Stereoselective Phenylation of Allylic Alcohol Derivatives by Palladium-Catalyzed Cross-Coupling with Hypervalent Silicon Complexes†

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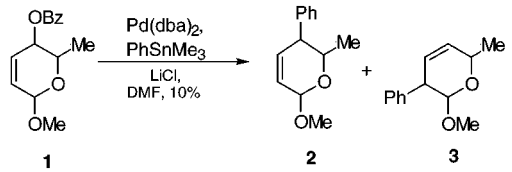
Palladium-catalyzed alkylation of allylic alcohol derivatives has been widely used in organic synthesis.[1] We and Curran have recently reported Pd-catalyzed reactions of dihydropyran derivatives in the synthesis of biologically active compounds such as pseudomonic acid A.[2] During the course of our studies, it was observed, however, that phenylstannanes did not couple efficiently to dihydropyran derivatives, such as **1** (Scheme 1). For example, Stille coupling[3] of pyran **1** with phenyltributylstannane gave <10% of dihydropyrans **2** and **3**. Homocoupling of the tin reagent led to the major product in the reaction mixture. Extensive experimentation did not improve the yields of phenylated materials.

Tin derivatives have several serious limitations as reagents for applications in cross-coupling reactions. Stille noted that the reactivity of the tin reagent is strongly affected by the nature of the substituents attached to tin.[3] As a practical concern, tin(IV) derivatives are also toxic, and the removal of tin byproducts is problematic. Recently, Fouquet has shown that stannylene derivatives can be employed in Pd(0)-catalyzed coupling reactions because these reagents yield tin byproducts that are easily removed from the reaction mixture.[4] An alternative strategy for the removal of tin reagents and byproducts has been reported by Curran using fluorous workup procedures.[5]

Legros and Fiaud have reported that tetraphenylborate underwent coupling with allylic alcohol derivatives in the presence of a Pd catalyst to afford phenylated adducts in good yields.[6]

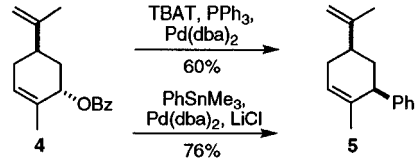
Hiyama and Hatanaka have studied fluoride-promoted cross-coupling of aryl- or vinylchloro- and fluorosilanes and allylic alcohol derivatives.[7] Aryl, vinyl, allyl, and alkyl

Scheme 1



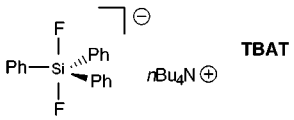
1 **2** **3**

Scheme 2



4 **5**

groups have been coupled under these conditions, and Hiyama has postulated that these cross-couplings proceed



through a pentavalent silicate complex.[8] Hiyama's *in situ* preparation of fluorosilicates followed by Pd-catalyzed cross coupling has three limitations: (1) the synthesis of fluorosilanes is a multistep process, (2) the polyfluorosilane derivatives are hydrolytically unstable, and (3) reaction conditions of the coupling protocol are strongly basic, precluding the use of base-sensitive functionalities.

In an effort to develop an efficient phenylation protocol for allylic alcohol derivatives employing silane rather than stannane reagents, the Pd(0)-catalyzed reaction of stable fluorosilicate complexes such as tetrabutylammonium triphenyldifluorosilicate (TBAT) was investigated. There are several attractive properties of fluorosilicates as transmetalating agents. For example, tetrabutylammonium triphenyldifluorosilicate (TBAT) is an air-stable, nonhygroscopic, nontoxic crystalline material. Previous studies have demonstrated that TBAT is an efficient fluoride source in organic synthesis,[9] and here we report that it is also an effective phenylation reagent in Pd-catalyzed coupling reactions.

