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MULTIPLE STEREOCONTROL USING ORGANOTRANSITION METAL TEMPLATES: ALKYLATION OF ENOLATES.

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Abstract: Generation and alkylation of enolates from (5-oxocyclohexenyl)$Mo(CO)_2Cp$ complexes 1 and 3 was accomplished regio- and stereospecifically and in high yield, allowing the preparation of stereospecifically substituted cyclohexene derivatives.

Previous work[1] in our laboratory has demonstrated the ability to achieve stereocontrolled multiple functionalization of six- and seven-membered rings via nucleophilic addition to dienyliron and dienemolybdenum complexes. Figure 1 depicts such a process for the cyclohexadiene-$Mo(CO)_2Cp$ system. While this generally works exceptionally well, there are a number of shortcomings. For example, using this methodology it is possible to functionalize only five carbon atoms out of a possible six or seven via organomolybdenum chemistry, and only six sites in the seven-membered ring using organoiron chemistry. We recently reported[2] the preparation of the oxo-substituted complex 1 and its monoalkylation to give, e.g., 2. We now describe modifications of this chemistry that allow stereocontrolled dialkylation as well as decomplexation to give potentially useful cyclohexene derivatives.

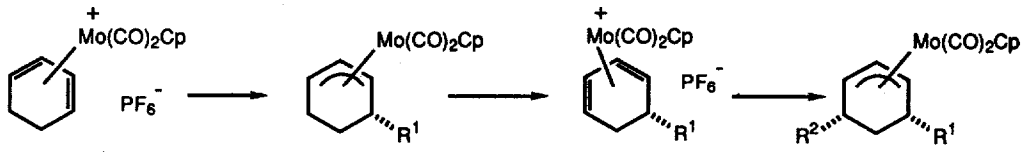
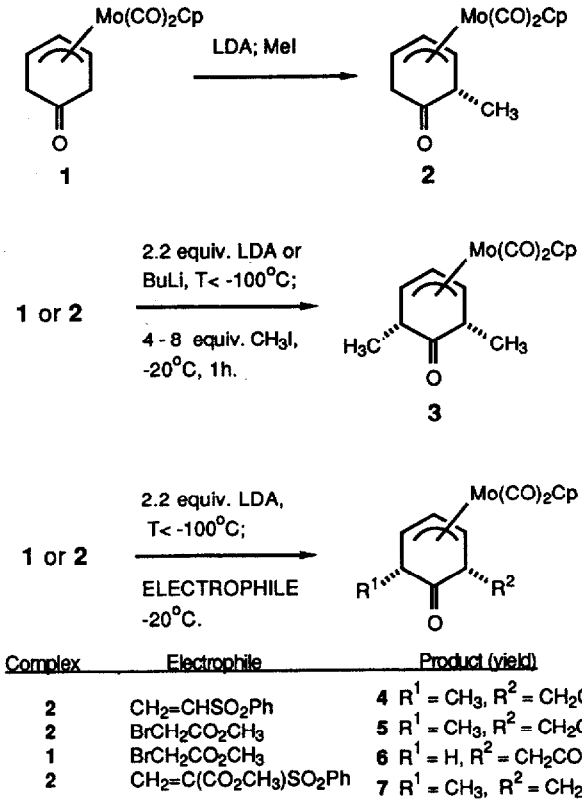


FIGURE 1. Stereocontrolled Double Functionalization via Nucleophile Addition to Cyclohexadiene - $Mo(CO)_2Cp$ Complexes (Cp = pentahapto-cyclopentadienyl).

