

ASYMMETRIC INDUCTION IN THE PALLADIUM CATALYZED [3+2] CYCLOADDITION
REACTION OF TRIMETHYLENEMETHANE WITH HOMOCHIRAL VINYL SULFOXIDES

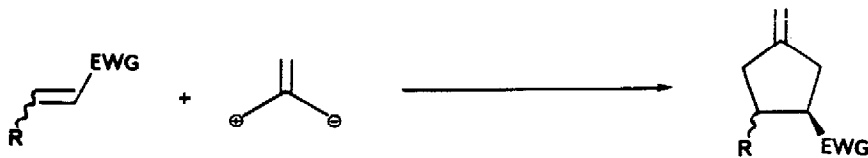
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Abstract: The palladium catalyzed [3+2] cycloaddition of trimethylenemethane with a variety of vinylsulfoxides led to cycloadducts in good to excellent chemical yields and with a good level of asymmetric induction.

In the course of synthetic studies directed towards the synthesis of diterpenes belonging to the Kaurane and Phyllocladane families¹ a diastereoselective method would be required to build up a 3,4-disubstituted methylenecyclopentane in an optically active form.

Recent developments of the [3+2] cycloaddition reaction by the Trost² or Binger³ methodologies showed the importance of this strategy for building up functionalized five membered rings having an exomethylene moiety (scheme 1).



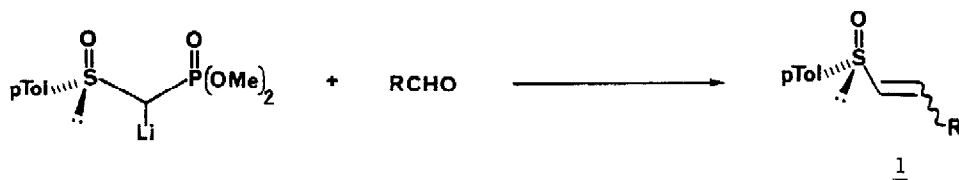
scheme 1

The methylenecyclopentane annulation catalyzed by palladium(0) requires olefins bearing electron withdrawing groups such as an ester, a nitrile, a sulfone or a ketone; but, as far as we know, no example has been described using a sulfoxide substituent, maybe because it is not supposed to be active enough or by fear of side reactions such as elimination⁴. However the presence of such a group in this reaction is very attractive because of the versatility offered by the adducts and in view of a possible asymmetric induction when working with a homochiral sulfoxide⁵. On the other hand the high asymmetric induction observed in the 1,3-dipolar cycloaddition of (R)-p-tolylvinylsulfoxide with acyclic nitrones⁶ and the recent development of asymmetric Diels-Alder reaction⁷ involving this type of dienophiles conformed us to undertake the study of their behavior in the Trost reaction.

We are now pleased to report the first asymmetric [3+2] cycloaddition by the Trost method using homochiral 2-substituted-R-p-tolylsulfinylethene (proceeding in good to excellent chemical yields and with a good level of asymmetric induction).

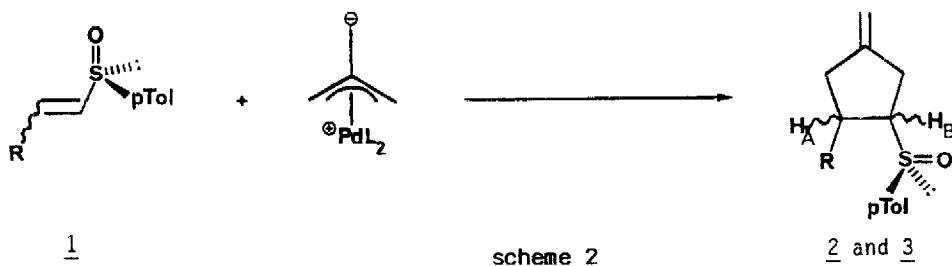
The enantiomerically pure α,β -unsaturated sulfoxides required, were prepared according to the Mikolajczyk procedure i.e. Wittig-Horner reaction of a variety of carbonyl compounds with the lithio derivative of (+)-(R)-dimethylphosphorylmethyl-p-tolyl sulfoxide⁸. In all cases, the reaction led to a mixture of Z and E isomers which were easily separable (table 1).

table 1:



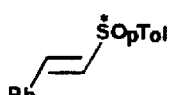
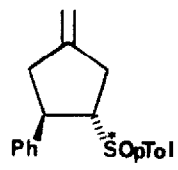
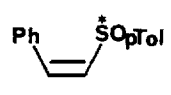
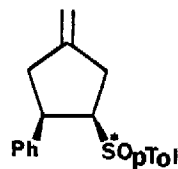
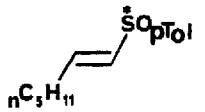
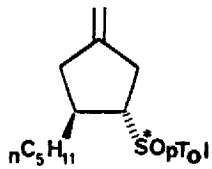
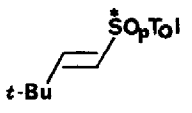
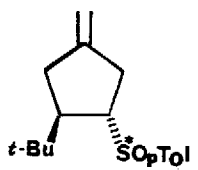
R	Yield (%)	Z/E	$[\alpha]_D^{20}$ in acetone (c=1)
Ph	88	<u>1b/1a</u> :24/76	Z: -740° E: +162°
nC ₅ H ₁₁	65	<u>1d/1c</u> :36/64	Z: -357° E: +148°
tBu	75	<u>1f/1e</u> :18/82	Z: -240° E: +33°

In a typical procedure for the cycloaddition a mixture of the olefin 1 (E or Z), two equivalents of 2-acetoxymethyl-3-allyltrimethylsilane, 5 mol% of palladium acetate and 20 mol% of triisopropylphosphite was refluxed in THF. All olefins afforded the desired 3,4-disubstituted methylenecyclopentane derivatives (scheme 2) in good to excellent chemical yields as a mixture of only two diastereomers 2 and 3 easily separable by flash chromatography on silica gel (table 2).



