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Planar Chiral *C*2-Symmetric Bisferrocenes: Stereoselective Pinacol Coupling of α-Substituted Ferrocenecarboxaldehydes

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Abstract: Planar chiral α-substituted ferrocenecarboxaldehydes were treated with samarium diiodide to give stereoselectively pinacol coupling products with a *threo*-configuration in good yields. The resulting dihydroxyl of the product was substituted with stereochemical inversion by an S_N1 reaction.

Keywords: pinacol coupling, ferrocenes, planar chirality, 1,2-diols, nucleophilic substitution, inversion

Enantiomerically pure 1,2-dihydroxy or diamine compounds and the related compounds have found widespread use as chiral ligands in asymmetric reactions. The optically active 1,2-diols have been conveniently synthesized by a catalytic asymmetric dihydroxylation of the olefins with high enantioselectivity.[1] Although the reductive coupling of carbonyl compounds, pinacol coupling, is the most direct way to synthesize the 1,2-diols, highly diastereoselective formation of the 1,2-diol is not so easy under most conventional reductive coupling methods.[2] Furthermore, the *threo* (*dl*) 1,2-diols could not be obtained in an enantiomerically active form by this pinacol coupling of the aldehydes or ketones. We have recently reported[3] that the planar chiral tricarbonylchromium complexes of *o*-substituted benzaldehydes or benzaldimines gave a single reductive coupling product, 1,2-diol or diamine with the *threo*-configuration. This highly stereoselective pinacol coupling reactions would be attributed to the stable configuration of the generated tricarbonylchromium-complexed ketyl radicals. We have been interested in the stereochemical influence of the metalcarbonyl fragment of other substrates in the asymmetric reactions. As part of our asymmetric synthetic exploration of the transition metal-coordinated planar chiral substrates, we have extended the intermolecular pinacol coupling to the chiral α-substituted ferrocenecarboxaldehydes.

The reaction results of samarium diiodide-mediated pinacol coupling of ferrocenecarboxaldehydes are summarized in Table 1. α-Unsubstituted ferrocenecarboxaldehyde (**1**) (R = H) produced a 1 : 1 diastereomeric mixture of *threo* (*dl*) and *erythro* (*meso*)-pinacols in 95 % yield. *Racemic* α-methylferrocenecarboxaldehyde gave a complex mixture of 1,2-diols based on the central and planar chiralities. However, an *enantiomerically pure* (+)-(*R*)-α-methylferrocenecarboxaldehyde (**1**) (R = Me) was coupled with samarium diiodide at 0 °C to give the corresponding three pinacol coupling products **2**, **3** and **4** in a ratio of 92 : 4 : 4 in 98 % yield (entry 2).

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The reductive coupling at lower reaction temperature (-78 °C) produced a single pinacol coupling 2 (R = Me) with *threo*-configuration in 92 % yield. Similarly, the planar chiral α-timethylsilyl, bromo or iodo substituted ferrocenecarboxaldehydes produced the corresponding 1,2-diols 2 with extremely high diastereoselectivity.

