Evans and co-workers also reported the isolation of the Dy^{III} complex $[Cp''_2Dy(\mu\text{-}N_2)DyCp''_2]$ from the reaction between DyI_2 and Cp″K in diethyl ether under nitrogen.[5] This clearly indicates the intermediacy of a Dy^{II} organometallic, although such an intermediate has yet to be isolated. It will be interesting to see whether, using the same reaction conditions as those used for the synthesis of **6**, the first Dy^{II} organometallic compound can be prepared, or whether the greater size and increased reduction potential of Dy^{II} will necessitate changes in the ligand and/or the reaction conditions to effect complex stabilization. The spectroscopic characterization and subsequent crystallization by Lappert and co-workers of compounds formulated as containing La^{II},[8] obtained by alkali metal reduction of $[Cp''_3La^{III}]$, suggests that even highly reducing La^{II} organometallic compounds may be readily accessible, provided that the correct supporting ligands and reaction conditions are chosen (E° (La^{3+}/La^{2+}) -3.1 V versus NHE).[3c]

Lanthanide(II) compounds now occupy a special place in the armoury of reagents available to the synthetic organic chemist due to their extremely useful redox potentials, their excellent functional group tolerance and the impressive stereo- and regioselectivities of many of their reactions.[9] Preliminary studies of the reduction chemistry of TmI_2 and DyI_2 have already indicated that these compounds have enormous potential as reagents in organic synthesis.[4d, 10] It remains to be seen whether new organolanthanide(II) compounds such as **6** will one day join the ranks of useful reagents.

Although they represent a significant advance in organolanthanide chemistry, the results outlined above beg several questions: 1) will it be possible to isolate organometallic compounds of the more reducing Ln^{II} ions such as Dy^{II} and Nd^{II} and, if so, to what extent must the ligand environment be modified in order to stabilize these highly reactive metal centers? 2) how will the reaction chemistries of **6** and related complexes compare with those established for **1** and **2**? and 3) will this chemistry be limited to sterically demanding cyclopentadienyl ligands such as Cp″ or will it be possible to further extend this range of compounds to include new σ-bonded organolanthanide(II) compounds?

Whatever the prospects for these new organolanthanide(II) compounds, it is evident that the future holds many challenges for the synthetic lanthanide chemist. We are on the brink of an exciting new era in organolanthanide chemistry which is certain to yield many novel compounds and unusual reactions.

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Catalytic, Enantioselective Syntheses of β-Lactones—Versatile Synthetic Building Blocks in Organic Chemistry

Christoph Schneider*

β-Lactones (2-oxetanones) combine the structural feature of a masked aldol product with the exceptional reactivity of a strained ring system that may be readily opened by nucleophiles.[1] Whereas soft nucleophiles typically add to β-lactones at the C(alkyl)–O bond with inversion of configuration, thereby furnishing chiral β-functionalized carboxylic acids, hard nucleophiles cleave the C(acyl)–O bond and unmask the aldol structure. Considering the significant synthetic value of β-lactones and the presence of this moiety in a number of biologically interesting natural products,[2] it is not surprising that great effort is currently being made to synthesize optically active β-lactones selectively and efficiently.[3]

The most direct synthesis of β-lactones involves the reaction of a ketene and an aldehyde which may proceed

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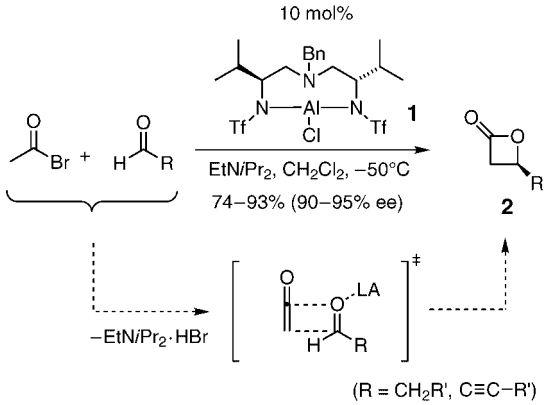
  1433-7851/02/4105-0744 $ 17.50+.50/0

either by way of a concerted [2+2] cycloaddition (HOMO(ketene)–LUMO(aldehyde) interaction) or, catalyzed by nucleophiles such as amines, through a stepwise aldol–lactonization reaction. The process developed by Wynberg and Staring in 1982[4] using cinchona alkaloids as nucleophilic catalysts—one of the earliest catalytic, enantioselective reactions—is an exceptional example for the latter variant which unfortunately allows only very reactive aldehydes, such as chloral, to be used as reaction partners. Recently however, substantial progress towards the development of more broadly applicable catalytic, enantioselective syntheses of β-lactones has been reported by several groups.

