

A versatile protocol for Stille–Migita cross coupling reactions†‡

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The combination of catalytic amounts of [Pd(PPh₃)₄], copper thiophene-2-carboxylate (CuTC) and [Ph₂PO₂][NBu₄] allowed a series of exigent Stille–Migita reactions to be performed with high yields; as the protocol is fluoride free, a variety of O-silyl and C-silyl groups remained intact.

Organotin derivatives are prominently featured amongst the different nucleophiles amenable to palladium catalyzed cross coupling reactions.¹ In many cases, they constitute a good compromise between availability, ease of handling, functional group tolerance and desirable reactivity towards the electrophilic partner. As a result, Stille–Migita reactions remain widely used in advanced organic chemistry, natural product total synthesis and material science, even though other methods for catalytic cross coupling are arguably more benign.^{2,3}

Over the years, the original Stille–Migita protocol⁴ has been considerably improved. The most noteworthy advances resulted from careful optimization of the ligand sets,⁵ as well as from the recognition of a significant co-catalytic effect exerted by copper(i) salts.^{6–8} Although the observed rate accelerations upon addition of CuX may have more than one cause,^{7a} transmetalation of the tin reagents with formation of organocopper species is almost certainly involved in reactions performed in polar media (Scheme 1). Since organocopper reagents are considered more nucleophilic, a positive effect on the rate and efficiency will ensue in all cases in which the transmetalation step of the catalytic cycle is rate determining.⁹ As the tin/copper exchange is likely reversible, however, the positive influence of Cu(i) will fade away with increasing conversion, as the built-up of R₃SnX in the mixture drives the equilibrium back to the left side.

Several methods have been devised to counteract this undesirable effect. A simple but effective means is to employ a large excess of CuCl (≥ 5 equiv.) in combination with LiCl (≥ 6 eq.).¹⁰ Alternatively, the use of copper thiophene-2-carboxylate (CuTC) has been recommended,^{8a} as the resulting tin carboxylates might be less prone to participate in the retro-reaction. Particularly successful was a procedure developed by Baldwin and co-workers,¹¹ which requires only catalytic amounts of CuI, provided that the mixture is complemented with CsF or TBAF (2 equiv.) to remove the generated R₃SnX

species from the equilibrium in form of sparingly soluble R₃SnF.

Despite the success of these and related protocols,¹² they essentially met with failure when applied to various late-stage Stille–Migita reactions planned to serve as key fragment coupling steps of different natural product syntheses pursued by our group. Not surprisingly, major problems arose from the incompatibility of the fluoride additives with the silyl protecting group regiments prevalent in target oriented synthesis.¹³ The sensitivity of certain substrates to the fairly basic conditions caused by the presence of fluoride in the medium constitutes another limiting factor.

We reasoned that these problems could be remedied by using a less nucleophilic and essentially neutral tin scavenger. We opted for the phosphinate salt [Ph₂PO₂][NBu₄]¹⁴ which had already previously been used to remove tin contaminants from difficult to purify mixtures,^{12b} and had also served very well in palladium-only¹⁵ as well as in palladium free cross coupling processes.¹⁶ To the best of our knowledge, however, this particular additive has not been exploited in Pd/Cu co-catalyzed Stille–Migita reactions prior to our work. We were therefore pleased to see that replacement of CsF by [Ph₂PO₂][NBu₄] allowed a series of challenging Stille–Migita cross coupling reactions to be performed with excellent results, which could not be effected otherwise.

The examples compiled in Table 1 are representative. Entry 1 shows a particularly challenging case as the skipped diene subunits of the substrate and the product are exceptionally sensitive and prone to double bond isomerization with formation of conjugated trienes under acidic as well as basic conditions, and even upon gentle heating;¹⁷ moreover, the terminal TBS-ether is incompatible with fluoride additives. Whereas the use of PdCl₂(MeCN) in combination with Ph₃As as a preferred ligand for Stille–Migita reactions^{5a} led to no reaction, the combination of [Pd(PPh₃)₄] (5 mol%), CuTC (1.5 eq.) and [Ph₂PO₂][NBu₄] (1.2 eq.) in DMF resulted in essentially quantitative cross coupling even at ambient temperature. Entry 2 confirms this rewarding result and shows that the reaction still proceeds in the presence of the potential S- and N-donor sites of a tetrazolyl thioether. Likewise, a conceivable Heck reaction between the iodide and a terminal alkene in the donor is not interfering (entry 3). The fact that cross coupling occurred at ambient temperature is key to success for the

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Scheme 1 Pre-equilibrium as one of the reasons for the co-catalytic effect of copper additives on Stille–Migita cross coupling reactions performed in polar media.

