Palladium-Catalyzed Allylic Substitution in γ-Oxygenated Vinyl Sulfones: One-Step Synthesis of Tetrasubstituted Dihydrofurans

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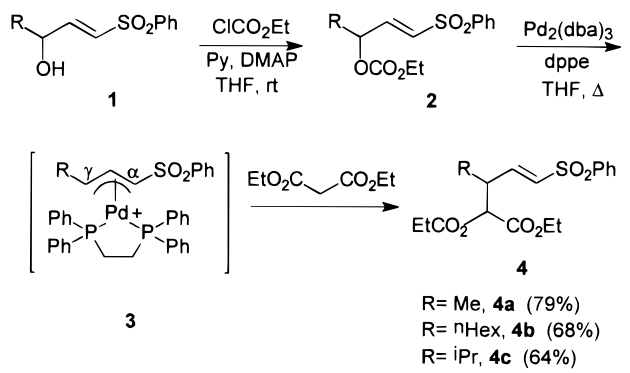
Received May 15, 1997 (Revised Manuscript Received July 14, 1997)

One of the most synthetically useful processes involving palladium-catalyzed reactions is the nucleophilic substitution of allylic alcohols and derivatives *via* their π-allylpalladium complexes. Both the regioselectivity and stereoselectivity of the reaction as well as the nature of the nucleophilic partners have been widely studied.[1] However, unlike allylic alcohols substituted with alkyl, aryl, or donating substituents, those substituted with electron-withdrawing groups at the double bond have been much less studied[2] because of their lower reactivity toward the palladium catalysts and their high tendency to undergo conjugate addition of the nucleophile.

Earlier work in our laboratory showed that γ-oxygenated vinyl sulfones are versatile intermediates in organic synthesis, mainly because they undergo highly stereoselective conjugate additions of a variety of nucleophiles.[3] We report here our preliminary results on their palladium-catalyzed allylic substitution with carbon nucleophiles, to give a new γ-substituted vinyl sulfone which could be used in further stereoselective conjugate additions. To the best of our knowledge, the only previous studies dealing with metal promoted allylic substitutions in this type of vinyl sulfones have been recently reported by Enders et al. who described the stoichiometric reaction of their cationic tetracarbonyl(η^3-allyl)iron derivatives with nucleophiles.[4]

The starting γ-hydroxy vinyl sulfones **1** were readily prepared by our usual one-step procedure based on the condensation of phenylsulfonyl arylsulfinyl methanes with aldehydes, followed by *in situ* olefin migration and sulfoxide−sulfenate [2,3] sigmatropic rearrangement.[5] However the reaction of their allylic acetates or chloroacetates with sodium diethyl malonate in THF at rt or reflux in the presence of $Pd_2(dba)_3$ (5 mol %) and a variety of ligands[6] afforded almost exclusively the Michael adducts, showing that the conjugate addition to the vinyl sulfone was much faster than the formation of the π-allylpalladium intermediate.

Scheme 1



Taking into account the impossibility of forming the π-allylpalladium complex when the malonate anion is present, we focused our attention on the use of their carbonates **2** (Tsuji's method),[7] which were readily prepared in high yield by reaction **1** with ethyl chloroformate (pyridine, DMAP, THF, rt).[2a] These substrates would allow to carry out the reaction in the presence of diethyl malonate instead of malonate anion, generating *in situ* the required nucleophile only after oxidative addition of Pd(0) to the allyl carbonate **2** with consequent formation of the π-allylpalladium intermediate and release of the alkoxide, which would then deprotonate the malonate.

We were pleased to find that the reaction of **2** with diethyl malonate in the presence of $Pd_2(dba)_3$ (5 mol %), dppe (20 mol %) as ligand,[8] and molecular sieves (4 Å)[9] in THF at reflux afforded exclusively the γ-substituted products **4**, which were isolated in good yields after chromatography (64−79%). Hence, under these conditions the nucleophile reacts with the intermediate π-allylpalladium complex **3** rather than adds to another molecule of **2**. Furthermore, the reactions were completely regioselective, with the nucleophile attacking at the γ-position of complexes **3** regardless of the steric size of the R group (Scheme 1).

Next, we extend this reaction to other soft carbon nucleophiles such as β-keto esters and 1,3-diketones (Table 1). Surprisingly, instead of the expected γ-substituted acyclic compounds **5**, tetrasubstituted dihydrofurans **6**−**8** were obtained as the major products. These results indicate that a tandem process, based on an initial γ-allylic substitution followed by cyclization of **5** *via* an intramolecular conjugate addition of its enol tautomer (or enolate) to the vinyl sulfone moiety, had taken place.[10] Dihydrofurans **6**−**8** were isolated in good yields (54−79% after chromatographic purification) excepting the case of

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(1) For some recent reviews, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Williams, J. M. J. *Synlett* **1996**, 705. (c) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: New York, 1995; p 290−422.

