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Pd-catalyzed Cross-Coupling of α-(Acyloxy)-tri-*n*-butylstannanes with Alkenyl, Aryl, and Heteroaryl Electrophiles

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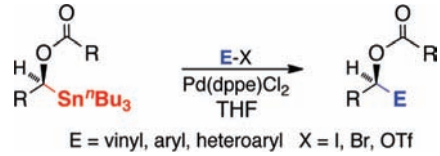
ABSTRACT



Racemic and scalemic α-(acyloxy)-tri-*n*-butylstannanes undergo Pd-catalyzed cross-couplings with alkenyl/aryl/heteroaryl iodides, bromides, and triflates in moderate to good yields in THF at 45 °C. Simple aryl iodides and unprotected aza-arenes, two classes of electrophiles that typically react sluggishly, are also good substrates. Cross-couplings proceed with retention of configuration at the alkenyl and stannyl-substituted stereocenters.

The Stille reaction,[1] i.e., the transition-metal-mediated cross-coupling of organostannanes with organic electrophiles, has achieved wide acceptance[2] as an exceptionally mild and efficient method for the creation of C−C bonds, especially between sp- and/or sp^2-hybridized centers.[3] Not surprisingly, the apparent advantages that would accrue from expanding the traditional scope and structural confines of the Stille reaction have attracted much interest.[4] In the early 1990′s, this laboratory[5] and others[6] explored the utility of tri-*n*-butylstannanes for the transfer of stereogenic carbons bearing heteroatoms and reported the stereospecific palladium/copper cocatalyzed cross-coupling of scalemic α-alkoxy- and α-aminoalkylstannanes with acid chlorides.[7,8] Subsequent studies led to copper-mediated cross-couplings with reactive electrophiles such as allylic and propargylic halides.[9] The utility of this methodology for the construction of chiral ethers and alcohols was cogently demonstrated during asymmetric total syntheses of the anticancer agent (+)-goniofufurone[10] and the potent endothelium-derived vasodilator 11,12,15-THE-

(1) Review: Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2004; Vol. 1, Chapter 3.

(2) Recent applications in natural products total synthesis: (a) Masters, K.-S.; Flynn, B. L. *Org. Biomol. Chem.* **2010**, *8*, 1290–1292. (b) Tang, B.; Bray, C. D.; Pattenden, G.; Rogers, J. *Tetrahedron* **2010**, *66*, 2492–2500. (c) Candy, M.; Audran, G.; Bienayme, H.; Bressy, C.; Pons, J.-M. *J. Org. Chem.* **2010**, *75*, 1354–1359. (d) Amans, D.; Bareille, L.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2009**, *74*, 7665–7674.

(3) Pascual, S.; Echavarren, A. M. In *Tin Chemistry*; Davies, A. G., Ed.; John Wiley & Sons Ltd.: Chichester, 2008; pp 579−606.

(4) For example: (a) Jensen, M. S.; Yang, C.; Hsiao, Y.; Rivera, N.; Wells, K. M.; Chung, J. Y. L.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2000**, *2*, 1081–1084. (b) Jarosz, S. *Tetrahedron Lett.* **1996**, *37*, 3063–3066.

(5) (a) Bhatt, R. K.; Shin, D. S.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **1992**, *33*, 4885–4888. (b) Belosludtsev, Y. Y.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5881–5882. (c) Falck, J. R.; Bhatt, R. K.; Reddy, K. M.; Ye, J. *Synlett* **1997**, 481–482.

(6) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438–7439.

(7) (a) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1–5.

(8) In 2004, α-sulfonamidoorganostannanes were introduced and shown to be highly efficacious: Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666–15667.

(9) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973–5982.

(10) Ye, J.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1993**, *34*, 8007–8010.

