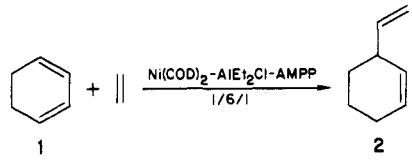
# Communications

## Threophos: A New Chiral Aminophosphine Phosphinite (AMPP) Ligand Highly Efficient in Asymmetric Hydrovinylation of Cyclohexa-1,3-diene Catalyzed by Nickel Complexes

*Summary:* Threophos is a potential tridentate ligand obtained from threonine. (*S*)-(+)-3-Vinylcyclohex-1-ene is produced quantitatively in 93% ee from asymmetric hydrovinylation of cyclohexa-1,3-diene catalyzed by the $Ni(COD)_2$–$AlEt_2Cl$–[(2*R*,3*R*)-threophos] system. A convenient route to determine both optical yield and absolute configuration of chiral cycloalkene compounds is reported.

*Sir:* Asymmetric C–C bond formation catalyzed by chiral transition-metal complexes is an objective of considerable current importance for the convenient synthesis of chiral synthons.[1-3] In this context, we have shown that chiral aminophosphines can be used as ligand in asymmetric codimerization reactions catalyzed by the nickel complexes.[4] We report here a new series of aminophosphine phosphinite ligands (AMPP) and their use in the catalytic synthesis of chiral 3-vinylcyclohex-1-ene (VCH, **2**) according to eq 1. This reaction is carried out quantitatively




and the ligand threophos gives rise to **2** with an optical purity approaching 100%.

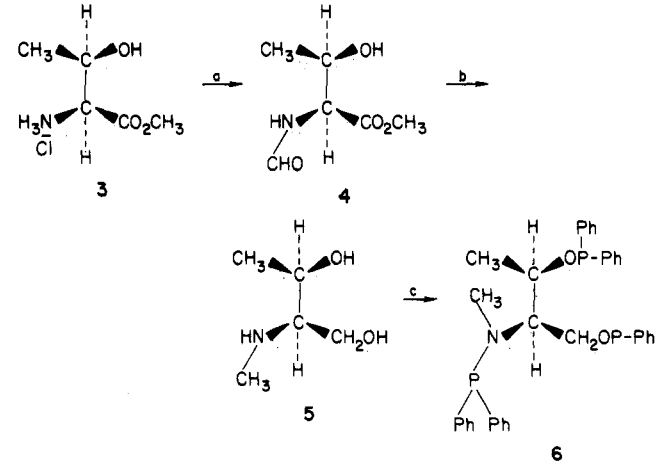
The AMPP ligands were readily prepared from commercial amino acids or amino alcohols, thus providing a cheap source of potential chiral bi- or tridentate ligands for asymmetric synthesis (Table I). We illustrate the general synthesis of these ligands by the preparation of threophos **6** (Scheme I).

The (2*S*,3*R*)-*N*-formyl compound **4**, $[\alpha]^{25}_D$ −3.4° (*c* 1.0, $CHCl_3$), was obtained in 74% yield by formylation[5] of the methyl ester hydrochloride of (2*S*,3*R*)-threonine (**3**), $[\alpha]^{25}_D$ −15.9° (*c* 2.0, $H_2O$). Compound **4** was converted into **5**, $[\alpha]^{25}_D$ −4.2° (*c* 2.0, $CHCl_3$), in 46% yield by reduction with $LiAlH_4$ in THF solution. Phosphinylation under usual conditions[6] of **5** afforded in 60% yield (2*R*,3*R*)-threophos **6** as a viscous oil, $[\alpha]^{25}_D$ +13.8° (*c* 2, $CHCl_3$).

Different AMPP ligands have been used in the asymmetric hydrovinylation of **1** catalyzed by the $Ni(COD)_2$–$AlEt_2Cl$–AMPP system. As shown in Table I, **2** was obtained in highest optical rotation $[\alpha]^{25}_D$ +250° at −30 °C with (2*R*,3*R*)-threophos.[7] For optically pure (+)-VCH a specific rotation $[\alpha]^{25}_D$ +268° ± 5° (*c* 1.0, toluene)[8] and *S* configuration were determined[9] from an unambiguous method as follows (Scheme II).

