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Enantiospecific synthesis of 4-(4′-methoxyphenyl)-hexan-3-one as precursor for optically active (p*S*) or (p*R*) isomer of (*Z*) or (*E*)-3-(2′-((*N*,*N*-dimethylamino)methylferrocenyl)-4-(4″-methoxyphenyl)-hex-3-ene

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Abstract

We describe herein an original method for the preparation of enantiomerically pure (*Z*)- or (*E*)-3-(2′-((*N*,*N*-dimethylamino)methylferrocenyl)-4-(4″-methoxyphenyl)-hex-3-ene possessing a p(*S*) or p(*R*) plane of chirality. The key step of the synthesis lies in obtaining enantiomerically pure (*R*) or (*S*) 4-(4′-methoxyphenyl)-hexan-3-one whose reaction with the lithiated *N*,*N*-dimethylaminomethylferrocene leads to two enantiomerically pure amino-alcohol diastereomers (p*S*,3*S*,4*R*) and (p*R*,3*S*,4*R*), or (p*S*,3*R*,4*S*) and (p*R*,3*R*,4*S*) respectively. Subsequent dehydration yields a mixture of three olefins, namely, two trisubstituted olefins and either the (*Z*)- or (*E*)-tetrasubstituted olefin with respect to the starting amino-alcohol diastereomer. Additionally we obtained the enantiomerically pure (*R*)- and (*S*)-4-phenyl-hexan-3-one and the corresponding diastereomeric amino-alcohols.

1. Introduction

The synthesis of heterobimetallic compounds possessing a conjugated electronic system connecting the two metallic sites has received considerable attention due to the opportunity for observing cooperative properties behavior.[1] A simple molecular wire might be composed of two metallocenic functions connected by a double bond. In such a case the charge can be selectively created at one of the two metallic centers depending on the nature of the metal.

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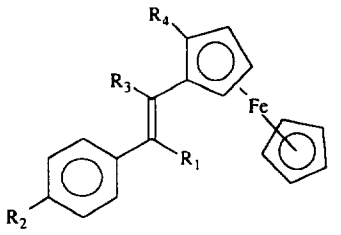
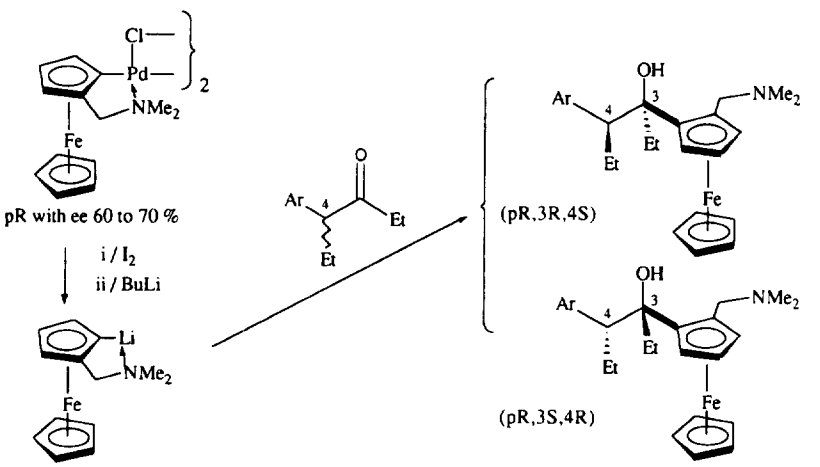


Fig. 1. Aryl ferrocenyl ethylene — type A

In addition, one of the two metallic π-complexes when properly disubstituted can present a plane of chirality and be obtained in the active form.[2] For our purpose the most useful models are the aryl ferrocenyl ethylenes (type A) (Fig. 1).

Some ferrocenic 1,2 or 1,3 disubstituted compounds are well known in enantiomerically pure forms[3] as well as those belonging to the arene complexes series.[4] Olefins of type A are generally obtained by a Wittig reaction starting from optically active 1,2 disubstituted ferrocene carboxaldehydes.[5] However, this reaction yields predominantly the (*E*)-olefins. Our objective was the synthesis of the (*Z*) and the (*E*)-3-(2′-((*N*,*N*-dimethylamino)methylferrocenyl)-4-(4″-methoxyphenyl)-hex-3-ene possessing a p(*S*) or p(*R*) plane of chirality[6] by using optically active amino-alcohols as precursors.

