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ASYMMETRIC [3 + 2] CYCLOADDITION OF 2-(SULFONYLMETHYL)-2-PROPENYL CARBONATE CATALYZED BY CHIRAL FERROCENYLPHOSPHINE-PALLADIUM COMPLEXES

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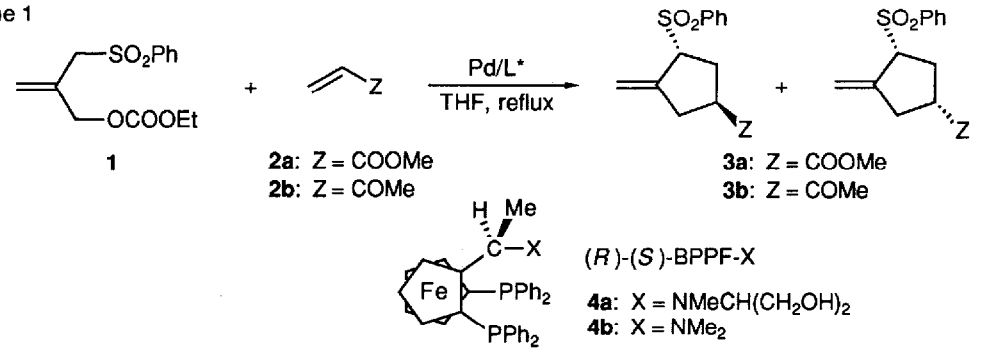
Summary: Cycloaddition reaction of ethyl 2-(benzenesulfonylmethyl)-2-propenyl carbonate with methyl acrylate and methyl vinyl ketone in the presence of a chiral ferrocenylphosphine-palladium catalyst gave optically active methylenecyclopentane derivatives of up to 78% ee.

Much attention has been paid to the development of methods for synthesis of cyclopentane systems.[1] One of the most effective methods is palladium-catalyzed [3 + 2] cycloaddition of 2-(trimethylsilylmethyl)-2-propenyl acetate with electron-deficient olefins forming methylenecyclopentanes, which has been developed by Trost and proposed to proceed via a (trimethylenemethane)palladium intermediate.[2] Tsuji has reported another approach to the palladium-catalyzed cycloaddition by the use of 2-(sulfonylmethyl)- or 2-(cyanomethyl)-2-propenyl carbonate.[3] In spite of extensive studies on asymmetric reactions catalyzed by chiral transition metal complexes, there have appeared few reports on asymmetric synthesis by means of the catalytic cycloaddition reactions.[4] Here we report the first efficient catalytic asymmetric synthesis of optically active methylenecyclopentanes, which was achieved by using a chiral ferrocenylphosphine-palladium catalyst for the cycloaddition of 2-(sulfonylmethyl)-2-propenyl carbonate.

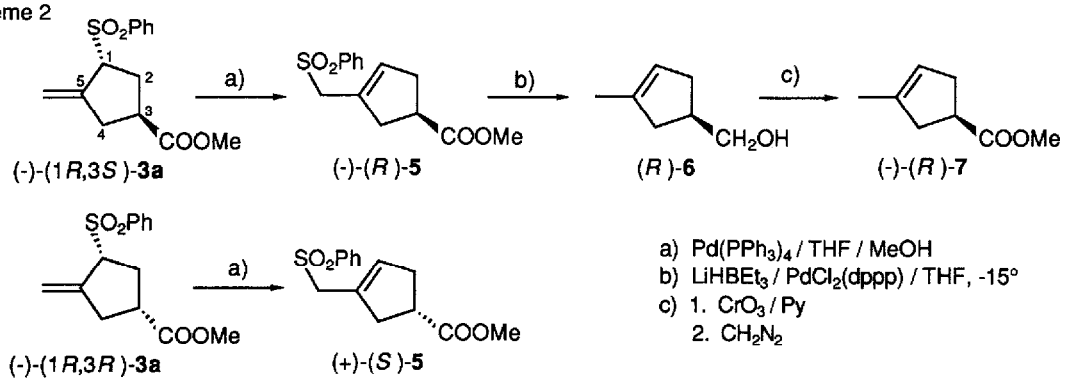
Chiral phosphine ligands including ferrocenylphosphines were examined for their stereoselectivity in the reaction of ethyl 2-(benzenesulfonylmethyl)-2-propenyl carbonate (**1**)[5] with methyl acrylate and methyl vinyl ketone (Scheme 1). The reaction conditions and results are summarized in Table 1. Reaction of carbonate **1** with methyl acrylate (**2a**) in the presence of 3 mol% of a palladium catalyst prepared in situ from $Pd_2(dba)_3 \cdot CHCl_3$ and (*R*)-*N*,*N*-dimethyl-1-[(*S*)-1'2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*S*)-BPPFA (**4b**)][6] in refluxing THF for 47 h gave 76% yield of methyl 1-benzenesulfonyl-5-methylenecyclopentane-3-

