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1-Amino-1-ferrocenyl-2-methyl-2-propanol: a case study on the conformational control of asymmetric induction

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Abstract—Evidence gathered both from X-ray diffraction data and from molecular modelling studies suggests that the introduction of a *gem*-dimethyl moiety at C1 in 2-amino-2-ferrocenylethanol should exert strong conformational control on the ferrocenyl group when this compound is incorporated into a heterocyclic ring. In order to test this hypothesis, we have developed an efficient, enantioselective and enantiodivergent route to 1-amino-1-ferrocenyl-2-methylpropan-2-ol. According to our expectations, the corresponding 1,3-oxazolidin-2-one (Fc-'SuperQuat') exhibited excellent diastereofacial selectivity in the Diels–Alder reaction of its *N*-crotonyl derivative with cyclopentadiene, in sharp contrast to the lack of diastereoselectivity observed when using the unsubstituted 4-ferrocenyl-1,3-oxazolidin-2-one. In a similar way, the presence of a *gem*-dimethyl group at C5 in a 2-(2-diphenylphosphinophenyl)-4-ferrocenyl-1,3-oxazoline (Fc-PHOX) ligand brings about a major change in the enantioselectivity of the palladium-catalyzed asymmetric allylic substitution by dimethyl malonate anion, and leads to unprecedented (for PHOX ligands derived from acyclic 2-amino alcohols) levels of asymmetric induction in substrates such as (*E*)-1,3-dimethyl-2-propenyl and 2-cyclohexenyl acetates.

1. Introduction

Chiral non-racemic β-amino alcohols are useful building blocks for the preparation of bioactive compounds[1] and since they form the basis of many ligands and auxiliaries, their importance in asymmetric synthesis cannot be over-emphasized.[2] Very often, the degree of asymmetric induction achieved by β-amino alcohol-based auxiliaries or ligands depends on the steric hindrance exerted by the β-substituent, as attested by the numerous chiral controllers derived from *tert*-leucinol.[3,4] The number of enantiopure β-amino alcohols bearing bulky substituents at the β-position is, however, rather limited and these compounds are usually obtained either by multistep synthetic sequences from some natural products[5] or by resolution of racemic mixtures.[6]

In light of the above considerations, and taking into account both the three-dimensional nature and the characteristic reactivity of the ferrocene moiety, we recently embarked into a research program aimed at the enantiodivergent synthesis of the previously unknown 2-amino-2-ferrocenylalkanols, 3-amino-3-ferrocenyl-1,2-alkanediols and 3-amino-3-ferrocenyl-2-hydroxy acids.[7] The properties of chiral auxiliaries or ligands bearing the 2-amino-2-ferrocenylethanol moiety were expected to be highly dependent on the orientation adopted by the ferrocenyl substituent, due to its cylindrical shape. The X-ray diffraction analysis of (4*S*,5*S*)-4-ferrocenyl-5-hydroxymethyl-1,3-oxazolidin-2-one **1** (performed as a stereochemical probe in our approach to (2*S*,3*S*)-3-amino-3-ferrocenyl-2-hydroxypropionic acid)[7a] showed that in the former compound the ferrocenyl group adopts a conformation such that the interactions with the vicinal hydroxymethyl substituent are minimized and are disposed away from the heterocyclic ring, thus exerting a substantial steric hindrance on one face of the sp^2-hybridized nitrogen atom (Fig. 1a). We therefore inferred that we could efficiently direct the conformational preferences of the ferrocenyl group in heterocyclic derivatives of 2-amino-2-ferrocenylalkanols by the introduction of substituents in the adequate positions. In particular, we anticipated that the presence of a *gem*-dimethyl group at C1 would strongly destabilize any conformation in which the vicinal ferrocenyl substituent is oriented towards the heterocyclic ring (IN), thus directing the conformational preferences of the system to conformers similar to those shown in Figure 1a (OUT).

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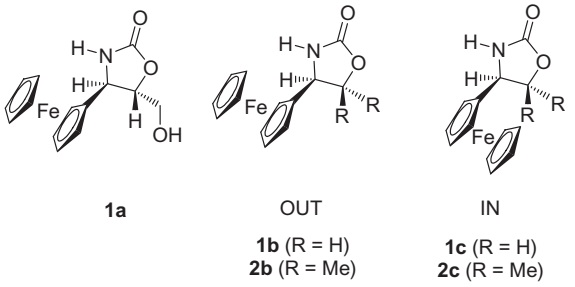


Figure 1. Compound **1a**: Solid-state conformation of 4-ferrocenyl-5-(hydroxymethyl)oxazolidinone **1**, according to X-ray diffraction data (Ref. 7a). Compounds **1b**,**c** and **2b**,**c**: Limiting conformations of 4-ferrocenyloxazolidinone and of 5,5-dimethyl-4-ferrocenyloxazolidinone **2**, respectively. In the OUT (**1b** and **2b**) conformers the ferrocenyl group is disposed away from the oxazolidinone ring, whereas in the IN (**1c** and **2c**) conformers, the same group points towards the heterocyclic moiety of the molecule.

Model theoretical calculations, performed by the semi-empirical PM3 method,[8] readily gave support to this hypothesis. Thus, whereas for 4-ferrocenyl-1,3-oxazolidin-2-one the two limiting conformers depicted in Figure 1b (OUT) and 1c (IN), respectively, differ by less than 0.6 kcal mol^{-1}, the OUT conformer of the 5,5-dimethyloxazolidinone **2** (Fig. 2b) is more stable than the IN one (Fig. 2c) by at least 3.0 kcal mol^{-1}.[9]

We report herein an efficient enantioselective synthesis of 1-amino-1-ferrocenyl-2-methyl-2-propanol **3**, as well as experimental studies on the performance of two of its derivatives in asymmetric Diels–Alder and palladium-catalyzed allylic substitution reactions, that provide clear-cut evidence on the high degree of conformational control of asymmetric induction that can be achieved by the introduction of geminal substituents at C1 in 2-amino-2-ferrocenylethanol derivatives.

2. Results and discussion

2.1. Enantioselective synthesis of 3-amino-3-ferrocenyl-2-propanol

We approached the preparation of 1-amino-1-ferrocenyl-2-methyl-2-propanol **3** in its highly enantiopure form with the belief that the methodology, which we had developed for the asymmetric synthesis of both enantiomers of 2-amino-2-ferrocenylethanol,[7a] would be easily amenable to this new target β-amino alcohol.[10] After some experimentation, we were pleased to find that this turned out to be the case and both (*R*)- and (*S*)-**3** could be readily obtained from ferrocenecarbaldehyde **4** with good overall yields and enantioselectivities. The synthetic pathway to (*R*)-**3** is summarized in Scheme 1.

1-Ferrocenyl-2-methylpropene **5**[11] could be readily secured (85–96% yield) from **4** via dehydration of the intermediate alcohol resulting from addition of the isopropyl Grignard reagent. The best conditions for the Sharpless asymmetric dihydroxylation[12] of **5**, which afforded the (*R*)-diol **6** in 82% yield and 96% ee, involved the use of $(DHQ)_2PYR$ as the chiral ligand and a 1:1 *tert*-butyl alcohol–water mixture as solvent, in accordance with the results obtained in the case of vinylferrocene.[7a,13] The treatment of (*R*)-**6** with acetic anhydride and triethylamine under 4-DMAP catalysis, and with accurate control of the reaction time produced the crude monoacetate **7**, which without further purification was submitted to nucleophilic substitution by an azide ion in aqueous methanol, thus providing the expected[14] (*R*)-azido alcohol **8** in 86% overall yield from **6**. The reduction of **8**, effected either by catalytic hydrogenation or by reaction with lithium aluminium hydride at low temperature, cleanly afforded (*R*)-1-amino-1-ferrocenyl-2-methyl-2-propanol in 93–94% yield. At this point, the enantiomeric excess of (*R*)-**3** was determined by HPLC and was shown to be identical with that of (*R*)-**6**, thus indicating that the whole synthetic sequence had taken place without detectable racemization. In a similar way, but by using $(DHQD)_2PYR$ as a ligand in the asymmetric dihydroxylation step, enantiomer (*S*)-**3** was obtained in good overall yield and high enantiomeric purity (94% ee).

Encouraged by the above results, we investigated the possibility of obtaining the 1,1′-disubstituted, C_2-symmetric analogue of **3**, hoping to take advantage from the benefits associated with performing a double asymmetric transformation in substrates bearing two homotopic prochiral functional groups.[15] To that end, 1,1′-ferrocenedicarbaldehyde **9** was treated with an excess of isopropylmagnesium chloride; without further purification, the intermediate mixture of the diastereomeric

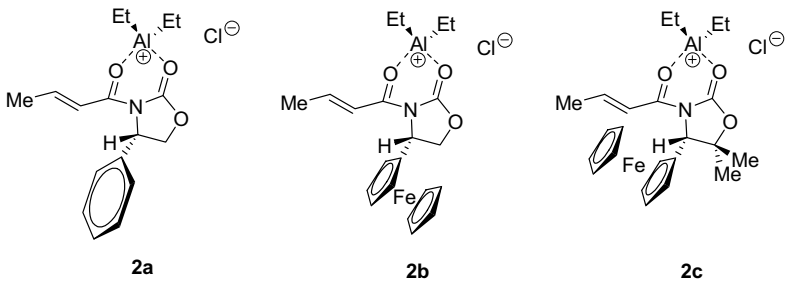
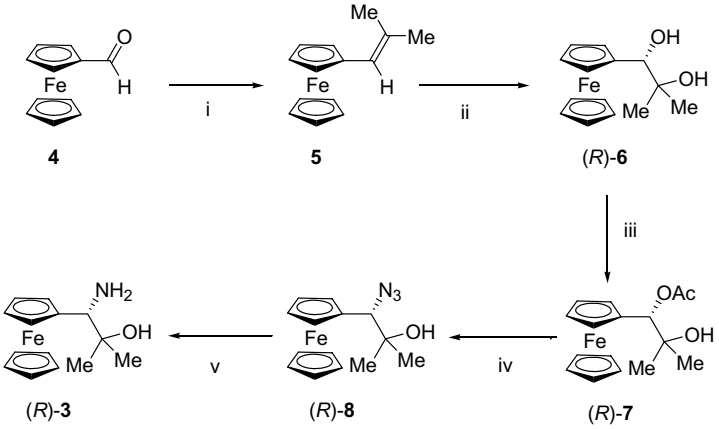
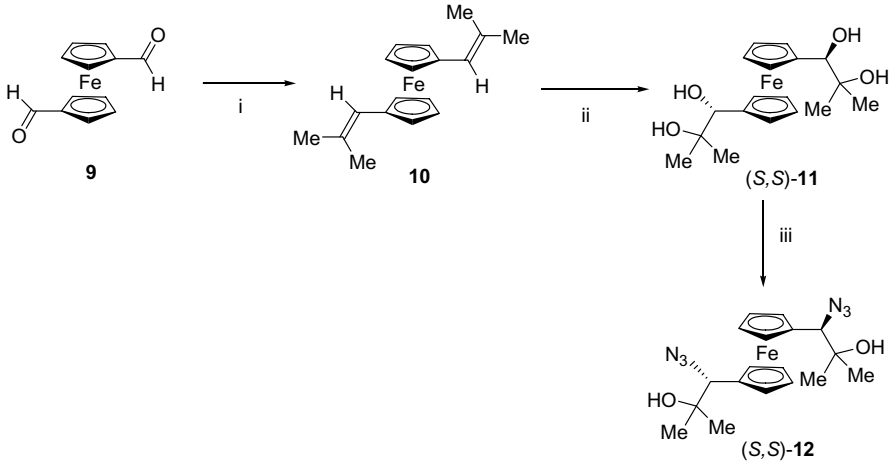


Figure 2. Compound **2a**: Reactive conformation of the aluminium-chelated complex of (*S*)-*N*-crotonyl-4-phenyloxazolidinone, according to Martinelli.[26] Compounds **2b**,**c**: Predicted reactive conformations of the aluminium-chelated complexes derived from (*R*)-**14** and from (*R*)-**15**, respectively.



