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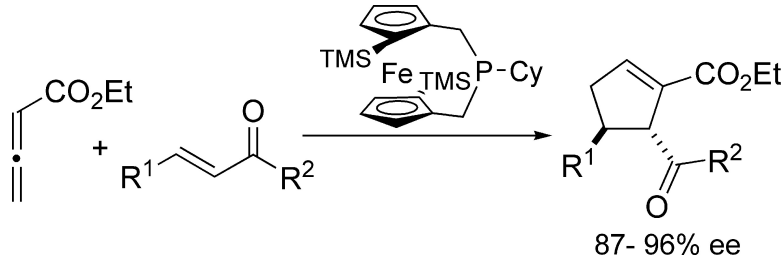

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2-Phospha[3]ferrocenophanes with Planar Chirality: Synthesis and Use in Enantioselective Organocatalytic [3 + 2] Cyclizations

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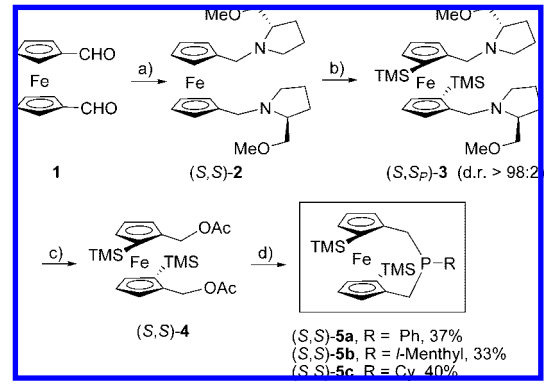
Nucleophilic phosphine organocatalysis has emerged recently as an attractive methodology in organic synthesis.[1] Though a wide variety of organic scaffolds are available by these methods, comparatively few advances have been made in the development of enantioselective variants of these reactions.[2] Notably, major contributions from Zhang,[3] Fu,[4] Miller[5] and Jacobsen[6] have highlighted the most efficient catalysts for annulation reactions disclosed so far. With the aim of further expanding the range of chiral phosphines for enantioselective organocatalytic processes, we have undertaken the development of a new class of specifically tailored compounds, the planar chiral 2-phospha[3]ferrocenophanes **5**. Relevant characteristics that make these phosphanes *a priori* amenable to enantioselective organocatalysis are their cyclic structure, with the related restricted conformational freedom, and their electron-rich nature and potentially nucleophilic character. The highly successful uses of many chiral phosphines with ferrocene backbones in organometallic catalysis[7] also supported our choice of **5** as privileged targets. Here we describe a stereoselective synthetic approach to the ferrocenophane scaffold as well as applications of **5c** as catalyst in highly enantioselective [3 + 2] cyclizations of ethyl 2,3-butadienoate with α,β-unsaturated esters and ketones.

Our synthetic approach to 2-phospha[3]ferrocenophanes **5** implies the building of an enantiomerically pure 1,1′,2,2′-tetrasubstituted ferrocene bearing on its α-carbons suitable leaving groups (OAc) that would allow introduction of the phosphorus function in the final step (Scheme 1).

The 1,1′,2,2′-tetrasubstituted ferrocene moiety has been prepared *via* diastereoselective di-*ortho*-lithiation of (*S,S*)-**2**[8] bearing 2-(methoxymethyl)pyrrolidine as the chiral directing groups.[9] The bislithiated intermediate obtained in Et_2O at −30 °C with *s*BuLi as the base, was conveniently quenched with TMSCl[10] to afford (S,S_P)-**3** in 66% yield, with excellent diastereoselectivity (dr > 98:2). In the next step, the chiral auxiliaries have been removed, and the required leaving groups have been introduced in a single process, by heating compound **3** in acetic anhydride at 85 °C. The cyclization step leading to **5** was performed then in acidic conditions[11] *via* two consecutive S_N1 substitutions on the α-carbons by a primary phosphine ($PhPH_2$, *l*-MenthylPH_2[12] or $C_6H_{11}PH_2$). Compounds **5** represent the first known phosphines with a planar chiral 2-phospha[3]ferrocenophane scaffold.[13]

The trivalent phosphines **5** (TMS-FerroPHANEs) showed good air stability in both solution[14] and solid state. Their structures as well as the expected (*S*)-configuration[9a] of the planar chiral ferrocene moiety have been unambiguously established by X-ray diffraction studies (Figure 1). In the solid state, the Cp rings of **5b** are almost perfectly eclipsed in a *syn*-periplanar conformation with a torsion angle of 2.0°. They are only slightly tilted toward each other (5.9°), which suggests a very low degree of ring strain induced by the three-atom tether.

