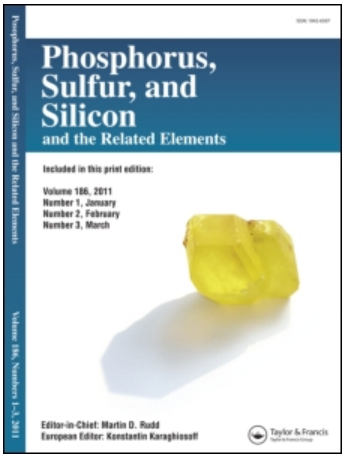

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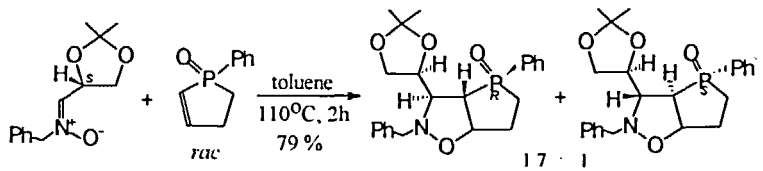
Asymmetric and Doubly Asymmetric 1,3-Dipolar Cycloadditons in the Synthesis of Enantiopure Organophosphorus Compounds

K. MICHAŁ PIETRUSIEWICZ[a], WIESŁAWA HOŁODY[a], MAREK KOPROWSKI[b], STEFANO CICCHI[c], ANDREA GOTI[c] and ALBERTO BRANDI[c]

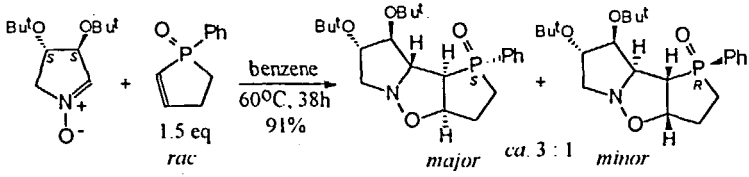
[a]*Department of Organic Chemistry, M. Curie-Skłodowska University, Gliniana 33, 20–031 Lublin, Poland,* [b]*Centre of Molecular and Macromolecular Studies, P.A.S, Sienkiewicza 112, Łódź, Poland. and* [c]*Dipartimento di Chimica Organica, Universita di Firenze, via Capponi 9, 50121 Firenze, Italy*

Enantiopure five-membered ring nitrones derived from *L*-tartaric acid and from *L*-malic acid undergo highly regio- and stereoselective cycloaddition reactions with an excess of racemic 2,3-dihydro-1-phenyl-1*H*-phospholes producing two readily separable tricyclic cycloadducts and concomitantly effecting kinetic resolution of the dihydrophosphole derivative. Stereochemistry of the cycloaddition process and scope of the kinetic resolution process have been established in details and adjusted to produce dihydrophosphole derivatives in good yields and in very high optical purity. To effect syntheses of single cycloadducts of 100% ee the techniques of doubly asymmetric synthesis and parallel kinetic resolutions have been employed. The resulting tricyclic cycloadducts feature 2,2'-connection of pyrrolidine and phospholane rings and five to seven contiguous stereogenic centers of which three have been induced and one or two kinetically resolved during the cycloaddition process.

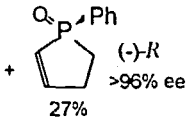
During our ongoing research[1-5] on the use of 1,3-dipolar cycloadditions for stereoselective construction of functionalized P-chiral systems we have found recently[6] that reaction of racemic 1-phenyl dihydrophosphole oxide (**1**) with enantiopure nitrone derived from *D*-glyceraldehyde gave a 1.7:1 mixture of only two stereoisomeric products

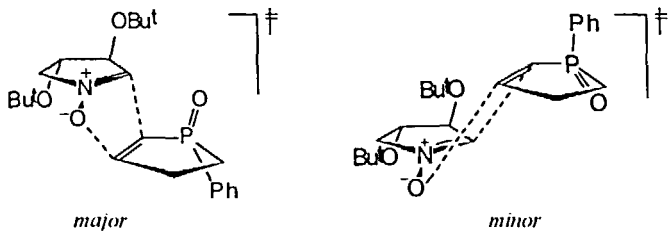


originating from the (*R*)-**1** and the (*S*)-**1**, respectively,[7] and left the unreacted portion of **1** enriched accordingly in the *S* enantiomer. Further research in the same vein and judicious use of five-membered ring nitrones derived from *L*- or *D*-tartaric acid[8,9] and *L*- or *D*-malic acid[10] in combination with various dihydrophosphole derivatives resulted in the development of a general and highly enantioselective 1,3-dipolar cycloaddition procedure which offers ready access to both the enantiopure P-chiral tricyclic cycloadducts and the resolved P-chiral dihydrophosphole derivatives of very high enantiomeric purity. The procedure is exemplified below with a reaction of the *L*-tartaric



