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Application of a diphosphinidenecyclobutene ligand in the solvent-free copper-catalysed amination reactions of aryl halides†

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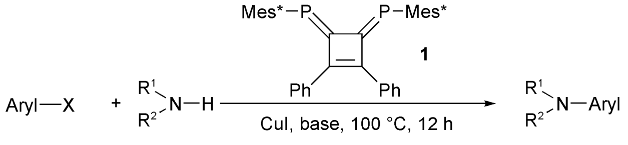
Received (in Cambridge, UK) 2nd June 2004, Accepted 23rd June 2004
First published as an Advance Article on the web 28th July 2004

DOI: 10.1039/b408232j

1,2-Diphenyl-3,4-bis[(2,4,6-tri-*tert*-butylphenyl)phosphinidene]cyclobutene was used as an additive ligand in copper-catalysed amination reactions of halobenzenes with amines in the presence of base to afford the corresponding secondary or tertiary amines in good to excellent yields.

Coupling reactions using copper powder or copper salts have long been known as the Ullmann reaction and are useful for obtaining diphenyls, ethers, amines, and amides. Conventionally these copper-mediated reactions require severe conditions such as high reaction temperature[1] and are carried out without using additive ligands.[2] However, the combination of a ligand such as phenanthroline and a copper source in the presence of base has provided a good methodology. Although palladium-catalysed coupling reactions have recently been extensively developed,[3] copper-mediated reactions remain promising in large and industrial scale reactions from an economic point of view. More importantly, copper-based methods have been used in cases where palladium methodology has failed. For example, the presence of functional groups at the *ortho* position in aromatic halides leads to a considerable decrease in reaction rates, as well as substantially lower overall yields.[4]

To date, sp^2-hybridised phosphorus compounds, *i.e.* low coordinated organophosphorus compounds,[5] have rarely been utilised as ligands for catalysts due to the lack of stability. However, owing to the recent progress in steric protection strategy,[6] such low coordinated phosphorus compounds have been prepared and used in coordination chemistry.[7] In the course of our studies on low coordinated phosphorus compounds, we have prepared various transition-metal complexes of 3,4-diphosphinidenecyclobutene ligands (DPCB)[8] and applied those complexes to several catalytic reactions,[9] since the DPCB ligands are air- and moisture-stable and have proved to act as efficient π-acceptors. Although a number of phosphine ligands are reported in the literature,[3] there is no report on low coordinated phosphorus compounds in the copper system.



X = Br, Cl; R^1= H, alkyl, aryl; R^2= alkyl, aryl; Mes*= 2,4,6-$tBu_3C_6H_2$.

We report here the copper-catalysed amination reactions of aryl halides in the presence of 1,2-diphenyl-3,4-bis[(2,4,6-tri-*tert*-butylphenyl)phosphinidene]cyclobutene **1**.

Reaction conditions were first investigated in the reaction of 1 equiv of *N*-methylaniline with bromobenzene (1 equiv) in toluene in the presence of **1** (2 mol%), CuI (2 mol%), and *t*-BuOK (1 equiv) at 100 °C for 12 h.† When an excess amount of *t*-BuOK (1.5 equiv) was used, the yield of *N*-methyldiphenylamine was slightly decreased from 80 to 73%. DMF and 1,4-dioxane were also evaluated as solvents; however, yields were inferior to those obtained with toluene (54 and 62% yield, respectively). After exploring a wide array of reaction conditions we determined that the best yield was obtained in the absence of solvent (85%, Table 1, entry 16).

Our optimised procedure can be applied directly to amination reactions with aryl bromides and chlorides as listed in Table 1, where the scope of the reaction is summarised. The reaction of aniline with 1 equiv of bromobenzene (entry 1) or bromobenzene derivatives bearing an electron-donating group at the *o*- or *p*-position (entries 4–9) gave the corresponding diphenylamine derivatives in good to excellent yields. The reaction of chlorobenzene with aniline also gave good results (entry 3). It should be noted that the reaction of aniline with 2 equiv of bromobenzene and 2 equiv of *t*-BuOK afforded mono-substituted product in 90% yield (entry 2). A most striking observation was that *o*-methoxybromobenzene gave an excellent result (entry 4). Primary alkylamines reacted with bromobenzene or chlorobenzene in moderate to good yields (entries 10–14). The long chain 1-hexadecylamine reacted with bromobenzene to afforded the corresponding product in good yield (entry 15). Similarly to entry 2, the reaction with 2 equiv of bromobenzene and 2 equiv of *t*-BuOK afforded only mono-substituted product (80% yield) in the reaction with phenethylamine (entry 13). Reaction of some secondary alkyl- or arylamines with bromobenzene or chlorobenzene gave the corresponding tertiary amines in good yields (entries 16–22). It should be noted that the intramolecular amination of *o*-bromophenethylamine proceeded to give indoline almost quantitatively (entry 23).

