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A Novel Route to 2-Cyclohexenones via Reaction of the Manganese Carbene Anions $[(\eta^5\text{-}MeC_5H_4)(CO)_2Mn{=}C(OEt)CHR]^-$ (R = H, Me) with α,β-Unsaturated Ketones

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*Summary: The carbene anions $[Cp'(CO)_2Mn{=}C(OEt)CHR]^-$ ([**1**]$^-$, $Cp' = \eta^5\text{-}MeC_5H_4$; R = H, Me) react at −78 °C with the α,β-unsaturated ketones $R^1(H)C{=}C(H)C\{O\}Me$ (**2**, R^1 = H, Me, Ph) to give the Michael adducts $Cp'(CO)_2Mn{=}C(OEt)CH(R)CH(R^1)CH_2C\{O\}Me$ (**3**) upon acidic hydrolysis at low temperature. By contrast, quenching the reaction after warming up to room temperature allows isolation of the cyclohexenone complexes $Cp'(CO)_2Mn(\eta^2\text{-}\overline{CH{=}CHCH(R)CH(R^1)CH_2C}\{O\})$ (**5**), from which the corresponding substituted 2-cyclohexenones (**9**) can be readily released by reaction with triphenylphosphine or carbon monoxide.*

Carbene anions formed upon deprotonation of Fischer-type carbenes at the β-carbon atom are known to react with a variety of electrophilic substrates,[1] including carbonyl compounds, to give aldol[2] or Michael[3] adducts. Until recently,[4] such reactions were almost exclusively developed with group 6 carbene anions. Our own interest in manganese derivatives $[Cp'(CO)_2Mn{=}C(OR')CHR]^-$ ([**1**]$^-$) stems in part on experimental evidences of their enhanced reactivity toward electrophiles as compared with the chromium and tungsten analogs $[(CO)_5M{=}C(OR')CHR]^-$.[5] This can be rationalized in terms of the relative acceptor abilities of the fragments $Cp'(CO)_2Mn$ ($Cp' = \eta^5\text{-}MeC_5H_4$) and $(CO)_5M$ (M = Cr, W). Keeping in mind the pioneering work of Casey *et al.* on the chromium *alkylalkoxy* carbene anion,[3a] we were curious to examine the reactivity of [**1**]$^-$ (R′ = OEt; R = H, Me) toward α,β-unsaturated ketones. This led us to observe the formation of cyclohexenone complexes, thus revealing an unprecedented reactivity pattern for these carbene anions.

The carbene anions $[Cp'(CO)Mn{=}C(OEt)CHR]^-$ ([**1a**]$^-$, R = H; [**1b**]$^-$, R = Me), generated *in situ* by treatment of $Cp'(CO)_2Mn{=}C(OEt)CH_2R$ (**1**) with ^{n}BuLi in THF at −78 °C,[5a] effectively readily react with the α,β-unsaturated ketones $R^1(H)C{=}C(H)C\{O\}R^2$ (**2**, see Table 1). After acidic hydrolysis *at low temperature*, the Michael-addition complexes $Cp'(CO)_2Mn{=}C(OEt)CH(R)CH(R^1)CH_2C(O)R^2$ (**3**, Scheme 1; Table 1, conditions A, entries 1−8) are obtained in moderate to excellent yields.[6] Only from the reaction between [**1a**]$^-$ and **2d** (Table 1, entry 4) is the aldol adduct $Cp'(CO)_2Mn{=}C(OEt)CH_2C(Me)(OH)CH{=}CH(Ph)$ (**4d**) detected in trace amounts. In contrast to the previously reported Michael additions of $[(CO)_5Cr{=}\overline{COCH_2CH_2CH}]^-$ to **2c** or **2d** that were not found to be diastereoselective,[3a] we find that **3e**, **3g**, and **3h** are, respectively, formed with diastereomeric excesses of 33%, 50%, and 70% (Table 1, entries 5, 7−8). Combinations of NMR and X-ray diffraction studies allowed us to establish an *anti* configuration for each of the major diastereomers.[7,8]

