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Vicinal di-functionalization of α,β-unsaturated ketones via manganese carbene intermediates: synthesis of γ-acyl-δ-lactones by cascade Michael addition/aldol/transesterification reactions

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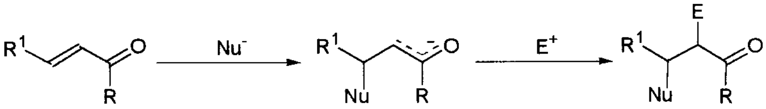
Abstract

The carbene–enolate complexes generated upon reaction of the carbene anion $[Cp'(CO)_2Mn{=}C(OEt)CH_2]^-$ with benzylidene acetone and chalcone react with benzaldehyde to form the 6-membered oxacyclocarbene complexes $Cp'(CO)_2Mn{=}CCH_2CH(Ph)CH(C\{O\}R)CH(Ph)O$ ($R = Me$, Ph). The latter, which can be regarded as the result of cascade Michael addition/aldol/transesterification reactions, are readily oxidized by air to release the corresponding γ-acyl-δ-lactones. © 2000 Elsevier Science Ltd. All rights reserved.

Tandem vicinal difunctionalization of α,β-carbonyl substrates has been extensively exploited in organic synthesis.[1] Yet, regio- and stereocontrol in each step remains a synthetic challenge without general solution.



Carbene anions generated upon deprotonation of the α-carbon atom of alkylalkoxy or alkylamino carbene complexes $L_nM = C(XR)CH_3$[2] are known to react with a variety of electrophilic substrates,[3] including enones.[4] Exclusive 1,4 addition is observed with a high degree of stereocontrol.[4b,d,e] Such anions could thus act as valuable nucleophiles for the above reaction ($Nu^- = [L_nM{=}C(XR)CH_2]^-$) provided the 'carbene-enolate' complexes formed upon the nucleophilic attack on the enone can be further functionalized in the vicinal position.

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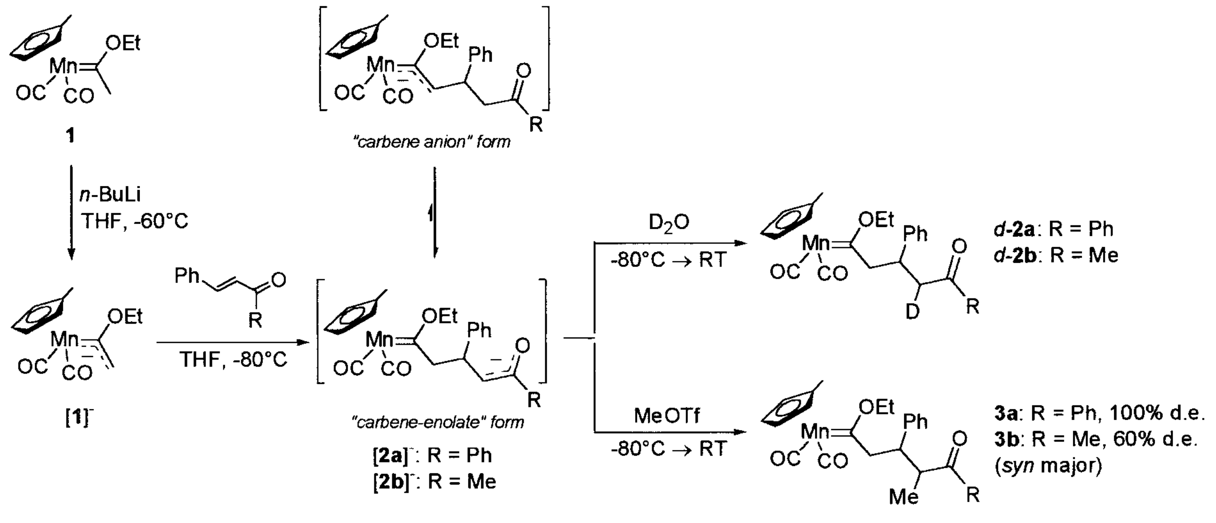
While pursuing our investigations on the reactivity of manganese carbene anions toward carbonyl substrates,[5] we were pleased to observed that when the reaction between [Cp′(CO)$_2$Mn=C(OEt)CH$_2$]$^-$ ([**1**]$^-$) and benzylideneacetone or chalcone was quenched with D$_2$O, deuteration of the incipient carbene–enolate [**2**]$^-$ occurred exclusively at the γ position relative to the carbene carbon atom to give Cp′(CO)$_2$Mn=C(OEt)CH$_2$CH(Ph)CHDC{O}R (*d*-**2**; *d*-**2a**: R = Ph, 94% yield, orange oil; *d*-**2b**: R = Me, 85% yield, orange oil) (Scheme 1). Alternatively, quenching with MeOTf resulted in selective methylation at the γ position, giving the complex Cp′(CO)$_2$Mn=C(OEt)CH$_2$CH(Ph)CH(Me)C{O}R (**3**; **3a**: R = Ph, 71% yield, orange oil; **3b**: R = Me, 71% yield, orange oil). Complex **3b** was formed with 60% d.e. and a careful analysis of NMR data[6] allowed to establish a *syn* configuration for the major diastereomer. For **3a**, only one diastereomer could ever be detected, though its configuration could not be unambiguously determined.