Scheme 1. Reagents and conditions: (i) ^{i}PrMgCl (1.2 equiv), diethyl ether, 0 °C, 5 min; Al_2O_3, toluene, Dean–Stark, reflux, 4 h, 96%. (ii) $K_3[Fe(CN)_6]$ (3 equiv), K_2CO_3 (3 equiv), $(DHQ)_2PYR$ (0.1 equiv), $K_2OsO_2(OH)_4$ (0.04 equiv), 1:1 *tert*-butyl alcohol/water, rt, 70 min, 82% (96% ee). (iii) Ac_2O (15 equiv), 4-DMAP (0.15 equiv), pyridine, rt, 100 min, 97%. (iv) NaN_3 (11.4 equiv), 1:3 methanol/water, 60 °C, 3 h, 89%. (v) 10% Pd/C (10% in weight), H_2 (1 atm), ethyl acetate, rt, 4 h, 94% (96% ee).



Scheme 2. Reagents and conditions: (i) ^{i}PrMgCl (1.5 equiv), diethyl ether, reflux, 10 min; Al_2O_3, toluene, Dean–Stark, reflux, 75 min, 58%. (ii) $K_3[Fe(CN)_6]$ (3 equiv), K_2CO_3 (3 equiv), $(DHQD)_2PYR$ (0.075 equiv), $K_2OsO_2(OH)_4$ (0.05 equiv), 1:1 acetonitrile/water, rt, 1 h, 60% (99.2% ee). (iii) Ac_2O (23 equiv), 4-DMAP (0.17 equiv), pyridine, 50 °C, 26 h; NaN_3 (10 equiv), 1:3 methanol/water, 60 °C, 27 h, 28%.

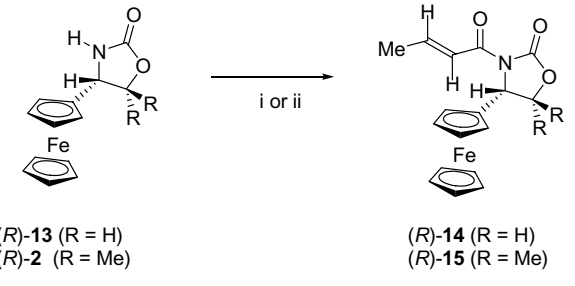
diols was submitted to dehydration with neutral alumina, to give 1,1′-bis(2-methylpropenyl)ferrocene **10** in 58% yield (Scheme 2). According to our expectations, the $(DHQD)_2PYR$-mediated asymmetric dihydroxylation of **10** furnished (*S*,*S*)-1,1′-bis(1,2-dihydroxy-2-methylpropyl)ferrocene **11** in moderate yield (60%) but with excellent enantiomeric purity (99.2% ee). The acetylation of **11** was however very difficult to control, leading invariably to a mixture of di-, tri- and tetraacetylated derivatives that upon treatment with sodium azide in aqueous methanol furnished, after chromatographic purification, the desired (*S*,*S*)-1,1′-bis(1-azido-2-hydroxy-2-methylpropyl)ferrocene **12** in disappointingly low yields (less than 30%). Due to these negative results, further investigations along these lines were not pursued.

2.2. Asymmetric Diels–Alder reactions

Chiral 4-substituted-5,5-dimethyl-1,3-oxazolidin-2-ones ('SuperQuats') were introduced by Davies as practical alternatives to Evans' oxazolidinones.[16,17] Even if the main usefulness of 'SuperQuats' is due to the fact that a *gem*-dimethyl moiety protects the oxazolidinone carbonyl from nucleophilic attack and consequently diminishes the extent of the undesired endocyclic cleavage in the removal step of the auxiliary from the elaborated *N*-acyl fragment, Davies also recognized the potential for concomitant conformational control of the C4-substituent, thus leading to enhanced degrees of facial selectivity in the reactions of *N*-acyl moieties. While as we have seen, conformational studies give support to this hypothesis,[9] only marginal increases in diastereoselectivity ascribable to the substitution of Evans' oxazolidinones by 'SuperQuats' have been observed in asymmetric processes such as enolate alkylations,[9b,18] Michael additions,[19] samarium-Reformatsky[20] and aldol[21] reactions and atom-transfer radical cyclizations,[22] the only exception being, to the best of our knowledge, some magnesium ion-mediated 1,3-dipolar cycloaddition reactions of nitrile oxides to *N*-acryloyl-4-benzyl-1,3-oxazolidin-2-ones.[23]

Chiral oxazolidinone auxiliaries have also played a pivotal role in the development of asymmetric Diels–Alder reactions.[24] In his seminal contributions to this field, Evans has demonstrated in particular that *N*-crotonyl-4-substituted-1,3-oxazolidin-2-ones derived either from norephedrine, valinol or phenylalaninol give rise to both excellent diastereoface selectivities and *endo*/*exo* ratios in their Lewis acid-catalyzed reactions with cyclopentadiene at low temperatures (−100 °C).[25] On the other hand, the phenylglycinol-based Evans' oxazolidinone is not a useful auxiliary for asymmetric Diels–Alder reactions. Martinelli[26] reported that when reacted with cyclopentadiene under a variety of conditions, its *N*-crotonyl derivative gave very high *endo* selectivity but no asymmetric induction, 1:1 mixtures of the two diastereomeric adducts being obtained in all instances. In order to account for this unexpected result,[27,28] the author suggested that in the chelated complex, the phenyl substituent adopted the conformation shown in Figure 2a, thus being unable to exert any significant facial discrimination on the dienophile. In light of the above precedents, we concluded that the chiral oxazolidinone-mediated Diels–Alder process would constitute an adequate benchmark reaction to gauge the degree of conformational control exerted by the *gem*-dimethyl group upon a vicinal ferrocenyl substituent. We anticipated that the most stable conformer of the chelated complex of *N*-crotonyl-4-ferrocenyl-1,3-oxazolidinone would be that shown in Figure 2b, which minimizes the steric interactions between the crotonyl and the ferrocenyl moieties, so that very little asymmetric induction would be observed in the reaction with cyclopentadiene; such a conformation would be strongly destabilized in the corresponding 5,5-dimethyl derivative, which would be forced to adopt a geometry similar to that depicted in Figure 2c; in this conformer, the ferrocenyl group efficiently blocks one of the faces of the dienophile, a phenomenon that should lead to a significant increase in the diastereoselectivity of the cycloaddition.

The two *N*-crotonyl-4-ferrocenyloxazolidinones were prepared as summarized in Scheme 3, by treatment of the corresponding oxazolidinones (*R*)-**13**[7a] and (*R*)-**2**[29] with *n*-butyl lithium in THF at low temperature followed by the addition of a slight excess of crotonic pivalic anhydride or crotonyl chloride; in this way, the target



(*R*)-**13** (R = H)
(*R*)-**2** (R = Me)

(*R*)-**14** (R = H)
(*R*)-**15** (R = Me)

Scheme 3. Reagents and conditions: (i) *n*-BuLi (1.1 equiv), tetrahydrofuran, −78 °C, 30 min; (*E*)-2-propenoic pivalic anhydride (1.8 equiv), tetrahydrofuran, rt, 15 h, 84% ((*R*)-**14**). (ii) *n*-BuLi (1.1 equiv), tetrahydrofuran, −78 °C, 15 min; (*E*)-2-propenoyl chloride (1.5 equiv), tetrahydrofuran, 0 °C, 30 min, 86% ((*R*)-**15**).

dienophiles (*R*)-**14** and (*R*)-**15** were obtained in 84% and 86% yields, respectively.

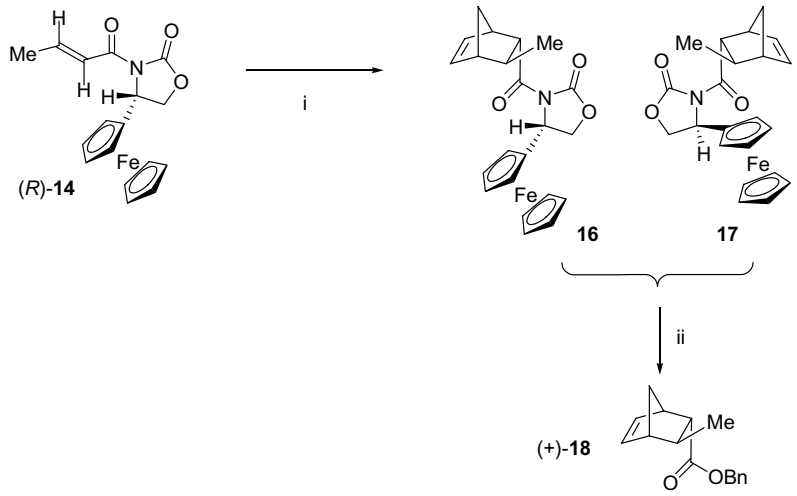
(*R*)-**14** was next treated with diethylaluminium chloride in dichloromethane at −78 °C, and reacted with an excess of freshly distilled cyclopentadiene. After 30 min at the same temperature, we isolated the cycloaddition product in 82% yield, following chromatographic purification, as an inseparable mixture of the two *endo* diastereomer adducts **16** and **17** (Scheme 4). The diastereomer ratio, determined by NMR, was 1.5:1, no trace of the *exo* adducts detected. The absolute configuration of the major isomer was deduced after conversion of the mixture to the known benzyl ester **18**[25] and examination of its rotatory power. As expected, these results closely match those obtained by Martinelli for (*S*)-*N*-crotonyl-4-phenyl-1,3-oxazolidin-2-one.[26]

We found, as anticipated, a completely different behaviour was observed in the case of (*R*)-**15** (Scheme 5). In effect, the diethylaluminium chloride complex of this compound failed to react with cyclopentadiene at −78 °C, even under prolonged reaction times. When the temperature was allowed to rise to −30 °C, the cycloaddition proceeded at a slow rate, taking 46 h for complete consumption of the starting material.[30] After chromatographic purification, the stereoisomerically pure (only one isomer was detected by NMR) *endo* **19** and *exo* **20** adducts were isolated in 60% and 12% yields, respectively. The absolute configuration of **19** was again determined upon conversion to the benzyl ester (+)-**18**. On the other hand, treatment of *exo* adduct **20** with lithium benzyloxide led to the isolation of diastereomeric ester (+)-**21**, whose relative configuration was ascertained by comparison of spectral data with those reported in the literature.[31] Since it is logical to expect that the diastereofacial selectivity of the cycloaddition will be the same for both the *endo* and *exo* approach of the diene, we assume that the absolute configuration of the *exo* adduct **20** is the one depicted in Scheme 5.

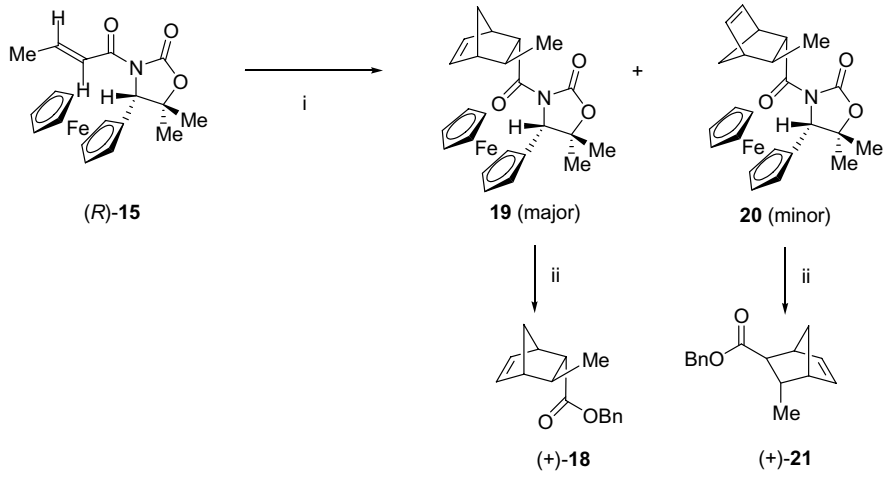
It is therefore clear that the presence of the *gem*-dimethyl group at C5 introduces significant changes over the course of the Diels–Alder cycloaddition, which can be easily rationalized by the conformational assumptions depicted in Figure 2; at the same time, these results suggest that the ferrocenyl 'SuperQuat' **2**, readily available in both enantiomeric forms, holds significant potential as a chiral auxiliary.

