



Chemoselectivity in the Kosugi-Migita-Stille coupling of bromophenyl triflates and bromo-nitrophenyl triflates with (ethenyl)tributyltin

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ABSTRACT

Kosugi-Migita-Stille cross coupling reactions of (ethenyl)tributyltin with all isomeric permutations of bromophenyl triflate and bromo-nitrophenyl triflate were examined in order to determine the chemoselectivity of carbon-bromine versus carbon-triflate bond coupling under different reaction conditions. In general, highly selective carbon-bromine bond cross couplings were observed using for example bis(triphenylphosphine)palladium dichloride (2 mol-%) in 1,4-dioxane at reflux. In contrast, reactions using the same pre-catalyst but in the presence of a three-fold excess of lithium chloride in *N,N*-dimethylformamide at ambient temperature were in most cases selective for coupling at the carbon-triflate bond. Overall, isolated yields and the selectivity for carbon-bromine bond coupling were significantly higher compared to carbon-triflate bond coupling.

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1. Introduction

The reactivity order usually observed in palladium catalyzed coupling reactions of aromatic halides is $I > Br \sim OTf > Cl > F$ ^{1,2} and it parallels the rate of oxidative addition of tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) to aromatic halides as established by Fitton and Rick in 1971.³ In Echavarren and Stille's seminal work on palladium catalyzed cross coupling reactions of organotin reagents with aromatic triflates, the chemoselectivity of carbon-bromine (C-Br) versus carbon-triflate (C-OTf) coupling of 4-bromophenyl triflate (**1**) with (ethenyl)tributyltin was dramatically modulated by proper choice of reaction conditions and additives.⁴ For example, treatment of 4-bromophenyl triflate (**1**) with (ethenyl)tributyltin in 1,4-dioxane in the presence of $Pd(PPh_3)_4$ at reflux gave product **2** derived from a highly selective oxidative addition to the C-Br bond (Scheme 1).⁵ In contrast, using bis(triphenylphosphine)palladium dichloride ($PdCl_2(PPh_3)_2$) as the catalyst precursor, in the presence of a three-fold excess of lithium chloride in *N,N*-dimethylformamide (DMF) at 24 °C, afforded selectively product **3** derived from oxidative addition to the C-OTf bond (Scheme 1).⁶ Furthermore, a completely selective cross coupling at the iodine bearing carbon was observed for 4-iodophenyl triflate even in the presence of lithium chloride.⁷

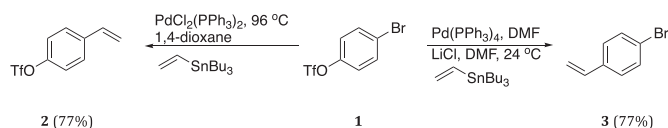
Echavarren and Stille thus established the overall reactivity order for cross coupling reactions of organotin reagents in the absence of LiCl as $I > Br > OTf > Cl$ and in the presence of LiCl as $I > OTf > Br > Cl$. This reactivity order should be used with some caution since the catalyst system can be tailored so that C-Cl coupling dominates over C-OTf. For example, treatment of 4-chlorophenyl triflate with (phenyl)tributyltin in the presence of tris(dibenzylideneacetone)dipalladium - bis(tri-*tert*-butylphosphine)palladium and cesium fluoride in 1,4-dioxane, at ambient temperature, gave exclusively the C-Cl coupling product **2**.^{8,9}

The change in selectivity in the presence of added LiCl is most likely due to more than one factor. An increase in the rate of oxidative addition has been observed upon addition of LiCl. The apparent rate (K_{app}) of oxidative addition of $Pd(PPh_3)_4$ to phenyl triflate in DMF at 20 °C was shown to increase nineteen-fold going from 0 to 150 equivalents of LiCl.¹⁰ In contrast, less than a two-fold change in K_{app} was observed using the more reactive 4-nitrophenyl triflate under the same reaction conditions. Thus, added LiCl accelerates the rate of oxidative addition but the magnitude of acceleration depends on additional functional groups present in the molecule.¹¹