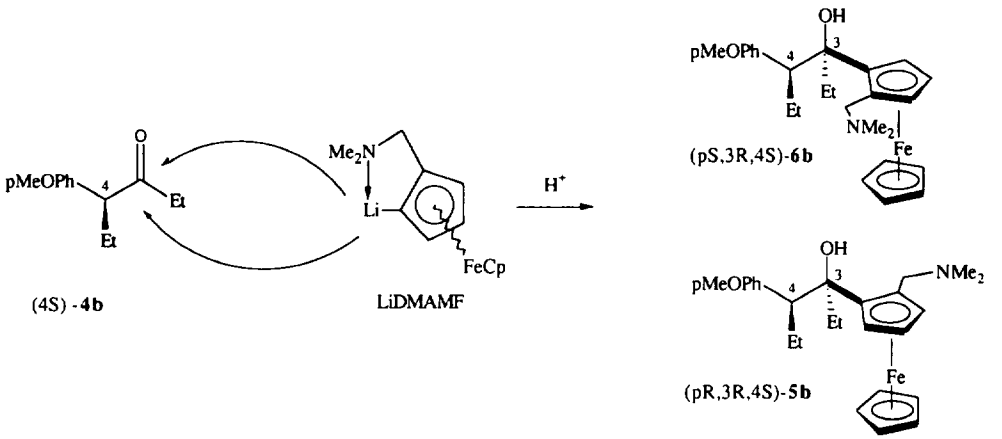
We have previously described the synthesis of the optically active ferrocenic amino-alcohols[7]: 3-(2′-((*N*,*N*-dimethylamino)methylferrocenyl)-4-(4″-methoxyphenyl)-hexan-3-ols. Their relative configurations were unambiguously determined for the racemic compounds by X-ray diffraction studies.[7] The absolute configurations were deduced from the configuration of the starting cyclopalladated ferrocenic compound previously described in the literature.[8] The carbon–carbon bond between the ferrocenic moiety and the six membered aromatic ring was built by action of the lithiated ((*N*,*N*-dimethylamino)-methyl)-ferrocene (LiDMAMF) on the appropriate ketone (Scheme 1).



Scheme 1. Control of the chirality by asymmetric cyclopalladation

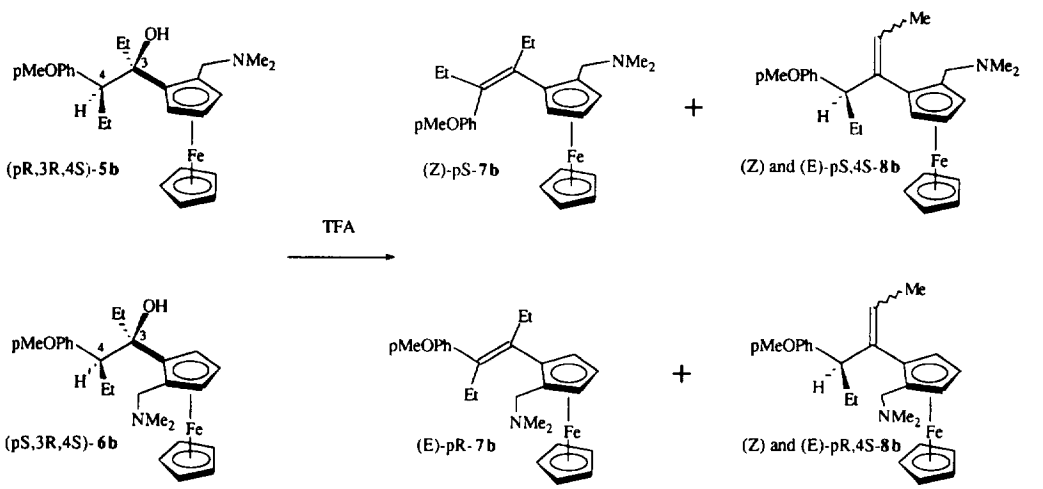
The main characteristic of this nucleophilic addition is the high diastereoselectivity of the reaction leading to two of the four possible isomers. The configuration of the generated new asymmetric carbon is, in most of the cases reported in the literature,[9] correlated to the configuration of the plane of chirality in the lithiated substituted ferrocene. In this example, the stereochemical course of the reaction is under the control of the configuration of the carbon adjacent to the ketone as described earlier for some

nucleophilic attacks.[10] In the previous approach[7] the control of the chirality was reached using the classical asymmetric cyclopalladation of DMAMF followed by the iodination and then the lithiation of the iodide. The optically active (p*S*) or (p*R*) lithiated ferrocene moiety reacts diastereoselectively with the racemic 4-(4′-methoxyphenyl)-hexan-3-one to yield two diastereomers (p*R*,3*S*,4*R*) and (p*R*,3*R*,4*S*) or (p*S*,3*R*,4*S*) and (p*S*,3*S*,4*R*) respectively with moderate enantiomeric excess (65 to 70%) according to those obtained for the cyclopalladated compounds. Based on these results, we planned to invert the synthetic strategy, i.e. to use optically pure 4-(4′-methoxyphenyl)-hexan-3-one and racemic LiDMAMF. We anticipated the formation of the target ferrocenic amino-alcohols in high enantiomeric excesses (Scheme 2).



