

A Homoannularly Bridged Hydroxyamino Ferrocene as an Efficient Catalyst for the Enantioselective Ethylation of Aromatic and Aliphatic Aldehydes.

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Abstract: Eleven aromatic and aliphatic aldehydes have been alkylated with Et_2Zn in the presence of the homoannularly bridged hydroxyamino ferrocene I. The resulting carbinols have e.e.'s varying from 66 to 97%. A mechanistic approach is presented to rationalize the preferred formation of the enantiomer observed.

Homoannularly disubstituted ferrocenes with different substituents R^1 and R^2 represent a C_1 symmetrical, so called "planar chiral" moiety. Introduction of appropriate substituents like CR_2OH , $\text{CR}_2\text{NR}'_2$, PPh_2 , etc. produce difunctional compounds which are likely to take part in asymmetric transformations as chiral auxiliaries. One of the most valuable applications is the C-C bond formation under chiral catalysis to produce optically active hydrocarbons by Ni- and Pd-catalyzed cross coupling reactions¹ or alcohols by alkylation of carbonyl compounds with R_2Zn^2 . The latter reaction was found to proceed with good to excellent enantioselectivity with aromatic and straight chain or α -branched aldehydes, when the reaction was carried out with Et_2Zn and aminoalcohol derivatives from camphor, prolin, ephedrin, etc. or ferrocenes of the general structure II as chiral modifiers. Only β -branched substrates gave unsatisfactorily chemical and optical yields.

Scheme 1

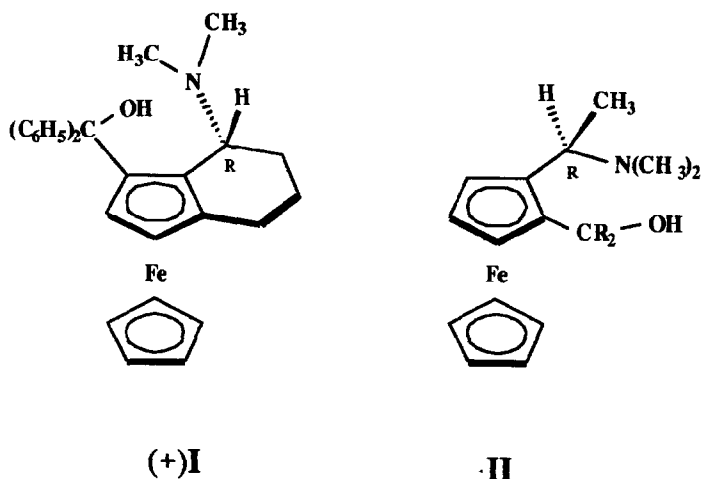
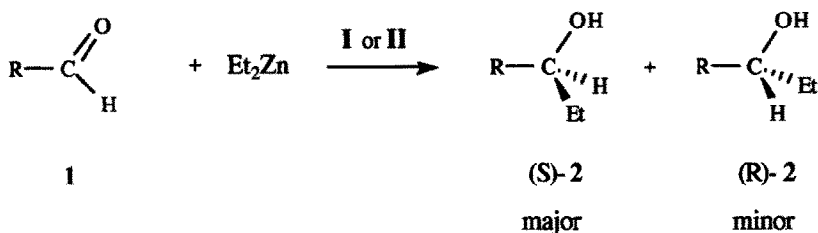


Table 1

entry	compound	R	T[°C]	t [hr]	isol.yield [%]	$[\alpha]_D^b$	e.e.[%] by (opt.rot. ^b / HPLC ^c / n.m.r.)
1	1a	C ₆ H ₅ -	25	12	87	-40.8	83.5
2	1a	C ₆ H ₅ -	40	12	90	-40.4	83
3	1a	C ₆ H ₅ -	0	12	87	-42.3	87 / 87
4	1b	p-CH ₃ C ₆ H ₄ -	25	4.5	93	-36.5	93 / / 94 ^d
5	1c	p-CH ₃ OC ₆ H ₄ -	25	4.5	81	-32.4	89 / 85 / 87 ^d
6	1d	p-ClC ₆ H ₄ -	25	4.5	88	-23.1	82 / 80
7	1e	1-furyl-	25	4	84	-15.4	83 / / 86 ^d
8	1f	C ₆ H ₅ CH=CH-	25	4	86	-5.4	86 / / 87 ^d
9	1g	C ₅ H ₁₁ -	25	4	72	+7.09	74 / / 70 ^e
10	1h	(CH ₃) ₂ CH-	25	4	30	n.e.	/ / 97 ^f
11	1i	(CH ₃) ₂ CHCH ₂ -	25	4	70	+20.1	85 / / 81 ^e
12	1j	(CH ₃) ₃ CCH ₂ -	25	4	68	+20.4	/ 85 ^e
13	1k	C ₆ H ₁₁ CH ₂ -	25	4	50	+16.6	66 / / 76 ^e

