Configurationally stable propeller-like triarylphosphine and triarylphosphine oxide†

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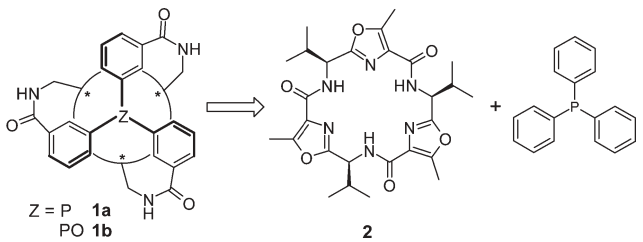
Configurationally stable, propeller-like triarylphosphine and triarylphosphine oxide can be synthesized; a chiral scaffold based on *Lissoclinum*-cyclopeptides linked *via* three peptide bonds with a triphenylphosphine and triphenylphosphine oxide moiety, respectively, prevents effectively epimerization at the chiral phosphorus atom.

Triphenylphosphine and triphenylphosphine oxide are valuable reagents, additives or ligands in synthetic chemistry.[1] Both molecules adopt propeller-like C_3-symmetrical conformations, thus minimizing intramolecular non-bonding repulsive interactions between their phenyl rings, and therefore are helically chiral substrates. However, organic compounds of this type, having the general chemical structure Ar_3Z (Z = N, P, PO), are regarded as achiral, since fast inversion of helicity occurs even at ambient temperature.[2] For this reason, in chemical reactions where the transfer of chirality is essential, phosphines[3] or phosphine oxides having an axial chirality, such as BINAP[4] and BINAP-dioxide,[5] are predominantly used. Numerous approaches to C_3-symmetrical, conformationally stable triphenylphosphines or triphenylphosphine oxides have already been undertaken; examples are the introduction of substituents with chiral centers in *ortho*- or *para*-positions,[6] the utilization of chiral counterions[7] or the introduction of bulky substituents[8] at the propeller blade aromatics for enhancing the barrier of racemization at the phosphorus atom. Although diastereospecific control over the helicity of triphenylphosphine metal complexes is well known,[9] these methods generally failed in the case of triarylphosphine and triarylphosphine oxide derivatives as free ligands. The only example for a stereochemically pure triarylphosphine oxide is a trisindolylphosphine oxide, where the stereochemical stability is the result of the immense steric demand of the indolyl substituents.[10]

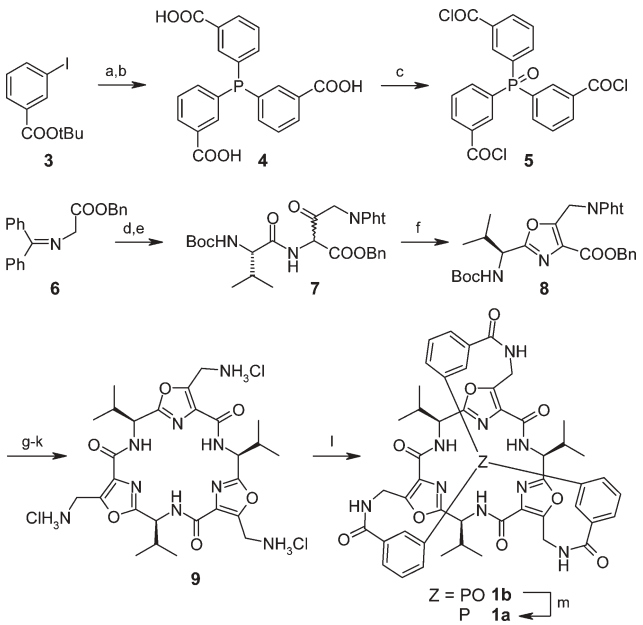
Recently we have shown that cyclic peptides can successfully be used as templates for the chirality transfer of C_3-symmetrical compounds.[11] Assuming that this concept is generally applicable, we decided to try and synthesize a triphenylphosphine derivative bound to a chiral, cyclic peptide scaffold. This scaffold should cause one of the possible configurations at the phosphorus centre



Scheme 1

to be stabilized to such an extent that only this is adopted at room temperature (**1** in Scheme 1). As chiral scaffold we chose the trisoxazole system **2**, which resembles the naturally occurring *Lissoclinum*-cyclopeptide *Westiellamide*.[12]

The desired triphenylphosphine oxide **1b** was obtained by cyclization of the chiral scaffold **9**, having three amino functions as coupling sites, with the tricarboxylic acid chloride **5** (Scheme 2). The latter compound is available in three steps starting from



