Highly stereoselective syntheses of arsenic and phosphorus macrocycles and cages

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ABSTRACT

The dimerization of certain 2-mercaptoethyl and 2-aminoethyl substituted tertiary arsines, chiral at arsenic, under appropriate condition produces high yields of 14-membered *trans*-As$_2$S$_2$ or *trans*-As$_2$N$_2$ macrocycles, with high stereoselectivities. The optical isomers of the macrocycles have also been isolated. Highly stereoselective syntheses of coordinated secondary and tertiary arsines and phosphines have also been performed. The first resolution of secondary phosphine, chiral at phosphorus, has been achieved by the method of metal complexation and a tricyclic tetra(tertiary phosphine) cage has been synthesised from 1,2-phenylene(bisphosphine) on copper(I) in the presence of base. Moreover, it has been shown that that the mould *Scopulariopsis brevicaulis* reductively methylates ethyl-*n*-propylarsinic acid with production of ethylmethyl-*n*-propylarsine of ca 80% optical purity.

INTRODUCTION

Asymmetric synthesis, once considered a rather exotic speciality in chemistry, is now a primary focus of activity for academic and industrial chemists (ref. 1). The asymmetric synthesis of one enantiomer or of one diastereomer of a substance is a very attractive proposition, because unlike a chemical resolution or separation the yield of the stereoisomer can be 100%. Although dominated by organic chemists employing natural products and their derivatives as chiral auxiliaries, the field is wide open to coordination chemists, who, with their superior knowledge of ligands and the chelate effect, have before them unparalleled opportunities for the development of stereoselective reactions. In this lecture I will show that highly stereoselective syntheses of optically active and diastereomerically homogeneous tertiary arsines (E_{inv} > 40 kcal mol^{-1}) and tertiary phosphines (E_{inv} 30 –35 kcal mol^{-1}) (ref. 2) are now possible, and that it is a realistic proposition for chemists to design and manufacture particular stereoisomers of tertiary arsines and phosphines, chiral at arsenic or phosphorus, for use in asymmetric synthesis. In this paper, emphasis will be placed on those reactions of chiral trivalent arsenic and phosphorus compounds that proceed with complete stereoselectivity (Note a).

MACROCYCLIC TERTIARY ARSINES

Given the wealth of chemistry, both organic (ref. 3) and inorganic (ref. 4) based upon the macrocyclic chelate effect on the one hand and the coordination chemistry of tertiary arsines on the other, it is surprising that few fully characterised macrocyclic tertiary arsines are known (ref. 5). In recent work, we showed that highly stereoselective syntheses of 14-membered macrocycles containing two chiral tertiary arsine groups occur in

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Note a: The term "complete stereoselectivity", or an equivalent expression, will henceforth mean that a synthesis has yielded a diastereomerically homogeneous product, as determined by high resolution NMR spectroscopy, or an enantiomerically homogeneous product, as determined by an appropriate method.

couplings of appropriate mono-tertiary arsines. For example, (±)-1 (L) readily forms the complex [Pd(L-H)$_2$], which, although it exists in solution as an equilibrium mixture of four diastereomers, yields, upon treatment with boron tribromide, diastereomerically pure (R^*,R^*)-2 (Note b) after removal of the metal (ref. 6). Although R^*,S^* diastereomers of [Pd(L-H)$_2$] are present in the reaction mixture, and there are six possible

