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Catalytic Asymmetric Dihydroxylation of 1-Substituted-1-ferrocenylethenes: An Enantioselective Entry to Chiral Tertiary Ferrocenylcarbinols and Ferrocenylalkylamines

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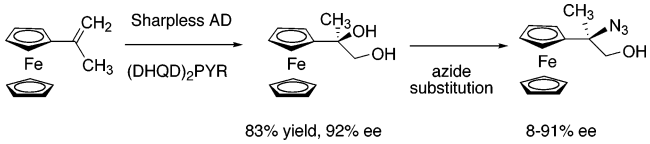
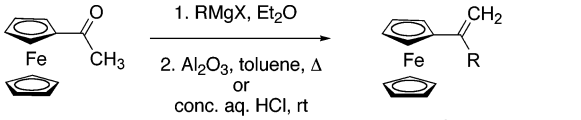


The Sharpless asymmetric dihydroxylation (AD) of 1-substituted-1-ferrocenylethenes takes place with good yields and with moderate to good enantioselectivities. The resulting 1-substituted-1-ferrocenyl-1,2-ethanediols are the first α-chiral tertiary ferrocenylcarbinols that have been prepared in optically active form. Their absolute configuration, ascertained by Induced Circular Dichroism (ICD), shows that in all cases the ferrocenyl moiety has the highest affinity for the SW binding pocket of the AD ligands. Depending upon the reaction conditions, significant racemization takes place during a side-chain azide nucleophilic substitution on 2-ferrocenyl-1,2-propanediol.

Introduction. Chiral ferrocene derivatives are currently the object of much interest, in view of their numerous applications in asymmetric catalysis,[1,2] in materials science,[2] and in biological chemistry.[3] Therefore, the development of general and preparatively useful methods for the synthesis of chiral, nonracemic ferrocene derivatives is a subject of unabated interest. Whereas much effort has been devoted to the asymmetric synthesis of planar chiral ferrocenes, less attention has comparatively been paid to the enantioselective preparation of ferrocene derivatives having only central chirality. Thus, while a number of secondary ferrocenylalkylamines and ferrocenylcarbinols have been obtained enantioselectively either by resolution of racemic mixtures

SCHEME 1. Synthesis of 1-Substituted-1-ferrocenylethenes 1a, 1c, and 1d



1a: R = CH_3, 91%
1c: R = -$CH(CH_3)_2$, 60%
1d: R = Ph, 61%

or by asymmetric addition reactions,[4] chiral tertiary ferrocenylcarbinols or α-ferrocenylalkylamines in which the tertiary, α-ferrocenic carbon is the sole element of chirality do not appear to have been ever prepared in optically active form. In the past few years, we have been involved in the synthesis of *β*-ferrocenyl-*β*-amino alcohols,[5,6a,c] a new class of central chiral ferrocene derivatives, as well as in the study of their applications in asymmetric synthesis[6b,d,e] or as starting products for the preparation of ferrocenyl amino acids.[6a] A key step in our route to *β*-ferrocenyl-*β*-amino alcohols is the Sharpless asymmetric dihydroxylation[7] (AD) of 1-ferrocenylethenes. This reaction takes place with excellent enantioselectivity (provided that ligands based on PYR heterocyclic spacers are used) for vinylferrocene[6a,8] and for other 2-substituted 1-ferrocenyl alkenes,[6a,c] and we felt that the study of its applicability to other types of 1-ferrocenyl alkenes would be worthwhile. We wish to report here that the asymmetric dihydroxylation of a set of 1-substituted-1-ferrocenylethenes affords the corresponding 1-substituted-1-ferrocenylglycols in good yields and with moderate to excellent enantiomeric purities. The enantiofacial selectivity of the process is dictated preferentially by the ferrocenyl moiety. Moreover, an initial exploration of the reactivity of (*S*)-2-ferrocenyl-1,2-propanediol indicates that side-chain substitutions at a tertiary α-ferrocene position are more prone to racemization than those taking place at secondary carbon atoms.