a) Et₂Zn in toluene (1.1 molar) was used for entry 1 - 6 and Et₂Zn in hexane (1 molar) for entry 7 -13.

b) (S)-1-Phenyl-1-propanol: $[\alpha]_D^{22}$ -47.6 (c: 6.11, CHCl₃), 98% e.e.^{3a}, (S)-1-(p-Tolyl)-1-propanol: $[\alpha]_D^{22}$ -20.4 (c: 5, C₆H₆), 52% e.e.^{3b}, (S)-1-(p-Methoxyphenyl)-1-propanol: $[\alpha]_D^{22}$ -17.2 (C₆H₆), 43% e.e.^{3c}, (S)-1-(p-Chlorophenyl)-1-propanol: $[\alpha]_D^{22}$ -10.4 (c: 5, C₆H₆), 43% e.e.^{3d}, (S)-1-(2-Furyl)-1-propanol: $[\alpha]_{578}^{22}$ -17.9 (c: 1.75, CHCl₃), 91% e.e.^{3e}, (S)-1-Phenylpent-1-en-3-ol: $[\alpha]_D^{22}$ -5.7 (CHCl₃), 96% e.e.^{3f}, (S)-3-Octanol: $[\alpha]_D^{21}$ 9.6° (c: 1.34, CHCl₃), 100% e.e.^{3g}, (S)-2-Methyl-3-butanol: $[\alpha]_D^{22}$ -6.05 (neat), 62% e.e.^{3h}, (S)-5-Methyl-3-hexanol: $[\alpha]_D^{24}$ 22.1 (c: 4.57, EtOH), 93% e.e.³ⁱ, (R)-5,5-Dimethyl-3-butanol: no opt. rot. reported, 1-Cyclohexyl-2-butanol: $[\alpha]_D^{23}$ -25.3 (c: 20, EtOH), 66% e.e.^{3j} c) HPLC: CHIRALCEL OB (4.6 x 250mm), 0.15ml / min, 1-Phenyl-1-propanol: i-PrOH / hexane (4:96), 42.5, 54.9 min; 1-(p-Methoxyphenyl)-1-propanol: i-PrOH / hexane (10:90), 61.3, 82.0 min; 1-(p-Chlorophenyl)-1-propanol: i-PrOH / hexane (5:95), 42.8, 47.8 min. d) MTPA - ester: ¹H - n.m.r. e) MTPA - ester: ¹⁹F - n.m.r. f) MTPA - ester: ¹³C - n.m.r.



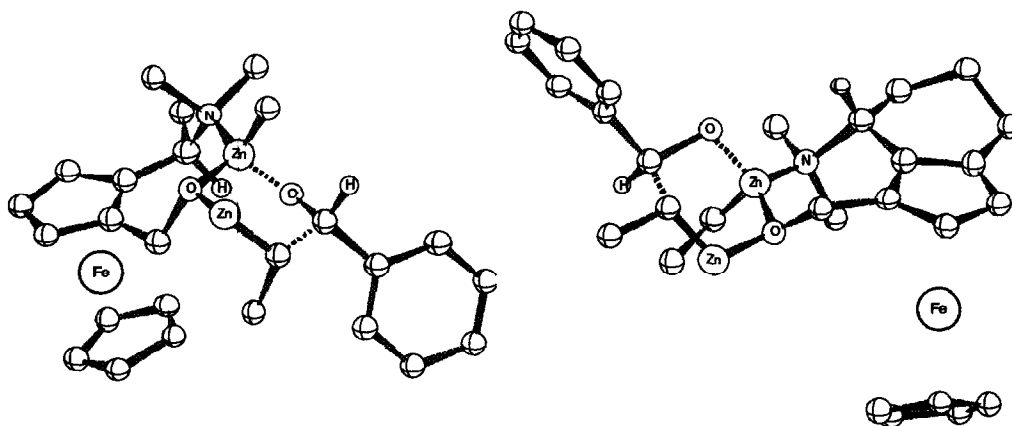
Here we report on the application of a new ferrocene catalyst **I**⁴ which was used successfully to alkylate aromatic and straight chain or branched aliphatic aldehydes to secondary alcohols with up to 97% e.e. Even with a β -branched aliphatic substrate (entry 12) an increased optical yield than that reported for **II** could be obtained. This seems to be a substantial improvement since **I** may become a valuable complement to the ferrocenyl aminoalcohols of type **II**.