Scheme 1



carboxylate (**3a**) which consists of trans and cis isomers in a ratio of 77 to 23.[7] The enantiomeric purities of trans-**3a** and cis-**3a** were determined to be 66% and 64%, respectively, by ^{1}H NMR in the presence of Eu(hfc)$_3$ (entry 2). Treatment of trans-**3a** with 3 mol% of Pd(PPh$_3$)$_4$ in THF/MeOH (3/1) for 28 h gave 91% yield of rearranged product (-)-**5** ([α]$_D^{20}$ -4.3° (c 1.6, chloroform)), which was converted into known (R)-(-)-4-carbomethoxy-1-methylcyclopentene (**7**)[8] by palladium-catalyzed reductive desulfonylation with LiHBEt$_3$[9] followed by oxidation and esterification (Scheme 2). Thus, the absolute configuration of trans-**3a** was determined to be (1R,3S). The allylic rearrangement of cis-**3a** gave (+)-**5**, demonstrating that cis-**3a** is a (1R,3R) isomer.

Scheme 2



Higher stereoselectivity was observed in the reaction with the ferrocenylphosphine containing N-methyl-N-bis(hydroxymethyl)methylamino group **4a**,[10] which gave (1R,3S)-**3a** of 73% ee (entry 1). Other types of chiral phosphine ligands such as (S,S)-chiraphos[11] and (+)-BINAP[12] were not so stereoselective (entries 3 and 4). Methyl vinyl ketone (**2b**) can be also used for the asymmetric cyclization (entries 5 and 6). Reaction with ferrocenylphosphine **4a** gave the cycloadducts trans-(1R,3S)-3-acetyl-1-benzenesulfonyl-5-methylenecyclopentane (**3b**) (75% ee) and cis isomer (1R,3R)-**3b** (78% ee) in a ratio of 66 to 34 in a high yield.[13]

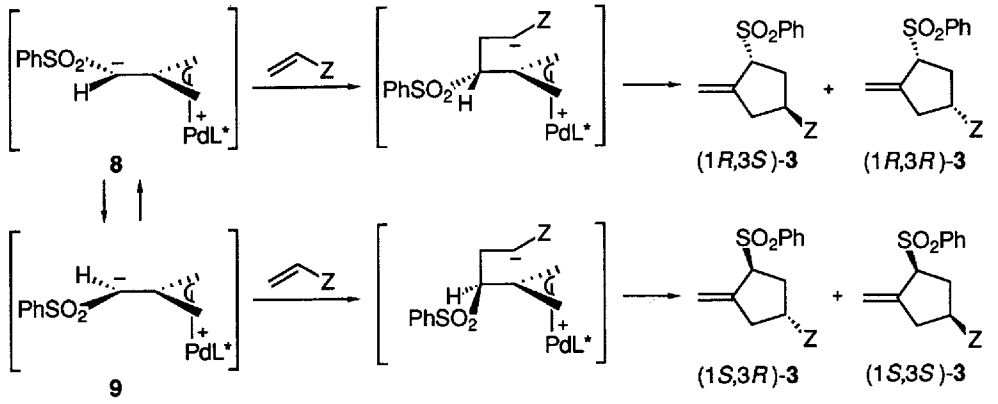
The stereochemical relationship between trans-**3** and cis-**3** is that the isomers have the same configuration R at the carbon center bearing sulfonyl group and the opposite configuration at the carbon bearing carbomethoxy or acetyl group. It is also noteworthy that both trans and cis isomers have almost the same enantiomeric purity in each entry. These results can be illustrated by the mechanism shown in Scheme 3. The key intermediates are zwitter ionic π-allylpalladium complexes **8** and **9**, which are diastereomeric isomers formed by oxidative addition of 1 to palladium(0) followed by deprotonation with the generated alkoxide anion.[3] The intermediates **8** and **9** will produce the methylenecyclopentanes **3** with (1R) configuration and (1S) configuration, respectively, since electron-deficient olefins **2** have been shown to approach the zwitter ionic intermediates from the side opposite to palladium.[14] The stereochemistry of the products must be determined at this step forming the chiral carbon center substituted with sulfonyl group. The subsequent cyclization step where the resulting enolate attacks the π-allyl carbon is not important for the enantioselection in the present cyclization. It may be concluded that the reaction proceeds mainly through the intermediate **8** which gives trans-(1R,3S)-**3** and cis-(1R,3R)-**3** of the same enantiomeric purity.

