Highly Selective Copper-Catalyzed Monoarylation of Aniline

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Dedicated to Joe P. Richmond on the occasion of his 60th birthday.

Abstract: A series of mono-, bi- and tridendate ligands was investigated in the copper-catalyzed monoarylation of aniline with *p*-chloronitrobenzene. Excellent selectivities at high conversions were observed when bridged bisimidazolidenes as well as biphenyl-bisalkylphosphines were employed. The X-ray crystal structure of bis(*tert*-butyl)biphenylphosphine-copper complex indicates a significant binding of the metal center to the aryl moiety and, thus, an almost bidendate coordination mode. Chelating bisphosphines, glycol, phenanthroline or other mono- to tridendate ligands led to less selective or productive catalysts.

Keywords: amination; copper; cross-coupling; homogeneous catalysis; ligand effects

The wide use of arylamines and arylamides in pharmaceutical, agrochemical, fine and polymer chemistry has led to the development of very broad and robust synthetic methods for the formation of C–N bonds. The copper-catalyzed coupling of aryl halides with amines and amides was first investigated by Ullmann[1] and Goldberg[2] in the beginning of the last century and is currently being intensively reinvestigated as an alternative to the palladium-catalyzed Buchwald–Hartwig amination.[3] Low costs, interesting functional group tolerances and high catalyst stabilities even under air emerged as major advantages of the copper-based approach.[4] Furthermore, various published investigations furnished a set of robust and versatile protocols that unveil a synthetic potential to a level almost comparable to the palladium-catalyzed reactions.

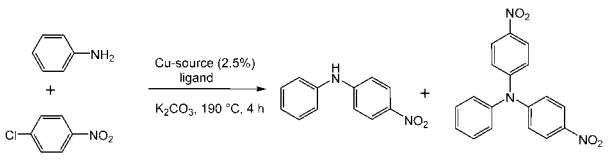
Initial studies towards the synthesis of triarylamines from mono- and diarylamines by a copper-catalyzed process were reported by Goodbrand[5] and Venkataraman[6] utilizing phenanthroline derivatives as ligands. Only recently, Chaudhari observed the accelerating and solubilizing effect of chelating additives in a screening of 22 ligands in the reaction of 2 equivalents of iodobenzene with aniline to obtain triphenylamine with high selectivity and yield.[7] In this case, however, the screening actually showed that the highest selectivities in double arylation were obtained when no ligand was added at all.

Nevertheless, one of the intriguing advantages of palladium-catalyzed arylations of primary amines is the high selectivity towards formation of the monoarylated species. In many cases the careful choice of the reaction conditions, mainly the phosphine, can result in a procedure that suppresses the formation of the bisarylated product below the detectable level.

However, the transfer of this observation to the copper-catalyzed version is not trivial. On the one hand, only very limited knowledge about the mechanism of the copper-catalyzed aromatic amination has been gathered to date. On the other hand, the catalytically active copper species might have completely different electronic and stabilizing demands compared to palladium.

In a recent investigation[8] we aimed at finding reaction conditions for the selective transformation of aniline to 4-nitrodiphenylamine thereby minimizing successive arylation to the corresponding 4,4′-dinitrotriphenylamine (Scheme 1). This side product is both a contaminant of 4-nitrodiphenylamine but also consumes two equivalents of chloronitrobenzene upon formation and therefore renders this coupling process less economical.

For our investigation we decided to examine not only the state of the art of copper-catalyzed aromatic amination,[4] but also the use of novel catalyst systems that were developed in our laboratories. Additionally, we investigated compounds that were known to coordinate transition metals and increase catalytic activity in other reactions. These groups include phosphines, phosphites,



Scheme 1. Copper-catalyzed nitrodiphenylamine synthesis.