(±)-1

(R*,R*)-(±)-2   (R*,S*)-2
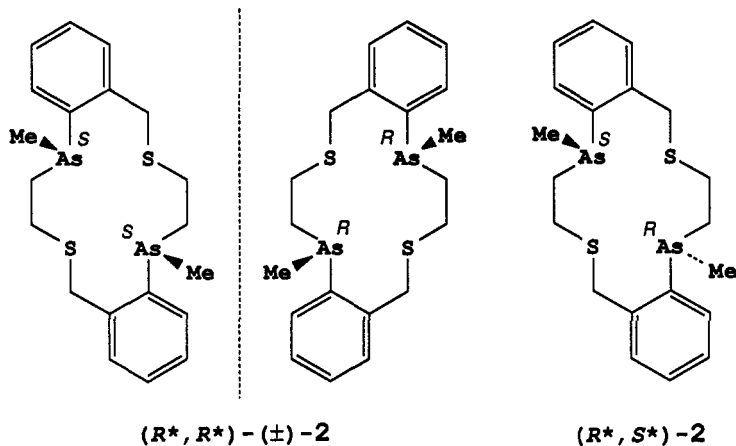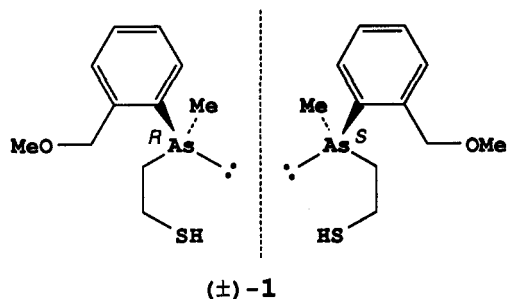
diastereomers of [Pd(2)]$^{2+}$ (the sulfurs are also chiral), one diastereomer of the macrocyclic complex is produced to the exclusion all others. Interestingly, pure (R^*,R^*)-2, when dissolved in chloroform to which a trace of aqueous hydrochloric acid has been added, rearranges with epimerization at arsenic to give an equilibrium mixture of (R^*,R^*)-2, and (R^*,S^*)-2. Under suitable conditions diastereomerically pure (R^*,S^*)-2 crystallizes from the acidic solution in quantitative yield in a typical second-order asymmetric transformation. On the other hand, if (R^*,S^*)-2 is converted into [Pd(R^*,S^*)-2](ClO$_4$)$_2$, and this complex is heated at 150 °C in dimethylsulfoxide for a few minutes, the coordinated arsines epimerise with quantitative formation of diastereomerically pure [Pd(R^*,R^*)-2](ClO$_4$)$_2$. Thus, by appropriate choice of conditions either diastereomer of 2 can be interconverted quantitatively with complete stereoselectivity.

Note b: The stereochemical nomenclature adopted here for diastereomers is consistent with Chemical Abstracts Service Index practice; R^* and S^* refer to the relative absolute configurations of the chiral centres. Enantiomers have simplified descriptors.

If (±)-1 is first resolved (and this can be achieved by the fractional crystallization of optically active palladium(II) diastereomers of deprotonated (±)-1, followed by displacem[5~ents of the optically pure arsine enantiomers from the diastereomers) and then converted into optically active [Pd(L-H)$_2$], cyclisation yields optically pure (R,R,)- or (S,S)-2, the first examples of optically active macrocyclic tertiary arsines.

(±)-3   (R*,S*)-4   (±)-5
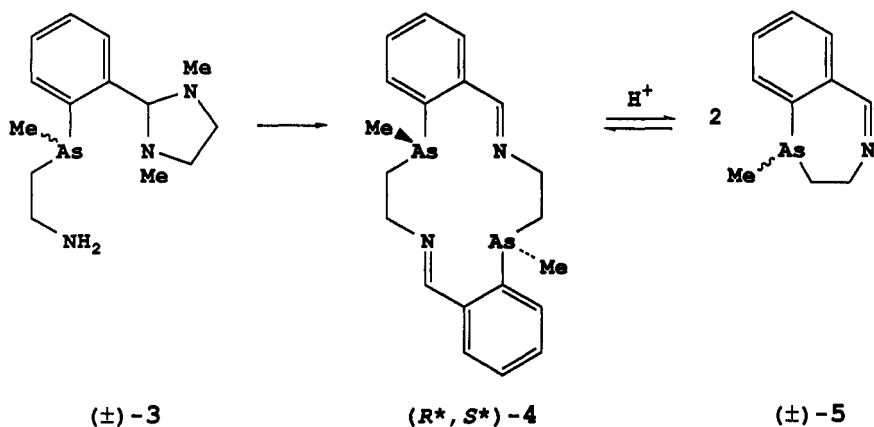
We have also isolated pure diastereomers and enantiomers of trans-As$_2$N$_2$ macrocycles (ref. 7). In a dramatic demonstration of stereospecificity, (±)-3, when heated at 80 °C in vacuo, yields diastereomerically pure (R*,S*)-4 in quantitative yield. The diimine rearranges quantitatively into 7-membered (±)-5 in chloroform; upon removal of solvent, (R*,S*)-4 is recovered. Thus, (R*,R*)-4 cannot be isolated and the synthesis of (R*,S*)-4 from (±)-3 is totally stereospecific. The individual enantiomers of (R*,R*)-4, *viz.* (R,R)- and (S,S)-4, however, can be isolated by asymmetric synthesis and each one is optically pure. Under acidic conditions (R*,S*)-4 reacts with R-6 to produce, after a work-up involving treatment of the reaction mixture with ammonium hexafluorophosphate, a diastereomerically pure palladium complex containing (R,R)-4. Optically pure (R,R)-4 can be liberated from the complex. Reductions of (R*,S*)- and (R,R)-4 with lithium aluminium hydride yield the corresponding diamines. Since (R*,R*)-4 is not available, the racemic diamine was obtained by heating [Pd(R*,S*)-4](ClO$_4$)$_2$ in dimethylsulfoxide for a few minutes at 150 °C, and then liberating from the metal the (R*,R*)-4 that had formed quantitatively by asymmetric transformation [see (R*,S*)-2 → (R*,R*)-2].


