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User-Friendly Methylation of Aryl and Vinyl Halides and Pseudohalides with DABAL-Me_3

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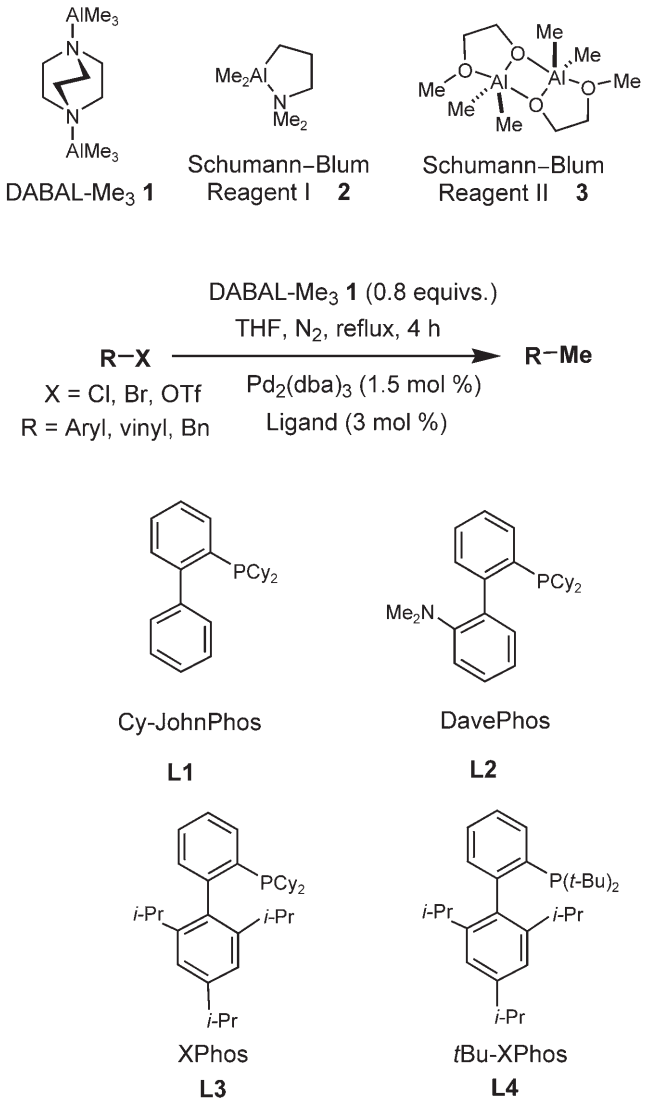
Abstract: An extremely technically simple cross-methylation of aryl and vinyl halides and pseudohalides using an air-stable adduct of trimethylaluminium with a Pd(0) catalyst supported by commercially available biarylphosphines gives excellent yields of methylated products (mainly >95%). Reactions can be run with either 0.5 mol % catalyst or without requiring the exclusion of atmospheric oxygen or the drying of solvents in some cases. A wide variety of functional groups is tolerated including CN, OH, CO_2R, CHO and NO_2.

Keywords: alkylation; aluminium; aryl halides; cross-coupling; palladium; vinyl halides

Palladium- and nickel-catalysed cross-alkylation of aryl and vinyl halides or pseudohalides with organometallic reagents represents an extremely powerful method of C–C bond formation.[1] A major drawback of this chemistry is often the air-sensitive nature of the organometallic reagents used. While tremendous developments have taken place in the use of organoboron[2] and organosilicon reagents,[3] the utility of air-stable organometallic reagents capable of transferring alkyl C(sp^3) nucleophiles, especially a simple CH_3 group, is relatively unexplored. Attempts to realise stabilised reagents derived from trimethylaluminium through the formation of Lewis acid/base pairs have been reported by Schumann, Blum and co-workers leading to the reagents **2** and **3** (among others).[4] While the use of **2** and **3** under nickel or palladium catalysis gives synthetically viable yields of the methylated products, starting from aryl halides, both **2** and **3** must be handled under inert atmospheres.[5] Recently, we demonstrated that the remarkably air-stable $AlMe_3$ adduct $(AlMe_3)_2 \cdot$DABCO (DABCO = 1,4-diazobicyclo[2.2.2]octane) (**1**), which we call DABAL-Me_3,[6] could be applied to the asymmetric methylation of aldehydes.[7] DABAL-Me_3 (**1**), formed in one step from DABCO and neat $AlMe_3$, although somewhat moisture sensitive can be easily handled without the need for an inert atmosphere. In comparison to the Schumann–Blum reagents **2** and **3** DABAL-Me_3 (**1**) is prepared directly from inexpensive, commercially available materials and is an extremely convenient source of methyl carbanions. Herein we report a convenient, robust and near quantitative method for the Pd-catalysed cross-methylation of aryl and vinyl halides or pseudohalides which utilises the reagent **1**.

