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An Efficient Low-Temperature Stille–Migita Cross-Coupling Reaction for Heteroaromatic Compounds by Pd–PEPPSI–IPent**

Meenakshi Dowlut, Debasis Mallik, and Michael G. Organ*[a]

Abstract: The reactivity of Pd–PEPPSI (Pyridine, Enhanced, Precatalyst, Preparation, Stabilization, and Initiation) precatalysts in the Stille–Migita cross-coupling reaction between heteroaryl stannanes and aryl or heteroaryl halides was evaluated. In general, Pd–PEPPSI–IPent (IPent = diisopentylphenylimidazolium derivative) demonstrated high efficiency over a variety of challenging aryl or heteroaryl halides with thiophene-, furan-, pyrrole-, and thiazole-based organostannanes when compared with Pd–PEPPSI–IPr (IPr = diisopropylphenylimidazolium derivative). The transformations proceeded at appreciably lower temperatures (30–80 °C) than triarylphosphine-based Pd catalysts, improving the scope of this useful carbon–carbon bond-forming process.

Keywords: biaryls · cross-coupling · heterocycles · Stille–Migita reaction · palladium

Introduction

The application of organostannanes in natural product synthesis is well known because of the relative ease of their formation and their high stability to air and moisture. In particular, the Stille–Migita cross-coupling reaction[1a,b] is an effective method for the formation of carbon–carbon bonds between two sp^2 centers.[1] Moreover, this protocol is a powerful route to the formation of heteroaromatic-containing compounds that are prevalent in the structure of drugs[2,3] and ligands[4] in metal catalysis.

By far, the majority of cross-coupling reactions to form heterobiaryls utilize phosphane-ligand-based Pd catalysts, such as tetrakis(triphenylphosphane)palladium(0).[5] These protocols are plagued by the requirement for very high temperatures, especially when aryl or heteroaryl chlorides are used as coupling partners. Recently, a few Stille–Migita couplings of active aryl bromides at room temperature were reported employing bulky phosphane ligands. The groups of Fu[6] and Verkade[7] have reported excellent yields with aryl bromides by using $P(t\mathrm{Bu})_3$ and proazaphosphatranes as the supporting ligand for Pd, respectively. Verkade and co-workers further extended the scope of the reaction to nonactivated chlorides, albeit at 110 °C. In addition, lower temperature (45 °C) couplings involving aryl iodides were reported by Baldwin and co-workers.[8] Most recently, Buchwald and Naber[9] have coupled activated aryl chlorides successfully at 80 °C by using the biaryl monophosphane ligand XPhos. Although some progress has been made towards lowering the temperature in Stille–Migita reactions of aryl bromides and iodides, reactions with aryl chlorides, especially nonactivated ones, remains a challenge.

Given the apparent requirement for higher temperatures in the Stille–Migita reaction, N-heterocyclic carbene (NHC) ligands have attracted some attention for this application in light of the high thermal stability of the Pd–NHC bond.[10] The first example of a high-temperature coupling of aryl chlorides by using NHC-based catalysts was reported by Nolan and Grasa.[11] We have prepared a family of air-stable, user-friendly Pd–NHC precatalysts and systematically varied the electronic and steric properties about the metal center.[12,13] Consistently, the *N*-(2,6-diisopropylphenyl) variants (i.e., **1** and **2**) were the most effective in a variety of cross-coupling reactions. Based on empirical data, Espinet and co-workers suggested that bulky ligands tend to promote a tri-coordinated palladium intermediate, thereby lowering the overall activation energy in cross-coupling reactions.[14] In a recent computational study of alkyl–alkyl Negishi couplings, we demonstrated that an increase in steric

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[**] PEPPSI = pyridine, enhanced, precatalyst, preparation, stabilization, and initiation.

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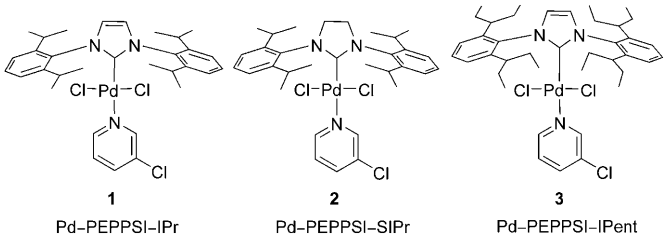
bulk close to the metal center in the case of Pd–NHC catalysts can play a role in promoting more than one step of the catalytic cycle, but that the largest effect is seen in transmetallation, which we believe is rate limiting for at least that particular coupling.[13c,d]