Scheme 2 *Reagents and conditions*: (a) *i*PrMgCl, PBr_3, THF, −78 °C → RT, 54%; (b) HCl–AcOEt, quant.; (c) $SOCl_2$, Δ, quant.; (d) $PhtNCH_2COCl$, KO*t*Bu, THF, then 2 M HCl–H_2O, −60 °C, 72%; (e) Boc–L–Val–OH, *i*BuOCOCl, NMM, THF, −20 °C → RT, 65%; (f) PPh_3, Et_3N, C_2Cl_6, CH_2Cl_2, RT, 52%; (g) $Pd(OH)_2$/C, H_2, MeOH, 98%; (h) HCl, AcOEt, 98%; (i) PyBOP, *i*Pr_2NEt, DMF, RT, 32%; (j) $NH_2NH_2{\cdot}H_2O$, Boc_2O, THF–CH_2Cl_2–EtOH; (k) HCl, Et_2O, RT, 90% (2 steps); (l) **5**, Et_3N, CH_2Cl_2, RT, 20%; (m) $HSiCl_3$, benzene, Δ, 78%.

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† Electronic supplementary information (ESI) available: Experimental details, calculated molecular structures of **(*P*1)-1**, atomic distances and dihedral angles of **1** obtained from NMR experiments and calculated values. See DOI: 10.1039/b709655k

Table 1 Relative energies of the conformers of **1a** and **1b** calculated with the TZVP basis set

Method		ΔE/kJ mol^{-1}			
		*P*1	*P*2	*M*1	*M*2
BP86	**1a**	0.0	51.4	19.3	40.2
BP86	**1b**	0.0	51.5	19.0	35.6
B3LYP	**1b**	0.0	56.6	24.1	33.7
SCS-MP2	**1b**	0.0	73.3	55.0	37.1

m-iodobenzoic acid *tert*-butyl ester. The chiral scaffold **9** could be synthesized in a few steps from the imine **6**. Reduction of the triphenylphosphine oxide **1b** with $HSiCl_3$ afforded the triphenylphosphine **1a**.

In principle, the triphenyl derivatives **1** can adopt four different conformations (*P*1, *P*2, *M*1 and *M*2): On the one side, the three phenyl rings can be present in two opposite helicities (*P*- or *M*-isomer), and on the other side, the amide bonds connecting the chiral scaffold to the triphenylphosphine system can adopt two different orientations. Viewing the molecule from the phosphorus atom along the main C_3-axis the hydrogen atoms of the three amide bonds are pointing clockwise in the case of conformers **(*P*2)-1** and **(*M*2)-1** and anticlockwise for isomers **(*P*1)-1** and **(*M*1)-1**.

To evaluate the relative stabilities of the stereoisomers, quantum chemical calculations were performed using the TURBOMOLE program.[13] The structures were determined by geometry optimizations at the DFT-level using the BP86-GGA functional.[14] For all calculations an AO-basis of triple-zeta quality with polarization functions (TZVP)[15] and the RI-approximation[16] was used. Applying other GGAs led to similar structures and similar relative energies (deviation < 5 kJ mol^{-1}) of the diastereomers. The structures optimized by BP86 were further used in single-point calculations with B3LYP[17] and SCS-MP2[18] methods, as well as for the calculation of (vertical) electronic CD spectra. All calculations reveal that the *P*1-isomers of **1a** and **1b** are strongly stabilized in preference to the others (Table 1, Fig. 1). The high energy differences between the *P*1-conformers and the other isomers indicate that phosphine **1a** as well as phosphine oxide **1b** adopt only the *P*1-conformation in solution at ambient temperature.

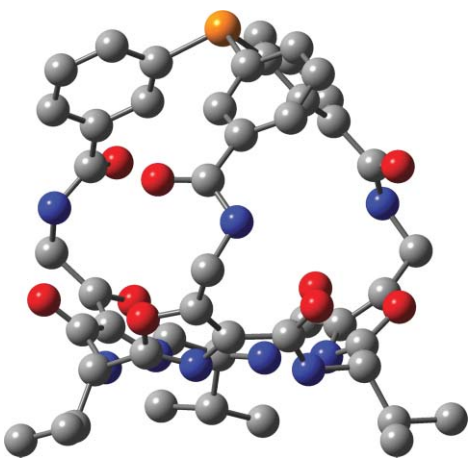

Fig. 1 Molecular structures of the energetically preferred conformer **(*P*1)-1a** calculated at the BP86/TZVP level; all hydrogen atoms have been omitted for clarity.

