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Novel formation and use of a Nicholas carbocation in the synthesis of highly substituted tetrahydrofurans†

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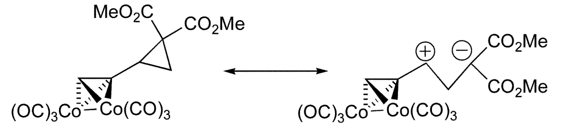
The first formation of a Nicholas carbocation through cleavage of a carbon–carbon σ bond has allowed the preparation of highly substituted tetrahydrofurans in a formal dipolar cycloaddition reaction.

The use of the Nicholas reaction is well established as a method for incorporating nucleophiles at propargylic cationic centres.[1] In particular, application to synthesis of ether ring systems is a popular step in the synthesis of many natural products.[2–10] The most common methods for achieving formation of Nicholas cations have been protonation of ethers, alcohols and alkenes.[1] To the best of our knowledge a Nicholas carbocation has never been created *via* cleavage of a C–C σ bond. Palladium catalysed ring opening of vinyl cyclopropanes and subsequent [3 + 2] cycloaddition with a double bond species is an extremely effective method for the construction of five-membered ring systems, and has previously been reported by Tsuji, Yamamoto and Trost and their co-workers.[11–15] These reports, together with Jamison and co-workers' account of a three component assembly of oxygen heterocycles using a bimetallic-alkyne carbonyl ylide and trapping with olefins,[16] led us to combine these methods to create a novel route to highly functionalised tetrahydrofuran species.

We now report the ring opening of dicobalthexacarbonyl complex of 2-ethynylcyclopropane-1,1-dicarboxylic acid dimethyl ester **1**, with boron trifluoride etherate ($BF_3{\cdot}OEt_2$) to form a doubly stabilised 1,3-dipole; the cobalt-alkyne unit stabilises the propargylic carbocation, while the malonate functionality stabilises the negative charge. The notable feature of this system is that the Nicholas carbocation is formed by cleavage of a carbon–carbon σ bond. (Scheme 1). The use of this dipole in organic synthesis is also explored.



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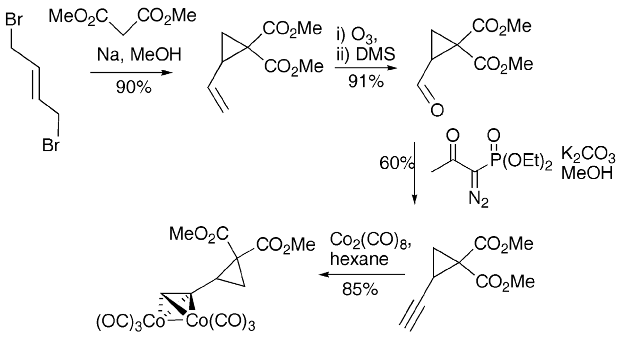
Scheme 1 Expected resonance form of cyclopropyl metal alkyne.

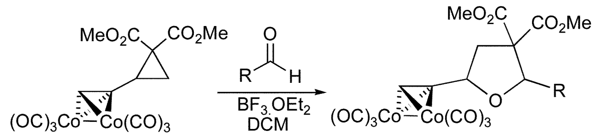
The starting alkynyl substituted cyclopropane was prepared in a straightforward manner, as shown in Scheme 2. The vinyl cyclopropane was synthesized by reaction of diethyl malonate with 1,4-dibromobut-2-ene.[11] Ozonolysis of this provided the corresponding aldehyde in 91% yield. Reaction with the Ohira–Bestmann reagent[17] allowed direct preparation of the alkyne in 60%, which was then complexed to cobalt, through reaction with dicobaltoctacarbonyl, in high yield (85%).

With the desired complex in hand, we wanted to assess its utility in the preparation of useful organic fragments.



Scheme 2 Formation of the cyclopropyl alkyne complex.

We postulated that aldehydes would represent a useful electrophile, producing tetrahydrofurans in the formal dipolar cycloaddition reactions with **1** (Scheme 3, Table 1). Optimisation of the reaction conditions quickly showed that reaction in dichloromethane with three equivalents of $BF_3{\cdot}OEt_2$ produced the highest yields. Use of only one equivalent of Lewis acid gave predominately a lactone by-product (*vide infra*). We suggest the Lewis acid may function in two ways: firstly, to aid the opening of the cyclopropane



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Scheme 3 Formal cycloaddition reaction with aldehydes.

