$AlAr_3$(THF): highly efficient reagents for cross-couplings with aryl bromides and chlorides catalyzed by the economic palladium complex of PCy_3†

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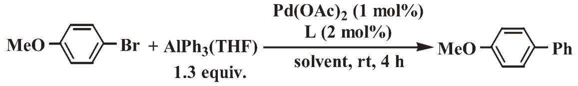
Novel and highly efficient cross couplings of aryl bromides and chlorides with $AlAr_3$(THF) (Ar = Ph, 2,4,6-$Me_3C_6H_2$, 2-naphthyl or 4-$Me_3SiC_6H_4$) catalyzed by the economic palladium catalyst of PCy_3 are reported without the use of a base and under mild reaction conditions at room temperature or temperatures $\leqslant 60$ °C even for couplings of bulky aryl halides and the Al(2,4,6-$Me_3C_6H_2)_3$(THF) reagent.

Since the discovery of cross-coupling reactions in the early 1970s,[1] a tremendous amount of catalytic systems[2] using organoborons,[3] organotins,[4] organosilicons,[5] organozincs or organozirconiums,[6] and organomagnesiums[7] as coupling reagents have been developed. Nowadays, cross couplings of organic halides are one of the most powerful synthetic techniques applied to material,[8] medicinal,[9] and other chemistry.[10] Earlier systems worked well for substrates of organic iodides, bromides and triflates. However, recent developments of cross coupling reactions focus on using the cheap but the more inert organic chlorides as substrates[11] and on developing catalytic systems for the formation of C–O[12] and C–N bonds.[13] It is established that catalytic systems of bulky and electron-rich phosphoranes and carbenes are effective for couplings of organic chlorides. In contrast, coupling reactions employing organoaluminium reagents are rare.[14] For aryl–alkyl coupling employing alkylaluminium reagents,[15] severe reaction conditions are required for coupling of aryl chlorides.[16] Organoaluminiums are more reactive than organoboron, organosilicon and organozinc reagents and are expected to facilitate coupling reactions of the inert organic chlorides.

We here report novel and highly efficient cross couplings of aryl bromides and chlorides with the easily prepared arylaluminium reagents, $AlAr_3$(THF) (Ar = Ph, 2,4,6-$Me_3C_6H_2$, 2-naphthyl or 4-$Me_3SiC_6H_4$).[17] In this study, the cheapest and commercial available PPh_3 and PCy_3 were selected as the ligands. Reaction conditions (eqn (1)) were optimized on the 4-methoxybromobenzene which is a sluggish substrate in many coupling systems. To our surprise, the reactions proceed at room temperature without the addition of a base which is an essential ingredient in coupling reactions. It is found that PCy_3 at 2 mol% along with 1 mol% $Pd(OAc)_2$ is a better catalytic system than the Pd complex of the less electron-rich PPh_3 (Table 1). The best yields of 99% were achieved in CH_2Cl_2 (entry 4) and DME (entry 10).



(1)

Generalities of the Pd/PCy_3 catalytic system were then studied on a variety of aryl bromides in DME with results listed in Table 2. The catalytic system works excellently to aryl bromides bearing either electron-donating substituents or an electron-withdrawing substituent. For examples, yields of coupling products ranged from 83 to 95% (entries 1–5) for electron-rich substrates such as 4-methoxybromobenzene, 4-*tert*-butylbromobenzene, 4-bromothioanisole, *p*-bromotoluene and 3,5-dimethylbromobenzene. For aryl bromides bearing an electron-withdrawing substituent such as 4-fluorobromobenzene, the coupling product was obtained in 93% yield (entry 6). However, a lower 65% yield (entry 7) was obtained for 4-nitrobromobenzene probably due to a higher affinity of the nitro group toward the aluminium reagent which retards access of the substrate to the catalytic metal centre. For sterically hindered 2-methoxybromobenzene and 2,4-dimethylbromobenzene, coupling products were obtained in 92 and 93% yields (entries 8 and 9). The system works well also to the most sterically hindered 2,6-dimethylbromobenzene to afford the product in a satisfactory 70% yield (entry 10). Coupling reactions of aryl chlorides bearing either an electron-donating or an electron-withdrawing substituent were also investigated and a higher reaction temperature at 60 °C and a prolonged reaction time of 12 h are required to furnish products in $\geqslant 91\%$ yields (entries 11–14). Nevertheless, $AlPh_3$(THF) is a superior reagent for aryl–aryl

