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Investigation of the scope of an enantioselective Co-mediated O→C rearrangement reaction

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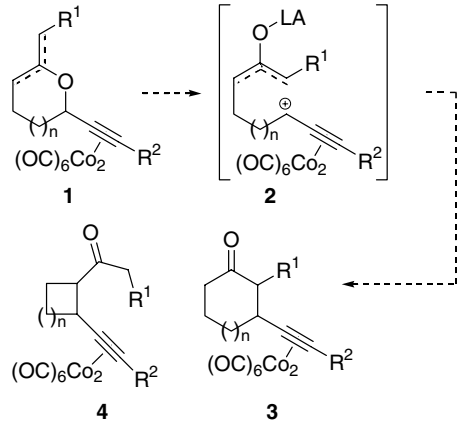
Abstract—A series of enantiomerically enriched functionalised pyrans bearing a dicobalt hexacarbonyl-alkyne moiety have been subjected to a Lewis acid mediated rearrangement to carbocyclic ketones. This process was found to provide cyclohexanones with good enantioselectivity, however, cyclobutanones were generated with complete loss of enantiocontrol.

Recent studies in our laboratories have uncovered a diastereoselective strategy towards 4-, 5-, 6- and 7-membered carbocyclic ketones via an O→C rearrangement[1] of functionalised cyclic ethers.[2,3] These approaches have all exploited latent electrophilic and nucleophilic moieties, generated by in situ molecular fragmentation of Co-alkyne complexed enol ethers. Specifically, as outlined in Scheme 1, Lewis acid activation of **1** promotes formation of a Nicholas carbocation[4] together with an enolate moiety (intermediate **2**) leading to C–C bond forming cyclisation to provide carbocyclic products **3** and **4**.

Both the starting enol ether complexes and ketone products contain a stereogenic centre at the propargylic position, and this raised an intriguing question as to the potential for stereochemistry to be maintained during the rearrangement process. In this context, Schreiber and co-workers carried out detailed studies into the nature of racemisation processes in Co-stabilised carbocations and found these to be relatively rapid.[5,6] Nonetheless, Muehldorf et al. confirmed that a Co-stabilised cation derived from an enantioenriched propargylic alcohol could be trapped by an intramolecular Friedel–Crafts reaction with minimal losses of enantiopurity in 6-membered ring forming reactions.[7] Notably however, the corresponding 5- and 7-membered ring



Scheme 1.

forming processes resulted in complete racemisation. These promising findings prompted us to investigate the scope of an enantioselective rearrangement of enantioenriched pyrans and we report our preliminary findings herein.[8]

Our initial studies focused on developing an efficient means to accessing enantioenriched pyrans. In this regard, we have shown that a [3+3] annelation strategy can be exploited towards the synthesis of enantioenriched nitrogen heterocycles by means of addition of the Büchi Grignard reagent to aziridines.[9] We therefore anticipated that an analogous process could be carried

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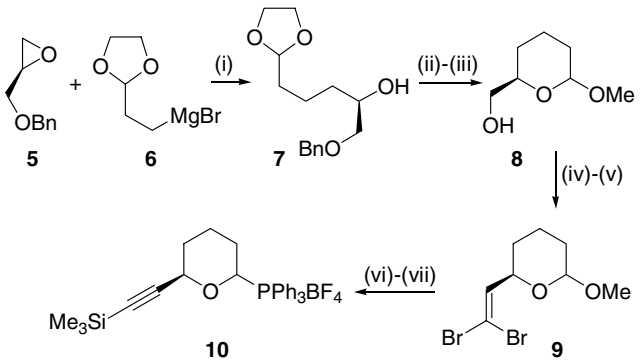


Scheme 2. Reagents and conditions: (i) 25 mol % CuBr·DMS, THF, −78 °C, 2 h, 99%; (ii) 1 M HCl, acetone–MeOH (1:5), rt, 4 h, 98%; (iii) H_2/Pd/C, MeOH, 16 h, 99%; (iv) $(COCl)_2$, DMSO, Et_3N, −78 °C; (v) CBr_4, PPh_3, DCM, −78 to 0 °C, 1 h, 75% over two steps; (vi) *n*-BuLi, THF, −78 °C, TMSCl, 88%; (viii) $HPPh_3BF_4$, MeCN, 4 Å MS, reflux, 16 h, 92%.

