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Synthesis of a Chiral Molecular Square with Two Organic Corners

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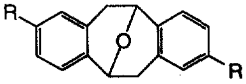
Summary: The bipyridyl ligand **5** was readily prepared in enantiomerically-pure form by coupling the appropriate stannanes with the bis-triflate 3. Mixing this ligand with a palladium ditriflate resulted in the formation of a chiral molecular square, according to spectroscopic analysis. © 1999 Elsevier Science Ltd. All rights reserved.

The synthesis of large, rigid macrocyclic species is currently of great interest.[1] These molecules may be prepared in a covalent fashion or they may be "self-assembled" through the formation of dative bonds between Lewis acids and bases. The latter approach is increasingly common. Using this methodology, many new molecular squares and other polygons have been prepared. Typically, these supramolecules possess corners at which a metal serves as the apex.[2] They are also generally achiral, though many chiral molecular squares are known.[3]

In an effort to develop chiral molecular squares which are also functional, we have undertaken the synthesis of a molecular square designed to possess at least two organic corners. The molecular framework chosen to serve at two opposite corners was Kagan's ether, **1**. It is known that this molecule and various congeners are chiral, rigid and possess an approximately 90° angle between the planes defined by the benzene rings.[4] While at this stage it remains uncertain, we also expect that facile functionalization of the benzylic positions of **1** or various analogues will enable the construction of chiral molecular squares in which endohedral functionality makes feasible processes such as enantiomer recognition or asymmetric catalysis. In this paper, we report the synthesis of the Kagan's ether analogue **5** and its reaction with a palladium (bis)triflate to produce a chiral molecular square.



1: R = H
2: R = OH
3: R = OTf

We recently reported the synthesis of both enantiomers of diol **2** as well as the corresponding triflates **3**.[5] Treatment of **3** with 4-tri-n-butylstannylpyridine **4** in the presence of 10 mol% tetrakistriphenylphosphine, lithium chloride and 2,6-dimethyl-4-t-butylphenol gave **5** in 75% yield (equation 1).[6] It was clear that the product still possessed C_2 symmetry by ^{13}C NMR. Both enantiomers of this compound were incorporated into a molecular square by a procedure adopted from Stang as shown in equation 2.[7] Reaction of 1,3-bis(diphenylphoshino)palladium ditriflate **6** with an equimolar amount of either enantiomer of **5** in methylene

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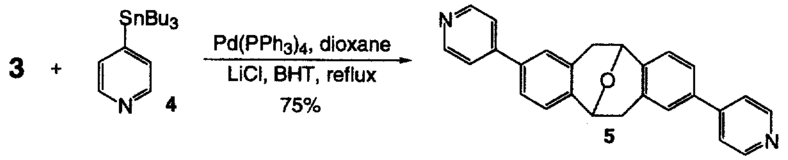
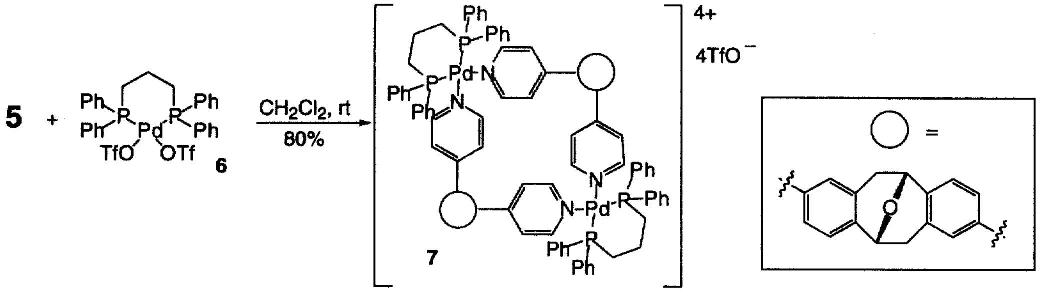


Equation 1

chloride at room temperature for about 8 hours resulted in the formation of the desired molecular square. We anticipated based on good precedent that **5** would easily displace the weakly coordinated triflate ligands of **6**.[1a] The shape of **4** was expected to drive the reaction toward square formation rather than oligomerization.