Results and Discussion. Ferrocenylethenes **1a**, **1c**, and **1d** were readily obtained from commercially available acetylferrocene by a two-step procedure involving addition of the appropriate Grignard reagent and alumina-[9] or acid-promoted dehydration of the intermediate alcohol (Scheme 1).

This procedure was not suitable for the preparation of 2-ferrocenyl-2-phenylpropene (**1b**), which was more conveniently obtained by Wittig methylenation of 2-phenyl-1-ferrocenylethanone[10] (Scheme 2).

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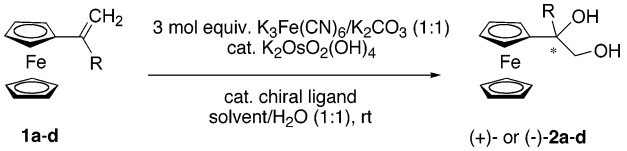
TABLE 1. Catalytic Asymmetric Dihydroxylation of 1-Substituted-1-ferrocenylethenes 1a−d

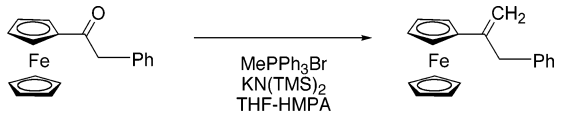


1a-d (+)- or (-)-**2a-d**

entry	alkene	ligand (% mol equiv)	Os(VI), % mol equiv	solvent	reaction time	diol product	% yield,[a] % ee (conf)
1	**1a** (R = CH_3)	$(DHQD)_2PYR$ (10)	10	CH_3CN	20 min	(+)-**2a**	83, 92[b] (*S*)[c]
2	**1a**	$(DHQ)_2PYR$ (10)	10	CH_3CN	75 min	(−)-**2a**	90, 84[b] (*R*)[c]
3	**1b** (R = CH_2Ph)	$(DHQD)_2PYR$ (10)	8	CH_3CN	15 min	(−)-**2b**	80, 90[b] (*S*)[d]
4	**1b**	$(DHQ)_2PYR$ (10)	8	CH_3CN	50 min	(+)-**2b**	81, 83[b] (*R*)[d]
5	**1c** (R = $CH(CH_3)_2$	$(DHQD)_2PYR$ (15)	15	^{t}BuOH	30 min	(−)-**2c**	80, 74[e] (*S*)[c]
6	**1c**	$(DHQD)_2PYR$ (10)	10	CH_3CN	25 min	(−)-**2c**	73, 84[e] (*S*)[c]
7	**1c**	$(DHQ)_2PYR$ (10)	10	CH_3CN	30 min	(+)-**2c**	69, 85[e] (*R*)[d]
8	**1d** (R = Ph)	$(DHQD)_2PYR$ (3.5)	3.4	^{t}BuOH	35 min	(−)-**2d**	66, 64[e] (*S*)[c]
9	**1d**	$(DHQ)_2PYR$ (7)	6	^{t}BuOH	18 h	(+)-**2d**	44, 43[e] (*R*)[c]
10	**1d**	$(DHQD)_2PYR$ (10)	8	CH_3CN	100 min	(−)-**2d**	73, 39[e] (*S*)[c]

[a] Yield of isolated product after chromatographic purification. [b] By ^{19}F NMR analysis of the Mosher derivative. [c] By ICD (see text). [d] Absolute configuration assigned by analogy. [e] By HPLC (Chiralcel OD column)

SCHEME 2. Synthesis of 2-Ferrocenyl-2-phenylethene (1b)



1b, 75%

With this set of 1-substituted-1-ferrocenylethenes (**1a**−**d**) in our hands, we proceeded to study their catalytic asymmetric dihydroxylation, using the $(DHQD)_2PYR$ and $(DHQ)_2PYR$ ligands.[11a] The results of this study are summarized in Table 1.

