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Planar chiral 2-ferrocenyloxazolines and 1,1′-bis(oxazolinyl)ferrocenes—syntheses and applications in asymmetric catalysis

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This article is dedicated to Dr. Antony Chesney, C.Chem., MRSC (1968–2001)

Abstract—The synthesis and reactivity of planar chiral 2-ferrocenyloxazolines and 1,1′-bis(oxazolinyl)ferrocenes is reviewed, with particular emphasis on their applications in asymmetric catalysis.

Contents

Definitions

Throughout the Schemes, unless otherwise stated, the following definitions apply: (**a**) R = H; (**b**) R = Me; (**c**) R = *i*-Pr; (**d**) R = *t*-Bu, (**e**) R = *s*-Bu; (**f**) R = Ph; (**g**) R = Bn; (**h**) R = CH_2SMe; (**i**) R = CH_2CH_2SMe; (**j**) R = CH_2OMe; (**k**) R = CH_2OTBS; (**l**) R = CH_2OCH_2OMe; (**m**) R = CMe_2OMe; (**n**) R = CEt_2OMe; (**o**) R = CO_2Me.

1. Introduction

Chiral ferrocene derivatives have attracted tremendous scientific interest over the past decade. Those that exhibit planar chirality have become especially important because of their involvement in asymmetric catalysis, and there is currently a surge of effort into the design and development of new enantiopure ferrocene derivatives. The syntheses of chiral planar ferrocenes containing an oxazoline fragment were initiated independently by Richards et al., Sammakia et al. and Uemura et al. by diastereoselective *ortho*-directed lithiation of parent 2-ferrocenyloxazolines with great success. These non-racemic 2-ferrocenyloxazolines [and the related 1,1′-bis(oxazolinyl)ferrocenes] where secondary

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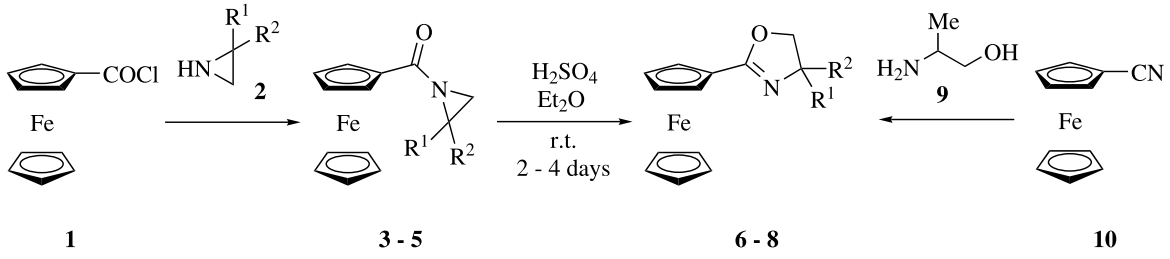
chelating substituents are either present or absent are very attractive ligands for transition metal mediated reactions and they have been successfully used for asymmetric catalysis.

Whereas a number of reviews have been published in recent years covering many aspects of both achiral[1,2] and chiral[3–5] ferrocene chemistry, there has been no comprehensive review of the synthesis and applications of 2-ferrocenyloxazolines and 1,1′-bis(oxazolinyl)ferrocenes in asymmetric processes. The aim of this report is to provide a thorough examination of the literature for 1994–2002, inclusive.

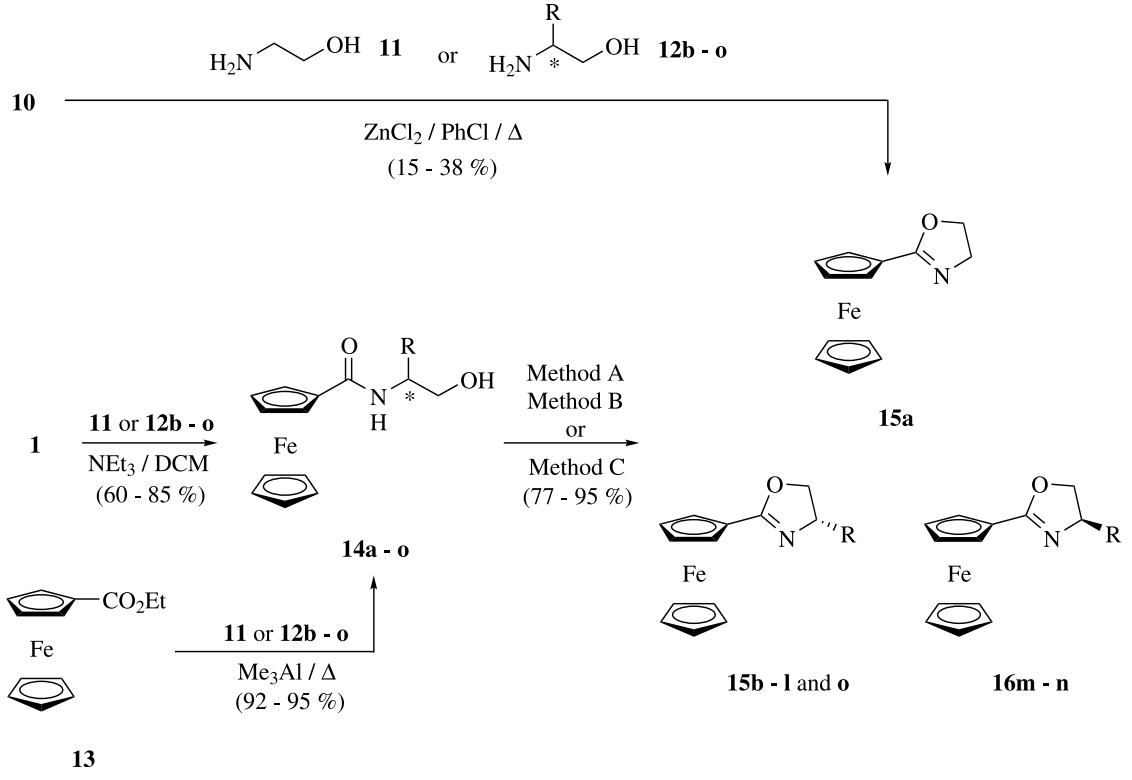
2. Synthesis of 2-ferrocenyloxazolines

Prior to the work of Richards et al., there appears to be only one report on the synthesis of 2-ferrocenyloxazolines, obtained by condensation of ferrocenoyl chloride **1** with aziridines **2** followed by acid catalysed ring expansion to generate derivatives **6**–**8** (yields 24–58%) (Scheme 1).[6] More conventional routes to 2-ferrocenyloxazolines have been reported to be unsuccessful, although two methods have been patented by BASF: (i) the reaction of 1-cyanoferrocene **10** (prepared from ferrocenecarbaldehyde) with 2-aminopropan-1-ol to give **7**, and (ii) the reaction of **1** with 2,2-dimethylaziridine **2** ($R^1=R^2=Me$) to furnish compound **8** (Scheme 1).[7]

More recently two methods have been established for the synthesis of 4-substituted 2-ferrocenyloxazolines. The first was developed by Uemura[8–10] and involves condensation of **10** with the chiral β-aminoalcohols **11**, **12** in the presence of a catalytic amount of $ZnCl_2$ (Scheme 2). Better results are achieved from the two-



Scheme 1. **3**, **6**, $R^1=R^2=H$; **4**, **7**, $R^1=H$, $R^2=Me$; **5**, **8**, $R^1=R^2=Me$.

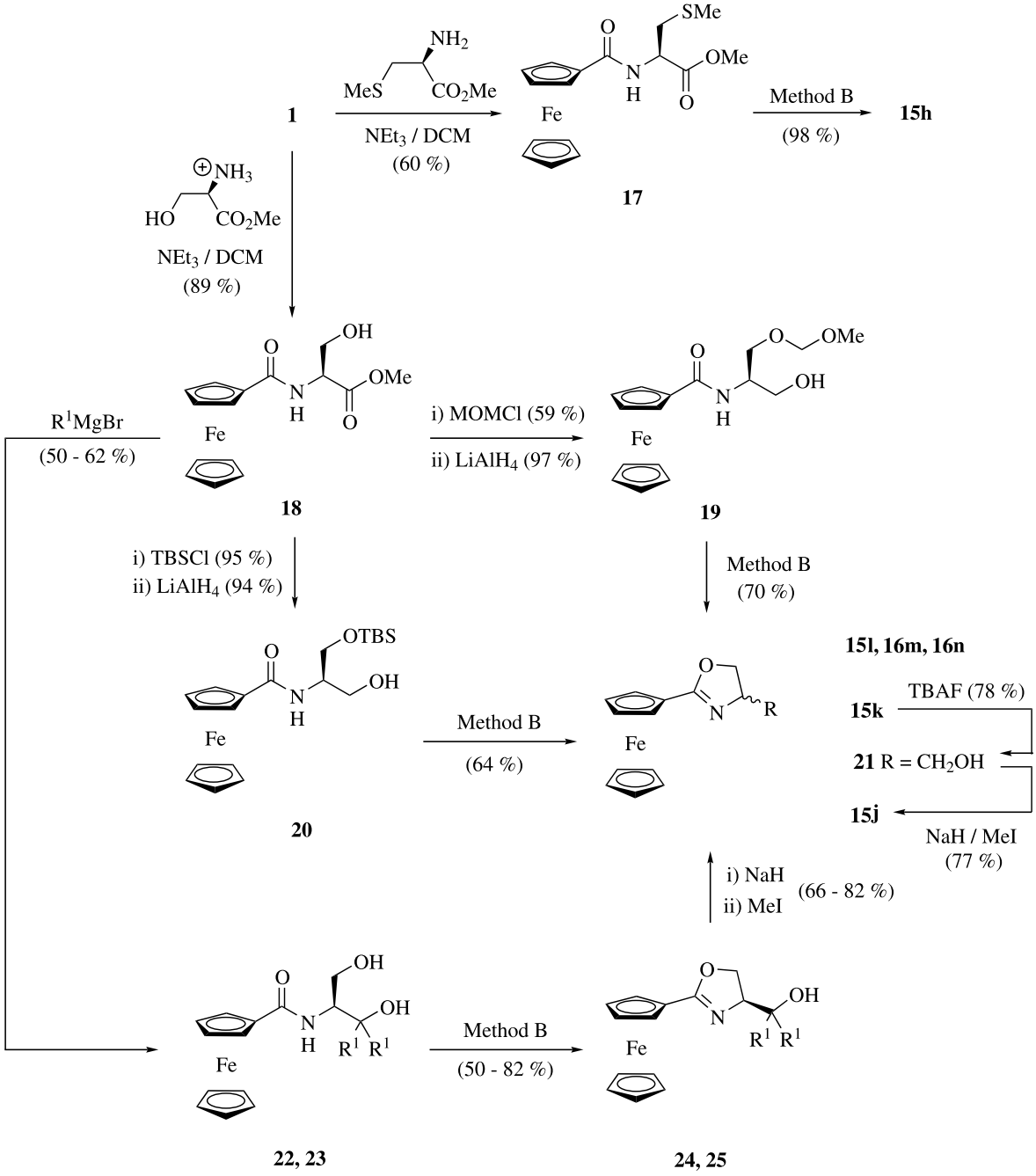


Scheme 2. **Method A** (Richards, 77–92% yields): PPh_3, CCl_4, NEt_3, MeCN (R = H, Me, *i*-Pr). **Method B** (Sammakia, 85–95% yields): *p*-TsCl, NEt_3, DMAP, CH_2Cl_2 (*i*-Pr, *t*-Bu, Ph, CH_2Ph) or (Ahn, 88–89% yields): *p*-TsCl, NEt_3, CH_2Cl_2 (*i*-Pr, *t*-Bu). **Method C** (Ikeda): MsCl, NEt_3 (R = H, Me, *i*-Pr, *t*-Bu, Ph) or (Bryce, 70–72% yields): MsCl, NaOH, MeOH (CH_2SMe, CH_2CH_2SMe).

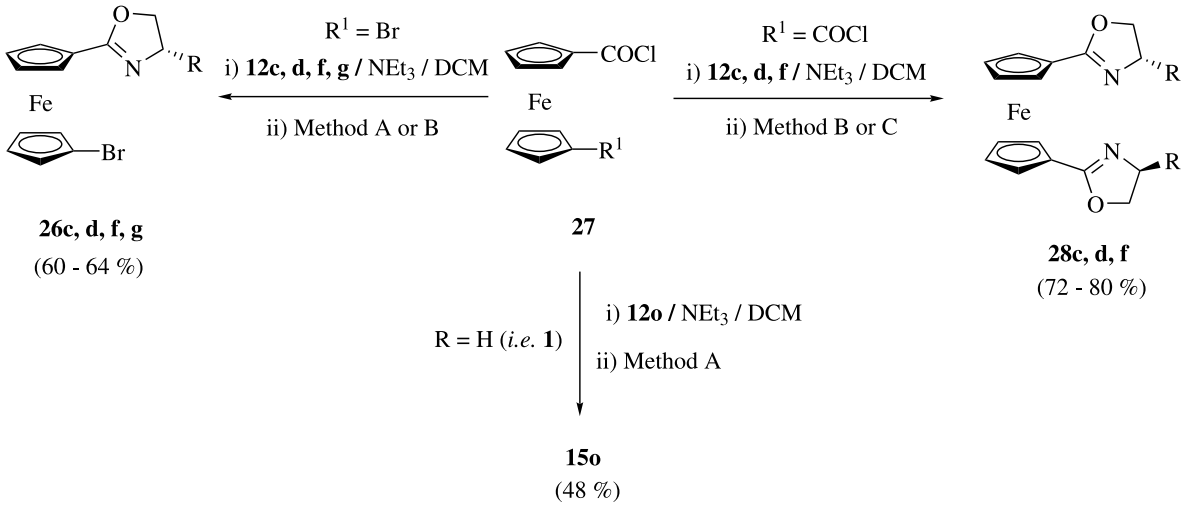
step methodology developed by Richards[11,12] and Sammakia.[13–15] Ferrocenoyl chloride **1** was combined with a number of chiral β-aminoalcohols to generate their corresponding β-hydroxyamides **14**. Subsequent dehydration under Appel conditions[16] with PPh_3, CCl_4 and NEt_3 (Method A) or using *p*-toluenesulfonyl chloride (*p*-TsCl) and NEt_3 (either in the presence or absence of DMAP) at room temperature (Method B) resulted in clean cyclisation to the desired products **15**, **16** (Scheme 2). Sammakia has thereby prepared derivatives which contain a variety of heteroatom containing substituents such as **15h**, **15k**, **15l**, **16m**, **16n**, **21**, **24** and **25** (Scheme 3).[13]

Ahn et al. have shown that oxazolines **15** (R = *i*-Pr or *t*-Bu) can also be prepared in high yield by cyclisation of β-hydroxyamides **14** [prepared by Weinreb transamidation[17] of ethyl ferrocenecarboxylate **13** with trimethylaluminium (2.0 equiv.) and either (*S*)-valinol or (*S*)-leucinol, respectively (yields 92–95%)] with *p*-TsCl (1.1 equiv.) and NEt_3 (2.2 equiv.) (Method B) (Scheme 2).[18–23] Using these methods a number of derivatives have been prepared, e.g. **26**[23] and the bis(oxazolinyl)ferrocenes **28** (Scheme 4).[19]

Bryce et al. reported the synthesis of **15o** and the bromo-derivative **26c** (Scheme 4)[24] and Aït-Haddou et al.



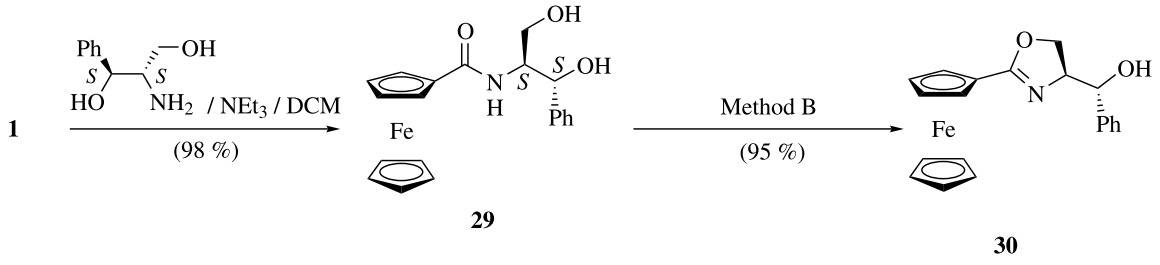
Scheme 3. **22**, **24**, $R^1 = Me$; **23**, **25**, $R^1 = Et$.



