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Stille Cross-Couplings of Unactivated Secondary Alkyl Halides Using Monoorganotin Reagents

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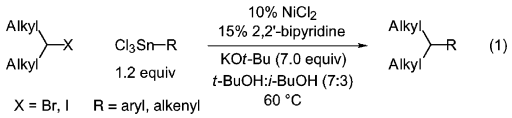
The Stille cross-coupling reaction[1] is a very powerful method for the construction of new carbon−carbon bonds that has found application in disciplines ranging from natural-products synthesis (e.g., chloropeptin I[2] and apoptolidin[3]) to materials science (e.g., conducting polymers[4]). A significant impediment to even more widespread use of this process is the toxicity of triorganotin compounds (R_3SnX),[5] which are the usual stoichiometric side products of Stille reactions. A second practical issue is the difficulty that is often encountered in separating R_3SnX from the desired cross-coupling adduct. A few clever approaches to circumventing these problems have been described, but none has yet found general use.[6]

Of course, one simple way to avoid trialkyltin-related issues is to employ an organotin coupling partner that does not generate R_3SnX as a side product. In fact, a few groups have reported Stille reactions of monoorganotin compounds.[7] The tin-based products of such processes are inorganic species that generally do not suffer from the purification and toxicity problems common to triorganotins.[8]

Recently, we and others have devoted considerable effort to expanding the scope of palladium- and nickel-catalyzed coupling reactions to include unactivated, β-hydrogen-containing alkyl halides as partners.[9] A particularly synthetically useful, although challenging (due to slow oxidative addition and facile β-hydride elimination), objective is the cross-coupling of *secondary* alkyl halides. To date, progress with this family of substrates has been limited to couplings with organozinc,[10] -boron,[11] -silicon,[9c] and -magnesium[12] reagents.[13] In this communication, we establish that a new family of partners, organotin compounds, can be cross-coupled with secondary alkyl halides (eq 1); monoorganotin reagents are the substrates of choice for this nickel-catalyzed process.

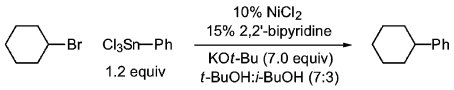


Unfortunately, the conditions that had previously been described for Negishi,[10] Suzuki,[11] and Hiyama[9c] couplings of secondary alkyl halides were ineffective for the corresponding Stille reactions. However, we determined that 10% $NiCl_2$/15% 2,2′-bipyridine, in the presence of KO*t*-Bu, catalyzes the cross-coupling of cyclohexyl bromide with $PhSnCl_3$ in good yield (Table 1, entry 1).

Essentially none of the desired carbon−carbon bond formation is observed in the absence of $NiCl_2$ (Table 1, entry 2) or in the presence of a range of palladium complexes (entry 3). Other nickel complexes can furnish reactivity that is comparable to $NiCl_2$ (entry 4); for the studies described below, we chose to use $NiCl_2$, since it is air-stable and inexpensive.[14]

If 2,2′-bipyridine is omitted, cross-coupling does not occur (entry 5), and other bipyridine-based ligands that we have explored have proved to be less effective (e.g., entry 6). The stoichiometry of KO*t*-Bu and the solvent have a significant impact on reaction efficiency (entries 7−11);[15] from the standpoint of convenience, it is worth noting that commercially available KO*i*-Bu in *i*-BuOH provides a useful amount of product (entry 11). Decreasing the catalyst loading leads to a somewhat diminished yield (entry 12), and virtually no cross-coupling is observed at room temperature (entry 13).

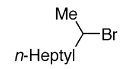
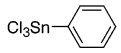
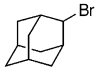
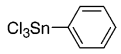
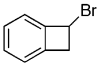
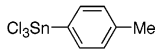
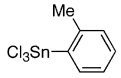
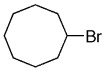
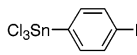
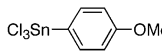
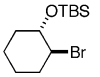
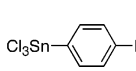
Table 1. Impact of Reaction Parameters on the Cross-Coupling of Cyclohexyl Bromide with $PhSnCl_3$



entry	variation from the "standard conditions"	yield[a] (%)
1	none	83
2	no $NiCl_2$	<5
3	10% $Pd(OAc)_2$ or $Pd_2(dba)_3$ [instead of $NiCl_2$]	<5
4	10% $Ni(cod)_2$, $NiBr_2$, or $NiBr_2$·diglyme [instead of $NiCl_2$]	82−86
5	no 2,2′-bipyridine	<5
6	15% bathophenanthroline [instead of 2,2′-bipyridine]	33
7	no KO*t*-Bu	<5
8	5.0 equiv of KO*t*-Bu [instead of 7.0 equiv]	55
9	*i*-BuOH [instead of *t*-BuOH/*i*-BuOH]	76
10	*t*-BuOH [instead of *t*-BuOH/*i*-BuOH]	<5
11	KO*i*-Bu in *i*-BuOH [instead of KO*t*-Bu in *t*-BuOH/*i*-BuOH]	61
12	5% $NiCl_2$, 7.5% 2,2′-bipyridine [instead of 10% $NiCl_2$, 15% 2,2′-bipyridine]	69
13	room temperature [instead of 60 °C]	<5

[a] Determined by GC analysis versus a calibrated internal standard (average of two experiments).