2.3. Asymmetric palladium-catalyzed allylic substitution reactions

4-Substituted-2-(2-diarylphosphinophenyl)-1,3-oxazolines (PHOX) constitute a very important class of chiral ligands derived from 2-amino alcohols.[32] These compounds were independently designed and synthesized by the research groups of Pfaltz,[33] Helmchen[34] and Williams,[35] with the aim of combining both electronic and steric effects in order to obtain highly efficient ligands for palladium-catalyzed allylic alkylations.[36] In fact, PHOX ligands derived from readily available acyclic amino alcohols, such as valinol, phenylglycinol and



Scheme 4. Reagents and conditions: (i) Et_2AlCl (2 equiv), cyclopentadiene (30 equiv), dichloromethane–hexanes, −78 °C, 30 min, 82% (**16** + **17**, 1.5:1 mixture). (ii) BnOLi (6 equiv), tetrahydrofuran, 0 °C, 20 h, 82%.



Scheme 5. Reagents and conditions: (i) Et_2AlCl (1.4 equiv), cyclopentadiene (25 equiv), dichloromethane–hexanes, −30 °C, 46 h, 60% **19** + 12% **20**. (ii) BnOLi (6 equiv), tetrahydrofuran, 0 °C, 26 h, 82% (+)-**18**, 85% (+)-**21**.

tert-leucinol were found to induce excellent enantioselectivities in palladium-catalyzed alkylations with 1,3-diphenylallyl acetate and other substrates bearing bulky substituents at both termini of the allyl moiety. The efficiency of these PHOX ligands is however strongly dependent on the size of the allyl substituents; for example, a maximum 71% ee was recorded by Pfaltz[33] in the substitution of (*E*)-1,3-dimethyl-2-propenyl acetate by dimethylmalonate anion when using *tert*-butyl-PHOX as a ligand, a result that could only be substantially improved by the incorporation of oxazoline moieties derived from conformationally blocked bicyclic *cis*-2-amino alcohols.[37] On the other hand, Helmchen[38] reported that simple PHOX ligands were totally ineffective in reactions with 2-cyclohexenyl acetate as a substrate, leading to nearly racemic products. In order to overcome these limitations, he devised PHOX[38] and phosphinocymanthrenyloxazoline[39] ligands bearing a stereogenic phosphorus atom. Other strategies involved the use of structurally different chiral P,N-,[40] P,P-[41] or P,S-[42] chelating ligands, or of monodentate chiral phosphines.[43]

In our recent studies on the use of 4-ferrocenyl-1,3-oxazolines as ligands for catalytic asymmetric allylation reactions,[7c] we found that the behaviour of the (π-allyl)palladium complex of 2-(2-diphenylphosphinophenyl)-4-ferrocenyl-1,3-oxazoline (Fc-PHOX)[7a] as a precatalyst was in complete accordance to these literature precedents (Fig. 3). In effect, while essentially complete enantioselectivity was achieved in the nucleophilic substitution of 1,3-diphenyl-2-propenyl acetate by dimethyl malonate anion, a moderate 44% ee was obtained in the case of 1,3-dimethylallyl acetate; on the other hand, (2-cyclohexenyl) dimethyl malonate could only be prepared in 11% optical purity. The degree of asymmetric induction exerted by the ferrocenyl group in the Fc-PHOX ligand was therefore, as described above for the asymmetric Diels–Alder reaction, roughly similar to that of a phenyl group (a 50% ee was reported for the

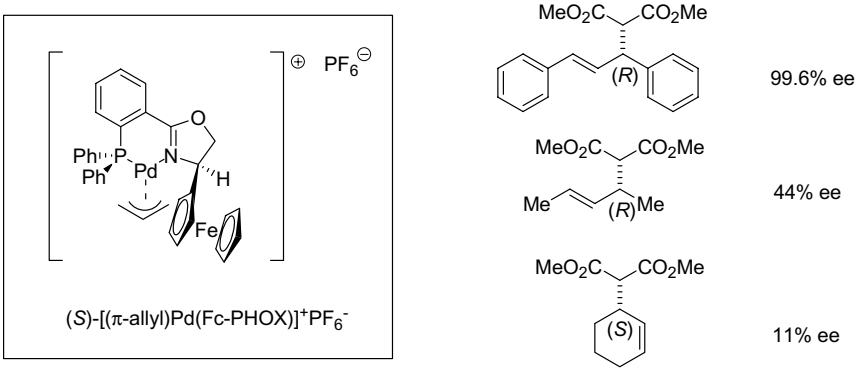


Figure 3. Enantioselectivity in the allylic substitution reactions with dimethyl malonate catalyzed by the (π-allyl)palladium complex derived from (*S*)-Fc-PHOX (Ref. 7c).

substitution of 1,3-dimethylallyl acetate by dimethyl malonate using Ph-PHOX as a ligand).[33]

Helmchen[37–39] has argued that the low enantioselectivities observed both for small acyclic and for cyclic substrates can be ascribed both to the lack of direct interactions between the C4-substituent and the phenyl group at phosphorus and of steric hindrance in the zone directly above the allyl system. Since according to our hypothesis the introduction of a *gem*-dimethyl group at C5 would direct the vicinal ferrocenyl group towards the (π-allyl)palladium moiety (see Fig. 4), we decided to synthesize 2-(2-diphenylphosphinophenyl)-4-ferrocenyl-5,5-dimethyl-1,3-oxazoline **22** (diMeFc-PHOX) in order to test its performance in palladium-catalyzed allylic substitutions. Our prediction was that this ligand would not be adequate for 1,3-diphenylallyl acetate, because in this case the fastest reacting *exo*-π-allyl complex would be destabilized by steric interactions between the phenyl and the ferrocenyl groups, and that on the other hand **22** would afford higher enantioselectivities than Fc-PHOX both for the less steric-demanding 1,3-dimethylallyl and 2-cyclohexenyl acetates.

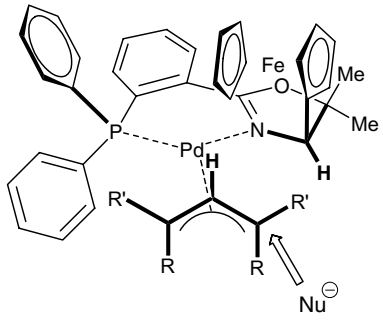


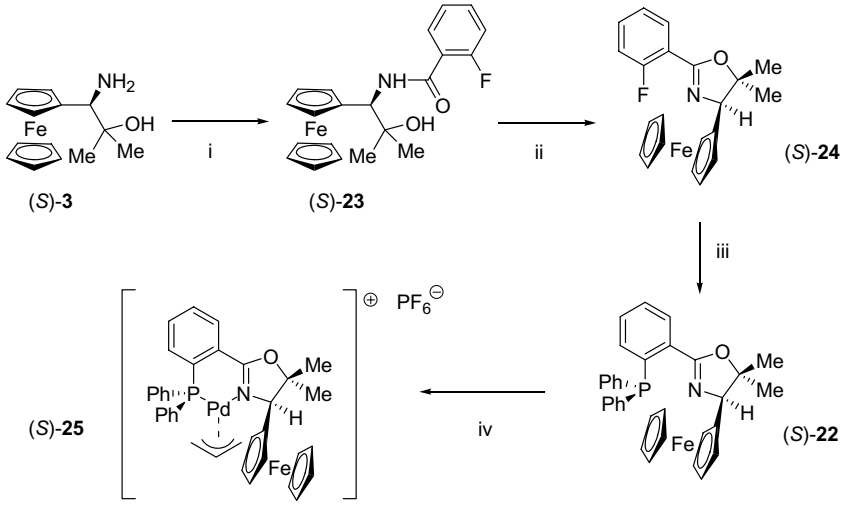
Figure 4. Predicted reactive conformation of an *exo* (π-allyl)palladium complex derived from (*S*)-diMeFc-PHOX **22**, showing the preferred site and facial selectivity for nucleophilic attack.

The (*S*)-enantiomer of **22** was prepared in good overall yield by adapting the procedure we had previously employed for Fc-PHOX,[7a] and subsequently converted into the corresponding (π-allyl)complex (*S*)-**25** (Scheme 6).

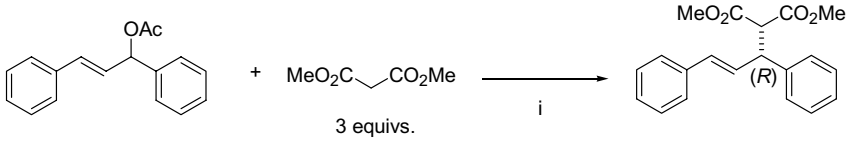
With the required pre-catalyst (*S*)-**25** in our hands, we proceeded to test its efficiency in the palladium-catalyzed allylation of dimethyl malonate for various substrates. It soon became evident that, as anticipated, **25** (Scheme 7) was less suitable for 1,3-diphenylallyl acetate than its unsubstituted counterpart (*S*)-Fc-PHOX, since after 6 days at room temperature in dichloromethane in the presence of 5 mol % of (*S*)-**25**, the reaction was still not complete, and the enantiomeric purity of the isolated substitution product was considerably lower (83% ee vs 99.6% ee).

We next turned our attention to 1,3-dimethylallyl acetate (Table 1). In this case, both the yields and the enantioselectivities were strongly dependent upon the reaction conditions, but (entry 1 of Table 1) the expected substitution product of (*R*)-configuration could be obtained in 82% yield and 80% ee (by GC). The introduction of the *gem*-dimethyl substituent resulted in a significant increase of 36 points in the enantiomeric excess of the product. It is also worth noting that the above enantiomeric excess is the highest observed for this reaction at room temperature with a PHOX-derived catalyst.[37]

An even more impressive increase in enantioselectivity (from 11% ee[7c] to 58% ee) was observed when using (*S*)-**25** in the allylation of dimethyl malonate by 2-cyclohexenyl acetate (Table 2). The maximum enantiomeric purity was attained when the reaction was run in THF solution at room temperature in the presence of 3 M equiv of dimethyl malonate, 3 M equiv of bis(trimethylsilyl)acetamide (BSA), 0.02 M equiv of lithium acetate and 0.05 M equiv of (*S*)-**25** (entry 2 of Table 2); these conditions afforded dimethyl (*S*)-(2-cyclohexenyl)malonate in a moderate 60% yield. When the temperature was raised to 70 °C, the yield increased to 72%, at the expense of a small decrease in the enantiomeric purity of the product (entry 3 of Table 2). Finally, a quantitative yield was obtained under the conditions of entry 5, together with a 53% ee. It is worth mentioning here that simple PHOX ligands are totally ineffective for this reaction, affording the racemic product in less than 30% yield.[39] These results, together with those described above for 1,3-dimethylallyl acetate, strongly suggest that, according to our hypothesis, in the diMeFc-

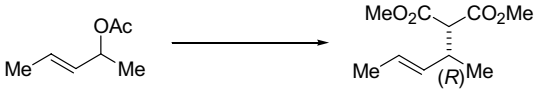


Scheme 6. Reagents and conditions: (i) 2-fluorobenzoyl chloride (1 equiv), NEt_3 (2 equiv), tetrahydrofuran, −45 °C, 20 min, 85%. (ii) $SOCl_2$ (4 equiv), NEt_3 (6 equiv), tetrahydrofuran, 0–60 °C, 40 min, 66%. (iii) Ph_2PLi (10 equiv), tetrahydrofuran, −78 °C, 2 h; rt, 12 h, 69%. (iv) $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (1.1 equiv), ethanol, rt, 45 min; NH_4PF_6, ethanol, 5 °C, 48 h, 78%.