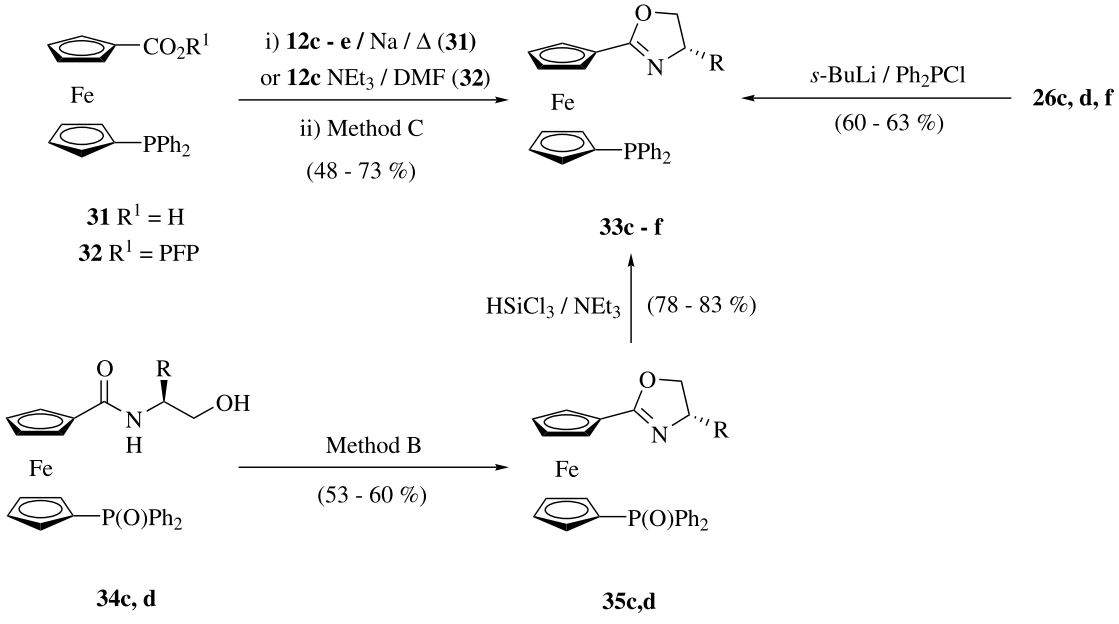
Scheme 4.

have published the preparation novel 2-ferrocenyloxazoline **30** containing two stereogenic centres from (1*S*,2*S*)-(+)-2-amino-3-(1,3-propanediol) and **1** followed by selective activation of the primary hydroxyl group via the tosylate and subsequent cyclisation (Scheme 5).[25]

Recently Dvorák published the synthesis of **33** by cyclisation of **34** with *p*-TsCl-NEt_3 to give the relatively unstable oxazolines **35** which were converted into the corresponding chiral 2-(1′-diphenylphosphanyl)-ferrocenyloxazolines **33** with trichlorosilane (Scheme 6).[26]



Scheme 5.



Scheme 6.

In certain cases standard Appel conditions fail to give a clean cyclisation. Mesylation of the free hydroxyl group of the β-amidoalcohols **14h**, **14i**, **36a**, **36c** and subsequent cyclisation with triethylamine[28] or sodium hydroxide in methanol[28] (Method C) has been used by Bryce et al. in the synthesis of disubstituted ferrocenyloxazolines **37a**[24] and **37c**[29] and the thioether derivatives **15h** and **15i** (Scheme 7).[30] Additionally chiral 2-(1′-diphenylphosphanyl)ferrocenyloxazolines **24** have been prepared by Ikeda et al. from either **31** or **32** and the corresponding β-aminoalcohols in the presence of catalytic sodium metal (R = *i*-Pr, *t*-Bu, Ph) or NEt_3-DMF (R = *i*-Pr), respectively, followed by cyclisation with MsCl-NEt_3 (R = *i*-Pr, *t*-Bu, Ph).[31] Debromo-lithiation of **26** with *s*-BuLi and quenching with PPh_2Cl has also been employed (Scheme 6)[23,32]

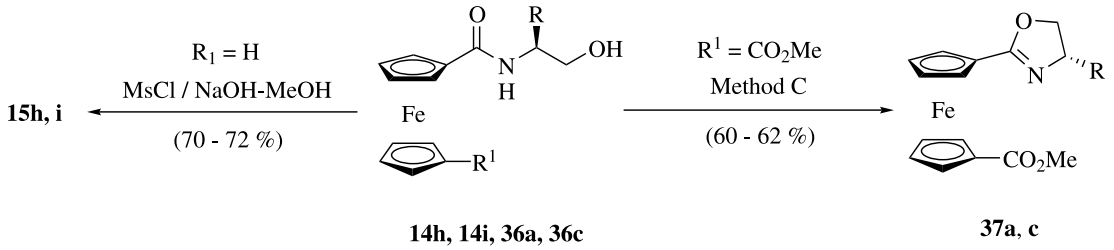
Cyclisation of amide **38** has been induced by Uemura et al. at −20°C with thionyl chloride (Method D) to give the hydrochloride salt, which is then neutralised with K_2CO_3 to give **39** (Scheme 8).[10]

2.1. Synthesis of 1,1′-bis(oxazolinyl)ferrocenes

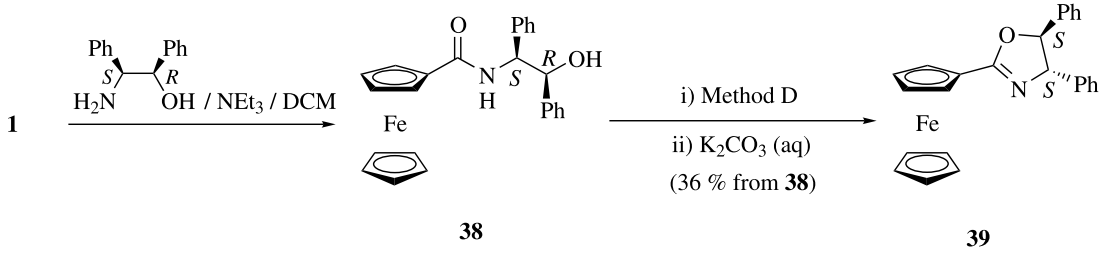
Routes to 1,1′-bis(oxazolinyl)ferrocene derivatives [19–22,27,30,31,33–41] are in general identical to those applied to their monosubstituted examples. Additionally, oxazolines **15c** and **15d** have been converted to the related bis(oxazolinyl)biferrocenes **40c** and **40d** via lithiation-transmetallation to their corresponding 'higher order' ferrocenylcuprates and concomitant dimerisation using oxygen (Scheme 9).[21,42]

3. *ortho*-Lithiation of 2-ferrocenyloxazolines and 1,1′-bis(oxazolinyl)ferrocenes

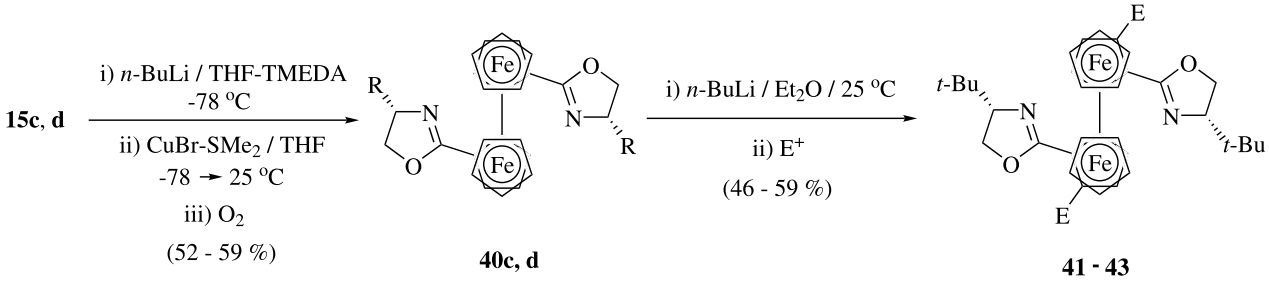
The synthesis of planar chiral ferrocene derivatives via the *ortho*-lithiation of 2-ferrocenyloxazolines has been an important topic since the mid-1990s. Richards, Sammakia and Uemura reported the ratio of diastereoisomers obtained by addition of *n*-butyl- or *s*-butyllithium to 2-ferrocenyloxazolines followed by TMSCl.[8,11,13]



Scheme 7.



Scheme 8. Method D (Uemura): $SOCl_2$, -20°C.

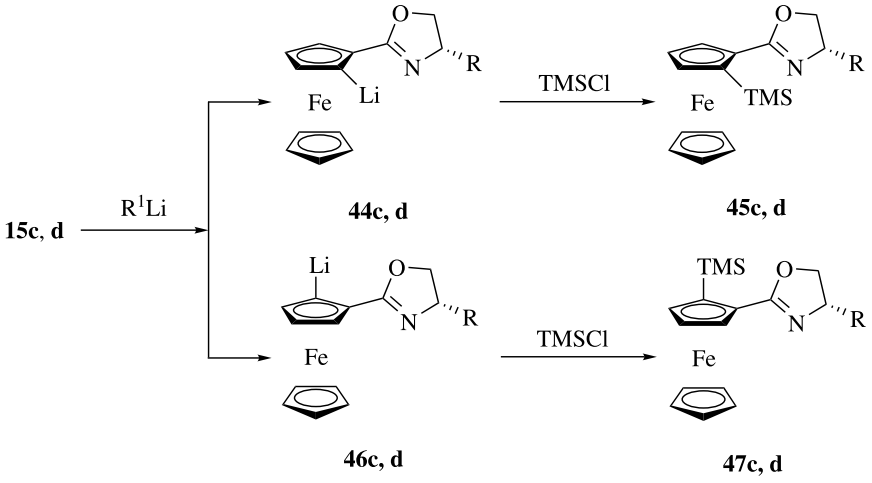


Scheme 9. 41, E = TMS (58%); **42**, E = TES (46%); **43**, E = $C(Ph)_2OH$ (59%).

Each of these studies involved *ortho*-metallation of 4-*i*-propyl-2-ferrocenyloxazoline **15c**, for which the distribution of the *ortho*-lithioferrocenyloxazolines **44** and **46** was shown to vary from 2.5:1 using *n*-BuLi at room temperature,[11] through 8:1 with *s*-BuLi/THF at −78°C,[11] to 39:1 with *s*-BuLi/Et_2O at −78°C (Scheme 10).[13] In each case the configuration of the major product was the same.

Sammakia developed what is now regarded as the method of choice for the *ortho*-lithiation of 2-ferrocenyloxazolines. It was shown that the combination of an additional chelating ligand, such as tetramethylethylenediamine (TMEDA) and the correct selection of solvent could vary the selectivity dramatically. The metallation of **15c** using TMEDA with *n*-BuLi in THF had little effect on the diastereomeric ratio; however, in either Et_2O or *n*-hexanes the selectivity was increased to 100:1. A further increase (>500:1) was observed by employing *s*-BuLi in the lithiation of **15c**, and similar selectivity was shown in the *ortho*-metallation of **15d** using either *n*-BuLi or *s*-BuLi (Table 1).[14]

The diastereoselection has been explained by considering the two rotamers **A** and **B**. Coordination of the organolithium species to the oxazoline nitrogen occurs such that it lies *exo* to the ferrocenyl unit. This forces the *i*-Pr group to be aligned either away from or towards the coordinated species, as in structures **A** and **B**, respectively. As the latter leads to an unfavourable steric interaction, deprotonation is preferred via **A**, even although the *i*-Pr group then lies *endo* to the ferrocenyl group, the distance between them is too great for any repulsive interaction to disfavour this rotamer (Scheme 11).

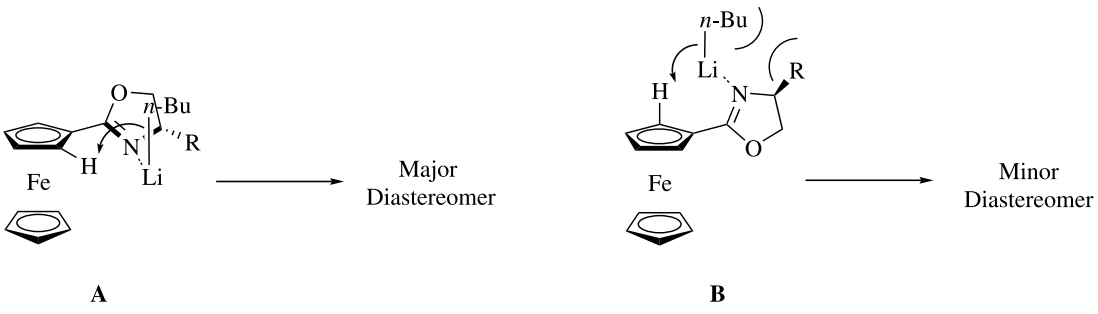


Scheme 10.

Table 1. Diastereoselective *ortho*-lithiation of **15c** and **15d**[14]

Compound	RLi	Solvent	Additive	**44**:**46**	% Yield **45**[a]
15c	*n*-BuLi	THF	TMEDA	3:1	>75
15c	*n*-BuLi	Et_2O	TMEDA	100:1	80
15c	*n*-BuLi	*n*-hexanes	TMEDA	100:1	75
15c	*s*-BuLi	*n*-hexanes	TMEDA	>500:1	94
15c	*t*-BuLi	*n*-hexanes	TMEDA	28:1	>75
15d	*n*-BuLi	*n*-hexanes	TMEDA	>500:1	>75
15d	s-BuLi	*n*-hexanes	TMEDA	>50:1	>75
15d	*t*-BuLi	*n*-hexanes	TMEDA	34:1	>75

[a] Isolated yield of major isomer **45** after chromatography.



Scheme 11.

Richards reported that in the absence of *n*-BuLi, molecular modelling showed that there is essentially no difference in the energies of **A** and **B** as the *i*-Pr group lies remote from the unsubstituted cyclopentadienyl ring in **A**.[11] Thus, it is generally accepted that the position of metallation is determined by the organolithium species avoiding repulsive interactions with both the ferrocenyl unit and the oxazoline R-substituent.[11,15] The fact that these reactions are mediated through nitrogen- rather than oxygen-directed metallation was proved by Sammakia via the macrocyclic derivative **48** which contains a rotationally constrained oxazoline moiety. Lithiation and subsequent quenching gave exclusively one diastereoisomer **49**/**50**, which was assigned by X-ray crystallography of **49** (Scheme 12). The oxygen atom in the tether of **48** is not thought to play a significant role in this reaction.[15]

A number of groups have shown that *ortho*-lithiation of 2-ferrocenyloxazolines **15** and in situ quenching with various electrophiles provides highly selective access to enantiopure (S,$_p S$)-*ortho*-substituted 2-ferrocenyloxazoline derivatives **45**, **51**–**61** (Scheme 13)[8,10–15,18] where the former prefix (*S*) indicates the configuration at the oxazoline ring carbon and the latter ($_p S$) the configuration at the ferrocene planar chirality.[10] The corresponding (S,$_p R$)-diastereoisomers **64** have been obtained through introduction of a TMS 'dummy' protecting group which is stable to further metallation and electrophilic substitution to give tri-substituted derivatives such as **63**: subsequent deprotection with TBAF gives the (S,$_p R$)-substituted-2-ferrocenyloxazolines such as **64** (Scheme 13)[11,12,18] The silylated derivative **45c** has also been isolated as a by-product of the reaction of ferrocenyloxazoline **15c** and bis(trimethylsilyl)peroxide (Scheme 14).[43]

The first report on the *ortho*-lithiation-electrophilic substitution of 1,1′-bis(oxazolinyl)ferrocenes appeared in 1995,[19] with additional studies by Ahn[20] and Ikeda.[27] Both the solvent and the structure of the alkyllithium reagent dictate which of the five possible products are obtained (Scheme 15). For example, the highest diastereoselectivity observed was 78:22 (**70**:**71**) using *s*-BuLi (2.6 equiv.) in THF.[27] This has subsequently been increased to 10:1 by Richards et al. in the preparation of **73c** by employing 2.6 equiv. of *s*-BuLi-TMEDA (2.6 equiv.) in diethyl ether.[39]

Dilithiation and subsequent methylation of the phenyl substituted derivative **28f** leads to the major product **74** arising from reaction at the benzylic positions (Scheme 16).[27]

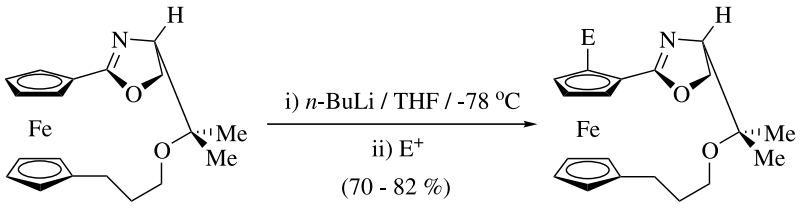
The stereochemical assignments of the 1:1 complex of **71b**-$PdCl_2$ [in which the palladium is bound by *P*,*N* chelation with the (*R*)-configuration oxazoline] is supported by X-ray crystallography.[19] Additionally X-ray structures of **69d**[20] and **73d** (obtained under similar lithiation conditions that gave **70**)[27] have also been reported. The X-ray crystal structure of **73** (obtained along with **75** by *ortho*-methylation, as shown in Scheme 17)[27,39] established that the molecule has a C_2-symmetric configuration and an ($_p S$)-configuration around the ferrocene axis for each ferrocene ring (Scheme 17). In the first work in this area **72** was incorrectly assigned as **70**, and that the crystal structure of **73d** represented is that of the wrong isomer.[19,27,36]

Ahn et al. have shown that 1,1′-bis(oxazolinyl)-biferrocenes can also be *ortho*-substituted. Silylated 1,1′-bis(oxazolinyl)biferrocenes **41** and **43** [obtained by reaction with *n*-BuLi and subsequent reaction with TMSCl or TESCl] are efficient ligands in the asymmetric intermolecular Cu(I)-catalysed cyclopropanation of styrene with diazoacetates in the presence of 5 mol% CuOTf-**41**/**42** complex (Scheme 18). The resulting cyclopropanes, **77**/**78**, were isolated in up to 99% ee with an *l*-menthyl derived diazoacetate, although with a low *cis*:*trans* selectivity (23:77).[21]

More recently these complexes have been utilised in the intramolecular Cu(I)-catalysed cyclopropanation of ene-diazoacetates (Scheme 18).[42] A slightly better enantioselectivity was obtained when **80** was used as a substrate, although the chemical yield of the product was greatly decreased.

