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Synthesis of Chiral 2-Phospha[3]ferrocenophanes and their Behaviour as Organocatalysts in [3+2] Cyclization Reactions

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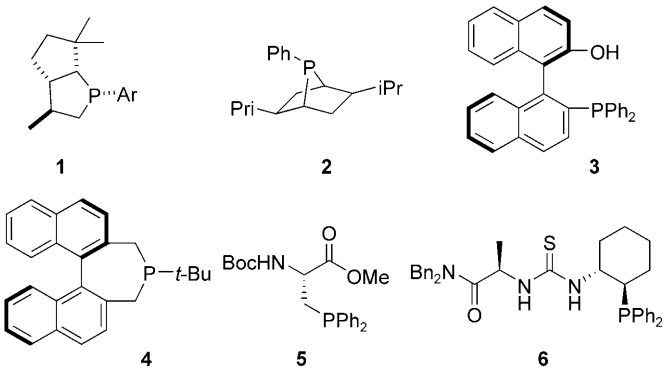
Abstract: Planar chiral 2-phospha[3]ferrocenophanes have been prepared *via* a stereoselective three-step synthesis. The key step is the lithiation of the 1,1′-disubstituted ferrocene **11** bearing (*S*)-2-(methoxymethyl)pyrrolidines as the chiral *ortho*-directing groups. The diastereoselectivity of these reactions has been mastered by an appropriate choice of the metallating agent, so as to afford a suitable access to C_2-symmetrical, tetrasubstituted ferrocenes. These compounds have been converted into the enantiomerically pure 2-phospha[3]-ferrocenophanes **16**, *via* the corresponding acetates and their reactions with primary phosphines. Phosphines **16** have been used as nucleophilic catalysts in model cyclization reactions. Unlike 2-phospha[3]-ferrocenophanes with stereogenic α-carbons, the planar chiral derivatives **16** proved to be suitable catalysts for these processes. Thus, for instance, phosphine **16c** successfully promotes the enantioselective [3+2] annulations of allenes and enones into functionalized cyclopentenes (*ee*s up to 96%). Among others, spirocyclic derivatives have been obtained in good yields and *ee*s in the range 77–85%. The robustness of this catalyst has been demonstrated by recycling experiments.

Keywords: cyclization; enantioselective organocatalysis; ferrocenophanes; *ortho*-metallation; phosphines

Introduction

In the field of organocatalysis, phosphines represent efficient auxiliaries,[1] whose peculiar reactivity often complements that of nitrogen-based[2] nucleophilic promoters. Since a number of synthetically useful processes have been highlighted, the development of asymmetric variants of phosphine-promoted transformations represents today a highly valuable challenge. Significant advances in this field have been reported mainly during the last decade: after the seminal work of Vedejs on enantioselective acylations,[3] several groups have investigated the use of chiral phosphines in Morita–Baylis–Hillman reactions,[4] [3+2] annulations of electron-poor unsaturated substrates (olefins, allenes and alkynes) with enones, unsaturated esters or imines,[5] [4+2] annulations with imines[6] and other miscellaneous reactions.[7] From these studies, only a few structural motifs have emerged as efficient scaffolds for phosphorus-based catalysts. Notably, the bicyclic phospholanes **1**[8] and **2**,[5a] the binaphthyl-based phosphines **3**[9] and **4**,[6] the α-amino acid-derived phosphine **5**[10] and the phosphinothiourea **6**[5d] have been highlighted as outstandingly efficient Lewis bases nucleophilic catalysts.



1 2 3 4 5 6

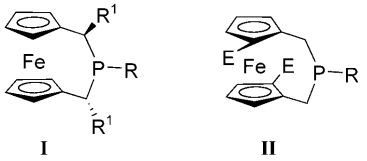
Given the reaction-catalyst and substrate-catalyst specificity which are usually distinctive for most catalytic transformations, it seems essential to further

expand the present range of efficient phosphines for enantioselective organocatalytic processes.

Our efforts toward this goal and the development of 2-phospha[3]ferrocenophanes as new scaffolds for Lewis base-type chiral organocatalysts are summarized herein. Part of this work has been reported previously as a preliminary communication.[11]

Results and Discussion

In our search for new phosphine organocatalysts, we targeted 2-phospha[3]ferrocenophane derivatives, with either stereogenic carbons (**I**)[12] or planar chirality (**II**),[11] since these ferrocenophane scaffolds display some peculiar structural features that are, *a priori*, amenable to enantioselective organocatalysis.



I **II**

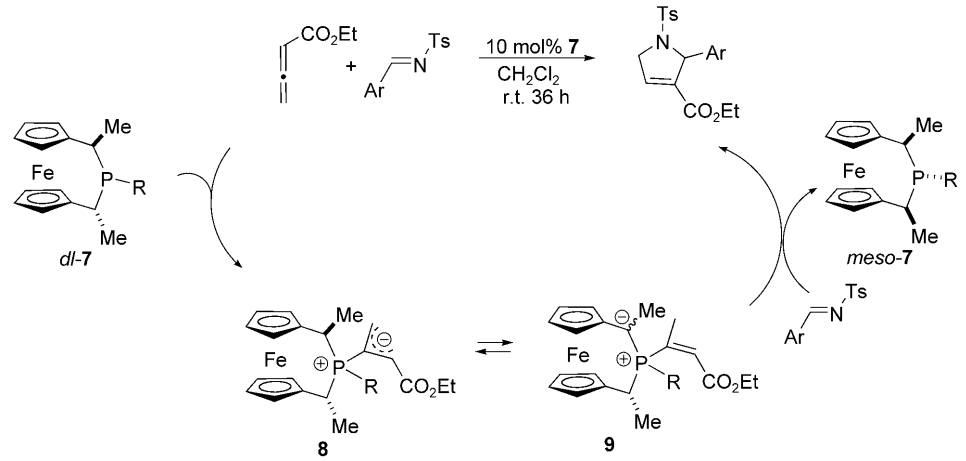
A first key point is that 2-phospha[3]ferrocenophanes are dialkyl- or trialkylphosphines, which credit them with an electron-rich nature and potentially nucleophilic character, a crucial requisite for good catalytic activity. Secondly, their cyclic structures, with the related restricted conformational freedom, are expected to favour chiral induction in catalytic processes. Finally, the bulky ferrocene moiety is expected to participate in steric discriminations as well as to increase the air-stability and ease of handling of these phosphines.

