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# Copper-Mediated Cross-Coupling of Organostannanes with Organic Iodides at or below Room Temperature

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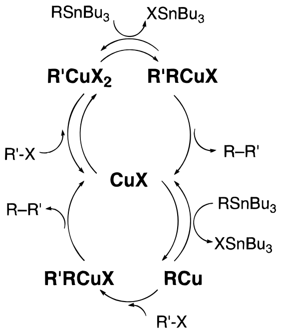
Nickel- and palladium-mediated cross-coupling reactions have revolutionized the practice of organic synthesis in academic and industrial laboratories over the past few decades. Kumada's[1] use of phosphine ligands to discipline the reactivity of organonickel intermediates allowed synthetically useful nickel-catalyzed couplings between Grignard reagents and vinyl/aryl/heteroaryl halides, thereby significantly extending earlier studies with simple transition metal salts by Kharasch and Fields.[2] Negishi expanded the cross-coupling concept to include aluminum, zirconium, and zinc reagents using both nickel- and palladium-based catalysts.[3] But it was the discovery of palladium-catalyzed cross-couplings of organic derivatives of tin (Stille,[4,5] Beletskaya[6] ), boron (Suzuki-Miyaura[7] ), and silicon (Hiyama[8] ) that meant carbon−carbon bonds could be formed under *neutral reaction conditions* between highly-functionalized substrates, a virtue that has led to the widespread acceptance of these powerful processes by the synthetic organic community.

In 1990, the beneficial influence of cocatalytic Cu(I) on nonproductive or sluggish Stille cross-coupling reactions catalyzed by palladium was first pointed out.[9] The practical utility of the "copper effect" was immediately recognized, and it was quickly extended to numerous other palladium-catalyzed carbon−carbon bond forming reactions (a few selected examples are documented in the bibliography).[10−17] In the original disclosure of the copper effect[9] it was suggested that transmetalation of the R group from $\mathrm{RSnBu_3}$ to CuI could be responsible for the catalysis, a process portending a synthetically useful cross-coupling protocol *mediated by simple copper salts alone*.[18,19] This suggestion has borne fruit. Recent studies support the tin to copper transmetalation,[20] and specific reaction subsets of organostannane cross-coupling reactions mediated by CuX salts have been documented by Piers[21] and Falck.[22]

In our laboratory, a cursory survey of the reaction of (4-chlorophenyl)-tri-$n$-butylstannane with 2-methyl-3-bromo-1-propene revealed a slow but efficient cross-coupling mediated by *catalytic* quantities of various Cu(I)X salts; for example, 5% $\mathrm{Cu(MeCN)_4BF_4}$ in $N$-methylpyrrolidone (NMP) gave 3-(4-chlorophenyl)-2-methyl-1-propene in 77% yield after 16 h at 80 °C. Monitoring of this reaction by GLC showed a rapid initial rate followed by a considerable rate retardation as the reaction approached 50% completion. *Significantly, the addition of 1 equiv of n-Bu$_3$SnCl at the start of the reaction produced only a trace of product under identical conditions*.

**Scheme 1**



These observations are consistent with a *reversible* transmetalation from tin to copper that is retarded by the formation of increasing concentrations of $n$-$\mathrm{Bu_3SnX}$ (X = halogen) as the cross-coupling reaction proceeds. Since mechanistic studies support the oxidative addition of certain organic halides to Cu(I) salts,[23,24] the transmetalation from $\mathrm{RSnBu_3}$ could occur either to a $\mathrm{RCuX_2}$ intermediate or to the CuX reagent, as depicted in the top and bottom cycles of Scheme 1, respectively. Regardless of the exact timing of the transmetalation step, recognition of its reversible nature suggests that the copper-mediated cross-coupling of organostannanes and organic halides should proceed most rapidly and efficiently either (1) by using an excess of CuX to drive an unfavorable transmetalation, a tactic explaining the requirement of *greater than 2 equiv* of CuCl in Piers's account of the *intramolecular* coupling of vinyl iodides with alkenyl trimethylstannanes;[21] or (2) by the design of reaction parameters to produce an organostannane byproduct, $n$-$\mathrm{Bu_3Sn}$**X**, that does not participate in a back reaction with RCu or $\mathrm{R'CuX_2}$.

As a first-stage solution to this problem,[25] a variety of Cu(I) carboxylates (CuOCOR: R = Me, Ph, ($E$)-CH═CHPh, 2-pyridyl, 2-furyl, 2-thienyl) were prepared and surveyed as stoichiometric mediators of the cross-coupling of ($E$)-$\beta$-(tri-$n$-butylstannyl)styrene with ($E$)-$\beta$-iodostyrene in NMP. Of these, copper(I) thiophene-2-carboxylate (CuTC)[26] possessed the best spectrum of properties (inexpensive, easy large-scale synthesis, air-stable, rapid reactions). *Most significantly, and in contrast to CuCl, CuBr, CuI, and CuCN,*[27] *1.5 equiv of CuTC mediated the rapid and very efficient intermolecular cross-coupling of aryl, heteroaryl, and vinylstannanes with vinyl iodides and certain aryl iodides within minutes in NMP at or below room temperature!*

Results of this study are depicted in Table 1. The cross-coupling possesses useful chemoselectivity; carbonyl groups

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[19] A synthetically powerful process based on transmetalation from organostannanes to higher order *cuprates* is well-known: Behling, J.; Babiak, K.; Ng, J.; Campbell, A.; Moretti, R.; Koerner, M.; Lipshutz, B. *J. Am. Chem. Soc.* **1988**, *110*, 2641. Behling, J.; Ng, J.; Babiak, K.; Campbell, A.; Elsworth, E.; Lipshutz, B. *Tetrahedron Lett.* **1989**, *30*, 27.