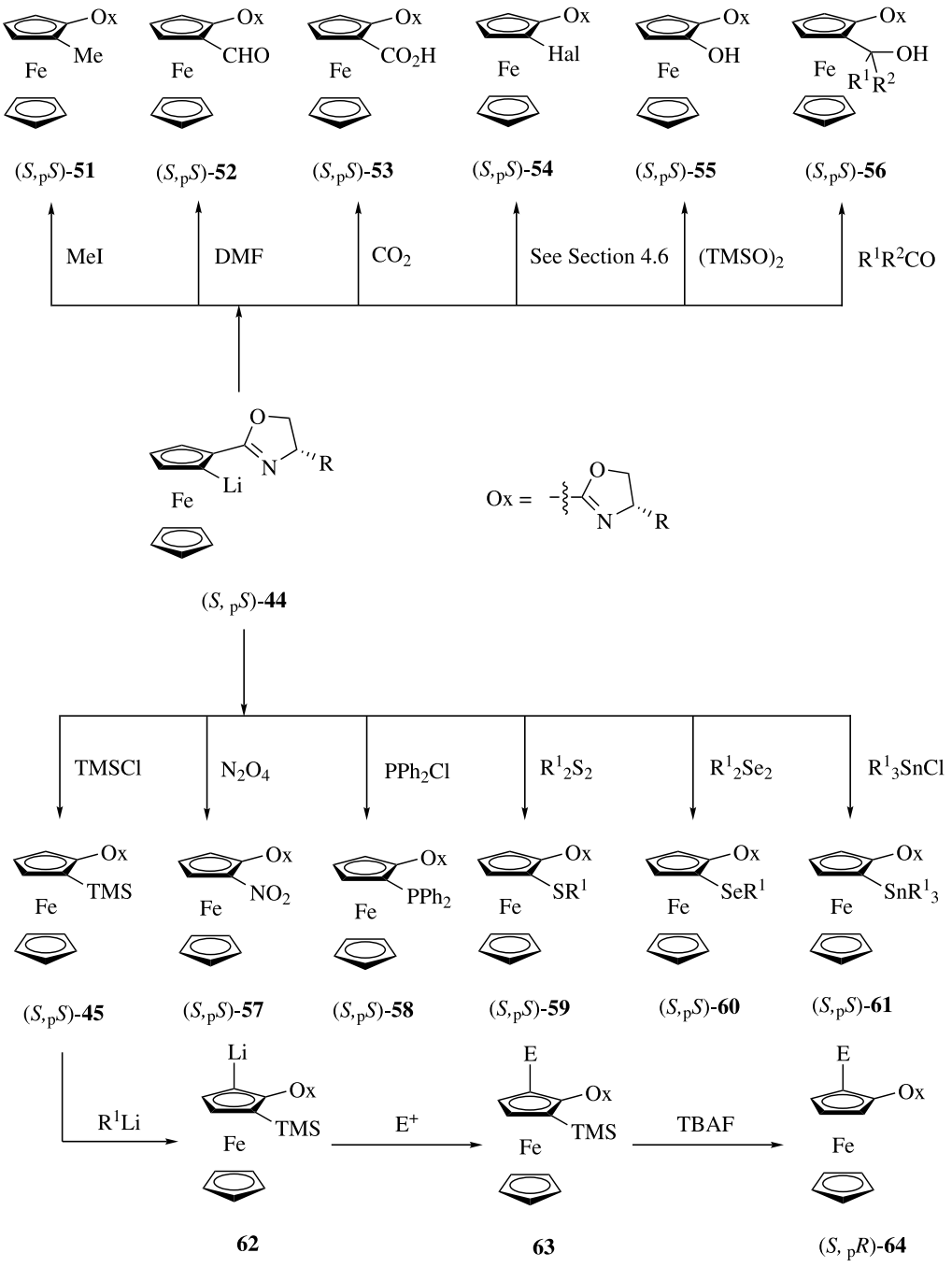
4. Applications in asymmetric synthesis

The importance of chiral recognition in biological systems has made the production of enantiomerically pure drugs a key requisite in lead design within the pharmaceutical industry. Consequently, great efforts have been made towards the development of asymmetric catalytic reactions and in the design of chiral ligands. Among them, ferrocene containing ligands are very interesting because of the ease in which planar chirality can be



48 **49, 50**

Scheme 12. **49**, E = Me; **50**, E = TMS.



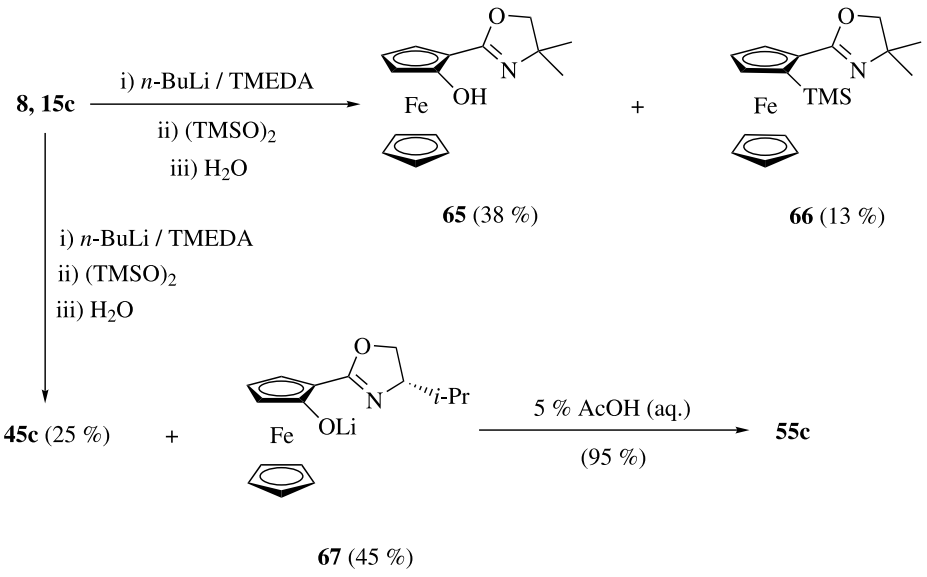
Scheme 13.

introduced and the inherent special electronic properties of ferrocene itself (see Section 5).

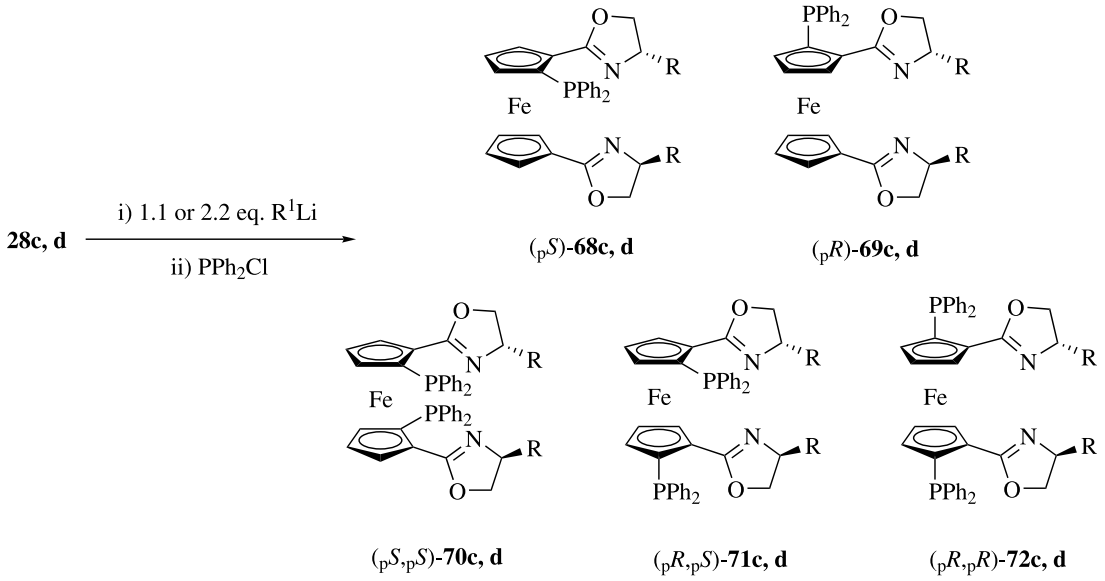
Through the pioneering work of Richards, Sammakia and Uemura, a robust and facile method of synthesising planar chiral 2-ferrocenyloxazolines containing secondary functional groups in both high yield and enantiopurity has been developed. A wide range of mono- and 1,1′-bis(oxazolinyl)ferrocene derivatives have been prepared by a number of groups and many have found application as chiral modifiers in asymmetric reactions. Additionally, a number of chiral 2-ferrocenyloxazolines[44–50] and 1,1′-bis(oxazolinyl)ferrocenes[37–39] serve as intermediates in the preparation of other chiral ligands used in asymmetric catalysis.

4.1. Nitrogen containing derivatives

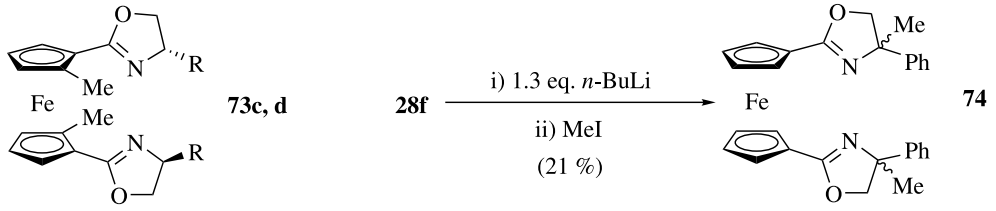
Until recently only one example of a chiral 2-ferrocenyloxazoline derivative with a secondary nitrogen-containing substituent had been reported, viz. (S_pS)-2-nitroferrocenyloxazoline **57c** prepared by Richards et al. by treatment of **15c** with *n*-BuLi and dinitrogen tetroxide. The (S_pR)-isomer was obtained from **15c** through use of a removable trimethylsilyl



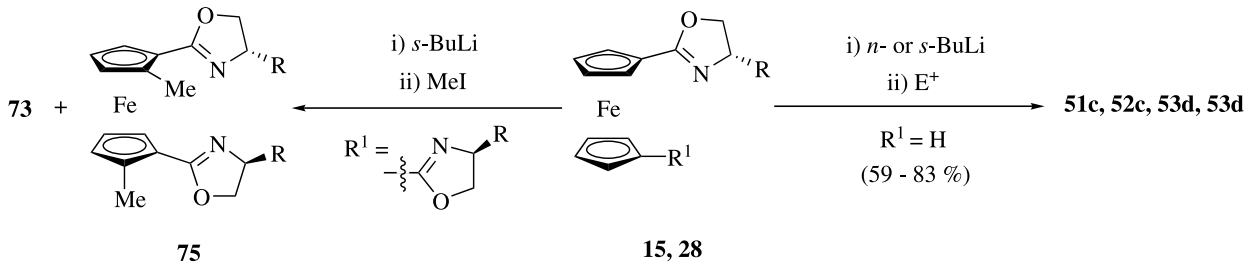
Scheme 14.



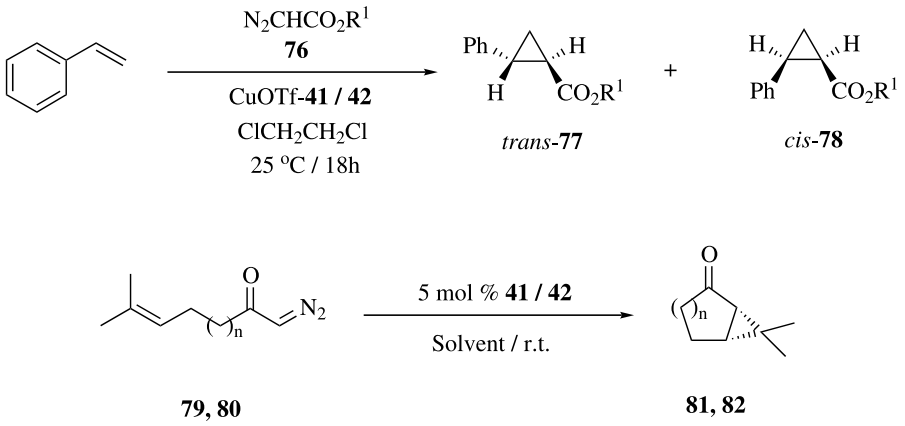
Scheme 15.



Scheme 16.



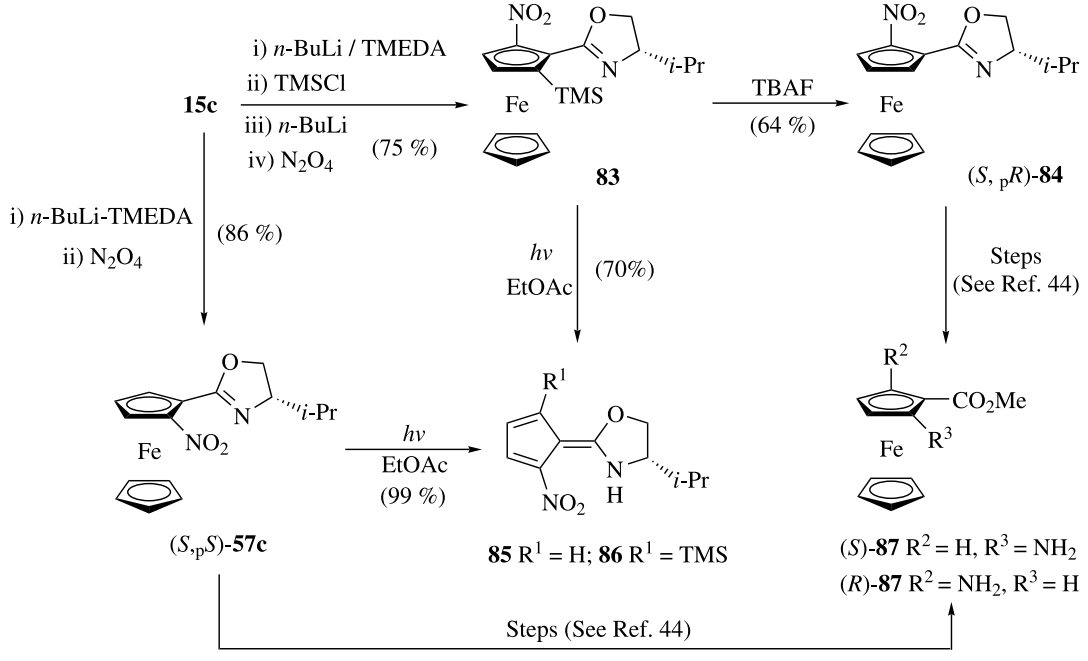
Scheme 17.



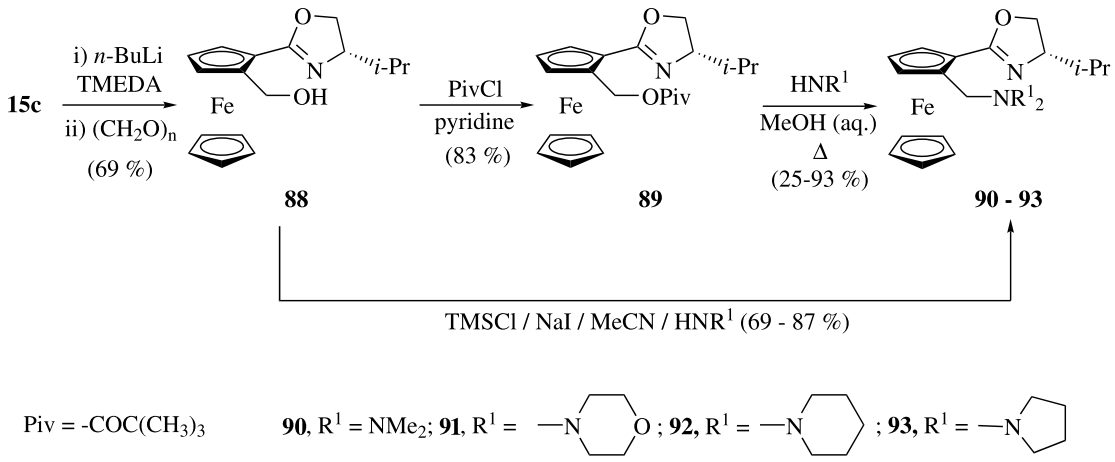
Scheme 18. **79**, $n=1$; **80**, $n=2$.

blocking group (which was introduced in a one-pot procedure) prior to further lithiation and addition of N_2O_4 (Scheme 19). These light-sensitive nitro-2-ferrocenyloxazolines could be further manipulated to give ($_pS$)- and ($_pR$)-2-aminoferrocenecarboxylic acid derivatives **87** and they also underwent facile photo-decomplexation to give nitrofulvalenes **85** and **86**.[44]

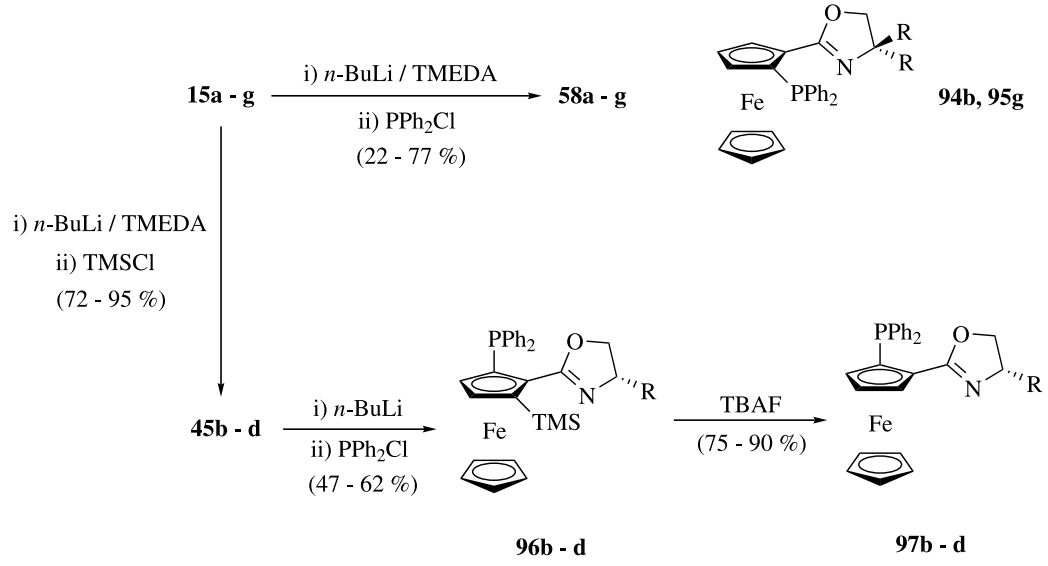
N,*N*-Disubstituted 2-ferrocenyloxazoline derivatives **90**–**93** have been reported by Sebesta et al. 2-Pivaloyloxymethyl derivative **89** (obtained from compound **88**)



Scheme 19.