Reaction of the aldehydes **1a** - **k** (Table 1) with Et_2Zn in toluene or *n*-hexane and 3 - 5 mol% of **I** afforded the secondary alcohols **2a** - **k** in good to excellent yield. The chemical purity of the isolated products was checked by ¹H n.m.r. and the optical purity was determined by at least two independent methods, except for entry 10 and 12 (see Table 1, footnotes b - f). The reaction proceeds smoothly with good chemical yields and without noticeable side reactions at ambient temperature, except in entry 10 where the isolated yield dropped to 30%, probably caused by elimination during work up (see below); an improvement of the procedure is presently under investigation. The effect of the reaction temperature on e.e. was found to be small (entry 1 - 3) with an optimum at about 0°C. The catalyst can be recovered by chromatography and reused without noticeable loss of selectivity.

A representative procedure is given for 5-methyl-3-hexanol (**2i**) (entry 11): A solution of 345 mg (4 mmol) of **1i** in 4 ml of dry toluene was degassed three times. To this was added subsequently 93 mg (5 mol%) of **I** and 6.4 mmol of Et_2Zn in hexane (1 molar) with stirring at 25°C. After 4 hr the reaction was quenched by addition of 5 ml of sat. NH_4Cl solution. The aqueous layer was separated and extracted with ether (3 x 5 ml) and the combined organic extracts were washed with brine and dried (MgSO_4). After removal of the solvent the crude carbinol was purified by bulb to bulb distillation to give 325 mg (70%) of **2i**.

Comparison of the sense of the asymmetric induction of **I** and **II** ($\text{R} = \text{C}_6\text{H}_5$ -) revealed the following interesting feature: When (+)(**R**)_c(**1S**)_m(**2R**)_m(**3R**)_m **I** - same absolute configuration as depicted in the scheme - was employed the (**S**) configured carbinol was formed predominantly. The same enantiomer was obtained when (-)(**R**)_c(**1R**)_m(**2S**)_m **II** was used, ($\text{R} = \text{Ph}$), the non bridged compound with *same* centrochirality but *opposite* metallocene chirality. This clearly indicates that the centrochirality dominates the sense of asymmetric induction, while the metallocene chirality seems to be less important. This rather surprising behavior may have its origin in the *endo* configuration of the amino group of **I**. The transition state depicted below accounts for this geometric situation and offers a suggestion how this observation can be rationalized. Transition states of the configuration determining step have been presented by Noyori⁵ and Butsugan². Both of them propose the participation of two molecules of Et_2Zn and the formation of a seven membered ring. This cycle adopts a chair-like conformation with Zn bonded covalently to O and coordinatively to N. Both substituents, the α -methyl group (**II**) or the tetramethylene bridge (**I**) as well as the ethyl group attached to Zn are arranged in equatorial positions. The Zn atom of the seven membered ring coordinates to the substrate, a second Et_2Zn unit to the ring O to give a chair-like six-membered transition state resulting in minimum steric repulsion. This geometry should highly favour an attack of the ethyl group to the *si*-side of the aldehyde.

Figure 1



Proposed transition states for the ethylation of benzaldehyde catalyzed by (R)_C-II (left) and (R)_C-I (right).
(One Zn - ethyl group omitted)

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