The product of equation 2 is a stable and amorphous solid. The solid decomposes between 280-5 °C. It is easily soluble in CH_2Cl_2, $CHCl_3$, CH_3NO_2 and acetone. This high solubility in organic solvents suggests a formation of a discrete molecule rather than oligomeric products. Based on the expected structure of the molecular square (Figure 1), we anticipated the formation of a species with relatively high symmetry (D_2 point group). The formation of a highly symmetric species was supported by ^1H and ^{13}C NMR. The ^1H NMR showed resonances corresponding to **5** and ligand **6** with slight chemical shift changes. The ^{13}C NMR spectrum showed 17 signals along with a quartet corresponding to the triflate ion. The ^1H NMR of the product



Equation 2

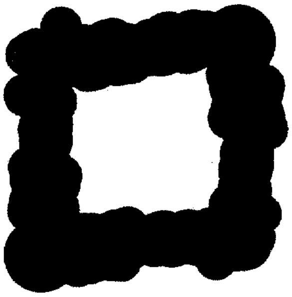


Figure 1. Anticipated structure of 7 without dppp ligands and triflate counterions.

formed from the reaction of **5** and **6** showed a downfield chemical shift for ortho-protons of the pyridine unit with respect to **5** of about 0.3 ppm. The formation of a complex was also supported by chemical shift changes in the ^{31}P NMR of the ligand. Ditriflate **6** shows a signal at 16.54 ppm relative to external phosphoric acid. After mixing with **5**, a clean singlet is observed at 7.09 ppm. This upfield shift is consistent with the displacement of the triflates by the pyridine units of **5**. Both enantiomers of **7** also show equal and opposite rotations, as expected for discrete species. The formation of a molecular square was also supported by FAB MS.[8] For instance, the M-OTf peak (m/z=2238) was the highest mass fragment observed. Its isotopic distribution agreed well with that calculated for $C_{109}H_{92}F_9N_4O_{11}P_4Pd_2S_3$. Peaks corresponding to the loss of **5** and $^-$OTf (1861), $^-$OTf and 2 x **5** (1485) and 3 x $^-$OTf and 2 x **5** were also observed, among others. A drawing (Chem 3D) of the anticipated structure of one enantiomer of the molecular square without the phosphorus ligands or counterions included is shown in Figure 1. Attempts to obtain crystals of the square which are suitable for X-ray analysis have not been successful.

In summary, we have used **5** to prepare a chiral molecular square. Further studies of square formation to produce similar squares with more functionalized conjeners of **5** are under consideration. Results will be reported in due course.

