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Diastereoselective addition of organozinc and organomagnesium reagents to 2-(2′-pyrimidyl)ferrocenecarbaldehyde

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Abstract

Addition of diisopropylzinc, diethylzinc, and isopropylmagnesium chloride to readily available 2-(2′-pyrimidyl)ferrocenecarbaldehyde takes place with high diastereoselectivity to afford exclusively the α-ferrocenyl alcohol of (*R**,p*R**) configuration. On the other hand, the addition of ethyl- and methylmagnesium bromide leads to diastereomeric mixtures in which the major isomer has the (*S**,p*R**) configuration. A unified mechanistic model accounting for this stereochemical outcome is proposed.

Keywords: Addition reactions; Asymmetric synthesis; Metallocenes; Organometallic reagents; Stereoselectivity

1. Introduction

Chiral ferrocene derivatives have been finding increasing application as ligands for asymmetric catalysis.[1] While the diastereoselective metalation of enantiopure ferrocene derivatives bearing stereogenic atoms at the α-position has been widely used for the stereocontrolled preparation of ligands with planar chirality,[2] the reverse strategy—i.e., the use of preexisting planar chirality in the stereoselective generation of α-ferrocenyl stereogenic centers—has been applied only in a limited number of instances.[3,4] In 1996, Brocard et al.[3a] studied the addition of ethyllithium, ethylmagnesium bromide, and diethylzinc to aldehyde **1** (Fig. 1). In all cases, the major diastereomer showed a (*R**,p*R**) configuration, and the diastereoselectivity increased from lithium (9:1 dr) to zinc (>99:1 dr). Later on, Fukuzawa and co-workers[3b,c] undertook a more detailed study of organometallic reagents to the enantioenriched aldehyde **2**. Both the yield and the diastereoselectivity were dependent on the nature of the organometallic reagent, but in all instances the major diastereomer was the (1*S*,2*R*,p*R*) one. However, when the same group used the structurally similar aldehyde **3**, the stereochemical outcome of the addition of dialkylzinc reagents was opposite to that of organolithium and organomagnesium compounds (2*S* vs 2*R* for the newly created stereocenter, respectively).[3d] Richards et al.[3e] have reported that the addition of Grignard reagents to aldehydes **4** and **5** takes place with moderate (2.7:1 dr) to high diastereoselectivities (45:1 dr), giving predominantly rise to alcohols of (*S**,p*S**) relative configuration. Very recently, Loh et al., have found that the zinc-mediated

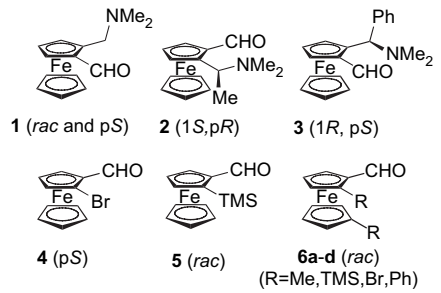

Figure 1. 2-Substituted ferrocenecarbaldehydes previously used in studies on the addition of organometallic reagents.

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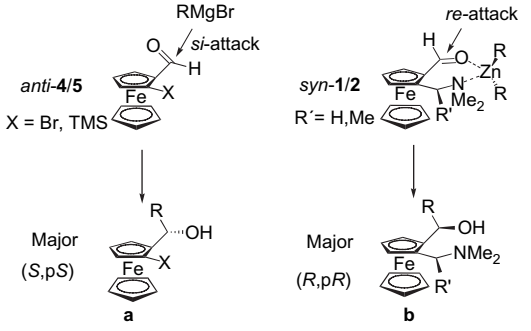


Figure 2. (a) Origin of Grignard addition selectivity to aldehydes **4** and **5**, according to Ref. 3e. (b) Chelation of the amino and the formyl group to zinc explains the organozinc addition selectivity to aldehydes **1** and **2** (Refs. 3a,c,d).

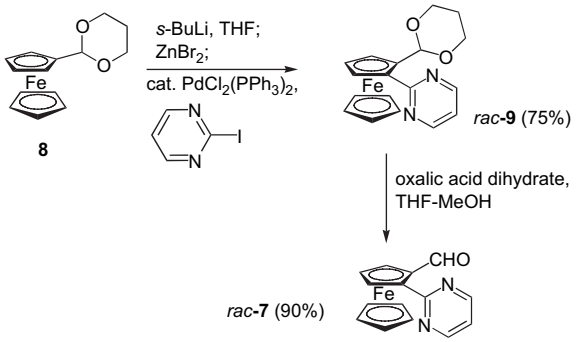
allylation of the 2,2′-disubstituted ferrocenecarbaldehydes **6a–d** takes place with the same diastereofacial selectivity.[3f]

For aldehydes **4** and **5**, the relative (*S**,p*S**) configuration of the major diastereomer agrees with an *exo* attack of the Grignard reagent to a carbonyl oriented *anti* to the α-ferrocenyl substituents in order to minimize the steric interactions (Fig. 2a);[3e,f] however, a unified mechanistic model that can rationalize the stereochemical outcome of the addition of organometallic reagents to ferrocenecarbaldehydes bearing α-nitrogenated 2-substituents, such as **1–3**, is still lacking. In fact, while Brocard et al. and, later on, Fukuzawa et al. suggested that for these aldehydes the reaction with dialkylzinc compounds takes place through activation of the organometallic species by coordination of the metal with the nitrogen atom and subsequent *exo* addition to the *syn*-oriented carbonyl group (Fig. 2b),[3a–c] the variable diastereoselectivities observed in the addition of methyl, ethyl, and phenyl Grignard reagents to aldehydes **2** and **3** cannot be easily rationalized.