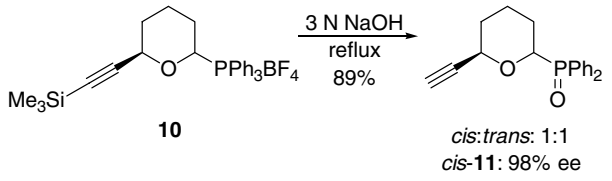
out towards pyrans from the corresponding epoxides,[10] and our route is outlined in Scheme 2.

Addition of Büchi Grignard **6** to commercial (*R*)-(+)-benzylglycidyl ether **5** proceeded in excellent yield to provide alcohol **7**, which was further transformed to pyran **8** upon hydrolysis and cleavage of the Bn-ether. Oxidation of the primary alcohol provided an unstable aldehyde that was immediately treated with CBr_4/PPh_3 to deliver dibromoolefin **9**. Finally, **9** was transformed to the desired phosphonium salt **10** in high yield over two steps.

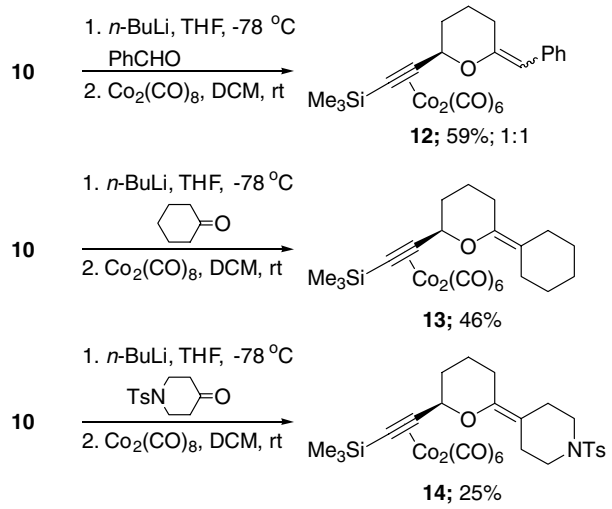
The enantiomeric purity of phosphonium salt **10** was established at this stage by conversion to the Horner–Wittig reagent by treatment with aqueous NaOH. Separation of the *cis*- and *trans*-diastereomers allowed us to determine the enantiopurity of *cis*-**11** by chiral HPLC (Scheme 3).[11]

We next turned our attention to the formation of a series of pyran based enol ether substrates in an effort to study the enantioselective rearrangement reaction. In the first instance, we prepared enol ethers *E*/*Z*-**12**, and more heavily substituted substrates **13** and **14** in modest to good yields over two steps (Scheme 4).

The *E*/*Z*-isomers of enol ether **12** were readily separated by chromatography and so we began our studies by examining their rearrangement, our results are summarised in Table 1. Subjection of *Z*-**12** to standard rearrangement conditions[2d] provided the corresponding ketone **15** in 84% yield and 87% ee (entry 1). We decided

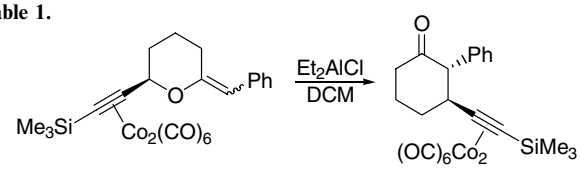


Scheme 3.



Scheme 4.

Table 1.

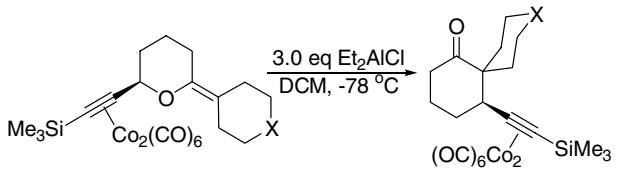


E/*Z*-**12** **15**

Entry	Substrate	Et_2AlCl (equiv)	*T* (°C)	Time (min)	Yield (%)	ee (%)
1	*Z*-**12**	1.5	−78	60	84	87
2	*Z*-**12**	1.5	−90	180	40	84
3	*Z*-**12**	1.5	−78 to rt	10	41	89
4	*Z*-**12**	3.0	−78	60	72	63
5	*E*-**12**	1.5	−78	60	84	77
6	*E*-**12**	1.5	−90	180	24	61
7	*E*-**12**	3.0	−78	60	85	47

to lower the reaction temperature in an effort to minimise racemisation processes but found that this had a deleterious effect on yield with little change to product ee (entry 2). Interestingly, reducing the reaction time by allowing the reaction to warm from −78 °C to room temperature over 10 min provided **15** in moderate yield but high ee (entry 3). Finally, increasing the quantity of Al-Lewis acid resulted in efficient rearrangement but delivered **15** with modest ee (entry 4). Notably, similar trends were observed in the rearrangement of *E*-**12** (entries 5–7).[12]