In attempts to optimize the reaction conditions of the above Michael addition, we to discovered that the nature of the resulting complexes is dramatically affected by the maximum temperature reached before the acidic workup. Indeed, once the carbene anions [**1**]$^-$ were allowed to react with the α,β-unsaturated ketones $R^1(H)C{=}C(H)C\{O\}Me$ (**2b**−**d**) at −78 °C, acidic hydrolysis carried out *at room temperature* afforded the 2-cyclohexenone complexes $Cp'(CO)_2Mn(\eta^2\text{-}CH{=}\overline{CHCH(R)CH(R^1)CH_2C}\{O\})$ (**5**, Scheme 1; Table 1, conditions B, entries 2−4, 6−8).[6,9] These complexes were characterized by the usual spectroscopic techniques and for some of them by X-ray diffraction. Complexes **5c**, **5d**, and **5f** were isolated as single diastereomers, each of them exhibiting an *exo* configuration.[10] Since partial decomposition to give paramagnetic species precluded NMR analysis of the crude reaction mixtures, the formation

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[2] (a) Wulff, W. D.; Gilbertson, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 503. (b) Wulff, W. D.; Anderson, B. A.; Toole, A. *J. Am. Chem. Soc.* **1989**, *111*, 5485. (c) Wulff, W. D.; Anderson, B. A.; Toole, A. J.; Xu, Y.-C. *Inorg. Chim. Acta* **1994**, *220*, 215 and references cited therein. (d) Powers, T. S.; Shi, Y.; Wilson, K. J.; Wulff, W. D. *J. Org. Chem.* **1994**, *59*, 6882.

[3] (a) Casey, C. P.; Brunsvold, W. R.; Scheck, D. M. *Inorg. Chem.* **1977**, *16*, 3059. (b) Anderson, B. A.; Wulff, W. D.; Rahm, A. *J. Am. Chem. Soc.* **1993**, *115*, 4602. (c) Iyoda, M.; Zhao, L.; Matsuyama, H. *Tetrahedron Lett.* **1995**, *36*, 3699.

[4] Yi, C. S.; Geoffroy, G. L.; White, C. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3806.

[5] (a) Kelly, C.; Lugan, N.; Terry, M. R.; Geoffroy, G. L.; Haggerty, B. S.; Rheingold, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 6735. (b) Rabier, A.; Lugan, N.; Mathieu, R.; Geoffroy, G. L. *Organometallics* **1994**, *13*, 4676. (c) Gimenez, C.; Lugan, N.; Mathieu, R.; Geoffroy, G. L. *J. Organomet. Chem.* **1996**, *517*, 133.

[6] The detailed experimental, spectroscopic, and crystallographic information are provided as Supporting Information.

[7] For a definition of the *syn*/*anti* convention used, see: Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

[8] (a) Assignments of the configurations have been made by ^{1}H 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. (b) The *anti* configuration of the Cp analog of *anti*-**3h** has been confirmed by X-ray crystallography; crystal data: monoclinic C_{2h},[5] $P2_1/c$, $a = 15.075(6)$ Å, $b = 8.766(2)$ Å, $c = 16.691(2)$ Å, $\beta = 111.06(7)$°, $V = 2058(2)$ Å^3, $Z = 4$, $R = 0.0394$, $R_w = 0.0423$ for 2171 observations and 244 variable parameters.

[9] The 2-cyclohexenone complex **5b** was originally obtained in 30% yield upon photolysis of $Cp'(CO)_3Mn$ in the presence of 2-cyclohexenone, see: Giffard, M.; Gentric, E.; Touchard, D.; Dixneuf, P. *J. Organomet. Chem.* **1977**, *129*, 371.

