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CHIRAL SYNTHESIS OF *Z*-2-BUTYLIDENECYCLOHEXAN-1-OL AND -1-YL PHENYLSULPHIDE FROM OPTICALLY ACTIVE PHOSPHINE OXIDES

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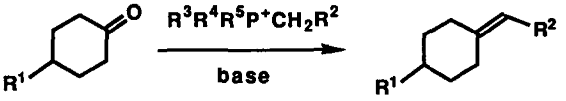
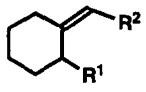
Optically active butyl(*ortho*-methoxyphenyl)phenylphosphine oxide is used to create three new chiral carbon atoms as a carbon framework is built up by stereoselective electrophilic attack on a cyclic allylic phosphine oxide. Elimination of the chiral auxiliary in a Horner-Wittig reaction gives the title compounds.

Optically active phosphorus compounds, e.g. DIPAMP,[1] are effective chiral auxiliaries in the synthesis of amino acids by asymmetric hydrogenation.[2] However, chiral synthesis by Wittig olefination with optically active phosphonium salts[3] is inevitably limited to those few cases where a chiral alkene, e.g. (2), can be made from a prochiral ketone, e.g. (1), as two chiral centres are created and then destroyed during the reaction. Our stereo-controlled approach to olefination using phosphine oxides[4] is more amenable to development as a chiral process since it allows the stereoselective creation of two,[4] three,[5] or four[6] new chiral centres while carbon-carbon bonds are formed. We now report the extension of this work to exocyclic alkenes (3) and, by replacing Ph_2PO with optically active (o-$MeOC_6H_4$-)PhPO, the synthesis of optically active compounds (3; R^2 =alkyl, R^1=OH or SPh). In these syntheses, the chirality originally introduced as a phosphorus atom is used to create a sequence of three new chiral carbon atoms, two of which are sacrificed to make an exocyclic double bond of defined configuration.



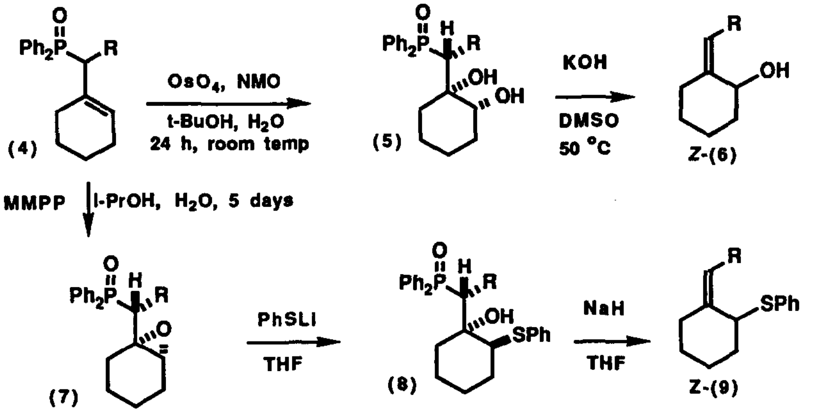
(1) (2)



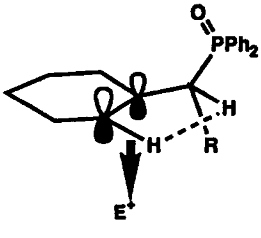
(3)

Hydroxylation of the cyclic allylic phosphine oxides[7] (4) with OsO_4 and *N*-methylmorpholine-*N*-oxide[8] (NMO) gave two diols (83:17, R=Pr). Elimination with KOH in DMSO[9] gave *Z*-(6)[10] from the major isomer,

Scheme 1



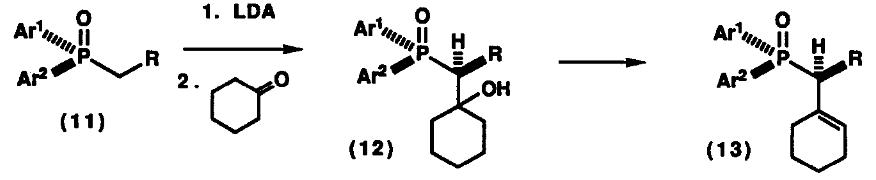
which must therefore be (**5**), and *E*-(**6**)[10] from the minor isomer. Epoxidation of the alkenes (**4**) with magnesium monoperoxyphthalate[11] (MMPP) gave a single epoxide (**7**) which could be opened[12] with PhSLi to give a single diol (**8**) and hence the sulphide *Z*-(**9**) (Scheme 1). Attack by both electrophiles occurred on the same diastereotopic face of the alkene, presumably by the Houk[13] selectivity (**10**).



(10)

We selected as chiral auxiliary a diarylphosphinoyl group with one phenyl and one *ortho*-MeO-phenyl group, partly inspired by DIPAMP,[14] but also in the hope that the MeO group might complex the lithium atom during the creation of the first chiral carbon atom. Addition[15] of the lithium derivative of racemic (**11**; Ar^1, Ar^2=Ph, 2-MeOC$_6$H$_4$, R=alkyl) to cyclohexanone gave adducts (**12**) in good yield and reasonable selectivity (Scheme 2). The diastereoisomers of (**12**) were separated by crystallisation. Elimination[15] gave the cyclic alkenes (**13**) which were treated with the same electrophiles as before (Table). Experiments with compounds lacking the chiral centre at carbon (**13**; R=H) (entries 1 and 2) or at phosphorus (**4**) (entries 7 and 8), and with different relative stereochemistry at C and P (entries 3-6), showed that the stereoselectivity of electrophilic attack is dominated by the chiral carbon atom and that there is virtually no match/mismatch effect.[16] The chiral phosphorus atom thus controls only the first new chiral centre: we suggest that the preferred diastereoisomer is formed by the transition state (**14**), but this is not definitely established.