In addition to an increased rate of oxidative addition, the effect of added chloride ions has been attributed to a chloride – triflate metathesis of the intermediate $Ar-Pd-OTf$ complex, i.e. $Ar-Pd-OTf$ to $Ar-Pd-Cl$, followed by a rapid transmetalation and reductive elimination.¹² For example, Jutand and Maes et al. have shown that transmetalation of tin reagents are faster for pyridyl- $Pd-Cl$

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Scheme 1. Kosugi-Migita-Stille cross coupling of **1** with (ethenyl)tributyltin.

complexes compared to pyridyl-Pd-I complexes.¹³ In a similar fashion, Casado and Espinet reported that transmetalation – reductive elimination from isolated *trans*-[3,5-dichloro-2,4,6-trifluorophenyl-Pd-X(AsPh₃)₂] complexes were in the order X = Cl > Br > I.¹⁴

In addition to the group being replaced, the rate of reaction depends on the electronic nature of additional substituents on the aromatic ring. Milstein and Stille reported an almost ninety-fold difference in the relative reaction rate in reactions of tetramethyltin with 4-methoxy-1-bromobenzene (1) < 4-methyl-1-bromobenzene (1.46) < bromobenzene (2.18) < 4-trifluoromethyl-1-bromobenzene (19.5) < 3-nitro-1-bromobenzene (87.9) in hexamethylphosphoramide (HMPA) at 63 °C using BnPd(PPh₃)₂Cl as the pre-catalyst.¹⁵ These results clearly demonstrate the significant rate accelerating effect of the electron withdrawing nitro group even when not in conjugation with the site of the oxidative addition. In a similar fashion, the usually unreactive aryl fluorides can participate in Kosugi-Migita-Stille couplings in the presence of two electron withdrawing groups. For example, cross couplings of 4-fluoro-3-nitrobenzaldehyde and 4-fluoro-3-nitrobenzonitrile with (ethenyl)tributyltin have been reported.^{16,17}

A chemoselective sequential introduction of two different alkenes was of interest to us for the synthesis of dinitro-dialkenylbenzenes, substrates suitable for a palladium catalyzed double reductive cyclization en route to pyrroloindoles. It was envisioned that the chemoselectivity observed by Echavarren and Stille would enable us to prepare a variety of cyclization precursors containing two different alkenes. Thus, 2,4-dinitro-5-bromophenyl triflate (**5**) was prepared in good yield by dinitration of 3-bromophenyl triflate (**4**) (Scheme 2). Treatment of **5** with (ethenyl)tributyltin under the Echavarren-Stille conditions described above that should result in oxidative addition to the C-OTf bond did not afford any identifiable coupling product. The solvent was changed from DMF to toluene in order to simplify the work up and the analysis of the crude ¹H NMR spectrum. A small amount of 2,6-di-*tert*-butyl-4-methylphenol (DTBMP) was added as a radical inhibitor. No reaction occurred at ambient temperature, however the starting material was completely consumed within 17 h when the reaction temperature was increased to 80 °C. The ¹H NMR spectrum of the resulting crude reaction mixture contained three alkenyl proton resonances suggesting a single coupling product. Surprisingly, a quartet resonance in the ¹³C NMR (*J* = 320 Hz) spectrum and a resonance at –72.9 ppm in the ¹⁹F NMR spectrum indicated the presence of an intact triflate group. The crude product was purified by chromatography to afford **6** in good isolated yield.

The site selectivity of palladium catalyzed coupling reactions of benzenes having two electrophilic centers depends on the position of additional functional groups present in the substrate. However, the two potential coupling sites in **5** should be similar if not equally

activated for oxidative addition by the two electron withdrawing nitro groups. In addition, the steric environments should be more or less equivalent since both sites have an *ortho*-nitro group and they are separated by an unsubstituted position. Thus, the absence of any apparent reaction at ambient temperature and the failure to obtain the expected C-OTf bond coupling product from **5**, under the reaction conditions reported to be selective for triflate coupling, were puzzling.

