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Pd-Catalyzed Arylation of Secondary α-Alkoxytricyclohexylstannanes

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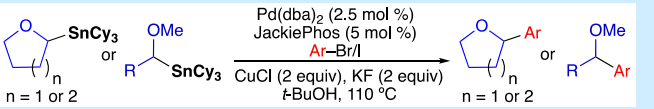
ABSTRACT: We have developed a general process for the formation of α-arylethers via the Pd-catalyzed arylation of secondary α-alkoxytricyclohexylstannanes. Incorporation of cyclohexyl spectator ligands into the alkylstannane and the use of the electron-deficient ligand JackiePhos (**1**) are critical for achieving selective alkyl transfer in this process. This system circumvents the need for a coordinating/directing oxygen-protecting group to promote selective alkyl transfer and enables α-tetrahydropyran, α-tetrahydrofuran, and open-chain secondary α-alkoxy groups to be employed efficiently in Pd-catalyzed Stille reactions with a broad range of aryl electrophiles. These findings suggest that selective transmetalation of a single marginally activated secondary alkyl unit from Sn to Pd should be broadly achievable provided that unactivated secondary alkyl ligands comprise the other three groups of the tetraalkylstannane.



The biological properties of organic molecules are greatly influenced by the presence of heteroatoms within their molecular structures.[1] Oxygen-containing heterocycles, commonly in furanose or pyranose forms, represent particularly significant components of biologically active molecules.[2] Therefore, reliable strategies to structurally modify oxygen-containing heterocycles, as well as open-chain ethers, constitute important synthetic tools for use in medicinal chemistry applications. Though Pd-catalyzed cross-coupling reactions have revolutionized the manner in which organic synthesis can be approached, these reactions are much more readily employed in the construction of $C(sp^2)-C(sp^2)$ bonds than $C(sp^3)-C(sp^2)$ or $C(sp^3)-C(sp^3)$ bonds.[3] Accordingly, the development of a general Pd-catalyzed approach for incorporation of α-oxygenated secondary alkyl groups into organic structures remains a significant and important synthetic challenge.[4−6]

Considering the expansive substrate scope and broad functional group tolerance commonly observed in Pd-catalyzed $C(sp^2)-C(sp^2)$ bond-forming Stille reactions, the development of $C(sp^3)-C(sp^2)$ Stille variants using alkylstannanes is an attractive goal.[7] However, the use of alkylstannanes in Pd-catalyzed Stille cross-coupling reactions is complicated by slow alkyl transmetalation as well as the general need for four substituents on the organotin nucleophile.[8] In traditional $C(sp^2)-C(sp^2)$ bond-forming Stille reactions, such complications are circumvented due to the greater migratory aptitude of $C(sp^2)$ substituents from tin, relative to $C(sp^3)$ substituents.[1,8] This enables alkyl groups to be employed as inert spectator ligands, thereby facilitating selective transfer of an aryl or alkenyl unit. Significant acceleration of alkyl transmetalation is thus necessary to effect successful cross-coupling reactions using alkylstannane nucleophiles. Development of a catalytic system that promotes alkyltin transmetalation does not completely solve this problem, however, as selectivity of alkyl transfer from the tetraalkylstannane then becomes the new hurdle, particularly when transfer of a secondary alkyl group is desired. To achieve selective activation and transfer of an otherwise unactivated secondary alkyl group from tin, we have introduced the use of secondary alkylcarbastannatranes[9,10] in Pd-catalyzed cross-coupling reactions supported by the electron-deficient biarylphosphine ligand JackiePhos (**1**) (Figure 1a).[11] This system combines the enhanced nucleophilicity of alkylcarbastannatrane reagents with the heightened Pd(II) electrophilicity that arises from ligation with electron-deficient **1**, enabling selective and stereospecific alkyl transfer. Alternatively, selective alkyl transfer has also been achieved when a α-heteroatom bearing a coordinating protecting group is incorporated into the secondary alkyltin nucleophile (Figure 1b).[12,13] Falck pioneered this approach for Pd-catalyzed cross-coupling reactions of secondary α-alkoxytributylstannanes. In this system, the presence of a directing/coordinating oxygen-protecting group is a critical structural requirement for achieving selective transmetalation of the secondary α-alkoxy group.[12] In the absence of a directing group, the activating effect of the α-oxygen substituent is insufficient to promote efficient transfer of the secondary α-alkoxy group, which results in low yields and/or competitive butyl transfer.[8,14] Recently, we demonstrated that a change from *n*-butyl spectator ligands to cyclohexyl spectator ligands is sufficient to enable the

