The Reaction of Chiral Nucleophiles with Organomanganese Arene Complexes

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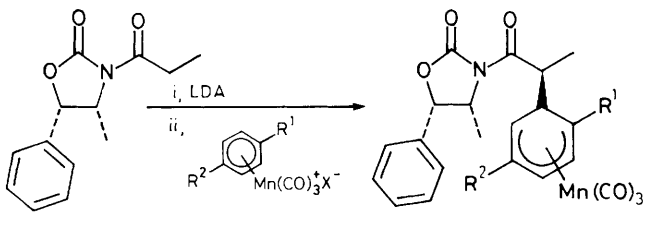
The reaction of the enolate derived from chiral *N*-acyloxazolidinone (**1**) and organomanganese arene complexes (**2**) gives η^5-dienyl complexes (**3**) which can be converted into chiral 2-arylpropionic acids by cleavage of the chiral auxiliary and oxidation of the η^5-dienyl moiety.

The reaction of nucleophiles with transition metal electrophiles has been extensively used in the synthesis of organic compounds.[1] Although asymmetric synthesis has been on the forefront of synthetic organic chemistry for the past decade,[2] there are only a few reports of the reaction of chiral nucleophiles with achiral transition metal electrophiles.[3] Herein we describe our initial studies of the reaction of chiral enolates derived from *N*-acyloxazolidinones[4] with organomanganese arene complexes[5] to give chiral η^5-dienylmanganese complexes. Cleavage of the chiral auxiliary and oxidation of the η^5-dienylmanganese moiety allows facile access to chiral 2-arylpropionic acids, a class of pharmaceutically important anti-inflammatory agents.[6]

The reaction of the enolate of (**1**) with $(C_6H_6)Mn(CO)_3PF_6$ (**2a**) (added as a solid at −78 °C, warmed to 0 °C) gave the

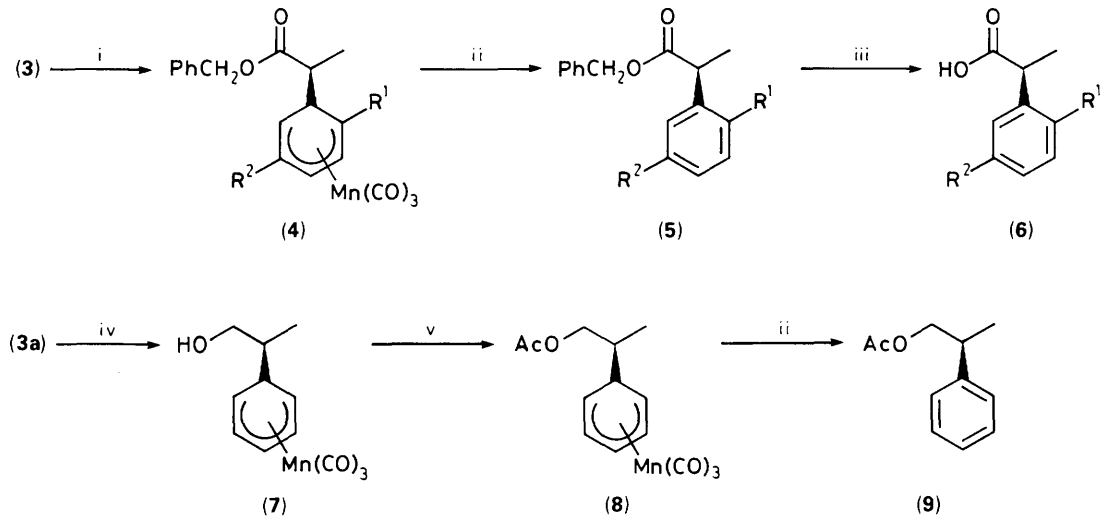


(**1**) (**2**) (**3**)

LDA = lithium di-isopropylamide

(**2a**) $R^1 = R^2 = H$, $X = PF_6$
(**2b**) $R^1 = H$, $R^2 = OMe$, $X = PF_6$
(**2c**) $R^1 = R^2 = OMe$, $X = BF_4$
(**2d**) $R^1 = H$, $R^2 = OPh$, $X = BF_4$

Scheme 1



Scheme 2. *Reagents and conditions:* i, $LiOCH_2Ph$, THF, 0 °C, 1—3 h; ii, DDQ (2 equiv.), MeCN, reflux, 6 h; iii, H_2, EtOAc–EtOH, Pd/C; iv, $LiAlH_4$ (1.5 equiv.), Et_2O, 0 °C, 1 h; v, MeCOCl–pyridine, benzene, reflux, 1 h.

η^5-dienyl complex (**3a**)† and its epimer (Scheme 1) as the major products after chromatography (75%; >9:1 diastereoselectivity). Further purification by recrystallization (CH_2Cl_2/hexane) afforded diastereoisomerically pure (**3a**) (>99% by ^1H NMR). Similar yields and diastereoselectivity were observed for the reaction of the enolate of (**1**) with organomanganese arene complexes (**2b–d**). The high regioselectivity (>95%) observed for the formation of (**3b**) and (**3d**) is consistent with previous observations for the reactions of nucleophiles with arene complexes.[5] There was relatively low diastereoselectivity in the formation of the second chiral centre on the ring of (**3b–d**), but this lack of selectivity was of no consequence in these studies since the chiral centre was destroyed in the subsequent aromatization step.