To the best of our knowledge, there is no reported systematic study on the chemoselectivity in Kosugi-Migita-Stille couplings of substituted bromophenyl triflates.

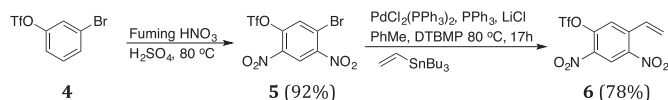
Herein is described a detailed study of the selectivity observed in palladium catalyzed coupling reactions of (ethenyl)tributyltin with all possible isomeric permutations of bromophenyl triflate and bromo-nitrophenyl triflate. Each isomeric compound was examined under bromide and triflate selective reaction conditions.

2. Results and discussion

In an attempt to corroborate the results reported by Echavarren and Stille, cross coupling reactions of 4-bromophenyl triflate (**1**) and (ethenyl)tributyltin were performed (Table 1). Under bromine selective conditions, a 33:1 ratio of C-Br to C-OTf (**2:3**) bond coupling was reported by the authors based on ¹H NMR of the crude reaction mixture (Table 1, entry 1). This reaction was repeated and in our hands only compound **2** was observed by ¹H NMR at 600 MHz (entry 2). The catalyst, Pd(PPh₃)₄, used in the initial study is not air stable and handling and extended storage of this compound often results in diminished catalytic activity. In order to minimize problems associated with Pd(PPh₃)₄, a combination of the significantly more stable precursor bis(dibenzylideneacetone)palladium (Pd(dba)₂) and triphenylphosphine (PPh₃) was used to generate Pd(PPh₃)₄ *in situ*. In the event, the same exclusive selectivity was observed using 2 mol% Pd(dba)₂ and 8 mol % PPh₃ in 1,4-dioxane at reflux (entry 3). Since the latter conditions gave the same selectivity as Pd(PPh₃)₄, the more convenient catalyst precursor Pd(dba)₂-PPh₃ was used in all subsequent reactions.

It is unclear why two different palladium catalyst precursors were used by Echavarren and Stille (Scheme 1). We found that PdCl₂(PPh₃)₂ without any added PPh₃ not only gave the same chemoselectivity as Pd(PPh₃)₄ in a reaction of **1** with (ethenyl)tributyltin and in the absence of LiCl, but this catalyst precursor also afforded a superior yield of product (entry 4). Under triflate selective conditions, employing PdCl₂(PPh₃)₂ in the presence of a three-fold excess of LiCl in DMF at 24 °C, Echavarren and Stille reported exclusive coupling derived from oxidative addition to the C-OTf bond (entry 5). In our hands, employing the same reaction conditions, a much lower selectivity C-Br/C-OTf = 1:6.7 (entry 6) was observed. This product ratio is similar to the ratio reported by Echavarren and Stille at a higher reaction temperature either in 1,4-dioxane (at reflux, entry 7) or DMF (70 °C, entry 8).¹⁸ It should be noted that products **2–3** decompose/polymerize to varying extent upon chromatographic purification on silica gel.

In contrast to cross coupling of **1** with (ethenyl)tributyltin, carbonylative reactions of **1** with (2-phenylethenyl)tributyltin in the presence of 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (PdCl₂(dppf)) was reported to afford exclusive C-OTf bond coupling with or without added LiCl (Scheme 3).^{19,20} A C-OTf selective carbonylation of **1** using Pd(OAc)₂ - dppf in DMF to give an amide was very recently reported by Jiao and Wu et al.²¹ Interestingly, switching the ligand to Xantphos and the solvent to toluene completely reversed the selectivity to C-Br. We assumed that the difference in site selectivity observed in the absence of LiCl when comparing Schemes 1 and 3 was the result of the PdCl₂(dppf) pre-catalyst and not the difference in tin reagents. Thus, **1** was



Scheme 2. Preparation and Kosugi-Migita-Stille reaction of **5**.

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