We report herein our studies on the addition of diorganozinc and Grignard reagents to 2-(2′-pirimidyl)ferrocenecarbaldehyde (**7**), a planar chiral formylferrocene in which the 2-substituent, contrary to the previously investigated aldehydes **1–3**, has an sp^2-hybridized nitrogen atom that can coordinate to the organometallic reagent. As we shall see, the addition of diorganozinc reagents is completely diastereoselective, while the stereochemical outcome of the reaction with Grignard reagents depends markedly on the size of the alkyl residue.

2. Results and discussion

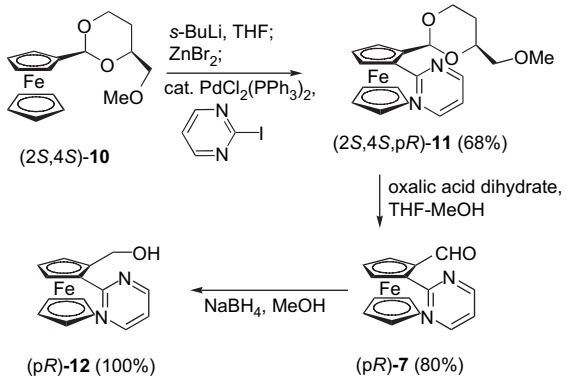
In the course of a research project devoted to the study of asymmetric autocatalysis,[5] we developed a short and efficient synthesis of 2-(2′-pyrimidyl)-ferrocenecarbaldehyde (**7**), both in racemic and in highly enantioenriched form, and we found that this compound readily reacts with diisopropylzinc to give the corresponding isopropyl alcohol with essentially complete diastereoselectivity. We decided to investigate the behavior of **7** toward other organometallic reagents. The synthesis of *rac*-**7** is summarized in Scheme 1.



Scheme 1. Preparation of aldehyde **7** in racemic form.

Following a literature procedure,[6] commercially available ferrocenecarbaldehyde was acetalized with 1,3-propanediol to afford the dioxane **8** in 90% yield. After some experimentation, we found that optimal conditions for the one-pot lithiation/transmetallation/Negishi coupling[7] involved treatment of **8** with 1.2 equiv of *sec*-butyllithium in tetrahydrofuran at low temperature, addition of 1.2 equiv of zinc bromide, and reaction with 2-iodopyrimidine[8] with $PdCl_2(PPh_3)_2$ as precatalyst. Using this protocol, the coupling product **9** was isolated in 75% yield after chromatographic purification. Finally, mild acidic hydrolysis of **9** (oxalic acid dihydrate in tetrahydrofuran–methanol)[9] afforded the desired aldehyde **7** in 90% yield.

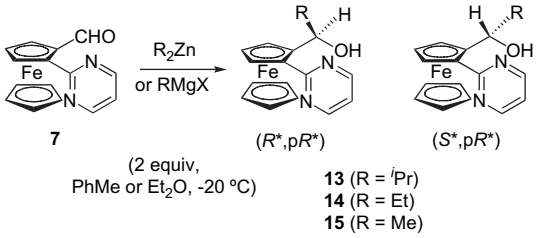
In a similar way (Scheme 2), the Negishi coupling of the organozinc reagent obtained by the diastereoselective lithiation/transmetallation of Kagan's chiral acetal **10**,[10] followed by acetal cleavage, afforded the scalemic aldehyde (p*R*)-**7** in good overall yield. After reduction with sodium borohydride to the alcohol **12**, HPLC analysis of this compound on a Chiralcel® OD column established a 94:6 er for (p*R*)-**7**.



Scheme 2. Enantioselective synthesis of aldehyde (p*R*)-**7**.

The reaction of **7** with diisopropylzinc (2 equiv) was next examined. In toluene solution at 0 °C, the reaction was complete in less than 2 h, giving rise to a single diastereomer (both by NMR and by HPLC). When the reaction temperature was lowered to −20 °C, no starting aldehyde remained after 5 h, a single isomeric alcohol **13** being again obtained in almost quantitative yield. Under the same conditions,

ferrocenecarbaldehyde gave less than 7% conversion. Both the reactivity and the stereoselectivity of the diisopropylzinc addition to **7** suggest that the reaction is autoactivated[3a] through coordination of zinc to the aldehyde oxygen and to one of the pyrimidine nitrogens, so that the addition takes place from the *exo* face of a *syn*-oriented carbonyl. At the light of this result, we decided to investigate the behavior of *rac*-**7** toward other organometallic reagents (Scheme 3 and Table 1).



