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Helical Chirality Transmission through a *p*-Phenylene Fragment in a Hexa-λ^5-phosphazene

Mateo Alajarín,* Carmen López-Leonardo, and José Berná

Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia,
Campus de Espinardo, 30100 Murcia, Spain

alajarin@um.es

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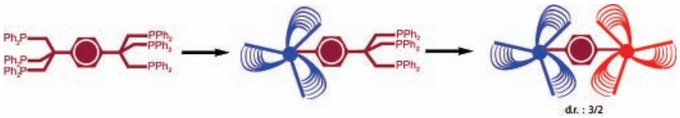
ABSTRACT



The helical chirality of a conformationally stable macrobicyclic tri-λ^5-phosphazene is propagated through to its C_3 symmetry axis and causes a measurable stereoinduction in the formation process of a second macrobicyclic tri-λ^5-phosphazene unit connected to the former one by a *p*-phenylene linker.

Molecular propellers are chiral molecules possessing two or more subunits, which can be considered as "blades", radiating from an axis of rotation.[1] Bicyclic organic compounds of local C_3 symmetry, constructed by linking two tripodal units, may exhibit this type of chirality.[2] In this regard, we have previously reported that the self-assembly of tripodal reactants such as tris(3-azidobenzyl)amines and triphosphanes of general formula $R_{piv}C(CH_2PPh_2)_3$ gave intermediate triphosphazides[3] which under mild heating in solution yielded the tri-λ^5-phosphazenes **1**[4] by the well-known two-step Staudinger reaction.[5] The macrobicycles **1** so obtained were shown to possess a propeller geometry (both in solution and in solid state), and the process occurs with total stereoselectivity in favor of the formation of the species in which both tripodal units, the upper tribenzylamine and the lower *tert*-pentane fragments, present the same sense of twist.

We have shown[6] that the sense of twist (*P*/*M*) of the helical asymmetry of cages **2**, bearing a single chiral carbon atom on one of their arms, is totally controlled by the absolute configuration of the stereogenic center (Figure 1).[7] This kind of control represents one of the scarce examples of center-to-propeller chirality transfer reported at the molecular level in discrete organic molecules until now.[8]

Whereas point chirality has been effectively transferred to a propeller,[7,8] or to an axis,[9] propeller-to-propeller chirality transfers are unknown processes in covalent architectures. To the best our knowledge, these kinds of transmission

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[1] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 1156.

[2] (a) Pascal, R. A., Jr.; West, A. P., Jr.; Van Engen, D. *J. Am. Chem. Soc.* **1990**, *112*, 6406. (b) L'Esperance, R. P.; West, A. P., Jr.; Van Engen, D. R.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 2672. (c) Dell, S.; Vogelaar, N. J.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 6421. (d) Chen, Y. T.; Baldridge, K. K.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 12082. (e) Dell, S.; Ho, D. M.; Pascal, R. A., Jr. *J. Org. Chem.* **1999**, *64*, 5626.

[3] Alajarín, M.; Vidal, A.; López-Leonardo, C.; Berná, J.; Ramírez de Arellano, M. C. *Tetrahedron Lett.* **1998**, *39*, 7807.

[4] (a) Alajarín, M.; López-Leonardo, C.; Berná, J. *Tetrahedron* **2006**, *62*, 6190. (b) Alajarín, M.; López-Leonardo, C.; Berná, J.; Steed, J. W. *Tetrahedron* **2007**, *63*, 2078. (c) Alajarín, M.; López-Leonardo, C.; Berná, J. *Tetrahedron* **2007**, *63*, 4450.

[5] (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. (b) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L F. *Tetrahedron* **1981**, *37*, 437. (c) Gololobov, Y. G.; Kasukhin, L F. *Tetrahedron* **1992**, *48*, 1353. (d) Johnson, A. W. *Ylides and Imines of Phosphorus*; Wiley: New York, 1993; p 403.