Despite the highly successful uses of many chiral phosphines with ferrocene backbones,[13] ferrocenophane derivatives have been seldom considered for applications in catalytic processes. As far as we know, only chiral ferrocenophanes bearing carbon tethers between the Cp rings and attached R_2P functions, have been used so far in asymmetric catalysis.[14]

We started our study by considering the use as catalysts of 2-phospha[3]ferrocenophanes with stereogenic carbon atoms in the tethering chain (**I**).[12] Their preliminary evaluations in a model organocatalytic reaction (Scheme 1) have highlighted, however, a major drawback of the targeted structures.

Indeed, when the racemic phosphane *dl*-**7** has been used as catalyst in the [3+2]cyclization reaction of ethyl 2,3-butadienoate with *N*-tosyl-1-naphthaldimine[5c,d,15] under the usual conditions, TLC monitoring showed that a significant amount of the putative catalyst was still present in the reaction mixture, after completion of the reaction. After isolation, this compound was shown to be the *anti-anti* (*meso*) isomer of the 2-phospha[3]ferrocenophane **7** initially employed. This experiment thus highlighted that the phosphaferrocenophane structure is remarkably stable in the conditions of the catalytic reactions which induce, however, inversion of the relative stereochemistry of the stereogenic centers.

A tentative rational for the observed isomerization process is shown in Scheme 1. According to the generally accepted mechanism,[16] the phosphane-promoted [3+2]cyclizations involve zwitterionic intermediates such as the phosphonium salt **8** which is generated by addition of the nucleophilic phosphane to the electron-poor allene. The zwitterionic phosphonium salt might very likely undergo reversible intra- or intermolecular proton exchange reactions[17] leading to phosphorus ylides such as **9**. This proton exchange reaction can account for the isomerization process, in so



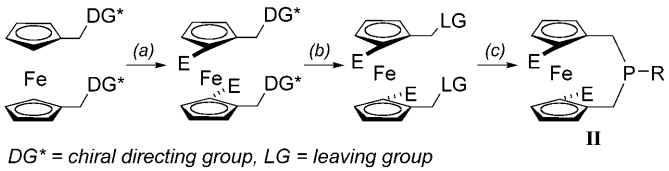
Scheme 1. Phosphine-promoted synthesis of pyrrolines. Proposed mechanism for the epimerization of *dl*-**7** into *meso*-**7** during the organocatalytic process.

far as the *anti-anti* isomer, *meso*-**7**, is expected to be the thermodynamically favoured isomer of the ferrocenophane catalyst.

Analogous epimerization or racemization processes *via* transient phosphorus ylides might take place, in principle, for other phosphines bearing stereogenic α-carbons. This might advise against using phosphines of this class as chiral auxiliaries, although some of them have already been applied to enantioselective organocatalytic processes.[5a,b,6,7a,18,19] No mention was made about possible racemization processes, but catalyst recovering was not mentioned either.

The observed epimerization of ferrocenophane **7** during the catalytic cyclization reactions mentioned above led us to consider planar chirality as a more reliable stereogenic element and ferrocenophanes **II** as *a priori* more convenient organocatalysts.

The envisioned access to structures **II** is the three-step procedure shown in Scheme 2, which involves the diastereoselective di-*ortho*-metallation of a 1,1′-disubstituted ferrocene bearing chiral *ortho*-directing groups (step *a*) as the key step.



DG = chiral directing group, LG = leaving group*

(*a*) diastereoselective ortho-lithiation;
(*b*) removal of the chiral auxiliary and introduction of the leaving group
(*c*) cyclization *via* nucleophilic substitution reactions with RPH_2

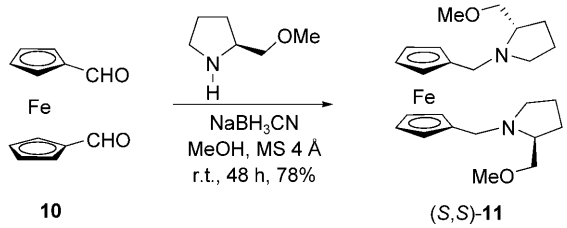
Scheme 2. Strategy for the synthesis of 2-phospha[3]ferrocenophanes with planar chirality.

The major issue of this synthetic approach was to identify a suitable chiral auxiliary as well as the experimental conditions allowing highly diastereoselective dilithiations of the disubstituted ferrocene.

