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One-Pot Preparation of Chiral 2-Vinyl-1,4-benzodioxane

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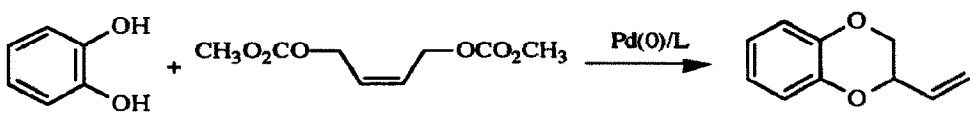
Abstract: 2-Vinyl-1,4-benzodioxane was obtained with e.e. up to 45 % by condensation of catechol and *(Z)*-2-butene-1,4-diylbis(methylcarbonate) in the presence of a catalytic amount of palladium(0) in association with chiral ligand such as BINAP.

The 1,4-benzodioxane ring system has aroused increasing interest due to its presence in a large number of structures of therapeutic agents having important biological activities, which are considerably influenced by the chirality of the 1,4-benzodioxane unit.[1] Most of the synthesis of optically pure 2-substituted-1,4-benzodioxanes started from 2-hydroxymethyl-1,4-dioxane in chiral form; this later compound could be obtained from D-mannitol,[2] by direct condensation of catechol with chiral glycidol [3] or chiral epichlorhydrin,[4] by Sharpless epoxydation of 1-aryloxy-4-hydroxy-2-butene substrate[5] or more recently by an enzymatic resolution of the racemic compound.[6]

Palladium-based methodology has been recently used for the synthesis of five- and six-membered oxygen heterocycles.[7] However only a few methods have been reported for catalytic asymmetric synthesis of oxygen heterocycles.[7a-b,8] The reports by Tsuda[9] and recently by Hayashi[10] of the asymmetric construction of morpholines and piperazines by palladium-catalyzed tandem allylic substitution reaction prompted us to publish our own results in the synthesis of chiral 1,4-benzodioxanes.

We recently described the alkylation of allylic carbonates by oxygen nucleophiles and particularly phenols.[11] We decided to explore the palladium(0)-catalyzed reaction of catechol **1**, a bifunctional nucleophile, with a bifunctional allylic dicarbonate **2** namely *(Z)*-2-butene-1,4-diylbis(methylcarbonate). When catechol **1** was reacted with allylic dicarbonate **2** in tetrahydrofuran at room temperature in the presence of the palladium(0) catalyst generated from $Pd_2(dba)_3$ (dba = dibenzylidene acetone) and dppb [dppb = 1,4-bis(diphenylphosphino)butane], 2-vinyl-1,4-benzodioxane **3** was obtained in 60 % chemical yield (Scheme 1).



1 **2** **3**

Scheme 1

In a similar manner 2-vinyl-1,4-naphtalenedioxane was obtained in 67 % yield using 2,3-dihydroxynaphtalene as the nucleophile.

The results obtained in the presence of chiral ligands and summarized in Table 1 reveal that the reaction did not occured in the presence of a 1,2-diphosphine such as Chiraphos or Norphos (entries 4-6). As expected

Table 1. Palladium(0)-Catalyzed Asymmetric Synthesis of 2-Vinyl-1,4-benzodioxane [a]

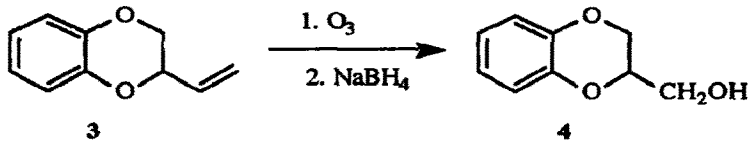
Entry	Ligand	Solvent	T °C	Yield (%) [b]	e.e. (%) [c]
1	(*S,S*) DIOP [d]	THF	25	72	0
2	(*S,S*) BDPP [e]	THF	25	63	14 (*R*)
3	(2*S*, 4*S*) BPPM [f]	THF	25	75	5 (*R*)
4	(2*S*, 3*S*) Chiraphos [g]	THF	25	0	-
5	"	THF	50	0	-
6	(*R, R*) Norphos [h]	THF	25	0	-
7	(*R, R*) BINAP [i]	THF	0	31	41 (*R*)
8	"	THF	25	70	37 (*R*)
9	"	THF	50	86	31 (*R*)
10	"	dioxane	25	62	40 (*R*)
11	"	dioxane	75	54	22 (*R*)
12	"	tetrahydropyrane	25	73	33 (*R*)
13	"	dimethoxyethane	25	45	45 (*R*)
14	"	C_6H_6	50	18	2 (*R*)
15	"	CH_2ClCH_2Cl	50	0	-
16	"	$CHCl_3$	25	45	43 (*R*) [j]