^{1}H-NMR spectra of **1a** and **1b** confirm the assumption that only one diastereomer is present in solution. Furthermore, the torsion angles ascertained from ^3J coupling constants approve both the rigidness of the triphenylphosphine moiety as well as the preference of the *P*1-conformation.[19]

A variable temperature ^{1}H-NMR measurement as well as 2D-NOESY experiments were carried out for **1b**.[20] VT-^{1}H-NMR measurements showed that there are no dynamic processes occurring between -60 °C and $+60$ °C. The comparison of H,H-distances in **1b** from 2D-NOESY measurements with those of the conformers calculated by BP86/TZVP shows that these are only consistent with the *P*1-conformation. The short distances between the amide hydrogen and one hydrogen of the adjacent methylene group (2.3 Å) on the one side and one aromatic proton (2.1 Å) on the other side indicate that **1b** is rigid and possesses no conformational flexibility.

Additionally, CD measurements were carried out to confirm that only the diastereomer **(*P*1)-1b** is present in solution. Fig. 2 shows CD spectra of chiral scaffold **2** and of triphenylphosphine oxide **1b**. Compared to the CD spectrum of **2** the $\Delta\varepsilon$-values of **1b** show a change of sign, as well as a substantial increase in intensity by a factor of up to six. The new bands at 265, 249, 233 and 205 nm of **1b** arise from the triphenylphosphine oxide chromophore and support the stabilization of one conformation. Furthermore, a CD spectrum was calculated for **(*P*1)-1b** by the time-dependent DFT (TDDFT) method.[21,22] To avoid artificial excited electronic states with charge-transfer character, which often appear for large molecules when using pure GGAs, TDDFT-calculations were carried out by the BH-LYP hybrid functional[23] with a HF-exchange fraction of 50%. This calculated spectrum is also depicted in Fig. 2 showing an evident accordance between experiment and theory.

In summary, we have demonstrated that it is possible to stabilize one conformation of a propeller-like triphenylphosphine and triphenylphosphine oxide by using a chiral scaffold based on *Lissoclinum*-cyclopeptides. The facile synthesis of such systems *via* combination of a chiral scaffold with an achiral phosphine allows us to develop novel triarylphosphines and triarylphosphine oxides and to investigate their applicability in catalysis and synthesis.

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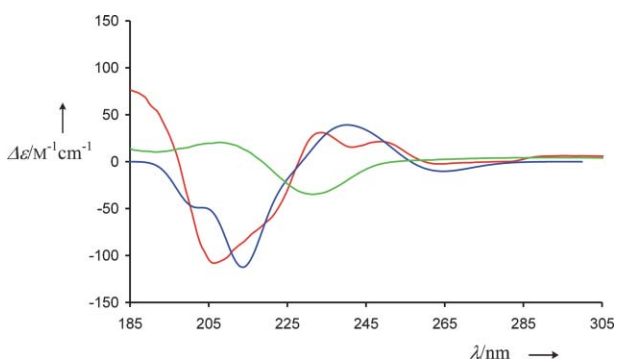

Fig. 2 CD spectra of peptide **2** (green) and of phosphine oxide **1b** [experimental: red; calculated at the TDDFT-BHLYP/TZVP//BP86/TZVP level for isomer *P*1 (intensity scaling factor: 0.22): blue].