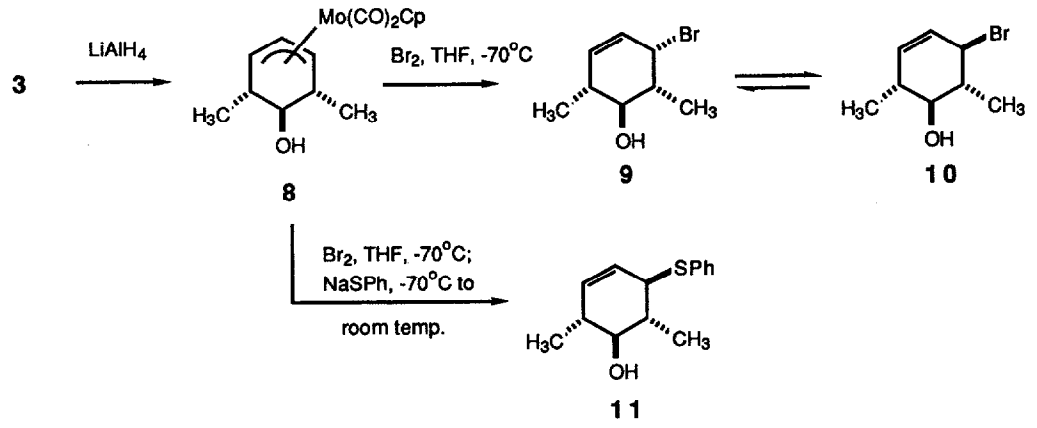
In our earlier work we encountered difficulties during attempted deprotonation of complex 2 using stoichiometric amounts of LDA. We now report that treatment of 2 with an excess (2.2 equiv.) of LDA in THF at temperature lower than -100°C for 20 min., produces a deep red solution of the enolate, which is then allowed to react with methyl iodide (4.4 equiv., warm to -20°C, 1h, quench at r.t. with sat. aq. NH_4Cl). Using this procedure the dimethylated compound 3 was obtained as a yellow high-melting solid in 49% yield,[3] together with 14% of recovered 2, which were readily separated by preparative TLC. Better yields of 3 were obtained by treating complex 1 directly with excess LDA or n-butyllithium (2.2 equiv., THF, T < -100°C)[4] followed by excess methyl iodide (-20°C, 1h; 61% yield using LDA; 77% yield using n-BuLi). General alkylations of 2 were accomplished using this procedure, and are shown in Fig. 2.



Complex	Electrophile	Product (yield)
2	$CH_2=CHSO_2Ph$	4 $R^1 = CH_3$, $R^2 = CH_2CH_2SO_2Ph$ (78%)
2	$BrCH_2CO_2CH_3$	5 $R^1 = CH_3$, $R^2 = CH_2CO_2CH_3$ (82%)
1	$BrCH_2CO_2CH_3$	6 $R^1 = H$, $R^2 = CH_2CO_2CH_3$ (68%)
2	$CH_2=C(CO_2CH_3)SO_2Ph$	7 $R^1 = CH_3$, $R^2 = CH_2CH(CO_2CH_3)SO_2Ph$ (100%)

FIGURE 2. Stereocontrolled Double Functionalization via Enolate Alkylation

In these reactions, the steric bulk of the $Mo(CO)_2Cp$ group is used to control the stereochemistry of alkylation. Similar control can be exercised over nucleophile addition to the ketone carbonyl of, e.g., 3, which gives a single product 8 in 99-100% yield on reduction with $LiAlH_4$ (8.0 equiv., THF, -30°C).[3,5] One problem remains if the methodology is to be useful for organic synthesis, viz., conversion of the π-allyl-$Mo(CO)_2Cp$ complexes to cyclohexene derivatives. Treatment of 8 with bromine[6] (1.1 equiv., THF, -70°C) gave a bromocyclohexene in high yield, tentatively assigned the structure 9 based on NMR spectroscopy. However, this compound was unstable, presumably due to the axial disposition of the bromine atom, and underwent facile rearrangement to give a mixture of 9 and 10. This problem was solved as follows. Complex 8 was allowed to react with bromine (2.0 equiv., THF-CH_2Cl_2, 2:1, -70°C, 2h) and then a solution of NaSPh (5 equiv.) in THF was added dropwise to the reaction mixture. After 5 min at -70°C, the mixture was allowed to warm to room temperature, quenched with water and extracted with ether in the usual way. Purification by flash chromatography afforded, in 87% yield, the sulfide 11 as a white crystalline solid, m.p. 61-63°C, R_f = 0.40 (CH_2Cl_2/EtOAc, 9:1). The stereochemistry of 11 was readily apparent from its NMR spectrum, which showed the all-equatorial nature of the substituents.[3]



In conclusion, selective high-yielding alkylations of enolates can be accomplished in the presence of a neighboring π-allyl-Mo(CO)$_2$Cp moiety. The organometallic group can be used as a template to control stereochemistry and regiochemistry (no alkylation of 2 at the methyl-substituted position is observed) and the metal can be removed to give organic products in high yield.