Scheme 2. Formation of the two diastereomeric amino-alcohol (p*R*,3*R*,4*S*)-**5b** and (p*S*,3*R*,4*S*)-**6b** from ketone (4*S*)-**4b**

The subsequent formation of the tri- and tetra-substituted olefins from the amino-alcohols was achieved by acidic treatment. The reaction is very specific in the sense that the geometry (*Z*) or (*E*) of the obtained tetrasubstituted olefins depends solely on the relative configuration of the starting amino-alcohol (Scheme 3).[11]

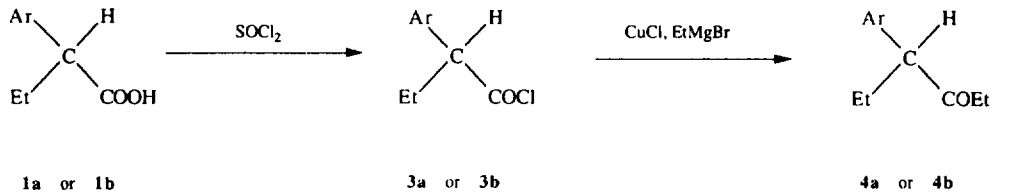


Scheme 3. Formation of the olefins from the amino-alcohols

2. Results and discussion

Several methods of preparation of 2-aryl-alkylketones as a racemic mixture[12] or as optically active compounds[13] were described earlier. They are most commonly formed in the reaction of a lithiated aliphatic compound with 2-phenylalkanoic acids.[14] Metallated chiral hydrazones can be used as intermediates in this synthesis.[15] Recently enzymatic oxidations of secondary alcohols were also reported.[16]

We propose therein a new and efficient way to prepare optically active 4-aryl-hexan-3-ones combining an enzymatic resolution of 2-aryl-butanoic acids followed by classical conversion of the carboyl into a ketone (Scheme 4).

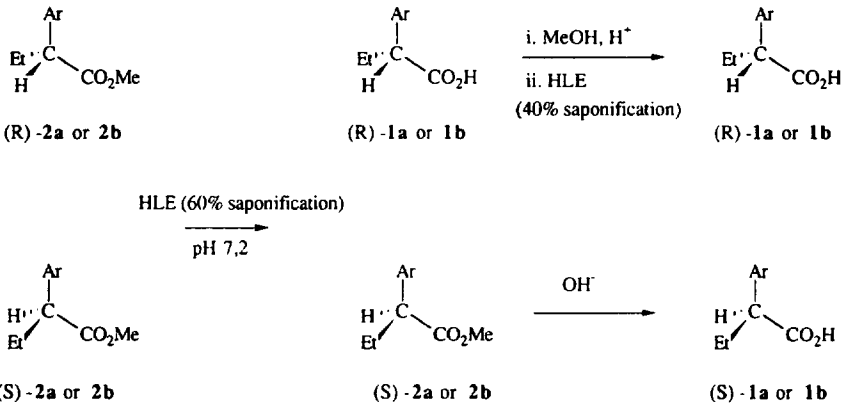


1a or **1b** **3a** or **3b** **4a** or **4b**

1a Ar = Ph ; **1b** Ar = pMeOPh

Scheme 4. Obtention of the ketones from the acids

Different methods have been used to achieve the resolution of aliphatic organic acids by bioconversion.[17] One of the most efficient and useful techniques uses the enzymatic resolution of the racemic methyl esters by enantioselective hydrolysis.[18] This approach, which usually gives good yields, requires very simple and inexpensive experimental conditions.[19] The enantiomerically pure (*R*)-or (*S*)-2-phenyl-(or-(4′-methoxyphenyl))-butanoic acids **1a** (or **1b**) were prepared from the methyl esters **2a** (or **2b**) by using horse liver esterase (HLE). [The reaction is also possible with pig liver esterase (PLE) but with no satisfactory ee (65% for the unreacted ester) at pH 7.2 at room temperature.] In this enzymatic reaction the (*R*) isomer is primarily hydrolyzed under the conditions described by Bloch.[20] (Scheme 5).