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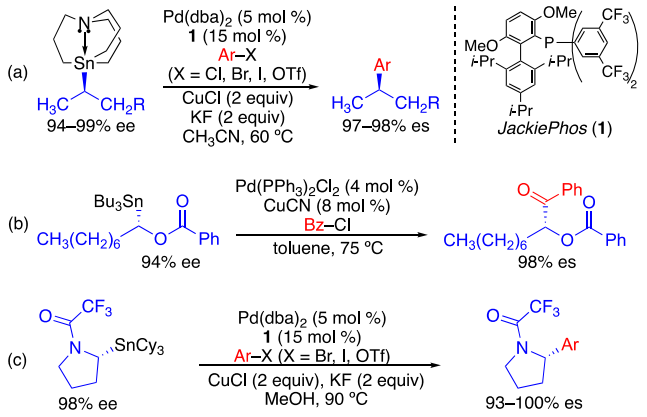
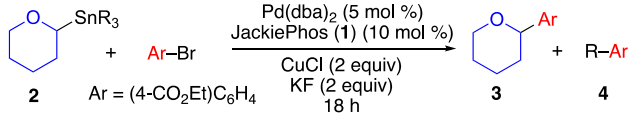


Figure 1. Examples of selective Pd-catalyzed Stille cross-coupling reactions using (a) unactivated and (b, c) activated secondary alkyl groups.

selective transmetalation and coupling of nitrogen-containing stereocenters in Pd-catalyzed cross-coupling reactions supported by ligand **1** (Figure 1c).[15] These results suggested that selective alkyl transfer of activated secondary alkyl groups should be broadly achievable using other marginally activated secondary alkyltricyclohexylstannane nucleophiles alongside ligand **1**. Herein, we describe the use of secondary α-alkoxytricyclohexylstannanes in Pd-catalyzed arylation reactions. We demonstrate that α-oxygenated secondary alkyl units without a directing group undergo selective transfer from tin when in the presence of cyclohexyl spectator ligands. Using this strategy, α-tetrahydropyran (THP), α-tetrahydrofuran (THF), and open-chain secondary α-alkoxy groups can be efficiently employed in Pd-catalyzed Stille reactions with a broad range of aryl electrophiles. In this system, the presence of cyclohexyl spectator ligands is essential to ensure selective transfer of the α-oxygenated secondary alkyl unit.

We initiated our investigations using α-tributylstannanyl tetrahydropyran (**2a**) in Pd-catalyzed cross-coupling reactions with ethyl 4-bromobenzoate. Reaction conditions previously used in stereospecific cross-coupling reactions with alkylcarbastannatranes[10a] predominately generated the corresponding *n*-butylation product **4a** (Table 1, entry 1). Though improved yields of α-arylated tetrahydropyran product **3** were obtained using *t*-butanol as solvent, **4a** remained a significant product

Table 1. Optimization of Tetrahydropyran Transfer in Pd-Catalyzed Stille Reactions