Scheme 3. Addition of dialkylzinc and Grignard reagents to **7**.

The addition of diethylzinc to *rac*-**7** also took place readily at −20 °C (entry 2 of Table 1), affording the alcohol **14** in almost quantitative yield and as a single diastereomer, in accordance with literature precedents on nitrogenated ferrocenecarbaldehydes **1**–**3**.[3a–c]

On the other hand, the stereoselectivity of the addition of Grignard reagents was clearly dependent on the size of the alkyl group: while the reaction of isopropylmagnesium chloride (entry 3) afforded the same isomer obtained with the zinc reagent (entry 1), both ethylmagnesium bromide (entry 4) and methylmagnesium bromide (entry 5) gave rise to diastereomer mixtures that could be separated by column chromatography.

The relative configuration of (*R**,p*R**)-**14** was unambiguously established by X-ray diffraction analysis of a monocrystal (Fig. 3).[11] Examination of the structure revealed the presence of an intramolecular hydrogen bond between the OH hydrogen and one of the pyrimidine nitrogens, clearly apparent in Figure 3. The O–N distance is 280.2 pm, the O–H–N angle is 141.5°, and the dihedral angle between the pyrimidyl and the upper cyclopentadienyl ring is very small (14.3°). Also in accordance with the existence of this hydrogen

Table 1
Addition of dialkylzinc and Grignard reagents to aldehyde **7**

Entry	Reagent	Product(s)	Yield[c] (%)	dr
1	$^{i}Pr_2Zn$[a]	(*R**,p*R**)-**13**	93	>30:1[d]
2	Et_2Zn[a]	(*R**,p*R**)-**14**	96	>30:1[d]
3	$^{i}PrMgCl$[b]	(*R**,p*R**)-**13**	61	>30:1[d]
4	EtMgBr[b]	(*R**,p*R**)-**14** (minor) (*S**,p*R**)-**14** (major)	87	40:60[e]
5	MeMgBr[b]	(*R**,p*R**)-**15** (minor) (*S**,p*R**)-**15** (major)	94	40:60[e]

[a] Dialkylzinc reagent (2 equiv), toluene, −20 °C, 5 h.
[b] Grignard reagent (2 equiv), diethyl ether, −20 °C, 30 min.
[c] Yield of isolated product after chromatographic purification.
[d] Only a single isomer was observed by NMR and HPLC.
[e] Determined by ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$).

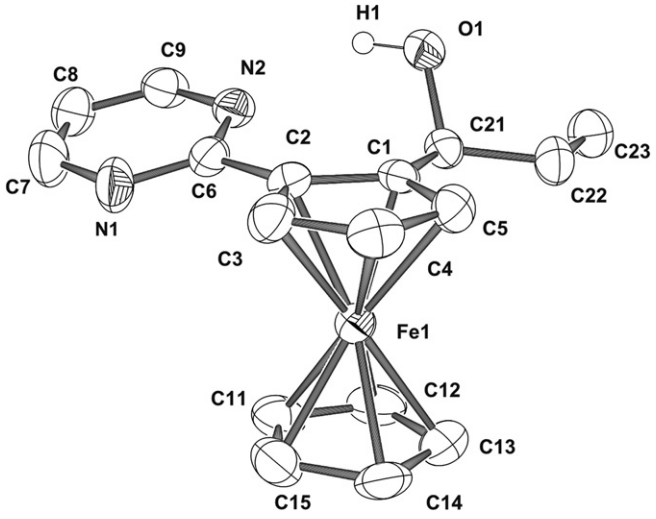


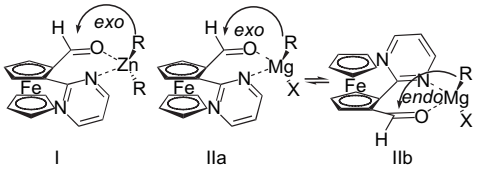
Figure 3. X-ray crystal structure of the isomer of **14** obtained in the addition of diethylzinc to *rac*-**7**. Selected bond lengths [pm] and angles [°]: Fe(1)–(upper Cp centroid): 165.0, Fe(1)–(lower Cp centroid): 166.1, O(1)–C(21): 144.1, C(1)–C(21)–O(1)–H(1) torsion angle: 70.8, (upper Cp centroid–Fe(1)–lower Cp centroid) angle: 178.8.

bond is the fact that in the ^{1}H NMR spectrum of (*R**,p*R**)-**14** the signal corresponding to the OH proton appears as a well-defined doublet (*J*=5 Hz) at 6.86 ppm.

The observed (*R**,p*R**) relative configuration of the diastereomer of **14** arising from the addition of diethylzinc to **7** is in complete agreement with the stereochemical outcome of the previously studied additions of dialkylzinc reagents to the α-nitrogenated ferrocenecarbaldehydes **1**,[3a] **2**,[3c] and **3**.[3d] We assigned therefore the same relative configuration to the alcohol **13**, and the opposite one (*S**,p*R**) to the major isomer of **14** arising from the addition of ethylmagnesium bromide. Finally, the stereochemistry of both isomers of alcohol **15** was deduced after careful comparison of their ^{1}H NMR spectra with those of (*R**,p*R**)-**14** and (*S**,p*R**)-**14**.

