J. Org. Chem. **1996,** *61,* 6492−6493

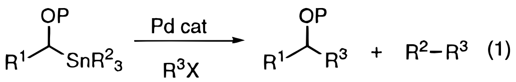
Selective Copper-Catalyzed Coupling Reactions of (α-Acetoxyhexyl)tricyclohexyltin

Russell J. Linderman* and James M. Siedlecki

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

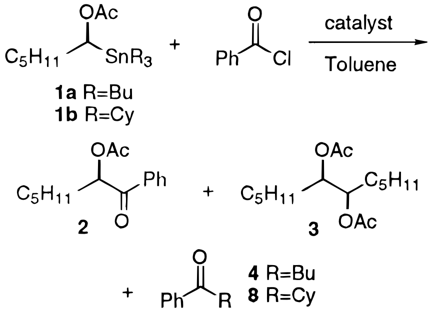
Received June 20, 1996

The selective coupling reactions of α-alkoxyalkyl groups from nonsymmetric tetraalkylstannanes has been a subject of study for some time (eq 1). Stille and co-workers examined Pd-catalyzed coupling reactions of $MOMOCH_2SnBu_3$ and $MOMOCH_2SnMe_3$ with benzoyl chloride.[1] Methoxymethyl group transfer occurred preferentially to Bu or Me group transfer; however, the selectivity was poor (2.5:1 or 3:1, respectively). Julia and co-workers reported coupling of $MPMOCH_2SnBu_3$ with a vinyl iodide in modest yields, but also noted significant butyl transfer.[2] Vedejs and co-workers reported a solution to the selective alkyl transfer problem via intramolecular activation of tin in a 1-aza-5-stannabicyclo[3.3.3]-undecane system.[3] In this example, selective transfer of primary alkyl groups including the CH_2OMOM group was realized in Stille coupling reactions. We employed an intramolecular variant of the Stille coupling reaction of an (α-alkoxyalkyl)stannane to provide a furanone; however, we subsequently found that the reaction was capricious, often resulting in no coupling product.[4] More recently, Falck and co-workers have shown that Pd/Cu cocatalyst systems are effective for the selective transfer of (α-acetoxy- or (α-(benzoyloxy)benzyl)tributylstannanes in coupling reactions with aryl or aliphatic acid chlorides.[5ab] (α-Acetoxyalkyl)tributylstannanes were not as effective in coupling reactions with aryl acid chlorides and were ineffective in attempted coupling reactions with aliphatic acid chlorides. (α-Methoxymethoxy- or (α-methoxyalkyl)tributylstannanes did not provide coupling products. Subsequently, Falck and co-workers achieved a significant advance by discovering that thiocarbamate or thionoacetoxy derivatives reacted with allyl bromides and aliphatic acid chlorides in the presence of a copper(I) catalyst alone.[5c] Intramolecular stabilization of a presumed copper intermediate by the sulfur atom was speculated as a probable rationale for the unique success of this class of derivatives. The intermediacy of a copper species in mixed Pd/Cu-catalyzed Stille couplings, as well as direct Sn−Cu transmetalations, have also been recently reported in other studies.[6]



(1)

We were intrigued by these results[5] given the low degree of butyl group transfer reported and the lack of a dimeric species.[7] We had earlier studied the reactions of α-alkoxyorganocopper and -cuprate reagents (obtained via initial Sn−Li transmetalation) with several electrophiles.[8] In these cases, formation of a dimeric species was frequently noted as a byproduct. We then examined the reaction of α-acetoxyhexyl(tributyltin) **1a** with benzoyl chloride in the presence of a Pd/Cu catalyst (eq 2).[9] The reaction led to the formation of three products, the α-acetoxyhexyl (α-OAcHex) coupling product **2**, the dimer **3**, and the Bu transfer product **4** (eq 2). The 57% isolated yield of **2** was similar to that reported,[5a] but the dimer **3** was also isolated in 39% yield as well as 42% of the Bu transfer product. Note that 96% of the α-OAcHex ligand of stannane **1a** is accounted for in this reaction. The molar ratio of the isolated products **2**:**3**:**4** was 48:16:36.[10]



(2)

Interestingly, dimer **3** formation increased and the amount of the α-OAcHex product **2** significantly decreased when the reaction was carried out without degassing the toluene solution. In fact, running the reaction in the presence of oxygen gas resulted in a 90% yield of the dimer with no trace of either the α-OAcHex or Bu group transfer products. The dimer could possibly arise via a radical coupling reaction, or via direct decomposition of an organocopper intermediate.[11] Adding radical inhibitors, TEMPO or galvinoxyl, to the

---

[1] (a) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634−4642. (b) For a review, see: Mitchell, T. N. *Synthesis* **1992**, 803−815. For additional examples of Pd catalyzed nonselective transfer of an α-alkoxyalkyl group, see: (c) Kosugi, M.; Sumiya, T.; Ogata, T.; Sano, H.; Migita, T. *Chem. Lett.* **1984**, 1225−1226. (d) Majeed, A. J.; Antonsen, O.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, *45*, 993−1006.