Although a number of ferrocenes bearing chiral *ortho*-directing groups are known to undergo diastereoselective metallation-substitution reactions,[20] di-*ortho*-metallations have been comparatively less considered.[21,22] The 1,1′-bis[(2-methoxymethylpyrrolidin-1-yl)methyl]ferrocene, (*S,S*)-**11** introduced by Pugin et al.,[21f] retained our attention as a suitable substrate because of the easy availability of the chiral auxiliary and its subsequent easy removal procedure, that will give a direct access to the desired ferrocenylmethyl units (see above).

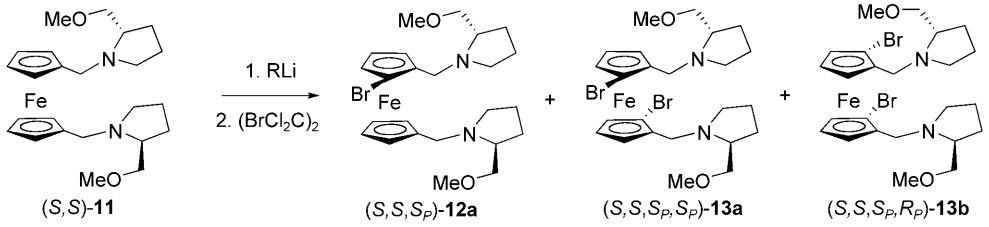
The ferrocene derivative (*S,S*)-**11** has been prepared on a multigram scale by reductive amination of the commercially available dialdehyde **10** with (*S*)-methoxymethylpyrrolidine (SMP) (Scheme 3).[23] This synthetic procedure compares favourably with the previously reported method based on the nucleophilic substitution between SMP and (ferrocenylmethyl)-trimethylammonium iodide.[24]

A detailed study of the *ortho*-metallation of (*S,S*)-**11** (step *a*) was then conducted. The lithiation-bromination reaction shown in Table 1 has been selected as



Scheme 3. Synthesis of (*S,S*)-**11** by reductive amination.

Table 1. Diastereoselective di-*ortho*-lithiation/bromination of (*S,S*)-**11**: effect of base and reaction conditions on the products ratio.



Entry	Base	Solvent	Products ratios			Yield[a] [%]
			12a	**13a**	**13b**	
1	*n*-BuLi[b]	Et_2O	47	50	3	**13a**, 38
2	*s*-BuLi[c]	Et_2O		95	5	**13a**, 80
3	*s*-BuLi	THF	57	40	3	**13a**, 25
4	*t*-BuLi[d]	Et_2O		25	75	**13b**, 55

[a] Reactions performed at 0 °C, on a 60 mg scale (0.15 mmol).
[b] 1.60 M in hexane.
[c] 1.40 M in cyclohexane.
[d] 1.7 M in pentane.

the model sequence because structural assignment of the final products could be easily performed in this series, including assignment of the planar configuration (see X-ray data below).

Lithiations have been performed with 2.5 equivalents of the base and the resulting metallated ferrocene has been reacted then with an excess 1,2-dibromotetrachloroethane. After aqueous work-up, the crude reaction mixture has been monitored by ^{1}H NMR.

n-Butyllithium proved unsuitable for dilithiations, as it led to a 1:1 mixture of the mono- and dibromo-substituted ferrocenes **12** and **13**.

With stronger bases such as *s*-BuLi or *t*-BuLi, 1,1′-dibromoferrocenes were obtained efficiently, for reactions performed in ether (entries 2 and 4). The two metallating agents led, however, to preferential production of two different isomers of the dibromoferrocene **13**.[25] Spectroscopic data allowed assignment of a C_2-symmetrical structure (S_P,S_P or R_P,R_P planar configurations) to the major isomer **13a** which was obtained with *s*-BuLi (entry 2), while the S_P,R_P epimer **13b** was preferentially formed when using *t*-BuLi (entry 4).[26] The first lithiation step might account for this reversal of stereochemical control since opposite senses of chiral induction are also observed when (*S,S*)-**11** undergoes mono-lithiation with *s*-BuLi and *t*-BuLi, respectively.[27] A clear rational for the stereochemical course of these reactions cannot be proposed at present, particularly since lithium coordination by either the vicinal and/or the remote pyrrolidine units might occur here.

Data in Table 1 show that an appropriate choice of the metallating agent is crucial to direct the outcome of these lithiations toward the desired tetrasubstituted C_2-symmetrical stereoisomer **13a** of the planar-chiral ferrocene. *s*-BuLi is the reagent of choice, giving **13a** with almost perfect diastereoselectivity.

The known sense of chiral induction from the (*S*)-methoxymethylpyrrolidine unit in the lithiation of monosubstituted ferrocenes[20d] could not be reliably used here to predict the stereochemical outcome of the di-metallations above, because these reactions clearly display a rather intricate behaviour. Thus, the major epimer **13a**, which was obtained from (*S,S*)-**11** by lithiation with *s*-BuLi (entry 2), has been submitted to X-ray diffraction studies in order to determine the relative configuration of the planar chiral moiety.