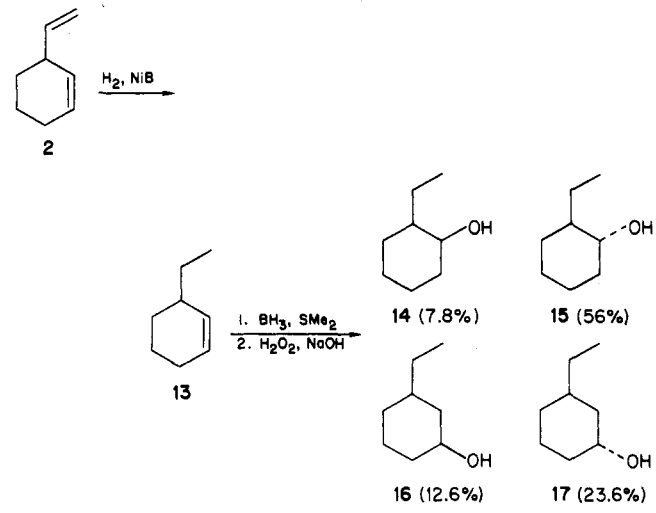
VCH (**2**), $[\alpha]^{25}_D$ +227.5°, was selectively reduced by the Brown's method[10] to (+)-3-ethylcyclohex-1-ene (**13**).[11]

Scheme I[a]




[a] (a) $CH_3COOCHO$, $CHCl_3$, NEt; (b) $LiAlH_4$, THF; (c) $3ClPPh_2$; $3NEt_3$, benzene.

Scheme II

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(7) This result involves that the previously estimated[4] specific rotation, $[\alpha]^{25}_D$ +170°, for optically pure VCH (**2**) is uncorrect for yet unknown reasons. Thus in this previous communication[4] on hydrovinylation of **1** with (−)-(*R*)-[*N*-(1-phenylethyl)amino]diphenylphosphine as ligand an optical yield of ca. 73% in **2** was overestimated by using a combination of Mosher's procedure (Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512) and lanthanide shift reagent (Yamagushi, S. "Asymmetric Synthesis; Morrison, J. D., Ed.; Academic Press: 1983; Vol. 1, Analytical Methods, p 125).

(8) From this value the previous optical yield (73%) reported[4] for **2** is lower (47%).

(9) Binuclear complexes obtained from either Ag(fod) or Ag(tfa) and a chiral lanthanide chelate such as $Yb(facam)_3$, $Pr(hfbc)$, and $Eu(tfac)_3$ failed to give differentiation by $^1H$ and $^{13}C$ NMR spectra for (*R*)- and (*S*)-3-vinylcyclohex-1-ene enantiomers (Wenzel, T. J.; Sievers, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 382–388).

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**Table I. Asymmetric Hydrovinylation of Cyclohexa-1,3-diene Catalyzed by the $Ni(COD)_2$–$AlEt_2Cl$–AMPP System[a] (AMPP Ligands $Ph_2PN(CH_3)CH^*RCH_2OPPh_2$)**

| | | 3-vinylcyclohex-1-ene | | | |
|---|---|---|---|---|---|
| starting amino acids | AMPP ligands,[b] R | $[\alpha]^{25}_D$, deg (c 1.00, toluene) | config[c] | T, °C | optical yields,[c] %ee |
| (2S,3R)-threonine | $CH_3CH^*(OPPh_2)$ (6) | +227.5 | S | 40 | 85 |
| | | +243.5 | | 10 | 91 |
| | | +248.5 | | 0 | 93 |
| | | +249 | | −20 | 93 |
| | | +250 | | −30 | 93[a] |
| (S)-phenylalanine | $PhCH_2$ (7) | −56.5 | R | 40 | 21 |
| | | −104.5 | | −5 | 39 |
| | | −139 | | −25 | 52 |
| (S)-alanine | $CH_3$ (8) | −45 | R | 40 | 17 |
| (S)-valine | i-Pr (9) | −26.5 | R | 40 | 10 |
| | | −30 | | −5 | 11 |
| (R)-phenylglycine | Ph (10) | −12 | R | −5 | 4 |
| (S)-aspartic acid | $CH_2CH_2OPPh_2$ (11) | −75 | R | 40 | 28 |
| (S)-glutamic acid | $(CH_2)_2CH_2OPPh_2$ (12) | −50 | R | 40 | 19 |

[a] An autoclave was successively charged with a pre-formed solution of AMPP ligands (0.4 mmol) and $Ni(COD)_2$ (0.4 mmol) in toluene (5 mL), a solution of $Et_2AlCl$ (0.2 mL) in toluene (5 mL), and 1 (7 g, 87.5 mmol). Then, the autoclave was pressurized with a stoichiometric amount of ethylene. The reactions were monitored by ethylene consumption and were conducted to completion within 15 min at 40 °C. Under these conditions the selectivities in 2 approached 100%. 2 was purified by spinning column distillation. The reaction time at −30 °C is 225 min. [b] All compounds described here gave NMR ($^{13}C$, $^1H$, and $^{31}P$) spectra consistent with their structures. [c] See text. Results were reproducible to within 0.5%. Duplicate experiments were run for each entry.