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6. **Synthesis of 5.** To a 10 mL flame-dried, round-bottomed flask equipped with a magnetic stir bar, a nitrogen balloon, a reflux condenser and a septum, ditriflate **3** (50 mg, 0.096 mmol) and freshly distilled dioxane (1.9 mL) were added. Into this solution, $Pd(Ph_3P)_4$ (11 mg, 0.0096 mmol), LiCl (13 mg, 0.3 mmol), and BHT (3 mg) were added in one portion, resulting in a yellow solution. To this solution, 4-tributylstannyl pyridine **4** (74 mg, 0.2 mmol) was added via a syringe. The mixture turned black immediately. This mixture was then gently refluxed for 24 hours. TLC showed the completion of the reaction. The flask was cooled down and placed on a rotary evaporator to remove solvent. The residue was purified by flash chromatography (first 100 mL methylene chloride, then 5% isopropyl alcohol in methylene chloride) to afford the product as a white solid. (27 mg, 75%). An analytical sample was obtained by taking a middle fraction from the flash chromatography. mp 120-122 ^{o}C. (*S*, *S*)-**5**: [α] = 130.36 (25 ^{o}C, sodium D, c=1.1, acetone-d_6), (*R*, *R*)-**5**: [α] = -123.20 (25 ^{o}C, sodium D, c=1.5, acetone-d_6). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.59 (d, 4H, J=4.0 Hz), 7.43-7.38 (m, 6H), 7.27-7.21 (m, 4H), 5.40 (d, 2H, J=5.9 Hz), 3.66 (dd, 2H, J=6.1 Hz, J=16.3 Hz), 2.88 (d, 2H, J=16.3 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 150.2, 147.8, 138.7, 136.9, 132.4, 127.7, 126.0, 124.8, 121.4, 69.3, 36.1. IR (KBr) 3427 (br, s), 3027 (w), 2928 (s), 1611 (s), 1555 (w), 1490 (w), 1428 (w), 1406 (w), 1290 (s), 1256 (s), 1228 (s), 1166 (s), 1085 (m), 1031 (s), 1011 (m), 986 (w), 812 (s), 789 (m), 719 (m) cm^{-1}. Exact mass calcd for $C_{26}H_{20}N_2O$: 376.1576. Found: 376.1550.
7. **Synthesis of 7 from (*S*,*S*)-5.** To a 25 mL flame-dried, round bottomed flask equipped with a magnetic stir bar, a nitrogen balloon and a septum, $Pd(dppp)_2(OTf)_2$ **6** (21.7 mg, 0.0265 mmol) was added and dissolved freshly distilled methylene chloride (5.3 mL) to give a 5 mM solution. To this solution, **5** (10 mg, 0.026 mmol) was added as a solution in 1 mL methylene chloride via a syringe and the mixture was allowed to stir at room temperature for about 8 hours. The resulting clear solution was concentrated to half of the actual volume on a rotary evaporator. To this, freshly distilled ether was added until a precipitate formed. This precipitate was then filtered off and washed with ether to give an off-white powder (27.2 mg, 86%). mp 280-285 ^{o}C (dec). [α] = 60.4 (25 ^{o}C, sodium D, c=1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, br, 8H), 7.64-6.94 (m, 66H), 5.28 (d, 4H,J=5.4 Hz), 3.50 (dd, 4H, J=5.8 Hz, 15.8 Hz), 3.18 (s, br, 8H), 2.67 (d, 4H,J=16 Hz), 2.24 (s, br, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 149.6, 139.8, 133.9, 133.1, 132.1 (2C), 129.5, 127.7, 126.1, 124.6, 123.2, 121 (q, J=320 Hz, OTf), 69.2, 36.1, 21.6-21.4 (m), 17.6. ^{31}P NMR (101 MHz, $CDCl_3$) δ 7.09. ^{19}F NMR (235 MHz, $CDCl_3$) δ -77.88. IR(KBr) 3449 (br, m), 3058 (w), 2924 (w), 1615 (m), 1489 (w), 1439 (w), 1283 (br, s), 1258 (s, br), 1225 (m, br), 1162 (m, br), 1034 (s, br), 818 (w) cm^{-1}. Mass Calcd. for $C_{110}H_{92}F_{12}N_4O_{14}P_4Pd_2S_4$: 2386.89398. Found (FABMS): m/z= (M-OTf=2238.1), 1861.1, 1710.2, 1485.0, 1187.1. **From (R,R)-5.** Yield 80%. mp 280-285 ^{o}C (dec). [α] = -57.4 (25 ^{o}C, sodium D, c=1.6, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, br, 8H), 7.64-6.94 (m, 66H), 5.29 (d, 4H, J=5.8 Hz), 3.51 (dd, 4H, J=6.0 Hz, 16.3), 3.18 (s, br, 8H), 2.67 (d, 4H, J=16.3 Hz), 2.24 (s, br, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 149.6, 139.8, 133.9, 132.1, 132.6, 132.06, 132.0, 129.5, 127.6, 126.1, 124.6, 123.2, 121 (q, J=320 Hz, OTf), 69.1, 36.0, 21.6-21.2 (m), 17.6. ^{31}P NMR (101 MHz, $CDCl_3$) δ 7.09. ^{19}F NMR (235 MHz, $CDCl_3$) δ -77.87. IR(KBr) 3473 (br, m), 2920 (w), 1617 (m), 1446 (w), 1280 (br, s), 1262 (s, br), 1229 (m, br), 1163 (m, br), 1104 (w), 1038 (s, br), 821 (w) cm^{-1}. Mass Calcd. for $C_{110}H_{92}F_{12}N_4O_{14}P_4Pd_2S_4$: 2386.89398. Found (FABMS): m/z=(M-OTf=2237.0), 1861.1, 1712.2, 1440.9.
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