Palladium-Catalyzed Cross-Methylation of Aryl Chlorides by Stabilized Dimethylaluminium and -Gallium Reagents

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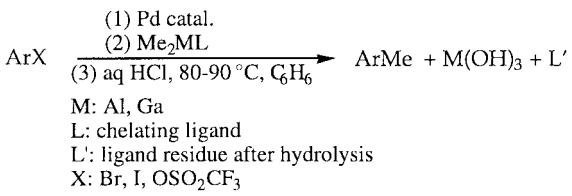
Abstract: Two methods for palladium-catalyzed cross-methylation of aryl chlorides by intramolecularly stabilized dialkylaluminium and -gallium complexes **6**−**13** have been studied. In one method, in which either tetrakis(triphenylphosphine)palladium (**1**) or dichlorobis(triphenylphosphine)palladium (**2**) is used as the catalyst at 80−90°C, the activation of the chlorine atom is affected by introduction of strong electron-withdrawing groups into the aromatic moiety. The second method is based on the application of either [1,3-bis(diisopropylphosphino)propane)]palladium (**4**) or homologous electron-rich palladium complexes as catalysts. Although **4** promotes smooth cross-alkylation of aryl chlorides it fails to activate simple aryl bromides.

Key words: aryl chlorides, aluminium complexes, gallium complexes, cross-coupling, palladium(0) catalysis

In a previous communication[1] we reported that intramolecularly stabilized alkylaluminium complexes can substitute Grignard and organolithium reagents in alkylation of many carbonyl compounds. Further studies revealed that at 80−90°C these aluminium reagents, as well as their gallium analogs, successfully cross-alkylate aryl bromides,[2] iodides[2] and trifluoromethanesulfonates[3] in the presence of either $Pd(Ph_3P)_4$ (**1**) or $PdCl_2(Ph_3P)_2$ (**2**), as illustrated in Scheme 1. Aryl chlorides, however, react under these conditions extremely slowly or not at all.



Scheme 1

In this paper we report two methods by which cross-methylation of aromatic chlorides becomes feasible: (i) activation of the halogen atom by introduction of the strong electron-withdrawing nitro moieties into the aromatic skeleton and (ii) replacement of the above palladium catalysts by electron richer phosphine complexes such as [1,2-bis(diisopropylphosphino)ethane]palladium [$Pd(dippe)_2$, **3**], [1,3-bis(diisopropylphosphino)propane]palladium [$Pd(dippp)_2$, **4**], or [1,4-bis(diisopropylphosphino)butane]palladium [$Pd(dippb)_2$, **5**][4] (Figure). Thus, although chlorobenzene reacts only sluggishly with dialkylaluminium and dialkylgallium complexes **6**−**13** (Figure) in the presence of **1**, and does not react at all in

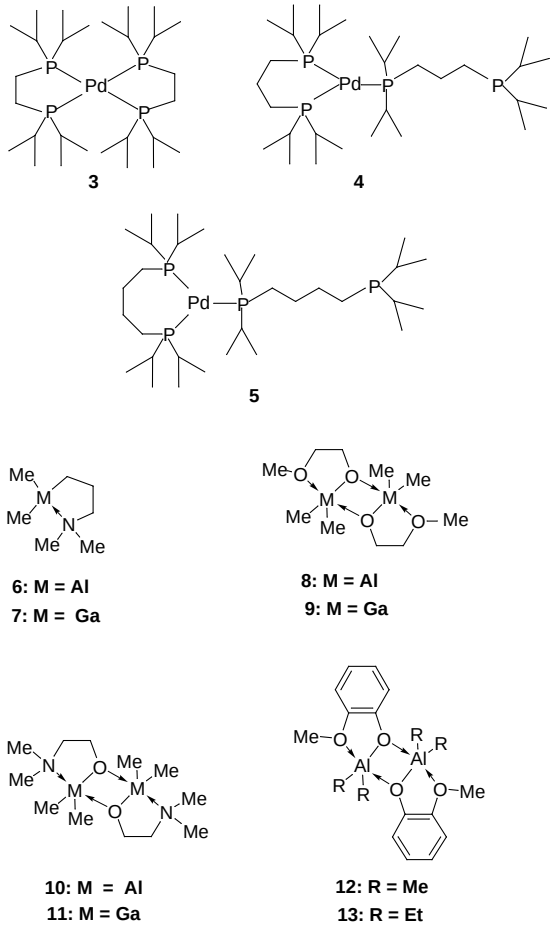


Figure Structures of Pd catalysts **3**−**5** and dialkylaluminium and dialkylgallium complexes **6**−**13**