Scheme 7. Reagents and conditions: (i) BSA (3 equiv), (*S*)-**25** (0.05 equiv), LiAcO (0.02 equiv), dichloromethane, rt, 6 days, 46% (83% ee).

Table 1. Asymmetric allylic substitution of *rac*-1,3-dimethylallyl acetate by dimethyl malonate using (*S*)-**25** as a pre-catalyst



Entry	Conditions[a]	Solvent	Temperature	Time	Yield (%)[b]	Ee (%)[c]
1	A	CH_2Cl_2	rt	4 days	82	80
2	A	THF	rt	4 days	n.d.[d]	68
3	A[e]	THF	70 °C	110 min	70	47
4	B	THF	rt	5 min	51	52
5	B	THF	−40 °C	22 h	61	63

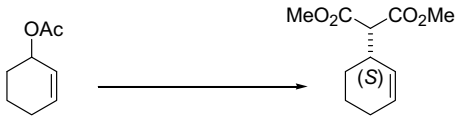
[a] Conditions A: 3 equiv dimethyl malonate, 3 equiv BSA, 0.05 equiv (*S*)-**25**, 0.02 equiv LiOAc; conditions B: 1.5 equiv sodium dimethyl malonate, 0.05 equiv (*S*)-**25**.
[b] Yield of isolated product after chromatographic purification.
[c] By GC.
[d] Conversion not complete.
[e] 0.02 equiv of (*S*)-**25** were used in this case.

PHOX ligand **22** the ferrocenyl moiety is able to block to a substantial degree, the area of space situated over the palladium atom in the corresponding metal complex.

3. Conclusions

In summary, our quest for the restriction of conformational mobility of the metallocene moiety in 2-amino-2-ferrocenyl derivatives has resulted in the highly enantioselective preparation of both enantiomers of 1-amino-1-ferrocenyl-2-methyl-2-propanol **3** in good overall yield and using readily available reactants and reagents. This new chiral β-amino alcohol can easily be transformed into the corresponding oxazolidinone **2** and phosphino-oxazoline **22** derivatives. The Fc-'SuperQuat' **2** has been shown to block very efficiently the access to one of the faces of a *N*-crotonyl substituent in the diethylaluminium chloride-catalyzed Diels–Alder reaction with cyclopentadiene. Moreover, the use of the diMeFc-PHOX ligand **22** in the palladium-catalyzed allylation of dimethyl malonate has allowed for the first time the achievement of sizable asymmetric induction in the PHOX-palladium-catalyzed substitution of 2-cyclohexenyl acetate. We therefore anticipate that the new ferrocenyl amino alcohol **3** is an excellent precursor for the

Table 2. Asymmetric allylic substitution of *rac*-2-cyclohexenyl acetate by dimethyl malonate using (*S*)-**25** as a pre-catalyst



Entry	Conditions[a]	Solvent	Temperature	Time	Yield (%)[b]	Ee (%)[c]
1	A	CH_2Cl_2	rt	7 days	31[d]	34
2	A	THF	rt	7 days	60	58
3	A	THF	70 °C	110 min	72	56
4	B	THF	rt	45 min	83	53
5	B	THF	0 °C	2 h	100	53
6	B	THF	−40 °C	6 days	46[d]	50

[a] Conditions A: 3 equiv dimethyl malonate, 3 equiv BSA, 0.05 equiv (*S*)-**25**, 0.02 equiv LiOAc; conditions B: 1.5 equiv sodium dimethyl malonate, 0.05 equiv (*S*)-**25**.
[b] Yield of isolated product after chromatographic purification.
[c] By GC.
[d] Conversion not complete.

preparation of useful chiral controllers for asymmetric synthesis. Work along these lines is currently in progress in our laboratory.

4. Experimental

4.1. General materials and methods

Melting points were determined in an open capillary tube and are uncorrected. Optical rotations were measured at room temperature (23 °C); concentrations are given in g 100 ml^{-1}. Infrared spectra were recorded in a Fourier transform mode, using the NaCl film technique. Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts are given in parts per million and referenced to TMS or $CHCl_3$. Carbon multiplicities were established by DEPT experiments. Exact mass measurements (HRMS) were performed by the 'Unidad de Espectrometría de Masas de la Universidad de Santiago de Compostela'. Reactions were generally run in flame- or oven-dried glassware under a N_2 atmosphere. Commercially available reagents were used as received. Diethyl ether and tetrahydrofuran used in the reactions were dried by distillation over metallic sodium and benzophenone (or fluorenone). Dichloromethane, triethylamine and pyridine were distilled from calcium hydride. Oxazolidinone (*R*)-**13**,[7a] *rac*-1,3-diphenylallyl acetate,[44] *rac*-1,3-dimethylallyl acetate[45] and *rac*-2-cyclohexenyl acetate[45,46] were prepared according to previously described procedures.

4.2. Synthesis of ferrocenyl amino alcohols

4.2.1. 1-Ferrocenyl-2-methylpropene 5

4.2.1.1. Dehydration with concentrated hydrochloric acid. To a cold (0 °C), stirred solution of ferrocenecarbaldehyde **4** (8.51 g, 39.8 mmol) in anhydrous diethyl ether (120 ml) a 2 M solution of isopropylmagnesium chloride in diethyl ether (30 ml, 60 mmol) was added dropwise. The resulting mixture was heated to reflux and after 15 min cooled again to 0 °C. The excess organomagnesium reagent was destroyed by the dropwise addition of water. At this point, the reaction mixture was treated with 25 ml of concentrated (37%) aqueous HCl and stirred at the same temperature for 40 min. After four additions, the intermediate alcohol had reacted completely (TLC). The reaction mixture was filtered through glass wool and washed with brine (2 × 80 ml). The aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic solution was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using hexanes as eluent, to give 8.10 g (85% yield) of the title compound as a red oil.

4.2.1.2. Dehydration with neutral alumina. To a cold (0 °C), stirred solution of ferrocenecarbaldehyde **4** (3.50 g, 16.3 mmol) in anhydrous diethyl ether (60 ml) a 2 M solution of isopropylmagnesium chloride in diethyl ether (10 ml, 20 mmol) was added dropwise. The resulting mixture was heated to reflux and after 15 min cooled again to 0 °C. Saturated aqueous ammonium chloride (20 ml) was added dropwise. After stirring for 15 min at room temperature, the aqueous phase was separated and extracted with ethyl acetate (3 × 100 ml). The combined organic phases were dried over magnesium sulfate, and evaporated under reduced pressure. The crude 1-ferrocenyl-2-methyl-1-propanol was not further purified. A solution of this alcohol in dry toluene (60 ml) was heated to reflux in a Dean–Stark apparatus in the presence of neutral alumina (3.0 g) for 4 h. After cooling to room temperature, the resulting solution was filtered through a Celite® pad. The solvent was eliminated under vacuum to afford 1.79 g (96% yield) of pure olefin **5**. The spectral data for this compound were identical to those reported in the literature.[11]

4.2.2. (*R*)-1-Ferrocenyl-2-methylpropane-1,2-diol (*R*)-6.

To a stirred solution of $K_3Fe(CN)_6$ (1.97 g, 6.0 mmol) and K_2CO_3 (0.83 g, 6.0 mmol) in 1:1 ^tBuOH–water (750 ml), were added $(DHQ)_2PYR$ (0.18 g, 0.2 mmol) and $K_2OsO_2(OH)_4$ (29 mg,

0.08 mmol), with stirring maintained at room temperature until complete dissolution of the osmate. At this point, 1-ferrocenyl-2-methylpropene **5** (0.48 g, 2.0 mmol) was added in one portion. The reaction was monitored by TLC. When no starting alkenylferrocene remained (70 min stirring at room temperature), sodium sulfite (3.6 g, 28 mmol) was added and stirring maintained for 25 min. The reaction mixture was extracted with ethyl acetate (5 × 40 ml); the organic extracts were dried over magnesium sulfate and the solvents removed at reduced pressure. Column chromatography of the crude product (silica gel, hexane–ethyl acetate mixtures as eluent) afforded 0.67 g (82% yield) of (*R*)-1-ferrocenyl-2-methylpropane-1,2-diol (96% ee) as a yellow solid. Mp: 106–107 °C. $[\alpha]_D^{23} = -102$ (*c* 1.15, $CHCl_3$). IR (NaCl film): ν_{max} = 3566, 3434, 2989, 1374, 1341, 1158, 1104, 1055, 1019, 820 cm^{-1}. ^1H NMR (200 MHz): δ 1.05 (s, 3H), 1.17 (s, 3H), 2.18 (br s, 1H), 2.38 (br s, 1H), 4.17–4.30 (m, 10H) ppm. ^{13}C NMR (50 MHz): δ 24.2 (CH_3), 26.2 (CH_3), 65.2 (CH), 67.9 (CH), 68.1 (CH), 68.4 (CH), 69.5 (CH), 72.5 (Cq), 76.9 (CH), 89.8 (Cq) ppm. MS (CI-NH_3) *m/e*: 292 (M+18, 49%), 275 (M+1, 4%), 257 (M−17, 100%). MS (EI) *m/e*: 274 (M, 48%), 185 (M−89, 100%). HRMS (EI) $C_{14}H_{18}FeO_2$ (M): calcd 274.0656, found 274.0663.

4.2.3. (*S*)-1-Ferrocenyl-2-methylpropane-1,2-diol (*S*)-6. In a similar way, but using $(DHQD)_2PYR$ as the chiral ligand, **5** (0.48 g, 2.0 mmol) afforded 0.69 g (85% yield) of (*S*)-1-ferrocenyl-2-methylpropane-1,2-diol (94% ee). $[\alpha]_D$ = +97.5 (*c* 0.135, $CHCl_3$). Conditions for the HPLC determination of the enantiomeric purity of **6**: Chiralcel OD column, 90% hexane–10% isopropyl alcohol, Φ = 0.5 ml min^{-1}, T = 25 °C, λ = 220 nm, $t_{R(R)}$ = 13.6 min, $t_{R(S)}$ = 17.0 min.

4.2.4. (*R*)-2-Hydroxy-1-ferrocenyl-2-methylpropyl acetate (*R*)-7. To a stirred solution of (*R*)-1-ferrocenyl-2-methylpropane-1,2-diol (*R*)-**6** (0.84 g, 3.1 mmol) and 4-DMAP (56 mg, 0.46 mmol) in anhydrous pyridine (6 ml), acetic anhydride (5.2 ml, 55 mmol) was added and the resulting mixture stirred at room temperature for 100 min. At this point, TLC monitoring revealed that no starting diol remained; excess acetic anhydride and pyridine were removed under vacuum, the addition of toluene being necessary to ensure the complete removal of pyridine. The residue was dissolved in toluene (10 ml) and washed with aqueous saturated copper(II) sulfate solution (4 × 10 ml) and brine (10 ml). After drying over magnesium sulfate and elimination of the solvent, 0.94 g (97% yield) of the crude monoacetate (*R*)-**7** were obtained as a brown oil. Without further purification, this product was directly used in the following reaction. IR (NaCl film): ν_{max} = 3097, 2986, 2942, 1740, 1435, 1370, 1232, 1140, 1107, 1046, 1023, 948, 939, 820 cm^{-1}. ^1H NMR (200 MHz): δ 1.08 (s, 3H), 1.11 (s, 3H), 1.58 (br s, 1H), 2.26 (s, 3H), 4.11–4.23 (m, 9H), 5.67 (s, 1H) ppm. ^{13}C NMR (50 MHz): δ 21.3 (CH_3), 25.0 (CH_3), 26.1 (CH_3), 66.2 (CH), 67.6 (CH), 68.1 (CH), 68.7 (CH), 69.0 (CH), 72.7 (Cq), 77.8 (CH), 85.0 (Cq), 172.5 (Cq) ppm. MS (FAB+) *m/e*: 316 (M, 100%). HRMS (FAB+) $C_{16}H_{20}FeO_3$ (M): calcd 316.0762, found 316.0753.