Table 1 Conditions and yields of cyclisation reaction

Electrophile (R)	Product	Temp/°C	Yield (%)
Ph–	**2a**	25	68
		40	83
4-$MeOC_6H_4$–	**2b**	0	0
		40	0
4-$NO_2C_6H_4$–	**2c**	0	65
		40	71
2-$NO_2C_6H_4$–	**2d**	25	23
		40	30
4-FC_6H_4–	**2e**	0	85
		40	81
4-BrC_6H_4–	**2f**	0	50
		40	61
C_5H_{11}–	**2g**	0	83
		40	83
CH_3–	**2h**	0	74
		40	65
–$CO_2C_2H_5$	**2i**	25	82
		40	85

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† Electronic supplementary information (ESI) available: experimental procedures and data for new compounds. See http://www.rsc.org/suppdata/cc/b4/b411367e/

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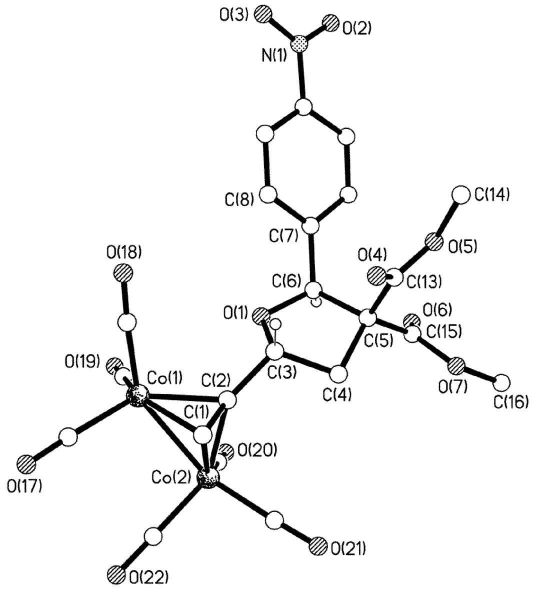


Fig. 1 X-Ray structure of complex *trans*-**2c**.

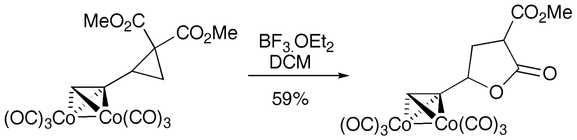
by activation of the malonate; secondly, through coordination with the aldehyde, thereby increasing its electrophilicity.

As may be expected, better yields were obtained with electron-deficient aromatic aldehydes. Electron-rich aromatic aldehydes, such as anisaldehyde, gave no reaction. Aliphatic (hexanal, acetaldehyde) and functionalised aldehydes (ethyl glyoxylate) were also found to be compatible. As indicated, the reaction takes place from zero to 40 °C. The *cis*- and *trans*-isomers were isolated as a 1 : 1 mixture in most of the reactions, with **2d** producing a maximum diastereomeric ratio (d.r.) of 2 : 1. However, in most cases, the diastereoisomers were separable by silica gel chromatography, allowing access to both complexes. The diastereoselectivity of the reaction was measured directly when the diastereoisomers were separable, otherwise the d.r. was determined by ^{1}H NMR spectroscopy.

In order to ascertain if interconversion of the diastereoisomers was responsible for the low d.r., we took the separated complexes *cis*-**2c** and *trans*-**2c** and subjected these to the reaction conditions. In each case, the pure *cis*- or *trans*-isomer gave a mixture of diastereoisomers, suggesting the mixture obtained is the thermodynamic ratio of products.

When the reaction was carried out without with an aldehyde substrate, we obtained a lactone by-product (Scheme 4). This presumably arises from the intramolecular cyclisation of one of the esters onto the Nicholas carbocation. This by-product was also obtained in the reaction with aldehydes when only one equivalent of Lewis acid was employed, or if the reaction mixture was contaminated with water.

Characterisation of one of the tetrahydrofuran products was completed when the X-ray crystal structure of *trans*-**2c** was obtained (Fig. 1).‡



Scheme 4 Formation of lactone by-product.

In conclusion, we have prepared a novel cyclopropyl alkynyl complex and successfully opened the ring to unveil a reactive 1,3-dipole. This reaction proceeds *via* cleavage of a C–C σ bond, providing a unique entry to the Nicholas carbocation system. This dipole can then be employed in the preparation of highly substituted tetrahydrofurans in good yield. Further work is underway to extend the scope of the reaction and to provide a means to control the stereochemistry. These studies will be reported in due course.

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Notes and references

‡ Crystal data for trans **2c**: $C_{22}H_{15}Co_2NO_{13}$, $M = 619.21$, triclinic, $a = 6.8834(15)$, $b = 8.1890(18)$, $c = 23.757(5)$ Å, $\alpha = 83.215(4)$, $\beta = 86.122(4)$, $\gamma = 67.370(4)^\circ$ $U = 1227.0(5)$ Å^3, $T = 150$ K, space group $P\bar{1}$, $Z = 2$, μ(Mo–Kα) = 1.422 mm^{-1}, 7010 reflections measured, 3195 unique ($R_{\text{int}} = 0.059$) which were used in all calculations. The final $wR2(F^2) = 0.1681$ (all data), $R1 = 0.0769$ (for 2122 data with $F^2 > 2\sigma(F^2)$). CCDC 246166. See http://www.rsc.org/suppdata/cc/b4/b411367e/ for crystallographic data in .cif format and a 3D Chime figure.

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