



An effective protocol for the synthesis enantiomerically pure 4-substituted oxetane-2-ones



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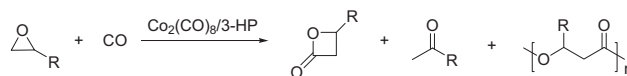
ABSTRACT

Six enantiomerically pure 4-substituted oxetane-2-ones (β-lactones) were obtained using the known Jacobsen's catalytic hydrolytic resolution of racemic epoxides, followed by atmospheric pressure carbonylation reaction.

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1. Introduction

Oxetane-2-ones (β-lactones) are attractive intermediates in organic synthesis, they are frequently presented as a structural unit of biologically active compounds and find a wide range of applications in biopolymer synthesis, e.g., via an anionic ring-opening polymerisation.^{1,2} However, their synthesis has been limited to only few methods. Among them, carbonylation is emerging as a versatile strategy because of the extensive availability of epoxides and high atom economy of the process. Recently, systematic investigations have been conducted on the catalytic synthesis of oxetane-2-ones through the carbonylation of epoxides, since epoxides are readily synthesised, inexpensive, and available in an enantiomerically pure form. Moreover, carbon monoxide used for this purpose is also cheap and readily available from synthetic gas. Catalytic carbonylation of epoxides leading to oxetane-2-ones was first discovered over a decade ago (Scheme 1).³ The catalytic system was composed of a cobalt source and a hydroxy-substituted pyridine, preferably dicobalt octacarbonyl, Co₂(CO)₈ and 3-hydroxypyridine (3-HP), respectively. The patent stated that a number of epoxides were carbonylated to form the corresponding β-lactones, and also noted that upon standing, or if the reaction run at high temperatures or for long times, a polymer was formed. Further development of the



Scheme 1. First epoxide carbonylation.

catalytic system proved that catalysts of the general formula [Lewis acid]⁺[Co(CO)₄][−] were the most efficient and selective.⁴ Among them, two groups were particularly promising, namely, the Jacobsen salen complexes (**1**) and tetraphenylporphyrins (**2**) (Fig. 1). These compounds combined a Lewis acidic cation and a nucleophilic metal-carbonyl anion into a single, well-defined complex that selectively carbonylates epoxides to oxetane-2-ones more quickly and under milder conditions than previous systems. The reaction involves Lewis acid (LA) inducing activation of the epoxide

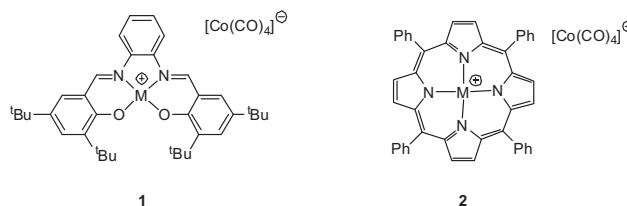


Fig. 1. Catalysts for epoxide carbonylation.

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followed by a ring-opening nucleophilic attack of $[\text{Co}(\text{CO})_4]^-$. Despite its undoubted advantages, the use of this method has been limited due to the necessity of expensive high-pressure (15–100 atm) equipment.

Thus, a catalyst efficient under mild conditions and low pressure of CO would be of value, enabling the widespread use of epoxide carbonylation as a route to oxetane-2-ones. In 2006, Coates et al.⁵ reported a synthesis of the salen type catalyst **1a** that was capable of epoxide carbonylation to produce a functionally diverse set of oxetane-2-ones with minimal side-product formation, at CO pressure as low as 1 atm (Fig. 2).

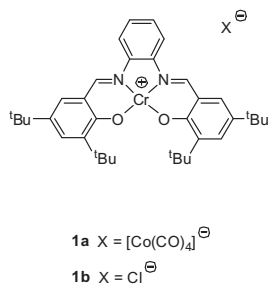


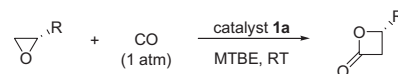
Fig. 2. Catalyst **1a** and its precursor **1b**.

However, the synthesis of the catalyst involves the preparation and handling of a highly oxygen-sensitive compound $\text{Na}[\text{Co}(\text{CO})_4]$. This requires the use of a glove box and Schlenk-line techniques, which impedes its use within non-specialised laboratories. Also isolation and handling of this catalyst is adversely affected by this sensitivity. Furthermore, commercially available catalysts lose their activity, even if stored under an inert gas atmosphere. Our hypothesis for this phenomenon assumes that the $[\text{Co}(\text{CO})_4]^-$ anion is slowly losing its carbonyl ligands. However, this inconvenience can be overcome due to the fact that sensitive anion $[\text{Co}(\text{CO})_4]^-$ can be generated in situ. It is based on the observation that free or complexed halide sources could catalyse the disproportionation of $\text{Co}_2(\text{CO})_8$ to generate nucleophilic $[\text{Co}(\text{CO})_4]^-$ ion.⁶ Ibrahim et al.⁷ proved that the use of a Lewis acid metal halide in conjunction with $\text{Co}_2(\text{CO})_8$ could form in situ a catalyst that would combine the Lewis acid activation of the epoxide with halide-assisted generation of $[\text{Co}(\text{CO})_4]^-$ ion. This circumvents the preparation and handling of highly air sensitive cobaltate salts.