4.2.5. (*R*)-1-Azido-1-ferrocenyl-2-methylpropan-2-ol (*R*)-8. To a stirred solution of the crude acetate (*R*)-**7** (0.70 g, 2.2 mmol) in 3:1 water–methanol (70 ml), sodium azide (1.64 g, 25.2 mmol) was added in one portion. The resulting mixture was stirred at 60 °C for 3 h (TLC monitoring) and allowed to cool at room temperature. After eliminating most of the methanol at reduced pressure, the mixture was extracted with dichloromethane (4 × 30 ml). The combined organic extracts were washed with brine (40 ml), dried over magnesium sulfate, stripped of solvents at reduced pressure and purified by column chromatography (silica gel, hexane–ethyl acetate mixtures of increasing polarity) to afford 594 mg (89% yield) of the azido alcohol (*R*)-**8** as an orange-coloured solid. Mp: 77–80 °C. $[\alpha]_D^{23} = -74.3$ (*c* 0.160, $CHCl_3$). IR (NaCl film): ν_{max} = 3448, 2977, 2934, 2105, 1373, 1263, 1161, 1108, 1044, 1003, 820 cm^{-1}. ^1H NMR (200 MHz): δ 1.08 (s, 3H), 1.11 (s, 3H), 1.78 (br s, 1H), 4.14–4.30 (m, 10H) ppm. ^{13}C NMR (50 MHz): δ 25.3 (CH_3), 26.0 (CH_3), 66.7 (CH), 67.7 (CH), 68.1 (CH), 68.6 (CH), 68.7 (CH), 68.9 (CH), 72.5 (Cq), 86.4 (Cq) ppm. MS (CI-NH_3) *m/e*: 317 (M+18, 31%), 300 (M+1, 4%), 272 (M−17, 100%). HRMS (CI) $C_{14}H_{18}FeN_3O$ (M+1): calcd 300.0799, found 300.0796.

4.2.6. (*R*)-1-Amino-1-ferrocenyl-2-methylpropan-2-ol (*R*)-3. To a stirred suspension of 10% Pd/C (17 mg) in ethyl acetate (3 ml) under a hydrogen atmosphere, a solution of the azido alcohol (*R*)-**8** (173 mg, 0.58 mmol) in ethyl acetate (3 ml) was added via cannula. The mixture was stirred at room temperature for 4 h, filtered through a Celite® pad and the solvent removed under vacuum, to afford 149 mg (94% yield) of the title compound (96% ee) as a yellow solid. Mp: 91–92 °C. $[\alpha]_D^{23} = -83.4$ (*c* 0.356, $CHCl_3$). IR (NaCl film): ν_{max} = 3929, 3398, 3095, 2971, 2244, 1651, 1464, 1373, 1235, 1167, 1105, 1024, 1001, 818 cm^{-1}. ^1H NMR (200 MHz): δ 0.96 (s, 3H), 1.15 (s, 3H), 2.17 (br m, 3H), 3.50 (s, 1H), 4.00–4.30 (m, 9H) ppm. ^{13}C NMR (50 MHz): δ 24.6 (CH_3), 27.2 (CH_3), 59.7 (CH), 65.3 (CH), 67.3 (CH), 67.5 (CH), 68.4 (CH), 69.3 (CH), 71.9 (Cq), 90.9 (Cq) ppm. MS (CI-NH_3) *m/e*: 291 (M+18, 100%), 274 (M+1, 52%), 257 (M−17, 100%). HRMS (CI) $C_{14}H_{20}FeNO_2$ (M+1): calcd 274.0894, found 274.0897.

4.2.7. (*S*)-1-Amino-1-ferrocenyl-2-methylpropan-2-ol (*S*)-3. In a similar way, diol (*S*)-**6** afforded amino alcohol (*S*)-**3** (94% ee). $[\alpha]_D^{23} = +71.5$ (*c* 0.397, $CHCl_3$). Conditions for the HPLC determination of the enantiomeric purity of **3**: Chiralcel OD column, 90% hexane–10% isopropyl alcohol, Φ = 0.5 ml min^{-1}, T = 25 °C, λ = 220 nm, $t_{R(R)}$ = 17.7 min, $t_{R(S)}$ = 19.8 min.

4.2.8. 1,1′-Di-(2-methylpropenyl)ferrocene 10. To a cold (0 °C), stirred solution of 1,1′-ferrocenedicarbaldehyde **9** (121 mg, 0.50 mmol) in anhydrous diethyl ether (5 ml) a 2 M solution of isopropylmagnesium chloride in diethyl ether (0.75 ml, 1.5 mmol) was added. The resulting mixture was heated to reflux and after 10 min, cooled to room temperature. Saturated aqueous ammonium chloride (10 ml) was added dropwise. After

stirring for 5 min at room temperature, the aqueous phase was separated and extracted with ethyl acetate (3 × 5 ml). The combined organic phases were dried over magnesium sulfate, and evaporated under reduced pressure. The crude diol mixture (*meso* + *dl*) was not further purified. A solution of this mixture in dry toluene (10 ml) was heated to reflux in a Dean–Stark apparatus in the presence of neutral alumina (0.50 g) for 75 min. After cooling to room temperature, the resulting solution was filtered through a Celite® pad. The solvent was eliminated under vacuum to afford after chromatographic purification (neutral alumina, hexanes) 85 mg (58% yield) of diene **10** as a red solid. Mp: 32–34 °C. IR (NaCl film): ν_{max} = 3046, 2967, 2914, 1654, 1447, 1374, 1245, 1225, 1065, 1030, 903, 808 cm^{-1}. ^1H NMR (200 MHz): δ 1.77 (d, J = 0.8 Hz, 6H), 1.79 (d, J = 1.4 Hz, 6H), 4.10 (m, 4H), 4.18 (m, 4H), 5.80 (m, 2H) ppm. ^{13}C NMR (50 MHz): δ 19.7 (CH_3), 27.1 (CH_3), 68.7 (CH), 69.4 (CH), 77.0 (CH), 120.9 (CH), 132.3 (Cq) ppm. The signal corresponding to the quaternary ferrocene carbons could not be observed. MS (CI-NH_3) *m/e*: 295 (M+1, 100%), 294 (M, 14%). HRMS (CI) $C_{18}H_{22}Fe$ (M): calcd 294.1071, found 294.1084.

4.2.9. 1,1′-Bis[(*S*,*S*)-1,2-dihydroxy-2-methylpropyl]ferrocene (*S*,*S*)-11. To a stirred solution of $K_3Fe(CN)_6$ (658 mg, 2.0 mmol) and K_2CO_3 (276 mg, 2.0 mmol) in 1:1 acetonitrile–water (100 ml), were added $(DHQD)_2PYR$ (44 mg, 0.05 mmol) and $K_2OsO_2(OH)_4$ (12 mg, 0.03 mmol), and stirring maintained at room temperature until complete dissolution of the osmate. At this point, diene **10** (98 mg, 0.33 mmol) was added in one portion. The reaction was monitored by TLC. When no starting alkenylferrocene remained (3.5 h stirring at room temperature), sodium sulfite (1.0 g) was added and stirring maintained for 20 min. The reaction mixture was extracted with ethyl acetate (3 × 30 ml); the organic extracts were washed with brine (50 ml), dried over magnesium sulfate and the solvents removed at reduced pressure. Column chromatography of the crude product (silica gel, hexane–ethyl acetate mixtures as eluent) afforded 72 mg (60% yield) of the title compound (99.2% ee) as a yellow solid. Mp: 137–139 °C. $[\alpha]_D^{23}$ = +33.5 (*c* 0.097, $CHCl_3$). IR (NaCl film): ν_{max} = 3386, 3098, 2977, 1466, 1382, 1164, 1067, 1023, 965, 911, 814 cm^{-1}. ^1H NMR (200 MHz): δ 1.02 (s, 6H), 1.17 (s, 6H), 2.13 (br s, 2H), 4.10–4.27 (m, 8H), 4.30 (s, 2H), 4.50 (br s, 2H) ppm. ^{13}C NMR (50 MHz): δ 23.5 (CH_3), 26.3 (CH_3), 67.7 (CH), 67.8 (CH), 67.9 (CH), 68.1 (CH), 73.4 (Cq), 77.4 (CH), 88.5 (Cq) ppm. MS (FAB+) *m/e*: 362 (M, 100%), 345 (M−17, 14%). HRMS (FAB+) $C_{18}H_{26}FeO_4$ (M): calcd 362.1180, found 362.1184. Conditions for the HPLC determination of the enantiomeric purity of **11**: Chiralcel OD column, 80% hexane–20% isopropyl alcohol, Φ = 0.5 ml min^{-1}, T = 25 °C, λ = 220 nm, $t_{R(S,S)}$ = 10.1 min, $t_{R(R,R)}$ = 17.2 min.

4.2.10. 1,1′-Bis[(*S*,*S*)-1-azido-2-hydroxy-2-methylpropyl]ferrocene (*S*,*S*)-12. To a stirred solution of tetraol (*S*,*S*)-**11** (171 mg, 0.47 mmol) and 4-DMAP (19 mg, 0.16 mmol) in anhydrous pyridine (3 ml), acetic anhydride (2.0 ml, 21 mmol) was added and the resulting mixture was stirred at 50 °C for 26 h (TLC monitoring). At this point, excess acetic anhydride and pyridine were removed under vacuum, the addition of toluene being necessary to ensure the complete removal of pyridine. The residue (a mixture of di-, tri- and tetraacetylated products, according to NMR) was dissolved in methanol (4 ml) and a solution of sodium azide (614 mg, 9.5 mmol) in water (12 ml) added in one portion. The resulting mixture was stirred at 60 °C for 27 h (TLC monitoring) and allowed to cool at room temperature. After eliminating most of the methanol at reduced pressure, the mixture was extracted with dichloromethane (3 × 10 ml). The combined organic extracts were dried over magnesium sulfate, stripped of solvents at reduced pressure and purified by column chromatography (silica gel, hexane–ethyl acetate mixtures of increasing polarity) to afford 55 mg (28% yield) of the bis(azido alcohol) (*S*,*S*)-**12** as a yellow solid. Mp: 105–106 °C. $[\alpha]_D^{23}$ = +99.3 (*c* 0.210, $CHCl_3$). IR (NaCl film): ν_{max} = 3416, 2989, 2105, 1463, 1378, 1306, 1264, 1127, 1019, 1003, 828 cm^{-1}. ^1H NMR (200 MHz): δ 1.10 (s, 6H), 1.13 (s, 6H), 1.83 (s, 2H), 4.12 (br s, 2H), 4.20–4.50 (m, 8H) ppm. ^{13}C NMR (50 MHz): δ 25.2 (CH_3), 26.0 (CH_3), 67.7 (CH), 69.1 (CH), 69.6 (CH), 69.9 (CH), 72.4 (CH), 73.8 (Cq), 87.5 (Cq) ppm. MS (CI-NH_3) *m/e*: 413 (M+1, 4%), 412 (M, 23%), 385 (M−28, 100%). HRMS (CI) $C_{18}H_{24}FeN_6O_2$ (M): calcd 412.1310, found 412.1322.

