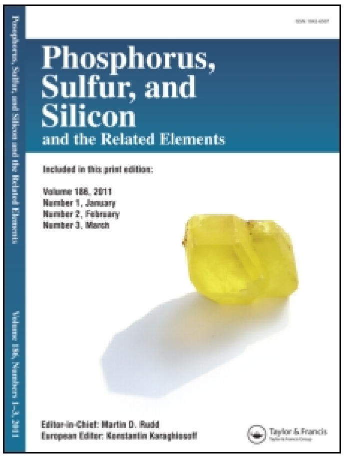

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Chiral Vinyl Phosphine Oxides: Double Asymmetric Induction in the 1,3-Dipolar Cycloaddition to Chiral Nitrones. Kinetic Resolution of a Racemic Phospholene Oxide

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CHIRAL VINYL PHOSPHINE OXIDES: DOUBLE ASYMMETRIC INDUCTION IN THE 1,3-DIPOLAR CYCLOADDITION TO CHIRAL NITRONES. KINETIC RESOLUTION OF A RACEMIC PHOSPHOLENE OXIDE

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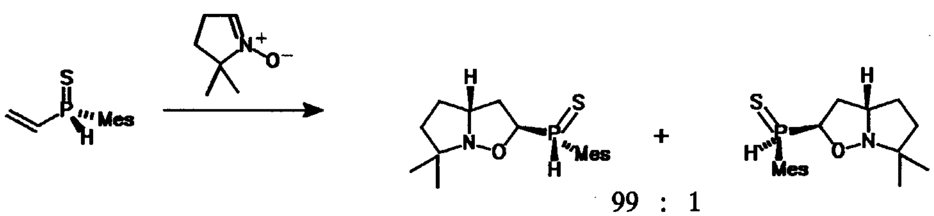
Abstract The 1,3-dipolar cycloaddition of nitrones with chiral vinylphosphine oxides or sulfides provides 5-phosphinyl substituted isoxazolidines with selectivity up to 99:1. Use of chiral nitrones allows a more generalized stereoselective synthesis of these compounds, also by means of a double asymmetric induction. With a racemic phospholene oxide, the high diastereofacial selectivity of the cycloaddition gives rise to a single 4-phosphinyl substituted isoxazolidine from each enantiomer. Moreover, a certain degree of enantiomeric discrimination permits a partial kinetic resolution of the phospholene oxide.

1,3-Dipolar cycloaddition reactions are useful means to control the stereochemistry in acyclic systems. Particularly, chiral isoxazolidine cycloadducts turned out to be highly valuable building blocks for stereoselective synthesis of functionalized molecules. Chiral isoxazolidines can be derived either from chiral nitrones or from chiral dipolarophiles. Our recent discovery of considerable stereoselectivity in nitrone cycloaddition to chiral and prochiral vinyl phosphine



SCHEME 1

derivatives[1] suggested the use of chiral organophosphorus dipolarophiles as chirality inducers in such cycloadditions. The best selectivity (>99:1) resulted from the use of a chiral vinylphosphine sulfide having the remaining two substituents (mesityl and hydrogen) highly differentiated in size (Scheme 1).

A suitable transition state model, having the largest group antiperiplanar to the incoming dipole and the polar group inside, has also been derived, which accounts for the formation of the major diastereoisomers (Figure 1).[1]

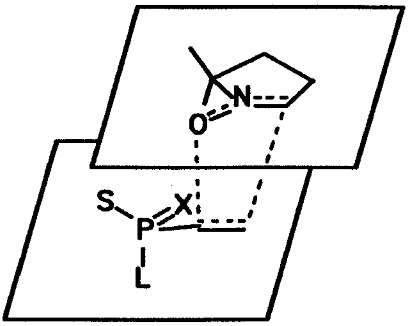
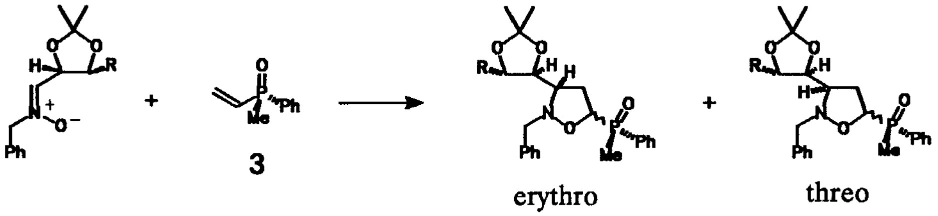


FIGURE 1 Transition State model for the cycloaddition leading to the major isomer (L = large, S = small, X = heteroatom).