[6] (a) Alajarín, M.; López-Leonardo, C.; Vidal, A.; Berná, J.; Steed, J. W. *Angew. Chem.* **2002**, *114*, 1253; *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1205. (b) Alajarín, M.; López-Leonardo, C.; Berná, J.; Sánchez-Andrada, P. *Tetrahedron Lett.* **2007**, *48*, 3583.

[7] A comparable situation has been found in the tricyclic 2-methyl-1-azonia[4.4.4]propellane cation; see: McIntosh, J. M. *J. Org. Chem.* **1982**, *47*, 3777.

[8] For a recent example of point-to-helix chirality transfer in a C_3-symmetric Ti(IV) alkoxide complex, see: Axe, P.; Bull, S. D.; Davidson, M. G.; Gilfillan, C. J.; Jones, M. D.; Robinson, D. E. J. E.; Turner, L. E.; Mitchell, W. L. *Org. Lett.* **2007**, *9*, 223.

[9] Stara, I. G.; Alexandrova, Z.; Teply, F.; Sehnal, P.; Stary, I.; Saman, D.; Budesinsky, M.; Cvacka, J. *Org. Lett.* **2005**, *7*, 2547.

10.1021/ol702183d CCC: $37.00

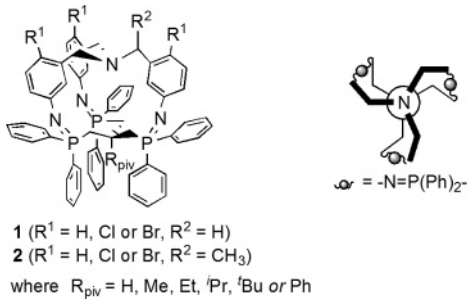


Figure 1. Tri-λ^5-phosphazenes **1** and **2** and schematic view along their C_3 axis, showing both tripods with the same sense of twist.

processes have been reported only in charged chiral complexes[10] where noncovalent diastereoselective interactions control the stereoselective formation of the asymmetric ion pairing.

Herein, we disclose our studies on propeller-to-propeller chirality induction using tri-λ^5-phosphazenes such as **1** as helical units. In particular, we wondered if the helical chirality of one of these macrobicycles can cause some effect in the helical sense of a second triphosphazene unit separated from the first one by an appropriate spacer.[11]

To carry out this study, a double and sequential tripod–tripod coupling strategy was designed by using a hexafunctional bis(tripod) to give in the first instance a macrobicycle capable of undergoing a second coupling with another reactant molecule and yielding a bis(macrobicyclic) compound (Figure 2).

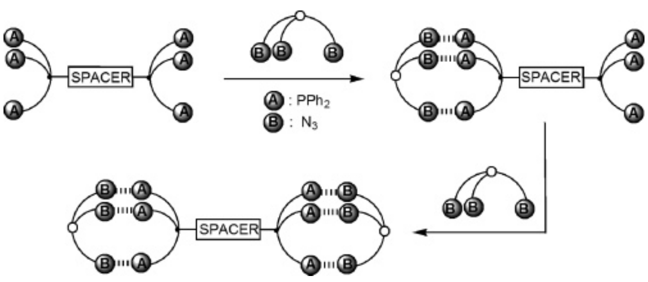
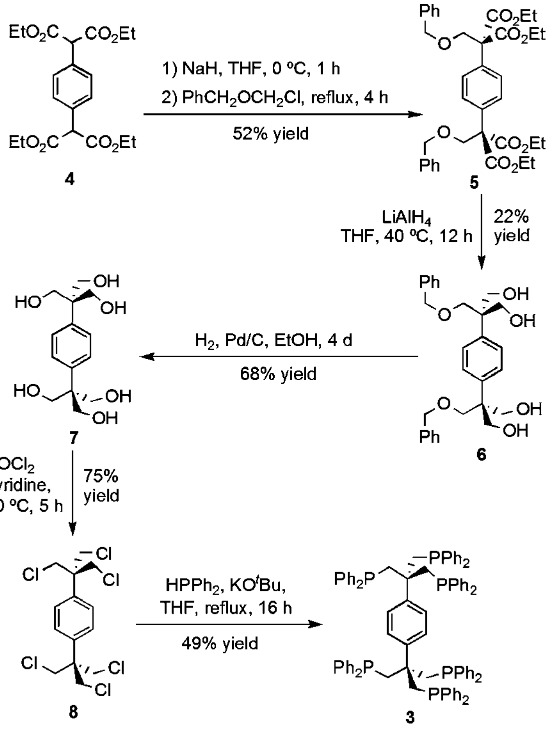