(2) For palladium-catalyzed allylic substitutions in γ-oxygenated-α,β-unsaturated esters, see: (a) Tanikaga, R.; Jun, T. X.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1185. (b) Tsuda, T.; Horii, Y.; Nakagawa, Y.; Ishida, T.; Saegusa, T. *J. Org. Chem.* **1989**, *54*, 977. (c) Tanikaga, R.; Takeuchi, J.; Takyu, M.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1987**, 386. (d) Tsuji, J.; Ueno, H.; Kobayashi, Y.; Okumoto, H. *Tetrahedron Lett.* **1981**, *22*, 2573.

(3) (a) Adrio, J.; Carretero, J. C.; Gómez Arrayás, R. *Synlett* **1996**, 640. (b) Carretero, J. C.; Gómez Arrayás, R.; Storch, I. *Tetrahedron Lett.* **1996**, *37*, 3379. (c) Carretero, J. C.; Gómez Arrayás, R. *J. Org. Chem.* **1995**, *60*, 6000. (d) De Blas, J.; Carretero, J. C.; Domínguez, E. *Tetrahedron Lett.* **1994**, *35*, 4603. (e) Domínguez, E.; Carretero, J. C. *Tetrahedron* **1994**, *50*, 7557.

(4) (a) Enders, D.; Jandeleit, B.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1949. (b) Enders, D.; Von Berg, S.; Jandeleit, B. *Synlett* **1996**, 18.

(5) (a) Domínguez, E.; Carretero, J. C. *Tetrahedron* **1990**, *46*, 7197. (b) Trost, B. M.; Grese, T. A. *J. Org. Chem.* **1991**, *56*, 3189.

(6) PPh_3, dppe, dppp and $P(OEt)_3$ were used as ligands.

(7) (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523. (b) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809.

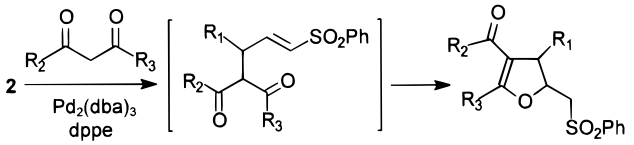
(8) Although other ligands, such as PPh_3, dppp, dppf and neocuproine were also tested, the best yields were obtained in the presence of dppe.

(9) A significant decrease in the yields of the γ-substituted products was observed when the reactions were performed in the absence of molecular sieves due to the competitive hydrolysis of the carbonates **2** to the corresponding alcohols **1**.

(10) For other recent synthesis of dihydrofurans based on tandem processes, see: (a) Lee, Y. R.; Kim, B. S. *Tetrahedron Lett.* **1997**, *38*, 2095. (b) Hagiwara, H.; Sato, K.; Suzuki, T.; Ando, M. *Tetrahedron Lett.* **1997**, *38*, 2103. (c) Hayashi, T.; Yamane, M.; Ohno, A. *J. Org. Chem.* **1997**, *62*, 204. (d) Hayashi, T.; Ohno, A.; Lu, S.-J.; Matsumoto, Y.; Fukuyo, E.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 4221.

S0022-3263(97)00864-5 CCC: $14.00

Table 1. Palladium-Catalyzed Reaction of Carbonates 2 with β-Keto Esters and 1,3-Diketones[a]



	substrate		nucleophile		product		
entry	**2**	R_1	R_2	R_3		*trans*/*cis*[b]	% yield[c]
1	**2a**	Me	OEt	Me	**6a**	78/22	76[e]
2	**2b**	*n*-Hex	OEt	Me	**6b**	>98/<2	79
3[d]	**2c**	*i*-Pr	OEt	Me	**6c**	>98/<2	38
4	**2a**	Me	Me	Me	**7a**	75/25	79[e]
5	**2b**	*n*-Hex	Me	Me	**7b**	>98/<2	67
6	**2c**	*i*-Pr	Me	Me	**7c**	>98/<2	14
7	**2a**	Me	OEt	Ph	**8a**	83/17	63[e]
8	**2b**	*n*-Hex	OEt	Ph	**8b**	>98/<2	57
9	**2c**	*i*-Pr	OEt	Ph	**8c**	>98/<2	18[b]

[a] Reaction conditions: **2**, $R_2COCH_2COR_3$ (4 equiv), $Pd_2(dba)_3$ (5 mol %), dppe (20 mol %), powdered molecular sieves[9] 4 Å (20 mg/mL) in 1:1 mixture of THF−toluene (0.1 M solution of **2**) at 100 °C. [b] Determined by ^{1}H-NMR on the crude mixtures. [c] In pure product after silica gel chromatography. [d] In this case the reaction was carried out in THF at reflux. [e] The *cis*+*trans* mixture could not be separated by chromatography.

