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Use of Thallium(I) Ethoxide in Suzuki Cross Coupling Reactions

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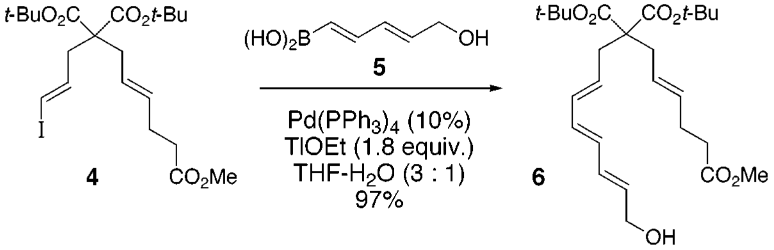
ABSTRACT



Thallium(I) ethoxide promotes Suzuki cross couplings for a range of vinyl- and arylboronic acids with vinyl and aryl halide partners in good to excellent yields. This reagent offers distinct advantages over thallium(I) hydroxide in terms of commercial availability, stability, and ease of use.

The Suzuki reaction is an important method for the synthesis of conjugated olefins, styrenes and biphenyls,[1−3] and is extremely useful in the context of complex natural products synthesis.[4−8] In the original version of the reaction,[2,9] a vinyl (or aryl) halide is combined with a vinyl (or aryl) boronic acid (or ester) or dialkylborane in the presence of bases such as NaOMe or K_2CO_3 and a Pd(0) catalyst in an organic solvent at temperatures between 60 and 90 °C for 2−24 h. In 1987 Kishi reported remarkable rate accelerations when the Suzuki reaction was performed using TlOH as the base, in which case the cross couplings were complete within minutes at ambient temperature.[4] We have found the TlOH method to be superior to many other procedures especially when 1,1-dibromoolefins or 1-iodo-1-trimethylsilylalkenes, which easily undergo base-induced elimination of HBr or HI, are used as the substrates.[7,10−12]

Despite its great utility in the Suzuki reaction, aqueous solutions of TlOH are both air and light sensitive and have an inferior shelf life. Moreover, commercial sources of the reagent have virtually disappeared, and to our knowledge only a single supplier of solid TlOH currently exists.[13] Dissolution of solid TlOH in water gives an initially clear solution from which a brown-black precipitate separates even under careful storage conditions.[14] Moreover, we have

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(13) While 10% aqueous solutions of TlOH have been available in the past from a variety of commercial vendors, a recent search revealed only a single supplier of solid TlOH. A conversation with a Johnson-Matthey customer service representative indicated that 10% TlOH solutions exhibited both air and light sensitivity and that they had ceased marketing the reagent for reasons of shelf life. While TlOEt is significantly more stable than TlOH, it is air and moisture sensitive and should be handled under inert atmospheres.
(14) The identity of the brown-black precipitate is unclear, but a likely suspect is Tl_2O_3: Tóth, I.; Gyõri, B. *Encyclopedia of Inorganic Chemistry*; King, B. R., Ed.; John Wiley and Sons: New York, 1994; Vol. 8, p 4134.