Table 1. Asymmetric [3 + 2] Cycloaddition of 2-(Sulfonylmethyl)-2-propenyl Carbonate Catalyzed by Chiral Ferrocenylphosphine-Palladium Complexes.[a]

entry	-X in (R)-(S)-BPPF-X	CH_2=CHZ (2)	time (h)	yield[b](%) of 3	trans /cis	% ee[c] (configuration)[d] trans-3	cis-3
1	$-NMeCH(CH_2OH)_2$ (**4a**)	CH_2=CHCOOMe	40	58	82/18	73 (1R,3S)[e]	58 (1R,3R)[f]
2	$-NMe_2$ (BPPFA, **4b**)		47	76	77/23	66 (1R,3S)	64 (1R,3R)
3	(S,S)-chiraphos		42	51	73/27	46 (1R,3S)	21 (1R,3R)
4	(+)-BINAP		46	63	78/22	19 (1R,3S)	4 (1R,3R)
5	$-NMeCH(CH_2OH)_2$ (**4a**)	CH_2=CHCOMe	64	77	66/34	75 (1R,3S)[g]	78 (1R,3R)[h]
6	$-NMe_2$ (BPPFA, **4b**)		38	86	72/28	54 (1R,3S)	61 (1R,3R)

[a] A mixture of $Pd_2(dba)_3 \cdot CHCl_3$ (0.015 mmol) and a ligand (0.033 mmol) in THF (4 mL) was stirred at room temperature for 30 min. Sulfonyl carbonate **1** (1.0 mmol) and 2 (5.0 mmol) were added and the mixture was refluxed under nitrogen. Evaporation of the solvent followed by preparative TLC on silica gel (hexane/ethyl acetate = 1/1) gave the product **3a** or **3b**. [b] Isolated yield. [c] Determined by ^1H NMR using chiral shift reagent Eu(hfc)$_3$. [d] See Scheme 2 and ref 13. [e] $[\alpha]_D^{20}$ -69.6° (c 1.4, $CHCl_3$). [f] $[\alpha]_D^{20}$ -64.0° (c 0.9, $CHCl_3$). [g] $[\alpha]_D^{20}$ -86.9° (c 1.7, $CHCl_3$). [h] $[\alpha]_D^{20}$ -63.7° (c 1.3, $CHCl_3$).

