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Synthesis of novel 1,1′-bis(oxazolinyl)metallocenes and their application in the asymmetric phenyl transfer from organozincs to aldehydes

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Dedicated to Professor Jean Normant on the occasion of his 65th birthday

Abstract

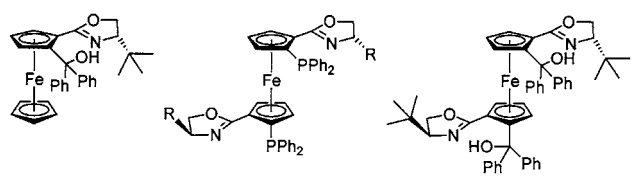
Two novel C_2-symmetric 1,1′-bis(oxazolinyl)metallocenes bearing two catalytic sites each have been employed in the asymmetric phenyl transfer from organozincs to aldehydes. Both, ferrocene (**3**) and ruthenocene (**10**) give very good yields and high enantioselectivities in the title reaction affording optically active diarylmethanols with up to 96% ee.

Keywords: 1,1′-bis(Oxazolinyl)metallocenes; Asymmetric phenyl transfer; Organozincs; Aldehydes

1. Introduction

Asymmetric catalysis has become a powerful tool in organic synthesis in recent years [1]. Among the vast variety of ligands, planar chiral ferrocenes [2] belong to the most successful which have also been applied in industrial processes [3]. Numerous compounds have been described [4], and it was found that the element of planar chirality often had a decisive influence on the stereoselectivity and efficiency of the resulting catalytic system [5]. In order to introduce planar chirality into the molecules, the ability of oxazolines to act as directing groups for diastereoselective *ortho*-lithiation [6] has frequently been applied, leading — after subsequent quenches with appropriate electrophiles — to the desired products in high yield and excellent stereochemical control [7]. Furthermore, the oxazoline moiety itself proved to be an excellent stereo-directing element in asymmetric catalysis, and thus in planar chiral systems its usefulness has exceeded the application as internal chiral auxiliary [8].

Recently, we reported on a highly enantioselective catalyst system for the phenyl transfer from organozincs to aldehydes consisting of ferrocene **1** and mixtures of $ZnPh_2$ and $ZnEt_2$ [9,10]. The best enantiomeric excesses were obtained with a catalyst loading of 10 mol%. In order to achieve a reduction of the required catalyst amount, we now investigated the use of metallocenes bearing duplicate catalytically active sites in a single molecule. Considering a strategy introduced by Park, Ahn [11] and Ikeda [12] in the ferrocene series (preparation of C_2 symmetric diphosphine **2**) several years ago, we expected a straighforward synthesis of the desired 1,1′,2,2′-tetrasubstituted ferrocene **3** by electrophilic quench of the dianion of **4** with benzophenone [13][1]. Other metallocenes having this substitution pat-



1 **2** **3**

Fig. 1.

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[1] After submission of this manuscript (September 29, 2000) a paper appeared in which the synthesis of **3** and its application in diethylzinc additions to benzaldehyde was described.

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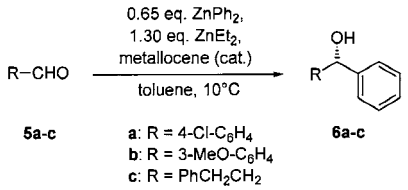
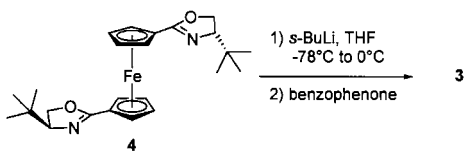
Table 1
Catalyzed phenyl transfer to various aldehydes with ferrocenes **1** and **3** [a]



Entry	Substrate	Catalyst amount (mol%)	Ee (%) [b] of products **6a–c** using		Absolute config. [c]
			Ferrocene **1**	Ferrocene **3**	
1	**5a**	10	97	96	*R*
2	**5a**	5	95	94	*R*
3	**5a**	2	92	86	*R*
4	**5b**	10	96	95	*R*
5	**5b**	5	96	95	*R*
6	**5c**	10	75	72	*S*
7	**5c**	5	75	71	*S*



Scheme 1.

tern were hoped to be accessible in an analogous manner (Fig. 1).