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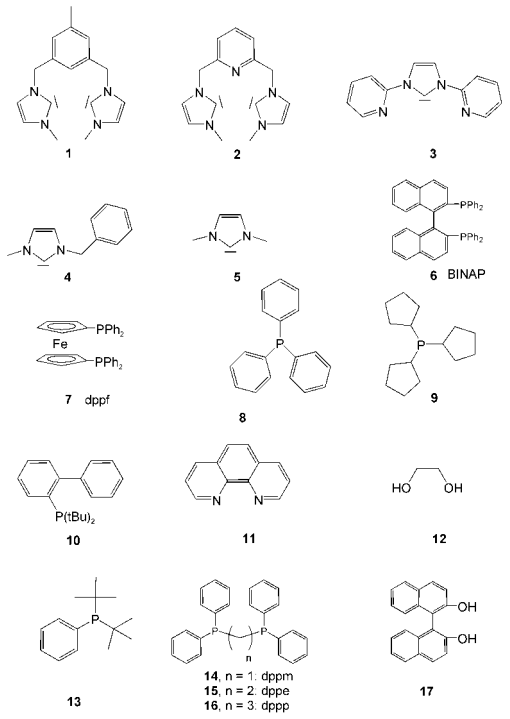


Scheme 2. Ligands for the formation of copper catalysts.

phosphonites, *N*-heterocyclic carbenes, imines, amines, oximes, alcohols and pyridine derivatives. A selection of these ligands is shown in Scheme 2.

Although a total of about 80 ligands was investigated in this random screening, only examples that resulted in a significant improvement of the ligand-free conditions are reported in Table 1.

The screening was set up in a 48-slot parallel synthesis reaction block (H+P Labortechnik GmbH, Munich/Germany)[9] with aniline both as solvent and starting material. To test the reproducibility, we repeated different examples several times. The reactions were monitored by HPLC using quantitative calibration. For better comparison, the data presented show the HPLC yields after 4 h.

Entry 1 shows the blank reaction without addition of any copper catalyst. In this case only 11% conversion was reached. The use of CuO without any ligand other than the starting materials of the reaction yielded 16% conversion, however, with high selectivity (entry 2).

For comparison with more classical additives in copper-catalyzed reactions, we investigated the effect of several di- to polyols, pyridines and phenanthrolines (entries 3 and 4).

Table 1. Ligand screening for the synthesis of 4-nitrodiphenylamine.[a]

Entry	Cu source/ligand	Metal/ligand ratio	Conversion of 4-nitrochlorobenzene [%]	Yield of 4-nitrodiphenylamine [%]	Yield of 4,4′-dinitrotriphenylamine [%]	4-NDPA selectivity[c] [%]
1	Absence of CuO/ligand	–	11	11	0	100
2	CuO	–	16	15,7	0,3	98
3	CuO/**11**	1:1	68	60	8	89
4	CuO/**12**	1:1	28	27	1	96
5	$CuBr_2$/**1**[b]	1:1	78	76	2	98
6	$CuBr_2$/**2**[b]	1:1	65	61	4	94
7	$CuBr_2$/**3**[b]	1:1	44	43	1	98
8	$CuBr_2$/**4**[b]	1:2	71	69	2	97
9	$CuBr_2$/**5**[b]	1:2	64	62	2	96
10	Cu(**6**)Br	1:1	71	69	2	97
11	Cu(**7**)Br	1:1	64	60	4	94
12	CuO/**8**	1:1	37	35	2	95
13	CuO/**8**	1:2	51	49	2	97
14	CuO/**8**	1:3	51	49	2	97
15	CuBr/**8**	1:2	41	40	1	97
16	CuBr/**9**	1:2	81	75	6	93
17	CuBr/**10**	1:1	90	89	1	99
18	$CuBr_2$/**13**	1:2	83	80	3	96
19	CuO/**14**	1:1	60	58	2	96
20	CuO/**15**	1:1	65	61	4	94
21	CuO/**16**	1:1	65	63	2	96
22	CuO/**17**	1:1	65	63	2	96

[a] 10 mmol *p*-nitrochlorobenzene, 40 mmol aniline, 6.9 mmol potassium carbonate, 0.25 mmol catalyst; reaction temperature: 190 °C, reaction time: 4 h.

[b] Catalysts were preformed by addition of the ligand to Cu(II)Br_2 in the presence of KO-*t*-Bu. The formed complexes were characterized by field desorption mass spectrometry.