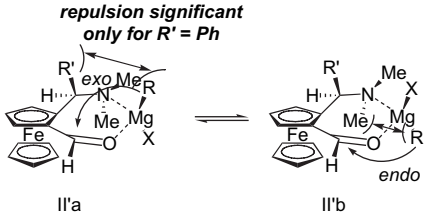
We believe that a single reaction model may account for the stereochemical outcome of the addition of both diorganozinc and Grignard reagents to **7**, as well as for the very fast reaction of the former. In particular, we suggest that additions to **7** could take place in an intramolecular fashion through a *N*,*O*-chelated intermediate, which disposes the formyl group in a *syn* orientation with regard to the 2-pyrimidyl moiety.[12,14] In the case of diorganozinc compounds, only one such intermediate is possible that leads to the exclusive formation of the (*R**,p*R**) isomer by *exo* attack of the upper R group (**I**, Scheme 4). For the addition of Grignard reagents, two different chelated intermediates (**IIa** and **IIb**, Scheme 4) are now possible. When the R group is bulkier than the halogen atom, intermediate **IIa** will be more stable than **IIb**, and intramolecular *exo* attack of R in **IIa** will lead again to the formation of the (*R**,p*R**) isomer; this is what happens in the case of isopropylmagnesium chloride. On the other hand, when X=Br and R=Et or Me, both **IIa** and **IIb** will exhibit a similar stability, and *endo* attack from intermediate **IIb** (also more favorable when R is a primary alkyl) will lead to the competitive formation of the (*S**,p*R**) diastereomer.[15] It is worth noting

here that the non-chelated addition to the formyl group that would explain the production of this isomer by a sterically preferred *exo* attack of the Grignard reagent to a carbonyl oriented *anti* to the 2-pyridyl substituent (cf. Fig. 2a),[3e,f] cannot easily rationalize the fact that with isopropylmagnesium chloride only the (*R**,p*R**) isomer is obtained.[17]



Scheme 4. Proposed origin of addition selectivity to **7**.

Moreover, this mechanistic model could help to rationalize the otherwise puzzling comparative behavior of aldehydes **1**, **2**, and **3** toward Grignard reagents:[3a–d] while in the case of both **1** and **2** the major isomer of the addition product has always an (*R**,p*R**) relative configuration, the opposite one (*S**,p*R**) is observed for **3**. The coordination model can explain satisfactorily this observation (Scheme 5); when the R′ substituent is small (R′=H or Me), the **II′b** chelated intermediate is destabilized with respect to **II′a**, by the steric repulsion between the *endo N*-Me and R groups, and *exo* attack from **II′a** leads to the predominant formation of the (*R**,p*R**) diastereomer. Only in the case of **3** (R′=Ph) the 1,3-diaxial interaction between R and R′ destabilizes the **II′a** intermediate with respect to **II′b**, and *endo* attack from the latter, leading to the (*S**,p*R**) isomer, becomes competitive.



Scheme 5. Proposed origin of the Grignard addition selectivity to aldehydes **1** (R′=H), **2** (R′=Me), and **3** (R′=Ph).

3. Conclusions

In summary, we have seen that aldehyde **7**, readily prepared in racemic or in highly enantioenriched form, undergoes addition of dialkylzinc compounds and secondary Grignard reagents in a totally diastereoselective fashion. The use of the resulting alcohols **13** and **14**, as well as that of the purely planar chiral compound **12**, as chiral ligands for asymmetric catalysis[19] is currently being evaluated in our laboratories. Finally, a mechanistic rationalization of the stereochemical outcome of the addition of organometallic reagents to planar chiral ferrocenecarbaldehydes bearing α-nitrogenated substituents at the 2-position, like **1**, **2**, **3**, and **7**, has been proposed.

4. Experimental section

4.1. General materials and methods

Melting points were taken on an Electrothermal apparatus and have not been corrected. Infrared spectra were recorded in a Fourier transform mode on a Nicolet 510 FT spectrometer, using NaCl film techniques. Only the most representative wavenumbers (cm^{-1}) are reported. NMR spectra were recorded in $CDCl_3$ solution. ^1H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were obtained on a Varian-Unity spectrometer; ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were obtained on a Varian-Mercury spectrometer. Chemical shifts (δ) are quoted in parts per million and referenced to internal TMS for ^1H NMR and to $CDCl_3$ (δ 77.0) for ^{13}C NMR; data are reported as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; coupling constants (*J*) are quoted in hertz. Low resolution chemical ionization mass spectra were recorded on a HP-5988 A spectrometer. High resolution mass spectra (HRMS) were obtained from the 'Servei de Espectrometría de Masses, Serveis Científico-Tècnics de la Universitat de Barcelona', using electron-spray ionization (ESI) techniques. Reactions were run in flame- or oven-dried glassware under a N_2 atmosphere. Commercially available reagents were employed as-received, with the exception of zinc bromide that was anhydrized prior to use by heating under vacuum (250 °C, 1 mmHg) in a round-bottomed flask that was cooled with a stream of argon and subsequently dissolved in dry THF. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium-benzophenone ketyl. Toluene was dried by storing over sodium wire. Acetals **8** and **10** were obtained according to literature procedures.[6,10] 2-Iodopyrimidine was prepared from 2-chloropyrimidine and aqueous hydriodic acid as described by Vlád and Horváth.[8]