Preliminary work demonstrated that in the presence of 3 mol % $Pd(PPh_3)_4$, in anhydrous THF at reflux and under an inert atmosphere, synthetically useful yields of methylated products are attained from the cross-alkylation of DABAL-Me_3 (**1**) using unfunctionalised aryl bromides and iodides (50–96%). However, in practice separation of the starting halides from their methylated products is not easily attained in preparative procedures and we sought to attain a process resulting in complete conversions and near quantitative yields under mild conditions. Simple *in situ* generation of the catalyst allowed the screening of the commercially available 1,1′-biphenylphosphines **L1**–**L4**. Primarily developed for the use in the Buchwald/Hartwig-type amination reactions, the electron-rich phosphines **L1**–**L4** have been shown to be highly effective for Pd(0)-catalysed cross-couplings.[8] A brief ligand optimisation study, using $Pd_2(dba)_3$ as the Pd(0) source revealed that Xphos **L3** was the best ligand for the chosen substrates, allowing complete conversion, and delivering the desired products in near quantitative yields (Table 1).

The Pd(0)/**L3** system is known to be a potent activator of Ar–X bonds. In line with this behaviour, highly effective methylation of a wide range of aryl and vinyl bromides, chlorides and triflates could be attained (Ta-



Scheme 1.

ble 2). Both electron-rich and electron-poor aryl substrates participated in the reaction and a wide range of functional groups including nitrile, vinyl, methoxy, esters, aldehydes and alcohols was tolerated. Similarly, a number of naphthalene and heteroaromatic-based substrates also performed well. Selective methylation of aryl–bromide bonds in the presence of aryl–chloride bonds required the use of **L1** which generated a less active catalyst (entry 6) allowing highly chemoselective coupling.

There are some limitations to the DABAL-Me_3 (**1**)/Pd(0)/**L3** system which deserve mention. Functional groups bearing enolisable protons were not tolerated. In the case of acetyl functional groups (Table 2, entry 27) we observed what appeared to be self-aldol condensation of the substrate and product initiated by the presence of the liberated DABCO base. The presence of strongly coordinating amine groups in heterocyclic halides depressed the yield of isolated products (Table 2, entries 35 and 36). The balance of the material was unidentified polar by-products.

In continued efforts to simplify the experimental procedure we were pleased to discover that for small-scale screening reactions high-throughput studies can be performed without recourse to the usual anaerobic procedures associated with palladium(0) and organoaluminium chemistry. Simply running the reactions in commercial undried solvents and in standard glassware open to the atmosphere resulted in clean conversion of representative starting materials. Little or no effect on the yield of methylated products was observed (Table 3). On a small-scale, deoxygenation of the THF might be achieved through heating to reflux, but reactions run below reflux temperatures (60 °C) also gave comparable results. Moisture is clearly removed from such reactions by the presence of the slight excesses of DABAL-Me_3. However, we recommend that large-scale reactions adhere to the anhydrous anaerobic protocol to minimise catalyst decomposition.

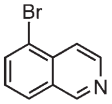
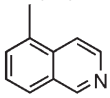
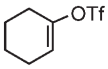
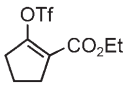
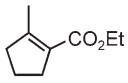
Variation of catalyst loading and reaction time using 4-bromotolunitrile as a test substrate indicated that reaction times of 30 min were sufficient for essentially quantitative conversion to the methylated product (Ta-

Table 1. Lead phosphine structure screening.[a]

Entry	Substrate	Ligand	Product	Yield [%][b]
1	4-NCC_6H_4Br	**L1**	4-NCC_6H_4Me	92
2	4-NCC_6H_4Br	**L2**	4-NCC_6H_4Me	93
3	4-NCC_6H_4Br	**L3**	4-NCC_6H_4Me	95
4	4-NCC_6H_4Br	**L4**	4-NCC_6H_4Me	60
5	4-(MeO)C_6H_4Br	**L1**	4-(MeO)C_6H_4Me	77
6	4-(MeO)C_6H_4Br	**L2**	4-(MeO)C_6H_4Me	97
7	4-(MeO)C_6H_4Br	**L3**	4-(MeO)C_6H_4Me	>99
8	4-(MeO)C_6H_4Br	**L4**	4-(MeO)C_6H_4Me	>99

[a] Reactions performed on a 0.25 mmol scale using 1.5 mol % $Pd_2(dba)_3$, 3 mol % Ligand, 0.8 equivs. DABAL-Me_3 (**1**), THF, N_2, reflux, 4 h.
[b] Yields determined by GC *vs.* an internal standard.