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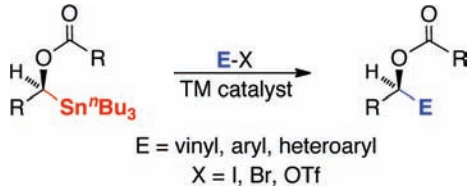
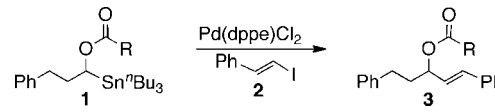
TA.[11] On the other hand, comparable unions between α-heteroatom-substituted triorganostannanes and alkenyl/aryl electrophiles were conspicuously absent[12] and suitable methodology has been elusive.[13] To address this methodological gap, we conducted an extensive survey of alternative reaction parameters including oxygen substituents[14] and herein describe a practical, stereospecific cross-coupling capable of using a broad range of sp^2-hybridized iodides/triflates/bromides (Scheme 1).

Scheme 1. Proposed Cross-Coupling



Since esters and alkenyl iodides were identified as the most promising pairing in our initial evaluations, α-(acetyloxy)stannane **1a** and (*E*)-*β*-iodostyrene (**2**) were selected as the test system. Screening an extensive collection of transition metals salts and complexes, tested individually or in combination, revealed palladium complexes were especially efficacious, and in particular freshly recrystallized Pd(dppe)Cl_2.[15] The yield of adduct **3a** increased proportionately with the amount of Pd(dppe)Cl_2 up to 10 mol % (62%; Table 1), but thereafter neither more catalyst nor alterations in mode of addition improved the outcome.[16] Yields of **3a** were patently better in THF as well as the reaction rate compared to other common solvents, *inter alia*, toluene, DME, and DMF; there was no cross-coupling in NMP, acetone, EtOAc, and CH_3CN. In contrast with the experience of others,[17] neither sources of fluoride (LiF, TBAF, KF, AlF_3, CsF) nor Lewis acids [$MgBr_2$, $AlCl_3$, $FeCl_3$, $ZnBr_2$, $BF_3{\cdot}Et_2O$, $Sc(OTf)_3$] have a beneficial effect.

Table 1. Cross-Coupling of α-(Acyloxy)stannanes with (*E*)-*β*-Iodostyrene[a]



compd	R	time (h)	yield (%)	compd	R	time (h)	yield (%)
a		12	62	f		12	68
b		10	71	g		12	72
c		10	72	h		10	72
d		12	70	i		8	81
e		10	68	j		8	**81**

[a] Reaction conditions: α-(acyloxy)stannane **1** (1 equiv), **2** (1.5 equiv), Pd(dppe)Cl_2 (10 mol %), THF, 45 °C, 8−12 h.

Replacement of the acetate of **3a** with a benzoate, i.e., **3b**, resulted in a modest improvement in yield. Electron-donating substituents (**3c**−**d**) had little influence above that of the parent aromatic **3b** and neither did electron-rich heterocycles like 2-carboxyfuran **3f** and 2-carboxythiophene **3g** despite the potential for intramolecular coordination in the transition state. In contrast, electron-withdrawing substituents (**3h**−**j**) offered an additional improvement in adduct yield and a modest rate enhancement. Because of its better handling characteristics and lower cost than the polyfluorinated aryls **3h**,**i**, *p*-trifluoromethylbenzoate **3j** was used in subsequent optimization studies.

Having standardized the reaction conditions, we next explored the scope of the cross-coupling of *p*-trifluoromethylbenzoate (TFMB) **1j** with a panel of representative sp^2-hybridized iodides, triflates, and bromides (Table 2). 3-Iodopropenoate **4**, despite its proclivity toward loss of HI and/or isomerization, smoothly cross-coupled using Pd(dppe)Cl_2 (catalyst A) to furnish **5** (entry 1) in excellent yield without complication or loss of the *Z*-configuration at the alkenyl center (>98% by $^1H/^{13}C$ NMR), thus precluding a conjugate addition mechanism. Under the same reaction conditions, 2-iodo-2-cyclohex-2-enone (**6**), (*Z*)-iodostyrene (**9**), (*E*)-triflate **12**, and unconjugated alkenyl iodide **15** led to adducts **8** (entry 2), **11** (entry 3), **14** (entry 4), and **16** (entry 5), respectively, although the reaction rates were somewhat slower than that for **4**. TFMB-benzyl alcohols **19** (entry 6), **22** (entry 7), and **24** (entry 8) were obtained analogously from aryl/heteroaryl iodides **17**, **20**, and **23**, respectively, in useful yields.

