 91.9541(19), γ = 104.8855(19)°, *U* = 1617.9(4) Å³, *T* = 150(2) K, *Z* = 2, μ(Mo-Kα) = 1.249 mm⁻¹, 12711 reflections measured, 5678 unique (*R*_{int} = 0.0322) which were used in all calculations, *wR*2 = 0.2425 for all data, *R*1 = 0.0774 for 4097 data with *F*² ≥ 2σ(*F*²). Modeled with two-fold disorder in one CO₂Me group and the solvent of crystallization.
- Crystal data for **18**: C₂₇H₂₀Co₂O₁₂, *M* = 654.29, triclinic, *P*-1, *a* = 8.0886(5), *b* = 11.7239(7), *c* = 15.7788(9) Å, α = 106.5335(8), β = 102.7961(9), γ = 91.9661(9)°, *U* = 1391.20(14) Å³, *T* = 150(2) K, *Z* = 2, μ(Mo-Kα) = 1.255 mm⁻¹, 16756 reflections measured, 8572 unique (*R*_{int} = 0.0176) which were used in all calculations, *wR*2 = 0.0807 for all data, *R*1 = 0.0313 for 6949 data with *F*² ≥ 2σ(*F*²).
- Crystal data for **19**: C₂₇H₂₀Co₂O₁₁S, *M* = 670.35, triclinic, *P*-1, *a* = 8.6480(5), *b* = 12.0683(7), *c* = 14.2184(9) Å, α = 107.2871(9), β = 93.7267(9), γ = 91.7003(9)°, *U* = 1412.03(15) Å³, *T* = 150(2) K, *Z* = 2, μ(Mo-Kα) = 1.308 mm⁻¹, 17036 reflections measured, 8495 unique (*R*_{int} = 0.0202) which were used in all calculations, *wR*2 = 0.0844 for all data, *R*1 = 0.0323 for 7011 data with *F*² ≥ 2σ(*F*²).
- Added in press:- J. Matsuo, S. Sasaki, T. Hoshikawa and H. Iahibashi, *Org. Lett.*, 2009, **11**, 3822; J. Matsuo, S. Negishi and H. Ishibashi, *Tetrahedron Lett.*, 2009, **50**, 5831.