As shown in Figure 1, the chiral tetrasubstituted ferrocene **13a** displays an (S_P,S_P) configuration. The pyrroline auxiliary displays here the same sense of chiral induction as that reported for the lithiations of monosubstituted ferrocenes.[20d]

Dimetallation of (*S,S*)-**11** with *s*-BuLi as the base was then used for the synthesis of the tetrasubstituted ferrocenes **14a–d** by quenching the reaction mixture with various silyl chlorides (step *a* in Scheme 4).[28]

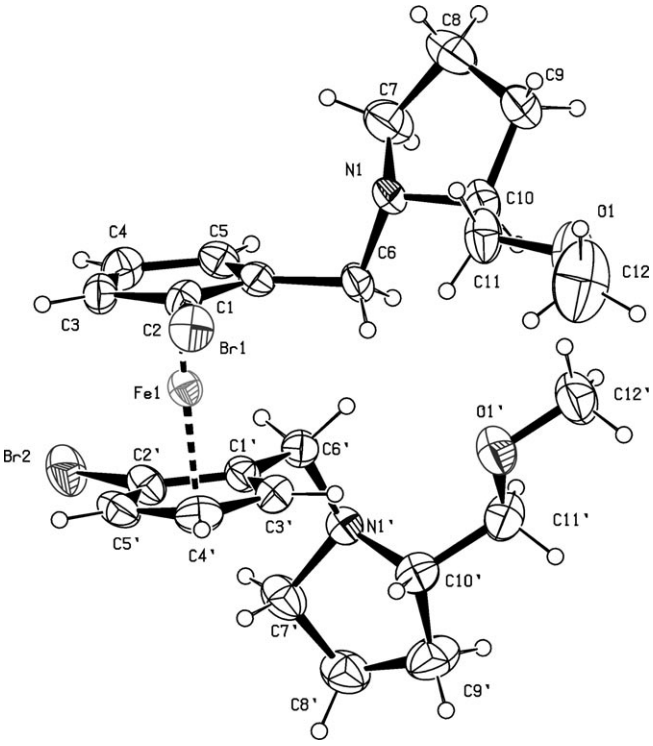


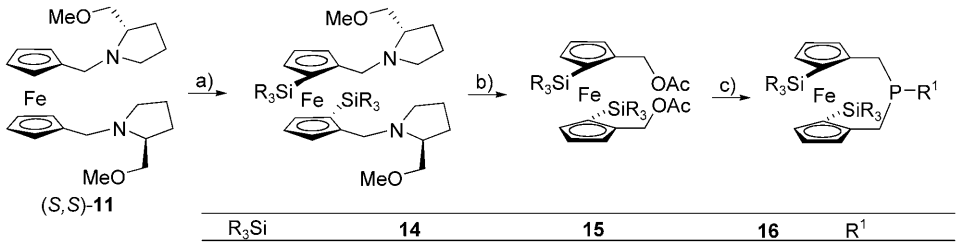
Figure 1. ORTEP diagram for the tetrasubstituted ferrocene (*S,S,S*$_P$,*S*$_P$)-**13a**.

NMR analysis of the crude reaction mixtures shows formation of the C_2-symmetrical silylated derivatives **14** in >95:5 diastereomeric ratios. The final products **14** have been obtained in diastereomerically pure form after purification by chromatography on silica gel. Yields are satisfying, although column chromatography may induce partial degradation of the product.

The silylated ferrocenes **14** were then converted into the corresponding 2-phospha[3]ferrocenophanes **16** following the two-steps sequence in Scheme 4.

Step *b*, that is, removal of the chiral auxiliary, has been performed following a known procedure,[20d,29] by heating **14** in acetic anhydride at 90 °C. The corresponding bis-acetates **15** were obtained in good yields from **14a–c**, while the dimethylsilyl-substituted derivative **14d** afforded an inseparable mixture of the desired diacetate (**15**, $R_3Si = Me_2HSi$) and the corresponding (acetoxy)dimethylsilyl-substituted ferrocene [**15**, $R_3Si = Me_2(OAc)Si$].

The pyrrolidine removal method above is especially convenient since it directly generates the acetate leaving groups which are required for the next step. In step *c*, the bis-(acetoxymethyl)ferrocenes **15** were subjected to nucleophilic substitution reactions[30] with equimolar amounts of primary phosphines, namely $PhPH_2$, (−)-menthylPH_2 or $C_6H_{11}PH_2$, to afford the corresponding 2-phospha[3]ferrocenophanes (*S,S*)-**16a–e** (called FerroPHANEs).



R_3Si	14	15	16	R^1	
Me_3Si	(S_P,S_P)-**14a**, 66%	(*S*,*S*)-**15a**, 80%	(*S*,*S*)-**16a**,	Ph,	37%
			(*S*,*S*)-**16b**,	(–)-Menth,	31%
			(*S*,*S*)-**16c**,	C_6H_{11},	42%
Et_3Si	(S_P,S_P)-**14b**, 73%	(*S*,*S*)-**15b**, 56%	(*S*,*S*)-**16d**,	C_6H_{11},	43%
Me_2PhSi	(S_P,S_P)-**14c**, 54%	(*S*,*S*)-**15c**, 78%	(*S*,*S*)-**16e**,	C_6H_{11},	44%
Me_2HSi	(S_P,S_P)-**14d**, 53%	---	---		

a) 1. *s*-BuLi 2.5 equiv., Et_2O, –20 °C; 2. R_3SiCl, –78 °C to r.t.; b) Ac_2O, 90 °C, 18 h; c) RPH_2, AcOH, 60 °C, 16 h.

Scheme 4. Synthesis of (*S*,*S*)-R_3Si-FerroPHANEs **16**.