4.3. Diels–Alder reactions of the *N*-crotonyl-4-ferrocenyl-1,3-oxazolidinones 14 and 15 with cyclopentadiene

4.3.1. (*R*)-4-Ferrocenyl-5,5-dimethyl-1,3-oxazolidin-2-one (*R*)-2. To a solution of the amino alcohol (*R*)-**3** (100 mg, 0.37 mmol) in dichloromethane (2 ml) were added 0.50 ml (3.1 mmol) of a 6 M aqueous NaOH solution. The resulting mixture was cooled to 0 °C and triphosgene (56 mg, 0.18 mmol) added in one portion; stirring was maintained for 20 min at the same temperature at which point TLC analysis showed that the reaction was complete. The dark-brown mixture was diluted with water (7 ml) and the aqueous phase was extracted with dichloromethane (3 × 5 ml). The combined organic extracts were dried over magnesium sulfate and the solvents were distilled off under vacuum to give 102 mg (93% yield) of the pure oxazolidinone (*R*)-**2**. Mp: 177–178 °C (dec). $[\alpha]_D^{23}$ = −194.3 (*c* 0.356, $CHCl_3$). IR (NaCl film): ν_{max} = 3284, 2986, 1752, 1719, 1407, 1373, 1347, 1304, 1263, 1105, 1005, 980, 828 cm^{-1}. ^1H NMR (200 MHz): δ 0.97 (s, 3H), 1.49 (s, 3H), 4.10–4.30 (m, 9H), 4.40 (s, 1H), 5.20 (br s, 1H) ppm. ^{13}C NMR (100 MHz): δ 23.2 (CH_3), 27.5 (CH_3), 62.8 (CH), 65.6 (CH), 67.6 (CH), 68.6 (CH), 69.0 (CH), 69.1 (CH), 84.0 (Cq), 84.3 (Cq), 158.5 (Cq) ppm. MS (FAB+) *m/e*: 300 (M+1, 64%), 299 (M, 100%). HRMS (FAB+) $C_{15}H_{17}FeNO_2$ (M): calcd 299.0609, found 299.0596.

4.3.2. (*R*)-4-Ferrocenyl-*N*-(2-(*E*)-propenoyl)-1,3-oxazolidin-2-one (*R*)-14. To a cold (−78 °C) solution of *trans*-crotonic acid (58 mg, 0.66 mmol) in anhydrous tetrahydrofuran (3 ml), triethylamine (96 μl, 0.68 mmol) and pivaloyl chloride (85 μl, 0.68 mmol) were added sequentially. After 15 min at −78 °C and 45 min at 0 °C, to the

resulting white suspension was added via cannula a cold (−78 °C) solution of the lithium salt of oxazolidinone (*R*)-**13** in anhydrous tetrahydrofuran (2.5 ml, prepared from 100 mg (0.37 mmol) of the oxazolidinone and 0.35 ml (0.41 mmol) of a 1.2 M solution of *n*-butyl lithium in hexanes). The resulting mixture was allowed to warm up to rt and stirred for 15 h; at this point TLC analysis showed that the reaction was complete. The reaction mixture was poured over water (25 ml) and extracted with ethyl acetate (3 × 25 ml). After drying over magnesium sulfate, elimination of the solvents followed by chromatographic purification on silica gel using hexane–ethyl acetate mixtures as eluents furnished 104 mg (84% yield) of the title compound as a dark yellow solid. Mp: 113–115 °C. $[\alpha]_D^{23} = +201$ (*c* 0.510, CH_2Cl_2). IR (NaCl film): ν_{max} = 3094, 2919, 1775, 1686, 1379, 1339, 1227, 1188, 1057, 970, 825 cm^{-1}. ^1H NMR (200 MHz): δ 1.92 (d, *J* = 5.2 Hz, 3H), 4.20 (m, 8H), 4.44 (m, 1H), 4.67 (m, 2H), 5.40 (dd, J_1 = 8.0 Hz, J_2 = 3.2 Hz, 1H), 7.03–7.22 (m, 2H) ppm. ^{13}C NMR (50 MHz): δ 18.5 (CH_3), 53.4 (CH), 65.6 (CH), 68.4 (CH), 68.5 (CH), 68.7 (CH_2), 68.8 (CH), 70.5 (CH), 84.8 (Cq), 121.8 (CH), 146.6 (CH), 153.5 (Cq), 164.4 (Cq) ppm. MS (EI) *m/e*: 339 (M, 100%), 289 (M−69, 17%), 69 (67%). HRMS (EI) $C_{17}H_{17}FeNO_3$ (M): calcd 339.0558, found 339.0557.

4.3.3. (*R*)-4-Ferrocenyl-5,5-dimethyl-*N*-(2-(*E*)-propenoyl)-1,3-oxazolidin-2-one (*R*)-15. To a cold (−78 °C) solution of oxazolidinone (*R*)-**2** (97 mg, 0.32 mmol) in anhydrous tetrahydrofuran (1 ml) was added a 1.4 M solution of *n*-butyl lithium in hexanes (0.25 ml, 0.35 mmol). After 15 min at −78 °C, (*E*)-2-propenoyl chloride (47 μl, 0.49 mmol) was added via syringe, and stirring maintained for 30 min at the same temperature. After stirring for 1 h at 0 °C, the reaction mixture was poured over saturated aqueous potassium bicarbonate (25 ml) and diethyl ether (10 ml) added. The aqueous phase was extracted with diethyl ether (2 × 10 ml), and the organic phase washed with saturated aqueous potassium bicarbonate (2 × 15 ml). After drying over magnesium sulfate, elimination of the solvents followed by chromatographic purification on silica gel using hexane–ethyl acetate mixtures as eluents gave 102 mg (86% yield) of the title compound as an orange-coloured solid. Mp: 111–113 °C. $[\alpha]_D^{23} = +45.5$ (*c* 0.150, $CHCl_3$). IR (NaCl film): ν_{max} = 3093, 2973, 1773, 1690, 1638, 1443, 1341, 1269, 1219, 1155, 1119, 1090, 1032, 969, 824 cm^{-1}. ^1H NMR (200 MHz): δ 0.92 (s, 3H), 1.43 (s, 3H), 2.02 (d, *J* = 5.6 Hz, 3H), 3.80–4.30 (m, 9H), 5.10 (s, 1H), 7.20–7.50 (m, 2H) ppm. ^{13}C NMR (50 MHz): δ 18.5 (CH_3), 22.5 (CH_3), 27.2 (CH_3), 61.4 (CH), 64.4 (CH), 67.91 (CH), 67.95 (CH), 68.0 (CH), 69.4 (CH), 83.6 (Cq), 85.8 (Cq), 122.4 (CH), 146.9 (CH), 153.5 (Cq), 164.5 (Cq) ppm. MS (FAB+) *m/e*: 367 (M, 100%), 289. HRMS (FAB+) $C_{19}H_{21}FeNO_3$ (M): calcd 367.0870, found 367.0880.

4.3.4. Diels–Alder reaction of the *N*-(crotonyl)oxazolidinone (*R*)-14 with cyclopentadiene. To a cold (−78 °C) solution of oxazolidinone (*R*)-**14** (82 mg, 0.19 mmol) in anhydrous dichloromethane (2 ml) was added a cold (−78 °C) 1 M hexane solution of diethylaluminium chloride (0.37 ml, 0.37 mmol). A colour change from yellow to red was immediately observed. At this point, freshly distilled cyclopentadiene (0.50 ml, 5.9 mmol) was added via syringe. After 30 min of stirring at the same temperature, no starting dienophile was present (TLC monitoring). The reaction mixture was poured over 1 M aqueous HCl (20 ml) and extracted with dichloromethane (3 × 25 ml). The organic extracts were dried over magnesium sulfate. Elimination of the solvent afforded a crude product that was then purified by column chromatography on silica gel, eluting with hexane–ethyl acetate mixtures of increasing polarity, to give 83 mg (82% yield) of a 1.5:1 mixture of the *endo* diastereomers **16** and **17** as a yellow solid. Mp: 113–116 °C. $[\alpha]_D^{23} = +17.2$ (*c* 0.62, CH_2Cl_2). IR (NaCl film): ν_{max} = 3093, 2963, 1775, 1701, 1653, 1559, 1458, 1377, 1331, 1221, 1055, 904, 821 cm^{-1}. ^1H NMR (200 MHz): (major isomer **16**) δ 1.09 (d, *J* = 7.0 Hz, 3H), 1.40 (dd, 2H), 2.13 (q, 1H), 2.46 (br s, 1H), 3.10 (br s, 1H), 3.50 (t, *J* = 3.6 Hz, 1H), 4.18 (m, 8H), 4.33 (s, 1H), 4.66 (m, 2H), 5.20 (dd, J_1 = 6.0 Hz, J_2 = 2.8 Hz, 1H), 5.31 (m, 1H), 6.21 (dd, J_1 = 5.8 Hz, J_2 = 3.0 Hz, 1H) ppm. (Minor isomer **17**) δ 1.07 (d, *J* = 7.0 Hz, 3H), 1.40 (dd, 2H), 2.13 (q, 1H), 2.46 (br s, 1H), 3.20 (br s, 1H), 3.50 (t, *J* = 3.6 Hz, 1H), 4.18 (m, 8H), 4.58 (s, 1H), 4.66 (m, 2H), 5.31 (m, 1H), 5.80 (dd, J_1 = 5.8 Hz, J_2 = 2.4 Hz, 1H), 6.36 (dd, J_1 = 5.8 Hz, J_2 = 3.0 Hz, 1H) ppm. ^{13}C NMR (50 MHz): (major isomer **16**) δ 20.4 (CH_3), 35.4 (CH), 46.7 (CH_2), 47.6 (CH), 49.5 (CH), 52.0 (CH), 53.5 (CH), 61.4 (CH), 64.9 (CH), 68.1 (CH_2), 68.5 (CH), 68.8 (CH), 70.7 (CH), 83.6 (Cq), 130.8 (CH), 139.2 (CH), 153.0 (Cq), 173.4 (Cq) ppm. (Minor isomer **17**) δ 20.5 (CH_3), 36.5 (CH), 47.2 (CH_2), 47.3 (CH), 49.5 (CH), 51.4 (CH), 54.2 (CH), 65.6 (CH), 68.1 (CH_2), 68.4 (CH), 68.6 (CH), 69.0 (CH), 70.9 (CH), 84.4 (Cq), 130.8 (CH), 139.6 (CH), 153.0 (Cq), 173.7 (Cq) ppm. MS (EI) *m/e*: 406 (M, 1%), 339 (M−67, 86%), 66 (100%). HRMS (EI) $C_{22}H_{23}FeNO_3$ (M): calcd 406.1061, found 406.1047.

When a solution of 80 mg (0.15 mmol) of this adduct mixture in anhydrous tetrahydrofuran (4 ml) was stirred at 0 °C for 20 h in the presence of lithium benzyloxide (0.60 mmol), 39 mg (82% yield) of the known[25] benzyl ester **18** {$[\alpha]_D^{23} = +37$ (*c* 1.20, CH_2Cl_2)} were obtained after chromatographic purification (preparative TLC, 5:1 hexane–ethyl acetate).

4.3.5. Diels–Alder reaction of the *N*-(crotonyl)oxazolidinone (*R*)-15 with cyclopentadiene. To a cold (−30 °C) solution of oxazolidinone (*R*)-**15** (0.13 g, 0.35 mmol) in anhydrous dichloromethane (2 ml) was added a 1 M hexane solution of diethylaluminium chloride (0.50 ml, 0.50 mmol). A colour change from yellow to red was immediately observed. After 5 min, freshly distilled cyclopentadiene (0.74 ml, 8.9 mmol) was added via syringe. After 46 h of stirring at the same temperature, no starting dienophile was present (TLC monitoring). The reaction mixture was poured over 1 M aqueous HCl (20 ml) and extracted with dichloromethane (3 × 5 ml). The organic extracts were dried over magnesium sulfate. Elimination of the solvent afforded a crude product that was purified by column chromatography on silica gel,

eluting with hexane–ethyl acetate mixtures of increasing polarity, to give 18 mg (12% yield) of the *exo*-adduct **20** and 92 mg (60% yield) of the *endo*-adduct **19**. Both compounds are yellow-orange solids.