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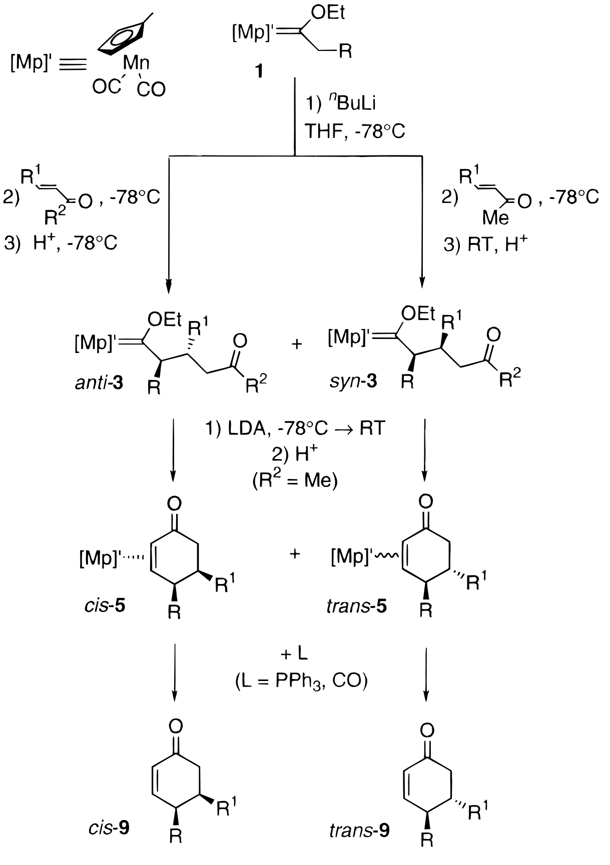
Table 1. Reactions of Carbene Complexes $Cp'(CO)_2Mn{=}C(OEt)CH_2R$ (1) with α,β-Unsaturated Ketones $R^1(H)C{=}C(H)C\{O\}R^2$ (2)

	carbene		α,β-unsaturated ketone			conditions A[a]			conditions B[b]		
entry		R		R^1	R^2	product(s)	yield[c]	*anti*/*syn*[d]	product(s)	yield[c]	*cis*/*trans*[e,f]
1	**1a**	H	**2a**	Ph	Ph	**3a**	98				
2		H	**2b**	H	Me	**3b**	66		**5b**	66	
3		H	**2c**	Me	Me	**3c**	88		**5c**	65	
4		H	**2d**	Ph	Me	**3d**[g]	85		**5d**	49	
5	**1b**	Me	**2a**	Ph	Ph	**3e**	85	66:34			
6		Me	**2b**	H	Me	**3f**	61		**5f**	59	
7		Me	**2c**	Me	Me	**3g**	82	75:25	**5g**	69	80:20
8		Me	**2d**	Ph	Me	**3h**	94	85:15	**5h**	90	91:9

[a] Conditions A: the carbene anion $[\mathbf{1}]^-$ was generated *in situ* by reaction of **1** with 1.1 equiv of ^{n}BuLi at −78 °C in THF, and after 20 min, 1.1 equiv of α,β-unsaturated ketone was added. After 15 min, the reaction was quenched by the addition of a saturated solution of NH_4Cl. [b] Conditions B: as in conditions A, except after the addition of the α,β-unsaturated ketone the reaction medium was allowed to reach room temperature, stirred for 2 h, and then the reaction was quenched by the addition of a saturated solution of NH_4Cl. [c] Isolated overall yield. [d] Estimated by ^1H NMR on crude reaction mixtures after a short filtration on alumina. [e] *cis*/*trans* refers to the relative position of the R and R^1 substituents within the cyclohexenone ring. [f] Ratio of isolated complexes after chromatographic workup. [g] 1,2-Addition product formed in trace amounts (<5%).