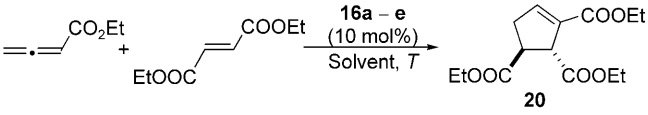
Phosphines **16a–c** have been described in our previous communication.[11] The [Cy]-Et_3Si-FerroPHANE **16d** and [Cy]-Me_2PhSi-FerroPHANE **16e** are orange oils which have been purified by column chromatography and fully characterized. Unlike FerroPHANE **16c** which hardly oxidizes in solution at room temperature (<5% oxidation after 24 h in $CDCl_3$ solution, in air), FerroPHANEs **16d** and **16e** are moderately air-sensitive compounds which are better handled and stored under inert atmospheres.

In an attempt to prepare FerroPHANEs with stereogenic phosphorus atoms, the trisubstituted 2-trimethylsilyl-1,1′-bis(acetoxymethyl)ferrocene **18** was reacted with cyclohexylphosphine (step *b* in Scheme 5). However, the cyclization reaction proved to be a non-stereoselective process which led to an inseparable mixture of the two diastereomeric FerroPHANEs **19** in about 1:1.6 ratios [^{31}P NMR ($CDCl_3$): $\delta = 13.6$ and 10.7 ppm].

Catalytic Studies

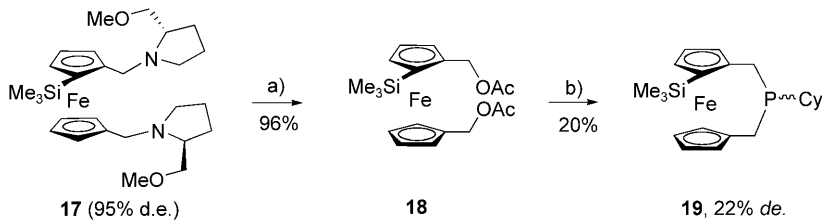
As a preliminary study, the properties of FerroPHANEs **16a–e** as nucleophilic organocatalysts have been evaluated in a model [3+2]cyclization reaction, that is, the annulation between ethyl 2,3-butadienoate and diethyl fumarate.[16a] Results are reported in Table 2.

Table 2. Cyclization of ethyl 2,3-butadienoate with diethyl fumarate promoted by FerroPHANEs **16**.[a]



Entry	Phosphine	Solvent	*T*	Yield [%][b]	*ee* [%][c]
1	**16a**	Toluene	r.t.	30	11 (–)
2	**16b**	Toluene	90 °C	34	12 (+)
3	**16c**	Toluene	r.t.	54	90 (+)
4	**16d**	Toluene	r.t.	63	84 (+)
5	**16e**	Toluene	r.t.	22	89 (+)
6	**16c**	CH_2Cl_2	r.t.	59	83
7	**16c**	Acetone	r.t.	61	84
8	**16c**	Toluene[d]	r.t.	68	90
9	**16c**	Toluene[d]	0 °C	28	93

[a] *Reaction conditions:* allene (0.2 mmol, 1 equiv.), fumarate (2 equiv.), solvent (1 mL), degassed solvents, under argon.
[b] Isolated yield after flash chromatography.
[c] Enantiomeric excesses were measured using chiral HPLC.
[d] Reactions performed at a 0.3 mmol mL^{-1} concentration.



a) Ac_2O, 90 °C, 18 h; b) $CyPH_2$, AcOH, 60 °C, 16 h.

Scheme 5. Attempted synthesis of P-stereogenic FerroPHANEs

In the presence of a 10% amount of the chiral phosphines, these reactions yield the *trans*-stereoisomer of cyclopentene **20** as the single product, implying that the process takes place, as expected, with retention of stereochemistry of the starting olefin.

From the data in Table 2 the catalytic properties of phosphines **16a–c** can be compared as a function of the phosphorus substituent (entries 1–3) as well as of the nature of the silyl groups (entries 3–5).

The *P*-cyclohexyl-FerroPHANE **16c** afforded **20** in 54% yield after 24 h (entry 3) at room temperature, while the *P*-phenyl-substituted phosphine **16a** afforded **20** in only 30% isolated yield under analogous conditions. With the *P*-menthyl-FerroPHANE **16b**, heating at 90 °C was required to achieve a reasonable conversion rate (entry 2). The lower reactivity of **16a** and **16b**, compared to the *P*-cyclohexyl-FerroPHANE **16c**, might be tentatively ascribed to a lower nucleophilic character for **16a** and to an increased steric hindrance for **16b**.

The nature of the phosphorus substituent in **16** is a crucial structural factor also with regard to asymmetric induction: the *P*-cyclohexyl-FerroPHANE **16c** gives indeed much higher enantioselectivity (90% *ee*) than phosphines **16a** and **16b**. It may be worth mentioning that the *P*-phenyl-FerroPHANE **16a** gives an opposite sense of chiral induction with albeit very low *ee* (entry 1).

The nature of the Cp-linked silyl groups modulates to some extent the enantioselectivity levels of the cyclization reaction, with enantiomeric excesses varying from 84 to 89 and 90% for FerroPHANES bearing Et_3Si, Me_2PhSi and Me_3Si groups, respectively (entries 3–5).