Nelson et al. developed the chiral, C_2-symmetric aluminum complex **1**, which was shown to be capable of catalyzing ketene–aldehyde cycloadditions under very mild conditions and in high yields and enantioselectivities (Scheme 1).[5] The

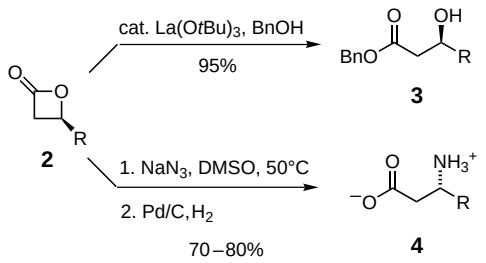


Scheme 1. [2+2] Cycloadditions of in situ generated ketenes and aldehydes according to Nelson et al.[5] Tf = trifluoromethanesulfonyl.

ketene component is generated in situ from acetyl bromide by treatment with Hünig's base and treated directly with the aldehyde complexed by the chiral Lewis acid **1** (10 mol%). Especially α-unbranched and acetylenic aldehydes have proved to be good substrates for this process, furnishing the optically active 2-oxetanones **2** typically in yields of 80–90% and enantioselectivities of 90–95% *ee*. By using propionyl bromide as ketene precursor in this scheme, 3,4-disubstituted 2-oxetanones are accessible with excellent *cis* diastereoselectivity as well.[6]

The free acetate aldol products **3** were obtained through reaction with alcohols catalyzed by $La(OtBu)_3$. Alternatively, the β-lactones **2** may be treated with NaN_3 in DMSO which resulted in the formation of β-azidocarboxylic acids with complete inversion of configuration. The latter were then hydrogenated with Pd/C to valuable β-amino acids **4** (Scheme 2).[7]

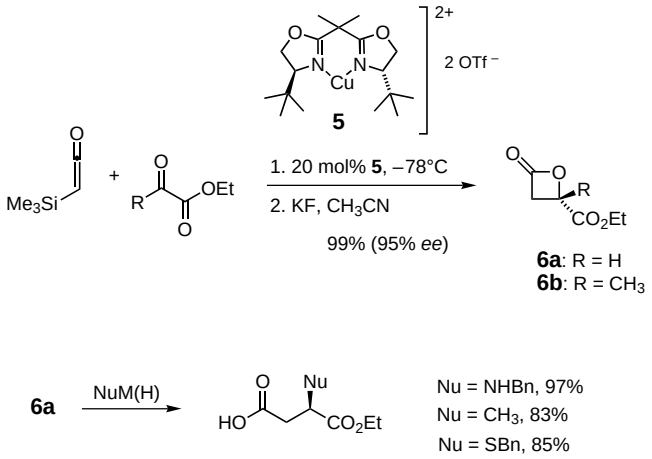
Crystallographic analysis of the aluminum triamine complex **1** revealed that the Lewis acidity of the a priori electron-rich complex stems from a trigonal-monopyramidal geometry around the aluminum center which leaves a fifth ligation site ideally disposed to accept the aldehyde. The X-ray structure of the **1**-DMF complex having a trigonal-bipyramidal geometry nicely supports this assumption. Interestingly, complexes



Scheme 2. Transformation of β-lactones **2** into acetate aldol products **3** and β-amino acids **4**.

lacking the additional heteroatom in the tether or complexes with a longer tether do not exhibit catalytic activity.[8]