Scheme 1



of the *endo* isomers cannot be excluded.[11] The disubstituted 2-cyclohexenone complexes **5g** and **5h** were isolated as two of four potential diastereomers *cis*-**5g** and *trans*-**5g** and *cis*-**5h** and *trans*-**5h** in 78:22 and 80:20 ratios, respectively. The structure of the major stereoisomer of *cis*-**5h** has been determined by X-ray crystallography:[12] the methyl and phenyl substituents within the cyclohexenone ring are found in a relative cis position, and the $Cp'(CO)_2Mn$ fragment is coordinated onto the opposite face. The configuration of the minor species *trans*-**5g** and *trans*-**5h** could not be fully elucidated, although the observed $^3J_{HH}$ of 9.1 and 10.1 Hz, respectively, between the protons of the adjacent CH(R) and CH(R^1) groups within the cyclohexenone ring indicate a relative *trans* position for the R and R^1 substituents in each complex.

Scheme 2 illustrates a possible mechanism for **5h** that would account for the unexpected formation of cyclohexenone complexes **5**. Nucleophilic attack of the carbene anion $[\mathbf{1b}]^-$ on benzylideneacetone **2d** would give the *anti* enolate anion [*anti*-**3h**]$^-$ as the major diastereomer. According to Casey *et al.*, related types of enolate anions generated from chromium carbene complexes readily equilibrate in favor of the corresponding carbene anions.[3a] Such a process would not predominate in the present case due to the destabilizing effect of the $Cp'(CO)_2Mn$ fragment toward carbene anions. Instead, a small portion of [*anti*-**3h**]$^-$ would isomerize to give the terminal enolate, allowing an intramolecular nucleophilic substitution for the ethoxy group on the carbene carbon to take place upon warming to room temperature, thus producing $[\mathbf{6h}]^-$,[13] in which the 4-Me and 5-Ph substituents are in a *cis* position, as found in the major final product *cis*-**5h**. The acidic hydrolysis of $[\mathbf{6h}]^-$ would lead to the neutral carbene complex **8h**, from which a final 1,2-hydride shift[14] would produce the cyclohexenone complex *cis*-**5h**. (Similarly, the minor cyclohexenone complex *trans*-**5h** would be produced from the minor *syn* enolate anion [**6h**-*syn*]$^-$, not represented on Scheme 2.)

As it can now be expected, cyclohexenone complexes **5** can be alternatively obtained from the corresponding

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[10] Crystal data for **5d**: monoclinic C_{2h},[5] $P2_1/n$, a = 9.516(2) Å, b = 14.691(3) Å, c = 12.447(3) Å, β = 105.26(2)°, V = 1678.7(7) Å^3, Z = 4, R = 0.0262, R_w = 0.0296 for 2088 observations and 217 variable parameters. Crystal data for **5f**: triclinic C_i,[1] $P1$, a = 6.826(3) Å, b = 9.506(1) Å, c = 11.789(2) Å, α = 69.23(1)°, β = 86.65(3)°, γ = 74.21(3)°, V = 687.6(4) Å^3, Z = 2, R = 0.0383, R_w = 0.0443 for 1805 observations and 172 variable parameters.

[11] Column chromatography of freshly prepared **5** on alumina shows a relatively fast moving band containing an extremely air-sensitive unidentified purple complex, along with traces of the corresponding free cyclohexenone. As this phenomenon disappears upon repeated chromatographic workup, we suspect it might be due to a selective decomposition of unstable stereoisomers. In few instances, after a first purification, traces of another complex could be observed along with **5d**, the ^{13}C NMR spectrum of which may correspond to the *endo* stereoisomers.[6]

[12] Crystal data for *cis*-**5h**: monoclinic C_{2h},[5] $P2_1/n$, a = 10.022(1) Å, b = 7.067(2) Å, c = 25.551(3) Å, β = 90.65(1)°, V = 1809.5(5) Å^3, Z = 4, R = 0.0543, R_w = 0.0623 for 1055 observations and 166 variable parameters.