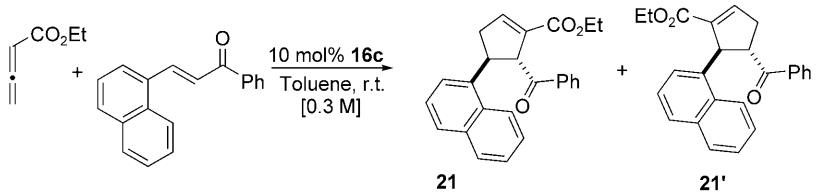
Thus, among the FerroPHANEs **16**, the *P*-cyclohexyl, trimethylsilyl-substituted derivative **16c** ([Cy]-TMS-FerroPHANE) proved to be the most efficient catalyst, with respect to both conversion rates and enantioselectivity. In the optimized conditions of entry 8 (Table 2), **20** was obtained in 68% yield and 90% *ee*. Previously, the enantioselective [3+2]cyclization between butadienoate and fumarate leading to **20** had been carried out by Zhang[5a] with the bicyclic phosphine **2** as the catalyst: the yield (49%) and enantiomeric excess (79%) were slightly lower than those obtained with FerroPHANE **16c**. For comparison purposes, we also tested Binepine **4** in the same cyclization reaction, which afforded **20** in high yield (80%) and enantioselectivity (93% *ee*) under the reaction conditions of entry 8.

The excellent catalytic behaviour of [Cy]-TMS-FerroPHANE **16c** has been demonstrated also in the enantioselective [3+2]cyclizations of ethyl 2,3-butadienoate with both ethyl acrylate and β-substituted enones. As disclosed in our preliminary communication,[11] in these reactions FerroPHANE **16c** performs as well as the best catalysts known so far,[5a,b] with *ee*s in the range of 84–96%. Moreover, a key property of FerroPHANE **16c** is its remarkable stability toward air oxidation. This allows phosphane **16c** to be stored for an indefinite period of time and the catalytic reactions to be routinely performed under standard conditions (no glove-box required). Most importantly, we also noticed that phosphane **16c** can be recovered after completion of the organocatalytic reaction and re-used then for a further run. This unprecedented recycling procedure of a chiral phosphane organocatalyst is illustrated in Table 3.

The cyclization reaction between ethyl 2,3-butadienoate and 3-(1-naphthyl)-1-phenyl-2-propenone was performed at room temperature for 24 h, with a 10% amount of FerroPHANE **16c** as the catalyst. At the end of the first run, the catalyst was isolated by chromatography and used again for a second run at the same catalyst loading. A third run was performed again in the same conditions. The three reactions led to comparable ratios of regioisomers and enantiomeric excesses, showing that the unchanged catalyst operates in these reactions.

Alternatively, the cyclization reaction leading to **21** has been carried out at an initial catalyst loading of 10%, and successive additions of the substrates have

Table 3. Recycling of catalyst **16c** in the [3+2]cyclization between ethyl 2,3-butadienoate and 3-(1-naphthyl)-1-phenyl-2-propenone.



21 21'

	Enone (mmol)	**21/21′**	Yield [%]	*ee* [%]
Initial run	0.50	20/1	87	96
1st catalyst recycling	0.26	20/1	76	96
2nd catalyst recycling	0.13	20/1	80	95

been performed after 24 h and 48 h. A 76% conversion rate (69% isolated yield) was observed after 70 h, which amounts to a product/catalyst ratio = 23.

These results demonstrate the efficiency of the new planar chiral 2-phospha[3]ferrocenophane scaffold in enantioselective organocatalytic processes, as well as the ease of handling, robustness and configurational stability of **16c** in the conditions of the catalytic reaction. When starting this project, the configurational stability of 2-phospha[3]ferrocenophane was confidently predicted, however, the possibility of some stereochemical scrambling could not be definitely ruled out, since in ferrocenophane derivatives haptotropic rearrangements of the cyclopentadienyl ligands may take place. Such rearrangements have been especially noticed with [1]- and [2]ferrocenophanes where ring strain favours η^3- and η^1-coordination of the Cp rings over the η^5-bonding mode.[31] The negligible ring strain of phospha[3]ferrocenophanes, where the three-atom tether makes the Cp rings only slightly tilted toward each other,[32] accounts for the strong preference for η^5-coordination and the subsequent configurational stability of **16c**.

In order to further explore the catalytic properties of FerroPHANE **16c** in [3+2]cyclization reactions, we have considered the annulations between 2,3-butadienoates and the cyclic enones **22** displaying exocyclic double bonds (Table 4). These reactions had been introduced by Fu during his studies on the (*S*)-Binepine **4** promoted cyclizations.[5b] The expected products are spirocyclic indanones with quaternary stereogenic centres.

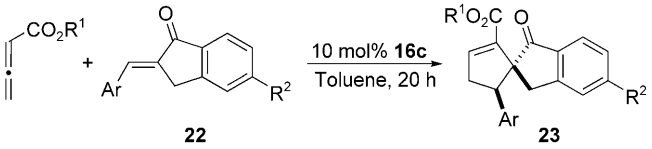
Under FerroPHANE catalysis, the annulation reactions between 2,3-butadienoates and enones **22** afforded the γ-cycloadducts **23**[33] in high yields and enantioselectivity. Only small amounts of the putative α-adducts have been observed in some experiments (entries 5, 7 and 8), which have never been unambiguously characterized, however.

The scope and limitations of these [3+2]annulation reactions have been considered, with respect to both the nature of the allenic ester and the substitution pattern of the cyclic enone substrate.

Of the three 2,3-butadienoates checked so far (R^1 = Et, Cy and Bn), the benzyl ester was found to afford the highest enantioselectivity level (84%, entry 3). It was used then as the preferred allene in further experiments.