[c] 4-NDPA selectivity is defined as: [moles 4-nitrodiphenylamine formed/(moles *para*-nitrobenzene converted)], formation of nitrobenzene by dehalogenation of pNCB was consistently found to be below 1% and was therefore neglected.

As the two best examples, phenanthroline (**11**) and ethylene glycol (**12**) have been reported to greatly enhance the activity of copper catalysts.[4] In our example, phenanthroline (**11**) yielded a rather active but unselective catalyst (entry 3), while ethylene glycol (**12**) provided almost no triphenylamine, but the conversion of starting material was rather poor (entry 4).

To check out a strongly basic and well coordinating ligand class, we turned our attention to the family of *N*-heterocyclic carbenes (entries 5–9). The monodentate compounds **4** and **5** showed outstanding selectivity towards formation of the desired monoarlyated product (entries 8 and 9) with already much increased conversion of starting aryl chloride compared to ethylene glycol (**12**) or phenanthroline (**11**). When applying chelating carbenes like ligands **1** to **3** (entries 5–7), again very high selectivities towards monoarylation were observed. Interesting to note is that ligand **3** (entry 7), principally chelating but still only a monocarbene, yields a catalyst with decreased activity compared to other monocarbenes like **4** and **5**. Pyridylbiscarbene **2** (entry 6) however, was found to be active but not very selective. The best data were gathered when investigating ligand **1**, as chelating biscarbene. To our delight, this was not only the most active and selective carbene (entry 5), it is also easily prepared from inexpensive and abundant starting materials, in this case *N*-methylimidazole and the corresponding benzyl bromide. Therefore, this ligand shows a high potential for industrial application. Interesting to note is that these yields could be retained when transferring this reaction to the kilogram scale without any problem at all.

Apart from the class of carbenes as ligands, a ligand class well-known from their applications in transition metal-catalyzed reactions using ruthenium, rhodium, palladium etc. was investigated next (entries 6 to 10, 13 to 16). This includes several mono- (entries 8–10, 13) and bidentate (entries 6, 7, 14–16) phosphines. In most cases the copper complex was preformed by mixing the ligand and copper(II) bromide in degassed methanol, in accord with the reports of Venkataraman.[10] To be sure that intermediate copper(I) species were not influenced by the presence of air, the solvent was carefully degassed. Characterization by field desorption mass spectrometry (FD-MS) indicated that the complexes had indeed formed.

The use of Cu(I) complexes with triphenylphosphine (**8**) as catalysts for the arylation of amines has been reported by Venkataraman.[10] When following his procedure, a complex with a molar ratio of copper to phosphine of 1:2 was formed. This catalyst again showed very high selectivity towards formation of monoarylated product, but when compared to the monodentate carbenes like **4** the catalytic activity was somewhat lower (entry 15). When copper oxide and triphenylphosphine (**8**) were added in a molecular ratio of 1:1 to 1:3, (entries 12 to 14) to the reaction, thus avoiding preformation of the complexes, the activity was slightly increased in the case of the ratio of 1:2 (entry 13). While the selectivity of the reaction compared to the preformed complex remained, a higher excess of triphenylphosphine did not increase either the activity or the selectivity of the catalyst (entry 14).

The use of more electron-rich phosphines, like triscyclopentylphosphine (**9**) yielded a higher conversion of the starting material (entry 16), however, the selectivity was slightly diminished compared to both triphenylphosphine (**8**) or monocarbene **4**.

In another case we used mixed arylalkylphosphines like di-*tert*-butylphenylphosphine (**13**) and a very active catalyst was generated. While the high selectivity of triphenylphosphine (**8**) could almost be retained, this ligand gave a catalyst with even higher activity compared to trialkylphosphine **9**. When ligand **13** is "stretched" by one phenyl group to ligand **10**, the class of biphenyldialkylphoshines, mostly known as ligands that assist palladium-catalyzed Suzuki and Buchwald–Hartwig reactions, is obtained. To our surprise, a catalyst from ligand **10** and copper(II) bromide proved to be very successful in this application. Following the trend from triphenylphosphine (**8**) to di-*tert*-butylphenylphosphine (**13**), biphenylphosphine **10** gave a highly active catalyst that almost exclusively yielded the diarylamine (entry 17). Again the reaction with this ligand was transferred to the kilogram scale. Also, just like in the case of the biscarbene **1**, the same results were monitored under these more "realistic" conditions.

