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Addition of aryl cuprates to azides: a novel approach for the synthesis of unsymmetrical diaryl amines

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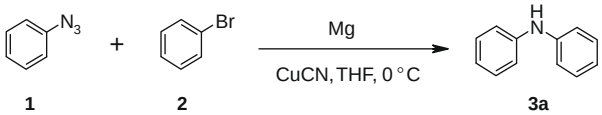
ABSTRACT

Aryl and benzyl azides react smoothly with aryl cuprates, generated in situ from aryl magnesium bromide and CuCN in THF to furnish a variety of unsymmetrical diaryl amines in good yields. This is the first report on the synthesis of diarylamines from aryl azides and aryl bromides via an organometallic approach.

Diaryl amines are important industrial intermediates and are frequently found in a variety of biologically active molecules such as natural products,[1] agrochemicals,[2] and HIV-1 protease inhibitors.[3] They are also widely used as stabilizers and antioxidants for rubber and polymers, stabilizers for explosives, as polymerization and corrosion inhibitors, and in dye preparation.[4] Traditionally, the N-arylation of amines has been carried out under copper-mediated Ullmann-type conditions involving the coupling of amines with aryl halides.[5] Although these copper-promoted reactions are useful, they usually require harsh reaction conditions and stoichiometric amounts of copper, and the yields are not reproducible.[6] Recently, various diaryl amines have been prepared by palladium-catalyzed cross-coupling reactions of amines with aryl halides.[7] Other transition metals such as copper[8] and nickel[9] have also been used for C–N bond-formation reactions. Oxidative coupling procedures between arylboronic acids and aromatic or heterocyclic amines mediated by Cu(II) salts are also effective.[10] Addition of aromatic Grignard reagents to nitroarenes has also been reported for the synthesis of diaryl amines.[11] Despite these significant recent improvements, there are still limitations such as the use of expensive catalysts and ligands in the present N-arylation methods. Furthermore, there have been no reports on the synthesis of unsymmetrical diaryl amines via aryl cuprate additions to organic azides.

In continuation of our work on metal-mediated reactions of organic azides,[12] we herein report a novel procedure for the preparation of unsymmetrical diaryl amines by means of addition of aryl cuprates to azides. Initially, we attempted arylation of phenyl azide (**1**) with phenyl magnesium bromide (**2**) in THF at 0 °C. To our surprise, no desired diphenyl amine was obtained using phenylmagnesium bromide alone. However, the corresponding diphenyl amine **3a** was obtained in 65% by phenyl cuprate generated in situ from phenyl magnesium bromide and CuCN (Scheme 1).

Next, we examined the reactivity of various azides and aryl halides. Interestingly, several aryl azides reacted readily with aryl cuprates to produce a wide range of diaryl amines (Table 1). This method worked well with aryl and benzyl azides. Though alkyl azides failed to react with aryl cuprates, benzyl azide reacted well with phenyl cuprate because of its high reactivity compared to alkyl azides. Furthermore, this method is highly selective for the monoarylation of azides, whereas Pd(II)/base-promoted arylation of amines produce a mixture of products. The reaction conditions are compatible with various functionalities such as chloro, nitro, and aryl ethers (Table 1). The steric and electronic factors had shown some effect on the conversion. In general, electron-rich azides gave higher conversion than electron-deficient counterpart (Table 1, entries d–f). Similarly, sterically hindered azides gave lower yields compared to simple aromatic azides (Table 1, entries i and l).



1 2 3a

Scheme 1.

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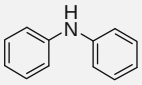
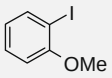
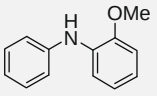
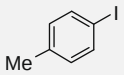
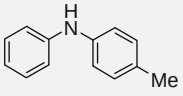
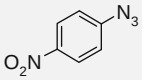
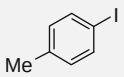
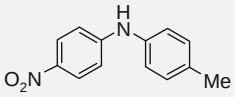
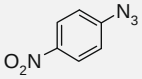
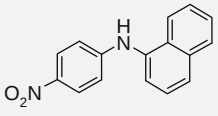
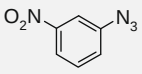
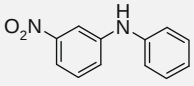
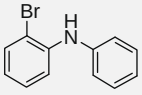
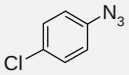
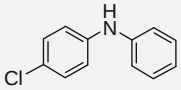
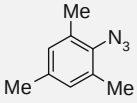
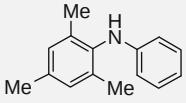
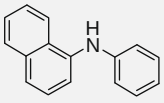
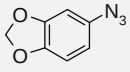
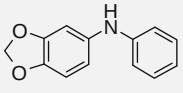
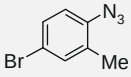
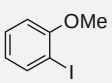
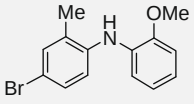
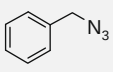
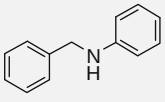
Table 1
Preparation of diaryl amines via the addition of aryl cuprates to azides

