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Copper-promoted C–N bond cross-coupling with phenylstannane

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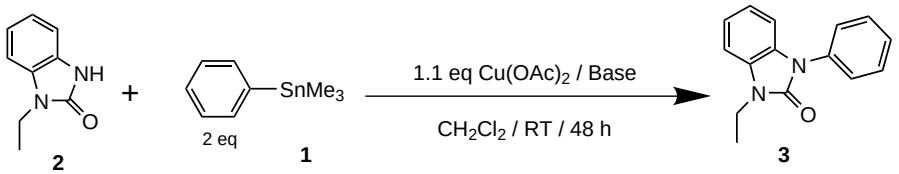
Abstract—Copper-promoted C–N bond cross-coupling of NH-containing substrates with phenylstannane at room temperature was accomplished with the addition of TBAF.

Copper-promoted carbon–nitrogen (C–N) bond cross-coupling reactions of NH-containing substrates with organometalloids have emerged as a powerful synthetic methodology since the initial reports.[1] This novel methodology is an important addition to the general transition-metal promoted C–N bond cross-coupling reactions[1–11] useful for the synthesis of nitrogen-containing compounds in pharmaceuticals, crop-protection chemicals and material sciences. Many extensions and applications of this new methodology have been reported.[2–7,10] Recently, this reaction has been rendered catalytic by Lam,[3] Buchwald[6] and Collman.[7] In addition to arylboronic acids, the scope of the cupric acetate ($Cu(OAc)_2$) methodology includes other organometalloids such as arylbismuth,[8] aryllead,[9] hypervalent aryl siloxanes[3] and hypervalent diaryliodonium salts.[10]

The use of aryltrialkylstannanes as coupling partners could be valuable as a result of their availability, air and moisture stability and compatibility with a variety of functional groups. However, previous attempts[1a] to use organostannanes gave poor or no yield of the arylated products. It was hypothesized that the transmetallation of the aryl group from stannane to copper was inefficient. It is well known that, like silicon, tin is fluorophilic.[12] We reasoned that, similarly to arylsiloxanes,[2] the addition of fluoride may form a hypervalent stannane anion that can accelerate the transmetallation step. In light of the fact that Stille

Table 1. Evaluation of bases



2 1 3

Entry	Base	Isolated yield (%)
1	TBAF (2 equiv.)	69
2	TBAF (2 equiv.)+TEA (2 equiv.)	58
3	CsF (2 equiv.)	58
4	TASF (2 equiv.)	47
5	TEA (2 equiv.)	14
6	Cs_2CO_3 (2 equiv.)	0
7	K_2CO_3 (2 equiv.)	0
8	Pyridinium fluoride (2 equiv.)	0
9	None	0

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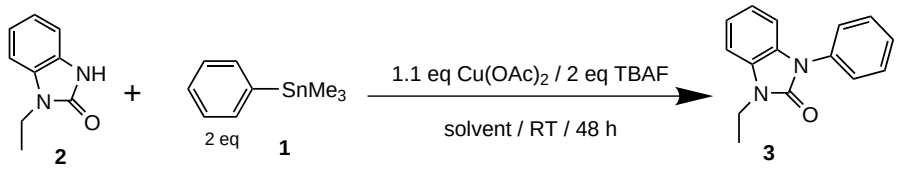
aryl–aryl (C–C) bond formation is accelerated with the addition of fluoride,[12] we investigated the effect of different fluoride species on our C–N cross-coupling reaction with phenylstannane.

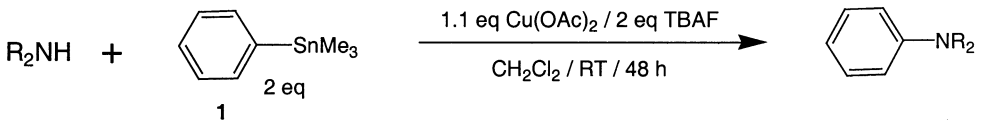
Indeed, we found that tetrabutylammonium fluoride (TBAF, 2 equiv.) is a very effective additive for the room temperature cross-coupling of trimethylphenylstannane **1** (2 equiv.) and benzimidazolinone **2** (Table 1, entry 1, 69%) in methylene chloride open to air.[13] Other fluoride sources such as CsF (entry 3, 58%) and tris-(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF, entry 4, 47%) gave acceptable yields but are less effective. Other bases such as triethylamine (TEA, entry 5, 14%), Cs_2CO_3 (entry 6, 0%), K_2CO_3 (entry 7, 0%) and pyridinium fluoride (entry 8, 0%) proved to be ineffec-

