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Stereospecific Cross-Coupling of α-(Thiocarbamoyl)organostannanes with Alkenyl, Aryl, and Heteroaryl Iodides

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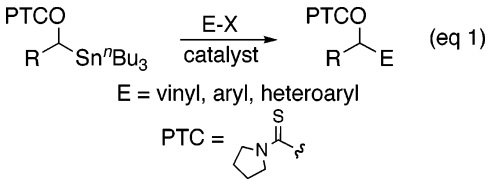
Abstract: Racemic and scalemic PTC-protected α-hydroxystannanes cross-couple with alkenyl/aryl/heteroaryl iodides in moderate to good yields using copper(I) thiophene-2-carboxylate (CuTC) in THF at or below room temperature. Simple aryl iodides and 1-iodocyclohexene, two classes of electrophiles that typically react sluggishly, are also good substrates. Cross-couplings proceed with retention of configuration at the alkenyl- and stannyl-substituted stereocenters.

Introduction

Cross-couplings of organostannanes mediated by transition metals have emerged over the past quarter century as one of the premier procedures for the creation of carbon−carbon bonds, especially with sp and sp^2-hybridized electrophiles.[1] Their numerous advantages, inter alia, applicability to a wide variety of substrates, high stereospecificity, mild and neutral reaction conditions, and compatibility with most functional groups, make them especially suitable for the preparation of complex and/or labile molecules.[2] In the early 1990s, our laboratory[3] and others[4] explored the utility of organostannanes for the transfer of stereogenic carbons bearing heteroatoms and described the palladium-mediated cross-coupling of scalemic α-alkoxy- and α-acyloxyalkylstannanes with acid chlorides.[5] We subsequently extended this to allylic and propargylic electrophiles and to α-nitrogen-substituted alkylstannanes.[6] 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[7] and the potent endothelium-derived vasodilator 11,12,15-THETA.[8] In stark contrast to these successes, alkenyl[9] and aryl[10] electrophiles were refractory and little, if any, cross-coupled adduct could be isolated. Consequently, we initiated a systematic investigation of this variant of the Stille reaction (eq 1) and report herein our progress.



Results and Discussion

The initial objective, i.e., the identification of a catalyst or promoter[11] competent to cross-couple α-hydroxystannanes with alkenyl and aryl electrophiles at room temperature, was conducted using pyrrolidinylthiocarbamoyl (PTC)-protected stannane **3** and *E*-alkenyl iodide **4** as the test system. Evaluation of a wide variety of transition metal salts and complexes, either individually or in combination, revealed copper salts[12,13] were uniquely suitable and, in particular, commercial copper(I)

(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.
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(3) (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.
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(5) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1−5.
(6) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973−5982.
(7) Ye, J.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1993**, *34*, 8007−8010.
(8) Falck, J. R.; Barma, D.; Mohapatra, S.; Bandyopadhyay, A.; Reddy, K. M.; Qi, J.; Campbell, W. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4987−4990.
(9) Recent examples of alternative chiral allylic alcohol syntheses: (a) Berkessel, A.; Roland, K.; Neudoerfl, J. M. *Org. Lett.* **2006**, *8*, 4195−4198. (b) Evans, D. A.; Aye, Y. *J. Am. Chem. Soc.* **2006**, *128*, 11034−11035. (c) Hilt, G.; Hess, W.; Harms, K. *Org. Lett.* **2006**, *8*, 3287−3290.
(10) Recent examples of alternative chiral benzylic alcohol syntheses: (a) Yang, S.-D.; Shi, Y.; Sun, Z.-H.; Zhao, Y.-B.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2006**, *17*, 1895−1900. (b) Zhu, D.; Yang, Y.; Hua, L. *J. Org. Chem.* **2006**, *71*, 4202−4205. (c) Grasa, G. A.; Zanotti-Gerosa, A.; Hems, W. P. *J. Organomet. Chem.* **2006**, *691*, 2332−2334.
(11) Since CuTC is used in stoichiometric amounts and apparently consumed to some extent, a reviewer suggested the term promoter instead of catalyst.
(12) Catalysis or promotion of the Stille reaction by copper salts in combination with other transition metals or alone is well established: (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364. (b) Wipf, P. *Synthesis* **1993**, 537−557. (c) Piers, E.; McEachern, E. J.; Burns, P. A. *J. Org. Chem.* **1995**, *60*, 2322−2323. (d) Wang, Y.; Burton, D. *Org. Lett.* **2006**, *8*, 1109−1111.
(13) Transmetalation of organostannanes with higher order cuprates is also known: Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641−2643.