Table 1 Amination reaction with aryl bromides and chlorides[a]

Entry	Amine	Halide	Yield (%)[b]
1	$PhNH_2$	PhBr	99
2	$PhNH_2$	PhBr[c]	90
3	$PhNH_2$	PhCl	80
4	$PhNH_2$	*o*-$MeOC_6H_4Br$	99
5	$PhNH_2$	*p*-$MeOC_6H_4Br$	71
6	$PhNH_2$	*p*-*tert*-BuC_6H_4Br	90
7	$PhNH_2$	*p*-MeC_6H_4Br	78
8	$PhNH_2$	*p*-MeC_6H_4Cl	60
9	*p*-$MeOC_6H_4NH_2$	PhBr	71
10	$PhCH_2NH_2$	PhBr	80
11	*p*-$MeC_6H_4CH_2NH_2$	PhBr	77
12	$PhCH_2CH_2NH_2$	PhBr	88
13	$PhCH_2CH_2NH_2$	PhBr[c]	80
14	$PhCH_2CH_2NH_2$	PhCl	50
15	$C_{16}H_{33}NH_2$	PhBr	65
16	PhNHMe	PhBr	85
17	PhNHMe	PhCl	75
18	Piperidine	PhBr	94
19	Piperidine	PhCl	78
20	Morpholine	PhBr	80
21	Morpholine	PhCl	70
22	THIQ[d]	PhBr	94
23	*o*-$BrC_6H_4CH_2CH_2NH_2$		99[e]

[a] Reaction conditions: halobenzene (1 equiv), amine (1 equiv), CuI (2 mol%), **1** (2 mol%), *t*-BuOK (1 equiv), 100 °C, 12 h, no solvent. [b] Isolated yield. [c] 2 equiv of PhBr and 2 equiv of *t*-BuOK were employed. [d] Tetrahydroisoquinoline. [e] Indoline was formed.

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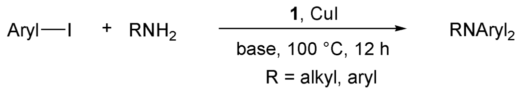
† Electronic supplementary information (ESI) available: details of general procedure for the solvent amination reaction; characterisation data of the products listed in Table 1 and Table 2. See http://www.rsc.org/suppdata/cc/b4/b408232j/

It appears that activity varies with aryl halides in the order Br > Cl. The chlorobenzene derivatives are less reactive (entries 3, 8, 14, 17, 19, 21) than the corresponding bromo derivatives. Although we have discovered that the DPCB–CuI system exhibits unique reactivity for amination reactions, we observed some limitations. No reaction was observed at 100 °C with anilines or bromobenzenes carrying an electron-withdrawing group *e.g.* p-EtOC(O)C_6H_4Br, p-MeC(O)C_6H_4Br, p-$NO_2C_6H_4Br$, p-CNC_6H_4Cl, p-$NO_2C_6H_4NH_2$.



We found that, when 2 equiv of iodobenzene were applied in place of bromo- or chlorobenzenes together with 2 equiv of *t*-BuOK in this copper-catalysed coupling reaction of primary amines, the corresponding tertiary amines were obtained in moderate to good yields, as shown in Table 2 (entries 2–6). It is notable that for the preparation of tertiary amines, a slight excess of iodobenzene gives better results, avoiding the formation of a mixture of secondary and tertiary amines (compare entries 4 and 5). Double arylation with p-tolyl iodide to aniline occurred to afford the corresponding tertiary amine (entry 6). The reaction of aniline with iodobenzene (entry 2) did not proceed either at room temperature or on irradiation with microwaves.

In summary, the copper-catalysed amination reactions of halobenzenes with amines proceed at 100 °C in the presence of **1** (2 mol%), CuI (2 mol%), and *t*-BuOK without solvent provide an efficient method for the introduction of one or two aryl groups into amines. Using iodobenzenes, the method offers an easy access to tertiary amines from primary amines.

Table 2 Amination reactions with iodobenzenes[a]

Entry	Amine	Aryl iodide	Equiv[b]	Product	Yield (%)[c]
1	$PhNH_2$	PhI	1	Ph_2NH	42[d]
2	$PhNH_2$	PhI	2	Ph_3N	90
3	p-$MeOC_6H_4NH_2$	PhI	2	p-$MeOC_6H_4NPh_2$	74
4	$PhCH_2CH_2NH_2$	PhI	2	$PhCH_2CH_2NPh_2$	67[e,f]
5	$PhCH_2CH_2NH_2$	PhI	2.25	$PhCH_2CH_2NPh_2$	84[g]
6	$PhNH_2$	p-MeC_6H_4I	2.25	(p-$MeC_6H_4)_2NPh$	87[h]

[a] Reaction conditions: amine (1 equiv), CuI (2 mol%), **1** (2 mol%), 100 °C, 12 h. [b] Equiv of aryl iodide and *t*-BuOK. [c] Isolated yield. [d] Ph_3N was also obtained in 24% yield. [e] Toluene (2 mL) was added. [f] $PhCH_2CH_2NHPh$ was also obtained in 20% yield. [g] $PhCH_2CH_2NHPh$ was also obtained in 17% yield. [h] p-MeC_6H_4NHPh was also obtained in 17% yield.

This work was supported in part by the Grants-in-Aid for Scientific Research (Nos. 13304049, 14044012, and 13640522) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. ASG is grateful to the Japan Society for the Promotion of Science for a Postdoctoral Fellowship for Foreign Researchers.

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