Notes and references

1 L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley, New York, 2000.
2 (*a*) K. Mislow, *Acc. Chem. Res.*, 1976, **9**, 26; (*b*) C. Bolm and K. B. Sharpless, *Tetrahedron Lett.*, 1988, **29**, 5101.
3 S. Enthaler, B. Hagemann, K. Junge, G. Erre and M. Beller, *Eur. J. Org. Chem.*, 2006, 2912.
4 (*a*) R. Noyori and H. Takaya, *Acc. Chem. Res.*, 1990, **23**, 345; (*b*) M. Berthod, G. Mignani, G. Woodward and M. Lemaire, *Chem. Rev.*, 2005, **105**, 1801.
5 (*a*) C. Ogawa, M. Sugiura and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2004, **43**, 6491; (*b*) M. Nakajima, S. Kotani, T. Ishizuka and S. Hashimoto, *Tetrahedron Lett.*, 2004, **46**, 157; (*c*) E. Tokuoka, S. Totani, H. Matsunaga, T. Ishizuka and S. Hashimoto, *Tetrahedron: Asymmetry*, 2005, **16**, 2391; (*d*) S. Kotani, S. Hashimoto and M. Nakajima, *Synlett*, 2006, 1116.
6 (*a*) M. T. Powell, A. M. Porte and K. Burgess, *Chem. Commun.*, 1998, 2161; (*b*) Y. K. Kim, S. J. Lee and K. H. Ahn, *J. Org. Chem.*, 2000, **65**, 7807; (*c*) P. Wyatt, H. Eley, J. Charmant, B. J. Daniel and A. Kantacha, *Eur. J. Org. Chem.*, 2003, 4216; (*d*) E. Brulé, Y. Pei, F. Lake, F. Rahm and C. Moberg, *Mendeleev Commun.*, 2004, 276.
7 (*a*) R. Dorta, L. Shimon and D. Milstein, *J. Organomet. Chem.*, 2004, **689**, 751; (*b*) B. Laleu, G. Bernardinelli, R. Chauvin and J. Lacour, *J. Org. Chem.*, 2006, **71**, 7412.
8 M. R. Whitnall, K. K. Hii, M. Thornton-Prett and T. P. Kee, *J. Organomet. Chem.*, 1997, **529**, 35.
9 (*a*) J. Polowin, S. C. Mackie and M. C. Baird, *Organometallics*, 1992, **11**, 3724; (*b*) S. E. Garner and A. G. Orpen, *J. Chem. Soc., Dalton Trans.*, 1993, 533; (*c*) H. Brunner, R. Oeschey and B. Nuber, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 866.
10 T. Benincori, G. Celentano, T. Pilati, A. Ponti, S. Rizzo and F. Sannicolò, *Angew. Chem., Int. Ed.*, 2006, **45**, 6193.
11 G. Haberhauer, T. Oeser and F. Rominger, *Chem. Commun.*, 2005, 2799.
12 P. Wipf, *Chem. Rev.*, 1995, **95**, 2115.
13 R. Ahlrichs, M. Bär, H.-P. Baron, R. Bauernschmitt, S. Böcker, P. Deglmann, M. Ehrig, K. Eichkorn, S. Elliot, F. Furche, F. Haase, M. Häser, H. Horn, C. Hättig, C. Huber, U. Huniar, M. Kattannek, A. Köhn, C. Kölmel, M. Kollwitz, K. May, C. Ochsenfeld, H. Öhm, H. Patzelt, O. Rubner, A. Schäfer, U. Schneider, M. Sierka, O. Treutler, B. Unterreiner, M. von Arnim, F. Weigend, P. Weis and H. Weiss, *TURBOMOLE (vers. 5.7)*, University of Karlsruhe, Karlsruhe, Germany, 2005, see http://www.turbomole.com.
14 (*a*) A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098; (*b*) J. P. Perdew, *Phys. Rev. B*, 1986, **33**, 8822.
15 A. Schäfer, H. Horn and R. Ahlrichs, *J. Chem. Phys.*, 1992, **97**, 2571.
16 (*a*) RI-DFT: K. Eichkorn, O. Treutler, H. Öhm, M. Häser and R. Ahlrichs, *Chem. Phys. Lett.*, 1995, **240**, 283; (*b*) RI-MP2: F. Weigend and M. Häser, *Theor. Chem. Acc.*, 1997, **97**, 331.
17 (*a*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; (*b*) S. H. Vosko, L. Wilk and M. Nusair, *Can. J. Phys.*, 1980, **58**, 1200; (*c*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
18 (*a*) S. Grimme, *J. Chem. Phys.*, 2003, **118**, 9095; (*b*) S. Grimme, *J. Phys. Chem. A*, 2005, **109**, 3067.
19 G. N. Ramachandran, R. Chandrasekaran and K. D. Kopple, *Biopolymers*, 1971, **10**, 2113.
20 Phosphine **1a** is readily oxidized under these conditions to the phosphine oxide **1b**.
21 (*a*) R. Bauernschmitt and R. Ahlrichs, *Chem. Phys. Lett.*, 1996, **256**, 454; (*b*) *Time-Dependent Density Functional Theory*, ed. M. A. L. Marques, C. A. Ullrich, F. Nogueira, A. Rubio, K. Burke and E. K. U. Gross, Springer, Berlin Heidelberg, Germany, 2006.
22 (*a*) F. Furche, R. Ahlrichs, C. Wachsmann, E. Weber, A. Sobanski, F. Vögtle and S. Grimme, *J. Am. Chem. Soc.*, 2000, **122**, 1717; (*b*) C. Diedrich and S. Grimme, *J. Phys. Chem. A*, 2003, **107**, 2524.
23 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 1372.