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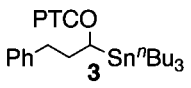
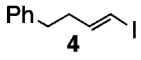
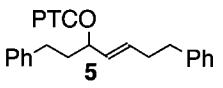
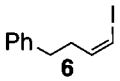
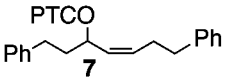
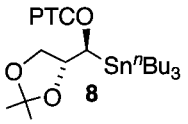
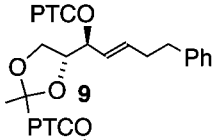
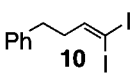
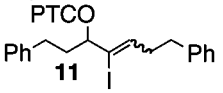
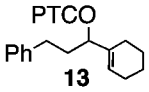
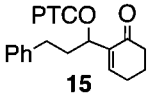
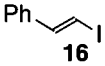
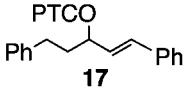
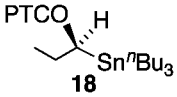
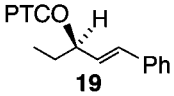
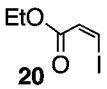
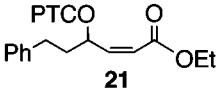
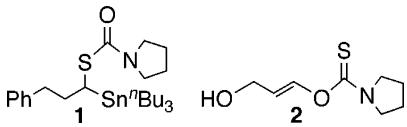
Table 1. Cross-Coupling of PTC-Protected α-Hydroxystannanes with Vinyl Iodides[a]

entry	stannane[b]	iodide	time (h)	adduct	yield (%)
1	 **3**	 **4**	0.15	 **5**	84
2	**3**	 **6**	0.3	 **7**	83
3	 **8**	**4**	0.1	 **9**	82 (>98% d.e.)
4	**3**	 **10**	0.25 1[c] 0.25[d]	 **11**	78 (4:1 *Z*/*E*)[e] 76 (9:1 *Z*/*E*)[e] 92 (4:1 *Z*/*E*)[e]
5	**3**	 **12**	1	 **13**	73
6	**3**	 **14**	0.5	 **15**	66
7	**3**	 **16**	0.25	 **17**	87
8	 **18**	**16**	0.25[f] 1.5[c] 7.5[g]	 **19**	85 (90% e.e.)[h] 76 (91% e.e.)[h] 70 (95% e.e.)[h]
9	**3**	 **20**	0.15	 **21**	81

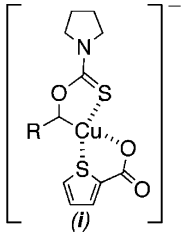
[a] See standard cross-coupling procedure. [b] Stannane **3** is racemic; **8** and **18** are >98% optically pure. [c] Conducted at 0 °C. [d] Stannane (2.5 equiv), iodide (1 equiv). [e] Ratio based on weight of pure, isolated adduct. [f] Conducted at 23 °C. [g] Conducted at −20 °C. [h] Determined by integration of chiral HPLC chromatogram.

thiophene-2-carboxylate[14] (CuTC; Liebeskind promoter[15]), albeit in stoichiometric amounts. The yield of adduct **5** increased as the portion of CuTC was raised: 0.1 equiv (51%), 0.5 equiv (64%), 1.0 equiv (73%), and 1.5 equiv (84%; Table 1, entry 1); more than 1.5 equiv of CuTC did not improve the outcome.[16] The remainder of the material balance was carbamothioate **1**, the result of an S→O rearrangement.[17] Control experiments showed **1** was generated almost quantitatively in *ca*. 15 min when **3** was exposed to CuTC under identical conditions in the absence of an electrophile. Yields of **5** were similar in many common solvents, *inter alia*, THF, DMF, NMP, toluene, acetone, dioxane, and EtOAc. However, the reaction rate was patently faster in THF (typically 10−60 min at rt) compared with the other aforementioned solvents; thus, it was used as the routine solvent in all subsequent experiments. In contrast to the experience of others,[18] sources of fluoride (LiF, TBAF, KF, AlF_3, CsF) did not have a significant effect nor did Lewis acids [$MgBr_2$, $AlCl_3$, $FeCl_3$, $ZnBr_2$, $BF_3{\cdot}Et_2O$, $Sc(OTf)_3$].[19]


1 **2**

Once we had secured a promising promoter and standardized the reaction conditions, we next explored the scope of the cross-coupling using a panel of representative alkenyl iodides (Table

(14) We speculate that CuTC is more effective than other copper salts because it is bidentate and can establish a highly coordinated intermediate, e.g., *i*, that resists *β*-elimination. This may explain, in part, why simple aryl iodides and 1-iodocyclohexene are satisfactory coupling partners, in contrast to the experience of Allred and Liebeskind (see ref. 15).