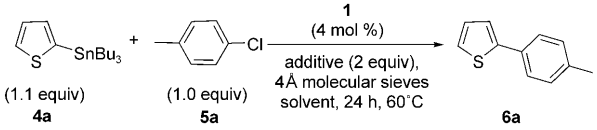
We[13] and others,[15] have recognized not only the need for bulk around the coordination sphere of the metal, but that the bulk must be "fluid" or possess "conformational flexibility" to exert a positive influence on the cross-coupling process. The high reactivity of Pd–PEPPSI–IPent, complex **3** (PEPPSI = pyridine, enhanced, precatalyst, preparation, stabilization, and initiation), relative to the less-bulky Pd–PEPPSI–IPr, complex **1**, in Suzuki–Miyaura cross-coupling reactions[13a] prompted us to explore the application of **3** in Stille–Migita reactions between heteroaryl stannanes and challenging aryl halides.

Results and Discussion

Beginning with commercially available **1**, we sought to develop general, optimized coupling conditions by using the model reaction outlined in Table 1. Attempts to couple 2-(tributylstannyl)thiophene (**4a**) and deactivated 4-chlorotoluene (**5a**) in the absence of an additive met with no reaction at all (Table 1, entries 1 and 2). Interestingly, when a number of well-established additives[16] were used to weaken the C–Sn bond by in situ stannate complex formation, no cross-coupled product was obtained (Table 1, entries 3–8). Switching the countercation from tetrabutylammonium to cesium showed some promise when the reaction was carried out in 1,2-dimethoxyethane (DME; Table 1, entry 9). Further improvement was seen with 1,4-dioxane as the solvent (Table 1, entry 10). Lithium or potassium fluoride (Table 1, entries 13 and 14) in 1,4-dioxane gave lower conversion, which could be an issue of solubility. We lowered the catalyst loading of **1** to 2 (Table 1, entry 23) and 1 mol% (Table 1, entry 24), which did not diminish conversion to the product. With these results in hand, we further explored the effect of temperature and found that 80°C led to better conversion (Table 1, entry 17).

When compound **3** was used under the initial conditions optimized for **1** at 60°C, conversion improved from 53 to 63% (Table 1, entry 18). Similar to **1**, catalyst **3** had an appreciable change in conversion when the temperature was increased to 80°C (Table 1, entry 20), thus application studies were conducted at that temperature. Initially, we investigated the versatility of **3** in the coupling reactions of **4a** to a wide variety of oxidative addition partners.

Table 1. Optimization of Stille–Migita cross-coupling conditions for **1**.



(1.1 equiv) **4a** (1.0 equiv) **5a** **6a**

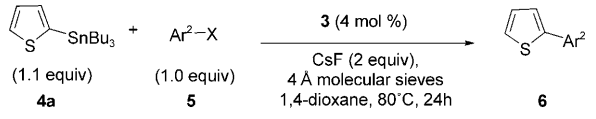
	Additive	Solvent	Conversion [%][a]
1	none	1,4-dioxane	0
2	none	THF	0
3	KOAc	THF	0
4	Na_2CO_3	THF	0
5	LiCl	THF	0
6	nBu_4NBr	THF	0
7	TBAF	THF	0
8	CsF	THF	0
9	CsF	DME	8[b]
10	CsF	1,4-dioxane	53[b]
11	CsF	1,4-dioxane	53[c]
12	CsF	1,4-dioxane	67[d,e]
13	LiF	1,4-dioxane	35[b]
14	KF	1,4-dioxane	43[b]
15	CsCl	1,4-dioxane	66
16	CsCl	toluene	52
17	CsF	1,4-dioxane	70[f]
18	CsF	1,4-dioxane	63[g]
19	CsF	1,4-dioxane	91[c,g]
20	CsF	1,4-dioxane	79[f,g] (76)[b]
21	CsF	1,4-dioxane	45[d,g]
22	CsF	1,4-dioxane	68[c,d,g]
23	CsF	1,4-dioxane	56[b,h]
24	CsF	1,4-dioxane	53[b,i]

[a] Determined by GC–MS with undecane as the calibrated internal standard (based upon an average of two runs). [b] Yield of the isolated product. [c] Reaction was run for 48 h. [d] Reaction was performed at 50°C. [e] Reaction performed with catalyst **2**. [f] Reaction was performed at 80°C. [g] Reaction performed with catalyst **3**. [h] Reaction was performed by using 2 mol% catalyst. [i] Reaction was performed using 1 mol% catalyst.