Variation of the Ar group in **22** did not affect the enantioselectivity levels, while it may have a major impact on the reactivity, since low conversion rates were observed at room temperature when starting from 1-naphthyl- and 4-chlorophenyl-substituted enones (entries 4 and 6). Good conversion rates could be attained, however, for reactions run at 80 °C (entries 5 and 7), with only a small decrease of the enantiomeric excesses to 80 and 77% *ee*, respectively. A small decrease of the regioselectivity (10:1 isomers ratio) is also observed in entry 7

Table 4. Asymmetric [3+2] annulations on exocyclic enones promoted by FerroPHANE **16c**.



22 23

	R^1	Ar	R^2	*T*	Product	Yield [%]	*ee* [%]
1	Et	Ph	Br	r.t.	**23a**	85	80
2	Cy	Ph	Br	r.t.	**23b**	80	77
3	Bn	Ph	Br	r.t.	**23c**	73	84
4	Bn	1-Naphth	Br	r.t.	**23d**	45	83
5	Bn	1-Naphth	Br	80 °C	**23d**	82	80
6	Bn	4-Cl-C_6H_4	Br	r.t.	**23e**	30	85
7	Bn	4-Cl-C_6H_4	Br	80 °C	**23e**	87	77
8	Bn	Ph	H	r.t.	**23f**	44	82
9	Bn	Ph	Me	r.t.	**23g**	35	84
10	Bn	Ph	Me	80 °C	**23g**	84	77

The Br-substituted indanone (**22**, R^2 = Br) turned out to be more reactive than unsubstituted (R^2 = H, entry 8) or Me-substituted (R^2 = Me, entry 9) indanones which require heating to 80 °C to produce **23** in high yields.

On the whole, the results in Table 4 show that conditions have been found, for each single pair of allene/enone substrates, where yields >80% and enantiomeric excesses of 77–86% can be obtained.

More exhaustive studies on the use of FerroPHANEs in enantioselective organocatalytic [3+2]cyclizations are ongoing. Results will be reported in due course.

Conclusions

In summary, this work shows that planar chiral, C_2-symmetrical 2-phospha[3]ferrocenophanes are easily available *via* a stereoselective approach allowing modulation of both the phosphorus and Cp rings substituents. The [Cy]-TMS-FerroPHANE **16c** represents a highly efficient nucleophilic promoter for enantioselective organocatalytic processes. It ranks among the best catalysts known so far for the [3+2]annulation reactions between allenoates and electron-poor olefins. These good catalytic properties can be ascribed to the electron-rich nature of **16c**, the C_2-symmetry of the chiral moiety, as well as to the bulk and restricted conformational freedom of the cyclic ferrocene unit. The remarkable stability of these catalysts has been demonstrated by recycling experiments.

Future studies on these new chiral phosphines will involve exploring their behaviour in other organoca-

talytic processes, as well as their properties as ligands in transition metal-promoted reactions.

Experimental Section

General Procedure for the Synthesis of the Silyl-Substituted Ferrocenes 14 from (*S,S*)-11 (Scheme 4)

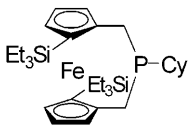
s-Butyllithium (1.4 M in cyclohexane, 2.5 equiv.) was added dropwise to a solution of (*S,S*)-**11** (1.0 equiv.) in anhydrous Et_2O, at −78 °C. The mixture was warmed then to −20 °C for 1 h and cooled again to −78 °C. Neat chlorosilane (3.0 equiv.) was added to the solution of lithiated ferrocene and the mixture was allowed to stir at −78 °C for 10 min, then at room temperature for 3 h. Water was added. The layers were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (0.5% Et_3N/Et_2O)

(*S,S,S*$_p$,*S*$_p$)-1,1′-Bis(triethylsilyl)-2,2′-bis[(2-methoxymethylpyrrolidin-1-yl)methyl]ferrocene (14b): Compound **14b** was prepared in 73% yield (0.78 g) from (*S,S*)-**11** (1.6 mmol) as an orange oil. R_f = 0.7 (0.5% TEA/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.20 (t, J = 2.0 Hz, 2H), 4.03 (bs, 2H), 3.95 (d, J = 12 Hz, 2H), 3.94 (bs, 2H), 3.49 (dd, J = 9.0, J = 5.5 Hz, 2H), 3.37 (s, 6H), 3.24 (dd, J = 9.0, J = 6.5 Hz, 2H), 2.96 (d, J = 12.5 Hz, 2H), 2.7–2.6 (m, 2H), 2.6–2.5 (m, 2H), 2.0–1.9 (m, 2H), 1.9–1.8 (m, 2H), 1.65–1.50 (m, 6H), 1.0–0.9 (m, 18H), 0.9–0.7 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 89.8 (C), 77.1 (CH_2), 76.4, 75.2, 70.9, 69.4 (C), 63.6, 59.1, 55.3 (CH_2), 54.2 (CH_2), 29.1 (CH_2), 22.5 (CH_2), 8.2 (Me), 4.9 (CH_2); HR-MS (ESI): m/z = 691.3748, calcd. for $C_{36}H_{64}FeN_2NaO_2Si_2$ $[M+Na]^+$: 691.3753; $[\alpha]_D^{24}$: −119 (*c* 1, $CHCl_3$).