(i)

(15) The Liebeskind laboratory developed CuTC and adroitly exploited it for the cross-coupling of organostannanes with aryl and alkenyl iodides: Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749.

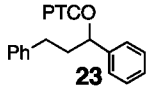
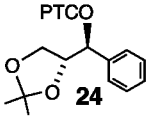
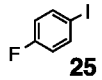
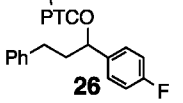
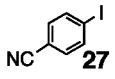
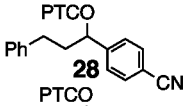
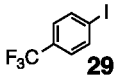
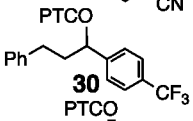
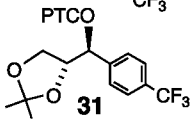
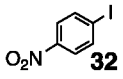
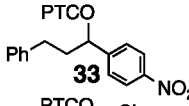
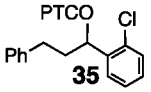
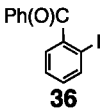
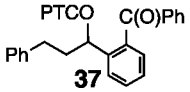
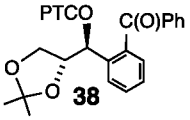
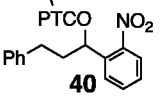
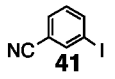
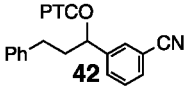
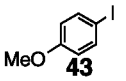
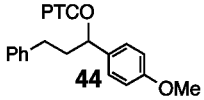
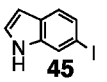
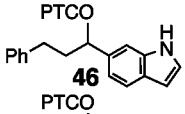
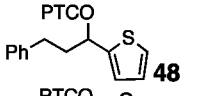
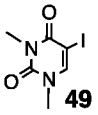
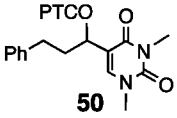
(16) Little, if any, tri-*n*-butylstannyl iodide or distannane is observed in the crude product at the end of the reaction. In light of the report by Allred and Liebeskind (ref. 15) that tri-*n*-butylstannyl thiophene-2-carboxylate is produced in their reactions, we speculate that the tri-*n*-butylstannyl byproduct is sequestered in this form. It would follow, therefore, that stoichiometric amounts of CuTC would be required, and this is what we found empirically to achieve maximum yields.

(17) Lewis acid catalyzed Newman−Kwart rearrangement: Fujii, K.; Shuto, Y.; Kinoshita, Y. *Agric. Biol. Chem.* **1990**, *54*, 2379−2384.

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

(19) Kagoshima, H.; Shimada, K. *Chem. Lett.* **2003**, *32*, 514−515.

Table 2. Cross-Coupling of PTC-Protected α-Hydroxystannanes with Aryl/Heteroaryl Iodides[a]

entry	stannane[b]	iodide	time (h)	adduct	yield (%)
1	**3**	 **22**	0.25	 **23**	65[c]
2	**8**	**22**	0.15	 **24**	63[d]
3	**3**	 **25**	0.3	 **26**	70
4	**3**	 **27**	0.25	 **28**	72
5	**3**	 **29**	0.3	 **30**	74
6	**8**	**29**	0.15	 **31**	72[d]
7	**3**	 **32**	0.3	 **33**	70
8	**3**	 **34**	0.25	 **35**	61
9	**3**	 **36**	0.25	 **37**	77
10	**8**	**36**	0.15	 **38**	75[d]
11	**3**	 **39**	0.3	 **40**	72
12	**3**	 **41**	0.25	 **42**	64
13	**3**	 **43**	0.25	 **44**	60
14	**3**	 **45**	0.3	 **46**	60
15	**3**	 **47**	0.3	 **48**	61
16	**3**	 **49**	0.5	 **50**	68

[a] See standard cross-coupling procedure. [b] Stannane **3** is racemic and **8** is >98% optically pure. [c] Stannane added over 0.5 h. [d] >98% de via NMR of crude product.

1). Notably, **3** and (+)-glyceryl stannane **8** added smoothly to *Z*-iodide **6** and *E*-iodide **4**, respectively, affording *Z*-allylic alcohol **7** (entry 2) and *E*-allylic alcohol **9** (entry 3) with complete stereospecificity at the alkenyl centers (>98% by $^{1}H/^{13}C$ NMR), thus precluding a radical chain mechanism. The latter cross-coupling was complete in less than 10 min at rt. Retention

of configuration at the stannyl-substituted stereogenic center, as indicated by the *erythro*-coupling[20] ($J_{2,3} \approx 4.8$ Hz) in the ^{1}H NMR of **9**, was consistent with prior experience using other classes of electrophiles,[5,6] but opposite to the inversion of configuration observed by Kells and Chong using scalemic α-(sulfonamido)organostannanes and Pd/Cu cocatalysis.[21] Not surprisingly, transmetalation of **8** with lithium or magnesium prior to conversion to an organocopper intermediate failed to give **9** and instead led to **2** (>90%) via facile β-elimination.[22]

