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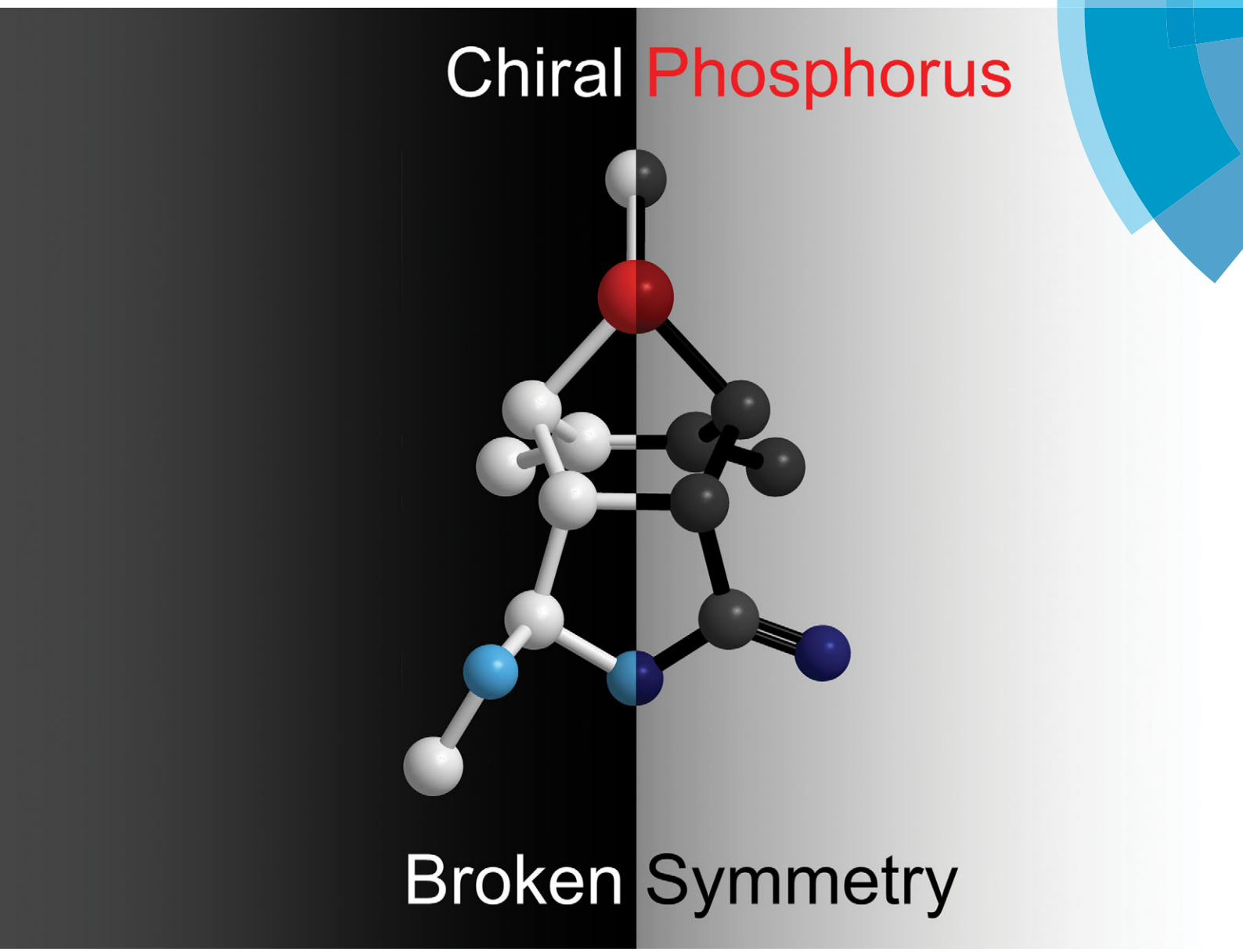

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P-chiral phosphorus heterocycles: a straightforward synthesis†

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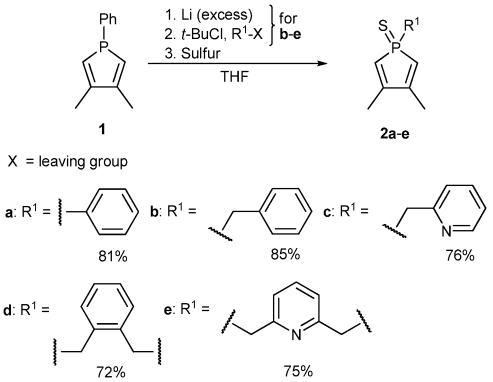
A straightforward synthesis of P-chiral polycyclic 7-phosphanorbornenes *via* an asymmetric Diels–Alder reaction is presented. The employed starting materials are cheap, easily accessible and of structural diversity facilitating a new flexible route towards differently functionalised P-chiral phosphanes.

