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A NEW "5+1" ROUTE TO ARENES. APPLICATION TO THE FACILE SYNTHESIS OF D_4-SYMMETRIC CHIRAL PORPHYRINS

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Abstract: A new synthesis of D_4-symmetric porphyrins is presented which provides chiral macrocycles in only five steps starting from optically active cyclic ketones. The efficacy of this approach is demonstrated with the synthesis of a new porphyrin derived from R-(+)-nopinone. The development of this flexible and general route should speed the development of porphyrin-based asymmetric catalysts.

Metal porphyrin complexes are efficient catalysts for a number of reactions, including alkene cyclopropanation[1], epoxidation[2] and alkane hydroxylation.[3] A number of groups have prepared porphyrins which catalyze these reactions in an asymmetric sense, and many novel ligands have been reported.[4] Unfortunately, these efforts have not resulted in catalysts with synthetically useful selectivities. A significant problem is that these chiral macrocycles are usually available only through tedious syntheses that often involve troublesome chromatographic separations, particularly of aryl porphyrin atropisomers. This has severely limited the amount of empirical experimentation with differently shaped ligands that is almost always necessary in the development of highly stereoselective catalysts. It was our aim to develop a convenient and general route to chiral porphyrins which would make these compounds much more readily available. D_4-symmetric tetraaryl porphyrins[5] have the major advantage that no atropisomerism is possible, eliminating the tedious chromatography that is required in the construction of C_2-symmetric porphyrins,[6] so we decided to focus on this class of macrocycles. We report here the concise synthesis of a D_4-symmetric porphyrin (**1**) from commercially available 1*R*-(+)-nopinone (Figure 1). We believe that this five step sequence will prove to be of general utility, allowing the facile synthesis of a large family of chiral porphyrin macrocycles from simple cyclic ketone precursors.

We planned to form the macrocycle by condensation of pyrrole with the appropriate chiral aldehyde, which would be obtained from stitching together two optically active cyclic ketones in a manner that would rapidly complete the central aromatic ring. To accomplish this, two molecules of commercially available 1*R*-(+)-nopinone were linked via a methylene bridge (60% yield) by the method of Kiyooka[7]