Figure 2. Sequential tripod–tripod coupling strategy.

In an initial attempt, this strategy was tested with the hexaphosphane $[(Ph_2PCH_2)_3CCH_2]_2O$ which was prepared by standard procedures from the commercially available dipentaerythritol (see Supporting Information for preparation details). However, no coupling product was obtained from its reaction with tris(3-azidobenzyl)amines, producing only irresoluble mixtures of oligomeric products under several different reaction conditions (e.g., Et_2O, 25 °C or $CHCl_3$, from 0 °C to reflux, using high dilution techniques). It was reasoned that the flexibility and the length (4.92 Å)[12] of the linker between both triphosphane fragments, CH_2OCH_2, modifies in such extension the suitable conformation of these tripodal moieties that prevent the formation of any coupling product. Then, a molecular modeling assisted design of the expected final product was employed to choose our next linker candidate: a *p*-phenylene fragment which is certainly more rigid and a little bit longer (6.03 Å)[12] than the CH_2OCH_2 one.

Thus we synthesized the new hexaphosphane α,α,α,α′,α′,α′-hexakis(diphenylphosphinomethyl)-*p*-xylene (**3**), taking as model the methodology developed by Huttner for the synthesis of tris(hydroxymethyl) compounds.[13] The alkylation of the tetraester **4**[14] with benzyl chloromethyl ether,[15] previously generating the corresponding dianion, gave compound **5** (Scheme 1). The reduction of **5** with lithium aluminum hydride followed by palladium-catalyzed hydrogenolysis produced sequentially the polyols **6** and **7**. Reaction

Scheme 1. Preparation of Hexaphosphane **3**



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(10) Lacour, J.; Frantz, R. *Org. Biomol. Chem.* **2005**, *3*, 15.

(11) For other examples of two linked helical subunits, see: (a) Okubo, H.; Yamaguchi, M.; Kabuto, C. *J. Org. Chem.* **1998**, *63*, 9500. (b) Yagi, S.; Yamada, R.; Takagishi, T.; Sakai, N.; Takahashi, H.; Mizutani, T.; Kitagawa, S.; Ogoshi, H. *Chem. Commun.* **1999**, 911. (c) Kwit, M.; Rychlewska, U.; Gawroński, J. *New J. Chem.* **2002**, 26, 1714. (d) Nakano, D.; Hirano, R.; Yamaguchi, M.; Kabuto, C. *Tetrahedron Lett.* **2003**, *44*, 3683. (e) Hamakubo, K.; Yagi, S.; Nakazumi, H.; Mizutani, T.; Kitagawa, S. *Tetrahedron* **2006**, *62*, 3619.

(12) Distance between the two connected quaternary carbons, as calculated from the corresponding fragments generated by Chem3D Ultra 8.0.

(13) Muth, A.; Asam, A.; Huttner, G.; Barth, A.; Zsolnai, L. *Chem. Ber.* **1994**, *127*, 305.