2. Results and discussion

Known 1,1′-bis(oxazolinyl)ferrocene (**4**) was prepared in two steps from 1,1′-bis(chlorocarbonyl)ferrocene following literature procedures [12a]. As hoped for, the synthesis of **3** was accomplished by dilithiation of **4** with *sec*-butyllithium in THF at −78°C and subsequent quenching of the dimetallated species with benzophenone (Scheme 1).

A 9:1 mixture of diastereomers was obtained in good yield, favoring of the product with (*R*,*R*)-configuration with respect to planar chirality. Preparative HPLC gave diastereomerically pure (S,S,R_p,R_p)-**3** which was subsequently used in asymmetric phenyl transfers to aldehydes according to our new protocol [9b]. Results of these catalyses are summarized in Table 1.

Compared to catalyses with ferrocene **1**, use of 10 mol% of C_2-symmetric **3** gave almost identical results with respect to both yield and enantioselectivity. Unfortunately, reactions with a lower catalyst loading led to a decrease in enantioselectivity. Based on an identical number of oxazoline diphenylhydroxymethyl units the catalyses with **3** even showed slightly inferior results. A possible explanation of this behavior was seen in a mutual interference of the two catalytic sites during the catalysis.

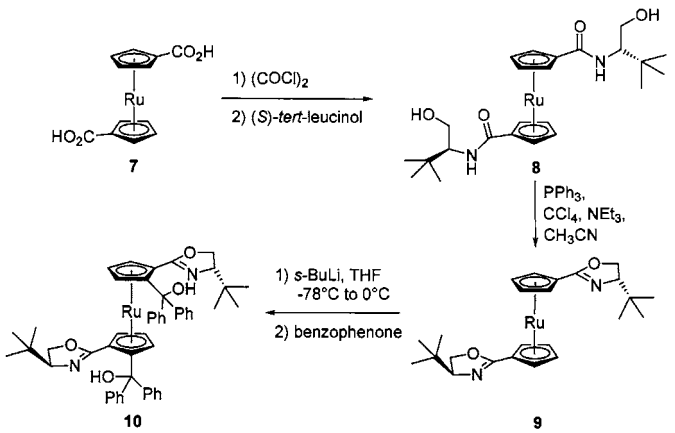
In order to disfavor and minimize such negative interaction, we prepared ruthenocene **10**. With respect to ferrocenes, the two cyclopentadienyl rings of ruthenocenes are ca. 0.34 Å further apart [14], thus increasing the spatial separation of the two catalytic sites. The synthesis of **10** was accomplished in the same manner as for ferrocene **3** starting from 1,1′-ruthenocene dicarboxylic acid (**7**), which was obtained via carboxylation of dilithiated ruthenocene [15] (Scheme 2). The diacid was reacted with an excess of oxalyl chloride, and the resulting 1,1′-bis(chlorocarbonyl)ruthenocene was treated with (*S*)-*tert*-leucinol to afford the corresponding bisamide **8**. Cyclization of **8** following the Appel protocol [16] gave 1,1′-bis(oxazolinyl)ruthenocene (**9**). Directed *ortho*-metalation of **9** with *sec*-butyllithium and subsequent quenching of the resulting dianion with benzophenone in the same manner as in the ferrocene series gave a diastereomeric mixture of ruthenocene **10** in a ratio of 9:1. The diastereomers were separated by flash chromatography, and diastereomerically pure (S,S,R_p,R_p)-**10** was used for further studies [13][2].

[2] In the synthesis of **3** the stereochemical assignment is based on the results by Ahn (Ref. [11b]) and Ikeda (Ref. [12a]). The analogous behavior of the Ru complex was established independently. The C_2 symmetry of complexes **3** and **10** is further suggested by the highly symmetrical NMR spectra.