Table 2. Methylation of aryl and vinyl halides and pseudohalides with DABAL-Me_3 (**1**).[a]

Entry	Substrate	L	Product	Yield [%][b]
1	C_6H_5Br	**L3**	C_6H_5Me	>99
2	C_6H_5OTf	**L3**	C_6H_5Me	>99
3	4-MeC_6H_4Br	**L3**	1,4-$Me_2C_6H_4$	>99
4	4-MeC_6H_4Cl	**L3**	1,4-$Me_2C_6H_4$	>99
5	4-FC_6H_4Br	**L3**	4-FC_6H_4Me	>99
6	4-ClC_6H_4Br	**L1**	4-ClC_6H_4Me 1,4-$Me_2C_6H_4$	96[c] 2
7	4-ClC_6H_4Br	**L3**	4-ClC_6H_4Me 1,4-$Me_2C_6H_4$	65 34
8	4-$(CF_3)C_6H_4Br$	**L3**	4-$(CF_3)C_6H_4Me$	>99
9	4-*t*-BuC_6H_4Br	**L3**	4-*t*-BuC_6H_4Me	96
10	4-NCC_6H_4Br	**L3**	4-NCC_6H_4Me	95
11	4-NCC_6H_4Cl	**L3**	4-NCC_6H_4Me	95
12	3-NCC_6H_4Br	**L3**	3-NCC_6H_4Me	95
13	2-NCC_6H_4Br	**L3**	2-NCC_6H_4Me	96
14	4-$(H_2C{=}CH)C_6H_4Br$	**L3**	4-$(H_2C{=}CH)C_6H_4Me$	>99
15	4-$(H_2C{=}CH)C_6H_4Cl$	**L3**	4-$(H_2C{=}CH)C_6H_4Me$	98
16	4-$(MeO)C_6H_4Br$	**L3**	4-$(MeO)C_6H_4Me$	>99
17	4-$(MeO)C_6H_4Cl$	**L3**	4-$(MeO)C_6H_4Me$	>99
18	4-$(MeO)C_6H_4OTf$	**L3**	4-$(MeO)C_6H_4Me$	>99
19	2-$(MeO)C_6H_4Br$	**L3**	2-$(MeO)C_6H_4Me$	>99
20	4-$(EtO_2C)C_6H_4Br$	**L3**	4-$(EtO_2C)C_6H_4Me$	99
21	4-$(EtO_2C)C_6H_4Cl$	**L3**	4-$(EtO_2C)C_6H_4Me$	98
22	4-HOC_6H_4Br	**L3**	4-HOC_6H_4Me	94[d]
23	4-$(O_2N)C_6H_4Br$	**L3**	4-$(O_2N)C_6H_4Me$	76
24	4-$(O_2N)C_6H_4Cl$	**L3**	4-$(O_2N)C_6H_4Me$	81
25	4-$(O_2N)C_6H_4OTf$	**L3**	4-$(O_2N)C_6H_4Me$	59
26	4-$(HOCH_2)C_6H_4Br$	**L3**	4-$(HOCH_2)C_6H_4Me$	79
27	4-$(MeOC)C_6H_4Br$	**L1**	4-$(MeOC)C_6H_4Br$	0
28	4-$(CHO)C_6H_4Br$	**L3**	4-$(CHO)C_6H_4Me$	88[e]
29	$C_6H_5CH_2Br$	**L3**	$C_6H_5CH_2Me$	72
30	1-$C_{10}H_7OTf$	**L3**	1-$C_{10}H_7Me$	>99
31	2-$C_{10}H_7OTf$	**L3**	2-$C_{10}H_7Me$	98
32	1-$C_{10}H_7Cl$	**L3**	1-$C_{10}H_7Me$	90
33	2-$C_{10}H_7Cl$	**L3**	2-$C_{10}H_7Me$	98
34	3-C_4H_3SBr	**L3**	3-C_4H_3SBr	90
35	3-C_5H_3NBr	**L3**	3-C_5H_3NMe	16
36		**L3**		59 [f]
37		**L3**		>99
38		**L3**		98[f]

[a] Reactions performed on a 0.25 mmol scale using 1.5 mol % $Pd_2(dba)_3$, 3 mol % Ligand, 0.8 equivs. DABAL-Me_3 (**1**), THF, N_2, reflux, 4 h. In all [all but entry 26 (91%)] cases quantitative conversions were attained.

[b] Yields determined by GC *vs.* an internal standard. In reactions run at larger scale the isolated yields were directly comparable and within 5% of the GC yields.

[c] 1.0 equivalents of DABAL-Me_3 (**1**) used.

[d] 1.6 equivalents of DABAL-Me_3 (**1**) used.