Scheme 2



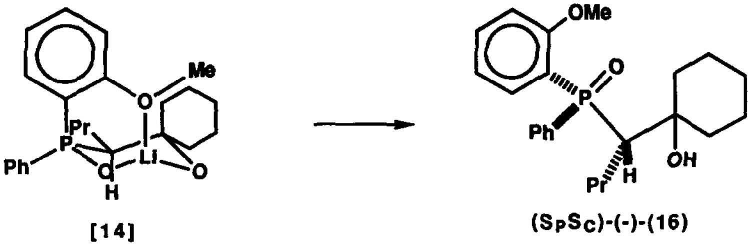
Ar^1, Ar^2 = Ph, 2-MeOC$_6$H$_4$

R	Ratio (yield)
R=Me	71:29 (93%)
R=Pr	63:37 (97%)
R=PhCH$_2$	64:36 (72%)
R=allyl	65:35 (89%)

Table: Asymmetric Induction in Electrophilic Attack on Allylic Phosphine Oxides

Entry	Starting Material (13)[a]			Reagent	Product Ratio	Yield[b]
	Ar^1	Ar^2	R			
1	An	Ph	H	MMPP	58:42	-
2	An	Ph	H	OsO$_4$/NMO	60:40	-
3	An	Ph	Pr	MMPP	>95:5	82%
4	Ph	An	Pr	MMPP	>95:5	c
5	An	Ph	Pr	OsO$_4$/NMO	80:20	60%
6	Ph	An	Pr	OsO$_4$/NMO	82:18	c
7	Ph	Ph	Pr	MMPP	>95:5	85%
8	Ph	Ph	Pr	OsO$_4$/NMO	80:20	50%

[a] An=2-MeOC$_6$H$_4$. [b] Isolated yield of major diastereoisomer. [c] Minor isomer not purified

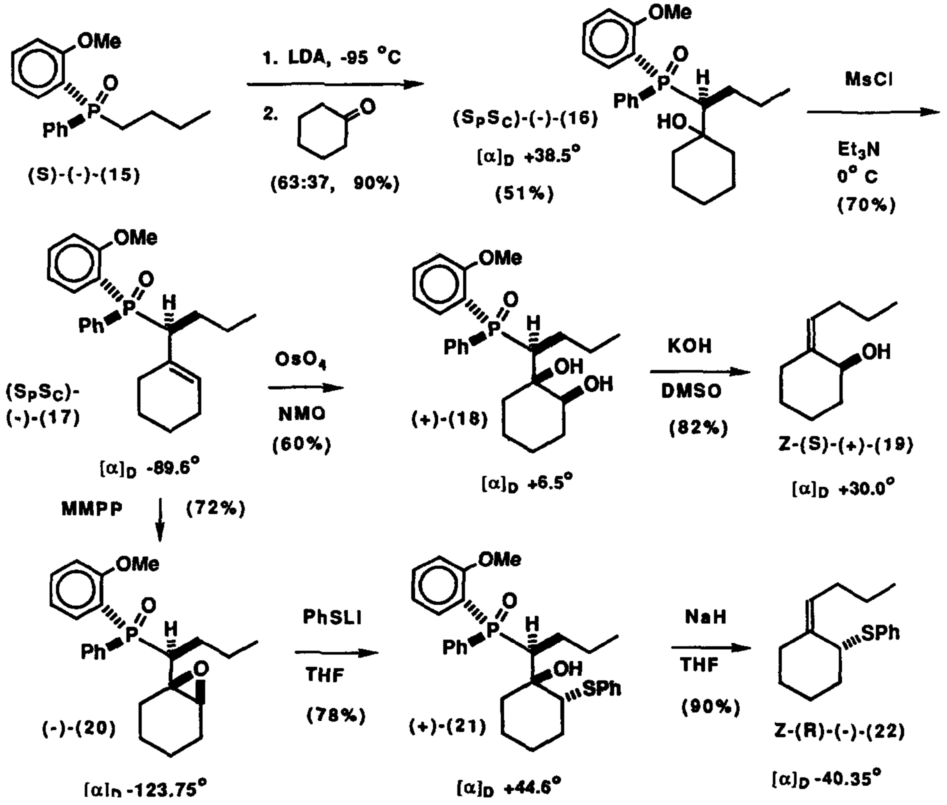


[14]

(SpSc)-(-)-(16)

The optically active phosphine oxide[17] (15) was converted into the optically active alcohol Z-(S)-(+)-(19) and into the optically active sulphide Z-(R)-(-)-(22) by the chemistry summarised in Scheme 3. The Z configuration of the double bond[10] in both products is dictated by the known relative configuration of two of the three chiral carbon atoms in (18) and (21). The absolute configuration of these chiral carbon atoms is determined by the known[1] absolute configuration of the original phosphine oxide (15). However the sense of the chiral transfer from P to C is not definitely established, but only predicted from transition state (14). Whether this prediction is correct or not, epoxide (20) is opened with inversion and so the absolute configuration of the surviving chiral centre in the sulphide (22) is opposite to that in the alcohol (19).

Scheme 3



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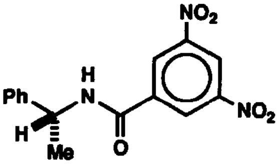

(i)

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