We next examined the rearrangement of substrates **13** and **14** towards enantiomerically enriched α-spirocyclic cyclohexanones. These sterically congested substrates had previously been investigated in the O→C process using 3.0 equiv of Al-Lewis acid. Given the poor results highlighted earlier in Table 1 when 3.0 equiv of Lewis acid were employed, together with the steric congestion present in these substrates, we were rather pessimistic as to the potential for generating enantioenriched products by this means. As outlined in Scheme 5 however, to our delight we found that the rearrangement of these sub-



X=CH_2; **13**
X=NTs; **14**

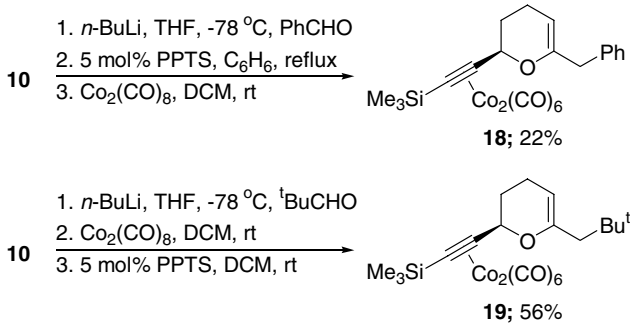
16; 83%, 87% ee
17; 51%; 74% ee

Scheme 5.

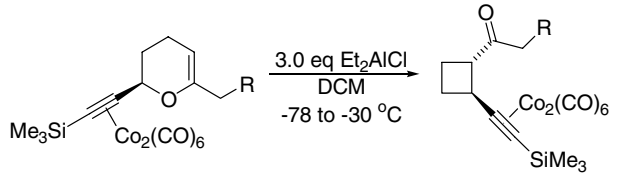
strates proceeded smoothly, allowing the corresponding products to be generated in good yields and enantioselectivities (Scheme 5).[13]

Finally, we wanted to extend these studies to include an enantioselective cyclobutane formation by a Co-mediated ring contraction process.[2e,f] Accordingly, dihydropyran complexes **18** and **19** were prepared from phosphonium salt **10** by a three-step sequence (Scheme 6).

Considering the results obtained in Table 1 and Scheme 5, we were hopeful that useful levels of enantiomeric purity would be retained in this process. In the event however, the rearrangement provided racemic material in both cases (Scheme 7).[14] We speculate that the reasons for the poor enantiocontrol in the ring contraction reactions to cyclobutanes is due to the relative sluggishness of 4-membered ring formation via cyclisation processes.[15] Indeed, this is manifested somewhat in the requirement for these reactions to be performed at elevated temperatures (−78 to −30 °C) relative to the cyclohexanone forming reactions described earlier.



Scheme 6.



R=Ph; **18**
X=^{t}Bu; **19**

20; 81%, 0% ee
21; 54%; 0% ee

Scheme 7.

In conclusion, we have found that enantioenriched pyranyl enol ethers undergo rearrangement to provide the corresponding cyclohexanones in high yield and good enantiocontrol. In contrast, the isomeric dihydropyrans appear to be subject to faster racemisation processes resulting in racemic cyclobutane products.

Acknowledgements

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11. Chiral HPLC analysis carried out on a Chiralpak OD column, 95:5 hexane/isopropanol, 1 mL/min; t_R(minor) = 21.75 min, t_R(major) = 23.92 min. Unfortunately, we were unable to separate the enantiomers of *trans*-**11**, and have therefore assumed *cis*-**11** to provide an adequate assay of enantiopurity at the propargylic stereocentre.
12. Substrate *E*-**12** gave rise to the cis-isomer of cyclohexanone **15**, this compound was isomerised to the corresponding trans-isomer (silica gel chromatography: petrol/

ether/Et_3N 50:10:1) to allow ee determination by chiral HPLC analysis.
13. The absolute stereochemistry of compounds **15**–**17** has not been elucidated but is assumed to be that shown based on the double inversion mechanism proposed by Schreiber.[5]
14. We were unable to assess the enantiopurity of complexes **18** and **19**, however, we were able to establish that they were not racemic samples by recording optical rotations: **18**; $[\alpha]_D^{23}$ 94.9 (*c* 0.158, $CHCl_3$). **19**; $[\alpha]_D^{30}$ −131.6, (*c* 0.114, $CHCl_3$).
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