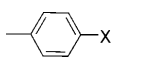
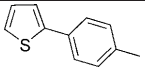
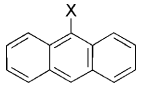
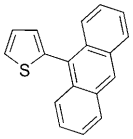
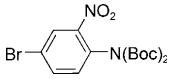
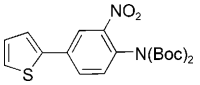
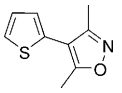
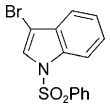
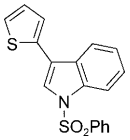
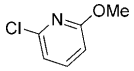
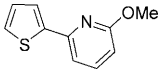
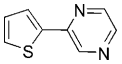
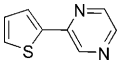
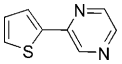
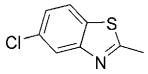
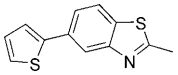
Couplings involving 2-(tributylstannyl)thiophene (4a): Thiophene-based biaryl motifs are found not only in natural products, but also in the structure of drug candidates and functional materials.[17] Although Suzuki–Miyaura aryl–aryl coupling is a popular choice to prepare heterobiaryls, protodeboration of 2-thiopheneboronic acids (or related derivatives) in polar, protic solvents necessitates the use of activated oxidative addition partners.[18] In general, the cross-coupling of aryl halides becomes more sluggish as the electrophilic partner becomes more sterically demanding or electron rich, which provides more opportunity for side reactions to occur, such as reduction. Drawing on our experience with hindered boronic acids treated with catalyst **3**,[13a] we envisioned that the flexible bulk of the flanking isopentyl groups in **3** would impart similar steric assistance to facilitate reductive elimination, and possibly even transmetallation,[13c,d] thereby enhancing coupling and minimizing byproduct formation with organostannanes. Sterically hindered halides (Table 2, entries 2 and 4) were coupled

smoothly in good yields and changing the chloride to a bromide allowed the anthracene-biaryl to form equally well at 60 °C; similar results were found for *p*-tolyl halides (Table 2, entry 1). There does not seem to be an obvious reliance on activated oxidative addition partners since aryl chlorides and bromides all coupled very well. Reactions involving chloropyridines and chloropiperazines (Table 2, entries 6–9) are known to be problematic under Suzuki–Miyaura reaction conditions;[17] with **3**, we observed near quantitative conversions in most cases involving **4a**.[19]

Table 2. Stille–Migita cross-coupling of aryl and heteroaryl halides with 2-(tributylstannyl)thiophene.



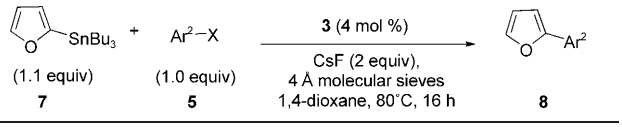
(1.1 equiv) **4a** | (1.0 equiv) **5** | **6**

	Aryl halide	Product		Conv.[a] (Yield)[b] [%]
1			**6a**	79 (X = Cl) (76) 75 (X = Br)[c,d]
2			**6b**	77 (X = Cl) 78 (X = Br) (74)[c]
3			**6c**	70 (62)
4			**6d**	93 (85)
5			**6e**	85 (84)
6			**6f**	99 (92)
7			**6g**	99 (86)
8			**6g**	99[e]
9			**6g**	99[d,f]
10			**6h**	74 (67)

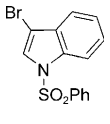
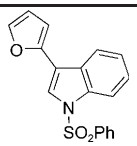
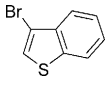
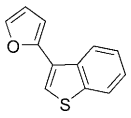
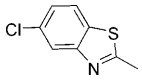
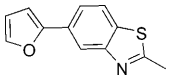
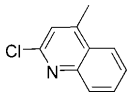
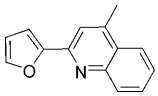
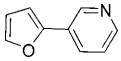
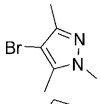
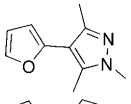
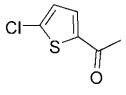
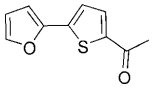
[a] Determined by ^{1}H NMR spectroscopy. [b] Yield of the isolated product following silica-gel chromatography (based upon an average of two runs). [c] Reaction performed at 60 °C. [d] Reaction performed with **1**. [e] Reaction performed with **2** at 30 °C for 30 h. [f] Reaction performed at 40 °C.