[2] Ferezou, J. P.; Julia, M.; Li, Y.; Liu, W.; Pancrazi, A. *Synlett* **1991**, 53−56.

[3] (a) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556−6558. (b) For an internally activated tin hydride reagent, see: Vedejs, E.; Duncan, S. M.; Haight, A. R. *J. Org. Chem.* **1993**, *58*, 3046−3050.

[4] (a) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438−7439. (b) Siedlecki, J. M. Unpublished results.

[5] (a) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1−5. (b) Ye, J.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1993**, *34*, 8007−8010. (c) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973−5982.

[6] (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911. (b) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749. (c) Piers, E.; McEachern, E. J.; Burns, P. A. *J. Org. Chem.* **1995**, *60*, 2322−2323. (d) Piers, E.; McEachern, E. J.; Romero, M. A. *Tetrahedron Lett.* **1996**, *37*, 1173−1176.

[7] Some butyl transfer is reported for α-phthaloylalkyl stannanes, but is not indicated for α-acetoxy stannane reactions in ref 5a. An interesting observation that carrying out the coupling reaction under CO favors Bu transfer is indicated in a footnote; however, no dimeric products (vida infra) are reported.

[8] (a) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491−5493. (b) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1990**, *55*, 5428−5430. (c) Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron* **1989**, *45*, 495−506 and references therein.

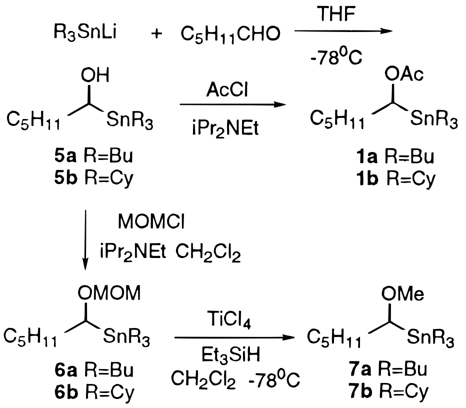
[9] Conditions for the Pd/Cu coupling reactions were typically 4 mol % $Pd(PPh_3)_2Cl_2$ and 8 mol % CuCN in refluxing toluene (ref 5a). Other Pd ($Pd(PPh_3)_4$, $Pd_2(dba)_3$) and Cu (CuI, CuCl, CuBr) sources and solvents (THF) were also examined.

[10] The yields of **2** and **3** are calculated based on **1a**. The yield of **4** is based on benzoyl chloride. The molar ratios were determined from the molar quantities of the isolated products and are therefore independent of starting material amounts. These data clearly indicate that dimer formation and Bu transfer are significant in reactions of stannane **1a**.

[11] The presence of oxygen is well known to induce oxidative coupling of organocopper and -cuprate species. For a recent synthetic example, see: Lipshutz, B. H.; Siegmann, K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9276−9282.

S0022-3263(96)01161-9 CCC: $12.00

Scheme 1



reaction mixture led to good yields of the dimer (>65%) along with a significant decrease in the yield of the α-OAcHex product. These data support the premise that an organocopper intermediate is formed. When the coupling reaction was carried out using only CuCN as catalyst, similar results were obtained. In this reaction, the yields of the coupling products were α-OAcHex **2** 34%, dimer **3** 26%, and Bu transfer **4** 22%. The molar ratio of isolated **2**:**3**:**4** was 44:17:34. The selectivity for α-OAcHex transfer was slightly enhanced using CuI in place of CuCN, but the yield of the α-OAcHex coupling product (30%) was attenuated. The molar ratio of **2**:**3**:**4** was 55:25:11 for the CuI-catalyzed reaction. In agreement with previous work,[2,5] the use of the ether derivatives, MOM **6a** or OMe **7a**, in the same reaction did not lead to coupling (α-OAcHex or Bu) products or dimer.

We noted that none of the studies to date had examined selective transfer of the α-acyloxyalkyl group from a tetraalkylstannane in which all of the Sn−C bonds were to secondary carbons. We reasoned that use of a secondary alkyl group on tin might eliminate or reduce competing alkyl group transfer from the R_3Sn moiety. Formation of (α-hydroxyhexyl)tricyclohexyltin was accomplished by Cy_3SnLi condensation with hexanal (Scheme 1).[12] The sensitive free alcohol **5b** was protected by acetylation with acetyl chloride to provide the α-acetoxy derivative **1b** in 95% overall yield. The corresponding MOM derivative **6b** was also prepared in 65% yield.[8] Lewis acid-catalyzed reduction of the MOM ether with Et_3SiH then provided the simple methyl ether derivative **7b**.[8a] Reaction of the tricyclohexyl derivative **1b** with benzoyl chloride and catalytic CuCN in toluene provided the desired coupling product in 78% yield (eq 2). None of the cyclohexylphenyl ketone **8** was observed, nor was the dimer **3** noted.[13] Results of coupling **1b** with aliphatic acid chlorides and allyl bromides (eq 3) are given in Table 1. The yields of **2** are uniformly high, from 73% for **2b** to 92% for **2e** derived from sterically demanding pivaloyl chloride. The reaction with cinnamyl bromide provided only the S_N2' product **2g** as a 1:1.5 mixture of diastereomers. Reaction of **1b** with iodobenzene did not result in any coupled product **2h**. As observed with the tributyltin species, attempted reactions of the MOM **6b** or MeO **7b** derivatives with acid chlorides or allyl bromide did not provide any coupling products.