Scheme 3



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7 ^{1}H NMR ($CDCl_3$) for trans-**3a**: δ 2.335 (dt, J = 14.4 and 8.2 Hz, 1 H), 2.505 (ddd, J = 14.4, 7.5, and 3.7 Hz, 1 H), 2.591 (ddt, J = 16.5, 6.7, and 2.0 Hz, 1 H), 2.71-2.81 (m, 1 H), 3.146 (broad quintet, J = 7.5 Hz, 1 H), 3.664 (s, 3 H), 4.06-4.10 (m, 1 H), 5.050 (q, J = 2.0 Hz, 1 H), 5.252 (q, J = 2.0 Hz, 1 H), 7.54-7.59 (m, 2 H), 7.63-7.69 (m, 1 H), 7.85-7.91 (m, 2 H). ^{1}H NMR ($CDCl_3$) for cis-**3a**: δ 2.32-2.49 (m, 3 H), 2.571 (ddd, J = 15.1, 7.0, and 1.0 Hz, 1 H), 2.759 (dddd, J = 12.1, 10.6, 7.9, and 7.0 Hz, 1 H), 3.681 (s, 3 H), 4.051 (tq, J = 8.4 and 1.8 Hz, 1 H), 5.19 (m, 1 H), 5.28 (m, 1 H), 7.54-7.58 (m, 2 H), 7.64-7.68 (m, 1 H), 7.85-7.92 (m, 2 H). The stereochemistry was assigned by the NOE studies on trans-**3a**. Irradiation at the methine mutiplet (δ 4.06-4.10, C-1) induced 6.9% signal enhancement in one of the methylene protons (δ 2.335, C-2), and irradiation at the methine broad quintet (δ 3.146, C-3) induced 3.7% signal enhancement in the other methylene proton (δ 2.505, C-2).

8 $[\alpha]_D^{27}$ -11.4° (c 1.1, methanol). The reported rotation is $[\alpha]_D^{27}$ +22.9° (methanol) for (S)-**7** of 88% optical purity (W. von. E. Doering and K. Sachdev, J. Am. Chem. Soc., **97**, 5512 (1975)). The loss of optical purity may be ascribed to partial racemization during the palladium-catalyzed reduction of (R)-**5** to (R)-**6**.

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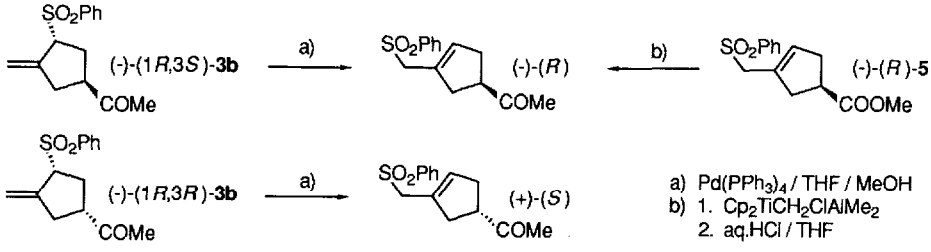
13 ^{1}H NMR ($CDCl_3$) for trans-**3b**: δ 2.165 (s, 3 H), 2.297 (dt, J =14.4 and 8.4 Hz, 1 H), 2.425 (ddd, J = 14.4, 7.3, and 3.3 Hz, 1 H), 2.505 (ddt, J = 16.4, 6.1, and 2.1 Hz, 1 H), 2.828 (ddq, J = 16.4, 9.2, and 2.1 Hz, 1 H), 3.320 (broad quintet, J = 7.2 Hz, 1 H), 4.03-4.07 (m, 1 H), 4.952 (q, J = 2.1 Hz, 1 H), 5.218 (q, J = 2.1 Hz, 1 H), 7.54-7.59 (m, 2 H), 7.63-7.69 (m, 1 H), 7.85-7.91 (m, 2 H). ^{1}H NMR ($CDCl_3$) for cis-**3b**: δ 2.15 (s, 3 H), 2.12-2.60 (m, 4 H), 2.84 (dddd, J = 7.0, 8.2, 10.2 and 12.2 Hz, 1 H), 4.07 (tq, J = 8.8 and 1.8 Hz, 1 H), 5.18 (m, 1 H), 5.28 (m, 1 H), 7.51-7.71 (m, 3 H), 7.86-7.93 (m, 2 H). Irradiation at the methine multiplet (δ 4.03-4.07, C-1) of trans-**3b** induced 6.5% signal enhancement in one of the methylene protons (δ 2.297, C-2), and irradiation at the methine broad quintet (δ 3.320, C-3) induced 4.1% signal enhancement in the other methylene proton (δ 2.425, C-2). The absolute configurations of trans- and cis-**3b** were determined by the following transformations.



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