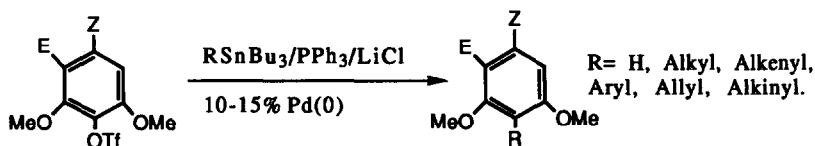


Palladium catalyzed cross-coupling of phenol triflates with organostannanes. A versatile approach for the synthesis of substituted resorcinol dimethyl ethers.

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Abstract.-2,6 Dimethoxy-substituted phenol triflates undergo efficient Pd(0) catalyzed cross coupling with organostannanes, thus providing an easy access to substituted resorcinol dimethyl ethers, a common building block of many aromatic polyketides.

The substituted resorcinol unit is a basic building block of a rather large number of valuable naturally occurring polyketide metabolites.¹ In spite of this skeleton being so simple there is no rational synthetic approach available for a rapid and flexible access to these important target molecules. We have now devised a concise and straightforward approach which allows for the synthesis of aromatic polyketides starting from easily available shikimic acid-type metabolites. As illustrated in Scheme 1, center to our plan was the introduction of several rests such as hydrogen, alkyl, vinyl, allyl, aryl, etc in place of the existing -OH group of 2,6-dimethoxy-substituted phenols.²



Scheme 1

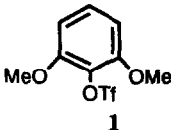
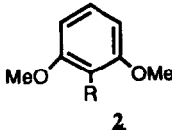
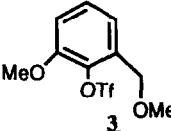
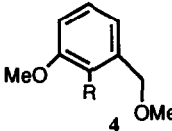
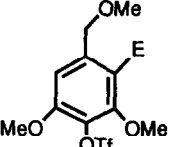
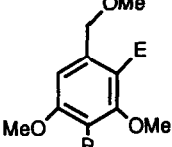
We have recently demonstrated that substituted 2,6-dimethoxyphenol triflates can undergo Pd(0) catalyzed reductive cleavage to the corresponding resorcinol dimethylethers, thereby suggesting that the targeted cross-couplings could be achieved.³ However, there was left a major question to be answered, namely whether or not the predicted unreactivity of 2,6-disubstituted aryl halides in Pd(0)

catalyzed cross-coupling reaction with organomagnesium compounds⁴ would also hold for the closely related deoxygenation reactions of aryl triflates catalyzed by Pd(0).⁵

In this report we would like to describe our preliminary results concerning the implementation of our objective, i.e. highly hindered phenol triflates easily derived⁶ from starting materials of shikimic acid origin, undergo Pd(0) catalyzed cross-coupling with a variety of organostannanes (methyl, vinyl, allyl, aryl, alkynyl) in medium to good yields, though alkyl groups other than methyl could not be introduced due to competitive β elimination. In spite of the wealth of publications⁵ on the subject appeared during the last two or three years, to our knowledge, no attempts have been made at studying these otherwise very important highly encumbered substrates, no doubt due to the well-known reluctance of aromatics substituted with electron-donating groups to undergo palladium catalyzed reactions.⁷

The salient features of the present study, for which we have employed model triflates **1**, **3**, **5**, **7** and **9** are collected in Table 1.⁸ In most cases, the best catalytic system found involved the use of (PPh₃)₂PdCl₂ (0.1-0.15 molar)/PPh₃ (0.4 molar)/LiCl (8 molar)/refluxing DMF (optimum conditions have been determined in regard with the following variables: palladium catalyst, phosphine ligand and added lithium chloride). Contrary to the standard conditions reported by Stille,^{5a} in our case the phosphine played a key role, as demonstrated by the fact that in its absence type **1** compounds did not cross couple. Moreover, for most cases triphenylphosphine worked best, followed by bisphosphines such as 1,1'-bis(diphenylphosphino)ferrocene (dppf), 1,3-bis(diphenylphosphino)propane (dppp) and 1,2-bis(diphenylphosphino)ethane (dppe).