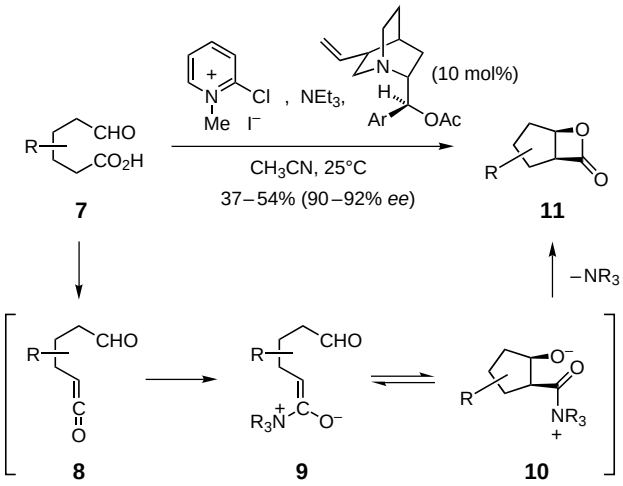
Evans et al. utilize C_2-symmetric copper(II)-bisoxazoline complexes **5** as chiral catalysts for the [2+2] cycloaddition of the more stable trimethylsilyl ketene with ethyl glyoxylate which affords the optically active β-lactone **6a** in very good yield and enantioselectivity (Scheme 3).[9] The observed



Scheme 3. [2+2] Cycloadditions of trimethylsilyl ketene and α-dicarbonyl compounds according to Evans et al.[9]

enantioselectivity is assumed to be derived from a double coordination of the chiral metal complex to the α-dicarbonyl moiety of the aldehyde and a square-planar geometry around the copper ion. Other α-oxygenated carbonyl compounds such as ethyl pyruvate and α-diketones are also good substrates for the cycloaddition and yield the corresponding β-lactones in good yields and enantioselectivities. The trimethylsilyl group is typically cleaved with fluoride after completion of the reaction. Futhermore, a series of stereospecific ring-opening reactions were conducted on the β-lactone **6a**, which gave rise to a range of optically active carboxylic acids (Scheme 3).

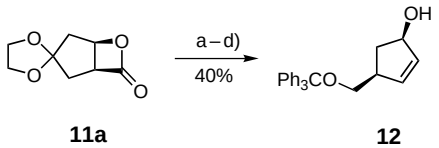
Romo et al. have synthesized some optically active bicyclic lactones **10** in moderate yields and very good enantioselectivities taking advantage of the cinchona alkaloid catalyzed aldol lactonization reaction (Scheme 4).[10] In a further development of the approach adopted by Wynberg and Staring they utilize ω-oxocarboxylic acids **7** and treat them with 2-chloro-*N*-methylpyridinium iodide (Mukaiyama reagent)



Scheme 4. Cinchona alkaloid catalyzed aldol–lactonization sequence to bicyclic β-lactones **11** according to Romo et al.[10]

and NEt_3 to furnish in situ the ω-oxo ketenes **8**. This strategy has two advantages: it avoids the otherwise necessary use of a ketene generator, and the intramolecular reaction course allows the employment of not specifically activated aldehydes. *O*-Acetyl quinidine (10 mol%) now adds in situ to ketene **8**, and the resulting ammonium enolate **9** engages the aldehyde in an intramolecular aldol reaction to yield aldolate **10**, which cyclizes to β-lactone **11** with concomitant regeneration of the chiral catalyst. The rate- and configuration-determining step is presumably the cyclization to the β-lactone, while the aldolate is formed reversibly. Owing to ring strain considerations only *cis*-fused bicyclic rings are formed, the *trans*-aldolates presumably revert back to the ammonium enolates in a retro-aldol reaction.

Bicyclic compounds **11** are characteristic structural elements of various natural products, such as spongiolactone,[2] and after ring-opening useful intermediates for the synthesis of pharmacologically interesting compounds. For this purpose **11a** was reductively opened and the enone moiety liberated through acid-catalyzed hydrolysis and elimination. Upon DIBAH reduction the highly enantiomerically enriched cyclopentenol **12** was obtained, which has been used previously as an intermediate in the synthesis of the antiviral, carbocyclic nucleoside aristeromycin (Scheme 5).



Scheme 5. Synthesis of an intermediate for aristeromycin from **11a**. a) $BH_3 \cdot SMe_2$, THF; b) 1N HCl, THF; c) Ph_3CCl, CH_2Cl_2; d) diisobutylaluminum hydride (DIBAH), THF.

In conclusion, these new methods for the catalytic, enantioselective synthesis of β-lactones constitute a significant advancement of synthetic methodology and should bring about more synthetic applications of β-lactones. The search for even more broadly applicable and more selective catalysts and processes will surely continue.

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