the presence of **2**, the introduction of a nitro group into the aromatic skeleton makes the chlorine atom (as in some other cases of aryl chloride activation)[5] susceptible to alkylation. When for example, a solution of 1 mmol of 4-nitrochlorobenzene and 0.02 mmol of **1** in anhydrous benzene is heated at 90°C under N_2 for 15 min, followed by treatment with an equimolar quantity of **8** for 22 hours at the same temperature, final quenching with 2% hydrochloric acid yields a mixture of 37% of 4-nitrotoluene and 63% of unreacted starting material. Further examples of cross-alkylations are listed in Table 1. A significant enhancement of the process is observed when the halogen is activated by an additional nitro group as e.g., in 2,4-$(NO_2)_2C_6H_3Cl$ (Entries 8−17). On the other hand, steric effects inhibit slightly the process [cf., e.g., the results of experiment 2 (Entry 2) with that of experiment 5 (Entry 5].

In the experiment described above we used equimolar amounts of the aryl chlorides and the methylating agent. Actually, one half of the aluminium or gallium compound is sufficient, as both methyl groups can be used in the process (see Entries 1, 4, 6, 8, 10 and 11). However, the second methyl group reacts significantly more slowly than the first one. Therefore, a period of 120 hours is needed to convert e.g., 2,4-$(NO_2)_2C_6H_3Cl$ to 80% of 2,4-$(NO_2)_2C_6H_3Me$ by half an equivalent of **8**. In order to achieve higher rates it is advisable to use a large excess of the alkylating agent. A ratio of 1:10 as in experiment 13 (Entry 13), yields 93% of 2,4-$(NO_2)_2C_6H_3Me$ under the standard reaction conditions within 22 hours (Scheme 2).

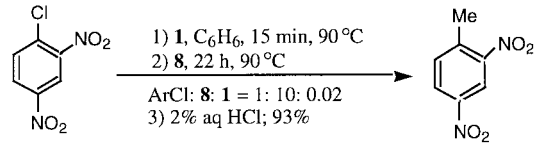
The rate of the cross-methylation was found to depend also on the nature of the alkylating agents. Usually, though not always, the aluminium complexes are more efficient than the gallium compounds (cf., e.g. Entries 2 and 3). Among the various aluminium complexes, compound **8** proved to be the most efficient one, and **9** was found to be the best gallium methylating agent. The ethylating agent **13** seems to be less reactive than the corresponding methylating complex **12** (see Entries 17 and 18 as well as Ref. 2). During the methylation of 4-$(NO_2)C_6H_3$-1,2-Cl_2 (Entry 20) only the halogen atom at position 1 is affected. No dimethyl compound is formed under our experimental conditions.

Comparison of the experiments described in Entries 10 and 11 indicate that the Pd(0) complex **1** is a better catalyst than complex **2**. This observation is compatible with the mechanism for palladium-catalyzed cross-methylation of aryl halides proposed previously.[2] Of greater efficiency than **1** and **2** are the electron rich complexes **3−5** [compare experiments 6, 7 and 12 (Entries 6, 7 and 12) in Table 1 with those listed in Table 2, Entries 1, 2 and 6-8, respectively]. Complexes **4** and **5** have already proven useful for activation of C−Cl bonds in catalytic carbonylation,[6] hydroformylation,[7] reductive dechlorination[8] and vinylation of aryl chlorides.[5,9] The alkylations could be conducted either in the presence of the isolated complexes **3−5** or in the presence of catalysts prepared in situ from $Pd(OAc)_2$ and the appropriate phosphine ligands.[10] By both techniques identical results were obtained. Entries 5, 10 and 11 in Table 2 reveal that nitrated fluoro-, bromo-