Chiral compounds are of great importance today and affect almost everybody's life. They are mainly applied in life sciences and drug development, but also in the food and fragrance industries, and their efficient and targeted syntheses are no longer solely of academic interest.[1] As a result, the fields of asymmetric synthesis and enantioselective catalysis, in particular, are still growing. For such an expanding field, new tools and reagents are permanently desired. Surprisingly, a class of such tools that was used in the very beginning of enantioselective catalysis has experienced a comeback recently: the class of P-chiral phosphanes.[2]

One of the main reasons why P-chiral phosphanes have been less applied in asymmetric catalysis than phosphanes having a chiral backbone is their challenging synthesis. Due to the immense interest in these compounds and the efforts made to expand their structural scope, this problem is about to be overcome.[2d–f,3] Thus, established synthetic strategies involve kinetic resolution and dynamic kinetic resolution of racemates, stereotopic face differentiation and desymmetrisation.[2d–f,3] Nevertheless, there is a major lack of stereoselective approaches to P-chiral phosphanes, in contrast to their C-stereogenic counterparts. In this regard, we have shown in a preliminary study that it is possible to apply the principle of stereotopic face differentiation to a P=C double-bond motif by using an asymmetric phospha-Diels–Alder reaction.[3] After establishing this stereoselective route to 1-phosphanorbornenes, it was apparent that this approach should also facilitate access to P-chiral 7-phosphanorbornenes with the phosphorus atom in the bridge position. To date, only two synthetic strategies have been reported which give access to this class of compounds.[4] The advantage of the approach presented here is the use of very cheap and easily accessible starting materials, which also offer the possibility for facile functionalisation and therefore a broad substrate scope.



Scheme 1 Facile synthesis of P-heterocyclic dienes.

An important aspect of this approach is the flexible synthesis of P-heterocyclic dienes (Scheme 1). Reaction of **1** with sulfur gives **2a**. Thiophospholes **2b–e** can be easily obtained from **1** *via* reductive P–C(Ph) bond cleavage, followed by addition of *tert*-butyl chloride to remove phenyllithium.[5] Then the phospholide is treated with an electrophile and sulfur to give **2b–e**. Compounds **2a–e** were fully characterised, and compounds **2d,e** were additionally characterised using X-ray crystallography (see ESI†).

Trivalent phospholes with exocyclic carbon substituents act as poor dienes, and often react only with very strong dienophiles or after rearrangement at higher temperatures[6] due to the conjugation of the lone pair of electrons at phosphorus and the hyperconjugation of the exocyclic σ-P–C bond with the dienic system.[6,7] Substitution of the exocyclic carbon substituent at the phosphorus atom by a heteroatom decreases the hyperconjugation effect and activates the phosphole towards cycloaddition reactions.[4f,8] However, if organyl-substituted derivatives are required, blocking the lone pair of

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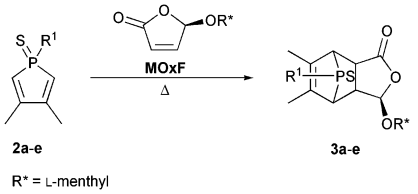
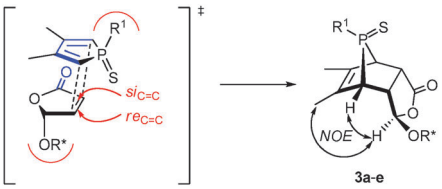
† Electronic supplementary information (ESI) available. CCDC 981039 (**2d**), 981040 (**2e**), 981041 (**3a**), 981042 (**3b**) and 981043 (**3c**), synthesis and full characterisation of **2a–e** and **3a–e**, and *in situ* synthesis of **4b,d,e**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00318g



Scheme 2 Asymmetric phospha-Diels–Alder reaction yielding P-chiral 7-phosphanorbornenes.