The AD of 2-ferrocenylpropene (**1a**) proceeded in good yields and with enantioselectivities only slightly inferior to those previously described for vinylferrocene,[6a,8] but the reaction times were considerably shorter. Thus, the dihydroxylation of **1a** in aqueous acetonitrile with $(DHQD)_2PYR$ as the chiral ligand (entry 1 of Table 1) took place in only 20 min at room temperature, affording the dextrorotatory diol (+)-**2a** in 83% yield and with 92% ee (determined by ^{19}F NMR analysis of its Mosher monoester). With the $(DHQ)_2PYR$ ligand (entry 2 of Table 1), the levorotatory enantiomer of **2a** (84% ee) was obtained in 90% yield. According to the observations made by Sharpless on the AD of α-aliphatic substituted styrenes,[11b] one could expect that both **1b** and **1c** would behave as relatively poor substrates in this reaction. We found out that this was not the case, and that the corresponding diols **2b** (entries 3 and 4 of Table 1) and **2c** (entries 5−7 of Table 1) were still obtained with acceptable enantioselectivities (74−90% ee). Even more interesting was the behavior of 1-ferrocenyl-1-phenylethene (**1d**). In this case, one could expect a strong competition between the phenyl and the ferrocenyl groups for the SW "binding pocket" of the ligand,[7] leading to the formation of nearly racemic products. However, the reaction still took place with reasonable levels of enantioselectivity (entries 9 and 10 of Table 1). As to the absolute configuration of the optically active diols, it is worth noting that the Sharpless mnemonic rule[7] is not directly applicable for 1,1′-disubstituted ethenes, due to the competition between aromatic and alkyl substituents for the binding pocket of the PYR class of ligands.[11b] This crucial issue could be easily addressed by the induced CD spectra (ICD) of the cottonogenic dimolybdenum tetraacetate derivatives, according to a methodology initially developed by Snatzke.[12] This is an exceptionally reliable method for the assignment of the absolute configuration of acyclic 1,2-diols, as demonstrated by Salvadori.[13] We have recently verified that this procedure correctly predicts the absolute (*S*) configuration of (+)-ferrocenyl-1,2-ethanediol,[6b] initially determined by anomalous X-ray diffraction.[8] In effect, when a DMSO solution of diol (+)-**2a** (for which a (2*S*) absolute configuration should be expected according to the AD mnemonic device assuming that the ferrocenyl group preferentially accommodates itself in the binding pocket of the $(DHQD)_2PYR$ ligand) was treated with a slight excess of dimolybdenum tetraacetate, the stationary state ICD exhibited a negative Cotton effect at ca. 310−320 nm (corresponding to a band of type IV, according to Snatzke's nomenclature),[12] which can be related to an (*S*) configuration for this compound (Figure 1).[13] By the same method, we could establish that diols (−)-**2a**, (+)-**2c**, and (+)-**2d**, arising from the $(DHQ)_2PYR$-mediated AD of α-substituted ferrocenylethenes **1a**, **1c**, and **1d**, respectively, have in all instances a (2*R*) absolute configuration (see the Supporting Information). The AD of 1-substituted-1-ferrocenylethenes is therefore an efficient process that allows for the first time the preparation of tertiary, α-chiral α-ferrocenylcarbinols in optically active form. The enantioselectivity of the reaction depends on the nature of the substituent, and decreases uniformly along the series Me > benzyl > ^{i}Pr > Ph.

We turned next our attention to the preparation of *β*-substituted-*β*-ferrocenyl-*β*-amino alcohols from the dihydroxylation products **2a**−**d**. In particular, we envisaged the transformation of (*S*)-2-ferrocenyl-1,2-propanediol ((+)-**2a**) into (*S*)-2-amino-1-ferrocenylpropanol (**4**). Originally, we planned to accomplish this transformation by means of the protocol developed earlier in our laboratory,[6] which called for the conversion of (+)-**2a** into the corresponding diacetate. In this event, the diacetylation