Scheme 20.



Scheme 21.

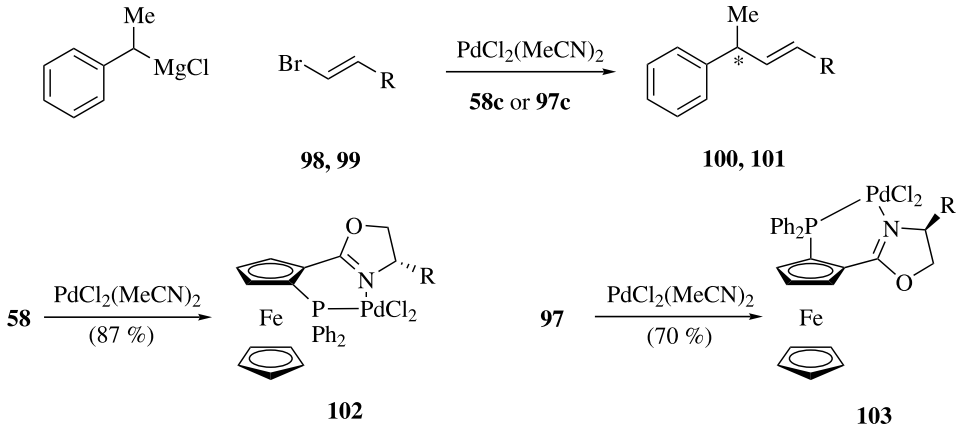
was converted into **90–93** as shown in Scheme 20. Compounds **90–93** were also prepared by treatment of **88** with TMSCl–NaI[51] and subsequent reaction with the amine.[52]

4.2. Phosphorus containing derivatives

A number of groups have shown that *ortho*-lithiation of 2-ferrocenyloxazolines **15** and in situ quenching with chlorodiphenylphosphine provides highly selective access to enantiopure ($S_{,p}S$)-*ortho*-phosphino substituted 2-ferrocenyloxazoline derivatives **58** (Scheme 21)[8,10–15,18] The corresponding ($S_{,p}R$)-diastereoisomers **97** have been obtained through introduction of a TMS blocking group, metallation and quenching with *n*-BuLi/Ph_2PCl and subsequent deprotection with TBAF.[11,12,18] Better yields of the ($S_{,p}R$)-diastereoisomers are obtained in a one-pot procedure (75–76% yields from **15**).[12]

Both **58c** and **97c** have been applied in the palladium-catalysed Grignard cross-coupling of 1-phenylethylmagnesium chloride with (*E*)-β-bromostyrene **98**, **99**. The former ligand gave the more encouraging result: use of 1 mol% of **58c**–$PdCl_2$ gave the (*S*)-configuration cross-coupled product **100**, **101** (74% yield, 45% ee), compared to the isomeric ligand **97c** (23% yield, 8% ee). The addition of $NiCl_2$ as a co-catalyst showed little improvement (Scheme 22).[53] X-Ray crystal structures of **102**[18] and **103**[53] reveal the differences in these complexes due to the opposite configurations of their elements of planar chirality.

Sammakia et al. have shown that the palladium catalysed 1,4-cross-coupling of *n*-butylmagnesium chloride to cyclohexenone proceeds cleanly in high yield and asymmetric induction in the presence **58b**,**c**,**d**,**f** and **g** with CuI.[54] Reaction of *n*-BuMgCl with cyclohexanone in the presence of 15 mol% of **58c** and 10 mol% of CuI, cleanly gave **A** (80% yield, 82% ee) (15:1 ratio



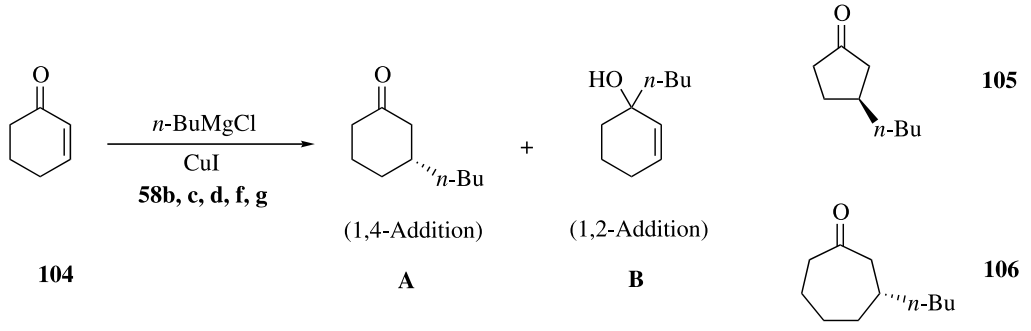
Scheme 22. **98**, **100**, R = H; **99**, **101**, R = Ph.

of **A**:**B**) (Scheme 23)—not surprisingly in the absence of CuI only 1,2-addition is observed. Slightly better results were obtained using **58f** (97% yield, 83% ee). Although variation of the alkyl group situated on the oxazoline ring was shown to have little influence on the reaction, the authors concluded that the additional planar chirality imparted by the ferrocenyl template is essential for producing high levels of asymmetric induction.

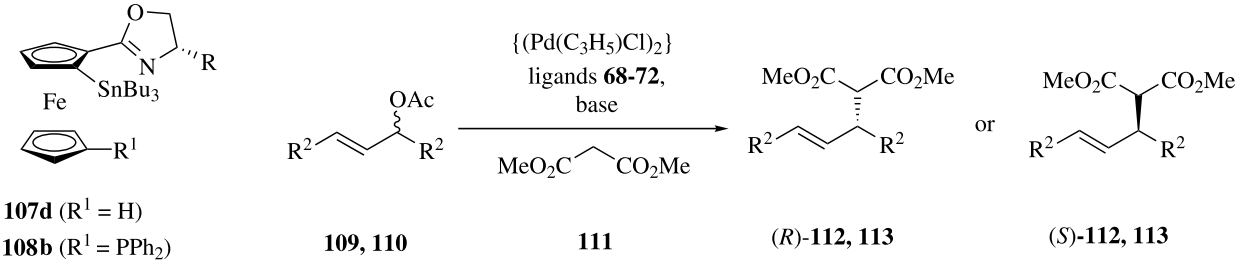
Other cyclic enones were studied under similar conditions with ligand **58f** and enantiomeric excesses of 63, 83 and 92% were obtained for cyclopentenone, cyclohexeneone and cycloheptenone, respectively, in reactions that proceed with >100:1 selectivity for 1,4-addition over 1,2-addition. The use of additives such as HMPA increased the selectivity of **A**:**B** (>100:1) but decreased the ee to 56%.

1,1′-Bis(oxazolinyl)ferrocene ligands **68**–**72** (Scheme 15) are catalysts for the Pd-catalysed allylic substitution of **109**, **110** with **111** to give (*S*)-**112**, **113** (Scheme 24).[22,35,50] The complexes derived from **70** and **71** are especially efficient suggesting that diphosphines may act in these reactions as *P*,*P*-chelating ligands, whereas the lower activity of **68** and **69** may be due to *P*,*N*-complexes being formed with $PdCl_2$.

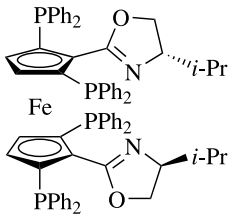
ortho-Functionalisation of chiral 2,2′-bis(oxazolinyl)-1,1′-bis(diphenylphosphino)ferrocenes **70**–**72** (Scheme 25) provided phosphorylated and silylated derivatives **114**–**121** which were employed by Park et al. in the allylic substitution of **110** with dimethyl malonate. The major product has (*S*)-configuration in the reactions employing **70c**, **71c**, **72c** and **116** and the monosilylated ligand **121** [derived from the ($_p$*S*,$_p$*S*)-diastereoisomer



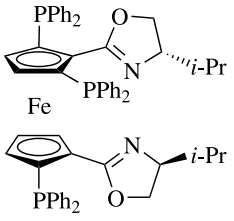
Scheme 23.



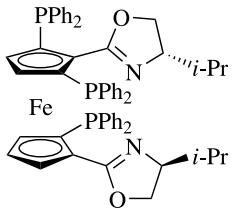
Scheme 24. **109**, **112**, R^2 = Me; **110**, **113**, R^2 = Ph.



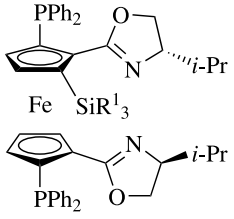
114



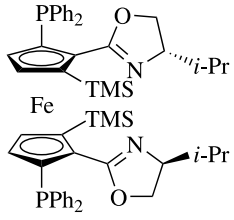
($_pR$)-**115**



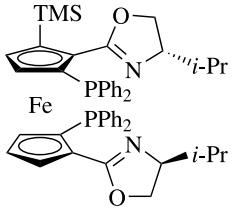
($_pS$)-**116**



($_pR$,$_pR$)-**117** (R^1 = Me)
($_pR$,$_pR$)-**118** (R^1 = Et)
($_pR$,$_pR$)-**119** (R^1 = Ph)



120



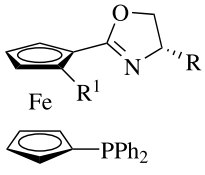
121

Scheme 25.

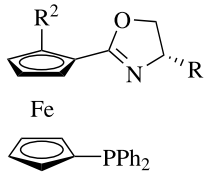
71c] with enantioselectivities up to 99% ee. In contrast, the enantioselectivity was reversed to give the (*R*)-product in the processes mediated by ligands derived from the ($_pR$,$_pR$)-diastereoisomer **71c** (up to 96% ee) (Scheme 24).[40]

In the above cases, the two coordinating groups are situated on the same Cp-ring. Dai and Hou examined the effects when they are disposed on two different Cp rings.[55,56] Ikeda's chiral *P*,*N*-ligand, (*S*)-**33c** (which has proved to be effective in Pd-catalysed allylic substitution with 91% ee)[31] was *ortho*-substituted to give the five planar chiral ligands, (S,$_pR$)-**122c**, (S,$_pS$)-**123c**, (S,$_pS$)-**108c**, (S,$_pR$)-**126c**, and (S,$_pS$)-**125c** (Scheme 26). The effectiveness of these ligands as chiral catalysts in the palladium-catalysed allylic substitution of acetate **110** with the nucleophile derived from dimethyl malonate (in the presence of BSA-KOAc) (Scheme 24) was examined and the results are shown in Table 2.

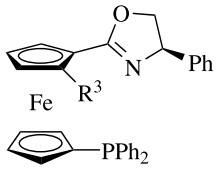
The authors found that a dramatic change in chiral induction occurred. From (*S*)-**33c** to (S,$_pR$)-**122c**, enantioselectivity decreased from 91% ee (*S*) to 34.2% ee (*R*) and from (*S*)-**33**c to (S,$_pS$)-**123c**, they observed a decrease from 91% ee (*S*) to 64% ee (*R*). Dai and Hou envisaged that matched isomers for this reaction which are (S,$_pS$)-**125c** and (S,$_pR$)-**126c** would show enhanced enantiocontrol. As expected (S,$_pR$)-**126c** showed an increased 98.6% ee (*S*); while that of (S,$_pS$)-**125c** was 98.5% ee (*S*). Introduction of a third group in a proper disposition favours the formation of one rotomer over the other, consistent with the % ee values of the products. Additionally it appears that the increase in enantioselectivity corrolates directly with the increased steric bulk of the third group (Table 2, entries 3 versus 11) as in the derivative **108c** which was shown to be effective chiral mediator (2.5 mol%) in the Pd-catalysed allylic alkylation of diphenylprop-2-enyl acetate **110** with dimethylmalonate [98% yield of (*R*)-**113**, 83.3% ee (1 equiv. KOAc) and 77.7% ee (no KOAc present)] (Scheme 24).[55]



122c (R^1 = Me)
123c (R^1 = TMS)
124g (R^1 = TMS)



125c (R^2 = Me)
126c (R^2 = TMS)
127g (R^2 = Me)
128g (R^2 = TMS)



129f (R^3 = TMS)
130f (R^3 = Me)

Scheme 26.

Table 2. The effect of different ligands on the enantioselectivity and configuration of the product in Pd-catalysed allylic alkylation[55]

Entry	Ligand	% Yield[a]	% ee[b]	Config.[c]
1	**33c**	99	91.0	(*S*)
2	**33c**	98	92.8[d]	(*S*)
3	**123c**	98	69.7	(*R*)
4	**123c**	99	64.0[d]	(*R*)
5	**124c**	98	34.2	(*R*)
6	**125c**	99	98.5[d]	(*S*)
7	**125c**	99	98.2	(*S*)
8	**125c**	99	87.8[e]	(*S*)
9	**126c**	99	98.6[d]	(*S*)
10	**126c**	99	97.8	(*S*)
11	**108c**	98	83.3	(*R*)
12	**108c**	98	77.7[d]	(*R*)

[a] Isolated yield.
[b] The ee value for **113** was determined by HPLC.
[c] Configurations were assigned by comparison of the sign of optical rotation.
[d] No KOAc was used.
[e] KOAc:ligand (10:1 equiv.) was used.

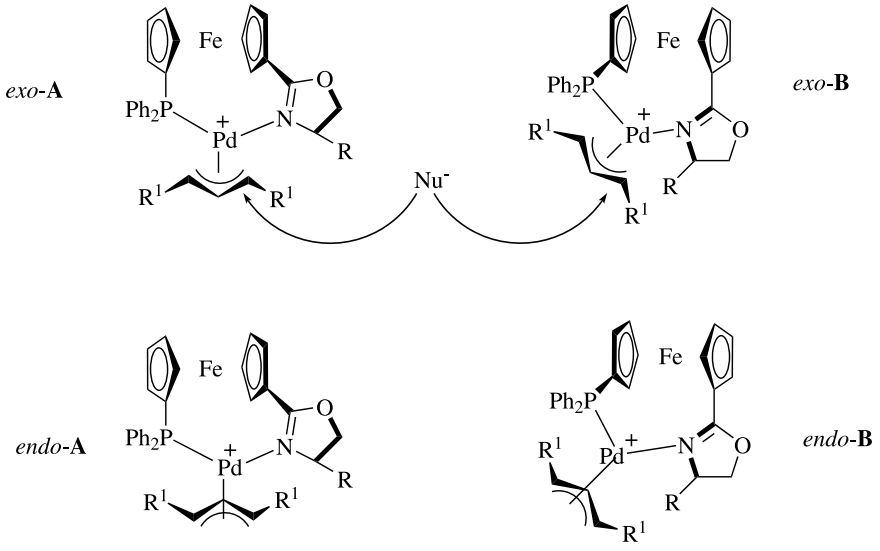
Similar results for Pd-catalysed asymmetric allylic substitution were obtained by Ahn et al. who explained the predominance of the (*S*)-configuration product in this reaction by preparing the four 1:1 complexes obtained from [(η^3-allyl)-$PdCl_2$] and [(η^3-1,3-diphenylallyl)-$PdCl_2$] with **33c** and **33d**. Analysis of the ^1H, ^{13}C and ^{31}P NMR data indicated that for simple (π-allyl)Pd(II) complexes, interconversion between isomers is rapid enough at room temperature to show only one set of resonance lines in ^1H NMR spectra via allyl isomerisation as well as rotation of the Cp-rings. However, the *exo*-isomers **A** and **B** seem to predominate with slow η^3-η^3 allyl isomerisation in the solutions of [(η^3-1,3-diphenylallyl)-Pd(**33**)]Cl, and nucleophilic attack *trans* to Pd–P bond of these isomers will lead to the (*S*)-product (Scheme 27).[23]

Table 3. Enantioselective allylic alkylations with chiral phosphaferrocenyloxazoline ligands[57]

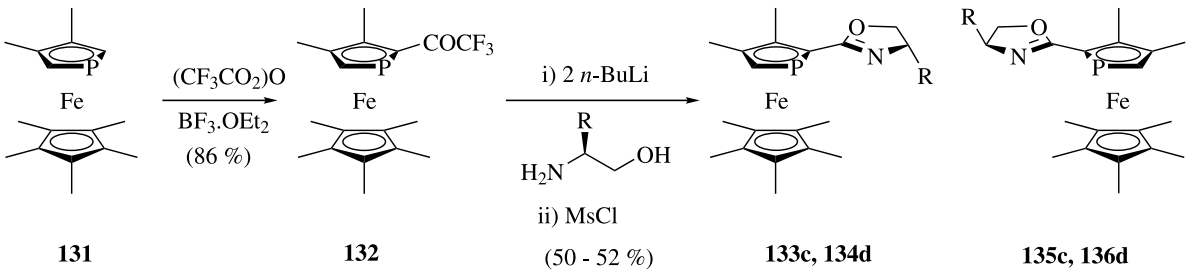
Entry	Ligand	Time (h)	% Yield[a]	% ee[b] (Config.[c])
1	**133c**	16	80	68 (*R*)
2	**135c**	4.5	94	79 (*S*)
3	**134d**	36	70	73 (*R*)
4	**134d**	4.5	92	82 (*S*)

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The absolute configuration was assigned by comparing the sign of its optical rotation with literature data.