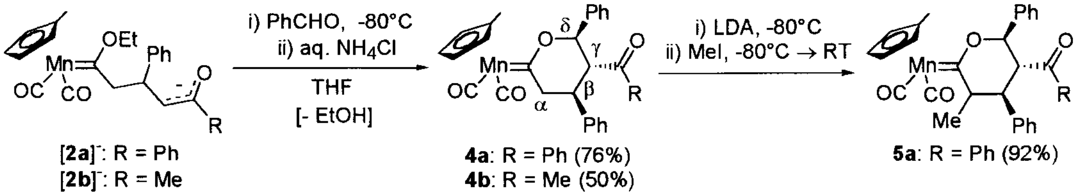


Scheme 1.

These experiments demonstrate that the carbene–enolate complex [**2**]$^-$ that initially forms upon the nucleophilic attack of the manganese carbene anion [**1**]$^-$ on the enone remains as the major species present in solution, at least under these reaction conditions.[7] This is in sharp contrast with early observation by Casey et al. who showed that related types of carbene–enolates generated from *chromium* carbene complexes readily equilibrate in favor of the corresponding carbene anions.[4a] This prompted us to investigate further the reactivity of [**2**]$^-$.

The carbene–enolates [**2**]$^-$ were found to react effectively with benzaldehyde. Upon quenching the reaction at low temperature, the new complexe Cp′(CO)$_2$Mn=CCH$_2$CH(Ph)CH(C{O}R)CH(Ph)O (**4**; **4a**: R = Ph, 76% yield, yellow solid, m.p. 95–97°C (dec)); **4b**: R = Me, 50% yield, yellow solid, m.p. 70–72°C (dec)) (Scheme 2) was obtained.

The structure of complex **4b** has been established by an X-ray diffraction study.[8] A perspective view of complex **4b** is given on Fig. 1. It consists of Cp′(CO)$_2$Mn fragment linked to a six-membered 2-oxacyclocarbene moiety. The ring adopts a chair conformation. The two phenyl ring attached to C(5) and C(7) and the acetyl group linked to C(6) are each in an equatorial position. In



Scheme 2.

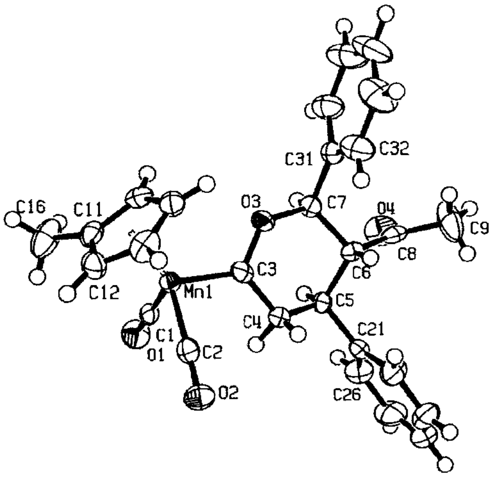


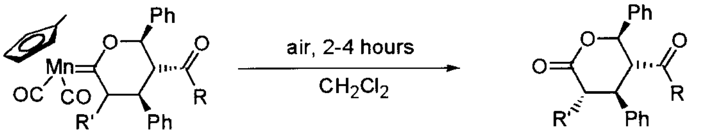
Figure 1. Perspective view of complex **4b**. Selected bond distances (Å) and angles (°): Mn(1)–C(3) = 1.880(4); O(3)–C(3) = 1.345(4); O(3)–C(7) = 1.476(4); C(3)–C(4) = 1.512(5); C(4)–C(5) = 1.530(5); C(5)–C(6) = 1.538(5); C(6)–C(7) = 1.527(5); Mn(1)–C(3)–O(3) = 119.4(3); Mn(1)–C(3)–C(4) = 125.1(3); O(3)–C(3)–(4) = 115.4(3)

solution, the coupling constants $J_{H\beta H\gamma}$ and $J_{H\gamma H\beta}$ of ca. 10 Hz measured in the ^{1}H NMR spectrum of **4b**—as well as in the NMR spectra of **4a**—are fully consistent with such a stereochemistry.

