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One-pot two-step stannylation/Stille homocoupling of aryl bromides and iodides under solvent-free conditions

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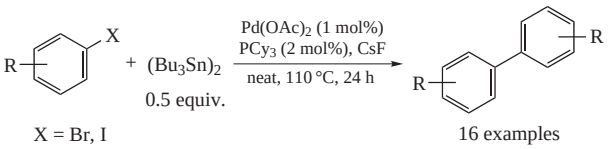
A new highly efficient solvent-free method for aryl bromide (iodide) homocoupling comprising the use of $Pd(OAc)_2/PCy_3$ system in the presence of CsF is suitable for substrates bearing functional groups not tolerant to lithium-, magnesium-, zinc-organic reagents and strong bases.



Development of new methods for the synthesis of symmetric biaryls is the subject of intense research.[1] Symmetric biaryls are important structural elements of polymers[2] and sensors;[3] they serve as starting compounds in synthesis of ligands for homogeneous catalysis,[4] and demonstrate diverse biological activity.[5] This type of compounds is widely used in medicinal[6] and synthetic organic chemistry.[7]

One of the most popular and easy methods of synthesis of biaryls bearing various functional groups from aryl halides is the Stille reaction.[8] Although there is a name reaction of intramolecular aryl halide coupling according to Stille–Kelly,[9] only 14 examples of symmetric biaryl preparation by intermolecular homocoupling comprising one-pot two-step stannylation/Stille coupling (SSC) reaction are known.[10] Therefore, one can conclude that development of one-pot two-step stannylation/Stille homocoupling (SSHC) is an attractive area of research.

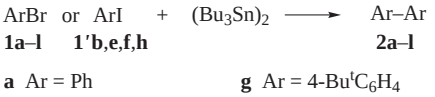
We found only three reports on one-pot two-step aryl halide SSHC. In a work by Vaquero,[11] a single homocoupling reaction was successfully completed through SSC in 26–56% yields. Microwave assisted one-pot two-step SSC reaction[12] was reported on 18 examples of aryl bromide homocoupling. Five cases of an *in situ* solvent-free homocoupling reaction under the effect of microwave irradiation were also desrcibed.[13] In addition to a narrow scope, the pitfalls of this work include the need for specific equipment (microwave labware), relatively high palladium loading (2 mol%), and the presence of DMF and Et_3N in the reaction mixture.

In continuation of our studies of solvent-free reactions catalyzed by transition metals, we turned to this problem.[14] In the current work, we performed a one-pot two-step SSHC under solvent-free conditions. Initially, catalytic systems for 4-bromotoluene homocoupling were screened using 0.5 equiv. $(Bu_3Sn)_2$, 1 mol% $Pd(OAc)_2$, 2–3 mol% ligand, and 1.5 equiv. base at 110 °C (Scheme 1). In our search for an optimal catalytic system (Table 1) we tested various bases using PCy_3 as a standard ligand for the Stille reaction.[15] Weak (LiCl, CsF),[16] mild (K_2CO_3, K_3PO_4, Cs_2CO_3), and strong (KOH, Bu^tONa) bases were tested. The use of LiCl, K_3PO_4, and K_2CO_3 resulted in low product yields (Table 1, entries 1, 3, 4). The utilization of strong bases, such as KOH, Cs_2CO_3, or Bu^tONa, considerably increased the product yield (entries 2, 5, 7). The highest yield of 87% was achieved in the presence of a weak base CsF (entry 6). We also studied the effect of a co-catalyst, CuI,[17] whose additive dropped the yield from 70 to 60% (entry 2).

Table 1 Screening of bases for homocoupling of 4-bromotoluene **1b**.[a]

Entry	Base	Yield of **2b** (%)	Entry	Base	Yield of **2b** (%)
1	LiCl	23	5	KOH	67
2	Bu^tONa	70 (60[b])	6	CsF	87
3	K_3PO_4	28	7	Cs_2CO_3	72
4	K_2CO_3	38			

[a] Reaction conditions: 4-bromotoluene (1 mmol), $(Bu_3Sn)_2$ (0.5 mmol), $Pd(OAc)_2$ (0.01 mmol), PCy_3 (0.02 mmol), base (1.5 mmol), neat, 110 °C, 24 h. [b] CuI (10 mol%) as a co-catalyst.



a Ar = Ph
b Ar = 4-MeC_6H_4
c Ar = 2-MeC_6H_4
d Ar = 2,4,6-$Me_3C_6H_2$
e Ar = 2-$MeOC_6H_4$
f Ar = 4-$MeOC_6H_4$
g Ar = 4-$Bu^tC_6H_4$
h Ar = 4-$NO_2C_6H_4$
i Ar = 4-$EtO_2CC_6H_4$
j Ar = 4-$PhOC_6H_4$
k Ar = 3-thienyl
l Ar = 2,4-$F_2C_6H_3$

Scheme 1 *Conditions*: Pd $(OAc)_2$, PCy_3, neat, 110 °C, 24 h.

After selection of the optimal base, we tested various palladium catalytic systems: $Pd(OAc)_2/PPh_3$, $[Pd(PPh_3)_2]Cl_2$, $Pd(OAc)_2/PBu^t_3 \cdot HBF_4$,[18] $Pd(OAc)_2$/SPhos, $Pd(OAc)_2$/DavePhos,[19] $Pd(OAc)_2/PCy_3$,[20] Bu^t-Indenyl(PCy_3)PdCl, and Bu^t-Indenyl(IPr)PdCl[21] (Table 2).