(R*,R*)-(±)-4
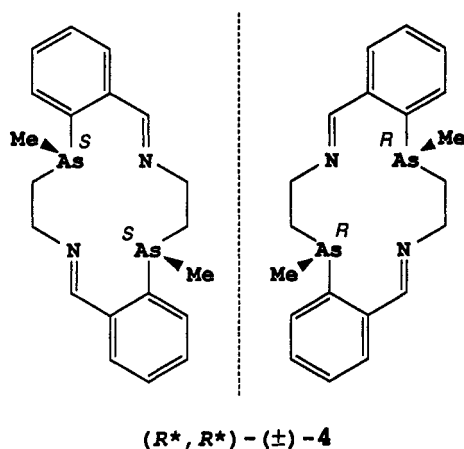
In recent work, we have explored the possibilities of resolving and stereoselectively alkylating secondary arsine complexes (ref. 8). Secondary arsine (±)-AsHMePh reacts with 7 in boiling methanol to give, in a second-order asymmetric transformation, a 90% yield of crystalline R-8, diastereomerically pure, the first example of a complex containing a resolved secondary arsine. Deprotonation of the secondary arsine in this complex with
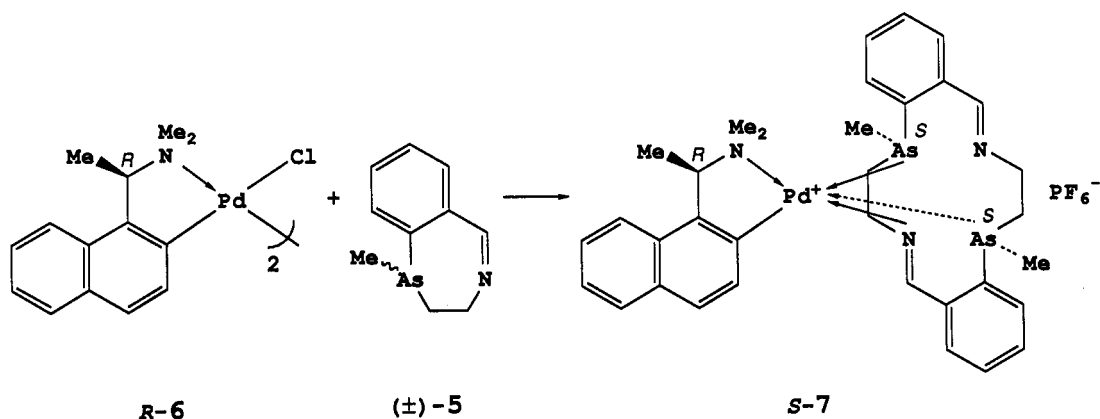
KOBu-*t* at -65 °C followed by treatment of the intermediate tertiary arsenido-iron
intermediate with ethyl iodide at the same temperature, yields diastereomerically pure
(*S*)-9. Thus, it is possible to synthesise a tertiary arsine from a free secondary arsine
with total stereoselectivity with use of the auxiliary 7. In another development, we have
found that 7 reacts with (±)-AsClMePh to give an equilibrium mixture of the expected
chloroarsine complexes. Treatment of tetrahydrofuran solutions of this mixture of epimers
with Grignard reagents gives the diastereomerically pure tertiary arsine complexes in >
90% chemical yield. Grignard reactions on diastereomerically homogeneous chlorophosphine
complexes, chiral at phosphorus, also proceed with complete (> 99%) stereoselectivity,
apparently with inversion at phosphorus. In another development, we have isolated a
platinum(II) complex containing a resolved secondary phosphine that can be liberated with
retention of configuration at phosphorus; this is the first resolution of a chiral
secondary phosphine. These results auger well for future stereoselective syntheses of
pure diastereomers and enantiomers of poly(tertiary arsines and phosphines) on metal ions.