Scheme 3 Transition state (blue = attractive, red = repulsive) and absolute configuration of **3a–e** including the supporting NOEs.

electrons is the only choice. One possibility is coordination to a metal, which activates the phosphole, but makes it synthetically less available as a substrate.[4a,9] Another possibility is sulfurisation, which leaves the substrate synthetically more accessible, but does not activate the diene further.[10]

In the key step, the Diels–Alder reaction, (5*R*)-(L-menthyloxy)-2(5*H*)-furanone (**MOxF**) was used as dienophile, since it had previously shown very good selectivities in stereoselective reactions (Scheme 2).[3,11] The cycloaddition reaction provides chiral C_1- (**3a–c**) and C_2-symmetric (**3d,e**) P-chiral 7-phosphanorbornenes (Table 1).

The applied conditions show that high activation energies are needed. Even at elevated temperatures, full conversion of the substrates occurred only after 5 d. However, in the case of **3a**, decomposition took place slowly even at room temperature; optimal conditions were found to be 110 °C for 3 d. The methylene group at the phosphorus atom in **2b–e** and **3b–e** seems to be important for full conversion and the stability of the formed product.

The stereoselectivities for the C_1-symmetric derivatives **3b,c** are good. For **3a**, the moderate d.r. could be attributed to the less flexible phenyl group at the phosphorus atom; furthermore, the *syn*/*anti* ratio for **3a** could not be determined, because numerous signals of decomposition products were present in the $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture. In the case of C_2-symmetric products (**3d,e**), the minor stereoisomers and hence their ratios could not be assigned because of the more complex mixture of possible cycloaddition products. Nevertheless, for both compounds the main stereoisomer could be assigned as the C_2-symmetric isomer. The main diastereomers of **3c–e** could be readily obtained in pure form.

The stated configuration of the main stereoisomers was supported by selective NOE NMR experiments (Scheme 3). Moreover, evidence for the *syn* orientation of R^1 and the C=C double bond can be taken from the ^{31}P NMR studies showing a strong downfield shift to 108–113 ppm for **3a–e**. This deshielding effect has been known for norbornenes and -norbornadienes for a long time, and was also observed for other elements in the bridge position.[12] It is caused by the C=C double bond, which is suspected to undergo σ–π interactions in such strained cage systems.[12f,13] Additionally, if R^1 in **3** were in a *syn* relationship with respect to the chiral auxiliary, the lone pair of electrons at phosphorus (blocked or free) would be above the C=C double bond and therefore in its shielding cone due to the anisotropic effect. Consequently, the ^{31}P NMR resonance would be more upfield shifted, as was observed before.[10a,12e,g] Single crystals could be obtained for **3a–c** and were analysed using X-ray diffraction measurements (see ESI†). As a representative example, the molecular structure of **3b** is shown in Fig. 1. The structure confirms the absolute configuration proposed and shows structural properties known for 7-phosphanorbornenes and -norbornadienes such as the small bond angle at the phosphorus bridge (C3–P1–C6 81.67(5)°).[14]

Table 1 Reaction conditions, selectivities and yields

	Conditions	*syn* : *anti*[a]	d.r. (of all *syn*)	Yield of **3** (%)
a	PhMe, 110 °C, 3 d	—[b]	68 : 21 : 7 : 4	49
b	PhCl, 130 °C, 5 d	96 : 4	85 : 7 : 5 : 3	52
c	PhCl, 130 °C, 5 d	98 : 2	93 : 5 : 2 : 0	70
d	PhCl, 130 °C, 5 d	—[b]	—[b]	50
e	PhCl, 130 °C, 5 d	—[b]	—[b]	51

[a] R^1 to C=C. [b] Not assignable.