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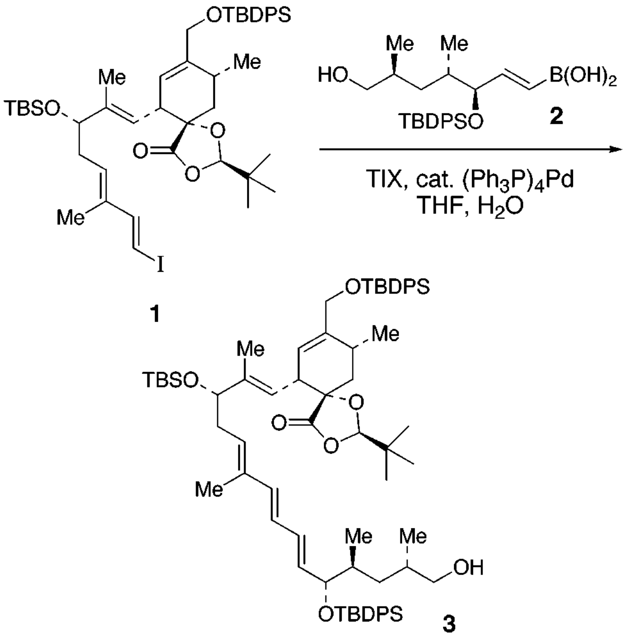
observed that the efficiency of Suzuki reactions promoted by TlOH is dependent on the age of the TlOH solution, with yields decreasing substantially with older batches of reagent. For example, during studies focusing on completion of a total synthesis of kijanolide,[15] the Suzuki coupling of **1** and **2**, using a 0.5 M stock solution of TlOH that had been prepared 1 month earlier and which had been employed successfully in our total synthesis of bafilomycin A,[8] provided **3** in 71% yield. However, when we repeated this reaction 4 months later using the same TlOH solution (after removing the brown-black precipitate by filtration), the yield of **3** fell to 50%. The next time this experiment was performed, an additional 6 months later, we prepared a fresh 0.5 M solution of TlOH from the same batch of solid TlOH, again with filtration to remove insoluble dark material, but the yield of **3** was still only 52%. The latter observations suggest that TlOH may also be somewhat unstable in the solid state. Thus, we turned our attention to identification of a suitable replacement for TlOH.

Although thallium(I) ethoxide (TlOEt) is an easily handled liquid that is readily available from several commercial suppliers at lower cost than TlOH, we are aware of only one published account in which this reagent has been used successfully as the base in a Suzuki cross coupling reaction.[16] However, there are several examples where TlOEt failed to give acceptable results,[17,18] including Kishi's original report.[4] In the later work, Kishi indicated that TlOEt gave only a 5-fold rate enhancement compared to experiments performed using KOH, while TlOH increased the rate a 1000-fold.

In a key initial experiment (Figure 1), we found that the Suzuki cross coupling of **1** and **2** using TlOEt in an aqueous THF solvent system, using conditions which otherwise mirrored the previous experiments performed using the 10% TlOH solutions, provided **3** in 83% yield**.** Interestingly, there was no significant difference in the rate of coupling of **1** and **2** using either TlOH or TlOEt.

We have demonstrated that TlOEt may be used with a range of functionalized vinyl and aryl halide and vinyl- and arylboronic acid coupling partners, as summarized in Figure 2.[19] As shown in these examples, vinyl iodides (**4**, **11**) 1,1-dibromo olefins (**7**), α-iodo vinylsilanes (**14**), and aryl iodides (**17**, **19**) are excellent coupling partners, and many potentially sensitive functional groups such as methyl esters, geminally alkylated malonate systems, silyl ethers, enones, etc. are fully compatible with these reaction conditions. In the accompanying paper, Chemler and Danishefsky have demonstrated that TlOEt also gives good results in intramolecular *B*-alkyl Suzuki macrocyclization reactions.[20]



TlX source	Reagent Age	Yield of **3**
TlOH (10% stock solution)	1 month old	71%
TlOH (10% stock solution)	5 months old	50%
TlOH (fresh, from solid)	12 months old	52%
TlOEt	--	83%

Figure 1.

The TlOEt-promoted Suzuki reactions summarized in Figures 1 and 2 are very fast, with TlBr or TlI precipitating from solution immediately upon addition of TlOEt to a mixture of the vinyl (or aryl) halide and vinyl (or aryl) boronic acid. Although we have not performed any detailed kinetic measurements, qualitatively these reactions appear to be as fast as Suzuki reactions we have previously performed using TlOH. Moreover, these reactions are substantially faster than those performed using AgO. For example, the coupling of **4** and **5** in the presence of AgO in 3:1 THF$-$H$_2$O gave only ca. 25% conversion to **6** after a 30 min reaction period, whereas the reaction of **4** and **5** in the presence of TlOEt is complete almost immediately after mixing of all reagents. Kishi reported that AgO is second only to TlOH in terms of rate acceleration (30-fold) of the Suzuki reaction;[4] however, our results suggest that TlOEt rivals TlOH in this capacity.