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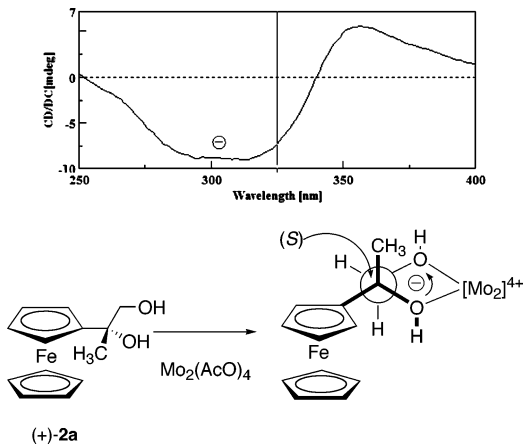

FIGURE 1. Induced circular dichroic spectrum of diol (+)-**2a**, and assignment of its absolute configuration according to the Snatzke−Salvadori rules (see text).[12,13]

of (+)-**2a** proved to be very troublesome, and we decided to explore the possibility of the direct azide substitution of the tertiary hydroxyl.[14] After some experimentation, we found out that the reaction of (+)-**2a** with a mixture of sodium azide and ammonium chloride in refluxing ethanol (reaction conditions previously employed by us for the regio- and stereoselective azide opening of *trans*-2-ferrocenyl-3-phenyloxirane)[5] reproducibly afforded the desired 2-azido-2-ferrocenyl-1-propanol (+)-**3** in acceptable yield. The reduction of the azide took place uneventfully, leading to the essentially quantitative formation of the target amino alcohol (+)-**4** (Scheme 3).

We were disappointed to find, however, that the enantiomeric purity of (+)-**3**, rigorously determined both by ^{19}F NMR of the Mosher ester and by HPLC, was only 44%. Ever since the work of Ugi in the early seventies,[15] it is generally accepted that ferrocenylalkane derivatives with leaving groups in the α position undergo nucleophilic substitutions with essentially complete retention of configuration, a paradigm that has been continuously invoked in the enantioselective preparation of chiral ferrocene derivatives.[2,5,6] The very few reported exceptions to this rule have occurred in substitution reactions performed in hot acetic acid as the solvent and in the presence of relatively poor, neutral nucleophiles.[16] It is worth noting moreover that, up to now, all known examples of retentive S_N1-type reactions at the α-position of ferrocene involve secondary carbons. We undertook therefore a systematic examination of the stereochemical outcome of the azide substitution on (+)-**2a** under various experimental conditions (Table 2).

Both the yield and the enantiomeric purity of the azido alcohol (+)-**3** strongly depend on the reaction conditions. The substitution does not take place in the absence of acid additives (entry 1 of Table 2), and becomes very slow with small concentrations of ammonium chloride (entry 2). While the yield of azido alcohol **3** increases with increasing amounts of ammonium chloride, the enantiomeric purity of the product follows the opposite behavior (entries 3 and 4). The use of lithium perchlorate as additive also led to slow reactions and, under prolonged reaction times, to oxidative decomposition of the reaction mixture (entry 5). The replacement of ammonium chloride by acetic acid led to improved yields and enantioselectivities (entries 6 and 7), but oxidative decomposition was again observed when it was used as the solvent (entry 8). When we assayed a stronger acid ((±)-camphorsulfonic acid, CSA) as the additive, we were pleased to find that under carefully controlled reaction conditions (entry 10; see the Experimental Section) the substitution took place rapidly with very little racemization, affording highly enantiopure (91% ee, determined by HPLC) azido alcohol **3**. Addition of water to the reaction mixture resulted in both low conversion and enantioselectivity (entry 12). The reaction could not be performed at room temperature, due to the low solubility of sodium azide. It is also worth noting that the enantiomeric excess of the recovered diol **2a** in entries 9 and 12 was identical with that of the starting material (92% ee), a fact that supports the hypothesis that the racemization takes place by rotation of the initially formed ferrocenyl cationic intermediate prior to its trapping by azide. Treatment of **2a** with other more soluble but less nucleophilic azide sources, such as titanium(diazido)(diisopropoxyde) or trimethylsilyl azide (entries 13 and 14, respectively), also resulted in the formation of **3**, although in low yields and enantioselectivities. In summary, the acid-mediated nucleophilic substitution by azide ion of 2-ferrocenyl-1,2-propanediol **2a** takes place with complete regioselectivity at the α-ferrocenic carbon, although with variable enantioselectivity. The presence of both a strong acid and an excess of azide anion appears to be necessary to ensure the rapid generation and trapping by the nucleophile of the α-ferrocenyl cation, to minimize the loss of the enantiomeric purity of the substitution product. This observation suggests that in general side-chain substitutions at a tertiary α-ferrocene position are more likely to proceed with racemization than those involving secondary carbon atoms, probably due to lower rotation barriers for the intermediate α-ferrocenyl cations. The potential use of the new *β*-ferrocenyl-*β*-amino alcohol (*S*)-**4** and of related compounds for the preparation of both chiral ligands for asymmetric catalysis and of conjugating units for functional biomaterials is currently being investigated in our laboratories.