Comparable couplings of alkenyl and aryl bromides using Pd(dppe)Cl_2 proved more challenging, and only poor yields of adduct could be obtained. Fortunately, we discovered that

(11) Falck, J. R.; Barma, D.; Mohapatra, S.; Bandyopadhyay, A.; Reddy, K. M.; Qi, J.; Campbell, W. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4987–4990.

(12) A catalyst-free cross-coupling of α-sulfur-substituted alkyltriorganostannanes with acid chlorides has been described: Kagoshima, H.; Takahashi, N. *Chem. Lett.* **2007**, *36*, 14–15.

(13) The copper(I) thiophene-2-carboxylate catalyzed cross-coupling of α-(thiocarbamoyl)tri-*n*-butylstannanes with sp^2-electrophiles was subsequently found to be accompanied by a facile Newman−Kwart O → S rearrangement that in many cases generated the corresponding thiolcarbamate as the major product: Falck, J. R.; Patel, P. K.; Bandyopadhyay, A. *J. Am. Chem. Soc.* **2007**, *129*, 790–793. Correction: *J. Am. Chem. Soc.* **2008**, *130*, 2372.

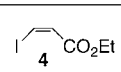
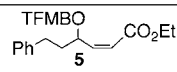
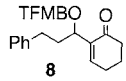
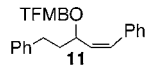
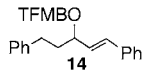
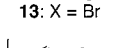
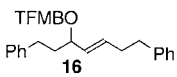
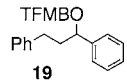
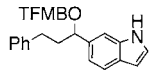
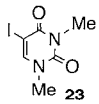
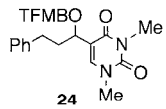
(14) Alternative sulfur-containing derivatives (e.g., thioesters, thiocarbonates, thiooxamides, thiophosphates) were evaluated, but it was not possible to completely suppress the rearrangement and still achieve acceptable yields of cross-coupled adduct (see Supporting Information).

(15) Catalyst quality varied widely with the source as revealed in cross-coupling yield of **3j**, e.g., Aldrich (brown color) mp 222 °C, 10%; TCI (light brown) mp 255 °C, 40%; Strem (pale yellow) mp 285 °C, 68%; Strem (recrystallized from EtOH, pale yellow) mp 298 °C, 78%; Strem (recrystallized from DMF/Et_2O, pale yellow) mp 301 °C, 81%; lit. mp >300, pale yellow: *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, NY, 1985; Vol. 3, pp 1675−1676.

(16) Modifications evaluated included reversing the order of reagent addition and slow addition of reagents via syringe pump.

(17) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Chem.—Eur. J.* **2005**, *11*, 3294–3308.

Table 2. Scope of Cross-Coupling Using α-(TFMB)stannane **1j**[a]

entry	electrophile	catalyst[b]	time (h)	adduct	yield (%)
1	 **4**	A	6	 **5**	86
2	 **6**: X = I **7**: X = Br	A B	10 12	 **8**	61 61
3	 **9**: X = I **10**: X = Br	A B	10 12	 **11**	61 52
4	 **12**: X = OTf **13**: X = Br	A	10 12	 **14**	60 72
5	 **15**	A	10	 **16**	66
6	 **17**: X = I **18**: X = Br	A B	8 12	 **19**	61 64
7	 **20**: X = I **21**: X = Br	A B	10 12	 **22**	65 62
8	 **23**	A	10	 **24**	62

[a] Reaction conditions: **1j** (1 equiv), electrophile (1.5 equiv), Pd catalyst (10 mol %), THF, 45 °C, 8−12 h. [b] Catalyst A = recrystallized Pd(dppe)Cl_2, catalyst B = chloro(2-di-*tert*-butylphosphino-2′,4′,6′-tri-*iso*-propyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II).

the Buchwald pallacyclic catalyst[18] chloro(2-di-*tert*-butylphosphino-2′,4′,6′-tri-*iso*-propyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXphos) restored efficacy (Table 2). While reaction times were modestly increased for bromides **10**, **13**, **18**, and **21**, adduct yields were generally comparable or even slightly better than those seen with alkenyl iodides/triflates. The exception was (*Z*)-bromostyrene (**10**) which likely reflects this electrophile's greater steric hindrance.