More recently Fu et al. have reported the synthesis of a number novel chiral phosphaferrocenyloxazolines, **133**, **134** and **135**, **136** (Scheme 28) and shown that they act



Scheme 27.



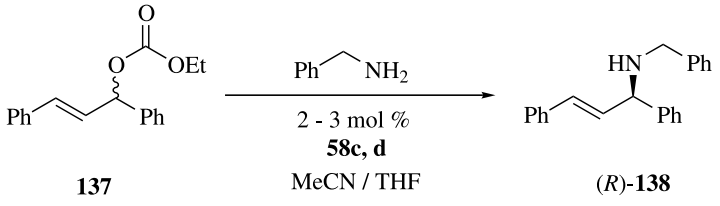
Scheme 28.

as efficient ligands for Pd-catalysed allylic alkylations (Table 3).[57] Interestingly, in contrast to ligands **58** and **97** which demonstrate that the chirality of the oxazoline ring is the primary determinant of the stereochemical outcome of these reactions,[22,58] the planar chirality of the phosphaferrocene subunit appears predominantly to control the stereochemistry of the products.

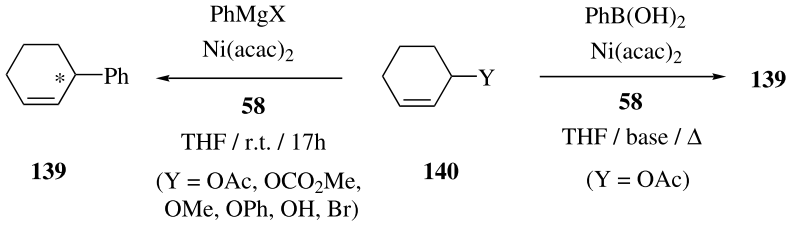
Guiry et al. have applied Pd complexes of ligands such as **58c** and **58d** in the palladium catalysed enantioselective allylic amination of ethyl (2*E*)-1,3-diphenylprop-2-enyl carbonate **137** with benzylamine. The (*R*)-product **138** was obtained in moderate to high yield and moderate enantioselectivity (Scheme 29).[59] Enantioselectivity was improved (up to 97.9% ee) by the addition of 2–4 equiv. of TBAF.[50]

Phosphino-substituted 2-ferrocenyloxazolines are also effective chiral *P*,*N*-ligands in the Ni(0)-catalysed cross-coupling of allylic compounds with Grignard reagents: products **139** were obtained in both high yield with good enantioselectivity (Scheme 30).[60] In addition, these ligands were also efficient in the Ni(0)-catalysed Suzuki-type coupling of arylboronic acids (Scheme 30).[61] Although the former coupling reaction proceeded at lower temperature than the latter, the chemical yields and enantioselectivities were much higher. Additionally both reactions illustrated that the ferrocene-based ligands with planar chirality are, in comparison, more effective than the phosphino-substituted 2-phenyloxazolines which have only central chirality.

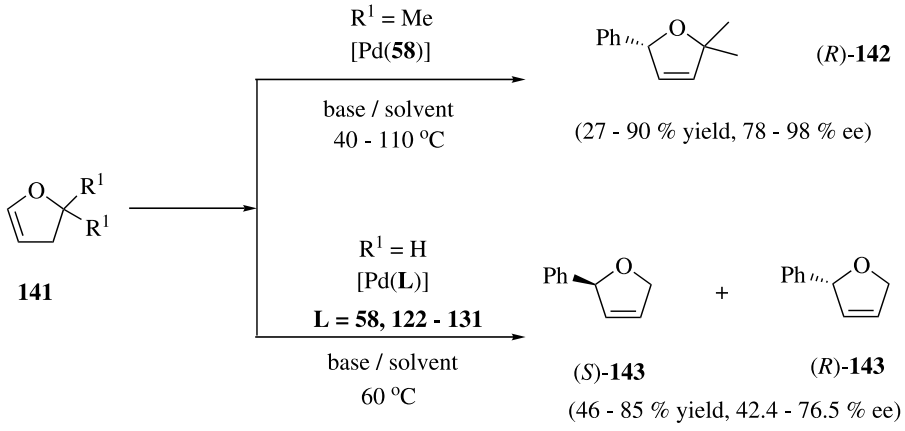
Similarly, **58c** and **58d** have been shown by Guiry et al. to be effective in the Pd-catalysed asymmetric Heck reaction of 2,2-dimethyl-2,3-dihydrofuran **141** (R^1 = Me) (Scheme 31).[62] Following this initial report Hou et al. studied the effect of placing the two chelating substituents on separate Cp rings. A number of 1,1′-*P*,*N*-ferrocene ligands were shown to be efficient chiral mediators. Interestingly, Guiry's ligands **58** were shown to have almost no catalytic activity even after 24 h. Considering the high reactivity of ligands **33g** and **33f**, the authors envisaged that the enantioselectivity and/or configuration of the product might be improved and/or inverted by introducing planar chirality into these ligands.[63]



Scheme 29.



Scheme 30.



Scheme 31.

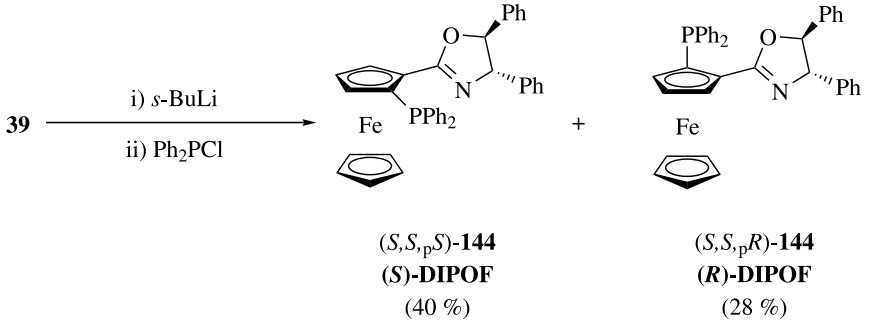
Table 4. Enantioselective Heck reaction of **141** and PhOTf with various ligands[63]

Entry	Ligand	Time (h)	% Yield[a]	% ee[c] (Config.[d])
1	(*S*)-**33g**	8	80	76.5 (*R*)
2	(S,$_p$*S*)-**124g**	8	72	83.5 (*S*)
3	(S,$_p$*S*)-**127g**	8	79 (82)[b]	88.5 (*R*)
4	(S,$_p$*R*)-**128g**	8	75	92.1 (*R*)
5	(*R*)-**33f**	8	79	42.4 (*S*)
6	(R,$_p$*R*)-**129f**	8	75	80.2 (*R*)
7	(R,$_p$*R*)-**130f**	8	85 (91)[b]	88.4 (*S*)

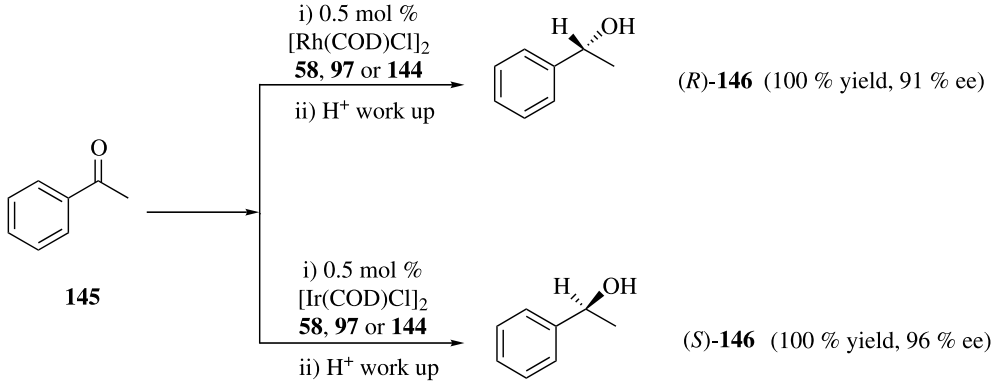
[a] Isolated yields based on PhOTf.
[b] Determined by GC.
[c] Determined by chiral GC.
[d] Configurations were assigned by comparison of the signs of optical rotation.

Planar chiral ligands (S,$_p$*S*)-**124g**, (S,$_p$*S*)-**127g** and (S,$_p$*R*)-**128g**, (R,$_p$*R*)-**129f** and (R,$_p$*R*)-**130f** were prepared and tested in the reaction using **141** (R^1 = H) as substrate. The enantioselectivity of the reaction product **143** changed from 76.5% (*R*) by using ligand **33g** to 83.5% (*S*) using (S,$_p$*S*)-**124g** (Table 4, entry 2) which represents a striking change in enantioselectivity. Similar phenomena were observed for other ligands indicating that the effect of planar chirality on the stereochemical outcome is significant in this reaction. Moreover, increasing the steric bulk of the planar chiral group also improved enantioselectivity.

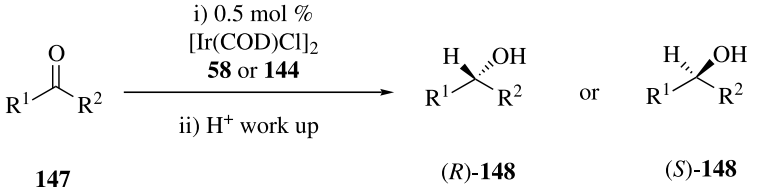
Uemura et al. used ligands **58c** and **58d** in the Rh-catalysed asymmetric hydrosilylation of acetophenone to give (*R*)-1-phenylethanol **146** with 48 and 60% ee, respectively.[8,9] The presence of an additional substituent on the oxazoline ring, as in **144** (prepared from **39**) (Scheme 32) can significantly improve this selectivity. Rh-catalysed reduction of acetophenone with **145**/$[Rh(COD)Cl]_2$ gave (*R*)-**146** in quantitative yield and high enantioselectivity.[9] Similar selectivities were also observed for other arylmethyl ketones (99–100% yield, 80–90% ee) and bulky alkylmethyl ketones (45–100% yield, 87–89% ee) (Scheme 33).[9]



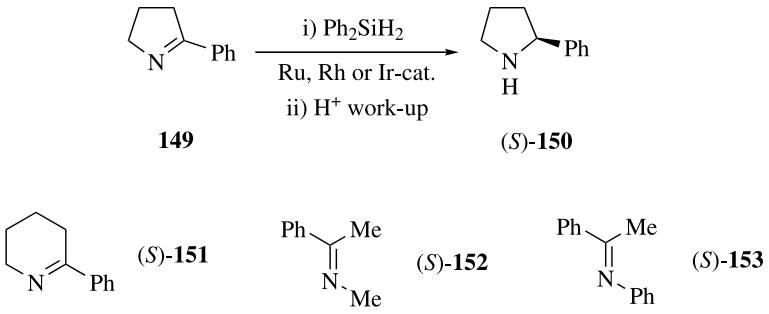
Scheme 32.



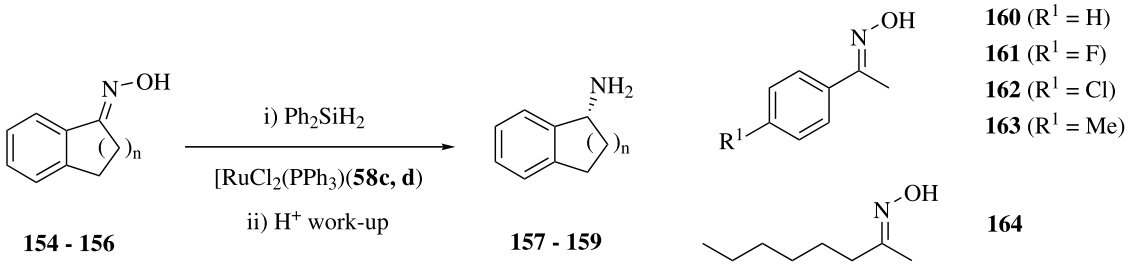
Scheme 33.



Scheme 34.



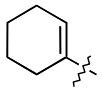
Scheme 35.



Scheme 36.

Replacing $[Rh(COD)Cl]_2$ by $[Ir(COD)Cl]_2$ gave the opposite enantiomer (*S*)-**146** with a slightly higher selectivity (100% yield, 96% ee) (Scheme 33). This result represents the first highly enantioselective Ir(I)-catalysed hydrosilylation of a ketone. Subsequently the DIPOF-Ir(I)-system has been successfully applied by Uemura et al. to the reduction of a number of other aryl-, heteroaryl-, alkyl- and alkenyl-ketones (Scheme 34, Table 5).[64] Five-coordinate Ru(II) species have been shown to provide even greater selectivities (42–80% yield, 43–97% ee).[65]

Table 5. Enantioselective Ir(I)-catalysed hydrosilylation of ketones[64]

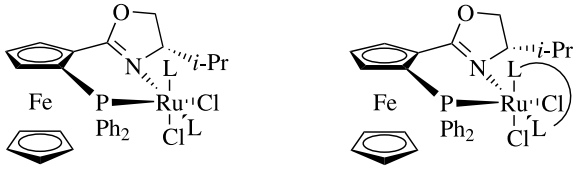
Entry	R	R_1	% Yield[a]	% ee[b] (Config.[c])
1	Ph	Me	100	96 (*R*)
2	Ph	Et	100	92 (*R*)
3	Ph	*n*-Pr	100	91 (*R*)
4	Ph	*i*-Pr	78	9 (–)
5	4-MeC_6H_4-	Me	100	91 (*R*)
6	4-ClC_6H_4-	Me	97	88 (*R*)
7	2-MeC_6H_4-	Me	98	88 (*R*)
8	2-Thienyl	Me	100	83 (*R*)
9	2-Furyl	Me	100	81 (*R*)
10		Me	100	84 (–)
11	$Me(CH_2)_5$-	Me	100	19 (*S*)

[a] Determined by GLC.
[b] Determined by HPLC and GLC.
[c] Determined by comparison of the sign of the optical rotation with literature values.

The Ru(II)-, Rh(II)- and Ir(I)-catalysts, $[RuCl_2(PPh_3)$(**58**)], $[M(COD)Cl]_2$-(**58**) (M = Rh or Ir), $[M(COD)Cl]_2$-(**144**) (M = Rh or Ir) (prepared from the phosphino-2-ferrocenyloxazolines **58** and **144**) are efficient catalysts for the asymmetric hydrosilylation of imines **149**, **151**–**153** to give the corresponding secondary amines after acid hydrolysis [Ru(II)-catalysts, 10–82% yield, 25–73% ee; Rh(II)-catalysts, 17–>95% yield, <5–34% ee and Ir(II)-catalysts, 18–>95% yield, 7–89% ee] (Scheme 35).[65,66]

Uemura et al. have also reported that ligands **58c** and **58d** are effective in the Ru(II)-catalysed asymmetric hydrosilylation of ketoximes **154**–**156** and **160**–**164** in conjunction with AgOTf to give the corresponding primary (*R*)-amines (70–>95% yield and up to 89% ee) (Scheme 36).[67]

In the context of chiral Ru(II) complexes, Gimeno et al. have recently published the stereoselective synthesis and X-ray structure of the first octahedral Ru(II)-complexes **165** and **166** containing the chiral ligand **58c** (FcPN) from the known complex $[RuCl_2(PPh_3)$(FcPN)] via phosphine exchange, paving the way for the preparation of novel derivatives for use in catalytic studies (Scheme 37).[68]



Scheme 37.

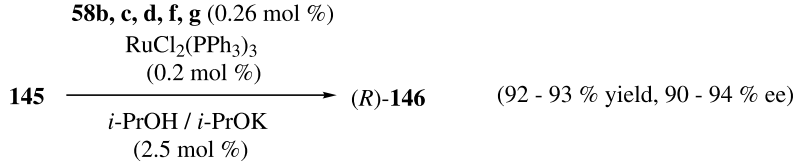
Sammakia et al. and Dai et al. have demonstrated that a number of the ligands **58b**,**c**,**d**,**f** and **g** can be used as catalysts for the asymmetric transfer hydrogenation (Meerwein–Ponndorf–Verley reduction) of ketones. The parent ligands **58b**,**c**,**d**,**f** and **g** (0.26 mol%) can efficiently transfer hydride from 2-propanol when used in tandem with $RuCl_2(PPh_3)_2$ (ca. 0.2 mol%) at 28°C. In each case acetophenone was reduced to (*R*)-**146** in high yield and high enantioselectivity (Scheme 38).