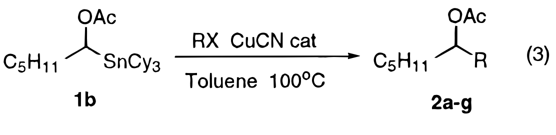


Table 1. Copper Cyanide-Catalyzed Coupling Reactions of 1b

entry	electrophile[a]	**2**, *R* =[b]		yield, %
1	PhCOCl	COPh	**2a**	78
2	CH_3COCl	$COCH_3$	**2b**	73[c]
3	$C_5H_{11}COCl$	COC_5H_{11}	**2c**	90
4	iPrCOCl	COiPr	**2d**	89
5	tBuCOCl	COtBu	**2e**	92
6	allyl bromide	$CH_2CH{=}CH_2$	**2f**	80[c]
7	cinnamyl bromide	$CH(Ph)CH{=}CH_2$	**2g**	85[d]
8	iodobenzene	Ph	**2h**	0[e]

[a] Two equivalents. [b] See eq 3 for structure of **2**. [c] Four equivalents of RX were used. [d] Obtained as a 1:1.5 diastereomeric mixture. [e] 93% recovery of **1b**.

These results indicate that intramolecular activation[3] or possible stabilization by sulfur[5] is not a prerequisite for selective (α-acetoxyalkyl) transfer reactions from nonsymmetric tetraalkylstannanes. The methyl ether derivatives **7a** and **7b** can be taken as a baseline value for ^{119}Sn chemical shifts, −38.1 ppm and −104.0 ppm, respectively, for a noncomplexed stannane. The MOM ether derivatives **6a** and **6b** ^{119}Sn NMR signals, −36.4 ppm and −103.7 ppm, respectively, reveal virtually no shift relative to the methyl ether. The Bu_3Sn acetate **1a** (−26.7 ppm) does show a modest upfield shift relative to methyl ether **7a**, while the Cy_3Sn acetate **1b** (−99.3 ppm) upfield shift relative to methyl ether **7b** is not as significant.[14] The slight degree of intramolecular interaction (intra- vs intermolecular supported by concentration studies) for **1a** compared to **1b** might provide a rationale for Bu transfer. One of the Bu groups could occupy an apical position in a trigonal bipyramidal Sn intermediate, and therefore may be activated toward transmetalation.[3a] A similar activation of a cyclohexyl group in **1b** appears to be less favorable.

In summary, we have shown that completely selective transfer of secondary α-acetoxyalkyl groups can occur from (α-acetoxyhexyl)tricyclohexyltin. In contrast, several examples of cross coupling reactions of (α-alkoxyalkyl)tributyl- or -methyltin compounds have resulted in nonselective transfer of both alkyl groups. The data in the literature and that from our present study indicate this reaction is complex and is likely dependent on a number of factors.

Acknowledgment. J.M.S. thanks the Burroughs Wellcome Fund and Glaxo for fellowships. Experimental procedures and spectral data for all new compounds **1a**,**b**, **2a**,**c**−**g**, **3**, **6b**, **7a**,**b**, and **8** (27 pages).

Supporting Information Available: Experimental procedures and spectral data for all new compounds **1a**,**b**, **2a**,**c**−**g**, **3**, **6b**, **7a**, and **8** (27 pages).

JO961161H

---

(12) For the preparation of Cy_3SnLi, see: Jousseaume, B.; Lahcini, M.; Rascle, M.-C. *Organometallics* **1995**, *14*, 685−689.

(13) Phenylcyclohexyl ketone **8** and dimer **3** were prepared independently. GC analysis of crude coupling reaction mixtures did not detect **3** or **8** in reactions using **1b**.

(14) For a recent paper examining intra- and intermolecular coordination of (alkyl)trichlorostannanes, see: Biesemans, M.; Willem, R.; Damoun, S.; Geerlings, P.; Lahcini, M.; Jaumier, P.; Jousseaume, B. *Organometallics* **1996**, *15*, 2237−2245. ^{119}Sn NMR data for the $SnCl_3$ derivatives typically revealed a >30 ppm upfield shift for complexed (trigonal bipyramidal at Sn) relative to uncomplexed (tetrahedral at Sn) species.