Table 2
Catalyzed phenyl transfer to various aldehydes with ruthenocene **10** [a]

Entry	Substrate	Catalyst amount (mol%)	Ee (%) [b] of products **6a–c** using ruthenocene **10**	Absolute config. [c]
1	**5a**	10	96	*R*
2	**5a**	5	95	*R*
3	**5a**	2	90	*R*
4	**5b**	10	94	*R*
5	**5b**	5	93	*R*
6	**5c**	10	74	*S*
7	**5c**	5	72	*S*

[a] All reactions gave good to quantitative yields on a 0.25 mmol scale.
[b] Determined by HPLC using a column with chiral stationary phase.
[c] Determined by comparison of the order of peak elution during HPLC with literature values, or tentatively assigned by assumption of an identical reaction pathway (entries 4,5).



Scheme 2.

The results of catalyses with the new ruthenocene **10** are summarized in Table 2. To our delight, we noted that compared to ferrocene **3**, ruthenocene **10** showed slightly better selectivities in the phenyl transfer to 4-chlorobenzaldehyde (**5a**) at lower catalyst loadings (entries 2 and 3). The same accounted for transformations of 3-phenylpropanal (**5c**). However, additions to 4-methoxybenzaldehyde (**5b**) were less efficient giving slightly lower enantioselectivies with **10** than with **3**, and again, ferrocene **1** having only a single catalytic site was more selective than ruthenocene **10** with two.

As a consequence of these results, we believe that possible steric interactions of the two catalytic sites in **3** and **10** are not the sole reasons for the lower enantioselectivities observed in catalyses with these 1,1′,2,2′-tetrasubstituted bis(oxazolinyl) metallocenes. Other factors might as well have an important impact, and current studies are directed towards a deeper understanding of the underlying principles of this synthetically useful C–C bond-forming catalysis.

3. Conclusion

In conclusion, we introduced new C_2-symmetric metallocenes **3** and **10** which catalyze the asymmetric phenyl transfer from organozincs to aldehydes with high enantioselectivities. Based on the number of oxazoline units present in the catalytic system, ferrocene **3** is inferior to its mono-substituted analogue **1**. Ruthenocene **10** showed comparable selectivities and yields.

4. Experimental

All manipulations except workup and purification were conducted under an inert atmosphere of Ar using standard Schlenk techniques. Diphenylzinc was obtained from Strem and handled in a glovebox under Ar. Tetrahydrofuran and toluene were distilled from sodium/benzophenone ketyl radical, dichloromethane from calciumhydride prior to use. *sec*-Butyllithium was purchased from Fluka as a 1.3 M solution in cyclohexane. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 and 75 MHz, respectively, and on a Varian Inova 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are given in ppm with internal referencing to the solvent peaks. IR spectra were measured on a Perkin Elmer 1760 S as KBr pellets, MS spectra on a Varian MAT 212 or a Finnigan SSQ7000 mass spectrometer with EI ionization. All experiments were conducted at least twice to ensure reproducibility.

*4.1. (S,S,R_p,R_p)-1,1′-bis-[(4-tert-Butyloxazolin-2-yl)]-2,2′-bis(diphenylhydroxymethyl)ferrocene (**3**)*

To a solution of 250 mg (0.57 mmol) of **4** in 10 ml of tetrahydrofuran is added 1.15 ml (1.50 mmol) of *sec*-butyllithium at −78°C. After stirring the mixture at