Other arylmethyl ketones similarly gave the corresponding (*R*)-alcohols (Scheme 39). Although sterically hindered or electron-rich substrates required elevated reaction temperatures (50–80°C) these conditions resulted in a less than 10% reduction in overall ee.[69]

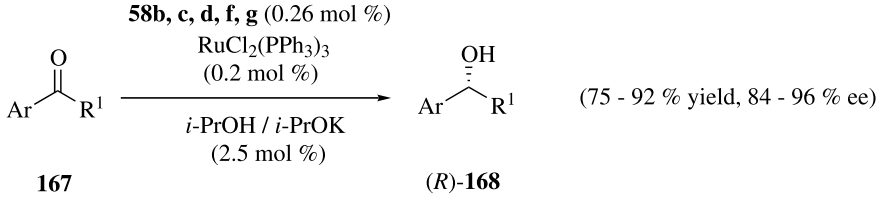
Similar results were obtained by Dai et al. who performed the transfer hydrogenations with **58c** and **97c** in refluxing *i*-PrOH. Although a number of (*R*)-alcohols were produced from the corresponding arylmethyl ketones with good conversions the enantioselectivites were lower (58–85% ee) (Scheme 40). Both groups observed that the higher temperatures and longer reaction times required for complete conversion led to a decrease in enantioselectivity and attributed this to the reversibility of the reaction with *i*-PrOH as the hydrogen source.[56,70]

More recently the Ru(II) complex **171** has been applied as a catalyst for the asymmetric transfer hydrogenation of not only alkylaryl ketones [to yield (*R*)-alcohols **173**], but also alkylmethyl ketones [to yield (*S*)-alcohols **173**] with *i*-PrOH/*i*-PrONa. Additionally, asymmetric Oppenauer oxidation of *rac*-secondary alcohols **174** with acetone via kinetic resolution using the same catalyst proceeds in moderate yield with extremely high enantioselectivity to afford (*S*)-alcohol **173** (Scheme 41).[71]

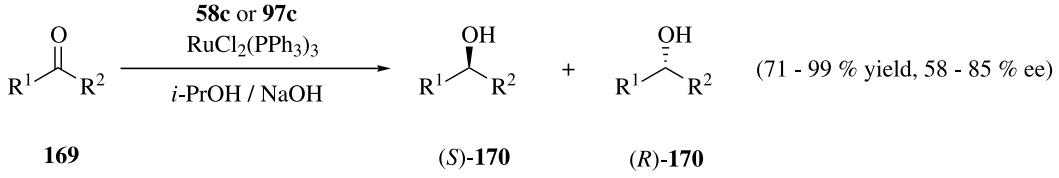
Phosphino-2-ferrocenyloxazolines **58d** and **123d** have been converted into the corresponding carboxylic acids **174**, **175** which are moderate mediators of Pd-catalysed asymmetric allylic alkylation (96–98% yield, 30–50% ee) (Scheme 42).[49]



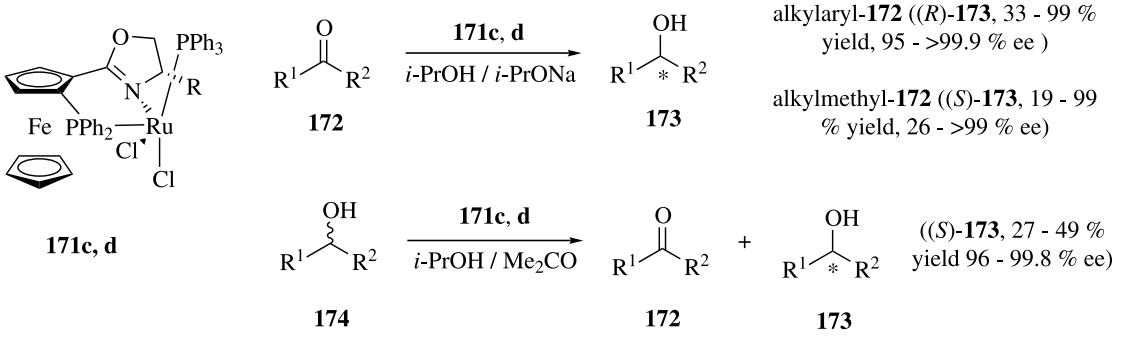
Scheme 38.



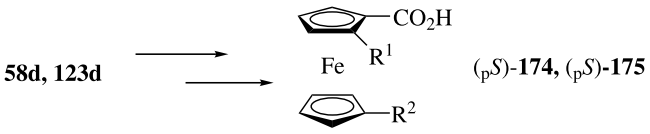
Scheme 39.



Scheme 40.



Scheme 41.



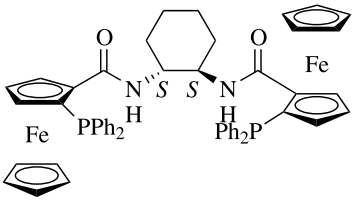
Scheme 42.

Additionally **58d** (which like **97d** is a poor catalyst in the asymmetric allylic alkylation of iminoesters with allyl carbonates) has been converted into the novel bis-*N*-[2-(diphenylphosphino)ferrocenylcarbonyl]diaminocyclohexane ligands (*S*,*S*)-**176** and (*S*,*S*)-**176** which are moderate mediators of this process (up to 75.3% ee) (Scheme 43).[47]

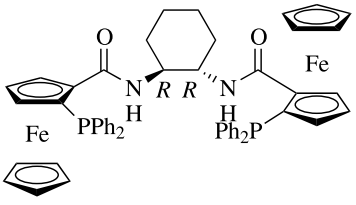
Bis(oxazolinyl)ferrocene-biphosphine ligand **71c** undergoes an irreversible fragmentation with elemental sulfur to give the fulvene derivative **190** (Scheme 44).[41]

4.3. Hydroxy, alkoxy and carboxy derivatives

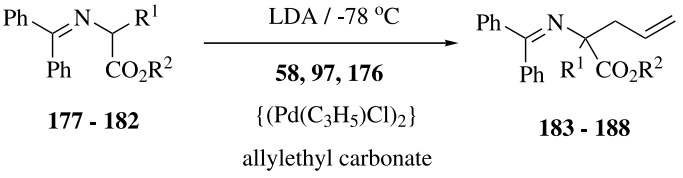
In 1995, Sammakia et al. reported the first examples of chiral 2-ferrocenyloxazoline bearing oxygen-based secondary substituents. *ortho*-Lithiation and quenching with TMSCl of **15c**, **15d**, **15f–h**, **15j**, **15l**, **16m** and **16n** gave the corresponding silylated derivatives **45c**, **45d**, **45f–h**, **45j**, **45l**, **191m** and **191n** (with the oxygen-based substituent attached to the oxazoline ring) where the diastereomer with matched central and planar chirality predominates. Interestingly, steric effects were shown to govern the outcome of the reaction, i.e. as the oxazoline substituent becomes larger—the diastereoselectivity increases (Scheme 45).[13]



(*S*, *S*)-**176**



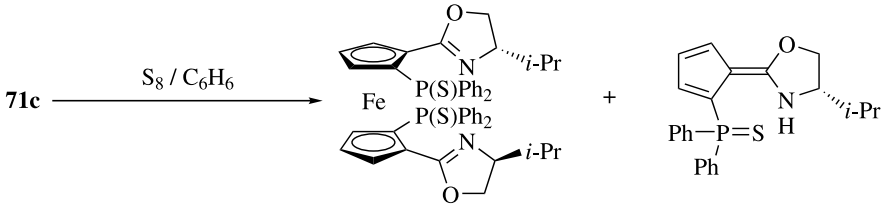
(*R*, *R*)-**176**



177 - 182

183 - 188

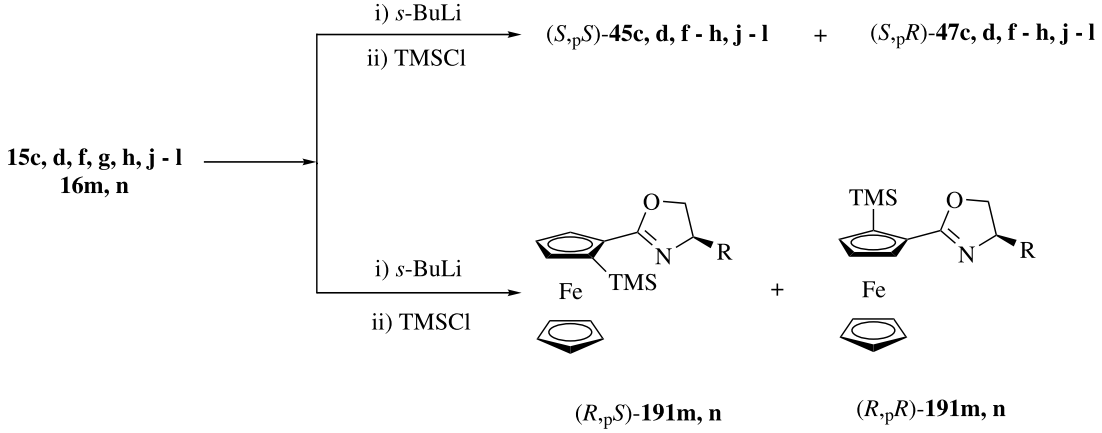
Scheme 43. 177, **183**, R^1 = Me, R^2 = Bn; **178**, **184**, $R^1 = R^2$ = Me; **179**, **185**, R^1 = *t*-Bu, R^2 = Me; **180**, **186**, R^1 = *t*-Bu, R^2 = H; **181**, **187**, R^1 = Et, R^2 = H; **182**, **188**, R^1 = Me, R^2 = H.



189 (trace)

190 (73 %)

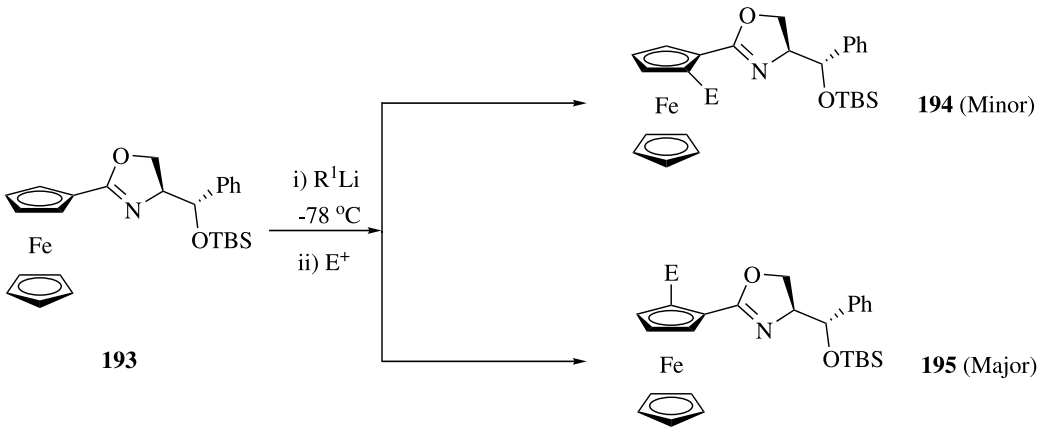
Scheme 44.



(*R*,p*S*)-**191m, n**

(*R*,p*R*)-**191m, n**

Scheme 45.



Scheme 46. 194, **195**, E = Me (95%, **195**); E = TMS (85%, **195**); E = I (48-66%, **195**); E = PPh_2 (68%, **195**); E = SPh (82%, **195**).

Subsequently, two other syntheses of chiral 2-ferrocenyloxazolines of this type were reported. These include tertiary alcohol **24** (prepared by Grignard addition to ester **15o**, and characterised by an X-ray crystal structure)[24] and Balavoine's compound **193** has been *ortho*-lithiated to give further derivatives for the enantioselective allylic alkylation of **110** with dimethylmalonate to give (*S*)-**113**, (95–98% yield, 79–95% ee)[25] (Scheme 46–see also Section 4.4).

Quenching **44** with DMF or CO_2 gave the corresponding formyl[18,72] and carboxylic acid[18] derivatives, **52c** and **53c**, respectively. Formyl derivative **52c** has shown by Fukuzawa and Kato to be a poor chiral mediator in the ethylation of aldehydes with $ZnEt_2$ [11% yield of (*S*)-**199**; 30% ee] compared to the amino derivative (*S*, *R*)-**197** [55–97% yield of (*R*)-**199**; 80–93% ee] (Scheme 47).[72]

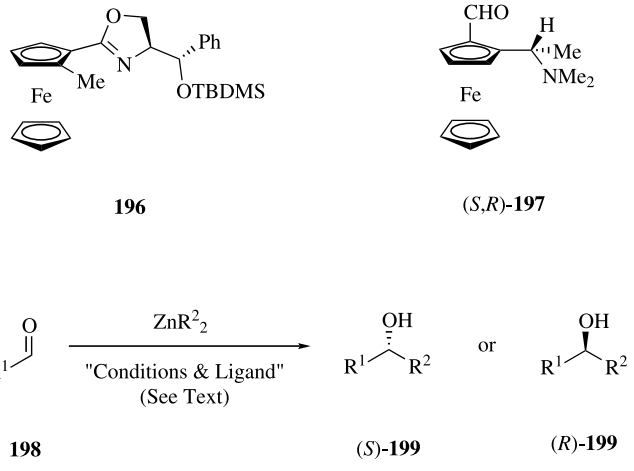
Bolm et al. have shown that *ortho*-lithiation of (*S*)-2-ferrocenyl-4-*tert*-butyloxazoline, **15d**, followed by addition of benzophenone gave diastereomerically pure alcohol derivative **201d** in 87% yield. [The (S_p,*R*)-isomer has also been prepared].[45,73] Other analogues such as **200**,[45] **201f**[45] and the related bis(oxazolinyl)biferrocenes **43**[21,42] have also been reported (Scheme 48). (2-Hydroxymethyl)-2-ferrocenyloxazoline **88** has been recently synthesised by Sebesta et al. and shown to be a useful intermediate in the preparation of (2-aminomethyl)-2-ferrocenyloxazolines **90-93** (Section 4.1).[52]

Ligands of this type (where the secondary substituent is located on the same Cp-ring as the oxazoline unit) have found application in the enantioselective addition of organozinc reagents to carbonyl compounds (Scheme 47).[45,73,74]

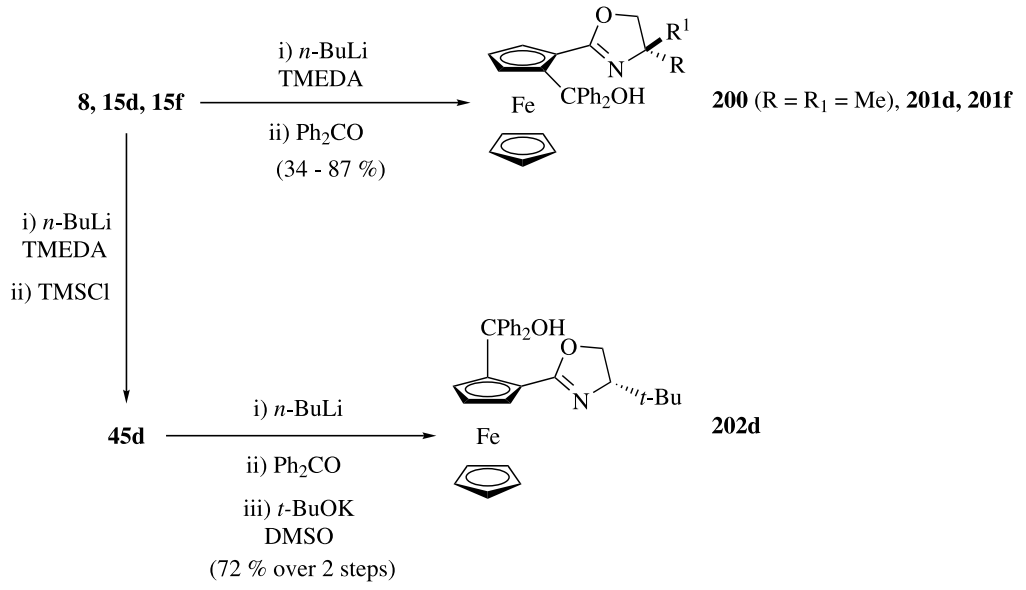
Bolm showed that the asymmetric ethylation of aromatic aldehydes [to give the corresponding (*R*)-alcohols **199**] mediated by 5 mol% of (S_p,*R*)-**201d** proceeded in high yield and with moderate to high enantioselectivity (Table 6). Aliphatic aldehydes are also shown to be reactive (entry 8). Comparing the results from two ligands (S_p,*R*)-**201d** and (S_p,*S*)-**202d** (and on the basis of X-ray crystal structures)[45] the authors determined the importance of planar chirality in this process (entry 1 versus entry 3) (Table 6). This work also highlighted the catalytic properties of stereochemically inhomogeneous mixtures of chiral hydroxymethyl-2-ferrocenyloxazolines in the addition of $ZnMe_2$ to benzaldehyde. The asymmetric catalysis of such reactions was shown not necessarily to require diastereomerically pure ligands for achieving high enantioselectivities (98% yield, 95% ee with a 1:1 mixture of ligands (S_p,*R*)-**201d** and (S_p,*S*)-**202d**).[74]

Hou et al. have shown that related chiral hydroxy(diphenyl)methyl-2-ferrocenyloxazolines **203c**,**d**,**f** and **g** (Scheme 49) are effective ligands in the addition of diethylzinc to aldehydes (especially aromatic derivatives) in high yield and moderate to high enantioselectivity.[75] 1,1′-Bis(oxazolinyl)ferrocene ligands, **204** and **205** have also been reported by Ikeda to be efficient catalysts for the addition of diethylzinc to benzaldehyde giving the (*R*)-alcohol in moderate to high yield (25–97%) and enantioselectivity (70–93% ee).[33]

Chiral hydroxy(diphenyl)methyl-2-ferrocenyloxazolines have also been applied by Bolm et al. in the enantiose-



Scheme 47.