Couplings involving 2-(tributylstannyl)furan (7): Furan compounds are important constituents of natural products, fragrances, flavors, and pharmacological agents.[17,20] A serious limitation in synthesizing substituted furans is the facile decomposition[21] of furan metalloids (e.g., 2-furanboronic acid and the corresponding trifluoroborate salt) under polar, protic conditions. Iodo- and bromo(hetero)aryl systems are common substrates in palladium-catalyzed cross-coupling reactions with a few activated chloride examples.[22] On the other hand, Verkade and co-workers reported the Stille–Migita reaction between 2-(tributylstannyl)furan and heteroaryl bromides at 50 °C.[7b] The application of our optimized conditions to couplings with **7** led to good conversions with both moderately activated and nonactivated aryl bromides and chlorides (Table 3). In addition, the reaction was compatible with reactive functional groups, such as sulfonamide and ketone moieties, illustrating the catalytic efficiency and versatility of catalyst **3**.

Table 3. Stille–Migita cross-coupling of aryl- and heteroaryl halides with 2-(tributylstannyl)furan.



(1.1 equiv) **7** | (1.0 equiv) **5** | **8**

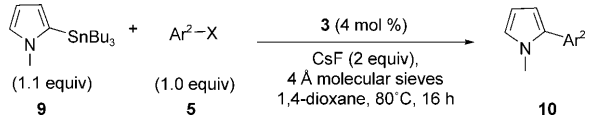
	Aryl halide	Product		Conv.[a] (Yield)[b] [%]
1			**8a**	75 (70)
2			**8b**	90 (81)
3			**8c**	99 (75)
4			**8d**	99 (88)
5			**8e**	99 (96)
6			**8f**	99 (91)
7			**8g**	99 (99)

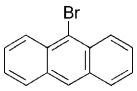
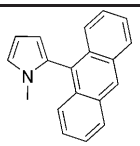
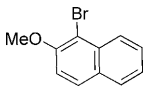
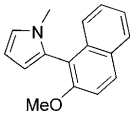
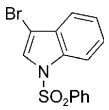
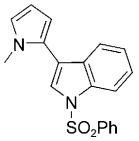
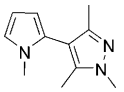
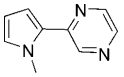
[a] Determined by ^{1}H NMR spectroscopy. [b] Yield of the isolated product following silica-gel chromatography (based upon an average of two runs).

Couplings involving 2-(tributylstannyl)-*N*-methyl pyrrole (9): The synthesis of biaryls containing a pyrrole motif by using organoboron derivatives is limited by the difficulty of reacting pyrrole-based metalloids with hindered or heteroaryl halides under standard Suzuki–Miyaura conditions.[23]

Recognizing the importance of pyrrole-containing compounds with pharmacological properties,[24] we sought to apply our Stille–Migita protocol to pyrrole-based stannanes. The reactions proceeded well and a variety of pyrrole-based biaryls were prepared in excellent yields from a diverse array of oxidative addition partners, including hindered aryl- and heteroaryl bromides (Table 4). It is noteworthy that poisoning of the palladium catalyst, which is a common cause for the failure of pyrrole-based cross-coupling reactions, was not observed with **3**; there was no clear formation of palladium black in any of the reactions performed in this study.

Table 4. Stille–Migita cross-coupling of aryl- and heteroaryl halides with 2-(tributylstannyl)-*N*-methyl pyrrole.



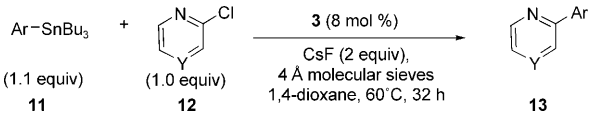
	Aryl halide	Product		Conv.[a] (Yield)[b] [%]
1			**10a**	79 (78)
2			**10b**	95 (90)
3			**10c**	95 (85)
4			**10d**	99 (98)
5			**10e**	99 (89)

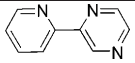
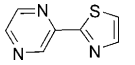
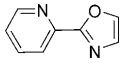
[a] Determined by ^{1}H NMR spectroscopy. [b] Yield of the isolated product following silica-gel chromatography (based upon an average of two runs).

Couplings involving highly electron-deficient heteroarylstannanes (11): Although the cross-coupling of heteroarylstannanes containing a single nitrogen or oxygen can be difficult, more electron-poor substrates with multiple heteroatoms are even more challenging. Moreover, competing side reactions (e.g., ring opening of thiazoles and oxazoles) further complicate the reaction. We were pleased to see quantitative conversions of electron-deficient organostannanes with both 2-chloropyridine and -pyrazine (Table 5). To the best of our knowledge, this is the first example of a palladium-catalyzed Stille–Migita cross-coupling reaction that has taken place at a temperature as low as 60 °C involving 2-(tributylstannyl)thiazole with N-hetero(aryl)chlorides.