Table 1 Couplings of 4-methoxybromobenzene with $AlPh_3$(THF) catalyzed by palladium complexes of phosphine[a]

Entry	L	Solvent	Yield[b] (%)
1	PPh_3	Toluene	41
2	PCy_3	Toluene	55
3	PPh_3	CH_2Cl_2	28
4	PCy_3	CH_2Cl_2	99
5	PPh_3	THF	65
6	PCy_3	THF	9
7	PPh_3	DMF	16
8	PCy_3	DMF	41
9	PPh_3	DME	82
10	PCy_3	DME	99

[a] 4-Methoxybromobenzene : $AlPh_3$(THF) : $Pd(OAc)_2$: ligand = 1.0 : 1.3 : 0.010 : 0.020 mmol; solvent, 4 mL. [b] Yields are based on ^1H NMR spectra.

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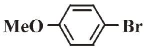
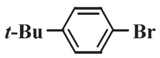
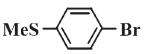
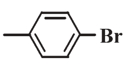
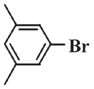
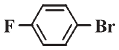
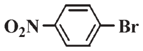
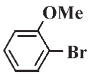
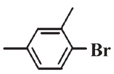
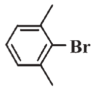
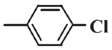
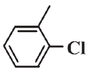
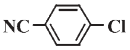
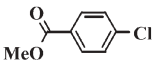
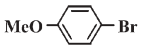
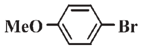
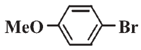
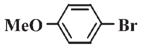
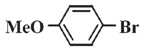
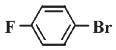
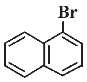
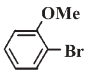
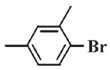
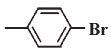
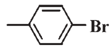
† Electronic supplementary information (ESI) available: Yields and ^1H and ^{13}C NMR data and spectra of coupling products. See DOI: 10.1039/b707703c

Table 2 Couplings of aryl bromides and chlorides with $AlPh_3(THF)$ catalyzed by the $Pd(OAc)_2/PCy_3$ catalytic system[a,b]

Entry	Substrate	T/°C	t/h	Yield (%)
1		rt	3	91
2		rt	3	95
3		rt	3	93
4		rt	3	83
5		rt	3	95
6		rt	3	91
7		rt	3	65
8		rt	3	92
9		rt	3	94
10		rt	3	70
11		60	12	91
12		60	12	94
13		60	12	93
14		60	12	95

[a] ArX : $AlPh_3(THF)$: $Pd(OAc)_2$: PCy_3 = 1.0 : 1.3 : 0.010 : 0.020 mmol; solvent, DME (4 mL). [b] Products are purified by column chromatography and isolated yields are reported as average values of two runs of reactions.

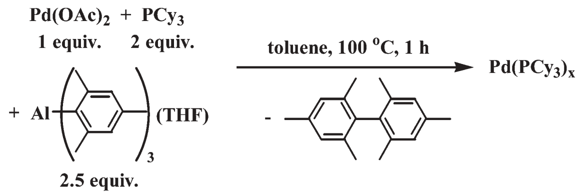
Table 3 Couplings of aryl bromides with $AlAr_3(THF)$ catalyzed by the $Pd(OAc)_2/PCy_3$ system[a,b]

Entry	Substrate	T/°C	t/h	Yield[c] (%)
1[d,e]		25	4	—
2[d,f]		25	4	—
3[d]		25	4	5
4[d]		40	8	83
5		40	4	90
6		40	5	94
7		60	5	92
8		60	5	96
9		60	5	92
10[g,h]		60	5	93
11[g,i]		60	5	85