Table 1 Cross Alkylation of Nitrated Aryl Chlorides by Dialkylaluminium and Dialkylgallium Complexes **6–13** in the Presence of Catalysts **1** and **2** under Comparable Conditions[a]

Entry	Substrate	Alkylating Agent	Catalyst	Molar Ratio (substrate:alkylating agent)[b]	Product	Yield (after 22 h, %)[c]
1	2-$(NO_2)C_6H_4Cl$	**8**	**1**	2:1	2-$(NO_2)C_6H_4Me$	12
2	2-$(NO_2)C_6H_4Cl$	**8**	**1**	1:1	2-$(NO_2)C_6H_4Me$	32
3	2-$(NO_2)C_6H_4Cl$	**9**	**1**	1:1	2-$(NO_2)C_6H_4Me$	18
4	4-$(NO_2)C_6H_4Cl$	**8**	**1**	2:1	4-$(NO_2)C_6H_4Me$	14
5	4-$(NO_2)C_6H_4Cl$	**8**	**1**	1:1	4-$(NO_2)C_6H_4Me$	37
6	4-$(NO_2)C_6H_4Cl$	**8**	**2**	2:1	4-$(NO_2)C_6H_4Me$	8
7	4-$(NO_2)C_6H_4Cl$	**9**	**1**	1:1	4-$(NO_2)C_6H_4Me$	25
8	2,4-$(NO_2)_2C_6H_3Cl$	**6**	**1**	2:1	2,4-$(NO_2)_2C_6H_3Me$	36
9	2,4-$(NO_2)_2C_6H_3Cl$	**7**	**2**	1:1	2,4-$(NO_2)_2C_6H_3Me$	35
10	2,4-$(NO_2)_2C_6H_3Cl$	**8**	**1**	2:1	2,4-$(NO_2)_2C_6H_3Cl$	49
11	2,4-$(NO_2)_2C_6H_3Cl$	**8**	**2**	2:1	2,4-$(NO_2)_2C_6H_3Me$	34
12	2,4-$(NO_2)_2C_6H_3Cl$	**8**	**1**	1:1	2,4-$(NO_2)_2C_6H_3Me$	58
13	2,4-$(NO_2)_2C_6H_3Cl$	**8**	**1**	1:10	2,4-$(NO_2)_2C_6H_3Me$	93
14	2,4-$(NO_2)_2C_6H_3Cl$	**9**	**1**	1:1	2,4-$(NO_2)_2C_6H_3Me$	51
15	2,4-$(NO_2)_2C_6H_3Cl$	**10**	**1**	1:1	2,4-$(NO_2)_2C_6H_3Me$	23
16	2,4-$(NO_2)_2C_6H_3Cl$	**11**	**1**	1:1	2,4-$(NO_2)_2C_6H_3Me$	30
17	2,4-$(NO_2)_2C_6H_3Cl$	**12**	**1**	1:1	2,4-$(NO_2)_2C_6H_3Me$	39
18	2,4-$(NO_2)_2C_6H_3Cl$	**13**	**1**	1:1	2,4-$(NO_2)_2C_6H_3Et$	21
19	4-$(NO_2)C_6H_3$-1,2-Cl_2	**6**	**1**	1:1	2-Cl-4-$(NO_2)C_6H_3Me$	21
20	4-$(NO_2)C_6H_3$-1,2-Cl_2	**8**	**1**	1:1	2-Cl-4-$(NO_2)C_6H_3Me$	58

[a] Reaction conditions: 1 mmol of the chloro compound and 0.02 mmol of the palladium catalyst in 2 mL benzene; heating for 15 min at 90°C under N_2; addition of the alkylating agent in 1 mL of the same solvent; quenching with 2% aq HCl.
[b] Calculated as for mononuclear alkylating agents.
[c] The remaining percentages reflect usually on the unreacted substrate.