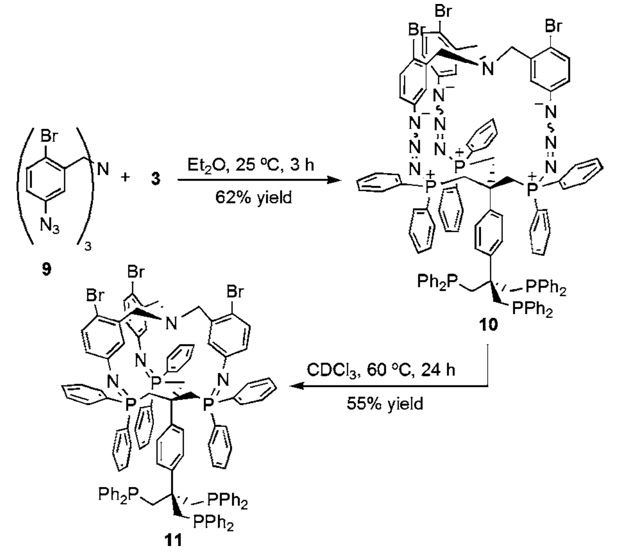
(14) Zvilichovsky, G.; David, M. *J. Org. Chem.* **1982**, *47*, 295.

(15) Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K., Jr.; Medwid, J. B. *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. VI, p 101.

of **7** with thionyl chloride gave the hexachloride **8**, which was treated with diphenylphosphane in the presence of potassium *tert*-butoxide to yield finally the hexaphosphane **3**.

The stoichiometric reaction of tris(5-azido-2-bromobenzyl)amine (**9**)[4a] and the hexaphosphane **3** led to the tripod−tripod coupling product, the triphosphazide **10** (Scheme 2) in 62% yield. Remarkably, no other byproducts as the putative hexaphosphazide were formed during this reaction. When we carried out a similar experiment with 2 equiv of **9**, again triphosphazide **10** was exclusively formed.

Scheme 2. Preparation of Tri-λ^5-phosphazene **11**



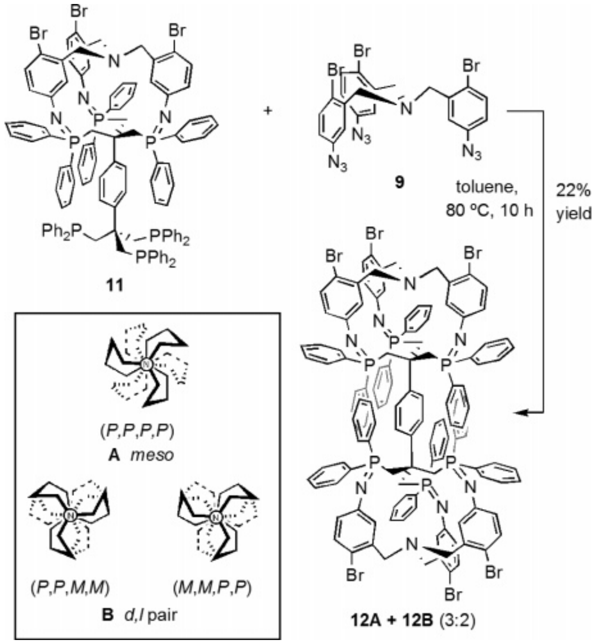
In order to explain why no double coupling product was obtained in these experiments, we reasoned that the conformation of the triphosphane moiety in **10**, optimal for the coupling with a second unit of **9**, was underpopulated due to the steric perturbation caused by the close pseudoaxial *P*-phenyl groups of its macrobicyclic fragment. Moreover, the low solubility of the macrobicycle **10** in the reaction medium (Et_2O) facilitates its isolation in pure form.

The ^{31}P NMR spectrum of **10** shows two signals, one at δ 4.43, as a broad singlet ($\Delta\nu_{1/2}$ = 714 Hz), and a sharp singlet at δ −28.88. The first one corresponds to the three equivalent phosphorus atoms of the intracyclic triphosphazide moieties, broadened by the equilibration between their *E*/*Z* forms,[3,4a] whereas the second is due to the triphosphane fragment. These data are in agreement with the existence of a C_3 axis passing through the two bridgehead atoms of the bicyclic cage. The propeller-like topology of compound **10** in solution is revealed by the diastereotopicity of the CH_2N protons that appear at δ 2.09 and 2.25 in its ^1H NMR spectrum, as two doublets with J_{gem} = 14.5 Hz. The trisphosphazide **10** was cleanly converted into its corresponding tri-λ^5-phosphazene **11** by heating at 60 °C in $CDCl_3$ solution and by stepwise triple extrusion of dinitrogen. The NMR data of compound **11** show unequivocally that it preserves the helical shape of its precursor (Scheme 2).