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[23] Cohen, T.; Cristea, I. *J. Org. Chem.* **1975**, *40*, 3649.

[24] Cohen, T.; Cristea, I. *J. Am. Chem. Soc.* **1976**, *98*, 748.

[25] As deduced from Scheme 1, production of an impotent form of $n$-$\mathrm{Bu_3Sn}$**X** requires control over all halide or pseudo-halide species that are introduced into the reaction; i.e., both the copper(I) salt, Cu**X**, and the organic halide, R′**X**, must possess a moiety **X** that produces the same form of $n$-$\mathrm{Bu_3Sn}$**X**. Therefore, effective catalysis with substoichiometric copper(I) salts should eventually be feasible if a viable reaction partner, R′**X**, can be found that both participates in efficient coupling with $\mathrm{RSnBu_3}$ and possesses a group **X** that leads to an unreactive form of $n$-$\mathrm{Bu_3Sn}$**X**.

[26] See Supporting Information for complete details.

[27] From control experiments, it was determined that a large excess of CuCl (but not CuBr, CuI, or CuCN) will induce *intermolecular* cross-coupling of organostannanes and alkenyl iodides. In contrast to the use of 1.5 equiv of CuTC, more than 5 equiv of CuCl is required to drive the reaction to completion.

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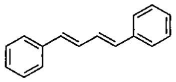
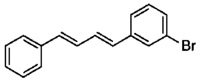
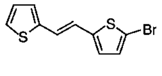
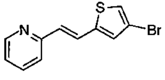
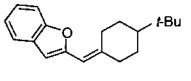
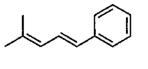
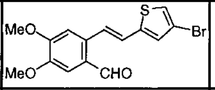
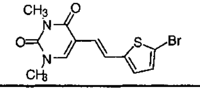
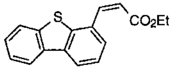
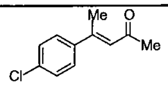
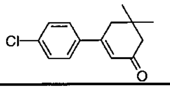
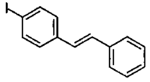
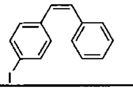
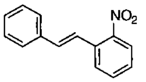
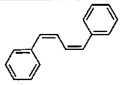
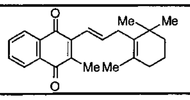
**Table 1.** Copper(I) 2-Thiophenecarboxylate (CuTC) Mediated Cross-Coupling Reactions

$$\mathrm{RSnBu_3} + \mathrm{R'I} \xrightarrow[\text{NMP, 0 °C to room temperature, minutes}]{\text{1.5 equiv of (2-thienyl)COOCu}} \mathrm{RR'}$$

| Entry | RSnBu$_3$<br>R'I | Product | Temp<br>Time<br>Yield |
|---|---|---|---|
| 1 | (*E*)-β-(*n*-Bu$_3$Sn)styrene<br>(*E*)-β-iodostyrene |  | 0 °C<br>5 min<br>89% |
| 2 | (*E*)-β-(*n*-Bu$_3$Sn)styrene<br>(*E*)-3-bromo-β-iodostyrene |  | 0 °C<br>5 min<br>93% |
| 3 | 2-(*n*-Bu$_3$Sn)thiophene<br>(*E*)-2-(2-iodovinyl)-5-bromothiophene |  | 0 °C<br>5 min<br>89% |
| 4 | 2-(*n*-Bu$_3$Sn)pyridine<br>(*E*)-2-(2-iodovinyl)-4-bromothiophene |  | 0 °C<br>5 min<br>83% |
| 5 | 2-(*n*-Bu$_3$Sn)benzofuran<br>4-*t*-butyl-1-iodomethylenecyclohexane |  | 23 °C<br>30 min<br>77% |
| 6 | 2-Me-1-(*n*-Bu$_3$Sn)-1-propene<br>(*E*)-β-iodostyrene |  | 23 °C<br>15 min<br>80% |
| 7 | 2-(*n*-Bu$_3$Sn)-4,5-dimethoxybenzaldehyde<br>(*E*)-2-(2-iodovinyl)-4-bromothiophene |  | 23 °C<br>5 min<br>78% |
| 8 | 5-(*n*-Bu$_3$Sn)-1,3-dimethyluraci<br>(*E*)-2-(2-iodovinyl)-5-bromothiophene |  | 23 °C<br>5 min<br>75% |
| 9 | 1-(*n*-Bu$_3$Sn)dibenzothiophene<br>ethyl (*Z*)-β-iodoacrylate |  | 23 °C<br>5 min<br>71% |
| 10 | 4-chlorophenyl-*n*-Bu$_3$Sn<br>(*E*)-4-iodo-3-pentene-2-one |  | 23 °C<br>15 min<br>89% |
| 11 | 4-chlorophenyl-*n*-Bu$_3$Sn<br>5,5-dimethyl-3-iodocyclohex-2-enone |  | 23 °C<br>30 min<br>81% |
| 12 | 4-iodoophenyl-*n*-Bu$_3$Sn<br>(*E*)-β-iodostyrene |  | 23 °C<br>5 min<br>97% |
| 13 | 4-iodoophenyl-*n*-Bu$_3$Sn<br>(*Z*)-β-iodostyrene |  | 23 °C<br>5 min<br>95% |
| 14 | (*E*)-β-(*n*-Bu$_3$Sn)styrene<br>*o*-iodonitrobenzene |  | 23 °C<br>30 min<br>74% |
| 15 | (*Z*)-β-(SnBu$_3$)styrene<br>(*Z*)-β-iodostyrene |  | 0 °C<br>5 min<br>94% |
| 16 | 2-Me-3-(*n*-Bu$_3$Sn)-1,4-naphthoquinone<br>(*E*)-1-iodo-3-(2,6,6-tri-Me-2-cyclohexenyl)-1-propene |  | 23 °C<br>15 min<br>93% |