(*S,S*)-1,1′-bis(Triethylsilyl)-2,2′-bis(acetyloxymethyl)-ferrocene (15b)

Compound **14b** (730 mg, 1.1 mmol) was dissolved in 8 mL of acetic anhydride. The solution was stirred at 90 °C for 16 h in a sealed tube. After evaporation of the solvent under vacuum, purification by column chromatography gave **15b** as an orange solid; yield: 340 mg (56%). R_f = 0.48 (30% Et_2O/heptane); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.92 (d, J = 12.0 Hz, 2H), 4.77 (d, J = 12.0 Hz, 2H), 4.35 (bs, 2H), 4.31 (bs, 2H), 4.08 (bs, 2H), 2.04 (s, 6H, Me), 1.01 (t, J = 8.0 Hz, 18H, Me), 0.90–0.75 (m, 12H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6 (CO), 85.8 (C), 76.1, 74.4, 72.3, 71.1 (C), 63.4 (CH_2), 21.0 (Me), 7.9 (Me), 5.0 (CH_2); HR-MS (ESI): m/z = 581.2187, calcd. for $C_{28}H_{46}FeNaO_4Si_2$ $[M+Na]^+$: 581.2182; $[\alpha]_D^{25}$: +46 (*c* 1, $CHCl_3$).

(*S,S*)-1,1′-Bis(triethylsilyl)-2,2′-(2-cyclohexyl-2-phosphapropanediyl)ferrocene (16d)



Cyclohexylphosphine (83 μL, 0.62 mmol, 1.1 equiv.) was added dropwise to a solution of the diacetate (*S,S*)-**15b** (0.31 g, 0.56 mmol) in degassed acetic acid (9 mL) at room temperature. The reaction mixture was heated at 60 °C for 16 h. The solvent was evaporated under vacuum, the crude product was taken up in dichloromethane and the solvent was evaporated again. Purification by flash chromatography on silica gel with heptane as the eluent afforded **16d**; yield: 135 mg (43%). R_f = 0.6 (1% EtOAc/heptane); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.54 (bs, 1H), 4.21 (bs, 1H), 4.18 (bs, 1H), 4.03 (bs, 1H), 4.01 (bs, 1H), 3.91 (bs, 1H), 2.39 (t, $J_{H,H} \sim J_{P,H}$ = 13.5 Hz, 1H, PCH_2), 2.31 (t, $J_{H,H} \sim J_{P,H}$ = 13.5 Hz, 1H, PCH_2), 2.05–1.80 (m, 6H), 1.78–1.70 (m, 1H), 1.60–1.50 (m, 1H), 1.40–1.28 (m, 5H), 1.03 [t, J = 8.0 Hz, 9H, Si(CH_2CH_3)$_3$], 0.99 [t, J = 8.0 Hz, 9H, Si(CH_2CH_3)$_3$], 0.88 [q, J = 8.0 Hz, 6H, Si(CH_2CH_3)$_3$], 0.79 [q, J = 8.0 Hz, 6H, Si(CH_2CH_3)$_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 87.7 (*C*), 87.3 (*C*), 77.16, 74.8, 74.5, 73.9 (d, $J_{P,C}$ = 10.6 Hz), 70.3, 69.9 (*C*), 69.7 (*C*), 69.0, 38.9 (d, $J_{P,C}$ = 12.9 Hz, *C*H), 30.5 (d, $J_{P,C}$ = 12.0 Hz, *C*H_2), 30.0 (d, $J_{P,C}$ = 10.6 Hz, *C*H_2), 27.3 (d, $J_{P,C}$ = 9.0 Hz, *C*H_2), 27.2 (d, $J_{P,C}$ = 8.0 Hz, *C*H_2), 26.7 (*C*H_2), 24.5 (d, $J_{P,C}$ = 23.0 Hz, P-*C*H_2), 22.8 (d, $J_{P,C}$ = 18.5 Hz, P-*C*H_2), 8.1 (Me), 7.8 (Me), 5.4 (CH_2), 5.3 (CH_2); ^{31}P NMR (202 MHz, $CDCl_3$): δ = 11.4 ppm; HR-MS (ESI): m/z = 555.2694, calcd. for $C_{30}H_{52}FePSi_2$ $[M+H]^+$: 555.2695; $[\alpha]_D^{25}$: −55 (*c* 1, $CHCl_3$).

Catalytic Asymmetric [3+2] Annulations of Buta-2,3-dienoates with Enones 22 (Table 4)

A mixture of enone **22** (0.15 mmol), buta-2,3-dienoate (0.30 mmol) and phosphine **16c** (10 mol%, 0.015 mmol, 7.1 mg) in degassed toluene (0.50 mL) was stirred at the given temperature for 24 h under an argon atmosphere. The crude mixture was concentrated under vacuum, and purified by flash chromatography on silica gel (EtOAc/heptanes). Enantiomeric excesses were measured by chiral HPLC (See supporting information). The shown configurational assignment for compounds **21** and **23** is based on $[\alpha]_D$ values, by comparison with known compounds from ref.[5b]

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[26] Assignment of an S_PR_P configuration to **13b** also relies on the fact that removal of the chiral auxiliaries from **13a** and **13b** with acetic anhydride, according to the procedure in Scheme 4, affords the *dl* and *meso* stereoisomers of the corresponding 1,1′-dibromo-2,2′-diacetoxymethylferrocene, respectively.

[27] Both **12a** (S_P-configuration) and the epimeric complex **12b** (R_P-configuration), produced with *t*-BuLi have been characterized: see supporting information.

[28] Other electrophiles such as MeI or DMF also afford the corresponding tetrasubstituted ferrocenes in good yields. Diastereomeric ratios are largely insensitive to the nature of the electrophilic trapping reagent.

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[32] For instance, **16c** displays a tilt angle of about 5.9° in its solid state structure, see ref.[11]

[33] The designation "γ-" refers to the allene carbon atom which adds to the β-carbon of the enone moiety.