this temperature for 2 h, and then at 0°C for 20 min, 271 mg (1.45 mmol) of benzophenone is added in one portion. Stirring is continued overnight, allowing the temperature to rise to ambient temperature. The reaction is then quenched with 10 ml of water and extracted with diethylether (3×25 ml). The collected organic layers are dried ($MgSO_4$) and evaporated. The crude product is obtained in a diastereomeric ratio of 9:1. The diastereomers were separated by preparative HPLC (silica gel; 10 μm; eluent: hexanes:MTBE = 9:1) to yield 277 mg (53%) of the title compound as an orange solid: m.p. 241–243°C. $[\alpha]_D = -125°$ [$c = 0.25$, $CHCl_3$]. ^{1}H-NMR ($CDCl_3$): δ 0.98 (s, 18H), 3.54 (dd, $J = 1.6$ Hz, 2.5 Hz, 2H), 3.58 (dd, $J = 9.6$ Hz, 2H), 4.07 (dd, $J = 9.3$ Hz, 2H), 4.15 (dd, $J = 8.8$ Hz, 10.2 Hz, 2H), 4.59 (dd, $J = 1.6$ Hz, 2.5 Hz, 2H), 5.17 (dd, $J = 2.7$ Hz, 2H), 7.00–7.20 (m, 20H), 9.13 (s, 2H). ^{13}C-NMR ($CDCl_3$): δ 26.5, 33.3, 67.9, 69.0, 72.0, 75.1, 75.6, 77.2, 78.6, 100.9, 126.5, 127.1, 127.3, 123.3, 127.4, 127.4, 145.3, 148.9, 167.1. MS (EI, 70 eV): m/z (%) 800 (26, [M^+]), 600 (70), 356 (100), 327 (30), 298 (958), 105 (20). IR (KBr): $\nu = 2957$, 1652, 700. HRMS Calc. for $C_{50}H_{52}N_2O_4Fe$: 800.3276. Found: 800.3275.

4.2. (S,S)-1,1′-bis-[N-(1-tert-Butyl-2-hydroxyethyl)-amido]ruthenocene (8)

A suspension of 1.00 g (3.13 mmol) of 1,1′-ruthenocenedicarboxylic acid (**7**) in 15 ml of dichloromethane is treated with 2.18 ml (25.06 mmol) of oxalyl chloride. Three drops of pyridine are added and the mixture is refluxed under ultrasonic irradiation until it becomes a clear solution (ca. 3 h). The solvent is removed into a trap, the residue is dried for 2 h and dissolved in 10 ml of dichloromethane. The solution is added slowly via cannula to a mixture of 1.31 g (11.11 mmol) of (*S*)-*tert*-leucinol and 2.30 ml (16.42 mmol) of triethylamine in 10 ml of dichloromethane. After stirring at ambient temperature overnight 20 ml of water are added. The organic layer is separated and the aqueous layer is extracted with dichloromethane (3×20 ml). The combined organic phases are dried ($MgSO_4$), evaporated and purified by column chromatography (silica gel; ethylacetate) to yield 931 mg (57%) of the title compound as a light yellow solid. m.p. 243–245°C (dec). $[\alpha]_D = -148°$ [$c = 1.0$, $CHCl_3$]. ^{1}H-NMR ($CDCl_3$): δ 0.95 (s, 18H), 3.57–4.10 (m, 6H), 4.75 (b, 4H), 4.83 (b, 2H), 5.20 (b, 2H), 5.91–6.00 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 26.9, 34.4, 58.8, 61.3, 77.8, 72.1, 73.2, 73.5, 82.2, 168.7. MS (EI, 70 eV): m/z (%) 518 (3, [M^+]), 402 (35), 303 (71), 257 (56), 231 (55), 86 (99), 60 (100). IR (KBr): $\nu = 3334$, 2963, 1626, 1539. HRMS Calc. for $C_{18}H_{22}NO_3Ru$ ($C_{24}H_{36}N_2O_4Ru$–$C_6H_{14}NO$): 402.0637. Found: 402.0638.

4.3. (S,S)-1,1′-bis-[4-tert-Butyl-oxazolin-2-yl]-ruthenocene (9)

To a solution of 822 mg (1.59 mmol) of **8** in 60 ml of acetonitrile is added 3.1 g (11.80 mmol) of triphenylphosphine, 2.0 ml of triethylamine and 2.6 ml of tetrachloromethane. The mixture is stirred overnight at ambient temperature, then quenched with 100 ml of water and extracted with diethylether (4×80 ml). The collected organic layers are dried ($MgSO_4$) and evaporated. Purification by column chromatography (silica gel; pentane:diethylether = 1:2) yields 605 mg (79%) of the title compound as a light yellow solid. m.p. 191–193°C. $[\alpha]_D = -117°$ [$c = 1.0$, $CHCl_3$]. ^{1}H-NMR ($CDCl_3$): δ 0.90 (s, 18H), 3.80 (dd, $J = 7.1$ Hz, 9.2 Hz, 2H), 4.04–4.20 (m, 4H), 4.67 (b, 4H), 5.05 (b, 2H), 5.15 (b, 2H). ^{13}C-NMR ($CDCl_3$): δ 25.8, 33.9, 68.2, 72.0, 72.2, 73.3, 73.3, 75.9, 75.9, 163.8. MS (EI, 70 eV): m/z (%) 482 (21, [M^+]), 425 (100), 325 (53). IR (KBr): $\nu = 3433$, 2960, 2225, 1660, 1483. HRMS Calc. for $C_{24}H_{32}N_2O_2Ru$: 482.1501. Found: 482.1503.