Scheme 2

and iodobenzenes can be methylated in the presence of **4** in a similar fashion as the respective chloro compound. The relative reactivity of the aryl halides is in the order F >Cl >Br >I which parallels the order of strength of the corresponding C-halide bonds. Aryl chlorides substituted in the 4 position with electron-withdrawing groups other than NO_2 (CF_3, CO_2Et, CN) are methylated in the presence of **4** as well, albeit at a lower rate than the analogous nitro compounds (Entries 12−14). 4-Chlorobenzaldehyde (Entry 15) is methylated slowly by the gallium complex **9** to give *p*-tolualdehyde. It reacts somewhat faster with the corresponding aluminum reagent **8**, but both the product and unreacted starting aldehyde undergo the Cannizzaro reaction upon quenching of the aluminum containing mixture with water.

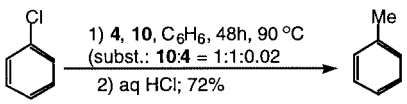
Table 2 Cross Alkylation of Various Aryl Halides by Dialkylaluminium and Dialkylgallium Complexes **6–13** in the Presence of Electron Rich Palladium Catalysts under Comparable Conditions[a,b]

Entry	Substrate	Alkylating Agent	Catalyst	Molar ratio (substrate: alkylating agent)	Product	Yield (%)[c]
1	4-$(NO_2)C_6H_4Cl$	**8**	**4**	2:1	4-$(NO_2)C_6H_4Me$	66
2	4-$(NO_2)C_6H_4Cl$	**9**	**4**	1:1	4-$(NO_2)C_6H_4Me$	47
3	4-$(NO_2)C_6H_4Cl$	**11**	**4**	1:1	4-$(NO_2)C_6H_4Me$	33
4	4-$(NO_2)C_6H_4Cl$	**13**	**4**	1:1	4-$(NO_2)C_6H_4Et$	30
5	2,4-$(NO_2)_2C_6H_3F$	**8**	**4**	1:1	2,4-$(NO_2)_2C_6H_3Me$	~100[d]
6	2,4-$(NO_2)_2C_6H_3Cl$	**8**	**3**[e]	1:1	2,4-$(NO_2)_2C_6H_3Me$	94[d]
7	2,4-$(NO_2)_2C_6H_3Cl$	**8**	**4**[e]	1:1	2,4-$(NO_2)_2C_6H_3Me$	~100[d]
8	2,4-$(NO_2)_2C_6H_3Cl$	**8**	**5**[e]	1:1	2,4-$(NO_2)_2C_6H_3Me$	~100[d]
9	2,4-$(NO_2)_2C_6H_3Cl$	**12**	**4**	2:1	2,4-$(NO_2)_2C_6H_3Me$	21
10	2,4-$(NO_2)_2C_6H_3Br$	**8**	**4**	1:1	2,4-$(NO_2)_2C_6H_3Me$	80
11	2,4-$(NO_2)_2C_6H_3I$	**8**	**4**	1:1	2,4-$(NO_2)_2C_6H_3Me$	43
12	4-$(CF_3)C_6H_4Cl$	**8**	**4**	1:1	4-$(CF_3)C_6H_4Me$	65
13	4-ClC_6H_4COOEt	**8**	**4**	1:1	4-MeC_6H_4COOEt	28
14	4-ClC_6H_4CN	**8**	**4**	1:1	4-MeC_6H_4CN	19
15	4-ClC_6H_4CHO	**9**	**4**	1:5	4-MeC_6H_4CHO	7
16	4-$(NO_2)C_6H_4$-1,2-Cl_2	**8**	**4**	1:1	2-Cl-4-$(NO_2)C_6H_3Me$	61
17	1,4-$C_6H_4Cl_2$	**8**	**3**[f]	1:1	1,4-$C_6H_4Me_2$	10
18	1,4-$C_6H_4Cl_2$	**8**	**5**[f]	1:1	1,4-$C_6H_4Me_2$	14
19	4-ClC_6H_4Br	**8**	**4**	1:1	4-ClC_6H_4Me	10
20	4-ClC_6H_4Br	**8**	**5**	1:1	4-ClC_6H_4Me	16
21	4-ClC_6H_4Me	**8**	**4**	1:1	1,4-$C_6H_4Me_2$	17
22	4-ClC_6H_4Me	**8**	**4**	1:10	1,4-$C_6H_4Me_2$	45
23	C_6H_5Cl	**8**	**4**	1:1	C_6H_5Me	37
24	1-$C_{10}H_7Cl$	**6**	**4**	2:1	1-$C_{10}H_7Me$	35
25	1-$C_{10}H_7Cl$	**7**	**4**	1:1	1-$C_{10}H_7Me$	10
26	1-$C_{10}H_7Cl$	**8**	**4**	2:1	1-$C_{10}H_7Me$	38
27	1-$C_{10}H_7Cl$	**8**	**4**	1:1	1-$C_{10}H_7Me$	56
28	1-$C_{10}H_7Cl$	**8**	**4**	1:5	1-$C_{10}H_7Me$	76
29	1-$C_{10}H_7Cl$	**8**	**4**	1:10	1-$C_{10}H_7Me$	83
30	1-$C_{10}H_7Cl$	**9**	**4**	1:1	1-$C_{10}H_7Me$	15
31	1-$C_{10}H_7Cl$	**10**	**4**	1:1	1-$C_{10}H_7Me$	7
32	1-$C_{10}H_7Cl$	**11**	**4**	1:1	1-$C_{10}H_7Me$	7
33	1-$C_{10}H_7Cl$	**12**	**4**	1:1	1-$C_{10}H_7Me$	20
34	1-$C_{10}H_7Cl$	**13**	**4**	1:1	1-$C_{10}H_7Et$	13[g]
35	1-$C_{10}H_7Br$	**8**	**3**[f]	1:1	1-$C_{10}H_7Me$	3
36	1-$C_{10}H_7Br$	**8**	**5**[f]	1:1	1-$C_{10}H_7Me$	15
37	BrC_6H_4-4-$CH_2C_6H_4$-4-Cl	**8**	**4**	1:1	BrC_6H_4-4-$CH_2C_6H_4$-4'-Me	36[h]

