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Asymmetric Synthesis of (Diene)Fe(CO)₃ Complexes via Catalytic Enantioselective Alkylation with Dialkylzinc

Yoshiji Takemoto, Yasutaka Baba, Izumi Noguchi and Chuzo Iwata*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-Oka, Suita, Osaka 565, Japan

Abstract: The reaction of meso-2,4-hexadien-1,6-dial $Fe(CO)_3$ complex **1** with several alkylzincs in the presence of 50 mol% of (*S*)-(+)-diphenyl-(1-methylpyrrolidin-2-yl) methanol **4a** proceeded with high enantiotopic group- and face-selectivity to give (2*R*,6*S*)-mono alcohol complexes **2a-c** as major products (>90% de and >98% ee). Copyright © 1996 Elsevier Science Ltd

Chiral (diene)$Fe(CO)_3$ complexes continue to attract attention as chiral synthons in asymmetric synthesis and have been used to prepare natural products.[1] The availability of these complexes as single enantiomers usually depends on the resolution method, such as recrystallization or column chromatographic separation of derived diastereomers.[2] Recently, however, more direct methods, involving auxiliary-directed[3] and reagent-controlled[4] stereoselective complexation, have been developed. Bifunctional meso-diene $Fe(CO)_3$ complexes would be ideal and useful starting materials for asymmetric synthesis of natural products, since $Fe(CO)_3$ complexation of meso-dienes does not give diastereoisomers and two-directional functionalization[5] using the $Fe(CO)_3$ chirality is possible. Despite the synthetic versatility of meso complexes, there have been only two reports concerning the differentiation of enantiotopic functionality: biochemical reduction,[4a] acetylation[4b] and allylboration using stoichiometrical chiral reagents.[4c] This encouraged us to investigate a more efficient approach; i.e., the catalytic enantioselective alkylation of meso-dienal $Fe(CO)_3$ complex **1** with dialkyl zincs.[6] While the enantioselective alkylation of metallocenecarboxaldehydes with alkylzinc reagents in the presence of a catalytic amount of chiral β-aminoalcohols has been successfully conducted to introduce the stereogenic center of chiral secondary alcohols,[7] the application of this reaction to the meso-dienal $Fe(CO)_3$ complex to construct two stereogenic centers involving a (diene)iron complex has not been reported. We report here the highly enantiotopic group- and diastereoface-selective alkylation of meso-dienal $Fe(CO)_3$ complex **1** with various dialkyl zincs, resulting in secondary alcohol complexes **2** bearing several alkyl substituents.

We initiated this study on **1** with diethyl zinc in the presence of a known catalyst [(*S*)-(+)-diphenyl-(1-methylpyrrolidin-2-yl) methanol **4a**][6a] under typical conditions. A solution of **1** in toluene was allowed to react with a 1 M solution of diethylzinc in hexane at 0℃ under a nitrogen atmosphere in the presence of 10 mol % of **4**. The reaction was not complete in 4 h, and gave rise to mono-alkylated adducts **2a**[8] and **3a**[8] along with mono-alkylated alcohol **5** from **2a**, dialkylated ketone **6**, and the starting material **1**. The diastereomeric ratio of **2a** and **3a** was very high [**2a** (R*f*: 0.26), and **3a** (R*f*: 0.37) could be easily separated by SiO_2 column chromatography with CH_2Cl_2/MeOH=30/1].[8] The enantiomeric purity of the major product **2a** was determined to be over 98% ee by ^{19}F-NMR analysis of the MTPA adduct derived from **2a** (entry 1 in Table 1). An increase in the reaction time so that all of the starting material would be consumed did not give improved results, and only gave increased amounts of byproducts **5** and **6**. Although the reaction with 0.5 equiv. of the chiral catalyst **4a** for 1 h resulted in a high yield of **2a** (78%) with no loss of ee (entry 2), the addition of more than 0.5 equiv. of **4a** did not give improved results. In addition, neither ether nor dichloromethane gave better results than the mixture of hexane and toluene (entries 3 and 4).