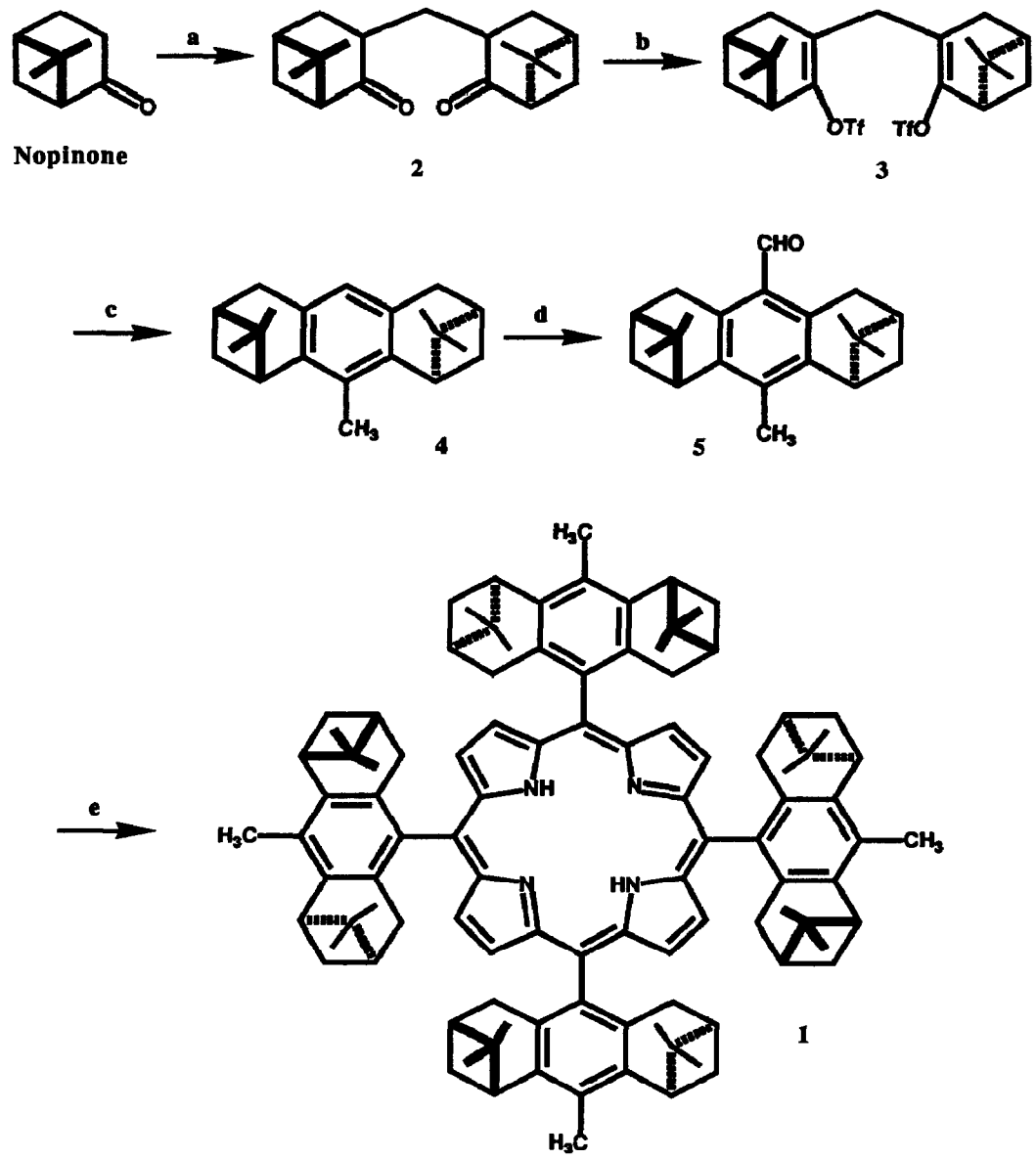

Figure 1. Synthesis of the chiral porphyrin **1** derived from nopinone. a) KH, DMF. b) KHMDS, Comins Reagent. c) $CH_2CHSnBu_3$, $Pd(PPh_3)_4$ (4%). d) Cl_2CHOCH_3, $TiCl_4$. e) i: Pyrrole, BF_3OEt_2; ii: *p*-chloranil.

(Figure 1). The 1,5-diketone **2** was then treated with potassium hexamethyldisilyl amide followed by Comins reagent (5-chloro-2-bistriflylamino-pyridine)[8] to provide the bis enoltriflate **3** in 65% yield. In the key step of the synthesis, **3** was mixed with $Pd(PPh_3)_4$ (4 mol %) in N-methylpyrrolidone solvent at 75°C, and vinyltributylstannane was added slowly by syringe pump to provide a 55% yield of arene **4**. We presume that the formation of **4** proceeds by an initial Stille reaction, resulting in the displacement of one of the triflates by the vinyl group.[9] Oxidative addition of the catalyst to the second triflate would then lead to an intramolecular Heck insertion[10] of the stannane-derived vinyl group into the palladium-carbon bond (Figure 2). Isomerization yields the desired pentasubstituted benzene. **4** was formylated[5] and the resultant optically pure[11] aldehyde **5** was then condensed with pyrrole under Lindsey conditions[12] to provide porphyrin **1** in 11% yield.[13]