Due to the limited availability of nonracemic chiral vinyl phosphorus compounds, however, the efficient production of functionalized phosphino-isoxazolidine synthons can be achieved by the use of optically active nitrones easily available from many sources.

In particular, when optically active nitrones such as (*S*)-(*Z*)-*N*-(2,2-dimethyl-1,3-dioxolan-4-yl)methylenebenzylamine *N*-oxide (**1**) or its 5-(*S*) methyl homologue **2** were reacted with enantiomerically pure (–)-(*S*)-methylphenylvinylphosphine oxide (**3**), high diastereoisomeric ratios have been obtained in the formation of 5-phosphinylisoxazolidines **4** and **5**. The major products **4a** and **5a** were found to have the C3-C4' *erythro* and C3-C5 *trans* relative stereochemistry (Scheme 2).[2]



R			a endo	b exo	c endo	d exo
R = H **1**	95 %	**4**	75	21	2	2
R = Me **2**	75 %	**5**	93	3	2	2

SCHEME 2

The obtained high diastereomeric ratios (up to 40:1 for an *endo* approach, according to the assumption that both nitrones react in their most stable *Z* configurations)[3] suggested that **3** and **1** (or **2**) constituted a matched pair of reactants. The experimental results thus confirm the prediction, based on the consideration of nitrone **3** and phosphine oxide **1** reactive conformations, that glyceraldehyde derived (*S*)-nitrones and (*S*)-phosphine oxide should compose a matched pair of reactants, since in the transition state leading to the major products both nitrone and phosphine oxide can present simultaneously their most favorable conformations (Figure 2).

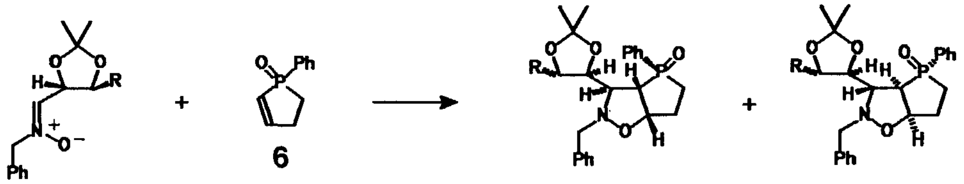
Matched interaction

Mismatched interaction

FIGURE 2 Matched and mismatched interactions in double asymmetric induction.

The stereochemical assignment for the two newly created centers in the two major products **4a** and **5a** (3*S*,5*R*) could then be made with sufficient confidence.

To study the double asymmetric induction in the formation of 4-phosphinyl isoxazolidines the chiral racemic 2,3-dihydro-1-phenyl-1*H*-phosphole 1-oxide **6** was considered for the high regio- and diastereoselectivity.[4] The cycloadditions of achiral nitrones with **6** give a single cycloadduct deriving from a highly diastereoselective approach of the nitrone *anti* to the phenyl ring of phospholene oxide. When nitrones **1** and **2** were used, only two diastereoisomers are produced in 1.7:1 ratio for **1**[5] and 1:1 ratio for **2** (Scheme 3).



1 R = H 79 % **7** 1.7 : 1 **8**

2 R = Me 90 % **9** 1 : 1 **10**

SCHEME 3

The structural assignment based on NMR data and X-ray analysis of **7**[6] established a *trans* C3-C4 stereochemistry (derived from *endo* TS with respect to nitrone) for all the products and a C3-C4' relative stereochemistry of *threo* type in the major isomer **7** (or **9**) and *erythro* in the minor one **8** (or **10**). To accommodate these results is necessary that each enantiomer of phospholene oxide **6** gives exclusively one cycloadduct with five contiguous stereogenic centres in an established and predictable absolute configuration. An analysis of the transition state trajectories in this cycloaddition accounts for the small or none differentiation between the two possible transition states. However, the small difference of reactivity of the two enantiomers of **6** with **1** allowed a partial kinetic resolution of the racemic phospholene oxide **6**, affording the (+)-(*S*) enantiomer with 90% enantiomeric excess.[5]

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