Component exchange as a synthetically advantageous strategy for the preparation of bicyclic cage compounds†

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Macrobicyclic triphosphazides are able to reversibly exchange one of their tripodal components by means of a dynamic disassembly–reassembly process; surprisingly this strategy provides better yields of cage compounds than a direct tripod–tripod coupling.

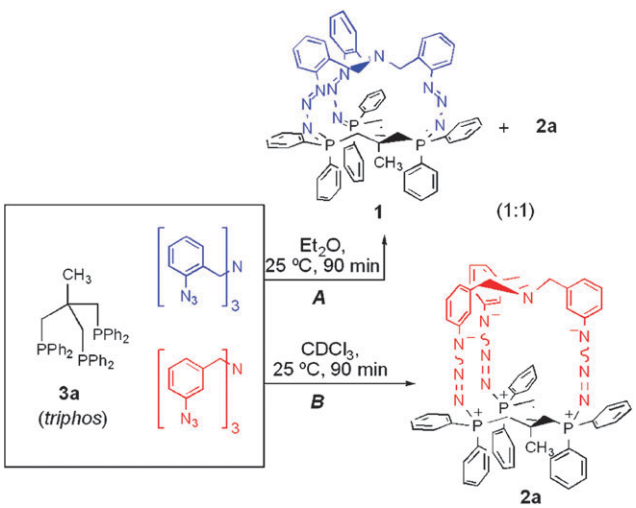
Self-assembly[1] is a key synthetic tool in both nature and abiotic systems. The reversible self-assembly of structurally complementary multifunctional building blocks to form large cage-type structures can work at both the molecular and supramolecular levels.[1,2] Molecular architectures obtained in this way are dynamic structures in which the reversible linkage of their components[3] enables structural reconfigurations by disassembly–reassembly events.[4] Recently, this particular feature has been implemented, at the molecular level, in component exchange processes aimed either at the generation of dynamic constitutional diversity[4b,c] or the interconversion of metallo–organic structures.[5]

We have previously described[6] the direct tripod–tripod coupling of tris(*ortho*- and *meta*-azidobenzyl)amines with 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos) to give macrobicyclic triphosphazides **1**[6a] and **2a**[6b] by a molecular self-assembly process[7] involving a triple phosphane–imination reaction which can be understood as the first mechanistic step of a Staudinger P^{III} imination.[8]

Herein we describe the dynamic behavior of these macrobicycles which are able to undergo exchange reactions of their triazide and triphosphane fragments through dynamic disassembly–reassembly processes which operate under very mild reaction conditions and without recourse to any templating agent. Interestingly, the preparation of macrobicyclic tri-λ^5-phosphazenes by this unprecedented protocol improves the yields obtained in their direct synthesis based on tripod–tripod coupling strategies.

Based on the different thermodynamic stability[6] of **1** and **2a** we first focused our attention on their selective assembly from a ternary mixture of equimolar amounts of tris(*ortho*- and *meta*-azidobenzyl)amines and triphos (**3a**). No selectivity was observed when the reaction is carried out in diethyl ether at room temperature, giving rise to an equimolar mixture of the triphosphazides **1** and **2a** (Scheme 1, path ***A***) which precipitated in the reaction medium. Gratifyingly, by changing the solvent to deuterated chloroform, in which both cages are soluble, the ternary mixture of reactants led exclusively to the less sterically congested triphosphazide **2a** (Scheme 1, path ***B***), the thermodynamically most stable product.

In these reversible conditions, the extreme selectivity of that dynamic process relies on the *metastable* nature of the phosphazide group at each arm of these bicycles, which is in a relatively fast equilibrium with their phosphane and azide precursors.[9] This fact apparently allows a proof-reading mechanism to operate such that if the reactants come together in an ''incorrect'', thermodynamically unfavorable manner then the system can readjust itself to yield the thermodynamically favored product.[5] In order to verify if such an underlying mechanism is working, we attempted a triazide exchange in **1**. In fact the addition of tris(*meta*-azidobenzyl)amine (1 equiv.) to a solution of the triphosphazide **1** in deuterated chloroform at room temperature quantitatively yielded a clean mixture of triphosphazide **2a** plus an equimolecular amount of the ejected tris(*ortho*-azidobenzyl)amine (Scheme 2).



Scheme 1 (a) Simultaneous self-assembly of triphosphazides **1** and **2a** (Path ***A***). (b) Selective formation of the triphosphazide **2a** from a ternary mixture of tris(azidobenzyl)amines and triphos (Path ***B***).