[a] Reaction conditions as in Table 1.
[b] Except otherwise stated, the reaction time was 22 h.
[c] The remaining percentages reflect usually on the unreacted substrate.
[d] 4.5 h.
[e] Identical results were obtained when the catalyst was prepared in situ from $Pd(OAc)_2$ and two equivalents of the corresponding free ligand.
[f] Practically no methylation occurred in the presence of **4**.
[g] Contaminated with 5% of naphthalene.
[h] ~1% of ClC_6H_4-4-$CH_2C_6H_4$-4'-Me was also formed.

Unlike the reaction of 4-(NO_2)C_6H_3-1,2-Cl_2 with **8** in the presence of either catalyst **1** or **4** (Table 1, Entry 20 and Table 2, Entry 16), the dichloride 1,4-$C_6H_4Cl_2$ undergoes bis-methylation with **8** in the presence of the electron-rich **3** or **5** to give chlorine-free *p*-xylene. Catalyst **4** proved to be inactive in this reaction. However, when 4-chlorotoluene rather than *p*-dichlorobenzene is used as starting material, **4** readily catalyzes its transformation to *p*-xylene (Table 2, Entries 21, 22). 4-Bromochlorobenzene reacts in the presence of **4** and **5** (but *not* in the presence of **3**) to give solely 4-ClC_6H_4Me (Entries 19, 20). This observation is unexpected in the light of the finding that **4** catalyzes the methylation of unsubstituted aryl chlorides but not the analogous aryl bromides (vide infra).