(R) -**2a** or **2b** (R) -**1a** or **1b** (R) -**1a** or **1b**

(S) -**2a** or **2b** (S) -**2a** or **2b** (S) -**1a** or **1b**

1c Ar = Ph ; **1d** Ar = pMeOPh

Scheme 5. Obtention of the optically pure acids **1a** or **1b** by horse liver esterase

Table 1

Product	$[\alpha]_D$ measured at 20°C*	Conc.	$[\alpha]_D$ lit.	ref.
2-Phenylbutanoic acid				
(S)-(+)-**1a**	+88	0.432	+93	21
(R)-(-)-**1a**	-95	2.18	-93	21
2-Phenylbutanoyl Chloride				
(S)-(+)-**2a**	+71	0.79		
(R)-(-)-**2a**	-82	2.37		
2-(4'-methoxyphenyl)-butanoic acid				
(S)-(+)-**1b**	+61	0.74	+61.1	22
(R)-(-)-**1b**	-62	0.53	-61.1	22
2-(4'-methoxyphenyl)-butanoyl chloride				
(S)-(+)-**2b**	+67	0.48		
(R)-(-)-**2b**	-68	0.64		

*All the measures were performed in Chloroform except for **1a** done in toluene.

The methyl esters with (*S*) configuration **2a** (or **2b**) were recovered in 34% yield and 93% ee based on the literature values of the acids[21,22] after three days of enzymatic treatment of the racemic mixtures of **2a** (or **2b**). Hydrolyses by KOH in aqueous ethanol solution yielded the corresponding acids (*S*)-**1a** (or (*S*)-**1b**). The (*R*) enantiomers of acids **1a** (or **1b**) were obtained after one step in 60% yield with an ee of 56%. The re-esterification followed by another cycle of enzymatic treatment afforded after one day the expected (*R*) isomers with ee of 96% in 35% yield.

The acids **1a** (or **1b**) were transformed into their corresponding acid chlorides **3a** (or **3b**) using thionyl chloride at 80°C for one hour and purified by distillation in vacuo (5 mmHg). Rotation values for **1a** and **1b** are reported in Table 1 and compared to those found in the literature.

The absence of racemization during the formation of the acid chlorides was confirmed by hydrolysis. The recovered acids present an identical specific rotation as the initial compounds. Attempts to prepare optically active ketones by the reaction of ethyl lithium with the corresponding acid **1a** (or **1b**) according to literature[23] failed, resulting in partially racemized ketone (ee 40–60%) even at low temperature. The (*R*) or (*S*)-4-phenyl-(or-(4′-methoxyphenyl))-hexan-3-one **4a** (or **4b**) were therefore prepared by the reaction of bromoethyl magnesium cuprate with the optically active (*R*) or (*S*)-2-phenyl-(or-(4′-methoxyphenyl))-butanoyl chloride **3a** (or **3b**) according to the method described by Dubois and Boussu[24] for the preparation of hindered ketones. The ketones **4a** (or **4b**) were obtained by addition of an ethereal solution of the butanoyl chlorides **3a** (or **3b**) at low temperature (−60°C) to a stoichiometric amount of bromoethyl magnesium cuprate. After acidic hydrolysis the ketones were isolated in 78% yield by flash-chromatography on silica gel (eluent pentane:ether=95:5). The optical rotations of ketones **4a** and **4b** were recorded in toluene[25] and are reported in Table 2. To our knowledge, the optically active form of **4b** has never been reported.

The next step in the synthesis was the reaction of the racemic lithiated DMAMF with the optically active ketones (*R*) or (*S*)-**4a** (or **4b**). This step was described earlier[7] and therefore we only report the optical rotation values, enantiomeric excesses and absolute configurations of each of the amino-alcohols

Table 2

Product	$[\alpha]_D$ measured (toluene, 20°C.)	e.e.*	ref.
4-Phenyl-hexan-3-one			
(S)-(+)-**4a**	+320	92	25
(R)-(-)-**4a**	-337	98	25
4-(4'-methoxyphenyl)-hexan-3-one			
(S)-(+)-**4b**	+306	93	
(R)-(-)-**4b**	-317	96	

* Measured by HPLC (column Chiralcel OJ isopropanol-heptane 0.5% flow 0.7ml/mn at 300nm)