Experimental Section

(*S*)-(+)-2-Ferrocenyl-1,2-propanediol ((+)-2a): To a stirred solution of $K_3[Fe(CN)_6]$ (0.49 g, 1.5 mmol) and potassium carbonate (0.21 g, 1.5 mmol) in 1:1 acetonitrile−water (40 mL) were added $(DHQD)_2PYR$ (44 mg, 0.05 mmol) and $K_2OsO_2(OH)_4$ (18 mg, 0.05 mmol), with stirring maintained at room temperature until complete dissolution of the osmate. At this point, 2-ferrocenylpropene[9] **1a** (113 mg, 0.50 mmol) was added in one portion. The reaction was monitored by TLC. When no starting ferrocenylalkene remained (20 min of stirring at room temperature), sodium sulfite (0.90 g, 7 mmol) was added and stirring was maintained for 20 min. The reaction mixture was extracted with ethyl acetate (5 × 10 mL); the organic extracts were dried over magnesium sulfate and the solvents removed at reduced pressure. Column chromatography of the crude product (silica gel, hexanes−ethyl acetate mixtures as eluent) afforded 108 mg (83% yield) of (+)-2-ferrocenyl-1,2-propanediol as a yellow solid. The enantiomeric excess of the diol, determined by ^{19}F NMR analysis of its (*S*)-MTPA ester, was 92%.

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(16) 1-Ferrocenylethanol undergoes extensive racemization by heating in acetic acid solution. See ref 15b. Racemization has also been observed in its substitution by imidazoles in acetic acid at 60 °C: Seo, H.; Kim, B. Y.; Lee, J. H.; Park, H.; Son, S. U.; Chung, Y. K. *Organometallics* **2003**, *22*, 4783−4791.

SCHEME 3. Synthesis of (*S*)-2-Amino-2-ferrocenylpropanol 4

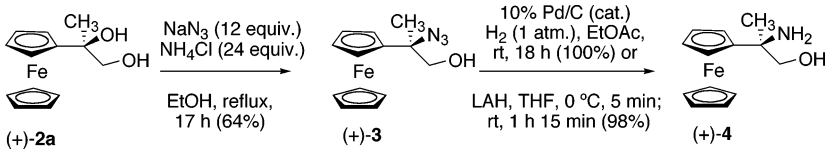

TABLE 2. Nucleophilic Azide Substitution on (+)-2a

entry	azide source (equiv)	additive (equiv)	solvent	temp, time	% yield,[a] % ee[b]
1	NaN_3 (12)		EtOH	reflux, 24 h	0, −
2	NaN_3 (12)	NH_4Cl (2)	EtOH	reflux, 15 h	36,[c] 78
3	NaN_3 (15)	NH_4Cl (15)	EtOH	reflux, 40 h	40, 70
4	NaN_3 (12)	NH_4Cl (24)	EtOH	reflux, 17 h	64, 44
5	NaN_3 (15)	$LiClO_4$ (15)	EtOH	reflux, 24 h	0,[d] −
6	NaN_3 (12)	AcOH (2)	EtOH	reflux, 17 h	45,[e] 78
7	NaN_3 (12)	AcOH (6)	EtOH	reflux, 5 h	70, 73
8	NaN_3 (12)		AcOH	80°C, 1.5 h	0,[d] −
9	NaN_3 (12)	CSA (2)	EtOH	reflux, 27 h	46,[f] 76
10	NaN_3 (12)	CSA (3)	EtOH	reflux, 0.5 h	52,[g] 91[g]
11	NaN_3 (12)	CSA (6)	EtOH	reflux, 17 h	30, 76
12	NaN_3 (12)	CSA (3)	EtOH/H_2O (7:1)	reflux, 8 h	45,[h] 77
13	$Ti(N_3)_2(O^iPr)_2$ (1.2)		CH_2Cl_2	reflux, 24 h	40,[i] 58
14	N_3SiMe_3 (5)	Et_2AlCl (1.1)	CH_2Cl_2	rt, 20 h	33,[j] 8