This result encouraged us to look in more detail at the coupling temperature. Certainly, the very high temperatures generally required for Stille–Migita coupling limits the attractiveness and applicability of this reaction. Catalyst **3** was able to perform the control coupling reaction in 45 % conversion at 50 °C (Table 1, entry 21), although only moderate conversion was attained when the temperature was lowered to 40 °C. When left for an additional 24 h, the conversion improved to a respectable 68 % (Table 1, entry 22). We have demonstrated previously in couplings involving Grignard reagents that the saturated NHC version of the catalyst was more reactive than the unsaturated one.[25] To this end, we repeated the control experiment with **2** and found that it was active at 50 °C (Table 1, entry 12), whereas catalyst **1** was ineffective at this temperature. It is possible that the increased conformational flexibility of **2**, relative to **1**, is, at least in part, responsible for the higher level of reactivity seen.

Table 5. Stille–Migita cross-couplings of electron-deficient heterostannyl compounds.



	Aryl halide	Product		Conv.[a] (Yield)[b] [%]
1			**13a**	99 (75)
2			**13b**	99 (98)
3			**13c**	99 (90)

[a] Determined by ^{1}H NMR spectroscopy. [b] Yield of the isolated product following silica-gel chromatography (based upon an average of two runs).

We next evaluated substrates at lower temperatures that would provide more biologically interesting, heterobiaryl products. Compound **4a** was coupled with 2-chloropyrazine quantitatively at 40 °C by using **1** (Table 2, entry 9). A further reduction in temperature for this coupling was possible by using **2** at 30 °C (Table 2, entry 8); reproducibly there was no reaction at room temperature (≈23 °C). Control experiments conducted under similar conditions with $PdCl_2$ (for the results shown in Tables 1–5) produced no cross-coupled biaryl products. We were also pleased to see quantitative conversion when 2-chloropyrazine was coupled to 2-(tributylstannyl)thiazole (Table 5, entry 2). To the best of our knowledge, this is the first example of a palladium-catalyzed Stille–Migita cross-coupling reaction that has taken place at a temperature as low as 60 °C involving 2-(tributylstannyl)thiazole with N-heteroaryl chlorides.

Conclusion

Stille–Migita cross-coupling reactions with **3** have shown that the flexible steric bulk of the IPent ligand plays a determining role in effective cross-coupling reactions of heterobiaryls. Pd–PEPPSI precatalysts helped solve a few major problems associated with Stille–Migita reactions: 1) The

coupling of readily available and cheaper nonactivated aryl chlorides generated good to excellent yields of a diverse array of interesting products. 2) Mild conditions were used for the high-yielding cross-coupling of electron-deficient heteroaromatic organostannanes (e.g., thiazole) with activated chlorides. 3) The decomposition of organostannanes or heteroaryl halides was minimized by successfully lowering the reaction temperature from the commonly used 100 °C to as low as 30 °C.

Experimental Section

General Stille–Migita cross-coupling procedure: The Pd–PEPPSI precatalyst (0.02 mmol, 0.04 equiv) and the aryl halide (if the halide was a solid) (0.50 mmol, 1.00 equiv) were added to a glass vial containing a magnetic stirrer bar, dry CsF (156 mg, 1.02 mmol, 2.0 equiv), and activated, crushed 4 Å molecular sieves (50 mg). The vial was then purged twice with argon and anhydrous 1,4-dioxane (1 mL) was added. If the aryl halide (0.50 mmol, 1.00 equiv) was a liquid, it was added after the addition of 1,4-dioxane. The mixture was stirred vigorously for 1 min at RT, after which time the organostannane (0.55 mmol, 1.10 equiv) was added. The reaction was stirred at the desired temperature for 16 h. At this time, the mixture was filtered through a prepacked pad of Celite/CsF (3:1 w/w) and the Celite/CsF pad was washed with CH_2Cl_2 (2×4 mL). The solvent was removed in vacuo and the crude product was diluted with hexanes or CH_2Cl_2 (2 mL). The solution was filtered through a prepacked pad of silica/CsF (1:1 w/w) to remove any remaining tin byproducts. The crude material was then loaded onto a Biotage KP-SiL samplet and purified by using a Biotage KP-SiL column containing an additional layer of CsF (200 mg) on top with hexanes/diethyl ether or hexane/CH_2Cl_2 as the eluent.

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