Table 3

Amino-alcohol*	$[\alpha]_D$ measured (Ethanol, 20°C)	Concentration	e.e.
4-Phenyl			
(pR,3R,4S)-**5a**	+32	0.54	92
(pS,3R,4S)-**6a**	-38	0.40	92
(pS,3S,4R)-**5a**	-71	0.45	98
(pR,3S,4R)-**6a**	+44	0.37	98
4-(4'-Methoxyphenyl)			
(pR,3R,4S)-**5b**	+54	0.61	93
(pS,3R,4S)-**6b**	-46	0.76	93
(pS,3S,4R)-**5b**	-55	0.69	96
(pR,3S,4R)-**6b**	+48	1.18	96

*4-aryl-3-(2'-(N,N-Dimethylamino)methylferrocenyl)-hexan-3-ol

in Table 3: (p*R*,3*R*,4*S*)-**5a**, (p*S*,3*S*,4*R*)-**5a**, (p*R*,3*S*,4*R*)-**6a** (p*S*,3*R*,4*S*)-**6a** (or **5b**, **6b**). It is noteworthy that the relations between the rotations of the amino-alcohols and their corresponding enantiomeric excesses based on those of the starting ketones, correlate perfectly with our previous results based on the ee of the starting ferrocenic cyclopalladated compounds.

The absence of racemization during the acidic hydrolysis renders possible the recycling of the starting ketone. This fact allowed us to obtain an overall yield of 55% of amino-alcohols. This opportunity does not exist in the asymmetric cyclopalladation approach in which the unreacted optically active material is lost. Finally, the target olefins (*Z*)-**7b** (or (*E*)-**7b**) were obtained by reaction of trifluoroacetic acid with the amino-alcohols **5b** (or **6b**) in dichloromethane at room temperature (Scheme 2). The yields, specific rotation values and ees are reported in Table 4. The yields of tetrasubstituted olefins are relatively low, however, it is possible to increase them by using the corresponding co-products trisubstituted olefins **8b** (Scheme 2) as new starting materials.

3. Conclusion

This work describes the preparation of ferrocenic amino-alcohols with high enantiomeric purity, exhibiting three elements of chirality including a ferrocenic plane. The key step of this synthesis is the easy preparation of optically active aryl-alkylketones with high ees and their diastereoselective condensation with the lithiated dimethyl aminomethylferrocene. The resulting amino-alcohols are selectively

Table 4

Olefins*	$[\alpha]_D$ measured (Ethanol,20°C)	Concentration	e.e.
(+)-(E)-3-ene-pR-7b	+ 113	0.784	93
(-)-(E)-3-ene-pS-7b	- 107	0.145	96
(-)-(Z)-3-ene-pR-7b	- 101	0.045	96
(+)-(Z)-3-ene-pS-7b	+ 96	0.49	93
(+)-(Z)-2-ene-pR,4R-8b	+ 300	0.40	96
(+)-(E)-2-ene-pR,4R-8b	+ 147	0.23	96
(+)-(Z)-2-ene-pR,4S-8b	+ 76	0.436	93
(+)-(E)-2-ene-pR,4S-8b	+ 154	0.456	93
(-)-(Z)-2-ene-pS,4R-8b	- 82	1.235	96
(-)-(E)-2-ene-pS,4R-8b	- 157	0.735	96
(-)-(Z)-2-ene-pS,4S-8b	- 295	0.38	93
(-)-(E)-2-ene-pS,4S-8b	- 145	0.392	93

* 3-(2'-((N,N-dimethylamino)-methylferrocenyl)-4-(4''-methoxyphenyl)-hex-2 or -3-ene

dehydrated to yield trisubstituted and tetrasubstituted olefins with predictible (*Z*) or (*E*) configuration, for which specific rotation has been determined.

4. Experimental methods

4.1. General information

All reactions were carried out under an atmosphere of dry argon. Solvents were dried and distilled using standard techniques. Diethyl ether was distilled from sodium:benzophenone, methylene chloride from sodium hydride, pentane was treated with sulfuric acid and distilled with sodium, triethylamine was dried with sodium. DMAMF was obtained from Aldrich and was distilled under reduced presure before use. Horse liver acetone powder was obtained from Sigma and used as received. ^1H and ^{13}C spectra were recorded on a Brucker AM 250 instrument, using standard programmes for proton (299.9 MHz) and carbon (75 MHz) spectra. NMR chemical shifts are reported in δ (ppm) relative to TMS (^1H, ^{13}C) J values are given in hertz. Elemental analyses were performed by Centre Régional de Microanalyse, Université Pierre et Marie Curie. Optical rotations were recorded on an Ameria AA-10 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 dm cell with a total volume of 1.3 mL. The enantiomeric excesses of the methylated acids and the ketones were determined by HPLC using a chiral column (Chiralcel OJ eluent isopropanol:heptane 0:5 to 1% with a flow of 0.5 to 1 ml/min, detector at 300 nm). The (*Z*) and (*E*) geometries have been determined by NMR analysis using an NOE DIFF programme.