[a] Preheating $AlAr_3(THF)$: $Pd(OAc)_2$: PCy_3 (0.0125 : 0.0050 : 0.010 mmol) in toluene at 100 °C for 1 h. [b] Substrate: $Al(2,4,6\text{-}Me_3C_6H_2)_3(THF)$: $Pd(OAc)_2$: PCy_3 = 0.50 : 0.65 : 0.0050 : 0.01 mmol; solvent, toluene (4 mL). [c] Isolated yields. [d] Without preheating the catalytic system. [e] In DME. [f] In THF. [g] 4-methylbromobenzene : $AlAr_3(THF)$: $Pd(OAc)_2$: PCy_3 = 1.0 : 1.3 : 0.010 : 0.020 mmol. [h] Ar = 2-naphthyl. [i] Ar = 4-$Me_3SiC_6H_4$.

coupling reactions in terms of the Pd/PCy_3 catalytic system. For couplings of aryl chlorides with arylboron or aryltin reagents, longer reaction times, higher reaction temperatures, and/or higher catalyst loading were required to afford products in satisfactory yields.[18]

Cross couplings of 4-methoxybromobenzene with the bulky $Al(2,4,6\text{-}Me_3C_6H_2)_3(THF)$ reagent were subsequently examined. It is surprisingly found that coupling reactions did not take place at all at 25 °C in 4 h in DME and THF (Table 3, entries 1 and 2). In toluene, the product was obtained in a yield of 5%. However, the product was obtained in 83% yield when the reaction time was extended to 8 h at 40 °C. If 1 mol% $Pd(OAc)_2$, 2 mol% PCy_3 and 2.5 mol% $Al(2,4,6\text{-}Me_3C_6H_2)_3(THF)$ were preheated in toluene at 100 °C for 1 h, the resulting solution catalyzed the coupling reaction of 4-methoxybromobenzene and the most sterically hindered $Al(2,4,6\text{-}Me_3C_6H_2)_3(THF)$ reagent in 90% yield in 4 h (Table 3, entry 5). The above result strongly suggests that the formation of the active Pd(0) species is a rate determining step for reactions using the bulkiest $Al(2,4,6\text{-}Me_3C_6H_2)_3(THF)$ reagent. To support the argument, reaction of $Pd(OAc)_2$, PCy_3 and $Al(2,4,6\text{-}Me_3C_6H_2)_3(THF)$ in a ratio of 1 : 2 : 2.5 was carried out at 100 °C in toluene for 1 h and the self-coupling 2,2′,4,4′,6,6′-hexamethylbiphenyl was obtained in 94% yield (eqn (2)), suggesting the formation of the Pd(0) species. Results in entries 6–9 were obtained employing the preheated catalytic system. For 4-fluorobromobenzene, the coupling product was obtained in 94% yield at 40 °C in 5 h (entry 6). For aryl bromides with an *ortho*-substituent, a higher reaction temperature at 60 °C is required to give products in ⩾92% yields (entries 7–9). The higher reaction temperature required for the *ortho*-substituted aryl bromides suggests that the transmetallation step is also slower for the hindered $Al(2,4,6\text{-}Me_3C_6H_2)_3(THF)$ reagent. In this study, couplings of 4-methylbromobenzene with two other arylaluminium reagents of Al(2-naphthyl)$_3$(THF) and $Al(4\text{-}Me_3SiC_6H_4)_3(THF)$ were conducted using the preheated systems to afford 2-*p*-tolylnaphthalene in 93% yield (entry 10) and 4-trimethylsilyl-4′-methylbiphenyl in 85% yield (entry 11).



(2)

In summary, novel and efficient cross couplings of aryl bromides and chlorides with AlAr$_3$(THF) catalyzed by the catalytic system of 1 mol% Pd(OAc)$_2$ and 2 mol% PCy$_3$ are reported. Several important features are demonstrated in this study. First, the relatively cheap and commercial available PCy$_3$ is used as an effective ligand. Second, a base is not required for the reaction. Third, the easily prepared AlAr$_3$(THF) are superior reagents for aryl-aryl coupling reactions. Fourth, the system works equally well for aryl halides bearing either an electron-donating or an electron-withdrawing substituent. Fifth, the catalytic system works well for couplings of the inert aryl chlorides to afford products in $>90\%$ yields at 60 °C in 12 h. Sixth, preheating the catalytic system at 100 °C for 1 h greatly shortens reaction times from 8 to 4–5 h for couplings of aryl bromides with the most bulky Al(2,4,6-Me$_3$C$_6$H$_2$)$_3$(THF) reagent at 40 or 60 °C, indicating that the formation of Pd(0) active species is a rate determining step.

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