TERTIARY PHOSPHINE MACROCYCLES AND CAGES

We have been concerned with the synthesis of chelating poly(tertiary phosphine)
macrocycles and cages for some time. Related work in this area has emanated from Kyba's
laboratories (ref. 9). One strategy for the synthesis of *trans*-P_2S_2 macrocycles involves
the metal template dimerization of appropriately substituted (±)-2-mercaptoethylphosphines
along the lines that proved successful for the synthesis of the diastereomers and
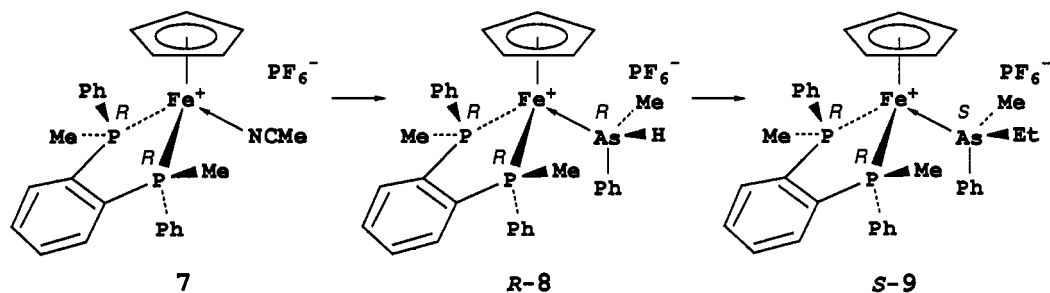
enantiomers of 2. Another approach has been to stereoselectively alkylate appropriate
primary and secondary phosphines in order to build-up rings at phosphorus. To date, our
work on the first approach has resulted in the resolution of the model compound (±)-
PhMePCH$_2$CH$_2$SH with use of *R*-6 as resolving agent and the corresponding 2-methoxymethyl
compound, as a racemate, has been cyclized on platinum(II) (as for 2) giving low yields of
the (*R**,*R**)-(±) and (*R**,*S**) forms of *trans*-P_2S_2 macrocycles.
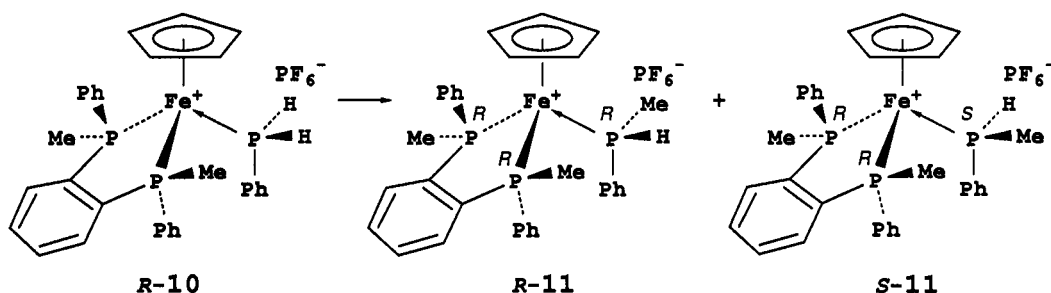
The second approach, which involves ring build-up by stereoselective alkylation of coordinated primary and secondary phosphines, seems particularly promising. Thus, reaction of *R*-10 with iodomethane in the presence of triethylamine at 20 °C produces a separable 4:1 mixture of *R*- and *S*-11 (ref. 10). Deprotonation of *R*-11 with KOBu-*t* at -90 °C, followed by treatment of the intermediate tertiary phosphido-iron complex with iodoethane at the same temperature, produces *S*-12 with complete stereoselectivity (refs. 11 and 12). Resolved secondary phosphine complexes can be converted therefore into resolved tertiary phosphine complexes with total stereochemical control at low temperatures. At elevated temperatures alkylations proceed under thermodynamic control due to the relatively low barrier to inversion of the tertiary phosphido-metal-*P* stereocentres in the intermediates.
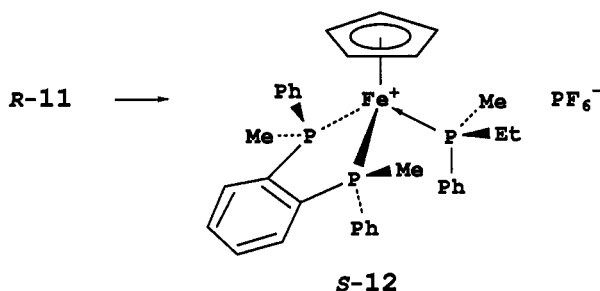