Chelating phosphines like bis-diphenylphosphinoferrocene (dppf) (**7**) or 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, **6**) (entries 10 and 11) unfortunately did not show any improvement compared to the monophosphines either in selectivity or in activity. Both, however, yielded results comparable to those of the chelating carbenes. Other common chelating bisphosphines like **14**, **15** and **16** showed comparable activities to **6** and **7** but with slightly diminished selectivities. Interesting to note is that with a growing carbon chain length between the phosphorus centers, a slight trend to increasing activity of the resulting catalyst can be observed (entries 19 to 21).

Finally, one example utilizing binaphthol **17** as ligand is presented (entry 22). When directly compared to ethylene glycol (**12**), this more rigid diol again yields a very selective catalyst, with a significant increase in catalytic activity. However, when compared to the most active catalysts in our screening, ligand **17** showed only moderate conversions.

When reviewing the activity of our best catalyst **10** (entry 17), we came across an uncommon X-ray structure (Figure 1). The white powder that was obtained on mixing the phosphine and copper(II) bromide in methanol consisted of a dimeric copper-phosphine complex. The distance between the copper center and C12 in the 2′ position of the biphenyl is about 2.54 Å and this

Table 2. Selected bond lengths [Å] and angles [°] for CuBr/**10**.

Br(1)–Cu(1)	2.4233(4)	Br(1)–Cu(1)–Br(1A)	102.599(15)
Br(1)–Cu(1A)	2.4692(4)	P(1)–Cu(1)–C(12)	92.03(7)
Cu(1)–P(1)	2.2161(8)	C(7)–C(12)–Cu(1)	89.57(17)
Cu(1)–C(12)	2.541(3)	Br(1)–Cu(1)–C(12)	108.67(7)
Cu(1)–Cu(1A)	3.0592(7)		

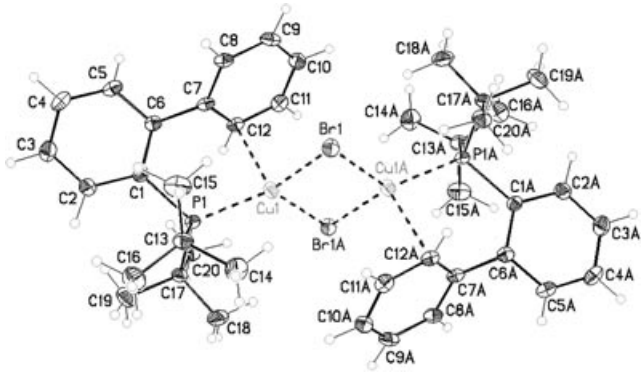


Figure 1. ORTEP plot of the CuBr/**10** complex with the numbering of the non-hydrogen atoms.

copper-carbon bond sets up an almost perpendicular angle to the plane of the phenyl moiety. It can be concluded that this aromatic group serves as a very weakly coordinating center. Therefore, we regard ligand **10** as a chelating ligand. The increased reactivity and selectivity might be explained by steric shielding of the catalytic center by the ligand on the one hand, quick cleavage of the dimer and therefore possibly higher productivity on the other hand.

In conclusion, we have shown that the selectivity and productivity in the monoarylation of aniline with *p*-chloronitrobenzene can be carefully tuned by ligand variation. The results achieved are very promising and reach a quality known only from the palladium-catalyzed counterpart of this reaction so far. Additional transformations with these copper catalysts are the subject of ongoing research and will be reported in due course.[11]

Experimental Section

Synthesis of 1,3-Bis-[*N*-(*N*′-methyl)imidazolidenemethyl]-5-methylbenzene (1)

A solution of 3,5-bis(bromomethyl)toluene (2.5 g, 9 mmol) and 1-methylimidazole (1.5 g, 18 mmol) in 100 mL of dioxane was stirred at 100 °C for 12 h. After cooling to room temperature the precipitate is filtered off, washed with dioxane and dried under vacuum to afford the pure product; yield: 3.01 g (77%); ^{1}H NMR (700 MHz, DMSO-d_6): δ = 2.31 (s, 3H, CH_3), 3.88 (s, 6H, CH_3), 5.41 (s, 4H, CH_2), 7.25 (s, 2H, Ph), 7.38 (s, 1H, Ph), 7.75 (s, 2H, imidazole-H), 7.82 (s, 2H, imidazole-H), 9.33 (s, 2H, imidazole-H); MS (CI): *m/z* = 282 (M – 2Br).