In the case of di-iodide **10**, there was a modest preference for addition to the less hindered side furnishing **11** as a 4:1 *Z*/*E*-mixture (entry 4). The *Z*/*E*-ratio improved to 9:1 at 0 °C. Repetition of the coupling at rt using an excess of stannane **3** gave rise to an excellent yield of adduct **11**, but had no influence on the stereochemistry. Other kinds of alkenyl iodides, e.g., cyclohexenyl[14] **12**, α-keto **14**, and β-iodostyrene (**16**), behaved analogously generating **13** (entry 5), **15** (entry 6), and **17** (entry 7), respectively, in synthetically useful yields. The coupling in entry 8 was more challenging since enantioenriched stannane **18** is both acyclic and nonbiased (i.e., unlike **8**, it has no other chiral centers to influence the stereochemical outcome). At rt, **19** was secured in good yield, but only 90% ee. As anticipated, the enantioselectivity could be elevated by lowering the temperature, 91% ee or 95% ee at 0 °C or −20 °C, respectively, albeit with some consequential effects on the yield and reaction time. The cross-coupling of **20** (entry 9) also merits attention as an indicator of the mildness of the reaction conditions. Despite the proclivity of **20** toward loss of HI and/or isomerization, its union with **3** proceeded without complication or loss of the *Z*-configuration to give **21**.

The applicability of aryl and heteroaryl iodides as electrophiles was also evaluated, and the results are summarized in Table 2. The simple, unactivated electrophile iodobenezene[14] (**22**) provided acceptable yields of **23** (entry 1) and **24** (entry 2) from **3** and **8**, respectively. The presence of electron-withdrawing substituents boosted the efficiency somewhat. Thus, benzyl alcohols **26**, **28**, **30**, **31**, and **33** were accessed in 70% or better yield from aryl iodides **25** (entry 3), **27** (entry 4), **29** (entries 5 and 6), and **32** (entry 7), accordingly. Even the more sterically demanding *o*-chloro **34**, *o*-benzoyl **36**, and *o*-nitro **39** aryl iodides reacted well to give **35** (entry 8), **37**/**38** (entries 9 and 10), and **40** (entry 11) all in comparable amounts. A *m*-cyano substituent seemed to have minimal effect (entry 12) while a *p*-methoxy (entry 13) had the anticipated equal but opposite influence of that observed with electron-withdrawing groups (*vide supra*). A variety of heteroaryl iodides, despite concerns that they might retard coupling by sequestering the promoter, were gratifyingly reactive. Indole **45**, thiophene **47**, and uracil **49** were readily transformed into **46** (entry 14), **48** (entry 15), and **50** (entry 16), respectively, within 30 min or less at rt under the standard reaction conditions.

Standard Cross-Coupling Procedure. A solution of PTC-protected α-alkoxystannane (0.19 mmol) in anhydrous THF (2 mL) was added to a stirring suspension of CuTC (0.28 mmol) and alkenyl/aryl/heteroaryl halide (0.28 mmol) in anhydrous THF (2 mL) under an argon atmosphere at the temperature indicated in Table 1 and 2. The heterogeneous mixture turned reddish-green as the reaction progressed. After TLC monitoring indicated all stannane was consumed (see Table 1 and 2 for times), the reaction mixture was diluted with Et_2O (20 mL) and filtered through a small bed of alumina. The filter bed was washed with fresh Et_2O (5 mL), and the combined filtrates were concentrated under reduced pressure. Chromatographic purification of the residue on SiO_2 gave the cross-coupled adduct in the indicated yield (Tables 1 and 2).

Conclusions

The Liebeskind promoter (CuTC) rapidly and stereospecifically cross-couples racemic and scalemic PTC-protected α-hydroxystannanes with alkenyl/aryl/heteroaryl iodides including secondary cycloalkenyl and unactivated aryl iodides in THF at ambient temperature. It is anticipated that the foregoing methodology will be compatible with a wide range of functionality and be of general utility in the synthesis of heteroatom-substituted stereogenic centers. Toward this end, preliminary results demonstrate CuTC can also mediate the cross-coupling of alkenyl bromides with PTC-protected α-hydroxystannanes. These data and extensions to other classes of electrophiles will be reported in due course.

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Supporting Information Available: Synthetic procedures, analytical data, chiral HPLC chromatograms, and ^{1}H/^{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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