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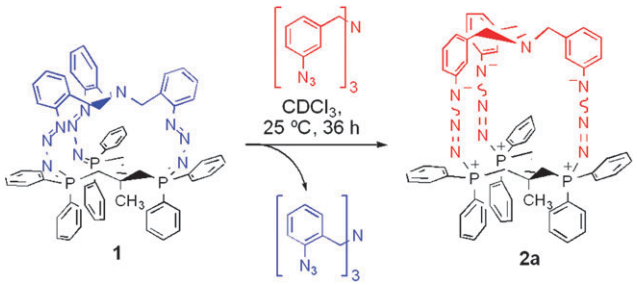
† Electronic supplementary information (ESI) available: CCDC 671014. For crystallographic data in CIF or other electronic format, and details of synthesis and structural characterization. See DOI: 10.1039/b801299g



Scheme 2 Synthesis of triphosphazide **2a** by triazide exchange.

We reasoned that exchange of the triphosphane fragment should also be possible if the equilibrium between *e.g.* **1** and a new triphosphane lies in favor of the new cage. This situation should arise with the longer-branched triphosphane **4** (Scheme 3) which could give rise to a less sterically constrained macrobicycle in which the second step of the Staudinger reaction, the extrusion of dinitrogen, might easily occur in each arm to give phosphazene functions. Indeed, the reaction of the macrobicyclic triphosphazide **1** with an equimolar amount of **4** at room temperature gave the new macrobicyclic tri-λ^5-phosphazene **5** in 84% yield (Scheme 3, path ***A***) by means of a triphosphane exchange followed by a triple expulsion of molecular N_2. In this case, this disassembly–reassembly process is kinetically trapped by the dinitrogen expulsion to give a non-dynamic macrobicycle of the type tri-λ^5-phosphazene.

In contrast with the macrobicyclic tri-λ^5-phosphazenes bearing a triphos-like phosphane moiety, which are rigid compounds with a propeller-like shape in solution,[10] macrobicycle **5** displays a time-averaged C_{3v} symmetry as determined by the magnetic equivalence of their CH_2N methylenic protons observed by ^{1}H NMR spectroscopy and also of the two phenyl rings of the Ph_2P groups observed in the ^{13}C NMR spectra.‡ The geometry of the compound in the solid state was determined by X-ray analysis§ (Fig. 1) which revealed an approximate C_3 symmetric conformation in which the two propeller fragments, the upper tribenzylamine core and the lower triphosphane moiety, adopt different helical senses (Fig. 1b), a remarkable difference compared to other reported macrobicyclic tri-λ^5-phosphazenes.[10]

Particularly striking is the fact that **5** was obtained in a much lower yield, 37%, in the direct tripod–tripod coupling of equimolar amounts of tris(2-azidobenzyl)amine and triphosphane **4** (Scheme 3, path ***B***). For some reason, the triphosphane exchange in the macrobicyclic triphosphazide **1** proceeds much more cleanly than the direct combination of triazide and triphosphane to give the tri-λ^5-phosphazene **5**. This surprising result led us to study if this trend is observed in the synthesis of other similar cage compounds. We find that the metastable cage **2b**[10c] is able to eject the triphosphane **3b** when reacted with one equivalent of the triphosphane **4**, or with its nitrogenated analog **6**, leading to the new macrobicyclic tri-λ^5-phosphazenes **7** and **8** in 60 and 76% yield, respectively (Scheme 4). For comparison, the direct tripod–tripod coupling approaches to **7** and **8** were also accomplished to afford these macrobicycles in 23 and 40% yield, respectively. Surprisingly again, in both cases a higher efficiency of the exchange protocol *vs.* the tripodal coupling was observed, validating the component exchange method as synthetically advantageous.

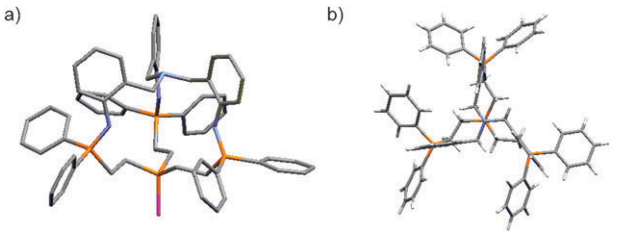
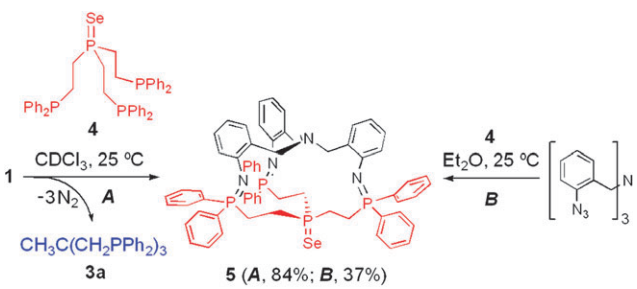