2 3 4

entry	R	solvent	temp (°C)	3 yield (%)[a]	4 yield (%)[a]
1	*n*-Bu (**2a**)	CH_3CN	80	19	78 (**4a**)
2	*n*-Bu	toluene	80	<5	<5
3	*n*-Bu	NMP	80	25	21
4	*n*-Bu	*t*-BuOH	80	31	23
5	*n*-Bu	*t*-BuOH	110	32	41
6	*n*-Bu	1,4-dioxane	110	16	31
7	Cy (**2b**)	CH_3CN	110	10	<5 (**4b**)
8	Cy	*t*-BuOH	110	81	<5

[a]Calibrated GC yields.

under these conditions. These results indicate that the activation effect arising from the presence of an α-alkoxy group on a secondary alkyltin substituent is insufficient to promote selective transfer of the secondary α-alkoxy substituent from the tributylstannane. In contrast, we found that use of α-tricyclohexylstannanyl tetrahydropyran **2b** successfully suppressed formation of undesired cross-coupling product **4b**, while also generating α-arylated tetrahydropyran product **3** in high yield. Thus, selective transfer of the tetrahydropyran group from tin can be achieved in the presence of cyclohexyl spectator ligands, which undergo markedly slower transmetalation from tin to palladium than the corresponding *n*-butyl ligands.

The broad application of our optimized cross-coupling conditions using α-tricyclohexylstannyl tetrahydropyran (**2b**) in arylation reactions results in the product scope depicted in Table 2. Electron-rich, electron-neutral, and electron-deficient aryl electrophiles undergo Pd-catalyzed cross-coupling reactions with **2b** in high yields. Aryl electrophiles bearing an ortho substituent or bearing an acidic NH or OH substituent are also well tolerated. Additionally, heteroaryl electrophiles show good compatibility with this process.[16] Importantly, none of these reactions shows more than a trace of cyclohexylated product.

The conditions developed for the Pd-catalyzed arylation of **2b** were extended to cross-coupling reactions involving α-tricyclohexylstannyl tetrahydrofuran (**5b**) (Table 3). Using the exact reaction conditions that were employed in Table 2, a similarly broad scope of α-arylated tetrahydrofuran products could be achieved. These identical reaction conditions were also employed in high-yielding arylation reactions with open-chain α-alkoxystannane **7** (Figure 2). Again, competitive transfer of the cyclohexyl ligand from tin is not observed in these reactions. Taken together, the reactions depicted in Tables 2−3 and Figure 2 suggest that selective transfer of a secondary α-alkoxy unit from an organostannane can be universally achieved without a coordination oxygen-protecting group when cyclohexyl spectator ligands are employed in combination with bulky, electron-deficient ligand **1**.

In addition to imparting improved selectivity in Pd-catalyzed cross-coupling reactions, use of cyclohexyl spectator ligands also has the following important practical advantages: (1) toxicity of X−$SnCy_3$ compounds is significantly lower than that of analogous X−$SnBu_3$ compounds;[17] (2) in contrast to $ClSnBu_3$, $ClSnCy_3$ is crystalline and odorless; (3) in contrast to $RSnBu_3$ compounds, which tend to be oils, $RSnCy_3$ compounds tend to be highly crystalline; and (4) $ClSnCy_3$ is easily prepared[18] from Cy_3SnOH (a decommissioned pesticide available in bulk). Based on these advantages, we feel that $RSnCy_3$ use in Stille couplings may transcend its application to cross-coupling reactions of activated secondary alkyl units and can reasonably be extended to more traditional $C(sp^2)-C(sp^2)$ cross-coupling processes where aryl or vinyl $SnBu_3$ derivatives are commonly employed.