To ascertain the stereochemistry of the C−C bond formation, enantioenriched benzoate **25** (98% ee), readily prepared from the corresponding aldehyde via the one-pot procedure of He and Falck,[19] was added to phenyl iodide using the standard conditions (Figure 1). Saponification of the resultant benzoate **26** gave rise to the known[20] 1,3-diphenylpropan-1(*R*)-ol (98% ee via chiral HPLC), thus demonstrating complete retention of configuration at the stannyl-substituted

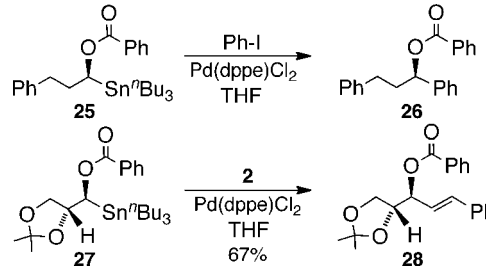


Figure 1. Cross-coupling of enantioenriched stannanes.

stereogenic center. This is consistent with prior experience using other classes of electrophiles but opposite to the inversion of configuration observed by Kells and Chong[8] using scalemic α-(sulfonamido)organostannanes and Pd/Cu cocatalysis. Analogous coupling of the diastereomeric glyceryl stannane **27**[21] to give **28** (Figure 1) was also instructive and revealed the adjacent stereocenter had no apparent influence on the outcome.

In conclusion, we have demonstrated the stereospecific Pd-mediated cross-coupling TFMB-protected α-hydroxystannanes with alkenyl/aryl/heteroaryl iodides/triflates/bromides including secondary cycloalkenyl and unactivated aryl iodides in THF under mild conditions.[22] When combined with the recently introduced methodology for the synthesis of racemic and scalemic α-hydroxystannanes,[19] we anticipate the foregoing methodology will find wide utility in the synthesis of heteroatom-substituted stereogenic centers.

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Supporting Information Available: Synthetic procedures, analytical data, chiral HPLC chromatograms, and $^1H/^{13}C$ spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) He, A.; Falck, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6586–6589.

(20) (a) Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H.; Obata, K. *J. Am. Chem. Soc.* **2000**, *122*, 1927–1936. (b) Anthony, R.; Stoner, H. E. J.; Peterson, M. J.; Grover, V. K. *J. Org. Chem.* **2003**, *68*, 8092–8096.

(21) Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4759–4762.

(22) Cross-Coupling Procedure: A Schlenk tube is charged with α-(acyloxy)-tri-*n*-butylstannane (0.16 mmol) and recrystallized Pd(dppe)Cl_2 (0.016 mmol, 10 mol %), when using an alkenyl/aryl/heteroaryl iodide/triflate, or chloro(2-di-*tert*-butylphosphino-2′,4′,6′-tri-*iso*-propyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) (*t*-BuXphos), when using an aryl/heteroaryl/alkenyl bromide, and then degassed via four alternating high-vacuum argon cycles. After dissolving in anhydrous THF (3 mL) under an argon atmosphere, a solution of electrophile (0.24 mmol) in THF (2 mL) is added via syringe and the mixture is warmed to 45 °C. After 6−12 h, the reaction mixture is diluted with Et_2O (10 mL) and filtered through a short pad of neutral alumina. The filter cake is washed with Et_2O (2 × 20 mL), and the combined organic filtrates are washed with water and brine and evaporated *in vacuo*. Chromatographic purification (SiO_2) of the residue furnishes the cross-coupled adduct in the indicated yield (Tables 1 and 2).