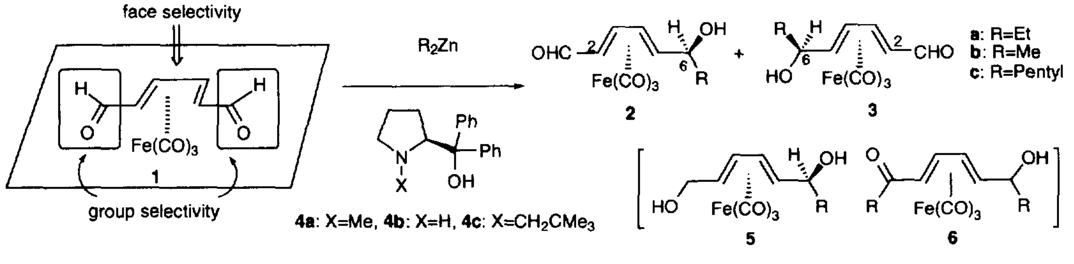

Table 1. Catalytic Asymmetric Alkylation of **1** with Several Dialkylzincs in the Presence of **4a-c**[a]

entry	R	ligand (eq.)	solvent[b]	time (h)	yield[c] (%)					ee of **2**[d] (%)
					2	**3**	**5**	**6**	**1**	
1	Et	**4a** (0.1)	T-H (4:1)	4	59	1	1	7	9	94
2		**4a** (0.5)	T-H (4:1)	1	78	3	3	2	9	>98
3		**4a** (0.5)	M-H (3:1)	5	53	4	-[e]	-[e]	28	>98
4		**4a** (0.5)	E-H (5:1)	3	29	2	-[e]	-[e]	52	>98
5		**4b** (0.5)	T-H (4:1)	2	59	3	3	1	29	96
6		**4c** (0.5)	T-H (4:1)	1	48	5	1	-[e]	34	70
7	C_5H_{11}	**4a** (0.5)	T	3	76	2	-[e]	-[e]	4	>98
8		**4a** (0.5)	M-T (3:1)	5	29	1	-[e]	-[e]	39	>98
9	Me	**4a** (0.5)	T-H (4:1)	2	12	4	-[e]	-[e]	61	86

[a] Reactions were carried out at 0℃ in the presence of 2.5 equiv. of dialkylzinc. [b] T=toluene, H=hexane, M=methylene chloride, E=ether [c] Isolated yield. [d] Determined by ^{13}F-NMR analysis of the MTPA-derivatives of **2a-c**. [e] Not detected.

The use of other catalysts **4b** and **4c**, which possess less- or more- hindered substituents than **4a**, gave **2a** and **3a** with lower diastereo- and enantioselectivity (entries 5 and 6). We next investigated other alkylations under optimized conditions. A pentyl group was introduced into **1** with dipentylzinc in a mixture of hexane and toluene with greater diastereo- and enantioselectivity than in CH_2Cl_2 to give **2b** in 76% yield (entries 7 and 8). On the other hand, methylation of **1** with dimethylzinc under similar conditions proceeded much more slowly than ethylation, and the methyl adduct was obtained in low yield even with a prolonged reaction time (entry 9). Furthermore, in the latter two cases, no di-alkylated product was detected regardless of the reaction time and the equivalence of dialkylzinc.

Thus, the mono-alkylation of **1** has been achieved with almost complete enantioselectivity and high diastereoselectivity. Although the cause of this high diastereoselectivity is not yet clear, the plausible transition state model in Fig. 1, which shows the dipole-dipole interaction of the metal carbonyl moiety with dialkylzinc to enhance enantiotopic group-selectivity, may well explain the major production of **2a-c**.[9] Further mechanistic studies and asymmetric synthesis of natural product with the use of **2a** are underway in our laboratory.

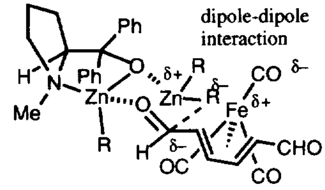

Fig. 1. Proposed transition state of the asymmetric alkylation of 1 with R_2Zn

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