Scheme 1

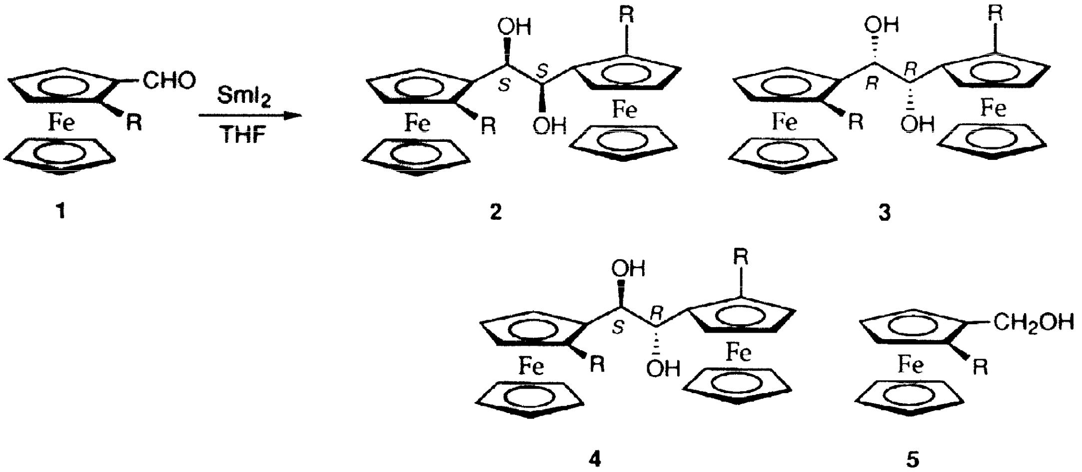


Table 1. Pinacol Coupling of α-Substituted Ferrocenecarboxaldehyde

Entry	R	Temp (°C)	Yield of diols 2,3,4 (%)	Ratio 2 : 3 : 4	2 [α]$_D$ (CHCl$_3$)	Yield 5 (%)
1[a]	H	0	95	25 : 25 : 50	–	0
2	Me	0	98	92 : 4 : 4		0
3	Me	-78	92	100 : 0 : 0	+89.5	0
4	TMS	0	88	91 : 8 : 1		5
5	TMS	-78	87	93 : 6 : 1	+69.5	8
6	I	0	94	92 : 4 : 4		0
7	I	-78	92	100 : 0 : 0	+37.4	0
8	Br	-78	93	100 : 0 : 0	+44.2	0
9[b]	PPh$_2$	0	41	52 : 24 : 24	–	20
10[c]	PPh$_2$	rt	80	30 : 40 : 30	*c*	

a; The compounds 2 and 3 are enantiomer to each other when R is hydrogen.
b; No pinacol coupling of 1 with α-diphenylphosphino substituent proceeded at -78 °C.
c; ref. 5.

The relative stereochemistry of the major coupling product 2 (R = I) was determined by a single crystal X-ray analysis after conversion of the diols to the corresponding acetonide, and found to be the (S_{Fc},1S,2S,$S_{Fc'}$)-configuration (Fig. 1). The structures of the other stereoisomeric coupling products could be easily assigned by NMR spectra. The compounds 2 and 3 have a C_2-symmetry, while 4 has a C_1-symmetry conformation.[4] However, no obvious diastereoselectivity was observed for the samarium diiodide-mediated pinacol coupling of α-(diphenylphosphino)ferrocenecarboxaldehyde. Thus, (S)-α-diphenylphosphino ferrocene 1 (R = PPh$_2$) produced all possible stereoisomers of the pinacol coupling products 2, 3 and 4 in a ratio of 52 : 24 : 24 in only 41 % yield along with ferrocenylmethyl alcohol 5 of 20 % yield (entry 9). A similar result was recently reported by Kagan et al,[5] in which the ratio of the diols 2, 3 and 4 was 30 : 40 : 30 (entry 10). In this way, the pinacol coupling of planar chiral α-substituted ferrocenecarboxaldehydes produced exclusively C_2-symmetrical 1,2-diols **2** except the α-(diphenylphosphino)ferrocenecarboxaldehyde.

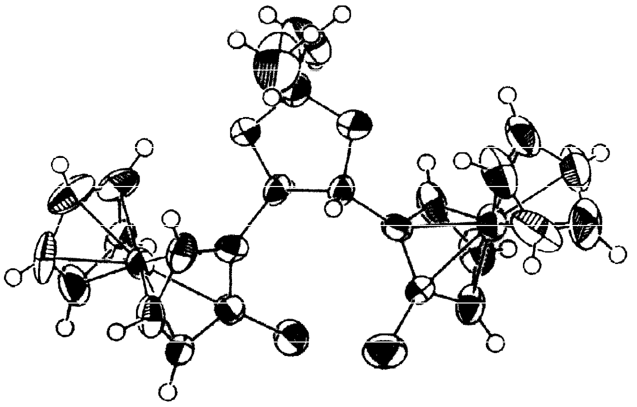


Fig. 1. X-ray structure of acetonide of **2** (R = I)

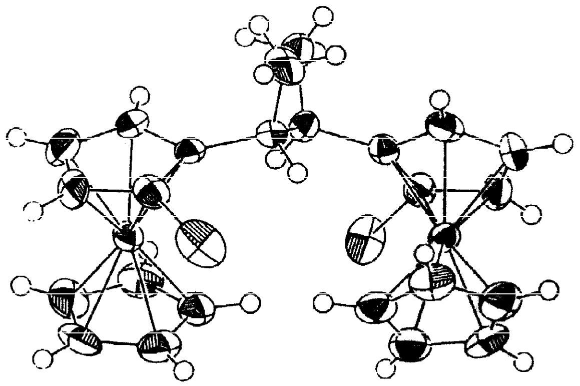
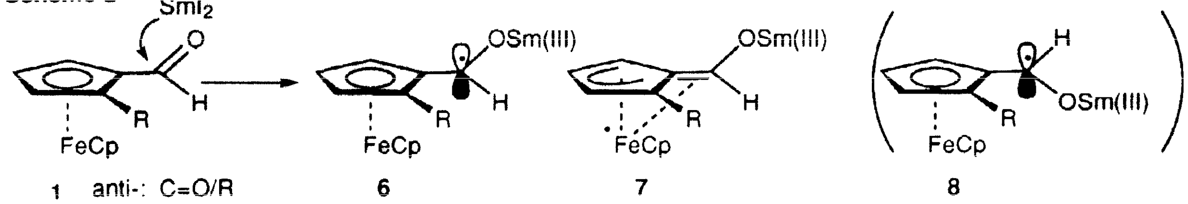