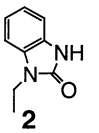
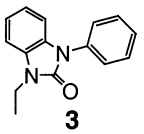
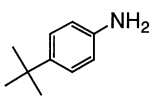
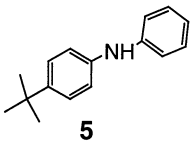
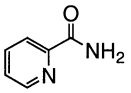
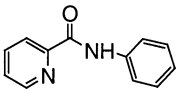
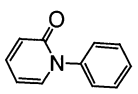
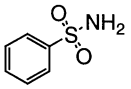
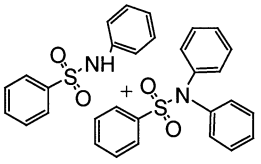
Table 2. Evaluation of solvents



Entry	Solvent	Isolated yield (%)
1	CH_2Cl_2	69
2	DMF	58
3	1,4-Dioxane	11

Table 3. C–N bond cross-coupling of trimethyl(phenyl)tin and NH-containing substrates



Entry	Substrate	Product	Isolated Yield
1	 **2**	 **3**	69 %
2	 **4**	 **5**	80 %
3	 **6**	 **7**	72 %
4*	 **8**	 **9**	77 %
5	 **10**	 **11a** **11b**	48 % (5 : 1)

* see footnote 16.

tive. The active arylating agent is probably a stannane fluoride anion by the fact that the yields are very low without fluoride additive (entries 5, 6, 7, 9). When using arylboronic acids, a base/ligand was required for the reaction. In the case of hypervalent stannanes, a base/ligand like TEA did not increase the yield (entry 3, 58%), similar to our observations for hypervalent arylsiloxanes.[2b] A brief screening of solvents (Table 2) showed that methylene chloride (entry 1, 69%) and DMF (entry 2, 58%) are preferred over 1,4-dioxane (entry 3, 11%).

A number of other NH-containing substrates can be arylated at room temperature (Table 3).[14] 4-*tert*-Butylaniline (entry 2) **4** gave 80% yield of **5**. Picolinamide **6** can be *N*-phenylated to **7** (entry 3, 72%) assisted by an α-nitrogen activating effect.[2a,15] 2-Pyridinone **8** (entry 4, 77%) easily undergoes *N*-arylation to **9**.[16] Finally mono- and bis-arylation products **11a** and **11b** (entry 5) were obtained from sulfonamide **10** in 48% yield (5:1). Water does not interfere with the reaction as the commercial solution of TBAF in THF contains 5% of water. An advantage of this method is that phenols or biphenyl ethers were never detected as side products, in contrast to the arylboronic acid cross-coupling.[1]

In summary, we have discovered the copper-promoted C–N bond cross-coupling with hypervalent phenylstannane at room temperature.[17] The large number of arylstannane reagents available commercially makes this new arylating agent a good complement to arylboronic acids, arylsiloxanes and other organometalloids. We continue to explore the scope and mechanism of this powerful copper-promoted C-heteroatom cross-coupling with organometalloids.

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13. Representative procedure for 1-ethyl-3-phenyl-2-benzimidazolinone **3**: To a 20 mL vial was added in sequence: 3 mL of dry dichloromethane, trimethylphenylstannane (121 μL, 0.667 mmol, 2.0 equiv.), 1-ethyl-2-benzimidazolinone (54 mg, 333 mmol, 1.0 equiv.), cupric acetate (66.7 mg, 0.367 mmol, 1.1 equiv.) and TBAF (0.67 mL of 1 M solution in THF, 0.667 mmol, 2.0 equiv.). The reaction was allowed to stir under air at room temperature for 48 h. The reaction was quenched with a solution of 2 mL of NH_3 in MeOH (2 M). The solvent was evaporated under reduced pressure and the residue was dissolved in 3 mL of dichloromethane and purified by silica gel chromatography (eluent: 7% methanol/chloroform) to give 54.6 mg (69%) of 1-ethyl-3-phenyl-2-benzimidazolinone **3**. MS (AP) m/z 239.4 (25%) $(M+H)^+$, 477.3 (100%) $(2M+H)^+$; ^1H NMR ($CDCl_3$) 7.54–7.49 (m, 4H), 7.39 (t, $J=6$ Hz, 1H), 7.17–7.03 (m, 4H), 6.96 (q, $J=7.3$ Hz, 2H), 1.41 (t, $J=7.1$ Hz) ppm; HRMS calcd for $C_{15}H_{15}N_2O$ $(M+H)^+$ m/e 239.1184, found m/e 239.1196.

14. In addition to the results in Table 3 arylation of the following substrates was attempted with results as follows: 4-phenyl-piperidine (31%), indazole (28%), benzimidazole (20%), isatin (<15%), phthalimide (10%), 3,5-di-*tert*-butyl-phenol (0%), oxazolidin-2-one (0%), saccharin (0%).
15. Benzamide can be *N*-phenylated in 19% yield with 76% unreacted benzamide recovered after 48 h.
16. For the lactam series under standard conditions the yields were low: 2-azetidinone (8%), 2-pyrrolidinone (5%), 2-piperdinone (0%).
17. We have attempted catalytic copper acetate with no success.