A typical example of this process is shown in Scheme 2. The conditions for the coupling are 5 mol % of both $Pd(dba)_2$ and PPh_3 and 2 equiv of TBAT in refluxing THF for 12 h. In contrast, standard conditions for the coupling with phenyltrimethylstannane (1.3 equiv) are 3 equiv of LiCl, 5 mol % of $Pd(dba)_2$ in DMF at rt for 24−48 h.[3]

It should be noted that 1 equiv of phosphine is tolerated in the TBAT reaction, whereas phosphine strongly inhibits the reaction with tin reagents.[3] Excess phosphine completely inhibits the TBAT coupling. Substitution of various phosphine ligands for triphenylphosphine was also investigated. Although electron-deficient phosphines enhance the cross-coupling in Stille coupling,[1d] we found coupling using TBAT failed with 2-trifurylphosphine. Electron-rich phosphines such as dppe and PPh_3 provided the highest yields of phenylated adducts, while low yields of products were obtained with highly nucleophilic *n*-tributylphosphine. Reduced yields of phenylation products were obtained with any of the typical Pd(0) sources ($Pd(PPh_3)_4$, $Pd(dppe)_2$, or $PdCl_2(CH_3CN)_2$) under these conditions.

To assess the stereoselectivity in Pd-catalyzed cross-coupling, the following substrates were tested under the optimized conditions (vide supra). Benzoate **4** was converted to *cis*-arene **5** in 60% yield (Scheme 2). The *cis*-benzoate (not shown) was transformed into the *trans*-alkene. As

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† Dedicated to Carl Johnson on the occasion of his 60th birthday.

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(4) Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242−5243.

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(7) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.*, **1994**, *66*, 1471−1478 and references therein.

(8) Preformed pentavalent silicates have been shown to couple with 4′-iodoacetophenone but not allylic substrates. The stereoselectivity has been studied with respect to double-bond geometry in acyclic alcohol derivatives and in chiral silane derivatives coupled to aryl substrates but not with respect to the leaving group in cyclic allylic alcohol derivatives. See ref 5 and references therein for additional details.

(9) (a) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166−5167. (b) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901−6905. TBAT is commercially available from Aldrich Chemical Co. and Eburon Chemicals.

S0022-3263(98)00069-3 CCC: $15.00
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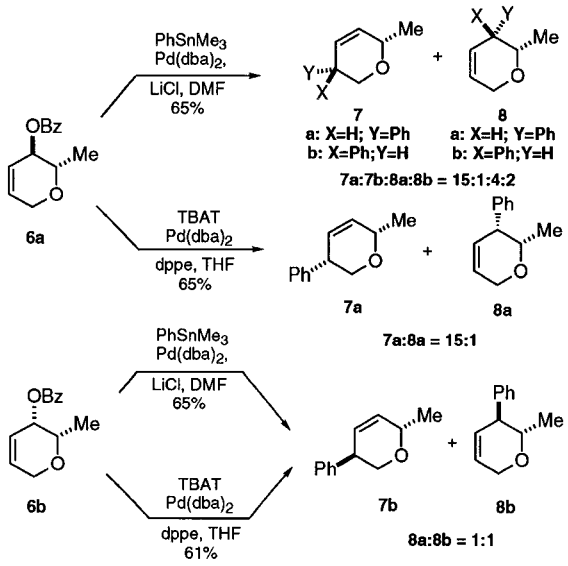
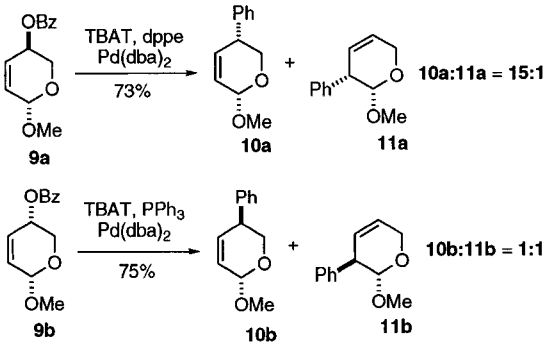
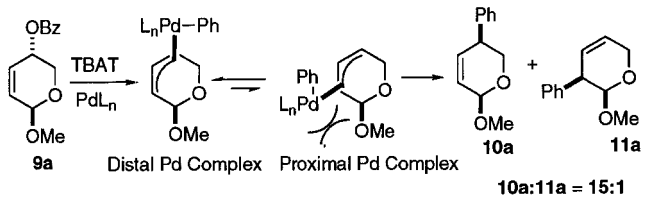
Scheme 3



Scheme 4



Scheme 5



anticipated, alkene **5** was produced with complete inversion of stereochemistry irrespective of whether tin or silicate reagents were employed.[1,3,10] Phenylation using phenyltrimethylstannane gave slightly higher yields than TBAT phenylation in this system, but removal of the tin byproducts was again problematic.