[13] At this stage, IR spectroscopy does indicate the formation of an anionic carbene complex (IR ν_{CO} (THF): 1897, 1830 cm^{-1}). Further evidence for the nature of the elusive intermediate $[\mathbf{6h}]^-$ was obtained by a methylation reaction leading to the fully characterized cyclic vinylcarbene **7h**.[6]

[14] (a) Casey, C. P.; Brunsvold, W. R. *Inorg. Chem.* **1977**, *16*, 391. (b) Roger, C.; Bodner, G. S.; Hatton, W. G.; Gladysz, J. A. *Organometallics* **1991**, *10*, 3266 and references cited therein.

Scheme 2

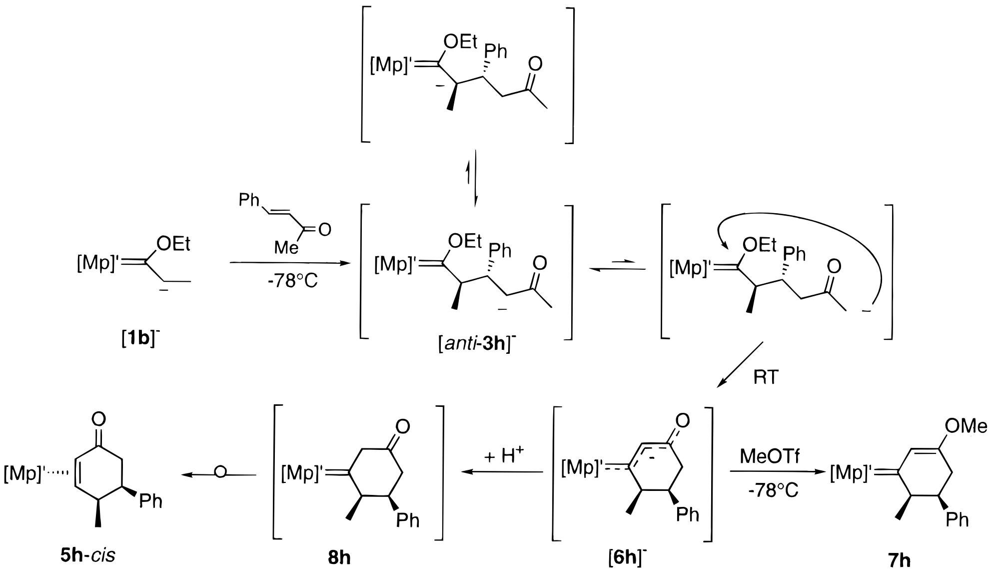

Table 2. Formation of Cyclohexenone Complexes 5 from Michael Adducts 3[a] and Demetalation Reactions[b]

	complex **3**				complex **5**		cyclohexenone **9**	
entry		R	R^1	R^2		yield		yield[c]
1	**3b**	H	H	Me	**5b**	90	**9b**	77
2	**3c**	H	Me	Me	**5c**	59	**9c**	82
3	**3d**	H	Ph	Me	**5d**	49	**9d**	92
4	**3f**	Me	H	Me	**5f**	95	**9f**	80
5	*anti*-**3g**	Me	Me	Me	*cis*-**5g**	72	*cis*-**9g**	75
6	*syn*-**3g**	Me	Me	Me	*trans*-**5g**	77	*trans*-**9g**	78
7	*anti*-**3h**	Me	Ph	Me	*cis*-**5h**	87	*cis*-**9h**	86
8	*syn*-**3h**	Me	Ph	Me	*trans*-**5h**	70	*trans*-**9h**	88

[a] LDA (1.1 equiv) was added at −78 °C to a solution of complex **3** in THF. The reaction medium was allowed to reach room temperature. After 2 h, the reaction was quenched by the addition of a saturated solution of NH_4Cl. [b] Triphenylphosphine (1.5 equiv) was added to a solution of cyclohexenone complex **5**, and the mixture was heated under reflux until total disapperance (by IR) of **5** (2 h). [c] Isolated yieds after chromatographic workup on alumina.