Scheme 1. Synthesis of the Planar Chiral 2-Phospha-[3]ferrocenophanes (*S,S*)-**5** via Diastereoselective *ortho*-Metalation[a]



[a] Reaction conditions: a) (*S*)-2-(methoxymethyl)pyrrolidine, $NaBH_3CN$, 4 Å MS, MeOH, 63%; b) i. *s*BuLi, Et_2O, −70 °C/−30 °C/−70 °C; ii. TMSCl −70 °C to rt, 66%; c) Ac_2O, 85 °C, 18 h, 87%; d) RPH_2, AcOH, 60 °C, 16 h.

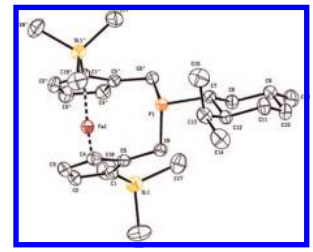


Figure 1. ORTEP view of phosphine **5b**.

Having in hand a suitable access to phosphines **5a**−**c**, their use as nucleophilic catalysts has been investigated then as a privileged potential application. Phosphines **5** have been evaluated in the [3 + 2] annulations of ethyl 2,3-butadienoate with α,β-unsaturated esters and ketones,[1d] leading to functionalized cyclopentenes with up to two contiguous stereogenic centers (see Table 1). These processes involve activation of the allenoate by addition of the nucleophilic phosphorus derivative to the central carbon, followed by stepwise formal [3 + 2] cycloadditions of the intermediate 1,3-dipole on the olefins.[15]

Initial experiments and optimization of the reaction conditions have been performed on the reaction between ethyl 2,3-butadienoate **6** and diethyl fumarate **7a**,[16,3] in the presence of a 10% amount of phosphines **5a**−**c**. The reactions yielded the *trans*-stereoisomer of cyclopentene **8a** as the single product, implying that the process takes place, as expected, with retention of the stereochemistry of the starting olefin. The nature of the phosphorus substituent in **5** proved to be a crucial structural factor with respect to both conversion rates and enantioselectivity. The *P*-cyclohexyl substituted phosphine **5c** ([Cy]-TMS-

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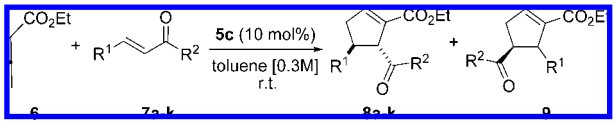
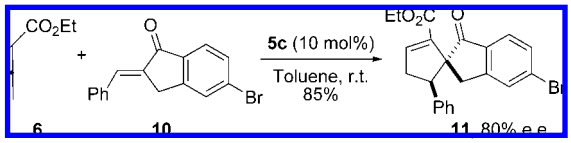
Table 1. [3 + 2] Annulation Reactions of Ethyl 2,3-Butadienoate **6** with the Unsaturated Esters **7a,b** and Enones **7c−k** Promoted by Phosphine **5c**



entry	R^1	R^2	**8**:**9** ratio	yield **8**+**9**	cmpd	ee[g] (%)
1[a]	CO_2Et	OEt	−	68	**8a**	90
2[a,b]	CO_2Et	OEt	−	28	**8a**	93
3[c]	H	OEt	1:1.5	53	**8b/9b**	88/84
4[d]	Ph	Ph	20:1	65	**8c**	92
5[d]	1-naphth	Ph	>20:1	87	**8d**	96
6[d]	4-$MeOC_6H_4$	Ph	>20:1	71	**8e**	93
7[e]	4-$NO_2C_6H_4$	Ph	10:1	63	**8f**	92
8[d,f]	2-furyl	Ph	8:1	71	**8g**	93
9[d]	Ph	4-$MeOC_6H_4$	>20:1	85	**8h**	95
10[e]	Ph	4-$NO_2C_6H_4$	>20:1	68	**8i**	89
11[e]	2-quinolyl	Ph	20:1	75	**8j**	87
12[e]	C≡CC_5H_{11}	Ph	15:1	70	**8k**	90

[a] **6**:**7** = 1:2. [b] Reaction at 0 °C. [c] **6**:**7** = 1:10. [d] **6**:**7** = 2:1. [e] **6**:**7** = 1.2:1. [f] In acetone. [g] Enantiomeric excesses have been measured by chiral HPLC.