4.1.1. *rac*-2-(2′-Pyrimidyl)ferrocenecarbaldehyde (*rac*-**7**)

To a cold (−78 °C) solution of 2-ferrocenyl-1,3-dioxane **8**[6] (670 mg, 2.46 mmol) in anhydrous THF (10 mL) under argon was added 2.4 mL of *sec*-butyllithium (1.24 M in hexanes, 2.95 mmol). After 10 min at −78 °C and 1 h at −30 °C, a solution of anhydrous zinc bromide (665 mg, 2.95 mmol) in dry THF (5 mL) was added with the aid of a cannula. After 10 min at −30 °C and 1 h at rt, the resulting mixture was added dropwise to a solution of 2-iodopyrimidine[8] (608 mg, 2.95 mmol) and $PdCl_2(PPh_3)_2$ (86 mg, 0.12 mmol) in anhydrous THF (15 mL), and the resulting mixture was stirred overnight under reflux. After cooling to rt, the reaction mixture was treated with brine (10 mL) and the aqueous phase was washed with ethyl acetate (3×10 mL). The combined organic extracts were dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. Chromatographic purification (SiO_2/NEt_3 10% v/v, hexanes/ethyl acetate) afforded 510 mg (75% yield) of *rac*-2-(2′-pyrimidyl)ferrocenyl-1,3-dioxane (**9**) as an orange-colored oil. IR (thin film) ν_{max}=3079, 2971, 2949, 1497, 1456, 1384, 1241, 1113, 1103, 1000, 821 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.62 (d,

J=4.8 Hz, 2H), 7.02 (t, J=4.8 Hz, 1H), 6.48 (s, 1H), 5.13 (m, 1H), 4.79 (m, 1H), 4.44 (m, 1H), 4.32 (dd, J=12.1 Hz, J'=4.8 Hz, 1H), 4.0–4.2 (m, 3H+s, 5H), 2.1–2.3 (m, 1H), 1.3–1.5 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.2 (C), 156.8 (2CH), 117.4 (CH), 100.3 (CH), 86.9 (C), 79.5 (C), 70.8 (CH), 70.7 (5CH), 70.2 (CH), 69.8 (CH), 67.8 (CH_2), 67.6 (CH_2), 26.2 (CH_2). MS (CI, NH_3): m/z=351 ([M+1]$^+$, 100%).

A mixture of *rac*-**9** (825 mg, 2.4 mmol) and oxalic acid dihydrate (1.96 g, 15.5 mmol) in 3:1 THF/MeOH (20 mL) was stirred at rt for 1 h. After cooling to 0 °C, a saturated aqueous solution of $NaHCO_3$ was added dropwise until no effervescence was observed. The mixture was filtered through a short pad of Celite® and washed with brine (10 mL). The aqueous phase was extracted with ethyl acetate (3×10 mL) and the combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents gave a crude product that was purified by column chromatography (silica gel, hexanes/ethyl acetate, 1:1) to give 614 mg (90% yield) of *rac*-**7** as an orange-colored solid. Mp 85–90 °C. IR (KBr) ν_{max}=2974, 1672, 1556, 1475, 810 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=11.13 (s, 1H), 8.67 (d, J=4.8 Hz, 2H), 7.13 (t, J=4.8 Hz, 1H), 5.51 (m, 1H), 5.20 (m, 1H), 4.84 (m, 1H), 4.20 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.1 (CH), 168.8 (C), 157.1 (2CH), 118.3 (CH), 84.7 (C), 79.7 (C), 75.6 (CH), 73.6 (CH), 71.5 (5CH), 71.1 (CH). MS (CI, NH_3): m/z=293 ([M+1]$^+$, 100%). HRMS (ESI): m/z calcd for $C_{15}H_{13}FeN_2O$: 293.0372; found for [M+H]$^+$: 293.0378.

4.1.2. (pR)-2-(2′-Pyrimidyl)ferrocenecarbaldehyde [(pR)-7]