Phenylation of benzoates **6a**,**b** (Scheme 3) was also studied, and in this system, TBAT was shown to be significantly more stereoselective than the stannane derivatives in the coupling reaction. As shown in Scheme 3, coupling of phenyltrimethylstannane with benzoate **6a** gave a mixture of all possible regio- and stereoisomers **7a**−**d**, while the silicate derivative gave exclusively the products of inversion of configuration. We attribute the loss of stereoselectivity in the tin coupling to intermediacy of a "distorted" π-allyl palladium intermediate[11] and the slow transmetalation from tin to the π-allyl complex. Under these conditions, when transmetalation from tin to palladium is slow, the initially formed π-allyl palladium complex reacts with Pd(0), resulting in formation of the diastereomeric Pd-complex.[12]

Phenylation of benzoate **6b**, in which there is a "symmetrical" π-allyl palladium complex as an intermediate, occurred without loss of stereoselectivity with both the tin and silicate reagent presumably due to facile transmetalation from tin/silicon to palladium for the intermediate π-allyl complex.

The generality of utilizing TBAT rather than tin reagents as the aryl donor in Pd-catalyzed cross-coupling reactions was further demonstrated using benzoates **9a**,**b** as summarized in Scheme 4. As in the results shown above, phenylation occurred with complete stereoselectivity with both **9a** and **9b** to provide a mixture of regioisomeric pyrans **10** and **11**. Again, one of the isomers, benzoate **9a**, displayed excellent regioselectivity in the phenylation process, while the other isomer gave no selectivity in the coupling reaction.

The high degree of regioselectivity in the phenylation of dihydropyran derivatives **6** and **9** can be explained by invoking "distorted" and "nondistorted" π-allyl Pd-complexes.[11] Examination of the Pd-complexes that precede reductive elimination showed that **9a** must proceed through a cis-distal ("distorted") Pd complex (Scheme 5). The distal π-allyl Pd complex is favored because it avoids the steric interactions between Pd and methoxy present in the proximal Pd complex. The preference for the distal Pd complex explains the high degree of regioselectivity for the phenylation of **9a** to give **10a** as the major product.

On the other hand, **9b** proceeds through a trans-Pd complex in which Pd and methoxy are on the opposite side of the ring and no steric interaction occurs between these two groups. Thus, the reaction proceeds through a symmetrical Pd complex. This symmetrical complex shows no preference for either the proximal or distal Pd complex and explains the lack of regioselectivity in the phenylation of *cis*-benzoate **9b**. The high degree of regioselectivity using trans-substrates and the absence of regioselectivity with cis-substrates is a general trend in these reactions (*vide infra*) that has been noted in other Pd-catalyzed reactions in our laboratory.[11]

The use of dppe as the Pd ligand is essential to maintaining the stereochemistry of *trans*-benzoates such as **9b**. Bäckvall has previously shown that the ligand change from PPh_3 to dppe minimizes the loss of stereochemistry when adding stabilized carbon nucleophiles and amines to allylic alcohol substrates.[12] However, Stille has shown that the Pd-catalyzed phenylation of allylic alcohol derivatives using stannanes is inhibited by the presence of phosphine.[3] Therefore, the ability of TBAT to cross-couple in the presence of phosphines makes the cross-coupling of pentavalent silicates superior to stannanes.

In summary, the hypervalent silicate complex TBAT has been shown to be a highly effective reagent for the phenylation of allylic benzoates. The Pd-catalyzed phenylations with TBAT are completely stereoselective with inversion of configuration and occur under mild reaction conditions. With certain substrates, the phenylations occur with excellent regioselectivity as well. The mild reaction conditions, availability of the silicate reagent, low toxicity of the silicates, and complete stereoselectivity of phenylation means that this protocol is superior to its tin counterpart.

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Supporting Information Available: Experimental procedures and spectral data for all novel compounds (5 pages).

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(10) Although the reaction occurred with complete inversion of stereochemistry with regard to the isopropylidene group, it should be noted that the absolute stereochemistry of the molecule was lost during the phenylation due to intermediacy of the achiral π-allyl complex.

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