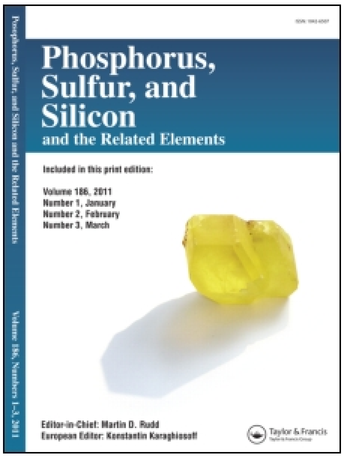

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Phosphino Isoxazolidines: an Approach to Regio and Stereoselective Synthesis

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PHOSPHINO ISOXAZOLIDINES: AN APPROACH TO REGIO AND STEREOSELECTIVE SYNTHESIS

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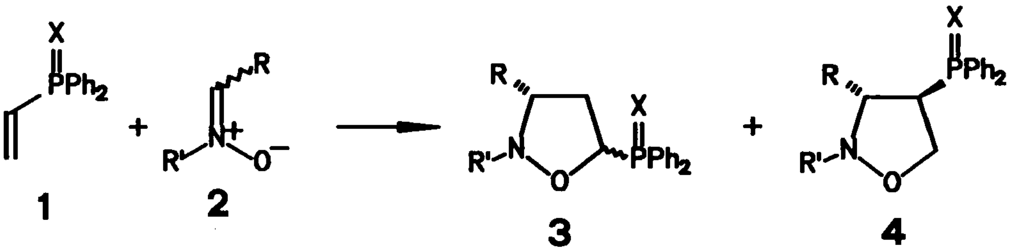
Abstract The 1,3-dipolar cycloaddition of nitrones to vinyl phosphorus derivatives, mainly phosphines and their oxides and sulfides, has been studied. The cycloaddition to chiral racemic phosphine oxides and sulfides gives adducts with considerable diastereofacial selectivity. The transition state model for the cycloaddition is discussed.

The 1,3-dipolar cycloaddition of nitrones to alkenes leads to isoxazolidine rings which are extensively used as useful synthetic intermediates. Many different synthetic strategies can originate by changing the functionality on the dipolarophilic alkene. Our interest in the synthesis of new classes of ligands for transition metal phosphine complexes prompted us to study the cycloaddition of nitrones to vinyl phosphorus derivatives as a general route to phosphino derivatives as a general route to phosphino isoxazolidines.

Despite the known deoxygenating ability of phosphines towards acyclic and cyclic nitrones, the reaction of phosphine **1** with nitrones **2** gives good yields (70-90%) of the cycloaddition products.[1] Oxygenation processes at phosphorus are almost absent, even in the presence of an excess of the nitrone. Only 5-substituted regioisomers **3** are obtained with cyclic nitrones, but formation of some 13% of the 4-substituted regioisomer **4** has been observed in the case of **2** (R = Ph, R' = Me). In case of **2** (R = R' = Ph) the oxidation of phosphine precedes the addition.

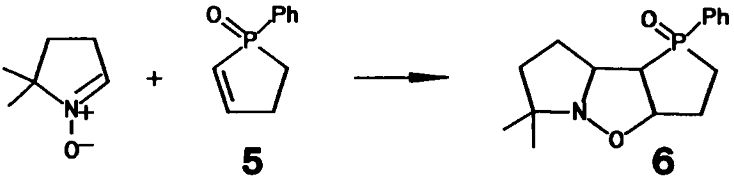
SCHEME 1



X = lone pair, O, S, Se

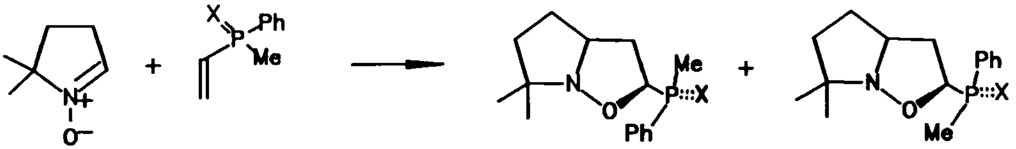
Cycloaddition of nitrones **2** to phosphine oxides **1** (as well as sulfides and selenides), which could be expected to provide the 4-substituted regioisomers **4** in greater amount, has also been studied as a complementary route to phosphino isoxazolidines considering the possibility of reduction at phosphorus in the cycloadduct. The corresponding phosphinyl isoxazolidines are formed in very good yields but again with the high preponderance of the 5-substituted regioisomers **3**. Only **2** (R = R' = Ph) with oxide **1** gives the 4-substituted phosphinyl isoxazolidine predominantly (60% of **4**).[2] Further increase of the selectivity in favor of the 4-regioisomer in this reaction is possible by replacement of oxide **1** with the corresponding sulfide or selenide which give products **4** with remarkable 80% selectivity. The exclusive formation of the 4-substituted phosphinyl isoxazolidines can be achieved by the use of 2-substituted vinyl phosphine oxides (e.g. **5**), as exemplified by the synthesis of **6** (Scheme 2).

SCHEME 2



The cycloaddition to vinyl phosphine oxides as a route to phosphino isoxazolidines becomes even more attractive if one considers that optically active vinyl phosphine oxides are easily available in high optical purity.[3] In this context we have studied the cycloaddition of several nitrones and nitrile oxides to a model racemic methylphenylvinylphosphine oxide **7**.[4] The additions to **7** favor 5-regioisomers to even a greater extent than to **1** (X = O) and provide the corresponding methylphenylphosphinyl isoxazolidines as mixtures of stereoisomers. As indicated in Scheme 3, considerable diastereofacial selectivity is observed and can be further improved by judicious matching of the two substrates. For example, on replacing **7** with **8** the diastereoselectivity increases from 2.5:1 to 4:1 (Scheme 3).

SCHEME 3



X = O : **7** 2.5 : 1

X = S : **8** 4 : 1

A similar regio and diastereoselection is observed also in cycloadditions of nitrile oxides to **7**. The structural assignments in this study are based on the NMR data and on the two X-ray analyses.

^{13}C-NMR spectroscopy is suggested to be the best means for regiochemical assignment in phosphorus substituted isoxazolidines and related compounds.[2]

From the collected results no definitive conclusion regarding the preferred transition state for the 1,3-dipolar cycloadditions to chiral vinyl phosphine oxides is at the moment apparent. Either a Felkin-type model with anti oxygen,[5] or the Houk and Jäger model[6] with the large group anti, or even s-cis $C=C-P=O$ conformation[7] in the transition state can be applied to explain the results. Further studies utilizing structurally modified phosphine oxides are in progress in our groups in order to unravel the origin of the observed stereoselection.

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