(entries 7−11, 16) and most aryl and heteroaryl bromides and iodides (entries 2−4, 7, 8, 12, 13) remain untouched. Since the latter react with organostannanes under typical Stille reaction conditions, this chemoselectivity should allow further functionalization of the products using various palladium-based protocols. The CuTC cross-coupling occurs with excellent retention of stereochemistry of both the organostannane and alkenyl iodide (entries 1, 15 and 12, 13), precluding a radical chain mechanism and supporting a cross-coupling mechanism composed of transmetalation, oxidative addition, and reductive elimination steps.

In some cases, the cross-coupling could also be effected with *catalytic* quantities of Cu(I) salts in the presence of stoichiometric carboxylate salts or alkali metal fluorides, although, to date, a general process has not been found. For instance, the addition of 1.2 equiv of CsF as an *in situ* tri-*n*-butylstannane scavenger to a mixture of 1.0 equiv of (4-chlorophenyl)-tributyltin, 1.2 equiv of *β*-iodostyrene, and 20% CuBr in NMP produced 4-chlorostilbene in 91% yield after 8 h at 60 °C.

Analysis of the reaction of (*E*)-*β*-(tri-*n*-butylstannyl)styrene with CuTC in NMP *in the absence of a reactive alkenyl iodide* showed slow (2 h) protodestannylation to styrene with concomitant formation of (*E*,*E*)-1,4-diphenylbutadiene and the appearance of a Cu(0) mirror, suggesting at least partial transmetalation from tin to copper(I). Providing further support for the direct oxidative addition of certain Cu(I) salts to alkenyl iodides,[24] excess CuTC reacted rapidly with various alkenyl iodides to produce symmetrical dienes in high yield.[28]

Although simple aryl iodides were ineffective coupling partners, *o*-iodonitrobenzene (but not *p*-iodonitrobenzene) reacted rapidly and efficiently with (*E*)-*β*-(tri-*n*-butylstannyl)-styrene (Table 1, entry 14). Steric and electronic factors imparted by the alkenyl iodide combine to play subtle and presently undefined roles in determining the success of the cross-coupling process. For example, *E*- and *Z*-monosubstituted and 2,2-disubstituted alkenyl iodides reacted well, as did 5,5-dimethyl-3-iodocyclohexenone, but 1-iodocyclohexene did not. Alkyl iodides and benzyl bromides were unreactive, while allyl bromides reacted rapidly, but suffered from competing esterification by the copper carboxylate.

In conclusion, the simplicity of this CuTC-mediated cross-coupling protocol, which features a rapid reaction rate at low temperature, should allow its use in many situations where thermally sensitive substrates are studied, or where copper-mediated coupling provides a functional group selectivity not achievable with palladium. Workup is straightforward. Products generally crystallized upon removal of solvent in vacuo after the reaction mixture was diluted with ether, filtered, washed with water, and dried. Though stoichiometric in copper, the new process is economical in terms of money and time, and it could prove competitive in many situations with traditional palladium-catalyzed protocols.

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**Supporting Information Available:** Complete description of the synthesis and characterization of all compounds in the paper (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[28] The addition of 2.5 equiv of CuTC to *β*-iodostyrene in NMP gave 1,4-diphenylbutadiene in 95% yield after only 30 min at room temperature. A study of this mild Ullman-like coupling of alkenyl iodides is underway (cf.: Cohen, T.; Cristea, I. *J. Am. Chem. Soc.* **1976**, *98*, 748).