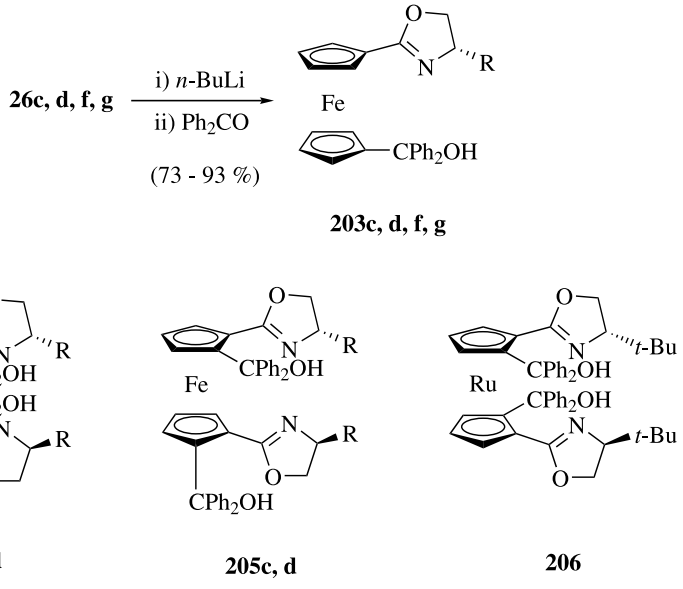


Scheme 48.

Table 6. Enantiomeric excesses resulting from the asymmetric addition of $ZnEt_2$ to several aldehydes in the presence of 5 mol % of ligands[45,76]

Entry	Aldehyde	Ligand	Time (h)	% Yield[a]	% ee[b] (Config.)
1	Benzaldehyde	(S_pR)-**201d**	6	83	93 (*R*)
2	Benzaldehyde	(S_pR)-**201d**	5	99	94 (*R*)
3	Benzaldehyde	(S_pS)-**202d**	59	55	35 (*R*)
4	Benzaldehyde	($_pR$)-**200**	20	97	51 (*R*)
5	Ferrocenecarbaldehyde	(S_pR)-**201d**	3	93	95 (*R*)
6	4-Methoxybenzaldehyde	(S_pR)-**201d**	9	93	91 (*R*)
7	5-(4-Chlorophenyl)-furancarbaldehyde	(S_pR)-**201d**	2	92	91[c] (*R*)[d]
8	Heptanal	(S_pR)-**201d**	26	94	87[e] (*R*)
9	4-Chlorobenzaldehyde	(S_pR)-**201d**	6	94	86 (*R*)
10	Cinnamaldehyde	(S_pR)-**201d**	6	89	78 (*R*)

[a] Isolated yield after column chromatography.
[b] Determined by HPLC analysis on a chiral stationary phase.
[c] >99 % ee after one recrystallisation.
[d] Tentatively assigned by assumption of an identical reaction pathway.
[e] Determined by ^{13}C NMR spectroscopy of corresponding MTPA esters.



Scheme 49.

lective addition of diphenylzinc to aromatic aldehydes giving enantioselectivities up to 96% (Scheme 47, Table 7) using 5–10 mol% of the ligand.[76] A major difficulty in developing an efficient asymmetric phenyl transfer from diphenylzinc to aldehydes is the rapid competitive uncatalysed pathway, which diminishes the enantioselectivity. A modified diphenylzinc reagent (formed in situ by mixing $ZnPh_2$ and $ZnEt_2$ in a ratio of 1:2) gave a dramatic increase in enantioselectivity. Phenylation of 4-chlorobenzaldehyde gave the (*R*)-alcohol **199** with 97% ee compared to 88% ee with the original system (Table 7, entry 5). Under these conditions the catalyst loading could even be reduced to 2.5 mol% giving the product with 93% ee. Other aliphatic and aromatic aldehydes gave the desired (*R*)-alcohols with up to 98% ee.[77] 1,1′-Bis(oxazolinyl)ferrocene **204** and the related ruthenocene ligand **206** are efficient catalysts for this reaction giving the alcohol in moderate to high yield and enantioselectivity (Scheme 49).[78] Recently Bolm has shown that this process can also be performed using a polymer-supported ferrocenyloxazoline catalyst (75–97% yield, 86–97% ee).[79]

4.4. Thiols and thioether derivatives

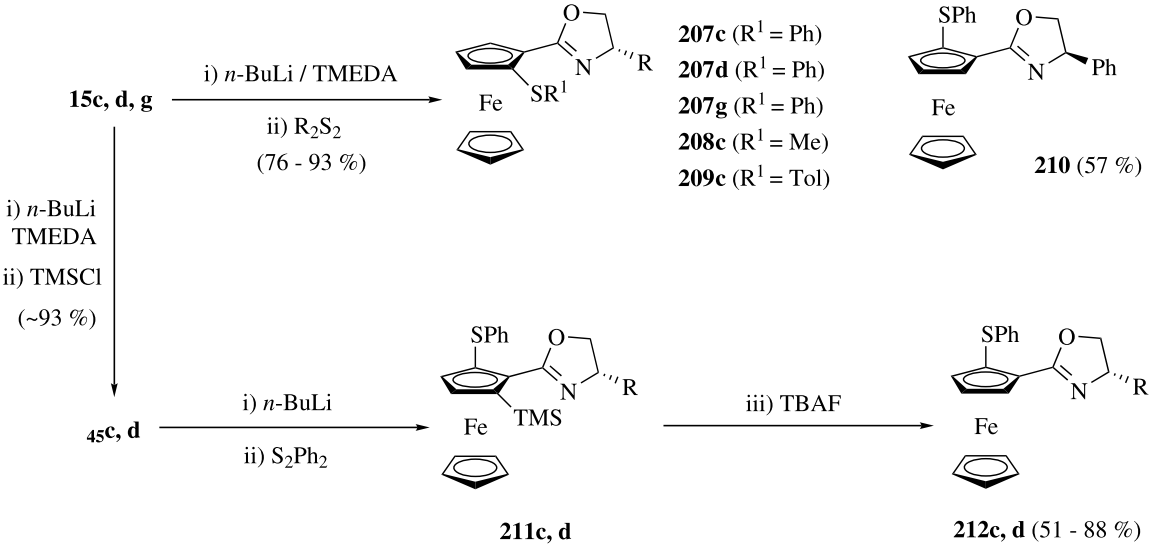
The first example of a chiral 2-ferrocenyloxazoline derivative containing a sulfur-based secondary chelating moiety (i.e. **15h** with the sulfur substituent situated on the oxazoline ring) was reported by Sammakia et al. in 1995.[13] Ahn et al. subsequently prepared both diastereomers **207c**,**d** and **212c**,**d** from **15c**,**d** using the standard *ortho*-lithiation strategy with *n*-BuLi–Ph_2S_2 (Scheme 50).[18] In 1998 these ligands were first reported in an asymmetric process (Scheme 24).[80]

Dai et al. prepared a number of derivatives **207c**–**g**, **208c**, **209c** (67–91% yields) and **212c** and showed that they could act as highly effective catalysts for the Pd-catalysed allylic substitution of **110** with dimethyl-

Table 7. Asymmetric addition of diphenylzinc to various aldehydes in the presence of ligands **201d** and **201f**[76]

Entry	R	Ligand (mol %)	Time (h)	% Yield[a]	% ee (Config.[d])
1	4-ClC_6H_4	**201d** (3)	12	99	64[b] (*R*)
2	4-ClC_6H_4	**201d** (5)	15	99	82[b] (*R*)
3	4-ClC_6H_4	**201d** (10)	14	99	88[b] (*R*)
4	4-ClC_6H_4	**201d** (10)	11	92	90[b] (*R*)
5	4-ClC_6H_4	**201f** (10)	13	99	88[b] (*R*)
6	Ferrocenyl	**201d** (5)	11	89	≥96[c,e] (*R*)
7	2-BrC_6H_4	**201d** (5)	14	98	31[c] (*R*)
8	1-Naphthyl	**201d** (5)	14	99	28[c] (*R*)
9	Me	**201d** (5)	15	94	75[c] (*S*)
10	$Ph(CH_2)_2$	**201d** (5)	10	91	50[c] (*S*)
11	*t*-Bu	**201d** (5)	16	99	56[c] (*S*)
12	2-Pyridyl	**201d** (5)	12	98	3[c] (*R*)

[a] Isolated yield after column chromatography.
[b] Determined by HPLC analysis on a chiral stationary phase (Chiralcel OB, *n*-hexane-*i*-PrOH = 4:1, 1.0 mL min^{-1}).
[c] Determined by HPLC analysis on a stationary phase.
[d] Determined by comparison of the optical rotation with literature values.
[e] Determined by ^1H NMR in the presence of $Eu(tfc)_3$.



Scheme 50.

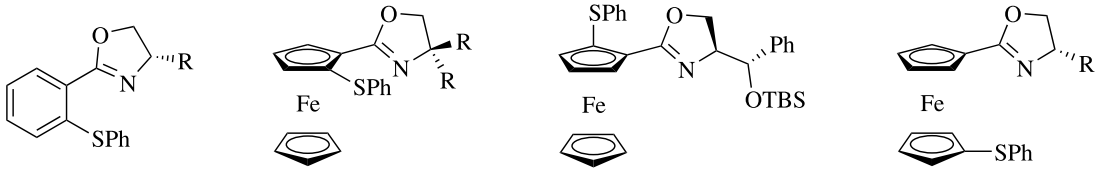
malonate to give the product (*S*)-**113** (cf. Scheme 24). The oxazolinylferrocenylthioethers derived from different β-aminoalcohols showed different effectiveness for enantioselectivities. The results showed that the R = *t*-Bu series (98% yield, 95.6–98% ee) is far superior to both the R = *i*-Pr (98% yield, 73.9–90.4% ee) and Bn series (98% yield, 87.8–95.6% ee), respectively. Dai et al. also observed that different salts (Li, Na, K, Cs) did not significantly change the enantioselectivity, although the reaction time was observed to vary.[80] These ferrocenyloxazoline ligands are more efficient than the comparable phenyloxazolines **213** reported by Williams et al.[81]

For ligands **214a** and **214b** only a low enantioselectivity was obtained (8.3 and 12.5% ee, respectively) but the absolute configuration of the product switched to (*R*)-**113**. Dai used this result to explain why the diastereoisomer ($S_{,p}R$)-**212c** achieved only a slightly higher enantioselectivity than ($S_{,p}S$)-**207c** (90.4 and 89.4% ee, respectively). The planar chirality is matched with the central chirality in ($S_{,p}R$)-**212c** for the oxazoline ring, whereas they are mismatched in ($S_{,p}S$)-**207c**. In this comparison, the central chirality seems to play a more important role (Schemes 50 and 51).[56,80]

Aït-Haddou and Balavoine have shown that hybrid ligand **215** also efficiently mediates Pd-catalysed allylic alkylation of *rac*-**110** with dimethylmalonate in the presence of NaH [(*R*)-**113**, 98% yield; 92% ee] or BSA–KOAc [(*R*)-**113**, 98% yield, 95% ee).[25] Additionally thioether derivatives, **216c**,**d**,**g** (where the secondary chelating substituent is situated on the second Cp ring of the ferrocene core) have been shown to mediate this asymmetric process–however, they give inferior results [(*S*)-**113**, 25–28% yield, 20–75% ee).[23]

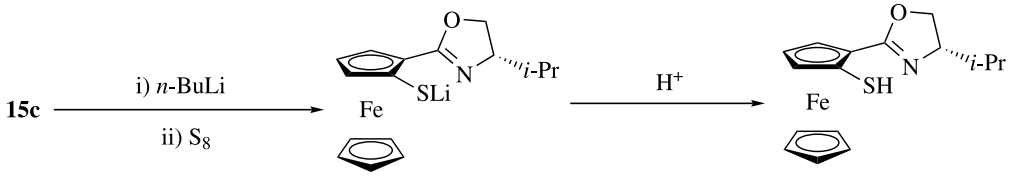
Recently, the relatively unstable ($S_{,p}S$)-*ortho*-thiol substituted 2-ferrocenyloxazoline derivative **218** was prepared in low yield from (*S*)-(+)-**15c** by Bäckvall et al. (Scheme 52). Treatment of **218** with copper iodide gave a catalyst which was used in the allylic substitution of acetate **219** with *n*-BuMgI to give product **220** (Scheme 53).[82]

New ferrocenyloxazolines containing a sulfur-based secondary chelating moiety e.g. **221** were reported by Bryce and Chesney.[30] Both **15h** and **15i** act as effective catalysts (10 mol%) in the Pd-catalysed allylic substitution of allylic acetate **110** and the sodium salt of dimethylmalonate to give the (+)-substitution product **113** in moderate to high yield (50–84%) and enantioselectivity



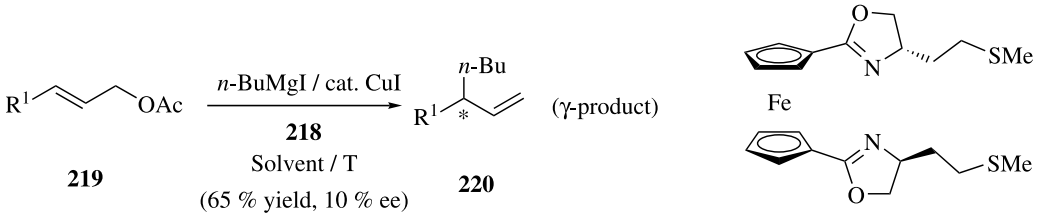
213c, d **214a, b, g** **215** **216c, d, g**
(70 - 80 %)

Scheme 51.



217 **218**

Scheme 52.



219 **220**

221 (93 % yield from **27** (R^1 = COCl))

Scheme 53.

(54–91%) (Scheme 24). Polar solvents, such as DMF, led to reasonable yields and enantioselectivities (whereas previous groups have shown that poor enantiocontrol is observed in DMF due to ligand displacement), whilst non-polar solvents such as THF gave better enantiocontrol but poor yields due to the insolubility of the nucleophile $NaCH(CO_2Me)_2$.

The use of *N*,*O*-bis(trimethylsilyl)acetimide (BSA) and dimethyl malonate [to overcome the insolubility problems encountered with $NaCH(CO_2Me)_2$] in the presence of ligands **15h** and **15i**, led to greatly improved yields and faster reaction times when compared to $NaCH(CO_2Me)_2$ (70–98% yields, 74–93% ee)—the use of dichloromethane as solvent with ligand **15i** providing the best results (98% yield, 93% ee).[30]

4.5. Selenols and selenoether derivatives

The first example of a diastereoselective synthesis of a chiral 2-ferrocenyloxazoline containing a selenium-based *ortho*-substituent was reported in 1995 by lithiation of **15c**,**d**,**g** and reaction with diphenyl diselenide (Scheme 54).[8] The structure of **60c** was confirmed by X-ray crystallography which established the (*S*)-configuration around the ferrocene core.[10] Compounds **60d**, **60g**, **222** and **224** were also obtained. Using established methodologies the phosphine derivative has also been prepared.[10]

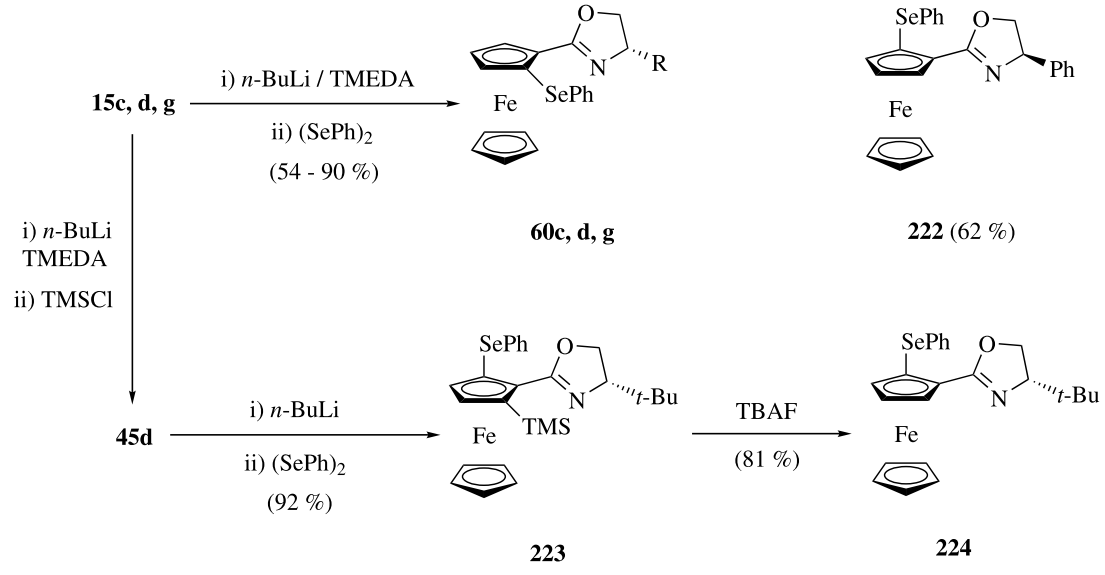
It was only recently that the first application of these types of ligand was published by Hou et al.[83] By analogy with the thioether derivatives **207**, **210**, **212** the chiral selenide derivatives **60c**,**d**,**g**, **222** and **224** were used in the palladium-catalysed allylic substitution[84] of acetate **110** (Scheme 24). Although the yields of the product **113** varied (17–80%), the enantioselectivity (70.8–99.3%) was high in all cases. Notably, unlike the thioether analogues, LiOAc did not accelerate the reaction rate but it was found to slightly increase the yield and enantioselectivity. In addition, the use of THF as solvent or sodium malonate showed a marked decrease in both chemical yield and chiral control.