[a] All entries were carried out under N_2 in the presence of palladium catalyst prepared in situ by mixing $Pd_2(dba)_3$ and the corresponding ligand; [1]/[2]/[Pd]/[L] = 20/30/1/1. [b] Isolated yields after column chromatography and not optimized. [c] Determined by GPC analysis with a chiral stationary phase column (Chiraldex ™ GC Column, type B-PH, 30 m x 0.32 mm). Absolute configuration in brackets. [d] [(4*S*, 5*S*)-(2, 2-Dimethyl-1, 3-dioxolane--4, 5-diyl)bismethylene)]bis(diphenylphosphine). [e] (1*S*, 3*S*)-(1, 3-Dimethyl-1, 3-propanediyl)bis(diphenylphosphine). [f] (2*S*, 4*S*)-4-(Diphenylphosphino)-2-(diphenylphosphinomethyl)-1-pyrrolidinecarboxylic acid-1,1-dimethylethyl-ester. [g] (1*S*, 2*S*)-(1, 2-Dimethyl-1, 2-ethanediyl)bis(diphenylphosphine). [h] (2*R*, 3*R*) Bicyclo [2,2,1]hept-5-ene-2, 3-diylbis(diphenylphosphine). [i] (*R*)-(1, 1'-Binaphtalene)-2, 2'-diylbis(diphenylphosphine). [j] $[\alpha]^{20}_D = 4.5°$ (*c* = 1, $CHCl_3$)

the most stereoselective phosphine ligand is (*R*)-(1,1'-binaphtalene)-2,2'-diylbis(diphenylphosphine) [(*R*)-BINAP] with e.e. up to 45% obtained in the formation of **3**. As shown in Table 1, the temperature and the solvent have an important influence on the enantioselectivity of the cyclisation. In tetrahydrofuran (entries 7-9) or in dioxane (entries 10-11) a higher reaction temperature gives a lower enantioselectivity. Oxygenated solvents seem to give higher activity and enantioselectivity (e.e. up to 45% in dimethoxyethane) than other solvents, although chloroform leads to **3** with 45% e.e.

The absolute configuration of compound **3** was determined by correlation with the known 2-hydroxymethyl-1,4-benzodioxane **4** (Scheme 2).[2,3] Transformation of **3** ($[\alpha]^{20}_D = 4.5°$) to **4** was carried out

by ozonolysis followed by reduction with sodium borohydride (80 % chemical yield), which turned out to be the (*R*)-isomer by measurement of the optical rotation ($[\alpha]^{20}_D = 7.5°$, $c = 0.5$, C_2H_5OH). It follows that the 2-vinyl-1,4-benzodioxane **3** obtained by cyclisation in entry 16 has the absolute configuration *(R)*.



3 **4**

Scheme 2

The reaction pathway involves a first nucleophilic allylic substitution of the catechol **1** on a π-allyl intermediate generated by the reaction of **2** with a palladium(0) species followed by an intramolecular attack of the second hydroxyl group on the new π-allyl system formed producing the benzodioxane **3**.

In conclusion chiral 2-vinyl-1,4-benzodioxane could be obtained by palladium-catalyzed tandem allylic substitution reactions in the presence of a chiral ligand. This methodology is now being extended to other heterocycles.

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