Synthesis of 1,3-Bis-[*N*-(*N*′-methyl)imidazolidenemethyl]-benzene (2)

A solution of 3,5-bis(bromomethyl)pyridine (2.5 g, 9 mmol) and 1-methylimidazole (1.5 g, 18 mmol) in 100 mL of dioxane was stirred at 100 °C for 12 h. After cooling to room temperature the precipitate is filtered off, washed with dioxane and dried under vacuum to afford the pure product; yield: 3.3 g (82%); ^{1}H NMR (700 MHz, DMSO-d_6): δ = 3.92 (s, 6H, CH_3), 5.58 (s, 4H, CH_2), 7.48 (m, 2H, Ph), 7.69 (s, 2H, imidazole-H), 7.78 (s, 2H, imidazole-H), 7.98 (m, 1H, Ph), 9.19 (s, 2H, imidazole-H); MS (CI): *m/z* = 271 (M – 2Br).

Synthesis of *N*,*N*′-Dipyridylimidazolium Bromide (3)

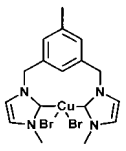
According to a literature procedure[12] a mixture of 2-bromopyridine (15 g, 95 mmol) and 1-methylimidazole (7.8 g, 95 mmol) was stirred at 190 °C for 20 h. After cooling to room temperature the residue was suspended in methanol/acetone (1:1, 100 mL). The precipitate is filtered off, washed with dioxane and dried under vacuum to afford the pure product; yield: 4.8 g (17%); ^{1}H NMR (700 MHz, DMSO-d_6): δ = 7.71 (m, 2H, pyr-H), 8.29 (m, 4H, pyr-H), 8.73 (m, 2H, pyr-H), 8.78 (s, 2H, imidazole-H), 10.9 (s, 1H, imidazole-H); MS-CI: *m/z* = 223 (M + 1 – Br).

Synthesis of *N*-Benzyl-*N*′-methylimidazolium Bromide (4)

A solution of benzyl bromide (17.1 g, 100 mmol) and 1-methylimidazole (8.2 g, 100 mmol) in 100 mL of dioxane was stirred at 100 °C for 12 h. After cooling to room temperature the oil was separated and dried under vacuum to afford the pure product; yield: 26.0 g (98%); ^{1}H NMR (700 MHz, DMSO-d_6): δ = 3.89 (s, 3H, CH_3), 5.48 (s, 2H, CH_2), 7.35–7.50 (m, 5H, Ph), 7.76 (s, 1H, imidazole-H), 7.85 (s, 1H, imidazole-H), 9.35 (s, 1H, imidazole-H).

Generation of Copper(II) Bromide/1 Catalyst

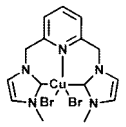
The biscarbene catalyst of ligand **1** was formed by dissolving the corresponding bisimidazolium dibromide (135 mg, 0.31 mmol) in 10 mL of toluene with potassium *tert*-butoxide (71 mg, 0.63 mmol) at 0 °C. After 2 h copper(II) bromide (70 mg, 0.31 mmol) was added and the resulting suspension stirred for 12 h before the solvent was removed under vacuum.



The white solid was transferred to the catalyst experiment without further purification. FD-MS: $m/z = 343$ (M – 2Br), 423 (M – Br), 503 (M + 2H).