Table 2. Stille Cross-Couplings of Secondary Alkyl Bromides with Aryltrichlorotin Reagents (eq 1)

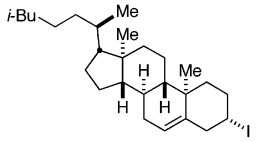
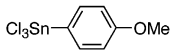
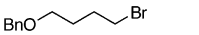
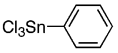
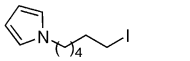
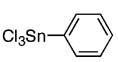
entry	R_{alkyl}—Br	Cl_3Sn—R	yield (%)[a]
1			72
2			74
3			83
4			47
5			67
6			68
7			48[b]

[a] Isolated yield (average of two experiments). [b] Catalyst: 20% $NiCl_2$/30% 2,2′-bipyridine. The unpurified product was a 96:4 *trans*/*cis* mixture. The reported yield is for the diastereomerically pure trans isomer.

$NiCl_2$/2,2′-bipyridine catalyzes a range of couplings of secondary alkyl bromides with aryltrichlorotin reagents (Table 2);[16] thus, both cyclic and acyclic bromides can be cross-coupled with a sterically and electronically diverse set of organotin compounds. The same catalyst system can also be applied directly to Stille reactions of

10.1021/ja0436300 CCC: $30.25

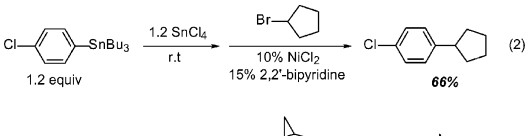
Table 3. Stille Cross-Couplings of Primary and Secondary Alkyl Bromides and Iodides with Aryltrichlorotin Reagents (eq 1)

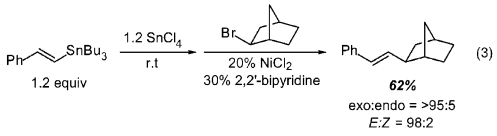
entry	R_{alkyl}–X	Cl_3Sn–R	yield (%)[a]
1			55[b]
2			61
3			62

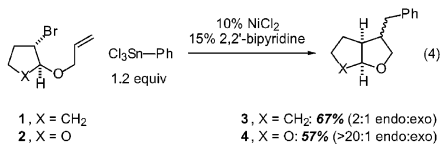
[a] Isolated yield (average of two experiments). [b] Only the 3*S* isomer is observed.

other families of alkyl electrophiles (secondary iodides, primary bromides, and primary iodides; Table 3).

Because a large number of aryl- and alkenyltributylstannanes are commercially available, we decided to determine if we could make use of these families of compounds in cross-couplings with alkyl electrophiles. These stannanes are not themselves suitable partners for $NiCl_2$/2,2′-bipyridine-catalyzed Stille couplings, but through a redistribution reaction with $SnCl_4$, they can be converted into aryl- and alkenyltrichlorotin reagents.[17] Upon the addition of the other components of the cross-coupling reaction, the desired carbon–carbon bond formation occurs (eqs 2 and 3).







In earlier studies, we suggested that nickel-catalyzed couplings of secondary alkyl halides may proceed through the initial generation of an alkyl radical, which then combines with nickel to afford an alkylnickel complex.[10,11,18] We subjected secondary bromides **1** and **2** to our Stille conditions and determined that both substrates undergo cyclization/cross-coupling to yield cis-fused 5,5 ring systems (eq 4); product **3** is formed with a low endo/exo ratio (2:1), whereas **4** is generated with high stereoselection (>20:1). Interestingly, these diastereoselectivities are independent of ligand structure (e.g., 2,2′-bipyridine, bathophenanthroline, or 4,4′-dimethoxy-2,2′-bipyridine), and they correlate with those observed in radical cyclizations of these compounds,[19,20] consistent with the possibility that an initially formed secondary alkyl radical cyclizes before reacting with nickel.

In summary, we have developed the first catalyst that achieves Stille cross-couplings of secondary (as well as primary) alkyl halides. The method employs easily handled and inexpensive catalyst components ($NiCl_2$ and 2,2′-bipyridine) and, through the use of monoorganotin reagents, avoids the formation of toxic and difficult-to-remove triorganotin side products. Efforts to expand the scope of Stille cross-couplings of alkyl electrophiles, as well as to achieve catalytic asymmetric reactions, are underway.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) The yields reported in Table 2 are for reactions conducted with 1.0 mmol of the electrophile. An increase in the scale of the process (without additional optimization) leads to a slightly lower yield (e.g., for entry 1, 1.28 g (63%) of the desired product was obtained when the cross-coupling was run with 10 mmol of the alkyl bromide). (b) Under these conditions, Cl_3Sn–Bu, secondary alkyl tosylates, and secondary alkyl chlorides are not suitable cross-coupling partners. (c) The presence of functional groups on the alkyl halide can lead to significantly diminished reaction efficiency. For example, certain substrates that contain ketones, secondary amines, imides, and nitriles cross-couple in <20% yield. (d) The reaction is moisture-sensitive. (e) According to ICP-MS analysis, the tin contamination in the product (after chromatography) is less than 5 ppm.

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