2. Results and discussion

Based on these findings, we developed methodology to enable the synthesis of optically active oxetane-2-ones. Chirality is an important factor influencing polymer structure and its biodegradable properties. In order to prepare chiral starting materials, we used the known Jacobsen hydrolytic catalytic resolution of epoxides.⁸ First, we tested the possibility of in situ generation of the catalyst **1a**. By using the above-described approach, the corresponding salen **1b** and $\text{Co}_2(\text{CO})_8$ were used to prepare the catalyst, which initially was tested on a small scale. Generation of the catalyst, setting up and carrying out the reaction is a one-pot process under ambient CO pressure enabling a high level of reproducibility because the properties of this catalytic system are perfectly controlled. Also after extensive solvent screening we found that, dimethoxyethane commonly used in epoxide carbonylation can be successfully replaced with cheaper methyl *tert*-butyl ether. To address this issue for multigram-scale procedures, we also tested the influence of catalyst loading on the reaction outcome. With this procedure in hand, we screened the carbonylation of a representative variety of epoxides

(Scheme 2, Table 1). Using our optimised conditions, we obtained several optically active oxetane-2-ones, in good yields. No racemisation was observed during reaction (confirmed by GC and HPLC experiments). The conclusions concerning stereochemistry are based on the work of Coates et al.^{4a} In this paper the authors proposed a mechanism of oxetane-2-ones formation and showed that the carbonylation reaction of terminal epoxides occurs with the retention of configuration (based on a chemical correlation, namely transformation of (*R*)-propylene oxide into (*R*)- β -butyrolactone). The carbonylation reaction was initially carried out with 2 mol % of the catalyst. In some cases, it was possible to decrease catalyst loading to 1 mol %, producing β -lactones in a very efficient manner (entry 1, 5 and 6). All optically active oxetane-2-ones were successfully used in further studies on synthetic analogues of aliphatic biopolyesters. For this purpose, metal free anionic ring-opening homo- and copolymerisation have been used. The results of the above-mentioned studies will be published in near future. Our attention was focused towards novel oxetane-2-ones with high potential of application in biopolymer synthesis, leading to materials of special properties. The variety of oxetane-2-ones (monomeric biopolymer precursors), accessible by catalytic carbonylation of epoxides, opens the chance for many applications not only as a niche product in the medicine sector (e.g., as artificial tissues or drug delivery systems) but also as a competitor to standard oil-based plastic materials. The packaging industry and agriculture are interested in this increasingly important class of materials.



Scheme 2.

3. Conclusion

In summary, we have reported scalable procedure for the epoxide carbonylation, offering the possibility for synthesis of optically active oxetane-2-ones. The procedure involves in situ formation of the catalyst in methyl *tert*-butyl ether and reaction proceeding effectively under an atmospheric pressure of CO. This methodology allows multigram synthesis of variety of oxetane-2-ones and should find application in organic synthesis as well as polymer science.

4. Experimental section

4.1. General considerations

NMR spectra were recorded using a Varian Mercury spectrometer (^1H NMR, 500 MHz; ^{13}C NMR, 125 MHz) and referenced against tetramethylsilane as an internal standard. The following abbreviations were used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; br, broad spin system; m, multiplet; coupling constants are reported in Hertz. High resolution mass spectra (HRMS) were performed unit using the ESI technique. Optical rotations were taken using Jasco P-2000 polarimeter. Gas chromatography was performed using a Trace 2000 GC unit equipped with a capillary chiral column β -dex 120 (permethyl- β -cyclodextrin, 30 m 0.25 mm I.D. Supelco, Bellefonte, USA), conditions: carrier gas nitrogen, 100 kPa; injection temp 200 °C; detector temp 250 °C. High performance liquid chromatography was performed using Hitachi EZ Chrom Elite unit equipped with AD-H chiral column. IR spectra in KBr pellets were recorded on a Perkin–Elmer 1640 FTIR spectrometer. Analytical TLC was carried out on commercial plates coated with 0.25 mm of Merck Kieselgel 60. Preparative flash silica

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