4.3.5.1. (4*R*)-3-[(3′*S*,4′*S*,5′*R*,6′*R*)-5′-Methylbicyclo-[2.2.1]hepten-4′-carbonyl]-5,5-dimethyl-4-ferrocenyl-1,3-oxazolidin-2-one 19. Mp: 136–138 °C. $[\alpha]_D^{23} = +64.9$ (*c* 0.160, $CHCl_3$). IR (NaCl film): $\nu_{max} = 3107$, 2965, 1753, 1701, 1464, 1375, 1327, 1271, 1215, 1159, 1097, 1024, 820 cm^{-1}. ^1H NMR (200 MHz): δ 1.03 (s, 3H), 1.17 (d, $J = 7.2$ Hz, 3H), 1.41 (s, 3H), 1.52 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H), 1.76 (d, $J = 8.4$ Hz, 1H), 2.16 (m, 1H), 2.55 (t, $J = 1.0$ Hz, 1H), 3.50–3.60 (m, 2H), 3.90–4.20 (m, 9H), 5.03 (s, 1H), 6.04 (dd, $J_1 = 5.6$ Hz, $J_2 = 2.6$ Hz, 1H), 6.42 (dd, $J_1 = 5.6$ Hz, $J_2 = 3.0$ Hz, 1H) ppm. ^{13}C NMR (50 MHz): δ 20.6 (CH_3), 23.1 (CH_3), 27.5 (CH_3), 37.2 (CH), 47.6 (CH_2), 48.3 (CH), 49.4 (CH), 51.7 (CH), 62.2 (CH), 65.2 (CH), 66.9 (CH), 67.4 (CH), 68.0 (CH), 69.6 (CH), 83.4 (Cq), 84.6 (Cq), 131.7 (CH), 139.3 (CH), 153.4 (Cq), 173.3 (Cq) ppm. MS (CI-NH_3) *m/e*: 450 (M+17, 14%), 434 (M+1, 100%), 433 (M, 18%), 300 (M−133, 4%). HRMS (CI-NH_3) $C_{24}H_{27}FeNO_3$ (M): calcd 433.1340, found 433.1322.

4.3.5.2. (4*R*)-3-[(3′*S*,4′*R*,5′*S*,6′*R*)-5′-Methylbicyclo-[2.2.1]hepten-4′-carbonyl]-5,5-dimethyl-4-ferrocenyl-1,3-oxazolidin-2-one 20. Mp: 139–141 °C. $[\alpha]_D^{23} = +33.7$ (*c* 0.170, $CHCl_3$). IR (NaCl film): $\nu_{max} = 3097$, 2967, 1761, 1701, 1369, 1327, 1273, 1214, 1162, 1096, 820 cm^{-1}. ^1H NMR (200 MHz): δ 0.80–0.95 (m, 6H), 1.40 (s, 3H), 1.50 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.3$ Hz, 1H), 1.80 (d, $J = 8.4$ Hz, 1H), 2.75–2.95 (m, 3H), 3.17 (br s, 1H), 3.94 (br s, 1H), 4.05 (br s, 1H), 4.14–4.25 (m, 7H), 5.06 (s, 1H), 6.18–6.23 (m, 1H), 6.43–6.48 (m, 1H) ppm. ^{13}C NMR (50 MHz): δ 18.9 (CH_3), 22.7 (CH_3), 27.0 (CH_3), 37.0 (CH), 47.1 (CH_2), 47.7 (CH), 50.2 (CH), 51.2 (CH), 62.1 (CH), 64.4 (CH), 67.3 (CH), 67.8 (CH), 67.9 (CH), 69.3 (CH), 83.7 (Cq), 85.3 (Cq), 135.5 (CH), 137.2 (CH), 153.5 (Cq), 174.1 (Cq) ppm. MS (CI-NH_3) *m/e*: 450 (M+17, 10%), 434 (M+1, 78%), 433 (M, 100%). HRMS (CI-NH_3) $C_{24}H_{27}FeNO_3$ (M): calcd 433.1340, found 433.1341.

When a solution of 76 mg (0.18 mmol) of the *endo*-adduct **19** in anhydrous tetrahydrofuran (2 ml) was stirred at 0 °C for 26 h in the presence of lithium benzyloxide (0.87 mmol), 35 mg (82% yield) of the known[25] benzyl ester 18 $\{[\alpha]_D^{23} = +91$ (*c* 1.13, $CHCl_3)\}$ and 41 mg (78% yield) of the oxazolidinone (*R*)-**2** were obtained after chromatographic purification (silica gel, hexane–ethyl acetate mixtures as eluent).

In a similar way, to a cold (0 °C) solution of benzyl alcohol (240 μl, 2.52 mmol) in anhydrous tetrahydrofuran (4 ml) were added 1.20 ml (2.0 mmol) of a 1.45 M solution of *n*-butyl lithium in hexanes. After 15 min, the alkoxide was transferred via cannula to a round-bottomed flask containing a cold (0 °C) solution of the *exo*-adduct **20** (19 mg, 0.043 mmol) in anhydrous tetrahydrofuran (1 ml). After 41 h, the reaction mixture was poured over aqueous saturated ammonium chloride (20 ml). The aqueous phase was extracted with dichloromethane (3 × 10 ml). The combined organic extracts were dried over magnesium sulfate. Elimination of the solvent afforded a residue that was purified by column chromatography on silica gel, eluting with hexane–ethyl acetate mixtures of increasing polarity, to give 9 mg (85% yield) of the known benzyl ester **21**[31] $\{[\alpha]_D^{23} = +17.1$ (*c* 0.170, $CHCl_3)\}$, and 9 mg (69% yield) of the oxazolidinone (*R*)-**2**.

4.4. Palladium-catalyzed allylic substitution reactions mediated by the diMeFc-PHOX ligand 22

4.4.1. (*S*)-2-Fluoro-*N*-(2-hydroxy-1-ferrocenyl-2-methylpropyl)benzamide (*S*)-23. To a cold (−45 °C), stirred solution of (*S*)-1-amino-1-ferrocenyl-2-methylpropan-2-ol (*S*)-**3** (328 mg, 1.20 mmol) and triethylamine (328 μl, 2.35 mmol) in anhydrous tetrahydrofuran (3 ml) a solution of 2-fluorobenzoyl chloride (142 μl, 1.18 mmol) in dry tetrahydrofuran (2.5 ml) was added via cannula. The resulting mixture was stirred at room temperature for 20 min (TLC monitoring) and the solvent and the excess triethylamine removed under vacuum. The oily residue was dissolved in dichloromethane (20 ml) and washed with aqueous saturated potassium bicarbonate (3 × 20 ml). After drying over magnesium sulfate, elimination of the solvents followed by chromatographic purification on silica gel using hexane–ethyl acetate mixtures as eluents gave 397 mg (85% yield) of the title compound as a yellow semi-solid. $[\alpha]_D^{23} = +53.3$ (*c* 0.250, $CHCl_3$). IR (NaCl film): $\nu_{max} = 3452$, 3089, 2977, 1650, 1615, 1532, 1482, 1324, 1208, 1108, 822 cm^{-1}. ^1H NMR (200 MHz): δ 1.12 (s, 3H), 1.22 (s, 3H), 1.60 (br s, 1H), 2.12 (br s, 1H), 4.05–4.35 (m, 9H), 4.99 (dd, $J_1 = 9.2$ Hz, $J_2 = 2.4$ Hz, 1H), 7.10–7.60 (m, 3H), 8.19 (m, 1H) ppm. ^{13}C NMR (50 MHz): δ 26.6 (CH_3), 26.8 (CH_3), 57.6 (CH), 64.9 (CH), 67.4 (CH), 68.1 (CH), 68.9 (CH), 70.0 (CH), 73.3 (Cq), 86.8 (Cq), 116.1 (d, $J_{C-F} = 24.6$ Hz, CH), 124.9 (d, $J_{C-F} = 3.2$ Hz, CH), 132.2 (d, $J_{C-F} = 1.9$ Hz, CH), 133.4 (d, $J_{C-F} = 9.1$ Hz, CH), 160.4 (d, $J_{C-F} = 240$ Hz, Cq), 162.8 (Cq), 162.9 (Cq) ppm. MS (CI-NH_3) *m/e*: 396 (M+1, 27%), 395 (M, 100%), 377 (M−18, 31%). HRMS (CI-NH_3) $C_{21}H_{22}FFeNO_2$ (M): calcd 395.0984, found 395.0979.

4.4.2. (*S*)-2-(2-Fluorophenyl)-4-ferrocenyl-5,5-dimethyl-1,3-oxazoline (*S*)-24. To a cold (0 °C), stirred solution of the benzamide (*S*)-**23** (79 mg, 0.20 mmol) and triethylamine (167 μl, 1.20 mmol) in anhydrous tetrahydrofuran (2 ml) freshly distilled thionyl chloride (44 μl, 0.80 mmol) was added in one portion. The resulting mixture was stirred at 0 °C for 10 min, at room temperature for 20 min and then at 60 °C for 10 min (TLC monitoring), poured over aqueous saturated potassium bicarbonate (10 ml) and extracted with ethyl acetate (3 × 10 ml). The organic extracts were washed with brine (20 ml) and dried over magnesium sulfate. Elimination of the solvents followed afforded a crude product that was purified by column chromatography purification on silica gel using hexane–ethyl acetate mixtures as eluents to give 60 mg (66% yield) of the title compound as a yellow solid. Mp: 77–79 °C. $[\alpha]_D^{23} = +364$ (*c* 0.335,

$CHCl_3$). IR (NaCl film): ν_{max} = 3450, 3093, 2971, 1735, 1613, 1488, 1457, 1212, 1108, 1025, 822 cm^{-1}. ^1H NMR (200 MHz): δ 1.00 (s, 3H), 1.51 (s, 3H), 4.00–4.20 (m, 4H), 4.29 (s, 5H), 4.75 (s, 1H), 7.10–7.30 (m, 2H), 7.40–7.55 (m, 1H), 7.93 (m, 1H) ppm. ^{13}C NMR (50 MHz): δ 23.1 (CH_3), 28.2 (CH_3), 66.9 (CH), 67.5 (CH), 67.6 (CH), 67.7 (CH), 69.1 (CH), 74.9 (CH), 86.5 (Cq), 116.6 (d, J_{C-F} = 21.9 Hz, CH), 123.8 (d, J_{C-F} = 4.1 Hz, CH), 126.9 (d, J_{C-F} = 10.0 Hz, Cq), 131.1 (d, J_{C-F} = 1.9 Hz, CH), 132.5 (d, J_{C-F} = 8.2 Hz, CH), 161.2 (d, J_{C-F} = 255.8 Hz, Cq), 163.9 (Cq) ppm. A signal corresponding to a quaternary carbon atom could not be observed. MS (CI-NH_3) *m/e*: 378 (M+1, 29%), 377 (M, 100%). HRMS (CI-NH_3) $C_{21}H_{20}FFeNO$ (M): calcd 377.0878, found 377.0878.

4.4.3. (*S*)-2-(2-(Diphenylphosphanyl)phenyl)-4-ferrocenyl-5,5-dimethyl-1,3-oxazoline (*S*)-22. To a cold (−78 °C), stirred suspension of the oxazoline (*S*)-**24** (259 mg, 0.69 mmol) in anhydrous tetrahydrofuran (2 ml), under an Ar atmosphere, a filtered tetrahydrofuran solution of lithium diphenylphosphide (prepared from 45 mg (6.5 mmol) of lithium, 910 mg (3.43 mmol) of triphenylphosphine and 67 mg (3.44 mmol) of ammonium bromide in 2 ml of anhydrous tetrahydrofuran) was added via cannula. The resulting mixture was stirred at −20 °C for 2 h and at room temperature for 12 h, and treated with a solution of sodium sulfate (1.50 g, 11 mmol) in water (2 ml). The organic layer was filtered through a short pad of silica gel, that was subsequently washed with ethyl acetate. Elimination of the solvents under vacuum afforded a crude product that was purified by column chromatography purification on silica gel, eluting with hexane–ethyl acetate mixtures of increasing polarity, to give 258 mg (69% yield) of the title compound as a yellow solid. Mp: 54–56 °C. $[\alpha]_D^{23} = +203$ (*c* 0.220, $CHCl_3$). IR (NaCl film): ν_{max} = 3072, 2977, 1729, 1646, 1461, 1436, 1370, 1275, 1090, 1046, 743 cm^{-1}. ^1H NMR (200 MHz): δ 0.80 (s, 3H), 1.36 (s, 3H), 3.80–4.20 (m, 9H), 4.60 (s, 1H), 6.80–7.00 (m, 1H), 7.20–7.50 (m, 12H), 7.80–8.00 (m, 1H) ppm. ^{13}C NMR (50 MHz): δ 23.0 (CH_3), 27.8 (CH_3), 66.6 (CH), 67.3 (CH), 67.5 (CH), 67.6 (CH), 69.1 (CH), 75.6 (CH), 86.5 (Cq), 86.7 (Cq), 128.0 (CH), 128.17 (CH), 128.25 (CH), 128.3 (CH), 129.57 (CH), 129.64 (CH), 130.3 (CH), 133.1 (d, J_{C-P} = 20.0 Hz, Cq), 133.7 (CH), 134.1 (CH), 134.2 (CH), 138.7 (d, J_{C-P} = 6.4 Hz, Cq), 138.8 (d, J_{C-P} = 19.3 Hz, Cq), 163.8 (Cq) ppm. MS (CI-NH_3) *m/e*: 544 (M+1, 46%), 543 (M, 3%), 359 (M−184, 100%). HRMS (CI-NH_3) $C_{33}H_{31}FeNOP$ (M): calcd 543.1414, found 543.1416.