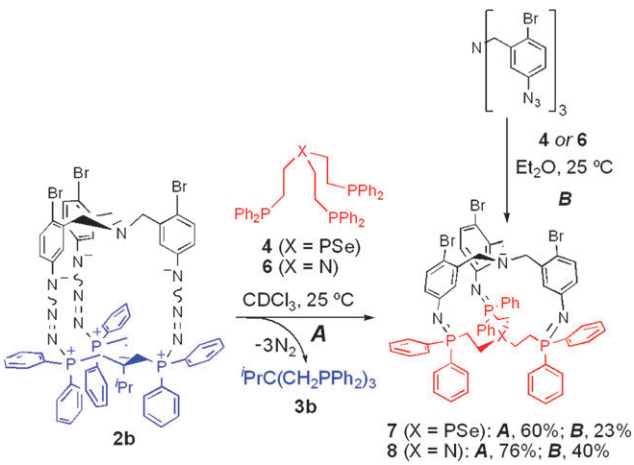
Fig. 1 (a) Molecular structure of **5** (hydrogen atoms omitted for clarity), (b) perspective view as projected along the threefold axis.

We reasoned that the higher efficiency of the syntheses of **5**, **7** and **8** by triphosphane exchange, when compared with their tripod–tripod couplings, might only be possible if, first, a stepwise disassembly[11] of **1** takes place to yield equilibrium species with one or two disassembled arms. Their free N_3 functions then sequentially react with the P atoms of the new triphosphane giving rise to a dynamic set of PN_3 intermediates in which both old and new triphosphane fragments become simultaneously linked to the triazide scaffolding,[12] which plays the role of a preorganized skeleton for building up the new cage compound.

The driving force for the selective formation of the tri-λ^5-phosphazenes **5**, **7** and **8** during the component exchange



Scheme 3 Synthesis of the macrobicyclic tri-λ^5-phosphazene **5** by (a) triphosphane exchange (Path ***A***) and (b) by tripod–tripod coupling (Path ***B***).



Scheme 4 Syntheses of the macrobicyclic tri-λ^5-phosphazenes **7** and **8** by (a) triphosphane exchange (Path ***A***) and (b) by tripod–tripod coupling (Path ***B***).

process is most probably the irreversible N_2 extrusion in the forming PN_3 arms of the new cage.

In summary, we have shown that macrobicyclic triphosphazides are able to exchange their tripodal components by means of a dynamic disassembly–reassembly process which clearly improves the conventional synthesis of flexible macrobyclic tri-λ^5-phosphazenes by direct tripod–tripod coupling.

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Notes and references

‡ *Selected spectral data* for **5**: ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ 2.40 (m, 6H, CH_2PN), 3.00 (m, 6H, CH_2PSe), 4.16 (s, 6H, CH_2N), 6.27 (m, 3H, H_{Ar}), 6.71 (dd, J(H,H) = 5.9, 3.5 Hz, 6H, H_{Ar}), 7.23–7.65 (m, 33H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ 24.62 (br d, ^1J(C,P) = 94.5 Hz, CH_2PSe); 25.98 (dd, ^1J(C,P) = 40.0, ^2J(C,P) = 7.2 Hz, CH_2PN), 53.97 (CH_2N), 117.81 (C_6), 120.72 (d, ^3J(C,P) = 9.3 Hz, C_3), 126.07 (C_4), 128.95 (d, ^2J(C,P) = 11.0 Hz, *o*C–PhP), 130.20 (d, ^1J(C,P) = 80.0 Hz, *i*C–PhP), 130.38 (C_5), 131.87 (br s, *p*C–PhP), 131.93 (d, ^3J(C,P) = 9.3 Hz, *p*C–PhP), 134.25 (d, ^2J(C,P) = 22.0 Hz, C_1–CH_2), 149.18 (C_2–NP). ^{31}P NMR (121.4 MHz, $CDCl_3$, 298 K): δ 3.50 (d, ^3J(P,P) = 47.4 Hz, 3 P, PN), 37.94 (q, ^3J(P,P) = 47.4 Hz, 1 P, PSe). Anal. calc. for $C_{63}H_{60}N_4P_4Se$: C, 70.32; H, 5.62; N, 5.21. Found: C, 70.11; H, 5.55; N, 5.18%.

§ *Crystal data* for **5**·$CHCl_3$·$(C_2H_5)_2O$: M = 1269.48, monoclinic, $P21/n$, a = 13.2007(4), b = 23.8974(6), c = 20.0702(6) Å, β = 97.571(2)°, V = 6276.2(3) Å^3, D_c = 1.344 g cm^{-3}, T = 110(2) K, Z = 4, R_1 = 0.0813 [$I > 2\sigma(I)$], wR_2 = 0.2021 (all data). CCDC 671014.

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12 See ESI for experimental evidence (NMR, ESI-MS) of species containing both triphosphane moieties in the reaction mixture†.