*4.2. (R) and (S)-2-Aryl-butanoic-acid **1a** (aryl=phenyl) or **1b** (aryl=4' methoxyphenyl)*

4.2.1. General procedure

In an 150 mL Erlenmeyer flask, 3 g (15 mmol) of ester **2b** in 90 mL of phosphoric buffer solution pH 7.2 (for 1 L: 53.7 g $Na_2HPO_4 \cdot 12H_2O$; 6.8 g KH_2PO_4) were stirred with 3 g of horse liver acetone powder (Sigma) at room temperature for 90 h. The mixture was acidified with 2 mL of conc. HCl and extracted five times with 50 mL of ether with the help of a centrifuge (5 min at 4000 t/min). The acidic organic ethereal layer was then basified with 150 mL of saturated Na_2CO_3 solution and the resulting

aqueous layer washed 5 times with ether (200 mL). The basic ethereal layers were filtered through silica gel and the removal of the solvent gave the optically active (*S*)-**2b** ester form (1.02 g, ee 93%; 61% saponification; yield 34%). The basic aqueous layer was then acidified with conc. HCl until precipitation was complete, extracted (ether, 3×120 mL) and filtered through silica gel to yield 1.46 g of the (*R*)-**1b** acid form (ee 56%; yield 52%).

The optically enriched acid was re-esterified for another cycle of 24 h with the enzyme (in the ratio: 2 g for 3 g of (*R*)-(−)-**2b**) and treated under the same conditions as described above, yielding 0.55 g of (*R*)-**1b** (38% saponification, 95% ee; yield 35%). (*R*)-**1a** $[\alpha]_D$=−95 (c=2.18, toluene). (*S*)-**1a** $[\alpha]_D$=+88 (c=0.432, toluene). (*R*)-**1b** $[\alpha]_D$=−62 (c=0.53, chloroform). (*S*)-**1b** $[\alpha]_D$=+61 (c=0.74, chloroform).

4.3. 2-Phenyl-butanoic-acid-methyl ester **2a**

Compound **2a** was obtained from the commercially available phenylbutanoic acid **1a** by refluxing it in CH_3OH in the presence of conc. H_2SO_4 for 3 h. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3, J=7.4); 1.76 (m, 1); 2.07 (m, 1); 3.42 (t, 1, J=7.7); 3.58 (s, 3); 7.20 (m, 5).

4.4. 2-(4′-Methoxyphenyl)-butanoic-acid-methyl ester **2b**

4-Methoxyphenyl-acetonitrile (Acros) was ethylated according to a previously described method.[7] 21 g (0.12mol) of 4-methoxyphenyl-butyronitrile was refluxed overnight in 140 mL of ethylene glycol with 130 g of KOH. After cooling to r.t., 200 mL of water were added followed by 100 mL of HCl (2 N). The white precipitate was filtered off, washed (Et_2O), extracted with ether and dried to give 22 g of a crude pale yellow viscous mixture containing the 2-(4′-methoxyphenyl)-butanoic acid **1b** and its demethylated form. The oil was dissolved in 25 mL of EtOH and warmed to 60°C. NaOH (5 g, 0.125 mol) in 7.5 mL of H_2O–Me_2SO_4 (15 g, 0.12 mol) were added alternately in 5 portions. After the additions, a further 1 g of NaOH in 2 mL H_2O was added to ensure an alkaline solution and the solution was heated in an oil bath at 82°C for 3.5 h. Then the solution was cooled, the ethanol removed and the residue washed (H_2O) and extracted (Et_2O). Evaporation of the solvent gave 21.5 g (0.10 mol) of 4-methoxyphenyl-butanoic acid methyl ester **2b** as a pale yellow oil (yield 83%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3, J=7.4); 1.77 (m, 1); 2.06 (m, 1); 3.42 (t, 1, J=7.7); 3.66 (s, 3); 3.79 (s, 3); 6.87 (d, 2, J=6.7); 7.23 (d, 2, J=6.7).