Michael adducts **3** upon treatment with LDA at −78 °C and subsequent acidic hydrolysis at room temperature (Scheme 1; Table 2).[6] Complexes *cis*-**5g** or *trans*-**5g** and *cis*-**5h** or *trans*-**5h** can, thus, be *selectively* obtained from, respectively, the separated *anti* or *syn* diastereomers of **3g** and **3h** (Table 2, entries 5−8).

Finally, the overall reaction sequence represented on Scheme 1 could be of synthetic use since 2-cyclohexenones **9** can easily be released upon treatment of the type **5** complexes either with triphenylphosphine in refluxing THF[15] or under a moderate pressure (4 atm) of carbon monoxide (Table 2).[16] It is noteworthy that this is the first diastereoselective synthesis of the 4,5-disubstituted 2-cyclohexenones **9g**[17] and **9h**[18] reported so far.[19,20]

We are now currently attempting to elucidate the factors which govern the diastereoselectivity of the initial nucleophilic attack of prochiral manganese carbene anions on Michael acceptors, as well as to explore further possibilities to functionalize the cyclohexenone ring within diastereomerically pure substituted cyclohexenone complexes.

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Supporting Information Available: Text giving experimental and spectroscopic data for all the new complexes and full experimental data for the X-ray studies, tables of atomic coordinates, anisotropic temperature factors, and bond distances and angles for *anti*-**3h** (Cp analog), **5d**, **5f**, and *cis*-**5h**, and figures showing perspective views of complexes *anti*-**3h** (Cp analog), **5d**, **5f**, and *cis*-**5h** (39 pages). Ordering information is given on any current masthead page.

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(15) (a) Angelici, R. J.; Loewen, W. *Inorg. Chem.* **1967**, *6*, 682. (b) Schinzer, D.; Blume, T.; Rojas Wahl, R. U. *Synlett* **1994**, 297.

(16) This procedure yields Cp′Mn$(CO)_3$ as the only organometallic "byproduct", which may be recycled to regenerate **1**.

(17) (a) Kugatova-Shemyakina, G. P.; Lutsenko, V. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1962**, *8*, 1429. (b) For the use of *cis*/*trans*-4,5-dimethyl 2-cyclohexenone as a flavoring agent, see: Flament, I. Fr. Pat. Appl. 73.28312, 1973.

(18) The synthesis of 5-phenyl-4-methyl 2-cyclohexenone (**9h**) as a *cis*/*trans* mixture has only recently been reported, see: Aurell, M. J.; Gaviña, P.; Mestres, R. *Tetrahedron* **1994**, *50*, 2571.

(19) For other metal-mediated stoichiometric syntheses of 2-cyclohexeneones, see, for instance: (a) Mortimer, M. D.; Carter, J. D.; McElwee-White, L. *Organometallics* **1993**, *12*, 4493. (b) McDaniel, K. F.; Kracker, L. R., II; Thamburaj, P. K. *Tetrahedron Lett.* **1990**, *31*, 2373. (c) Potter, G. A.; McCague, R. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1172. (d) Muzart, J.; Pale, P.; Pete, J.-P. *J. Chem. Soc., Chem. Commun.* **1981**, 668. (e) Birch, A. J.; Pearson, A. J. *J. Chem. Soc., Chem. Commun.* **1976**, 601.

(20) For relevent syntheses in terms of bond disconnections of substituted 2-cyclohexenones, see for instance: (a) Yamada, S.-I.; Otani, G. *Tetrahedron Lett.* **1969**, 4237. (b) Ito, Y.; Sawamura, M.; Kominami, K.; Saegusa, T. *Tetrahedron Lett.* **1985**, *26*, 5303.-