Chlorobenzene and 1-chloronaphthalene undergo smooth alkylation. An example in which chlorobenzene yields 72% of toluene (together with 28% of unreacted starting material) after 48h at 90°C is illustrated in Scheme 3. Further experiments with chlorobenzene and 1-chloronaphthalene are listed in Table 2 (Entries 23−34). Experiments 26−29 (Entries 26−29) demonstrate that in analogy to the methylation of nitrated aryl chlorides, the ratio substrate:alkylating agent strongly effects the reaction rate. Although many non-activated aryl chlorides are alkylated in the presence of **4**, the analogous bromine compounds are usually *not* affected. All attempts to methylate bromobenzene, 4-bromoanisole, ethyl 4-bromobenzoate and 1- and 2-bromonaphthalene by complexes **6−9** in the presence of **4**, gave under our standard experimental conditions, at most 2% of methylated products. The bromides were hardly affected even when the temperature was increased to 130°C. The palladium catalysts **3** and **5** promoted however, slow methylation of some aryl bromides as demonstrated in entries 35 and 36 of Table 2. Only in two cases did we observe significant activation of aryl bromides by **4**: (i) in the cross methylation of 2,4-(NO_2)$_2C_6H_3Br$ (Table 2, Entry 10) and (ii) in the transformation of 4-ClC_6H_4Br to 4-chlorotoluene (Table 2, Entry 19) (vide supra). On the other hand, **4**-catalyzed methylation of BrC_6H_4-4-$CH_2C_6H_4$-4'-Cl[11] took place preferentially on the chlorine atom. Attempts to alkylate a mixture of 1 mmol of C_6H_5Cl and 1 mmol of C_6H_5Br in the presence of 2 equivalents of **8** by **4** under the conditions of Table 2, affected solely the chlorobenzene (35% of toluene was obtained after 22 h) while the bromobenzene remained completely unreacted.



Scheme 3

The ethylation reagent **13** was shown to alkylate both NO_2-activated aryl chlorides in the presence of catalyst **1** (Table 1, Entry 18 and Table 2, Entry 4), as well as the non-activated 1-chloronaphthalene (Table 2, Entry 34). The rate of ethylation was found to be slower than that of the corresponding methylation reaction, and in the case of 1-chloronaphthalene led to the formation of some methyl-free naphthalene as side product.[5] The preferred alkylation of aryl chlorides over that of aryl bromides (except with 4-bromochlorobenzene) catalyzed by the electron-rich complexes **3-5** is surprising, in view of the fact that complex **4** oxidatively adds to Ar−Br faster than to Ar−Cl.[12] Indeed, the reaction of BrC_6H_4-4-$CH_2C_6H_4$-4'-Cl with an equimolar amount of complex **4** leads exclusively to the C−Br oxidative addition product,[13] in contrast to the result of catalytic methylation of this compound (Table 2, Entry 37). Thus, we believe that the expected mechanism involving C-X oxidative addition to **3−5** followed by alkylation of the resulting palladium complex is unlikely in this case. It is possible that the alkylation agent reacts with the Pd(0) complex to generate an anionic palladium complex which activates the chloroarene. Further studies aimed at mechanistic clarification are in progress.

Catalysts **3**, **4** and **5** were prepared from [(2-methylallyl)PdCl]$_2$ and the appropriate phosphines.[5] The aluminium and gallium derived alkylating agents **6−13** were synthesized as described previously.[2]

Alkylation of Aryl Chlorides; Genereal Procedure

A solution of the substrate (1 mmol) and the palladium catalyst (0.02 mmol) in anhyd benzene (2 mL) or toluene was heated at 90°C in a pressure tube under exclusion of air for 15 min. To this mixture was added the appropriate amount of the alkylating agent (indicated in Tables 1 and 2) in the same solvent (1 mL). The heating was continued for the length of time indicated in the Tables. The cooled mixture was treated with an excess of aq 2% HCl. Phase separation and extraction of the product from the aqueous layer by an appropriate organic solvent, were followed by concentration of the organic extracts and purification of the product by column chromatography. The products were characterized either by direct comparison with authentic samples, or analyzed by IR, GC/MS, ^1H and ^{13}C NMR spectroscopy.

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