To a cold (−78 °C) solution of (2*S*,4*S*)-4-(methoxymethyl)-2-ferrocenyl-1,3-dioxane **10**[10] (1.12 g, 3.50 mmol) in anhydrous THF (10 mL) under argon was added 3.4 mL of *sec*-butyllithium (1.24 M in hexanes, 4.25 mmol). After 10 min at −78 °C and 1 h at −30 °C, a solution of anhydrous zinc bromide (960 mg, 4.25 mmol) in dry THF (5 mL) was added with the aid of a cannula. After 10 min at −30 °C and 1 h at rt, the resulting mixture was added dropwise to a solution of 2-iodopyrimidine (880 mg, 4.25 mmol) and $PdCl_2(PPh_3)_2$ (124 mg, 0.18 mmol) in anhydrous THF (10 mL), and the resulting mixture was stirred overnight under reflux. After cooling to rt, work-up and chromatographic purification as described above afforded 955 mg (68% yield) of (2*S*,4*S*,p*R*)-4-(methoxymethyl)-2-[2-(2′-pyrimidyl)ferrocenyl]-1,3-dioxane (**11**) as an orange-colored oil. IR (thin film) ν_{max}=2922, 2855, 1563, 1488, 1397, 1106, 996, 944, 817 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.61 (d, J=4.8 Hz, 2H), 7.01 (t, J=4.8 Hz, 1H), 6.51 (s, 1H), 5.11 (m, 1H), 4.80 (m, 1H), 4.43 (m, 1H), 4.3–4.4 (m, 1H), 4.0–4.2 (m, 2H+s, 5H), 3.3–3.5 (m, 2H), 3.27 (s, 3H), 1.84 (m, 1H), 1.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.1 (C), 157.1 (2CH), 117.5 (CH), 100.3 (CH), 86.7 (C), 79.8 (C), 76.5 (CH), 75.8 (CH_2), 70.8 (5CH), 70.4 (CH), 69.7 (CH), 67.3 (CH_2), 59.4 (CH_3), 28.8 (CH_2). MS (CI, NH_3): m/z=395 ([M+1]$^+$, 100%). HRMS (ESI): m/z calcd for $C_{20}H_{23}FeN_2O_3$: 395.1053; found for [M+H]$^+$: 395.1052.

A mixture of **11** (940 mg, 2.4 mmol) and oxalic acid dihydrate (1.98 g, 15.7 mmol) in 3:1 THF/MeOH (20 mL) was stirred at rt for 1 h. After cooling to 0 °C, a saturated aqueous solution of $NaHCO_3$ was added dropwise until no effervescence was observed. The mixture was filtered through a short pad of Celite® and washed with brine (10 mL). The aqueous phase was extracted with ethyl acetate (3×10 mL) and the combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents gave a crude product that was purified by column chromatography (silica gel, hexanes/ethyl acetate, 1:1) to give 545 mg (80% yield) of (p*R*)-**7** as an orange-colored solid. $[\alpha]_D$ +30.0 (*c* 1.10, $CHCl_3$; er=94:6).

4.1.3. rac-2-(2′-Pyrimidyl)ferrocenylmethanol (rac-12)

To a stirred solution of the ferrocenylcarbaldehyde *rac*-**7** (50 mg, 0.17 mmol) in methanol (2 mL), sodium borohydride (6.4 mg, 0.17 mmol) was added in one portion and the resulting solution was stirred at rt for 20 min (TLC monitoring). After cooling down to 0 °C, aqueous saturated ammonium chloride (4 mL) was added dropwise, and the reaction mixture was extracted with diethyl ether (2×5 mL). The combined extracts were washed with water (10 mL) and with brine (10 mL), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The title compound (50 mg, quant. yield) was obtained as an orange-colored solid. Mp 70–72 °C. IR (KBr) ν_{max}=3359, 3091, 2927, 1571, 1554, 1484, 1455, 1399, 1000, 811 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.64 (d, J=4.9 Hz, 2H), 7.09 (t, J=4.9 Hz, 1H), 5.91 (t, J=6.0 Hz, 1H), 5.17 (m, 1H), 4.71 (dd, J=12.7 Hz, J'=5.8 Hz, 1H), 4.47 (m, 1H), 4.40–4.50 (m, 1H), 4.41 (m, 1H), 4.13 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.3 (C), 157.0 (2CH), 117.4 (CH), 89.5 (C), 80.2 (C), 73.6 (CH), 71.8 (CH), 70.3 (5CH), 69.1 (CH), 60.2 (CH_2). MS (CI, NH_3): m/z=295 ([M+1]$^+$, 100%); 277 ([M−17]$^+$, 97%). HRMS (ESI): m/z calcd for $C_{15}H_{14}FeN_2NaO$: 317.0347; found for [M+Na]$^+$: 317.0347; m/z calcd for $C_{15}H_{13}FeN_2$: 277.0422; found for [M−OH]$^+$: 277.0422.

4.1.4. (pR)-2-(2′-Pyrimidyl)ferrocenylmethanol [(pR)-12]

Prepared by the same method as above in 100% yield from (p*R*)-**7** (0.07 mmol) and from sodium borohydride (0.07 mmol). Orange-colored solid. $[\alpha]_D$ +2.0 (*c* 0.5, $CHCl_3$; er=94:6).

The enantiomeric purity for this compound was established by HPLC (Chiralcel® OD column, 7:3 hexane/isopropyl alcohol, 0.7 mL min^{-1}, λ=254 nm; t_R(p*S*): 10.9 min, t_R(p*R*): 19.6 min).