Generation of Copper(II) Bromide/2 Catalyst

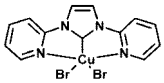
The biscarbene catalyst of ligand **2** was formed by dissolving the corresponding bisimidazolium dibromide (131 mg, 0.31 mmol) in 10 mL of toluene with potassium *tert*-butoxide (71 mg, 0.63 mmol) at 0 °C. After 2 h copper(II) bromide (70 mg, 0.31 mmol) was added and the resulting suspension



stirred for 12 h before the solvent was removed under vacuum. The white solid was transferred to the catalyst experiment without further purification. FD-MS: $m/z = 330$ (M – 2Br), 410 (M – Br), 490 (M + 2H).

Generation of Copper(II) Bromide/3 Catalyst

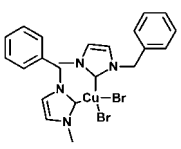
The biscarbene catalyst of ligand **3** was formed by dissolving the corresponding bisimidazolium dibromide (92 mg, 0.31 mmol) in 10 mL of toluene with potassium *tert*-butoxide (71 mg, 0.63 mmol) at 0 °C. After 2 h copper(II) bromide (36 mg, 0.31 mmol) was added and the resulting suspension



stirred for 12 h before the solvent was removed under vacuum. The white solid was transferred to the catalyst experiment without further purification. FD-MS: $m/z = 364$ (M – Br).

Generation of Copper(II) Bromide/4 Catalyst

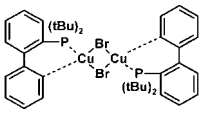
The monocarbene catalyst of ligand **4** was formed by dissolving the corresponding bisimidazolium dibromide (300 mg, 1,2 mmol) in 10 mL of toluene with potassium *tert*-butoxide (138 mg, 1.2 mmol) at 0 °C. After 2 h copper(II) bromide (120 mg, 0.6 mmol) was added and the resulting suspension



stirred for 12 h before the solvent was removed under vacuum. The white solid was transferred to the catalyst experiment without further purification. FD-MS: $m/z = 316$ (M – 2Br).

Generation of Copper(I) Bromide/10 Catalyst

Dry methanol (50 mL) was carefully degassed and heated to reflux under an argon atmosphere. Di-*tert*-butylphosphinobiphenyl (2.36 g, 7.905 mmol) was added slowly and stirring was continued until the phosphine was fully dissolved. Copper(II) bromide (0.589 g, 2.635 mmol) was added in small por-



tions over 10 minutes. Heating was continued for 15 min. and the suspension was allowed to cool to room temperature. The solid was isolated by filtration, washed with small amounts of ethanol and ether, then dried under vacuum to afford bis(di-*tert*-butylphosphinobiphenylcopper(I) bromide; yield: 0.93 g (1.05 mmol, 80%). ^{31}P NMR: $\delta = 41.6$; FD-MS: $m/z = 803$ (M – Br); (Cambridge Crystallographic Data Centre CCDC 239715).

Experimental Test Procedure for Catalytic Activity in the C–N Coupling of 4-Nitrochlorobenzene with Aniline

HPLC analyses were performed on a Hewlett-Packard 1100 chromatograph equipped with a ZORBAX SB C18 column (5 μ, 3.0 × 250 mm), column temperature 23 °C; eluent A: 90% v/v water, 10% v/v acetonitrile, 1 mL trifluoroacetic acid/L eluent; eluent B: 90% v/v acetonitrile, 10% v/v water, 1 mL trifluoroacetic acid/L eluent; eluent C: methanol, flow 1.0 mL/min, detection at 254 nm, 5 mL injection volume. For quantitative determination of pNCB, 4-NDPA and 4,4′-dinitrotriphenylamine calibration curves for each substance were recorded prior to catalytic tests.

In a 10-mL reaction tube 3.75 g (40 mmol) aniline were added to 1.58 g (10 mmol) *para*-nitrochlorobenzene, 0.95 g (6.9 mmol) potassium carbonate and 0.25 mmol catalyst (copper complex or copper precursor + ligand as denoted in Table 1) were added. A cooling tube filled with molecular sieve was set on top of the reaction tube and the reaction mixture was stirred with 530 rpm at 190 °C in a multiple screening block. After 4 hours the reaction was stopped, the reaction tubes cooled to 40 °C and samples were taken for HPLC analysis.

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