Scheme 2. [3 + 2] Annulation Reaction on a Trisubstituted Enone



FerroPHANE) gave the highest conversion rates[17] and enantiomeric excesses,[18] with a 90% ee for reactions performed in toluene at room temperature (entry 1). The enantiomeric excess could be further increased to 93% for reactions run with **5c** at 0 °C (entry 2). These are the highest ee's reported so far for cyclization reactions between ethyl 2,3-butadienoate and fumarate esters.[3]

Following these initial successful experiments, the annulation reactions of ethyl 2,3-butadienoate, **6**, with ethyl acrylate **7b** and various enones, **7c−k**, were surveyed in the presence of a 10% amount[19] of phosphine **5c** (entries 3−12). With such unsymmetrical alkenes as the dipolarophiles, two regioisomeric [3 + 2] cycloadducts **8** and **9** can be obtained, following γ- and α-addition modes of the intermediate phosphine−allene adduct to the olefins. In the presence of **5c**, the annulation reaction with ethyl acrylate afforded indeed the expected cyclopentenes as a 1:1.5 mixture of regioisomers **8b** and **9b**, in 88% and 84% ee, respectively (entry 3). An (*S*)-absolute configuration has been assigned to **9b**, based on $[\alpha]_D$ values.[3,20]

Starting from the α,β-unsaturated enones **7c−k**,[4a,5] the corresponding cyclopentenes were produced with high regioselectivity (**8**:**9** ratios from 8:1 to >20:1), *via* preferential γ-addition. Cyclopentenes **8c−k** were obtained in 87−96% ee from both electron-rich and electron-deficient chalcone derivatives. Enones **7g** and **7j** bearing heterocyclic substituents could be also converted into the corresponding cyclopentenes in 87−93% ee (entries 8 and 11). The possible use of β-alkynyl-substituted enones in the annulation reactions has been typified by converting **7k** into the corresponding cyclopentene **8k** in 90% ee (entry 12).[21]

Finally, high regioselectivity (20:1 regioisomeric ratio) and substantial enantiocontrol were observed in the synthesis of the spirocyclic derivative **11**[4a,5] from the corresponding exocyclic enone **10** (Scheme 2).

In summary, we have developed a stereoselective access to a new class of chiral phosphines based on a planar chiral 2-phospha[3]ferrocenophane scaffold, and we have highlighted the efficiency of phosphine **5c** as enantioselective nucleophilic organocatalyst in model [3 + 2] annulation reactions. In these reactions, phosphine **5c** compares favorably with the previous best catalysts.[3,4a,5] Its practical utility should rely on, among others, its good air-stability and ease of handling, combined with a yet satisfying nucleophilicity. The modular nature of ferrocenophanes **5** as well as the versatile synthetic approach should allow subtle and extensive variations of both the phosphorus substituent and the cyclopentadienyl substituents as a key to the fine-tuning of single organic and organometallic catalytic processes.

Supporting Information Available: Complete experimental procedures, characterization data, ee determinations, and crystallographic data for (*S,S*)-**5b** (CCDC 686645) and (*S,S*)-**5c** (CCDC 686646). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The lower reactivities of **5a** and **5b**, compared to that of **5c**, can be tentatively ascribed to a lower nucleophilic character for **5a** and to an increased steric hindrance for **5b**.

(18) In analogous conditions phosphine **5a** afforded **8a** in 11% ee, while **5b** gave a 12% ee for reactions run at 90 °C.

(19) The catalyst amount can be reduced, while retaining a significant catalytic activity and the same levels of enantiocontrol: for reaction in entry 5, conversion rates of 74% and 40% were observed after 40 h at rt, at catalysts amounts of 5% and 1% respectively (96% ee).

(20) For preliminary considerations on the sense of asymmetric induction and a model for the phosphine−allene adduct, see Supporting Information.

(21) Conversion rates lower than 10% were obtained in the annulations between ethyl butadienoate and both ethyl maleate and the alkyl-substituted enone $C_5H_{11}CH{=}CHCOPh$.

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