4.4. (S,S,R_p,R_p)-1,1′-bis-[4-tert-Butyloxazolin-2-yl]-2,2′-bis(diphenylhydroxymethyl)ruthenocene (10)

To a solution of 100 mg (0.21 mmol) of **9** in 4 ml of tetrahydrofuran is added 0.42 ml (0.54 mmol) of *sec*-butyllithium at −78°C. After stirring the mixture at this temperature for 2 h, and then at 0°C for 20 min, 100 mg (0.55 mmol) of benzophenone is added in one portion. The reaction is quenched after 2 h at 0°C with 10 ml of water and extracted with diethylether (3×10 ml). The collected organic layers are dried ($MgSO_4$) and evaporated. The crude product is obtained in a diastereomeric ratio of 9:1. Purification by flash chromatography (silica gel; pentane:diethylether = 6:1) yields 130 mg (74%) of the title compound as a light yellow syrup. $[\alpha]_D = -179°$ [$c = 1.0$, $CHCl_3$]. ^{1}H-NMR ($CDCl_3$): δ 0.90 (s, 18H), 3.50–3.60 (m, 2H), 3.84 (b, 2H), 3.98–4.15 (m, 4H), 5.01 (b, 2H), 5.15 (b, 2H), 6.90–7.30 (m, 20H), 8.90 (s, 2H). ^{13}C-NMR ($CDCl_3$): δ 26.4, 33.9, 69.2, 73.1, 74.2, 75.5, 77.1, 77.1, 81.8, 105.4, 126.4, 126.6, 126.9, 127.2, 127.3, 127.8, 145.5, 148.5, 166.4. MS (EI, 70 eV): m/z (%) 847 (15, [M^+]), 829 (26), 75 (55), 287 (22), 183 (28), 105 (100). IR (KBr): $\nu = 3086$, 2960, 1656, 1448. HRMS Calc. for $C_{50}H_{52}N_2O_4Ru$: 846.2964. Found: 846.2964.

4.5. Standard procedure for the asymmetric phenyl transfer to aldehydes

In a glovebox, a well-dried Schlenk flask is charged with diphenylzinc (36 mg, 0.16 mmol). The flask is sealed and removed from the glovebox. Freshly distilled toluene (3 ml) is added, followed by diethylzinc (33 μl, 0.33 mmol). After stirring for 30 min at room temperature the metallocene is added and the resulting solution

is cooled to 10°C. Stirring is continued for additional 10 min at this temperature, and then the aldehyde (0.25 mmol) is added in one portion. The Schlenk flask is sealed and the reaction mixture stirred at 10°C overnight. The solution is quenched with water, extracted with diethylether (3×10 ml), dried ($MgSO_4$) and evaporated. Column chromatography (silica gel; eluent: pentane/diethylether) affords the pure secondary alcohol.

4.6. HPLC analysis of the secondary alcohols

α-(4-Chlorophenyl)phenylmethanol (**5a**): Chiralcel OB, heptane/*i*-PrOH, 80:20, 0.9 ml min^{-1}, (*R*): 8.8, (*S*): 13.3 min.

α-(3-Methoxyphenyl)phenylmethanol (**5b**): Chiralcel OD, heptane/*i*-PrOH, 95:5, 0.8 ml min^{-1}, (*S*): 35.0, (*R*): 54.3 min.

1,3-Diphenyl-1-propanol (**5c**): Chiralcel OD, heptane/*i*-PrOH, 95:5, 0.9 ml min^{-1}, (*S*): 24.3, (*R*): 27.3 min.

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