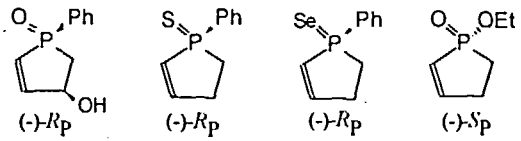
acid derived nitrone with a 50% excess of racemic **1** which yielded selectively only two readily separable enantiopure cycloadducts and left nearly entire excess of **1** almost completely resolved.[11] The analysis of the stereochemical





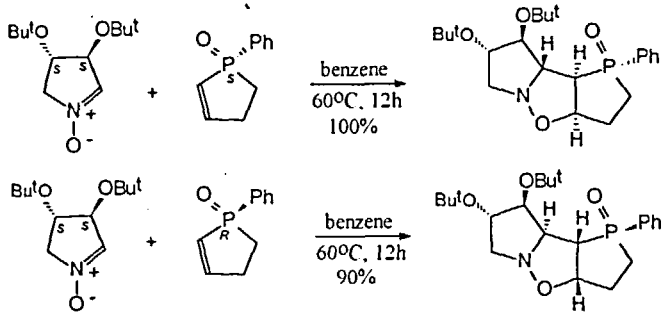
course of this cycloaddition has been facilitated by the X-ray structures of the two cycloadducts and pointed out to the two plausible TS constructs which are delineated above. As it follows, **1** has been approached by the nitrone exclusively from the face bearing the smaller P=O substituent and exclusively in the exo mode. The enantiomers of

1 have thus been discriminated by the proximal (C3) OBu^t group in the nitrone which could effectively hinder the approach in the *minor* path but apparently could not exert such an effect in the *major* path. This clear-cut enantiodiscriminating pattern has then been exploited in the equally facile and efficient kinetic resolutions utilizing the same *L*-tartaric acid derived nitrone and a series of 1-phenyl dihydrophosphole chalcogenides possessing similarly well differentiated faces of the dihydrophosphole ring. The resolved 1-phenyl dihydrophosphole chalcogenides were obtained in ca 31% yield and were found



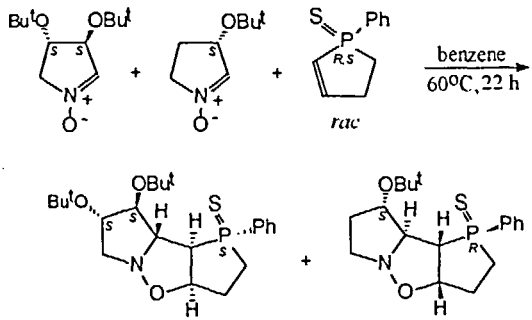
to be of 98-100% optical purity. They are listed above in their absolute configurations together with the 1-ethoxy derivative which was analogously resolved with the aid of the *L*-malic acid derived nitrone, albeit somewhat less cleanly and less efficiently.

The cycloadducts formed in these kinetic resolution experiments are also highly valuable as they feature five to seven contiguous stereogenic centers of the unique configuration and can serve as immediate precursors to a family of enantiopure amino alcohols and amino phosphines incorporating the 2,2'-coupled pyrrolidino-phospholane ring system in their structure. They are usually easily isolated from the reaction mixtures



by chromatography or prompt crystallization but they can be also conveniently obtained

by means of the doubly asymmetric cycloadditions which, with the appropriate pairing of substrate enantiomers as exemplified above, afford enantiopure cycloadducts of the desired absolute stereochemistry as the single products. Alternatively, use of a racemic dihydrophosphole derivative and the technique of parallel kinetic resolution[12] leads to



the highly selective production of two distinct easily separable cycloadducts, each derived from a different nitrone and a different dihydrophosphole enantiomer.

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