Catalytic systems based on PPh_3 ligands give moderate yields (Table 2, entries 1, 2). In a combination of $Pd(OAc)_2$ with PBu^t_3 (entry 3), the phosphine was generated *in situ* from its HBF_4 salt,[22] thus providing the product yield of 72%. Catalytic systems on the basis of DavePhos and SPhos ligands gave 78 and 71% yields, respectively (entries 4, 5). The yields of product for catalytic systems Bu^t-Indenyl(PCy_3)PdCl and Bu^t-Indenyl(IPr)PdCl varied

Table 2 Screening of catalytic systems for homocoupling of 4-bromotoluene **1b**.[a]

Entry	Catalytic system	Base	Yield of **2b** (%)
1	$Pd(OAc)_2/PPh_3$	CsF	52
2	$[Pd(PPh_3)_2]Cl_2$	CsF	51
3	$Pd(OAc)_2/PBu^t_3{\cdot}HBF_4$[b]	CsF	72
4	$Pd(OAc)_2$/SPhos	CsF	71
5	$Pd(OAc)_2$/DavePhos	CsF	78
6	Bu^t-Indenyl(PCy_3)PdCl	KOH	72
7	Bu^t-Indenyl(PCy_3)PdCl	Bu^tONa	56
8	Bu^t-Indenyl(IPr)PdCl	KOH	31
9	Bu^t-Indenyl(IPr)PdCl	Bu^tONa	41

[a] Reaction conditions: 4-bromotoluene (1 mmol), $(Bu_3Sn)_2$ (0.5 mmol), [Pd] (0.01 mmol), ligand (0.02 mmol), base (1.5 mmol), neat, 110 °C, 24 h. [b] 3 mol% of $PBu^t_3{\cdot}HBF_4$ as a ligand.

from moderate to good (entries 6–9). Since activation of such systems requires strong bases, we used Bu^tONa and KOH. According to the results of optimization of a catalytic system, the highest yield of target 4,4′-bitolyl (87%) was provided by simple and available $Pd(OAc)_2/PCy_3$ (entry 6).

Next, we studied the scope and limitations of the developed procedure (Table 3).† Under solvent-free conditions $Pd(OAc)_2/PCy_3$ demonstrates high activity with respect to electron withdrawing (**1h**,**i**,**l**) and electron donating substituted (**1e**,**g**,**j**), sterically hindered (**1c**,**e**,**l**), and heterocyclic (**1k**) aryl bromides. This catalytic system also provided high yields in homocoupling of aryl iodides (**1′b**,**e**,**f**,**h**). However, homocoupling of mesityl bromide bearing two *ortho*-substituents gave low yield of **2d**. Interestingly, some substrates bearing *ortho*-substituents (**1c**,**e**) give higher yields than analogous *para*-substituted substrates (**1b**,**f**).

Table 3 Homocoupling of aryl bromides **1** and iodides **1′**.[a]

Entry	(Het)aryl halide	Product	Yield (%)	Entry	(Het)aryl halide	Product	Yield (%)
1	**1a**	**2a**	92	9	**1′f**	**2f**	51
2	**1b**	**2b**	87	10	**1g**	**2g**	64
3	**1′b**	**2b**	83	11	**1h**	**2h**	>99
4	**1c**	**2c**	94	12	**1′h**	**2h**	64
5	**1d**	**2d**	11	13	**1i**	**2i**	>99
6	**1e**	**2e**	80	14	**1j**	**2j**	83
7	**1′e**	**2e**	81	15	**1k**	**2k**	69
8	**1f**	**2f**	65	16	**1l**	**2l**	68

[a] Reaction conditions: aryl bromide or iodide (1 mmol), $(Bu_3Sn)_2$ (0.5 mmol), $Pd(OAc)_2$ (0.01 mmol), PCy_3 (0.02 mmol), CsF (1.5 mmol), neat, 110 °C, 24 h.

Notably, in the first stage of the reaction, namely, halogen–metal exchange, no lithium-, magnesium-, or zinc-organic compounds (reagents in Murahashi,[23] Kumada,[24] Negishi[25] coupling) were used. In the second stage, coupling, no strong bases (Suzuki–Miyaura,[26] Hiyama[27] coupling) were required. Thus, the most prominent advantage of the developed SSHC protocol is the possibility to obtain biaryls bearing reactive functional groups not tolerant to RLi, RMgX, RZnX and strong bases (**2h**,**i**,**l**).

† *General procrdure.* A screw-cap vial equipped with a magnetic stir bar was charged with aryl halide (1 mmol), hexa-*n*-butylditin (0.5 mmol), palladium acetate (0.01 mmol) and tricyclohexylphosphine (0.02 mmol), followed by anhydrous cesium fluoride (1.5 mmol). The resulting mixture was manually homogenized with a magnet. A vial was transferred to a preheated oil bath (110 °C). After 24 h, the mixture was cooled, dissolved in CH_2Cl_2–H_2O mixture (1:1), the organic phase was separated, the solvent was evaporated *in vacuo* and the product was isolated by flash chromatography on a silica gel by elution with hexane–CH_2Cl_2 mixture.

In conclusion, a simple and efficient one-pot two-step SSHC under solvent-free conditions has been elaborated. The most efficient catalyst is the easily available and rather cheap $Pd(OAc)_2$ (1 mol%)/PCy_3 (2 mol%) system. Homocoupling of various electron donating and electron withdrawing substituted, sterically hindered aryl and heteroaryl bromides and iodides can be performed in high yields. The new protocol is suitable for homocoupling of aryl halides bearing functional groups not tolerant to lithium-, magnesium-, zinc-organic reagents and strong bases. The proposed procedure has a number of advantages: no solvent is used; aerobic conditions; low catalyst loading; easily available base (CsF); the reaction is activated with conventional heating (no milling, sonication, *etc*. needed). Thus, we developed a versatile, highly efficient, step-economical, low waste (solvent-free) procedure for the synthesis of highly functionalized biaryls.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.05.032.

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