Fig. 2. X-ray structure of **10** (Nu = Me)

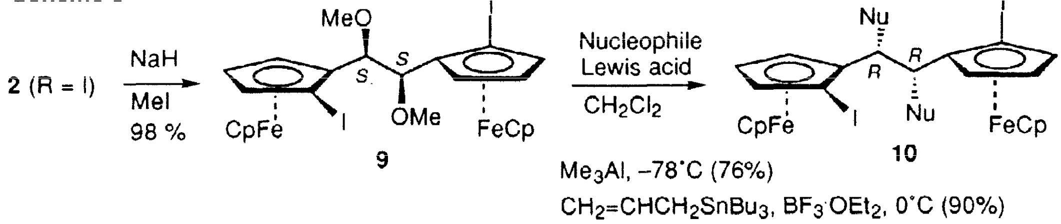
The reaction mechanism for giving the *threo*-diol **2** as the major product would be proposed as follows (Scheme 2). The samarium metal attacks the *anti*-carbonyl[6] of **1** from the *exo*-side to generate a ketyl radical intermediate **6**, which incorporates a substantial amount of the exocyclic double bond character **7** owing to an interaction of the *d*-orbital of the iron with the *p*-orbital of the carbon. This, in turn, implies that a rotation about the C_α-C_{ipso} bond giving **8** will be restricted. Then, the generated ketyl radical intermediate **6** would be coupled to each other, giving the *threo*-diol **2**. But, with the α-diphenylphosphino substituent, the initially formed ketyl intermediate **6** might be equilibrated with a diastereoisomeric ketyl radical **8** before the cross-coupling step under reaction conditions.[7]

Scheme 2



It is well known[8] that the substitution at the psuedo-benzylic position of α-ferrocenylethyl acetates and the related derivatives proceeds in high stereoselectivity with heteroatom and some carbon nucleophiles in the presence of Lewis acid. We next turned our attention to the reactivity and stereoselectivity on the substitution of (bisferrocenyl)ethane-1,2-diols and the related compounds. The dimethyl ether of bis-ferrocenylethanediol **9** was

Scheme 3



treated with trimethylaluminum to give a single nucleophilic substitution product **10** (Nu = Me), without any formation of stereoisomers or rearrangement products, in 76 % yield (Scheme 3). Similarly, the treatment of **9** with allyl tributylstanane in the presence of trifluoroborane etherate afforded a single product **10** (Nu = $CH_2CH=CH_2$) in 90 % yield. The relative stereochemistry of **10** (Nu = Me) was determined by X-ray crystallography, and found to be an S_{Fc},1*R*,2*R*,$S_{Fc'}$-configuration (Fig. 2).

It is noteworthy that the nucleophilic substitution of **9** via a carbonium ion intermediate proceeded with stereochemical inversion, while the (S_{Fc},*R*)-α-substituted ferrocenylethyl acetate and the related compounds afforded the stereochemical retention products by S_N1-type reaction at the pseudo-benzylic position.[8,9] We are now actively investigating the development of these C_2-symmetric bisferrocene compounds aschiral ligand in asymmetric reactions.

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4 ^{1}H-NMR ($CDCl_3$): δ for **2** (R = Me); 1.32 (6H, s), 2.66 (2H, br), 3.77-3.97 (4H, m), 4.07 (10H, s), 4.20-4.21 (2H, m), 4.24 (2H, s). for **3** (R = Me); 2.10 (6H, s), 2.24 (2H, br), 3.99-4.07 (6H, m), 4.14 (10H, s), 4.21 (2H, s). for **4** (R = Me); 1.69 (3H, s), 1.77 (3H, s), 2.38 (2H, br), 3.99-4.07 (6H, m), 4.10 (5H, s), 4.11 (5H, s), 4.44 (2H, br).

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7 An addition of MeLi to the α-diphenylphosphino ferrocenecarboxaldehyde gave predominantly one diastereomer via probably *anti*-carbonyl conformation. Therefore, even with the α-diphenylphosphino substituent, samarium metal would attack the *anti*-carbonyl, giving ketyl radical intermediate **6**.

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9 In the case of diastereomeric S_{Fc},*S*-configuration ferrocene, stereoselectivity at the pseudo-benzylic position for S_N1 reaction was largely dependent on the substrate, nucleophile and reaction conditions.