The Reaction of Chiral Nucleophiles with Organomanganese Arene Complexes

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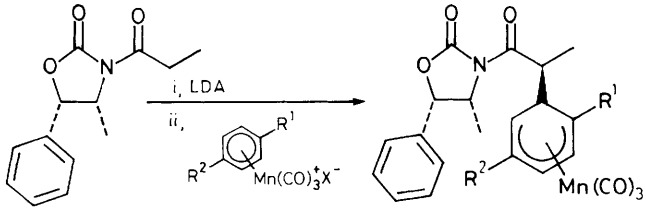
The reaction of the enolate derived from chiral *N*-acyloxazolidinone (**1**) and organomanganese arene complexes (**2**) gives η^5-dienyl complexes (**3**) which can be converted into chiral 2-arylpropionic acids by cleavage of the chiral auxiliary and oxidation of the η^5-dienyl moiety.

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

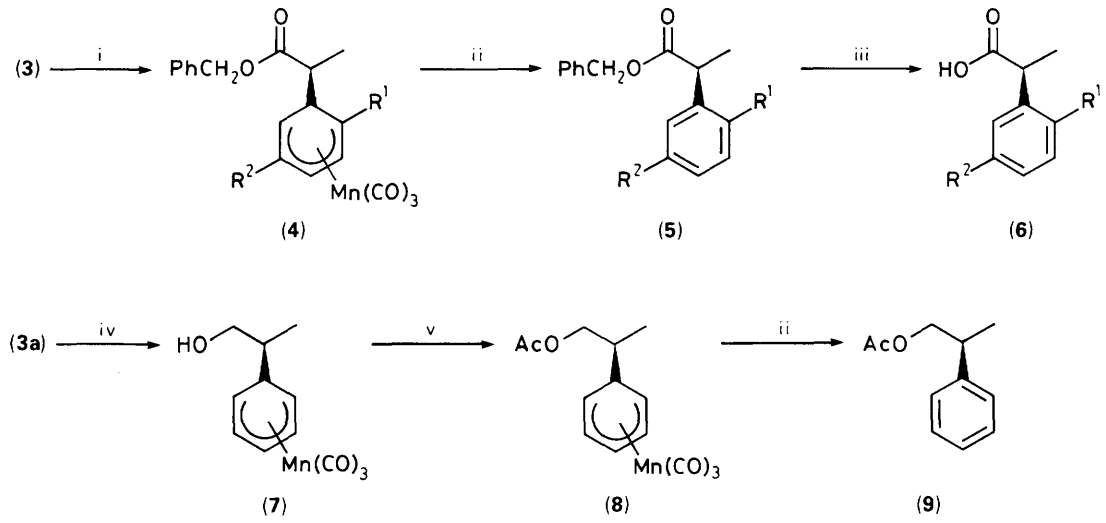


(**1**) (**2**) (**3**)

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.

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† 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**).

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