As previously noted, we have observed that *n*-butyl transfer competes extensively with THP and THF transfer when tributylstannane analogues **2a** and **5a** are employed in Pd-catalyzed cross-coupling reactions. Thus, we were surprised to find a report of high-yielding Pd-catalyzed arylation reactions using **2a** and **5a** in which competitive *n*-butyl transfer was seemingly suppressed.[19] Intrigued by this finding, we attempted to replicate the reported results using **2a** and **5a**. Direct comparison of our method using **2b** and **5b** (conditions B) and the reported method using **2a** and **5a** (conditions A)

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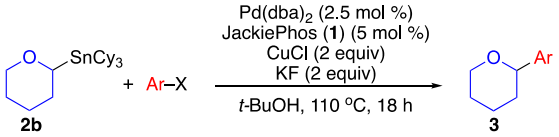
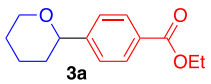
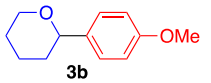
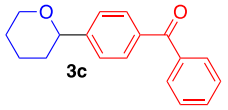
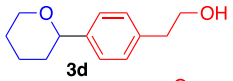
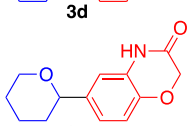
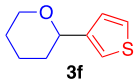
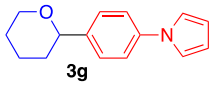
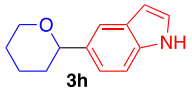
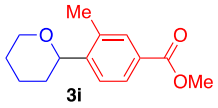
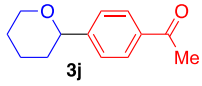
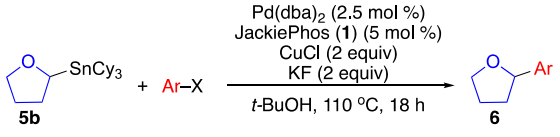
Table 2. Pd-Catalyzed Couplings of α-Tricyclohexylstannyl Tetrahydropyran (2b) and Aryl Electrophiles

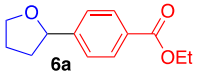
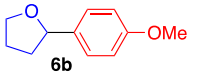
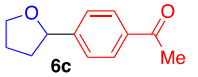
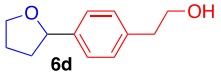
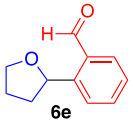
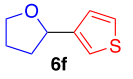
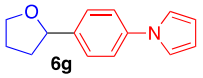
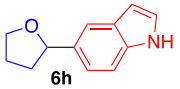
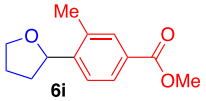


entry	X	product	yield (%)[a]
1	Br	 **3a**	79
2	Br	 **3b**	59
3	Br	 **3c**	76
4	Br	 **3d**	71
5	Br	 **3e**	81
6	Br	 **3f**	58
7	Br	 **3g**	70
8	I	 **3h**	57
9	Br	 **3i**	58
10	Br	 **3j**	83

[a]Isolated yields from duplicate runs.

Table 3. Pd-Catalyzed Couplings of α-Tricyclohexylstannyl Tetrahydrofuran (5b) and Aryl Electrophiles



entry	X	product	yield (%)[a]
1	Br	 **6a**	79
2	Br	 **6b**	75
3	Br	 **6c**	77
4	Br	 **6d**	78
5	I	 **6e**	57
6	Br	 **6f**	80
7	Br	 **6g**	52
8	I	 **6h**	80
9	Br	 **6i**	75

[a]Isolated yields from duplicate runs.

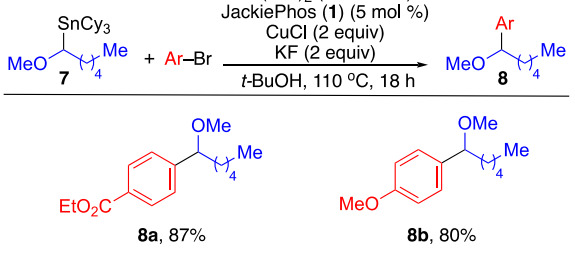


Figure 2. Use of open-chain α-alkoxytricyclohexylstannane **7** in Pd-catalyzed cross-coupling reactions.

are shown in Table 4. In our hands, reaction conditions A resulted in substantial formation of *n*-butylarene products alongside low yields of the desired THP and THF cross-coupling products. In contrast, only traces of cyclohexylarene products were observed using reaction conditions B, and the desired THP and THF cross-coupling products were obtained in high yield. We cannot explain the discrepancy between the reported results using conditions A and those obtained in our lab. However, based on our findings, use of cyclohexyl spectator ligands is essential for selective THP and THF transfer from tin in Pd-catalyzed Stille reactions.