Most interesting, whereas chemoselective cross-coupling (OTf vs. Cl, entry 12) was observed for the conversion of **5** -> **6a**, the inverse was true for the bromo derivative **7** (OTf vs. Br) which yielded **8c** though only by working (no LiCl added) with a limited quantity of palladium (1.5% molar). Actually, the use of 10% molar amount of palladium (LiCl added) produced the doubly allylated **8cc** (entry 13). Regioselectivity (OTf vs. Br) was not significantly modified by changing the catalyst [Pd(PPh₃)₄], in contrast with the results of Stille et al.^{5a, 5b} Furthermore, the reported^{5a} isomerization of the allyl group was not observed with our substrates (entries 3, 9, 11), a result which, in our view, might be of enormous synthetic value. It is also noteworthy to remark that all attempts (not shown) at reacting the above substrates **1** and **3** with alkenes (such as methyl vinyl ketone) or acetylenes (such as phenylethyne) under the conditions reported by Heck and others⁹ invariably led to the recovery of starting material. These observations are in accordance with the recently reported unreactivity of a highly congested bromo derivative in a similar reaction.^{10b} Somewhat as expected, the more reactive iodo compounds react.¹⁰

Entry	Substrate	Organostannane	Product (Yield, ^a %)
	 1	$\xrightarrow{\text{RSnBu}_3}$	 2
1	1	R= Me ^b	2a (92%)
2	1	R= Ph	2b (74%)
3	1	R= CH ₂ CH=CH ₂	2c (84%)
4	1	R= CH=CH ₂	2d (85%)
5	1	R= C=C-Ph	2e (50%)
6	1	R= n-Bu	2f (0%) ^c
	 3	$\xrightarrow{\text{RSnBu}_3}$	 4
7	3	R= Me	4a (96%)
8	3	R= Ph	4b (79%)
9	3	R= CH ₂ CH=CH ₂	4c (98%)
10	3	R= CH=CH ₂	4d (90%)
	 5, 7, 9	$\xrightarrow{\text{RSnBu}_3}$	 6, 8, 10
11	5 E= Cl	R= CH ₂ CH=CH ₂	6a E= Cl; R= CH ₂ CH=CH ₂ (63%)
12	7 E= Br	R= CH ₂ CH=CH ₂	8c E= CH ₂ CH=CH ₂ ; R= OTf (55%) ^{d,e}
13	7 E= Br	R= CH ₂ CH=CH ₂	8cc E= R= CH ₂ CH=CH ₂ (47%) ^e
14	9 E= SMe	R= Me	10a E= SMe; R= Me (58%)

a) Isolated yields. b) Me₄Sn was used .c) An 86% yield of deoxygenated material (R= H) was obtained. d) A limited quantity of Pd (1.5%) was employed. e)Unoptimized yield.

Table 1

Although it is clearly premature to advance a detailed mechanistic overview of the reaction, we speculate that perhaps the rate determining step might be the reductive elimination (of the associative type).¹¹ This is borne out by two facts: 1) the strict need of triphenylphosphine for the cross-couplings of type **1** substrates, and 2) the exceedingly faster reactions undergone by substrates **3** and **7** (compared to **1**), both possessing a coordinating side arm capable of intervening in the key elimination step (actually the strict requirement of triphenylphosphine for **1** is not applicable for **3** and **7**).

The application of this simple methodology for the synthesis of naturally occurring polyketides is underway.

Acknowledgement.-Financial support by the DCICYT (Project B87/0019) is gratefully acknowledged. One of us (G.M.) warmly thanks the Ministry of Education and Science (Spain) for a predoctoral fellowship.

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(Received in UK 8 March 1990)