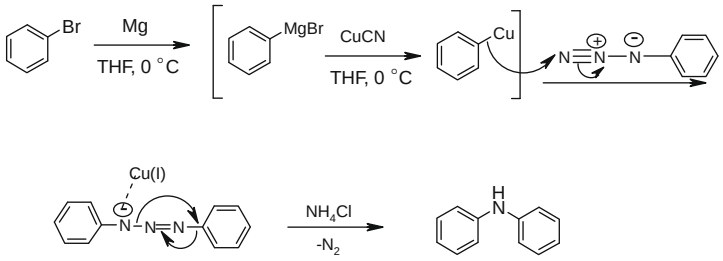
Entry	Azide	Aryl halide	Diaryl amine[a]	Time (h)	Yield[b,c] (%)
a				1.5	65
b				2.0	62
c				2.0	58
d				2.5	56
e				2.5	54
f				2.0	61
g				1.5	70
h				1.5	63
i				2.0	60
j				2.0	67
k				1.5	75
l				3.0	57
m				1.5	60

[a] The products were characterized by ^{1}H NMR, IR, and mass spectrometry.
[b] Yield refers to pure products after chromatography.
[c] The reactions were performed in 1 mmol scale at 0 °C.

Table 2
Effect of various Cu(I) salts in the preparation of **3a**

Entry	Cu(I) salt	Quantity[a] (mmol)	Yield[b] (%)
1	CuI	0.2	10
2	CuI	1.2	32
3	CuBr	0.2	8
4	CuBr	1.2	24
5	CuCN	0.2	15
6	CuCN	1	60
7	CuCN	1.2	65
8	CuCN	2	65
9	CuCN	3	65

[a] The reaction was carried out with phenyl azide (1 mmol), bromobenzene (1.2 mmol), and magnesium (2.5 mmol).
[b] Yield refers to pure products after chromatography.



Scheme 2.

The products were characterized by ^{1}H NMR, IR, and mass spectrometry. No improvement in yield was observed either by increasing the reaction time or by increasing the amount of copper(I) salt. In the absence of CuCN, 1,4-diaryl triazene was formed from arylmagnesium halide and azide, which was unstable and decomposed rapidly to give the respective orange-red diazo compound. The reaction was successful only with aryl cuprates. The scope and generality of this procedure is illustrated with respect to various organic azides and aryl halides and the results are presented in Table 1.[13]

The effect of various Cu(I) salts such as CuI, CuBr and CuCN, CuCN was studied in the reaction of phenyl azide (1 mmol), bromobenzene (1.2 mmol), and magnesium (2.5 mmol). Low yields (10–24%) were obtained when CuI and CuBr were used as additives. The use of catalytic amount of CuCN (0.2 equiv) gave the desired product **3a** in 15% yield. Under optimized conditions, 1.2 equiv of CuCN is essential to achieve high conversion. No increase in the yield was observed even by increasing the quantity of the CuCN (Table 2).

It is noteworthy to mention that the reaction needs to be carried out under anhydrous conditions to obtain the desired product. Mechanistically, the reaction proceeds via the formation of arylmagnesium halide, from aryl halide and magnesium metal, which subsequently reacts with CuCN to produce aryl cuprate. This aryl cuprate may attack on azide to give the diaryl amine with concomitant loss of nitrogen (Scheme 2).

In conclusion, we have developed a novel approach for the synthesis of unsymmetrical diaryl amines by means of addition of aryl cuprates to aryl azides. This is a versatile method to accomplish the synthesis of a series of diaryl amines from azides in a single-step operation.