4.1.5. (1R*,pR*)-1-(2-(2′-Pyrimidyl)ferrocenyl)isobutanol (rac-13)

To a cold (−20 °C), stirred solution of *rac*-**7** (80 mg, 0.27 mmol) in dry toluene (5 mL) under argon was added 0.55 mL of diisopropylzinc (1 M in toluene, 0.55 mmol). After 5 h at −20 °C (TLC monitoring), 1 M aqueous HCl (3 mL) was added, and the reaction mixture was allowed to warm up to rt. The pH of the solution was adjusted to 7 by slow addition of 1 M aqueous NaOH. The reaction mixture was

filtered through a small pad of Celite® in order to remove the precipitate of zinc chloride, the phases were separated and the aqueous one was extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. Chromatographic purification (SiO_2, 9:1 hexanes/ethyl acetate) afforded 80 mg (87% yield) of *rac*-**13** as an orange-colored oil. IR (thin film) ν_{max}=3249, 3094, 2956, 1570, 1473, 1399, 1257, 1041, 815 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.62 (d, J=4.8 Hz, 2H), 7.47 (d, J=10.1 Hz, 1H, OH), 7.07 (t, J=4.8 Hz, 1H), 5.17 (m, 1H), 4.44 (m, 1H), 4.40 (m, 1H), 4.15 (s, 5H), 4.07 (dd, J=10.1 Hz, J′=7.4 Hz, 1H), 1.75 (m, 1H), 1.01 (d, J=6.7 Hz, 3H), 0.71 (d, J=6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.2 (C), 156.7 (2CH), 117.1 (CH), 91.5 (C), 80.2 (C), 76.7 (CH), 74.4 (CH), 70.6 (CH), 70.4 (5CH), 69.0 (CH), 36.3 (CH), 20.7 (CH_3), 19.5 (CH_3). MS (CI, NH_3): m/z=337 ($[M+1]^+$, 28%), 319 ($[M-17]^+$, 100%). HRMS (ESI): m/z calcd for $C_{18}H_{20}FeN_2O$: 336.0919; found for M^+: 336.0919; m/z calcd for $C_{18}H_{19}FeN_2$: 319.0892; found for $[M-OH]^+$: 319.0900.

The same compound was obtained in 61% yield (49 mg) by reaction of *rac*-**7** (70 mg, 0.24 mmol) with isopropylmagnesium chloride (2 M in diethyl ether, 0.48 mmol) in anhydrous diethyl ether (3 mL) at −20 °C during 30 min, after usual work-up and chromatographic purification.

*4.1.6. (1R,pR)-1-(2-(2′-Pyrimidyl)ferrocenyl)isobutanol [(1R,pR)-**13**]*

Prepared by the same method as above in 95% yield from p*R*-**7** (0.27 mmol) and 1 M diisopropylzinc in toluene (0.35 mmol). Orange-colored solid. $[\alpha]_D$ +217.1 (*c* 0.12, $CHCl_3$; er=94:6).

The enantiomeric purity for this compound was established by HPLC (Chiralcel® OD column, 9:1 hexane/isopropyl alcohol, 0.5 mL min^{-1}, λ=254 nm; t_R(1*S*,p*S*): 6.9 min, t_R(1*R*,p*R*): 9.9 min).

4.1.7. (1R,pR*)-1-(2-(2′-Pyrimidyl)ferrocenyl)propanol [(1R*,pR*)-**14**]*

To a cold (−20 °C), stirred solution of *rac*-**7** (100 mg, 0.34 mmol) in dry toluene (5 mL) under argon was added 0.63 mL of diethylzinc (1.1 M in toluene, 0.68 mmol). After 5 h at −20 °C (TLC monitoring), 1 M aqueous HCl (4 mL) was added, and the reaction mixture was allowed to warm up to rt. The pH of the solution was adjusted to 7 by slow addition of 1 M aqueous NaOH. The reaction mixture was filtered through a small pad of Celite® in order to remove the precipitate of zinc chloride, the phases were separated and the aqueous one was extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. Chromatographic purification (SiO_2, 9:1 hexanes/ethyl acetate) afforded 105 mg (96% yield) of the title compound. Orange-colored solid. Mp 101–105 °C. IR (KBr) ν_{max}=3274, 3094, 2958, 1572, 1555, 1480, 1398, 1106, 811 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.65 (d, J=4.8 Hz, 2H), 7.10 (t, J=4.8 Hz, 1H), 6.86 (d, J=5 Hz, 1H, OH), 5.17 (m, 1H), 4.55 (m, 1H), 4.47 (m, 1H), 4.42 (m, 1H), 4.12 (s, 5H), 1.82 (q, J=6.8 Hz, 2H), 1.04 (t, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.4 (C), 156.8 (2CH), 117.3 (CH), 93.8 (C), 78.8 (C), 72.2 (CH), 71.7 (CH), 71.5 (CH), 70.5 (5CH), 69.2 (CH), 30.5 (CH_2), 11.6 (CH_3). MS (CI, NH_3): m/z=323 ($[M+1]^+$, 13%), 305 ($[M-17]^+$, 100%). HRMS (ESI): m/z calcd for $C_{17}H_{18}FeN_2O$: 322.0763; found for M^+: 322.0757; m/z calcd for $C_{17}H_{17}FeN_2$: 305.0735; found for $[M-OH]^+$: 305.0740.