We initiated these studies on the assumption that TlOH is an obligatory intermediate[4] and that TlOEt would be rapidly converted to TlOH under the aqueous reaction conditions. To determine if it is necessary to run the TlOEt-promoted Suzuki cross couplings in the presence of water, the reaction of **4** and **5** was performed in anhydrous THF (Figure 2). Tetraene **6** was obtained in 92% yield, compared to 97% for the original experiment in the 3:1 THF$-$H$_2$O solvent system, with no noticeable difference in reaction rate. A better yield of **18** was obtained from the coupling of phenyl

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[19] All new compounds were fully characterized by ^{1}H and ^{13}C NMR, IR, and high-resolution mass spectroscopy.

[20] Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695. We thank the Sloan-Kettering group for sharing their results with us prior to publication.

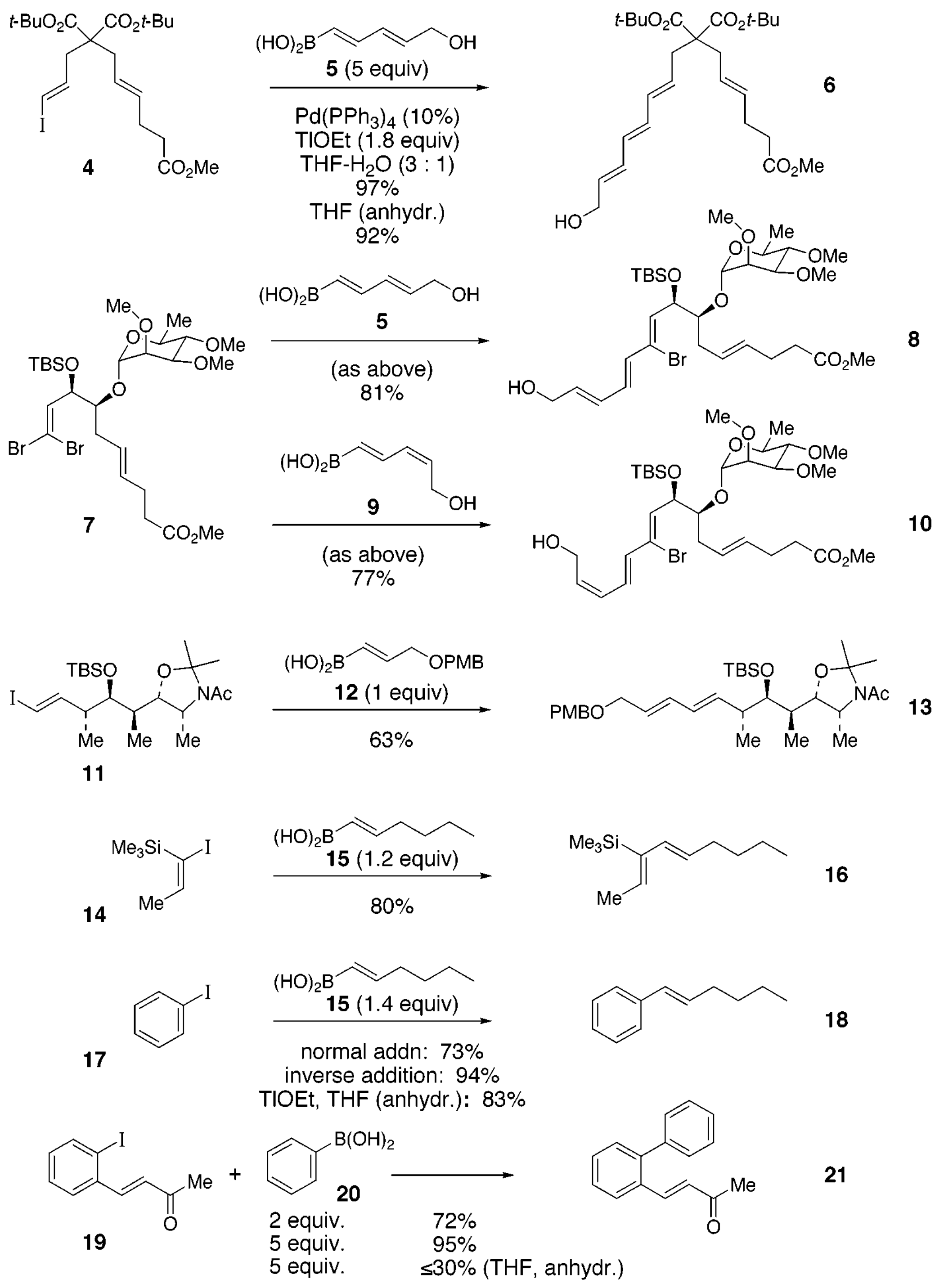
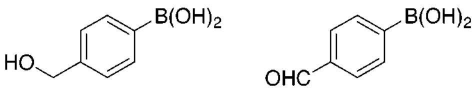