The roles of central and planar chirality in each of the catalysts were also investigated. It was concluded that the central chirality is probably a more decisive factor in the control of the product configuration as products with (*S*)-configuration were obtained when ligands **60c**,**d**,**g** and **224** were used (all have the same central chiral configuration), while the product with (*R*)-configuration was afforded using **222** which has a central chiral configuration which is different from that of **60c**,**d**,**g** and **224**.

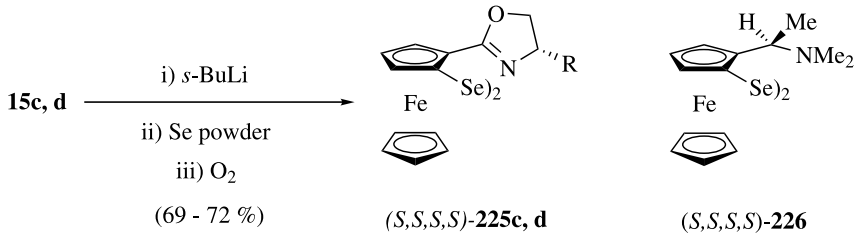
The related bis(2-ferrocenyloxazolinyl)diselenides **225c** and **225d** have been prepared independently by Fukuzawa[85] and Bolm[86] by treatment of the corresponding 2-ferrocenyloxazolines **15c** and **15d** with *s*-BuLi followed by reaction with elemental selenium and concomitant oxidation in air (**225c** 72% and **225d** 69% yields, respectively) (Scheme 55).

The first example of a chiral process using these types of ligand was reported by Fukuzawa et al. in 1997.[85] The asymmetric methoxyselenation of alkenes was studied by using a number of chiral ferrocenylselenium compounds. Although the best results for this transformation were obtained using chiral amino-substituted derivative **226** (20–99% yield, 89–98% ee), the chiral oxazolinyl derivative **225c** also showed efficient chiral control as well (99% yield, 66% ee) (Scheme 56).

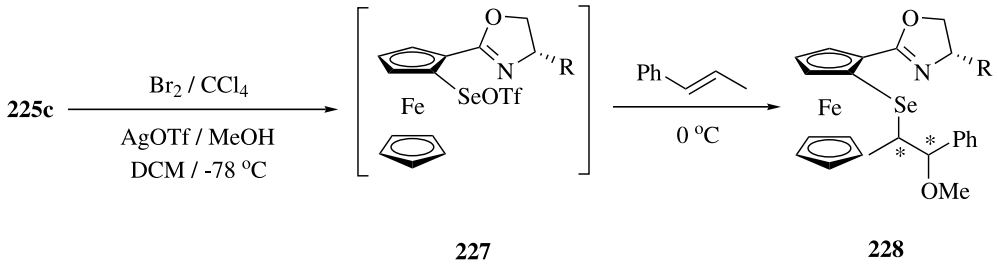
Bolm et al. recently observed that these ligands act as efficient chiral mediators in the catalytic asymmetric transfer of dialkylzinc reagents to aldehydes (Scheme 47).[86] The addition of diethylzinc to both aliphatic and aromatic aldehydes in the presence of **225d** gave disappointing results (68–79% yields, 20–44% ee) which were improved by using a mixture of diethylzinc and diphenylzinc modified diarylzinc (65–96% yields, 76–



Scheme 54.



Scheme 55.



Scheme 56.

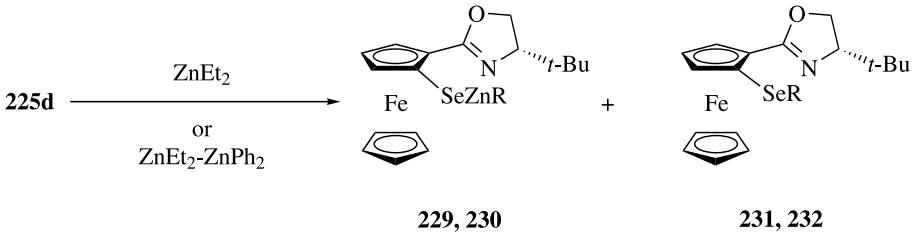
85% ee). The authors proposed that the catalytically active species are zinc selenides **229** and **230** formed by heterolytic cleavage of diselenide **225d** (Scheme 57)[87–89] with the selenoethers **231** and **232** playing only a minor role in determining the stereochemical outcome of the reaction.

4.6. Miscellaneous examples

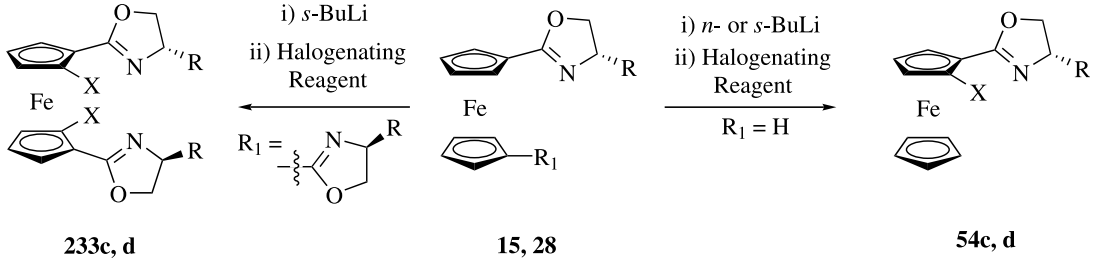
1,1′-Derivatives typified by **26** were first reported by Bryce (R = *i*-Pr; X = Br) in 1998[24] and more recently by Ahn (R = *i*-Pr, *t*-Bu, Ph; X = Br)[23] and Hou (R = *i*-Pr, *t*-Bu, Ph, CH_2Ph; X = Br).[32,55] *ortho*-Halo-substituted 2-ferrocenyloxazolines such as **54** [and the related 1,1′-bis(oxazolinyl)ferrocenes **233**] have been prepared from **15** and **28** with an alkyllithium and subsequent reaction with electrophilic halogenating reagents such as I_2,[44] CH_2I_2,[25] $(CH_2I)_2$,[25,40,90] $(CF_2Br)_2$,[55] $C_2Br_2Cl_4$[39,48] and C_2Cl_6[39] (Scheme 58).

Bolm has shown that planar chiral 2-(α-iodoferrocenyl)oxazoline ($_pS$)-**234** can be synthesised from **54d** by adapting Meyers' methodology[37,91,92]—this derivative can then be transformed into **200** using an iodine-lithium exchange followed by reaction with Ph_2CO (Scheme 59).[45]

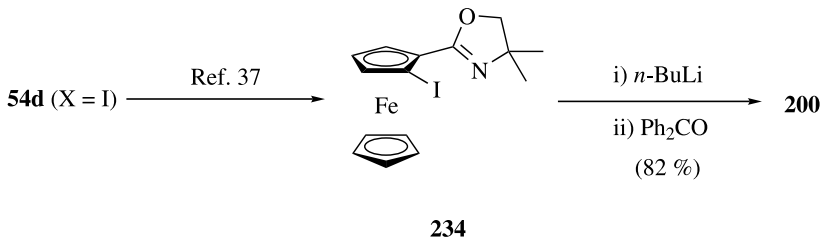
Facile halogen–lithium exchange on oxazolines **26** and concomitant trapping with electrophiles has been extensively used to give a wide range of derivatives where the



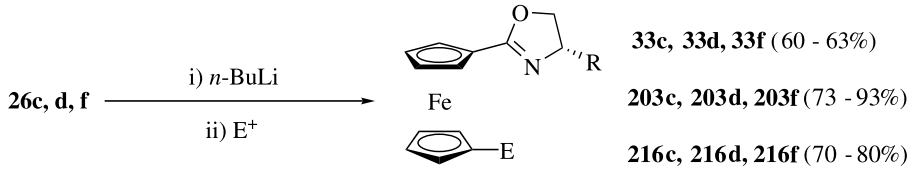
Scheme 57.



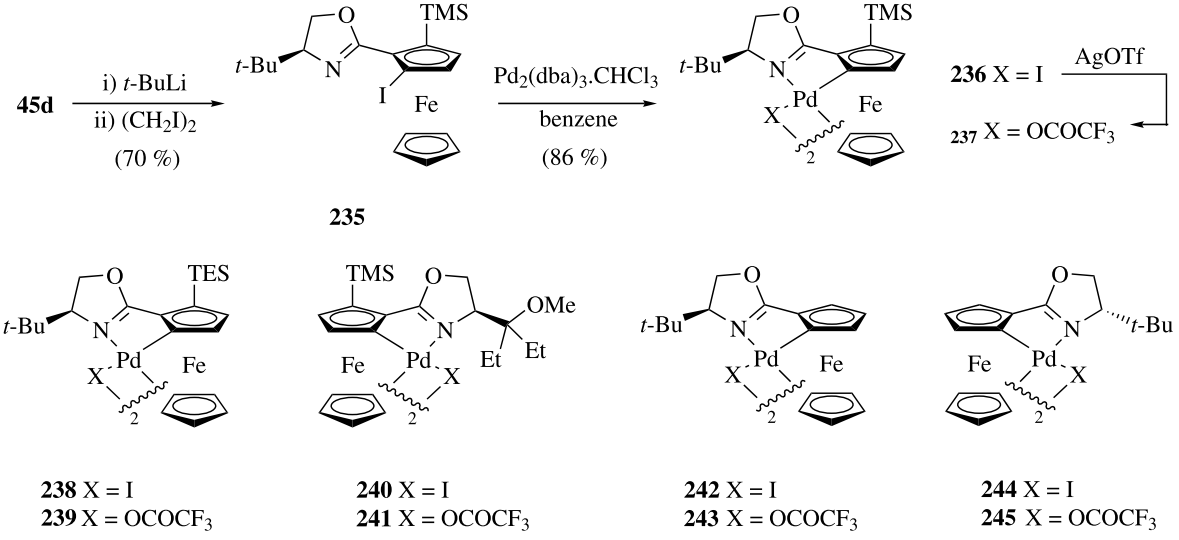
Scheme 58.



Scheme 59.



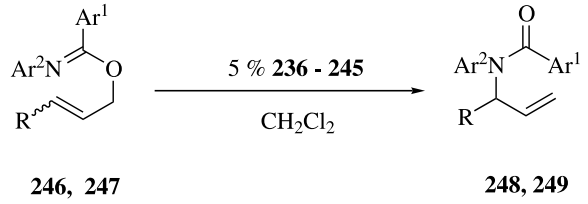
Scheme 60.



Scheme 61.

secondary chelating substituent is situated on the second Cp ring) including **33** (E = PPh_2),[31,55,56] **203** (E = CPh_2OH)[32] and **216** (E = SPh)[23] (Scheme 60).

Donde and Overman studied ferrocenyloxazoline palladacycles such as **236** in the asymmetric rearrangement of allylic imidates, **246**, **247** (Schemes 61 and 62). The palladacycles were prepared from iodo-derivative **235** by treatment with $Pd_2(dba)_3{\cdot}CHCl_3$. Although the iodine-bridged complexes **236**, **238**, **240**, **242**, **244** were inactive, 5 mol% of the trifluoroacetate complexes **237**, **239**, **241**, **243**, **245** generated in situ by reaction of the corresponding iodine-bridged dimer with 2 equiv. of $Ag(OCOCF_3)$, promoted the rearrangement of **246**, **247** in $CHCl_3$ at room temperature (Table 8). The scope of the rearrangement catalysed by complex **237** has also been investigated. A range of alkyl groups (R) and phenyl or substituted phenyl groups (Ar) are tolerated and yields and ee values are generally high.[90]



Scheme 62.

5. Applications as voltammetric metal sensors

The study of redox-active moieties in which a change in electrochemical behaviour in solution can be used to monitor complexation of a guest species is an important topic in molecular recognition chemistry.[93] Cation binding at an adjacent receptor site induces a positive shift in the redox potential of the ferrocene/ferrocenium couple by through-space electrostatic interactions, and the complexing ability of the ligand can be switched on

Table 8. Enantioselective formation of amide **248** from imidate **246**[90]

Entry	Catalyst	Imidate	Time	% Yield	% ee[a] (Config.)
1	**237**	*E*	2 days	57	79 (*S*)
2	**237**	*Z*	3 days	67	91 (*R*)
3	**239**	*E*	63 h	76	76 (*S*)
4	**239**	*Z*	6 days	89	90 (*R*)
5	**241**	*E*	3 days	95	72 (*R*)
6	**241**	*Z*	6 days	81	92 (*S*)
7	**243**	*E*	2 days	77	69 (*S*)
8	**243**	*Z*	2 days	15	49 (*R*)
9	**245**	*E*	2 days	86	8 (*S*)
10	**245**	*Z*	3 days	28	53 (*R*)

[a] Determined by HPLC.

and off by varying the applied electrochemical potential. We recognised that metal binding to the oxazoline substituents in ferrocenyloxazolines could be monitored in this way by conducting titration experiments in an electrochemical cell during cyclic voltammetry (CV) experiments. For example, palladium coordination to **15h**, **15i** and **221** results in the appearance of a new redox peak positively shifted by 100–190 mV compared to the free ligand.[30] The binding is cleanly reversible on the CV timescale. Remarkable selectivity for the coordination of Mg^{2+} and Ca^{2+} in the presence of a range of other metal cations has also been reported for **15c** resulting in positive shifts as large as 360 mV.[94] It is an attractive proposition that these processes may enable chiral recognition of metal-containing species and thereby offer a method for electrochemically modifying asymmetric metal-catalysed reactions.

The π-extended derivative **252** was synthesised according to Scheme 63 and its X-ray crystal structure was determined.[94,95] The observed voltammetric shift upon cation binding to **252** was reduced, compared to **15c**, due to the increased distance between the oxazoline binding site and the ferrocene unit. An advantage of compound **252** is that due to the extended chromophore, cation binding can be clearly detected by changes in the UV–Vis spectra: on addition of Mg^{2+} or Ca^{2+} a new absorption peak appeared at lower energy, with a concomitant colour change of the solution from pale yellow to purple. The diimine-containing system **253** is responsive to Ca^{2+}, Cu^{2+} and Zn^{2+}.[95]

6. Conclusions and future directions

The work described in this report demonstrates that 2-ferrocenyloxazolines have rapidly emerged as a very important class of ligands for metal-catalysed asymmetric synthesis. The stability of both the ferrocene and oxazoline moieties to an array of synthetic transformations has enabled a wide range of functional groups to be appended, and the ferrocene scaffold holds the substituents in a well-defined spatial proximity suitable for metal coordination. Oxazolines are among the most universally useful ligands; nonetheless, optimal ligand structures vary from one substrate to another, even within a single reaction type.[96] Future advances can be expected in the design and synthesis of specifically-functionalised ferrocenyloxazoline derivatives possessing secondary chelating groups to fine-tune the enantioselectivity in their reactions: in this respect, the synthesis of unsymmetrical multi-substituted ferrocene derivatives is still a challenging topic. The extension of these ligands to entirely new asymmetric catalytic processes can also be anticipated, and the redox-addressability of the ferrocene unit provides additional opportunities in this regard.

The potential of ferrocenyloxazolines is far from exhausted!

Acknowledgements

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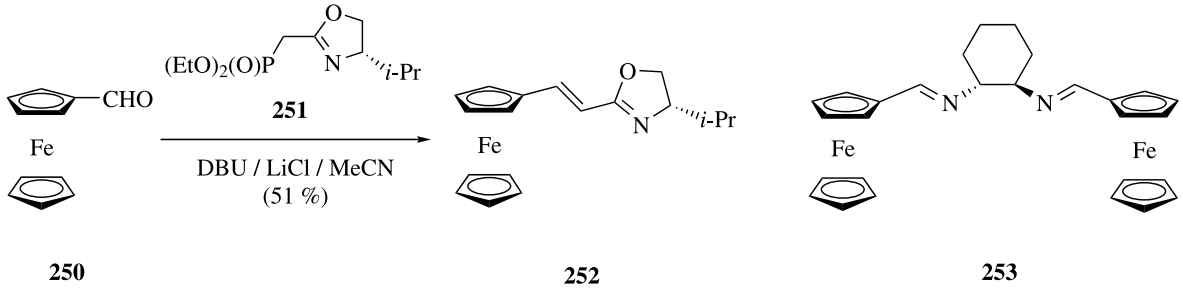

250 **252** **253**

Scheme 63.

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