In summary, we have developed a general process for the formation of α-arylethers via the Pd-catalyzed cross-coupling reaction of secondary α-alkoxytricyclohexylstannanes and aryl halides. Incorporation of cyclohexyl spectator ligands into the alkylstannane and the use of the bulky electron-deficient ligand JackiePhos (**1**) are critical for achieving selective alkyl transfer in this process. This system circumvents the previous need for a coordinating/directing oxygen-protecting group to promote selective alkyl transfer and enables α-tetrahydropyran, α-

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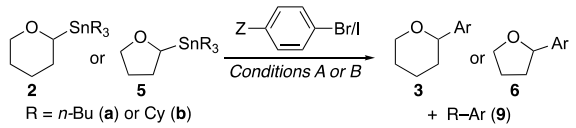
Table 4. Comparison of Pd-Catalyzed Arylation Reactions Using Tricyclohexylstannanes 2b and 5b to Arylation Reactions Using Tributylstannanes 2a and 5a



					yield (%)[b]	
entry	stannane	R	Z	conditions[a]	3 or 6	9
1a	**2a**	*n*-Bu	C(O)Me	A	26	27
1b	**2b**	Cy	C(O)Me	B	83	<5
2a	**2a**	*n*-Bu	CO_2Et	A	32	26
2b	**2b**	Cy	CO_2Et	B	79	<5
3a	**2a**	*n*-Bu	OMe	A	23	9
3b	**2b**	Cy	OMe	B	59	<5
4a	**5a**	*n*-Bu	C(O)Me	A	32	26
4b	**5b**	Cy	C(O)Me	B	77	<5
5a	**5a**	*n*-Bu	CO_2Et	A	40	29
5b	**5b**	Cy	CO_2Et	B	79	<5
6a	**5a**	*n*-Bu	OMe	A	35	8
6b	**5b**	Cy	OMe	B	75	<5

[a]Conditions A (ref 19): $RSnBu_3$ (2 equiv), ArI (1 equiv), $Pd_2(dba)_3$ (5 mol %), JackiePhos (20 mol %), CuCl (3 equiv), KF (2 equiv), 1,4-dioxane, 110 °C, 72 h; Conditions B: $RSnCy_3$ (1.2 equiv), ArBr (1 equiv), $Pd(dba)_2$ (2.5 mol %), JackiePhos (5 mol %), CuCl (2 equiv), KF (2 equiv), *t*-BuOH, 110 °C, 18 h. [b]Calibrated GC or NMR yields of **3** and **6** using conditions A (average of three runs) and for all yields of **9**; isolated yields of **3** and **6** using conditions B (average of two runs).

tetrahydrofuran, and open-chain secondary α-alkoxy groups to be employed efficiently in Pd-catalyzed Stille reactions with a broad range of aryl electrophiles. These findings are particularly noteworthy as they show that use of JackiePhos (**1**) supports the selective transmetalation of marginally activated secondary alkyl units from Sn to Pd when unactivated secondary alkyl ligands comprise the other three groups on tin. Thus, we expect that alkylstannane activation arising from the presence of an α-heteroatom, an α-C(sp^2) group, or ring strain will broadly enable selective alkyl (R) transfer from $RSnCy_3$ reagents. As a result, use of carbastannatranes should only be necessary in instances where the transmetalation of completely unactivated secondary alkyl units is desired. We are currently investigating stereospecific extensions of these methods for the formation of enantioenriched α-aryl ethers, as well as the use of other activated alkyl groups in coupling reactions involving $RSnCy_3$ reagents.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03729.

Procedural details, compound characterization, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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