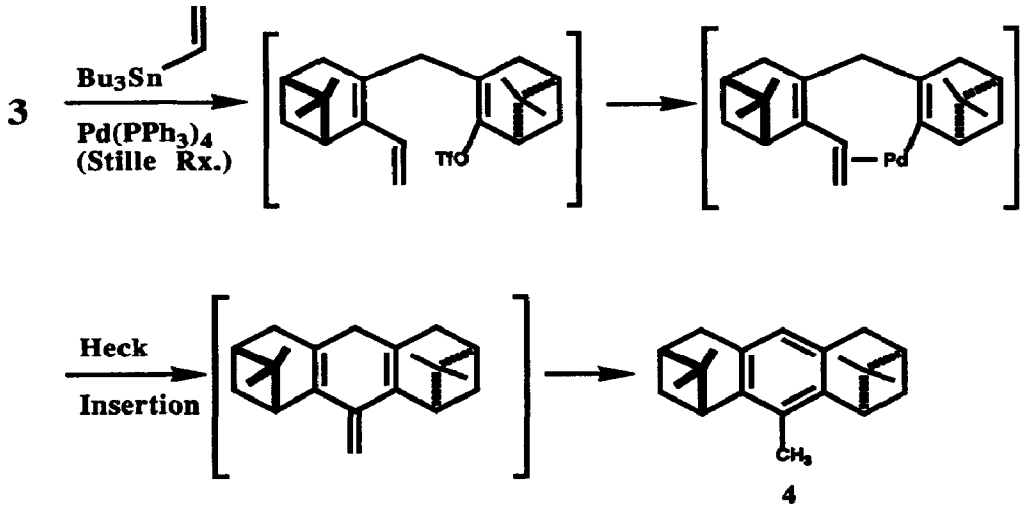

Figure 2. Postulated mechanism of the palladium-catalyzed reaction of vinyltributylstannane with bisenoltriflate **3** to provide arene **4**.

Metal derivatives of porphyrin **1** were not expected to be highly enantioselective catalysts. We viewed **1** as a model target to evaluate the efficacy of the synthetic scheme. As expected, the % e.e.'s observed in asymmetric epoxidation[4] and cyclopropanation[1b] reactions catalyzed by Mn(III) and Rh(III) derivatives of **1** were low (5-20%), but thousands of turnovers were observed in each case. We expect that future constructs, with the chiral directing groups more proximal to the "active site", will prove to be more selective catalysts.

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References and Footnotes

1. a) Callot, H.; Metz, F.; Piechoki, C. *Tetrahedron* **1982**, 2365-2369. b) Maxwell, J.L.; O'Malley, S.; Brown, K.C.; Kodadek, T. *Organometallics* **1992**, *11*, 645-652.
2. Groves, J.T.; Nemo, T.E., Myers, R.S. *J. Amer. Chem. Soc.* **1979**, *101*, 1032-1033. Traylor, T.G., Marsters, J.C., Nakano, T.; Dunlop, B.E. *J. Amer. Chem. Soc.* **1985**, *107*, 5537-5539. Collman, J.P.; Kodadek, T.; Raybuck, S.A.; Meunier, B. *Proc. Natl. Acad. Sci. USA* **1983**, *80*, 7039-7041.
3. Smegal, J.A.; Hill, C.L. *J. Amer. Chem. Soc.* **1983**, *105*, 3515-3521. Collman, J.P.; Tanaka, H.; Hembre, R.T.; Brauman, J.I. *J. Amer. Chem. Soc.* **1990**, *112*, 3689-3690.
4. Collman, J.P.; Zhang, X.; Lee, V.J.; Uffelman, E.S.; Brauman, J.I. *Science* **1993**, *261*, 1404-1411.
5. For the synthesis of the first D_4-symmetric chiral porphyrin, see: Halterman, R.L.; Jan, S.-T. *J. Org. Chem.* **1991**, *30*, 5253-5255.
6. O'Malley, S.; Kodadek, T. *Organometallics* **1992**, *11*, 2299-2302. O'Malley, S.; Kodadek, T. *J. Amer. Chem. Soc.***1989**, *111*, 9116-9117.
7. Kiyooka, S.; Yamashita, T.; Yamamoto, A.; Fujiyama, R. *Bull. Chem. Soc. Japan* **1989**, *62*, 1364-1366.
8. Comins, D.L.; Dehaghani, A.L. *Tetrahedron Lett.* **1992**, *33*, 6299-6303.
9. Stille, J.K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524.
10. Heck, R.F. *Acc. Chem. Res.* **1979**, *12*, 146-151.
11. Commercial nopinone is not optically pure. The minor isomer is carried through the synthesis to the aldehyde stage. Fortunately, **5** crystallizes readily, providing optically pure material.
12. Lindsey, J.S.; Schreiman, I.C.; Hsu, H.C.; Kearney, P.C. Marguerettaz, A.M. *J. Org. Chem.* **1987**, *52*, 827-836.
13. The yields reported in this communication, particularly that of the porphyrin-forming step, have not been optimized.

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