In recent work, we have discovered that 1,2-phenylenebis(phosphine) (ref. 13) can be per-alkylated in the complex [Cu{1,2-C_6H_4(PH_2)$_2$}]CF_3SO_3, 13. Thus, treatment of 26 with KOBu-*t* (8 equiv.) and iodomethane (8 equiv.) at 20 °C affords 1,2-phenylenebis(dimethylphosphine) in 80% yield after displacement from the metal. With dibromo-1,3-propane as alkylating agent, the tetrahedral cage 14 can be isolated in ca 50% yield. A full structural investigation of 14 and some of its complexes is in progress.

13   14
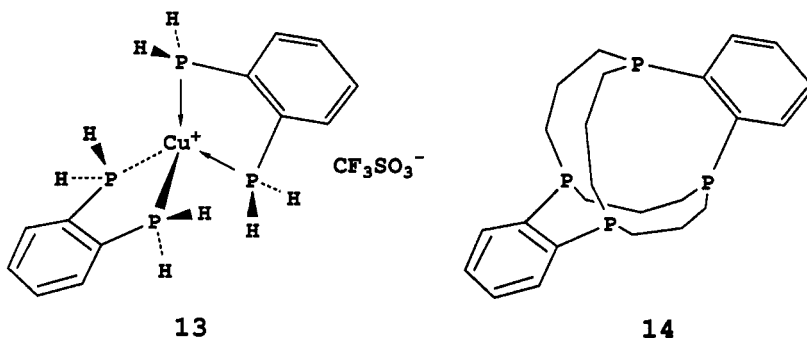
BIOLOGICAL SYNTHESIS OF CHIRAL TERTIARY ARSINES

The mould *Scopulariopsis brevicaulis* in bread cultures reductively methylates prochiral
dialkylarsinic acids under aerobic conditions to produce chiral tertiary arsines in
considerable yields (ref. 14). We have shown that the reduction is highly stereoselective
by trapping the tertiary arsines in solutions of optically active palladium complexes and
analysing the products by high resolution ^{1}H NMR spectroscopy. Thus, when growing on
bread treated with ethyl-*n*-propylarsinic acid, 15, the mould produces enantiomerically
enriched (±)-ethylmethyl-*n*-propylarsine, 16, of 80% optical purity. The progress of the
reaction, as well as the stereoselectivity of the reaction, was monitored by the
appearance of the diastereomers of the arsine with *R*-6. Present work is concerned with an
investigation of the scope of this reaction with related substrates, as well as with the
establishment of the identities of the major enantiomers of the products by X-ray analyses
of crystalline palladium diastereomers. We are optimistic that the mould will produce
optically active tertiary arsines, chiral at arsenic, with total stereoselectivity with
arsinic acids containing bulkier alkyl substituents.
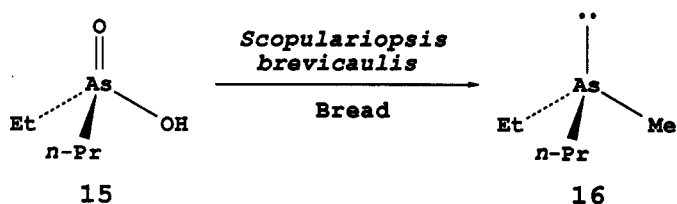
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