[a] Yield of azido alcohol (+)-**3** isolated after chromatographic purification. [b] By HPLC (Chiralcel OD column). [c] 65% conversion. [d] Acetylferrocene isolated as the main product. [e] 67% conversion. [f] 88% conversion. [g] Average of three reactions. [h] 73% conversion. [i] 62% conversion. [j] 75% conversion.

Mp 62.1−63.9 °C. $[\alpha]_D$ +14.8 (*c* 0.123, $CHCl_3$). IR (KBr) ν_{max} 3348, 2987, 2943, 1412, 1374, 1383, 1246, 1144, 1106, 1040, 999, 951, 822 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, TMS_{int}) δ 1.50 (s, 3H), 2.05 (s, 1H), 2.23 (s, 1H), 3.56 (m, 2H), 4.1−4.3 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$, TMS_{int}) δ 25.4 (CH_3), 65.4 (CH), 66.5 (CH), 68.1 (CH), 68.2 (CH), 68.4 (CH), 71.1 (CH_2), 71.2 (C), 95.3 (C). MS (CI, NH_3), *m*/*e* 260 ($[M]^+$, 2%), 243 ($[M - 17]^+$, 100%). HRMS ($C_{13}H_{16}FeO_2$, M) calcd 260.0500, found 260.0493.

(*S*)-(+)-2-Azido-2-ferrocenylpropanol ((+)-3): To a stirred suspension of sodium azide (0.63 g, 9.6 mmol) and diol (+)-**2a** (0.21 g, 0.80 mmol; 92% ee) in refluxing absolute ethanol (10 mL) was added a solution of (±)-camphorsulfonic acid (0.56 g, 2.4 mmol) in absolute ethanol (8 mL) dropwise over a period of 5 min. During the addition, the color of the mixture changed from yellow to dark red. At the end of the addition, stirring was maintained for 30 min. At this point, TLC monitoring showed the complete disappearance of the starting diol. Upon cooling to room temperature, aqueous saturated sodium bicarbonate (20 mL) was added, and the resulting yellow mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes−ethyl acetate mixtures as eluent) to give 0.14 g (62% yield) of the azido alcohol (+)-**3** as a yellow semisolid. $[\alpha]_D$ +41.9 (*c* 0.860, CH_2Cl_2) (91% ee, by HPLC). IR (NaCl film) ν_{max} 3352, 3097, 2934, 2105, 1651, 1560, 1457, 1260, 1144, 1046, 1002, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS_{int}) δ 1.68 (s, 3H), 1.93 (br s, 1H, OH), 3.55−3.64 (m, 2H), 4.14 (m, 1H), 4.21−4.25 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS_{int}) δ 21.7 (CH_3), 64.9 (C), 65.7 (CH), 65.9 (CH), 68.1 (CH), 68.3 (CH), 68.9 (CH), 70.4 (CH_2), 90.9 (C). MS (CI, NH_3), *m*/*e* 285 ($[M]^+$, 3%), 243 ($[M - 42]^+$, 100%). HRMS ($C_{13}H_{15}FeN_3O$, M) calcd 285.0564, found 285.0564.

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Supporting Information Available: General and analytical methods; detailed experimental procedures and characterization data, including copies of the ^1H and ^{13}C NMR spectra, for all new compounds; ICD spectra of diols (−)-**2a**, (+)-**2c**, and (+)-**2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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