4.1.8. (1S,pR*)/(1R*,pR*)-1-(2-(2′-Pyrimidyl)ferrocenyl)-propanol by addition of ethylmagnesium bromide to rac-**7***

To a cold (−20 °C), stirred solution of *rac*-**7** (60 mg, 0.21 mmol) in anhydrous THF (5 mL) under argon was added 0.14 mL of ethylmagnesium bromide (3 M in diethyl ether, 0.42 mmol). After stirring for 30 min at the same temperature (TLC monitoring), the reaction mixture was warmed up to 0 °C, treated with aqueous saturated ammonium chloride (5 mL), and extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated under reduced pressure, to give 57 mg (87% yield) of the product **14** as a 3:2 diastereomer mixture (by NMR). Chromatographic purification (SiO_2, toluene/ethyl acetate mixtures of increasing polarity) allowed the partial separation of diastereomers.

Spectral data of the minor isomer coincided with those obtained before for (1*R**,p*R**)-**14**, so that we assigned the (1*S**,p*R**) relative configuration to the major isomer. IR (KBr) ν_{max}=3276, 3094, 2960, 1571, 1555, 1479, 1398, 1106, 1037, 1002, 811 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.64 (d, J=4.9 Hz, 2H), 7.08 (t, J=4.9 Hz, 1H), 6.58 (br s, 1H, OH), 5.17 (m, 1H), 4.58 (m, 1H), 4.57 (m, 1H), 4.42 (m, 1H), 4.19 (s, 5H), 1.91 (q, J=7.2 Hz, 2H), 1.16 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.7 (C), 156.9 (2CH), 117.3 (CH), 96.8 (C), 78.5 (C), 71.8 (CH), 70.3 (5CH), 70.2 (CH), 68.7 (CH), 67.8 (CH), 28.8 (CH_2), 11.4 (CH_3).

4.1.9. (1S,pR*)/(1R*,pR*)-1-(2-(2′-Pyrimidyl)ferrocenyl)-ethanol by addition of methylmagnesium bromide to rac-**7***

To a cold (−20 °C), stirred solution of *rac*-**7** (240 mg, 0.82 mmol) in anhydrous THF (4 mL) under argon was added 0.41 mL of methylmagnesium bromide (3 M in diethyl ether, 1.24 mmol). After stirring for 30 min at the same temperature (TLC monitoring), the reaction mixture was warmed up to 0 °C, treated with aqueous saturated ammonium chloride (5 mL), and extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated under reduced pressure, to give 242 mg (94% yield) of the product **15** as a 3:2 diastereomer mixture (by NMR). Chromatographic purification (SiO_2, toluene/ethyl acetate mixtures of increasing polarity) allowed the partial separation of diastereomers.

4.1.9.1. (1S,pR*)-1-(2-(2′-Pyrimidyl)ferrocenyl)ethanol (major isomer).* IR (KBr) ν_{max}=3274, 3097, 2971, 2925, 1573, 1556, 1478, 1398, 1107, 811 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.63 (d, J=4.8 Hz, 2H), 7.10 (t, J=4.8 Hz, 1H), 7.09 (br s, 1H, OH), 5.18 (m, 1H), 4.80 (q, J=5.2 Hz, 1H),

4.53 (m, 1H), 4.41 (m, 1H), 4.21 (s, 5H), 1.58 (d, J=5.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5 (C), 156.8 (2CH), 117.2 (CH), 97.3 (C), 78.1 (C), 72.4 (CH), 70.5 (CH), 70.2 (5CH), 68.7 (CH), 62.5 (CH), 21.7 (CH_3).

4.1.9.2. (1R,pR*)-1-(2-(2′-Pyrimidyl)ferrocenyl)ethanol (minor isomer).* IR (KBr) ν_{max}=3299, 3069, 2958, 2924, 1572, 1557, 1482, 1398, 1291, 1105, 811 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.65 (d, J=4.8 Hz, 2H), 7.11 (t, J=4.8 Hz, 1H), 6.49 (br s, 1H, OH), 5.19 (m, 1H), 5.05 (br m, 1H), 4.52 (m, 1H), 4.43 (m, 1H), 4.09 (s, 5H), 1.58 (d, J=5.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.0 (C), 156.9 (2CH), 117.4 (CH), 93.1 (C), 80.1 (C), 72.6 (CH), 70.5 (CH), 69.2 (5CH), 68.4 (CH), 65.3 (CH), 21.7 (CH_3). MS (CI, NH_3): m/z=309 ($[M+1]^+$, 86%), 291 ($[M-17]^+$, 100%). HRMS (ESI): m/z calcd for $C_{16}H_{16}FeN_2O$: 308.0606; found for M^+: 308.0606; m/z calcd for $C_{16}H_{15}FeN_2$: 291.0579; found for $[M-OH]^+$: 291.0585.

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16. As implemented in the SPARTAN® package of programs.
17. The structures depicted in Scheme 4 are purely descriptive and do not attempt to represent the actual transition states. However, inspection of molecular models show that by rotation of the formyl and 2-pyrimidyl groups the organometallic fragment can adopt a geometry[18] suitable for the intramolecular transfer of an alkyl group.
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