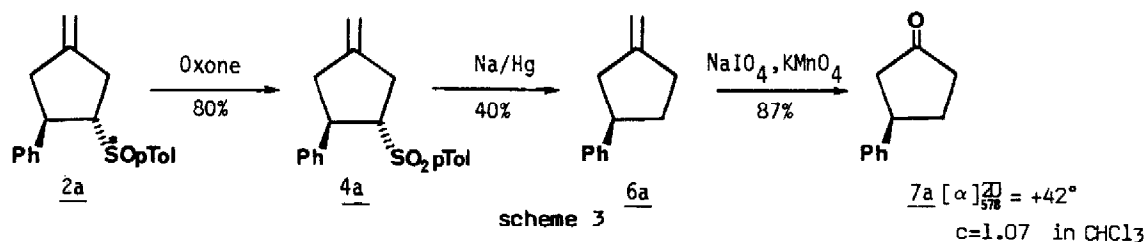
Complete structural assignments and stereochemical features of the reaction were established by spectral analyses⁹ and chemical modifications. For example, when R=Ph both ¹H and ¹³C NMR data confirmed that each isolated cycloadduct was a single stereomer, from E olefins virtually pure E products were obtained [³J(H_AH_B)=10.1Hz for 2a and 3a], the same stereospecificity was observed from Z olefins [³J(H_AH_B)=6.1Hz for 2b and 3b]¹⁰. In addition, both 2a ($[\alpha]_D^{20}=+126^\circ$) and 3a ($[\alpha]_D^{20}=-87^\circ$) after oxone oxidation¹¹ afforded two chiral sulfones (respectively 4a and 5a) having identical NMR data but of opposed optical activity ($[\alpha]_D^{20}=+10^\circ$ c=0.5 in acetone). These features allowed us to give unambiguously the extent of asymmetric induction indicated in table 2.

table 2: [3+2] cycloaddition

olefins	/	cycloadducts (i)	/	reaction time(h)	diastereomeric ratio (2/3)	yield(%) (ii)	de(%) (iii)
				2	90/10	80	80
				6	75/25	47	50
				8	77/23	62	54
				4	82/18	82	64

(i) only the major diastereomer **2** is depicted, **3** refers to the minor diastereomer.
(ii) isolated yields of pure products.
(iii) small amounts of unreacted vinylsulfoxide was recovered enantiomerically pure, showing that no racemization occurred under these reaction conditions.

Finally, in order to know the sense of chiral induction we proceeded to a straightforward transformation of **2a** (scheme 3) into a known chiral compound, 3-phenylcyclopentanone:



Carbon-sulfur bond cleavage of **4a** was accomplished according to the Trost procedure¹². Lemieux oxidation¹³ of the resulting **6a** yielded the dextrorotatory **7a** which indicated according to the Taber assignment¹⁴ the R absolute configuration at the chiral center.

Detailed kinetic and theoretical studies are required to fully understand the reason of the sense of asymmetric induction observed. This work is under progress.

In conclusion, we have shown that chiral vinylsulfoxides are suitable olefins for the palladium catalyzed [3+2] cycloaddition and exhibited a good degree of asymmetric induction. This opens a new route to enantiomerically pure, functionalized cyclopentane, reasonable precursors to a wide variety of cyclopentane-containing natural products. Studies aiming at increasing the degree of asymmetric induction and applying it to the synthesis of natural compounds are currently under active investigation in our laboratory.

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- All new compounds described in the work exhibited satisfactory spectral and analytical data. For example:
2a: ¹H NMR (300 MHz, CD₂Cl₂, 5.30 ppm) 7.38-7.23(m,9H), 4.93(brs,1H), 4.87(brs,1H), 3.47(td,J=10.1,8.2Hz,1H), 3.15(td,J=10.1,8.2Hz,1H), 2.93-2.81(m,2H), 2.60(ddq,J=16.2,10.1,2.3Hz,1H), 2.38(s,3H), 2.07(ddq,J=16.2,8.2,2.3Hz,1H).
3a: ¹H NMR (300 MHz, CD₂Cl₂, 5.30 ppm) 7.42-6.95(m,9H), 4.65(brs,2H), 3.60(td, J=8.7, 8.1Hz, 1H), 3.33(dt, J=8.7, 6.1Hz, 1H), 2.88(ddq, J=16.2, 8.7, 1.8Hz, 1H), 2.78(ddq, 16.2, 8.7, 1.8Hz, 1H), 2.64(ddq, J=16.2, 6.1, 1.8Hz, 1H), 2.48(ddq, J=16.2, 6.1, 1.8Hz, 1H), 2.34(s, 3H).
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