Figure 2. Representative TlOEt-promoted Suzuki reactions. Unless otherwise noted, all reactions were performed using TlOEt in 3:1 THF−H_2O using the conditions described in text for the coupling of **5** and **7**.

iodide and vinylboronic acid **15** in wet THF (94%) than in anhydrous THF (83%), although the former result was obtained using an inverse addition protocol (addition of a mixture of **17** and $Pd(PPh_3)_4$ to a mixture of **15** and TlOEt in wet THF; the yield of **18** was only 73% using the normal addition). However, the aqueous reaction conditions were essential to the successful, high-yield coupling of **19** and **20**.

One variable that is critical to the success of these reactions is the solubility of an intermediate generated from the reaction of the vinyl(aryl)boronic acid and TlOEt. For example, exposure of THF solutions of **15** or **20** to TlOEt in the absence of the other reaction components leads to the immediate precipitation of white solids, which we presume to be the thallium ate complexes of the boronic acids.[21] The precipitate generated from **15** and TlOEt partially dissolves when H_2O is added; however the solid analogously generated from **20** does not appear to dissolve at all under these conditions, or in other solvents such as MeOH, CH_3CN, or DMF. Therefore, to maximize the yield of biphenyl **21** from the coupling of **19** and **20**, it was necessary to use 5 equiv of the phenylboronic acid in the aqueous solvent system. Attempts to use arylboronic acids **22** and **23** (Figure 3) in these reactions were unsuccessful, presumably due to the insolubility of the boronic acid−TlOEt reaction product. For this reason, an excess of the boronic acid component was utilized in many of the experiments summarized in Figure 2.[22]



22 **23**

Figure 3. Unsuccessful reaction partners.

In summary, we have demonstrated that TlOEt is an excellent alternative to TlOH for use in Suzuki cross coupling reactions. This reagent has advantages compared to TlOH in terms of stability and ease of use. Most importantly, the commercial availability of TlOEt makes it significantly more attractive than TlOH for use in this important cross coupling reaction.

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(21) Dewar, M. J. S.; Jones, R. *J. Am. Chem. Soc.* **1967**, *89*, 2408.

(22) **Representative experimental procedure:** A solution of **5** (0.42 g, 3.28 mmol) and **7** (0.74 g, 1.09 mmol) in THF and water (12 mL, 3:1) was degassed thoroughly (3×) by using the freeze−pump−thaw method. Tetrakis(triphenylphosphine)palladium(0) (0.13 g, 0.11 mmol) was added as a solid, and the yellow solution was stirred for 5 min at ambient temperature. Thallium ethoxide (0.14 mL, 1.96 mmol) was added by syringe, and a bright yellow precipitate immediately formed. (**NOTE**: *thallium salts are generally quite toxic and should be handled with extreme care*.) The reaction was stirred 30 min and then was diluted with ether (25 mL) and a 1 N sodium bisulfate solution (10 mL). The biphasic mixture was filtered through Celite, and the organic layer was separated, washed with brine, and dried over $MgSO_4$. Concentration of the filtrate and purification of the crude tetraene by column chromatography afforded 0.60 g (81%) of **8**.