At this point, the next step was to build a second macrobicycle over the triphosphane fragment of **11** in order to elucidate if the axial chirality of the first one is able to stereocontrol to some extent the formation of the new bis(propeller).

Not surprisingly, when the reaction of **11** with **9** was assayed under standard conditions (diethyl ether at room temperature), the unchanged starting materials were recovered. Again, the *P*-phenyl groups of the tri-λ^5-phosphazene backbone seem make the tripod−tripod coupling difficult. However, when the reaction was performed in hot toluene, we obtained a material which analyzed correctly for the expected hexa-λ^5-phosphazene **12**,[16] along with other unknown oligomeric byproducts which were removed by column chromatography. This coupling process was optimized by controlled heating at 80 °C and employing high dilution conditions to obtain **12** in 22% yield (Scheme 3).

Scheme 3. Synthesis of Hexa-λ^5-phosphazene **12**



The NMR spectra of **12** ($CDCl_3$, 25 °C) display two sets of signals revealing the presence of two isomers (**A** and **B**, inset of Scheme 3). Its ^{31}P NMR spectrum shows only two well-resolved signals, at −2.59 and −1.64 ppm, which are in the typical range for phosphazenes,[17] in a 3:2 ratio. The

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(16) Hexa-λ^5-phosphazenes **12A** + **12B** (diastereomers ratio 1.5:1): yield 22%; ^1H NMR ($CDCl_3$, 300 MHz, 298 K) δ 3.09 [d, 3 H, *J* = 16.3 Hz, CH_AH_BN (b)], 3.11 [d, 3 H, *J* = 16.7 Hz, CH_AH_BN (a)], 3.48 [d, 3 H, *J* = 16.3 Hz, CH_AH_BN (b)], 3.50 [d, 3 H, *J* = 16.7 Hz, CH_AH_BN (a)], 3.64 [qv, 3 H, *J* = 6.7 Hz, CH_AH_BP (b)], 3.81 [qv, 3 H, *J* = 7.8 Hz, CH_AH_BP (a)], 4.22 [tv, 3 H, *J* = 15.9 Hz, CH_AH_BP (a)], 4.36 [tv, 3 H, *J* = 16.1 Hz, CH_AH_BP (b)], 5.94 [br s, 4 H, C_6H_4 (b)], 6.03 [br s, 4 H, C_6H_4 (a)], 6.86−7.00 [m, 30 H, H_{Ar} (a + b)], 7.05−7.36 [m, 138 H, H_{Ar} (a + b)], 7.40−7.56 [m, 12 H, H_{Ar} (a + b)]; ^{31}P NMR ($CDCl_3$, 121 MHz) δ −2.59 [s, (a)], −1.64 [s, (b)]; IR (Nujol) ν 1332, 1142, 1100, 948, 812, 692 cm^{-1}; MS (FAB) *m/z* 2423 (M^+ + 9, 10), 2422 (M^+ + 8, 8), 2421 (M^+ + 7, 18), 2420 (M^+ + 6, 10), 2419 (M^+ + 5, 10), 2418 (M^+ + 4, 8), 663 (36), 399 (46), 383 (80), 307 (100).

same proportion holds for the relative integration of some well-separated signals of its ^{1}H NMR spectrum, which mainly features two identical splitting patterns in the methylenic region similar to that observed in the macrobicycles **1**. The appearance of this spectrum also proves the equivalence of all arms of each isomer of **12** and consequently speaks for the elevated symmetry of these compounds. Additionally, the protons of the *p*-phenylene fragment appear as two singlets, one for each isomer of **12**. It is interesting to note that their chemical shifts ($\delta = 5.94$ and 6.04) are 0.86 and 0.76 ppm upfield relative to the analogous signal in the hexaphosphane **3** ($\delta = 6.80$), respectively. These values are consistent with a conformation in solution in which six interdigitated pseudoaxial *P*-phenyl groups, three per macrobicyclic unit, are flanking the *p*-phenylene linker. Also, their appearance as a singlet points out that this group is freely spinning around the propeller axis which contains the four bridgehead atoms of each bis(macrobicycle).