The conversion of (**3**) into wholly organic products was accomplished by several procedures (Scheme 2). Transesterification of (**3a**) with $LiOCH_2Ph$ in tetrahydrofuran (THF) gave (**4a**) in 79% yield. Oxidation of (**4a**) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[7] in acetronitrile gave benzyl (*S*)-2-phenylpropionate (**5a**) in 71% yield. Hydrogenolysis of (**5a**) gave (*S*)-2-phenylpropionic acid (**6a**) in 87% yield and in greater than 95% enantiomeric excess.‡ Conversion of (**3b–d**) into their respective 2-arylpropionic acids was accomplished under similar conditions in comparable chemical yields. The synthesis of (*S*)-2-(3-phenoxylphenyl)propionic acid (**6d**) is notable since it is the more biologically active enantiomer of Fenoprofen,[8] an anti-inflammatory drug marketed by Eli Lilly as the calcium dihydrate salt. Although cleavage of (**3**) by LiOH in tetrahydrofuran and oxidation of the resulting carboxylic acid provided a more expedient route to the 2-arylpropionic acids, the yields were lower and purification of (**6**) was problematic. Alternatively, reductive cleavage of (**3a**) with $LiAlH_4$[4a] gave alcohol (**7**) in 64% yield. Since oxidation of (**7**) with DDQ gave unsatisfactory yields of the desired aromatic product, (**7**) was converted into its acetate (**8**) in 83% yield and then oxidized with DDQ to give chiral (**9**) in 73% yield.

Not surprisingly, the chiral *N*-acyloxalidinone derived from (*S*)-valinol[4] can be converted into (*R*)-2-phenylpropionic acid in three steps, allowing the synthesis of both enantiomers of 2-phenylpropionic acid. Ester enolates also exhibit high diastereoselectivity. The dianion of ethyl 3-hydroxylbutanoate and complex (**2a**) react to give good yields and high diastereoselectivity[9] of the corresponding *threo*-η^5-dienyl complex. The demonstrated ability of these enolates to react in a stereospecific fashion with organomanganese arene complexes offers a unique approach to the synthesis of chiral aromatic compounds of biological interest.

We thank the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also thank the National Science

† All new compounds were fully characterized by IR and NMR spectroscopy, and by elemental (C, H) analysis. [Complexes (**4**) and (**8**) did not give satisfactory microanalysis.] Spectral data are given for some representative compounds (**3a**): ^1H NMR (C_6D_6) δ 7.0 (5H, m, Ph), 5.00 (1H, t, *J* 5.3 Hz, H-3), 4.61 (1H, d, *J* 7.7 Hz, CHO), 4.2 (3H, m, overlapping H-2, H-4 and CHN), 3.19 (1H, m, COCH), 2.88 (2H, m, overlapping H-1 and H-6), 2.65 (1H, m, H-5), 0.83 (3H, d, *J* 7.0 Hz, CHMe), 0.58 (3H, d, *J* 6.6 Hz, NCMe); IR (CH_2Cl_2) 2018, 1940, 1933, 1781, 1695 cm^{-1}. (**4a**): ^1H NMR (C_6D_6) δ 6.9 (5H, m, Ph), 4.6 (3H, m, H-3 and CH_2–O), 3.78 (1H, t, *J* 6.3 Hz, H-2), 3.71 (1H, t, *J* 6.3 Hz, H-4), 2.48 (1H, br. t, *J* 6.0 Hz, H-1), 2.25 (1H, m, H-6), 2.13 (1H, br. t, *J* 6.0 Hz, H-5), 1.08 (1H, m, CHMe), 0.29 (3H, d, J 7.0 Hz, CHMe); IR (cyclohexane) 2022, 1950, 1941, 1738 cm^{-1}. (**7**): ^1H NMR (C_6D_6) δ 4.92 (1H, t, *J* 5.2 Hz, H-3), 4.07 (2H, m, overlapping H-2, H-4), 2.90, 2.80 (2H, br. AB, *J* 10.0 Hz, diastereotopic CH_2), 2.64 (1H, m, H-1), 2.55 (1H, m, H-5), 2.07 (1H, m, H-6), 0.37 (4H, apparent s, CHMe); IR (cyclohexane) 3400, 2014, 1937 cm^{-1}.

‡ The enantiomeric purity of (**5**) was determined by conversion of (**5**) into its (*S*)-α-methylbenzylamide and assaying the diastereotopic purity by ^1H NMR. The stereochemistry for (**5b**) and (**5c**) was assumed to be (*S*), based on the definitive assignment of stereochemistry for (**5a**) and (**5d**).

Foundation for a grant used to purchase a GE-300 NMR spectrometer.

Received, 17th July 1989; Com. 9/03021B

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