Table 1 Palladium/copper co-catalyzed Stille–Migita cross coupling reactions promoted by $[\text{Ph}_2\text{PO}_2][\text{NBu}_4]^a$

Entry	Electrophile	Stannane	Product	Yield
1				84 %
2				87 %
3				80 %
4				56 %
5				71 % ^b
6				79 % ^b
7				89 % ^c
8				65 % ^{d,e}
9				76 %
10				77 %
11				85 % ^f
12				75 % ^f

^a $[\text{Pd}(\text{PPh}_3)_4]$ (5 mol%), CuTC (1.2–1.6 eq.) and $[\text{Ph}_2\text{PO}_2][\text{NBu}_4]$ (1.1–1.6 eq.) in DMF at RT, unless stated otherwise. ^b Using 10 mol% $[\text{Pd}(\text{PPh}_3)_4]$. ^c Using $[\text{Pd}(\text{PPh}_3)_4]$ (70 mol%), CuTC (3 eq.) and $[\text{Ph}_2\text{PO}_2][\text{NBu}_4]$ (4 eq.). ^d 86% based on recovered starting material. ^e The stannane was slowly added to the mixture. ^f In THF.

example depicted in entry 4, as the resulting product rapidly decomposes when heated to $\geq 35\text{ }^{\circ}\text{C}$.¹⁷

The examples shown in entries 5–7, which model a key fragment coupling *en route* to amphidinolide H,¹⁸ are also highly demanding. Apprehensive that a previous approach to this sensitive target based on a late-stage intramolecular Stille–Migita reaction at the 1,3-diene site had met with failure,¹⁹ much effort was dedicated to optimize this step. Grati- fyingly, the new protocol worked exceedingly well, providing the sterically hindered products in good to excellent yields. Most notable is the fact that the reaction tolerates unprotected hydroxy epoxides, which undergo Payne rearrangement under basic conditions. Likewise, a sensitive aldol unit remained intact (entry 7), attesting to an essentially neutral medium operative under the chosen conditions. As expected, various O-silyl groups as well as a vinylsilane entity (entry 5) posed no problems for this fluoride free protocol.

It is well precedented that steric hindrance adversely affects Stille–Migita and other palladium catalyzed processes.^{2,3} Therefore it was rewarding to see that the congested alkenyl triflate shown in entry 8 coupled without incident with the hindered biaryl donor to give product **8** in good yield, which is the key intermediate of a formal total synthesis of the marine alkaloid haouamine A.²⁰ The silylated alkyne terminus in **8** remained unaffected by the admixed $[\text{Ph}_2\text{PO}_2][\text{NBu}_4]$ salt.

Finally, we revisited the formation of compound **9** which represents the common polyketide sector of the crocacin family of antibiotics. Its formation was plagued by poor reproducibility and mostly low yields when performed under conventional conditions ($\text{Pd}_2(\text{dba})_3$ cat., tris-(2-furyl)phosphine, NMP, 40–60 $^{\circ}\text{C}$, 32%),²¹ whereas the 2-trimethylsilyl-ethyl ester moiety precludes the use of fluoride based protocols.^{11,13} In line with our expectations, the new method delivered this product without incident (entry 9). Together with the other model studies displayed in Table 1, this example corroborates the notion that the use of $[\text{Ph}_2\text{PO}_2][\text{NBu}_4]$ in combination with CuTC and a suitable palladium source accounts for a valuable protocol for challenging Stille–Migita cross coupling reactions. Although the use of each individual ingredient has precedence, their combination is unique and allows to cope with fragile functional groups as well as the C- and O-silyl protecting group regimens frequently encountered in target oriented synthesis.

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