All these NMR data are in agreement with two diastereoisomers of **12**, both with a C_3 axis, which only differ in the helical sense of their macrobicyclic moieties, a *meso* form **12A** (S_6 symmetric),[18] and a D,L-pair **12B** (D_3 symmetric) (Scheme 3). The similarity between the two sets of signals observed in the NMR spectra of **12** precluded the unequivocal configurational assignment of both diastereoisomers.

The estimated difference in energy between **12A** and **12B** is 1.1 kcal mol^{-1} in favor of the *meso* form **12A** (Figure 3) on the basis of mechanical molecular calculations.[19] This small energy value is enough to justify the observed diastereoisomeric excess during the tripod coupling between **11** and **9**. Variable temperature NMR experiments (193–373 K) of the mixture **12A** + **12B** in toluene-d_8 did not show significant variations of its ^{1}H and ^{31}P NMR spectra, in agreement with a substantial free energy of activation[20] for a presumable equilibration process involving **12A** and **12B**.

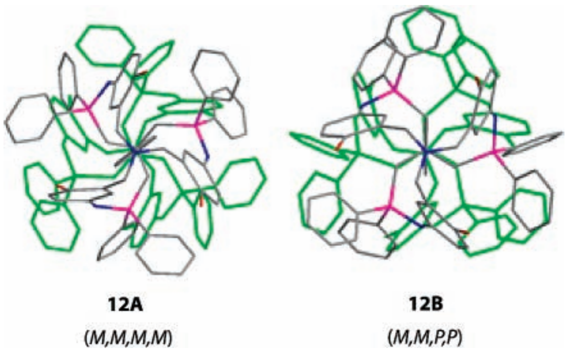

Figure 3. Molecular modeling structures of diastereoisomers **12A** and **12B** in a perspective view as projected along their respective threefold axes. One of the macrobicyclic moieties of each isomer is drawn in green color for showing neatly the helical sense of both propellers in each structure.

In conclusion, we have shown the preparation of a conformationally stable hexa-λ^5-phosphazene as a mixture of two diastereoisomers by means of an unprecedented synthetic route based on a double and sequential tripod–tripod coupling. The helical chirality transfer from the first produced macrobicycle to the second one results in a measurable excess of one of the two obtained diastereoisomeric bis(macrobicycles). This study has also shown that the helical sense of one moiety of the hexa-λ^5-phosphazene **12** is controlled in some extent by the peripheral chirality of its tri-λ^5-phosphazene precursor. Further studies of axial helical induction from these kinds of macrobicyclic tri-λ^5-phosphazene moieties to other different structural scaffolds are currently underway in our laboratory.

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Supporting Information Available: Experimental details for the synthesis of all products and their full characterization; estimation of energy barriers for the exchange between **12A** and **12B** are also given therein. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Tebby, J. C. *CRC Handbook of Phosphorus-31 NMR Data*; CRC Press: Boca Raton, FL, 1991; p 409.

(18) For the determination of the symmetry group of each diastereoisomer, we have considered that their two macrobicyclic units are connected by a single bond because, as stated in the text, the connecting aryl group rotates freely around the main symmetry axis, in solution at room temperature.

(19) MM+ force field as implemented in the HyperChem 6.0 molecular modeling program (Hypercube, Inc.; http://www.hyper.com).

(20) See Supporting Information for an estimation of the energy barrier for this equilibration process.