4.5. (R) and (S)-2-Aryl-butanoyl chloride **3a** *(aryl=phenyl) and* **3b** *(aryl=4′-methoxyphenyl)*

Acid chlorides **3a** (or **3b**) were obtained quantitatively by refluxing the acid form **1a** (or **1b**) for 1 h with 2 eq. of thionyl chloride followed by vacuum distillation. They were stored under argon at −30°C. **3a**: ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3, J=7.4); 1.92 (h, 1, J=7.4); 2.28 (h, 1, J=7.4); 3.94 (t, 1, J=7.5); 7.40 (m, 5). (*R*)-**3a** $[\alpha]_D$=−82 (c=2.37, chloroform). (*S*)-**3a** $[\alpha]_D$=+71 (c=0.79, chloroform). (*R*)-**3b** $[\alpha]_D$=−68 (c=0.64, chloroform). (*S*)-**3b** $[\alpha]_D$=+67 (c=0.88, chloroform).

4.6. (R) and (S)-4-Aryl-hexan-3-one **4a** *or* **4b**

4.6.1. General procedure

2.2 g (0.02 mol) of CuCl (Acros) were dried for 2 h at 120°C under vacuum. After cooling to −70°C, 15 mL of ether were added dropwise followed by 0.02 mol of ethyl magnesium bromide prepared from magnesium turnings and ethyl bromide in ether using standard procedures. After 15 min, 1.8 g (9.9 mmol) of (*S*)-(+)-**3b** was directly added with a syringe and the solution was stirred for 15 min before pouring

the mixture into an acidic (150 mL of 5% HCl) ice–water bath. The solution was extracted with ether (100 mL) dried ($MgSO_4$) evaporated and flash-chromatography carried out on silica gel (Merck 60G) starting with pure pentane and mixing it with 10% of ether. Removal of solvent led to 1.36 g (7.7 mmol, yield 78%) of the optically active ketone (*S*)-(+)-**4b**. **4a**: ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3, J=7.4); 0.97 (t, 3, J=7.3); 1.66–1.780 (m, 1); 2.01–2.13 (m, 1); 2.31–2.48 (m, 2); 3.55 (t, 3, J=7.4); 7.20–7.35 (m, 5). ^{13}C NMR ($CDCl_3$) δ 8.02, 12.3, 25.5, 35.3, 60.7, 127.2, 128.4, 128.9, 139.4, 211.4. (*R*)-**4a** $[\alpha]_D$=−337 (c=2.24, toluene). (*S*)-**4a** $[\alpha]_D$=+320 (c=1.13, toluene). **4b**: ^{1}H NMR ($CDCl_3$) δ 0.81 (t, 3, J=7.4); 0.95 (t, 3, J=7.3); 1.59–1.76 (m, 1); 1.94–2.09 (m, 1); 2.24–2.48 (m, 2); 3.48 (t, 3, J=7.4); 3.77 (s, 1); 6.85 (d, 2, J=8.7); 7.12 (d, 2, J=8.7). (*R*)-**4b** $[\alpha]_D$=−317 (c=0.49, toluene). (*S*)-**4b** $[\alpha]_D$=+306 (c=0.50, toluene). Recently a series of phenylalkylketones was reported for which the ees were determined by HPLC.[26] These values are in close agreement to our results. In particular these authors published a value of $[\alpha]_D$=−48 with 33% ee for the (*R*)-2-phenyl-pentan-3-one in $CHCl_3$; taking into account the solvent effects resulting in a two-fold increase of optical rotation values in toluene as compared to chloroform, and also the similar values for α-methyl and α-ethyl compounds.[27]

*4.7. (pR,3S,4R) and (pS,3S,4R)-3-(2′-((N,N-Dimethylamino)methylferrocenyl)-4-aryl-hexan-3-ol (**5a** and **6a**)(aryl=phenyl) or (**5b** and **6b**)(aryl=4″-methoxyphenyl)*

4.7.1. General procedure

To 0.80 g (3.3 mmol) of (*N,N*-dimethylamino)methylferrocene (Strem) in 10 mL anhydrous ether under argon at room temperature was added 3.1 mmol of butyllithium. After 1 h, 0.6 g (2.9 mmol) of optically active ketone (*R*)-(−)-**4a** dissolved in 2 mL of ether, was added at −40°C. After 15 min the mixture was poured into an acidic ice–water bath (100 mL, 5% HCl) and extracted 4 times with ether. This acidic ethereal layer was dried, evaporated and flash-chromatography was carried out to yield 0.21 g (1 mmol) of unreacted ketone. The aqueous solution was basified by addition of Na_2CO_3 and extracted 5 times with ether. Removal of solvent gave a dark orange oil which after chromatography on plates (silica gel 60G, eluent pentane: Et_3N 3% Rf 0.45 and 0.40) led to 0.20 g (0.45 mmol) of (p*S*,3*S*,4*R*)-**5a** (a more polar isomer) as an oil and 0.17 g (0.38 mmol) of (p*R*,3*S*,4*R*)-**6a** as an oil (total yield of amino-alcohols 28%).