the bulkiest substrate, **2c** (R_1 = ^{i}Pr), which afforded much lower yields (14−38%, entries 3, 6, and 9).[11] A second important issue concerns the stereoselectivity of the cyclizations. These occurred in all cases in a *trans*-stereoselective manner, but whereas the stereocontrol was almost complete from substrates **2b** and **2c** (R_1 = ^{n}Hex or ^{i}Pr, de ≥ 96%) the stereoselectivity was significantly lower from **2a** (R_1 = Me, de = 50−66%).[12]

By performing the palladium-catalyzed reaction of **2a** with ethyl acetoacetate under milder conditions (26 h at rt), we could isolate a mixture of the acyclic intermediate **5a** and the dihydrofuran **6a**, which were separated by chromatography (43% and 25% yield, respectively). With intermediate **5a** in hand no cyclization at all was observed in the absence of the phosphine both in the absence and in the presence of $Pd_2(dba)_3$. In contrast, the cyclization of **5a** into **6a** occurred in some extent in the presence of dppe (20 mol %) but in the absence of the palladium catalyst, although at a slower rate (70% conversion in THF at 68 °C for 5 h) than the reaction in the presence of both dppe (20 mol %) and $Pd_2(dba)_3$ (5 mol %) (100% conversion after 2 h in THF at 68 °C). These results suggest that the cyclization step is both a phosphine- and a palladium-catalyzed reaction, playing the phosphine the most important role.[13]

In summary, a convergent and stereoselective one-step synthesis of highly substituted dihydrofurans by Pd(0)-catalyzed reaction of the carbonates of γ-hydroxy vinyl sulfones (**2**) with β-keto esters and 1,3-diketones has been described. Since vinyl sulfones **1** can be readily prepared in enantiomerically pure form,[14] this method should provide a general new access to enantiopure tetrasubstituted tetrahydrofurans. This point as well as more detailed mechanistic studies are currently being investigated in our laboratory.

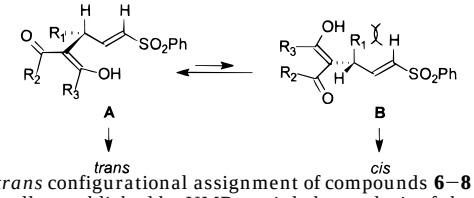
Acknowledgment. Financial support from Dirección General de Investigación Científica y Técnica (Grant No. PB93-244) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data of the new compounds (7 pages).

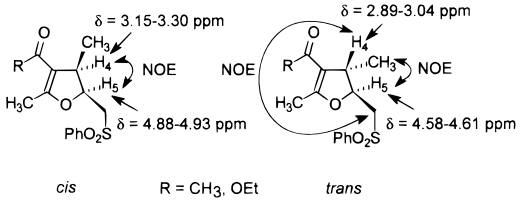
JO970864B

(11) Substrate **2c** reacted to give a mixture of products, predominating the formation of 4-methyl-1-benzenesulfonyl-1,3-pentadiene (24−37% yield) likely due to the competitive β-elimination process on the π-allylpalladium intermediate.

(12) The high *trans*-stereoselectivity can be explained on the basis of the major participation of the conformation **A**, which minimizes the allylic 1,3-strain between α and γ positions (see, Hoffmann, R. W. *Chem Rev.* **1989**, *89*, 1841). This model can also explain that the stereoselectivity increases as the size of the R_1 chain increases.



The *cis*/*trans* configurational assignment of compounds **6**−**8** has been unequivocally established by NMR, mainly by analysis of the chemical shifts of H_4 and H_5 (δ *cis* > δ *trans*) and by NOESY experiments (see figures below; data in $CDCl_3$).



(13) The phosphine could act as catalyst by means of its conjugate addition to the α,β-unsaturated sulfone to form a zwitterionic intermediate, which would deprotonate the acid hydrogen of another molecule of **5a** to form the enolate that would cyclize into **6a** by intramolecular conjugate addition. On the other hand, the role of $Pd_2(dba)_3$ in this cyclization step may be due to its reversible coordination with the double bond, thus activating the conjugate addition of either the phosphine or the formed enolate. For metal-promoted Michael reactions requiring the presence of free phosphine, see: Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553 (and references cited therein). For some recent phosphine-catalyzed nucleophile additions, see: (a) Zhang, C.; Lu, X. *Synlett* **1995**, 645. (b) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819.

(14) Carretero, J. C.; Domínguez, E. *J. Org. Chem.* **1992**, *57*, 3867.