Hydroboration[12] of **13** gave quantitatively a mixture of the four diastereoisomeric alcohols **14**–**17**. Optical yields were determined by GLC either on urethanes prepared from isopropyl isocyanate by using König's method[13] (glass capillary column, 50 m, coated with XE-60–*S*-valine–*S*-α-phenyl ethylamide, isotherm at 75 °C) or on urethanes from (+)-(*R*)-1-phenylethyl isocyanate (capillary column, 50 m, SE 52 isotherm at 160 °C). All optical yields evaluated by the two methods agreed within the experimental errors (±0.5%). Along hydrogenation and hydroboration reactions, the configuration of the asymmetric carbon in **2** was maintained, thus the *S* configuration of (+)-VCH has been deduced from the following reference compounds. (i) *trans*-(1*S*,2*S*)-2-Ethylcyclohexanol and *trans*-(1*S*,3*S*)-3-ethylcyclohexanol were prepared respectively from the corresponding racemic ketones by specific enzymatic reduction catalyzed by HLADH with recycling NADH.[14] (ii) *trans*-(1*R*,3*R*)-3-Ethylcyclohexanol and *cis*-(1*R*,2*S*)-2-ethylcyclohexanol were obtained from a stereospecific esterification with lauric acid carried out in organic phase and catalyzed by a lipase[15] (from the yeast *Candida cyclindracea*).

Optical yields for the different AMPP are reported in Table I. Relative to the optical yield of 85% obtained at 40 °C from threophos (**6**), the other ligands AMPP, particularly **9** and **10**, were much less enantioselective and, although AMPP ligands such as (*S*)-proliphos and D-ephos, obtained respectively from (*S*)-proline and D-ephedrine, have proved to be very effective toward asymmetric hydrogenation[6] and hydroformylation,[16] they were practically inefficient for reaction 1, as far as asymmetric induction is concerned. Potential tridentate ligand (2*R*,3*R*)-threophos (**6**) was one of the most effective ligands, giving quantitatively (+)-(*S*)-3-vinylcyclohex-1-ene. The extent of optical induction was readily upgraded to 93% ee by lowering the reaction temperature to 0 °C. Undoubtly, the antipode (2*S*,3*S*)-threophos would be able to produce (−)-(*R*)-3-vinylcyclohex-1-ene, with the same enantiomeric excess, so that this reaction could be a useful tool for production of chiral synthons; thus, we are preparing optically pure *trans*-perhydro-1-indanone from a Brown's annelation.[17]

**Registry No.** **1**, 592-57-4; (*S*)-**2**, 76152-63-1; (*R*)-**2**, 95421-88-8; **3**, 39994-75-7; **4**, 2313-74-8; **5**, 95421-89-9; **6**, 95421-90-2; **7**, 91662-87-2; **8**, 95421-91-3; **9**, 95421-92-4; **10**, 90032-62-5; **11**, 95421-93-5; **12**, 95421-94-6; **13**, 95421-95-7; **14**, 95529-72-9; **15**, 69854-63-3; **16**, 87759-26-0; **17**, 69854-64-4; $Ni(COD)_2$, 1295-35-8; $Et_2AlCl$, 96-10-6; $CH_2{=}CH_2$, 74-85-1; (2*S*,3*R*)-threonine, 72-19-5; (*S*)-phenylalanine, 63-91-2; (*S*)-alanine, 56-41-7; (*S*)-valine, 72-18-4; (*R*)-2-phenylglycine, 875-74-1; (*S*)-aspartic acid, 56-84-8; (*S*)-glutamic acid, 56-86-0; (±)-2-ethylcyclohexanone, 64870-41-3; (±)-3-ethylcyclohexanone, 64847-85-4.

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## Tandem Claisen–Diels–Alder Reactions in Synthesis. A Facile Approach to Anthracyclines

*Summary:* Acid **8b** is available in seven steps from ketone **1**. Quinone **5** represents a useful intermediate for the synthesis of anthracyclines.

*Sir:* The rearrangement of allyl phenyl ethers to *o*-allylphenols, termed the Claisen rearrangement,[1] has been less

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