4.4.4. [(*S*)-Diphenyl-(2′-(4-ferrocenyl-5,5-dimethyl(1,3-oxazolin-2-yl)phenyl))phosphine]-[π-allyl]palladium(II) hexafluorophosphate (*S*)-25. To a stirred suspension of di-μ-chloro-bis(π-allyl)palladium (25 mg, 0.068 mmol) in absolute ethanol (2 ml), a solution of phosphinooxazoline (*S*)-**22** (70 mg, 0.129, mmol) in absolute ethanol (2 ml) was added via cannula at room temperature. The resulting mixture was stirred for 45 min at room temperature, at which point a homogeneous orange-coloured solution was obtained. Solid ammonium hexafluorophosphate (22 mg, 0.135 mmol) was added in one portion, and the mixture left in the refrigerator (5 °C) for 48 h. The precipitate was isolated by filtration, washed with cold (0 °C) absolute ethanol and dried in vacuo to afford 84 mg (78% yield) of the title compound as an orange solid. According to the NMR spectra, compound **25** exists in solution as a 1:1.8 mixture of *endo* and *exo* isomers. Mp: 167–169 °C. $[\alpha]_D^{23} = -161$ (*c* 0.52, EtOH). IR (NaCl film): ν_{max} = 3855, 3749, 2921, 1736, 1699, 1651, 1541, 1458, 839 cm^{-1}. ^1H NMR (400 MHz): δ 1.30 (s, 3H, *exo*), 1.35 (s, 3H, *endo*), 1.69 (s, 3H, *endo*), 1.72 (s, 3H, *exo*), 2.80 (d, *J* = 12.4 Hz, 1H, *exo*), 2.99 (d, *J* = 12.4 Hz, 1H, *endo*), 3.26 (br s, 1H, *exo*), 3.33 (d, *J* = 5.6 Hz, 1H, *endo*), 3.48 (d, *J* = 6.8 Hz, 1H, *exo*), 3.55 (br s, 1H, *endo*), 3.60 (m, 1H, *endo*), 3.83 (br s, 1H, *exo*), 3.89 (br s, 1H, *endo*), 3.97 (br s, 1H, *exo*), 4.02 (s, 5H *endo* + 5H *exo*), 4.14 (br s, 1H, *endo*), 4.08 (m, 1H, *exo*), 4.78 (br s, 1H, *endo*), 4.81 (m, 1H, *endo*), 4.85 (br s, 1H, *exo*), 5.16 (m, 1H, *exo*), 5.69 (m, 1H, *exo*), 5.93 (m, 1H, *endo*), 7.00–7.21 (m, 2H *exo* + 2H *endo*), 7.24–7.72 (m, 11H *endo* + 11H *exo*), 8.24 (m, 1H, *endo*), 8.30 (m, 1H, *exo*) ppm. ^{13}C NMR (100 MHz): δ 22.3 (CH_3, *endo*), 22.6 (CH_3, *exo*), 27.3 (CH_3, *endo*), 27.4 (CH_3, *exo*), 54.8 (allyl CH_2, *exo*), 59.3 (allyl CH_2, *endo*), 67.1 (CH), 67.4 (CH), 67.6 (CH), 67.8 (CH), 68.9 (CH), 69.4 (CH), 79.2 (d, J_{C-P} = 118.8 Hz, allyl CH_2, *endo*), 79.5 (CH), 80.6 (CH), 82.5 (d, J_{C-P} = 112.8 Hz, allyl CH_2, *exo*), 84.2 (Cq, *endo* + *exo*), 90.0 (Cq, *exo*), 90.4 (Cq, *endo*), 121.9 (d, J_{C-P} = 24.4 Hz, allyl CH, *exo*), 122.7 (d, J_{C-P} = 24.4 Hz, allyl CH, *endo*), 127.6 (Cq, *endo*), 128.1 (Cq, *exo*), 128.5 (CH), 129.4 (CH), 129.9 (CH), 130.0 (Cq, *exo*), 130.6 (Cq, *endo*), 131.7 (Cq), 133.2 (CH), 132.7 (CH), 135.0 (CH), 138.6 (CH), 160.4 (Cq, *endo* + *exo*) ppm. ^{31}P NMR (121 MHz): δ 22.8 (s) ppm. MS (FAB+) *m/e*: 690 (M−PF_6, 100%). HRMS (FAB+) $C_{36}H_{35}F_6FeNOP_2Pd$ (M): calcd 835.0482, found 835.0520.

4.4.5. Palladium-catalyzed allylic substitution of (*E*)-1,3-diphenyl-2-propenyl acetate. To a stirred suspension of complex (*S*)-**25** (11.7 mg, 0.014 mmol) and lithium acetate (0.4 mg, 0.006 mmol) in anhydrous dichloromethane (1 ml) a solution of (*E*)-1,3-diphenyl-2-propenyl acetate (71 mg, 0.28 mmol) in anhydrous dichloromethane (2 ml) was added and stirring maintained for 30 min at room temperature. Bis(trimethylsilyl)acetamide (0.21 ml, 0.84 mmol) and dimethyl malonate (0.10 ml, 0.84 mmol) were added with the aid of a calibrated syringe and the solution stirred at room temperature for 6 days. The reaction mixture was diluted with dichloromethane (5 ml) and washed with water (3 × 2 ml). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane–ethyl acetate mixtures of increasing polarity). (*R*)-2-((*E*)-1,3-Diphenylallyl)malonic acid dimethyl ester (83% ee) was isolated as a colourless oil (42 mg, 46% yield), together with 28 mg (40% recovery) of the starting allyl acetate.

Conditions for the HPLC determination of the enantiomeric purity of 2-((*E*)-1,3-diphenylallyl)malonic acid dimethyl ester: Chiralcel ODH column, 99% hexane–1% isopropyl alcohol, Φ = 0.3 ml min^{-1}, *T* = 25 °C, λ = 254 nm, $t_{R(R)}$ = 44.0 min, $t_{R(S)}$ = 46.9 min.

4.4.6. Palladium-catalyzed allylic substitution of (*E*)-3-pentenyl acetate

4.4.6.1. With dimethyl malonate-bis(trimethylsilyl)acetamide. To a stirred suspension of complex (*S*)-**25** (18 mg, 0.021 mmol) and lithium acetate (0.60 mg, 0.009 mmol) in anhydrous dichloromethane (2 ml), a solution of (*E*)-3-pentenyl acetate (55 mg, 0.43 mmol) in anhydrous dichloromethane (2 ml) was added and stirring maintained for 30 min at room temperature. Bis(trimethylsilyl)acetamide (0.32 ml, 1.3 mmol) and dimethyl malonate (0.15 ml, 1.3 mmol) were added with the aid of a calibrated syringe and the solution was stirred at room temperature for 4 days. The reaction mixture was diluted with dichloromethane (5 ml) and washed with water (3 × 3 ml). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane–ethyl acetate mixtures of increasing polarity). (*R*)-2-((*E*)-1-Methyl-2-butenyl)malonic acid dimethyl ester (80% ee) was isolated as a colourless oil (71 mg, 82% yield).

4.4.6.2. With sodium dimethyl malonate. A cold (−40 °C) solution of complex (*S*)-**25** (14 mg, 0.017 mmol) and (*E*)-3-pentenyl acetate (42 mg, 0.33 mmol) in anhydrous tetrahydrofuran (2.5 ml) was added via cannula to a stirred suspension of sodium dimethylmalonate (0.47 mmol, obtained from 12 mg of sodium hydride and 0.07 ml of dimethyl malonate) in anhydrous tetrahydrofuran (1.5 ml). The resulting mixture was stirred for 22 h at −40 °C, after which time aqueous saturated ammonium chloride (4 ml) was added in one portion. The aqueous phase was extracted with dichloromethane (2 × 5 ml), and the combined organic phases washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 98:2 hexane–ethyl acetate). (*R*)-2-((*E*)-1-Methyl-2-butenyl)malonic acid dimethyl ester (63% ee) was isolated as a colourless oil (41 mg, 61% yield).

Conditions for the GC determination of the enantiomeric purity of 2-((*E*)-1-methyl-2-butenyl)malonic acid dimethyl ester: β-DEX column, $T = 80$ °C, $t_{R(S)} = 135.2$ min, $t_{R(R)} = 137.4$ min.

4.4.7. Palladium-catalyzed allylic substitution of 2-cyclohexenyl acetate

4.4.7.1. With dimethyl malonate-bis(trimethylsilyl)acetamide. To a stirred suspension of complex (*S*)-**25** (12 mg, 0.014 mmol) and lithium acetate (0.4 mg, 0.006 mmol) in anhydrous tetrahydrofuran (3 ml) a solution of 2-cyclohexenyl acetate (41 mg, 0.29 mmol) in anhydrous tetrahydrofuran (1 ml) was added and stirring was maintained for 30 min at room temperature. Bis(trimethylsilyl)acetamide (0.22 ml, 0.88 mmol) and dimethyl malonate (0.10 ml, 0.88 mmol) were added with the aid of a calibrated syringe and the solution was stirred at 70 °C for 110 min. The reaction mixture was diluted with dichloromethane (5 ml) and washed with water (3 × 2 ml). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane–ethyl acetate mixtures of increasing polarity). (*S*)-2-(Cyclohex-2-enyl)malonic acid dimethyl ester (56% ee) was isolated as a colourless oil (44 mg, 72% yield).

4.4.7.2. With sodium dimethyl malonate. A cold (0 °C) solution of complex (*S*)-**25** (15 mg, 0.018 mmol) and 2-cyclohexenyl acetate (55 mg, 0.39 mmol) in anhydrous tetrahydrofuran (3 ml) was added via cannula to a stirred suspension of sodium dimethylmalonate (0.59 mmol, obtained from 15 mg of sodium hydride and 0.09 ml of dimethyl malonate) in anhydrous tetrahydrofuran (1.5 ml). The resulting mixture was stirred for 2 h at 0 °C (TLC monitoring); at this point, aqueous saturated ammonium chloride (4 ml) was added in one portion. The aqueous phase was extracted with dichloromethane (2 × 5 ml), and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 98:2 hexane–ethyl acetate). (*S*)-2-(Cyclohex-2-enyl)malonic acid dimethyl ester (53% ee) was isolated as a colourless oil (85 mg, 100% yield). Conditions for the GC determination of the enantiomeric purity of 2-(cyclohex-2-enyl)-malonic acid dimethyl ester: β-DEX column, $T = 110$ °C, $t_{R(S)} = 157.6$ min, $t_{R(R)} = 160.5$ min.

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30. When the reaction was performed at 0 °C, the reaction time was reduced to 24 h, and the same 5:1 mixture of stereoisomerically pure adducts **20** and **21** was obtained in a lower global yield (56%).
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