Considering the analogy that may exist between carbene anions and ester enolates,[3a] complex **4** can be regarded as the result of cascade Michael addition/aldol/intramolecular transesterification reaction between the carbene complex **1**, an enone and an aldehyde. Significantly, the substrates we have chosen lead to final complexes possessing three chiral carbon atoms, whose relative configuration would be determined in the aldolisation step. A striking feature is that only one diastereomer, among the four discernible ones, could ever been detected.[9]

In addition, the 2-oxacyclocarbene complex **4a** could easily be methylated in the α-position upon treatment by LDA at –80°C in THF followed by methyl iodide (Scheme 2), thus producing a fourth chiral atom in the resulting complex $Cp'(CO)_2Mn{=}CCH(Me)CH(Ph)CH(C\{O\}Ph)C(Ph)O$ (**5a**, 92% yield, yellow oil), and this in a totally stereoselective manner. The $J_{H\alpha H\beta}$ coupling constant of 2.2 Hz in **5a** suggests a *cis* arrangement of the two protons H_α and H_β. Considering that α-alkylation of β-substituted δ-lactones are particularly *trans* selective,[10] the *cis* selectivity of the present reaction is surprising. We will remain, however, quite circumspect since NOE experiments aimed at confirming such a stereochemistry stayed inconclusive due to inescapable paramagnetic impurities.

The oxidation of manganese carbene complexes to release the corresponding carbonylated organic compound is known to take place upon treatment by either $KMnO_4$,[11a] or Me_3NO.[11b] In the present case, complexes **4** and **5** can readily be oxidized by air to liberate the corresponding diastereoisomerically pure γ-acyl-δ-lactones **6** and **7** in nearly quantitative yields (**6a**: R = Ph, R′ = H, 95% yield, white needles, m.p. 85–87°C; **6b**: R = Me, R′ = H, 80% yield, pale yellow oil; **7**: R = Ph, R′ = Me, 91% yield, pale yellow oil) (Scheme 3).



4a: R = Ph, R' = H
4b: R = Me, R' = H
5a: R = Ph, R' = Me

6a: R = Ph, R' = H (95%)
6b: R = Me, R' = H (80%)
7a: R = Ph, R' = Me (91%)

Scheme 3.

NMR data for **7a** indicates that H_α and H_β are in a *trans* position ($J_{H\alpha H\beta} = 11.4$ Hz): it remains unclear, however, whether these two hydrogen atoms were already in such a position in **5a** (vide supra) or if an epimerization at the α carbon atom occurred during the oxidation procedure.

γ-Acyl-δ-lactones are important synthetic intermediates.[12] It is worth noting that the lactone **6a** had previously been synthesized by tandem Michael addition/aldol reactions from ketene silyl acetals, α,β-unsaturated ketone, and aldehydes but with a different configuration.[12,13]

In summary, we have shown that the carbene anion deriving from a *manganese* alkylalkoxy carbene complexe is a suitable nucleophile for the vicinal difunctionalization of α,β-unsaturated ketone. It is remarkable that such a type of reaction has never been observed from the by far more studied group 6 carbene anions: this is very likely due to the poor acceptor ability of the $Cp(CO)_2Mn$ fragment compared to a $(CO)_5M$ (M = Cr, W) fragment, which in fact helps in stabilizing the key carbene–enolate intermediate complex shown on Scheme 1 versus. its—here unwanted—carbene anion form.

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6. Assignment of the configuration has been made by ^1H NMR considering the upfield chemical shift of the substituent gauche to the phenyl ring for the most stable rotamer (hydrogens *anti*) in each diastereomer. See: Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.

7. For R = Me, we have previously shown that quenching the reaction after warming up to room temperature allows isolation of the cyclohexanone complex $Cp'(CO)_2Mn(\eta^2\text{-}CH{=}CHCH_2CH(Ph)CH_2C\{O\})$.[4a]
8. Crystal data for **4a**: monoclinic, $C_{2h}^5\text{-}P2_1/c$, a = 5.7690(10) Å, b = 28.352(2) Å, c = 13.835(1) Å, β = 94.220(10)°, V = 2256.8(5) Å^3, Z = 4, R = 0.0556 for 2286 reflections and 291 variable parameters.
9. For R = Ph, NMR analysis of the crude reaction mixture showed the presence of **4a**, **1**, and traces the Michael adduct **2a**,[4a] whereas for R = Me, it showed **4b**, traces of **1**, **2b**[4a] (25% estimated by ^{1}H NMR), and traces of the 1,2 addition complex $Cp'(CO)_2Mn{=}C(OEt)CH(OH)(Me)C(H){=}C(H)Ph$.[4a]
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