[e] 0.5 equivalents of DABAL-Me_3 (**1**) used

[f] Isolated yield.

Table 3. Methylations using DABAL-Me_3 (**1**) under aerobic conditions.[a]

Entry	Substrate	Ligand	Product	Yield [%][b]
1	C_6H_5Br	**L3**	C_6H_5Me	79
2	4-$(CF_3)C_6H_4Br$	**L3**	4-$(CF_3)C_6H_4Me$	91
3	4-NCC_6H_4Br	**L3**	4-NCC_6H_4Me	>99
4	4-$(MeO)C_6H_4Br$	**L3**	4-$(MeO)C_6H_4Me$	98
5	4-$(EtO_2C)C_6H_4Br$	**L3**	4-$(EtO_2C)C_6H_4Me$	92
6	4-$(O_2N)C_6H_4Br$	**L3**	4-$(O_2N)C_6H_4Me$	71
7	1-$C_{10}H_7OTf$	**L1**	1-$C_{10}H_7Me$	>99
8	2-$C_{10}H_7OTf$	**L1**	2-$C_{10}H_7Me$	96

[a] Reactions performed on a 0.25 mmol scale using 1.5 mol % $Pd_2(dba)_3$, 3 mol % Ligand, 0.8 equivs. DABAL-Me_3 (**1**), undried THF, open to air, reflux, 4 h.
[b] Yields determined by GC *vs.* an internal standard.

Table 4. Summary of condition variation on the methylation of 4-bromotolunitrile.[a]

Entry	Catalyst mol [%]	*T* [h]	Conditions[a]	Conversion [%][b]	Yield [%][b]	TOF [h^{-1}][c]
1	3	4	A	>99	95	8
2	3	2	A	>99	96	16
3	3	0.5	A	>99	97	65
4	3	4	B	>99	>99	8
5	1	4	A	>99	95	24
6	0.5	4	A	>99	95	48
7	0.5	0.5	B	15	7	28

[a] Reactions performed on a 0.25 mmol scale using 1.5 mol % $Pd_2(dba)_3$, 3 mol % **L3**, 0.8 equivs. DABAL-Me_3 (**1**), reflux with conditions A: anhydrous THF, N_2 or conditions B: undried THF, open to air.
[b] Conversions and yields determined by GC *vs.* an internal standard.
[c] TOF values based on amount of Xphos-**L3** used.

ble 4, entry 3). Reduction of catalyst loading to 0.5 mol % also had negligible effect on the yield (entry 6). However, at these reduced catalyst loadings the reaction becomes much more sensitive to exposure to such impurities (Table 4, entry 7).

While we have focused on methylation here, the analogous higher organoaluminium reagents appear to participate. For example, the analogous ethylation chemistry using $(AlEt_3)_2 \cdot$DABCO [formed *in situ* from $AlEt_3$ and DABCO in THF] gave, under the standard anaerobic conditions, the desired ethylated products in excellent yields (>85%) for a range of simple substituted aryl bromides. Remarkably we observed only negligible β-hydride elimination derived by-products.

In conclusion, we have demonstrated a highly efficient and practical Pd-catalysed cross-methylation of a wide range of functionalised aryl halides and pseudohalides using the DABAL-Me_3 (**1**) reagent. This method utilises an air-stable organometallic reagent, commercially available phosphine ligands and palladium precursors and requires no precautions to exclude air or moisture from the reaction mixture. As such we expect the reaction to be of widespread use.

Experimental Section

General Procedure for Palladium-Catalysed Methylation of Aryl and Vinyl Halides and Triflates

To a flame-dried Schlenk tube under an inert atmosphere $Pd_2(dba)_3$ (6.8 mg, 7 μmol, 1.5 mol %) and Xphos **L3** (7.2 mg, 15 μmol, 3 mol %) were added. To this anhydrous THF (3 mL), 4-bromoanisole (62 μL, 0.50 mmol) and DABAL-Me_3 (**1**) (104 mg, 0.4 mmol, as a solution in 1.0 mL THF) were added and the red solution was heated at reflux for 4 h with stirring. The reaction mixture was cooled to ambient temperature and quenched with aqueous HCl (2 M, 2 mL) followed by extraction by *tert*-butyl methyl ether (10 mL). The organic phase was separated and filtered through a small plug of silica. Removal of the solvent under reduced pressure gave 4-methylanisole as colourless oil; yield: 57.7 mg (95%).

Alternatively yields were calculated from direct GC analysis of reaction mixtures against internal standards. All compounds were identified by GC/MS and ^1H NMR spectroscopy by comparison with authentic samples.

Further details of the experimental procedures (open air and $AlEt_3$) are detailed in the Supporting Information, which also contains characterization data for the compounds made.

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