To ensure a satisfactory separation of the amino-alcohols the plates of silica had to be precoated with the eluent and dried to prevent tail formation. The separation can be improved by drying the plates after a first migration and operating a second migration. (p*S**,3*S**,4*R**)-**5a** (aryl=phenyl): ^{1}H NMR ($CDCl_3$) δ 0.49 (t, 3, J=7.3); 1.17 (t, 3, J=7.3); 1.24 (m, 1); 1.45 (m, 1); 1.77 (m, 1); 2.08 (m, 1); 2.11 (s, 6); 2.50 (dd, 1, J=11.9, 2.9); 2.51 (d, 1, J=12.2); 3.94 (m, 1); 4.01 (m, 1); 4.11 (t, 1, J=2.5); 4.16 (s, 5); 7.22 (m, 5). ^{13}C NMR ($CDCl_3$) δ 8.9, 13, 24, 29.9, 36.5, 44.5, 44.8, 58.7, 60.1, 66.1, 69.2, 69.6, 70.1, 82.1, 99.1, 126, 127.7, 130.4, 142.5. IR (CCl_4) 3188, 2930, 1455 cm^{-1}. Anal. Calcd for $C_{25}H_{33}ONFe$: C, 71.60; H, 7.93; found: C, 71.67; H, 7.96. (p*R*,3*R*.4*S*)-**5a** $[\alpha]_D$=+32 (c=0.54, ethanol, ee 92%). (p*S*,3*S*.4*R*)-**5a** $[\alpha]_D$=−71 (c=0.45, ethanol, ee 98%). (p*R**,3*S**,4*R**)-**6a**: ^{1}H NMR ($CDCl_3$) δ: 0.36 (t, 3, J=7.3); 0.79 (t, 3, J=7.3); 1.31 (m, 2); 2.04 (m, 2); 2.19 (s, 6); 2.73 (d, 1, J=12.4); 2.84 (m, 1); 3.91 (m, 1); 4.11 (m, 1); 4.13 (m, 1); 4.14 (s, 5); 7.23 (d, 2, J=6.9); 7.28, t, 1, J=7.0); 7.36 (d, 2, J=7.1). ^{13}C NMR ($CDCl_3$) δ 8.6, 13, 24.1, 29.9, 37.4, 42.1, 44.8, 58.5, 59.4, 65.4, 68.6, 69.7, 70.9, 82.3, 99, 126.1, 127.9, 130.1, 143.4. IR (CCl_4) 3570, 3192, 2930, 1455 cm^{-1}. Anal. Calcd for $C_{25}H_{33}ONFe$: C, 71.60; H, 7.93; found: C, 71.54; H, 8.08. (p*R*,3*S*.4*R*)-**6a** $[\alpha]_D$=+44 (c=0.37, ethanol, ee 98%). (p*S*,3*R*.4*S*)-**6a** $[\alpha]_D$=−38 (c=0.40, ethanol, ee 92%).

4.8. Compounds **5b**, **6b**, **7b** and **8b** were described early[7,11]

(p*R*,3*R*,4*S*)-**5b** $[\alpha]_D$=+54 (c=0.61, ethanol, ee 93%). (p*S*,3*S*,4*R*)-**5b** $[\alpha]_D$=−55 (c=0.69, ethanol, ee 96%). (p*R*,3*S*,4*R*)-**6b** $[\alpha]_D$=+48 (c=1.18, ethanol, ee 96%). (p*S*,3*R*,4*S*)-**6b** $[\alpha]_D$=−46 (c=0.76, ethanol, ee 93%). When compounds **5b** and **6b** were chromatographed, another more polar isomer was also present but in very small amounts. ^{1}H NMR ($CDCl_3$) δ: 0.57 (t, 3, J=7.3); 1.29 (t, 3, J=7.3); 1.74 (m, 2); 1.77 (s, 6); 2.23 (q, 2, J=7.9); 2.42 (d, 2, J=12.1); 2.65 (m, 1); 3.70 (s, 3); 3.81 (q, 1, H_a-H_b); 3.90 (m, 1); 3.93 (m, 1); 4.00 (t, 1, J=2.5); 4.10 (s, 5); 6.62 (d, 2, J=8.7); 6.91 (d, 2, J=8.7).

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