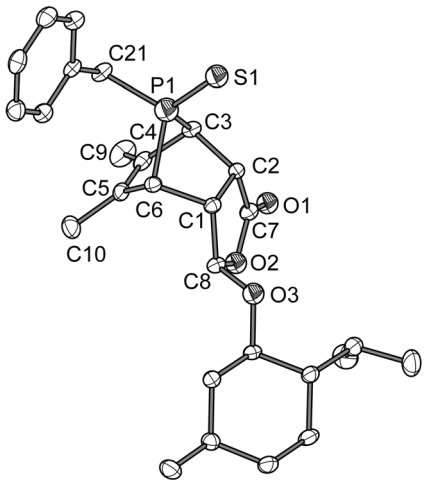
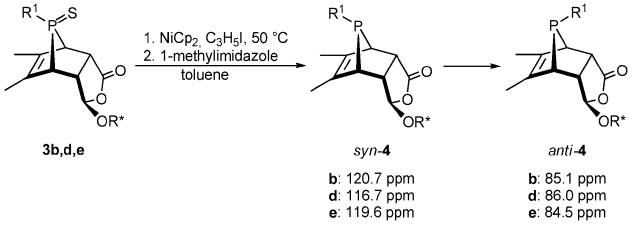


Fig. 1 Molecular structure of **3b** in the solid state showing the absolute configuration of the main stereoisomer; thermal ellipsoids are drawn at 50% probability. Hydrogen atoms are omitted for clarity.‡

An explanation for the occurrence of mainly one out of eight stereoisomers (per phosphanorbornene system) can be drawn from the transition state showing one attractive and two repulsive interactions (Scheme 3): (1) the attractive *endo* mode of transition states in Diels–Alder reactions is well known and attributed to secondary orbital interactions of the HOMO (diene) and LUMO (dienophile).[15] (2) Furthermore, steric shielding of the *re* side of **MOxF** by the bulky menthyloxy substituent causes approach of the thiophosphole from the *si* side. (3) In this approach, the sulfur atom, which is sterically less demanding than R^1, points towards the dienophile resulting in a *syn* orientation of the substituent R^1 at the phosphorus atom and the double bond in 7-phosphanorbornenes **3a–e**.

It is remarkable that these three interactions cause very good selectivities in a single concerted step and yield such complex structures of high rigidity. This feature is what makes the Diels–Alder reaction so unique and facilitates access to P-chiral



Scheme 4 Desulfurisation of **3b,d,e** and isomerisation of **4b,d,e**; $^{31}P\{^{1}H\}$ NMR chemical shifts without lock.

phosphorus heterocycles. In this respect, the scope of products is very variable due to the facile route and cheap and easily accessible substrates. Moreover, the introduced chiral auxiliary enables further functionalisation, such as substitution reactions or reductive cleavage of the auxiliary, which are of interest for subsequent ligand design and applications in asymmetric catalysis.

For this purpose, **3a–e** must be deprotected. Desulfurisation of the stable compounds **3b–e** was attempted with RANEY® nickel or triethylphosphane but only resulted in elimination of "P(*S*)R^1" to give the cyclohexadiene–**MOxF** fragment. This behaviour was observed for 7-phosphanorbornenes before and shows their tendency towards elimination reactions.[16] With trichlorosilane, no reaction was observed. The method of choice for **3b,d,e** was treatment with nickelocene/allyl iodide and subsequently 1-methylimidazole, which was also previously used for the desulfurisation of 7-phosphanorbornenes.[10a] The trivalent compounds **4b,d,e**, (Scheme 4) were obtained *in situ*. After two days at room temperature in solution, transformation of the *syn* to the *anti* isomer had occurred (singlet at 84–86 ppm in the $^{31}P\{^{1}H\}$ NMR spectra).[10a]

These phosphanes could become valuable tools in asymmetric catalysis; the corresponding applications of the *in situ* generated phosphanes **4b,d,e** are now underway and will be reported elsewhere.

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Notes and references

‡ wR_2 = 0.0662. Absolute structure parameter = −0.01(4). Selected bonds lengths [pm] and angles [°]: S1–P1 194.00(7), P1–C21 182.8(1), P1–C3 185.0(1), P1–C6 185.5(1), C1–C2 154.3(2), C1–C6 155.4(2), C1–C8 153.4(1), C2–C3 155.8(2), C2–C7 151.8(2), C3–C4 150.7(2), C4–C5 134.4(2), C5–C6 151.7(2); C21–P1–C3 109.44(5), C21–P1–C6 110.10(6), C3–P1–C6 81.67(5), C21–P1–S1 113.21(4), C5–C6–P1 99.38(7), C1–C6–P1 98.78(7), C4–C3–P1 99.54(7), C2–C3–P1 98.78(7).

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