Acknowledgement We are grateful to the United States Public Health Service, National Insitutes of Health, for financial support of this research.

References and Notes

1. a) Dienyliron complexes: A. J. Pearson and C. W. Ong, *J. Org. Chem.*, 1982, **47**, 3780; A. J. Pearson, S.L. Kole, and T. Ray, *J. Am. Chem. Soc.*, 1984, **106**, 6060. b) Dienemolybdenum complexes: A. J. Pearson, M. N. I. Khan, J. C. Clardy, and H. Cun-heng, *J. Am. Chem. Soc.*, 1985, **107**, 2748; A. J. Pearson and M. N. I. Khan, *J. Org. Chem.*, 1985, **50**, 5276.

2. A. J. Pearson and M. W. D. Perry, *J. Chem. Soc. Chem. Commun.*, 1989, 389. See also: M. Green, S. Greenfield, J. Grimshire, M. Kersting, A. G. Orpen and R. A. Rodriques, *J. Chem. Soc. Chem. Commun.*, 1987, 97.

3. All new compounds were obtained as racemic mixtures and were fully characterized using IR, 200 MHz ^{1}H NMR, and high resolution mass spectrometry. Satisfactory combustion analyses were obtained for compounds 3, 4, 5 and 7, and all other compounds were shown to be at least 95% pure by NMR and TLC. Typical data are as follows:

(3): m.p.: decomp. at 215°C. IR ($CHCl_3$) ν_{max} 1950, 1870, 1697 cm^{-1}. NMR ($CDCl_3$) δ 5.22 (5H s), 4.17 (1H, t, J = 7.0), 3.80 (2H, d, J = 7.0), 2.80 (2H, q, J = 7.3), 1.27 (6H, d, J = 7.3). Anal. calcd for $C_{15}H_{16}MoO_3$: C, 52.63; H, 4.71. Found: C, 52.97; H, 4.84%.

(8): m.p. 124-126°C. IR ($CHCl_3$) ν_{max} 3590, 3545, 1938, 1855 cm^{-1}. NMR ($CDCl_3$) δ 5.19 (5H, s), 4.29 (1H, t, J = 6.6), 3.39 (2H, d, J = 6.6), 2.35 (1H, t, J = 8.8), 1.54 (2H, dq, J = 8.8, 7.6), 1.49 (1H, s, exch. D_2O), 1.13 (6H, d, J = 7.6). HRMS calcd for $C_{14}H_{18}{}^{98}MoO_2$ (M-CO): 316.0366. Found: 316.0371.

(11) m.p. 61-63°C. IR ($CHCl_3$) ν_{max} 3520, 2960, 1588, 1475, 1460, 1265, 1045, 1023 cm^{-1}. NMR ($CDCl_3$) δ 7.47-7.39 (2H, m), 7.33-7.23 (3H, m), 5.66 (1H, dt, J = 10, 2.5), 5.40 (1H, dt, J = 10, 1.9), 3.36 (1H, ddt, J = 10, 3.6, 2.2), 3.06 (1H, br. dd, J = 10.3, 10.2), 2.04 (1H, br, exch. D_2O), 1.73-1.57 (2H, m), 1.33 (3H, d, J = 6.5), 1.07 (3H, d, J = 7.0). HRMS calcd for $C_{14}H_{18}OS$: 234.1078. Found: 234.1080.

4. Controlled temperature is critical for the success of these reactions. In general, all deprotonations were performed at T < -100°C. If the temperature is raised above -98°C, significant amounts of phenol are formed. Presumably, this arises via double deprotonation of 1 and subsequent decomposition of the resulting dianion. When 1 is treated with excess LDA and the temperature is raised in the absence of electrophile, phenol is the major product.

5. We have previously established that reduction of complex 1 using $LiAlH_4$ occurs stereospecifically trans to the $Mo(CO)_2Cp$ group. The stereochemical assignment of 8 is further supported by its conversion to 11.

6. For the use of this method for converting π-allyl-$Mo(CO)_2Cp$ complexes to allylic bromides, see: A. J. Pearson and V. D. Khetani, *J. Am. Chem. Soc.* 1989, 111, in press; V. D. Khetani, Ph.D. dissertation, Case Western Reserve University, 1989.

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