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References and notes

1. (a) Negwer, M. *Organic-Chemical Drugs and their Synonyms (An International Survey)*, 7th ed.; Akademie GmbH: Berlin, Germany, 1994; (b) Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112–113; (c) Hong, Y.; Senanayake, C. H.; Xiang, T.; Vandenbossche, C. P.; Tanoury, G. J.; Bakale, R. P.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 3121–3124; (d) Romero, D. L.; Morge, R. A.; Genin, M. J.; Biles, C.; Busso, M.; Resnick, L.; Althaus, I. W.; Reusser, F.; Thomas, R. C.; Tarpley, W. G. *J. Med. Chem.* **1993**, *36*, 1505–1508; (e) Evans, D. A.; DeVries, K. M.. In *Glycopeptide Antibiotics, Drugs and the Pharmaceutical Sciences*; Nagarajan, R., Ed.; Marcel Decker: New York, 1994; Vol. 63, pp 63–104; (f) Pettit, G. R.; Singh, S. B.; Niven, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 8539–8540; (g) Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909–4913; (h) Atkinson, D. C.; Godfrey, K. E.; Myers, P. L.; Philips, N. C.; Stillings, M. R.; Welbourn, A. P. *J. Med. Chem.* **1983**, *26*, 1361–1364; (i) Nicolaou, K. C.; Christopher, N. C. B. *J. Am. Chem. Soc.* **2002**, *124*, 10451–10455.
2. *CRC Handbook of Pesticides*; Milne, G. W. A., Ed.; CRC Press: Boca Raton, FL, 1994.
3. Turner, S. R.; Strohbach, J. W.; Tommasi, R. A.; Aristoff, P. A.; Johnson, P. D.; Skulnick, H. I.; Dolak, L. A.; Seest, E. P.; Tomich, P. K.; Bohanon, M. J.; Horng, M. M.; Lynn, J. C.; Chong, K.-T.; Hinshaw, R. R.; Watenpaugh, K. D.; Janakiraman, M. N.; Thaisrivongs, S. *J. Med. Chem.* **1998**, *41*, 3467–3476.
4. (a) Goodson, F. E.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 1700–1703; (b) Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 7527–7530; (c) Singer, R. A.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 213–214.
5. (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384; (b) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670–674; (c) Ullmann, F. *Chem. Ber.* **1904**, *37*, 853–854.
6. (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456; (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1370.
7. (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146; (b) Wolfe, J. P.; Wagan, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818; (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067; (d) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000.
8. (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729; (b) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803–3805; (c) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333–1336; (d) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. J. *Org. Chem.* **1999**, *64*, 2986–2987.
9. (a) Lipshutz, B. H.; Ueda, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 4492–4494; (b) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 247–250.
10. (a) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077–2079; (b) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233–1236; (c) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418; (d) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600–7601.
11. Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390–9391.

12. (a) Kumar, H. M. S.; Anjaneyulu, S.; Reddy, B. V. S.; Yadav, J. S. *Synlett* **1999**, 551; (b) Kumar, H. M. S.; Reddy, B. V. S.; Anjaneyulu, S.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 8305–8306; (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, G. S. K. K. *New J. Chem.* **2000**, *24*, 571.
13. *Typical procedure*: a mixture of bromobenzene (188 mg, 1.2 mmol), activated magnesium turnings (0.060 mg, 2.5 mmol), and a small iodine granule in anhydrous THF (5 mL) was stirred under nitrogen atmosphere to generate phenyl magnesium bromide. The thus-obtained aryl Grignard reagent was added slowly to the solution of CuCN (128 mg, 1.5 mmol) in dry THF (4 ml) at 0 °C. After obtaining bluish-green colour, a solution of phenyl azide (119 mg, 1 mmol) in THF (1 mL) was added slowly in a dropwise manner. The resulting mixture was stirred for 1 h at 0 °C. After the completion of the reaction, as indicated by TLC, the mixture was quenched with saturated ammonium chloride solution (5 mL) and filtered off under vacuo. The filtrate was extracted with ethyl acetate (2×10 mL), dried over Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate/hexane, 2:98) afforded pure diphenyl amine (109 mg, 65% yield). In case of substituted aryl iodides, the corresponding Grignard reagent was generated in dry diethyl ether. *Spectral data for selected products*: compound **3k**. *N-(1,3-Benzodioxol-5-yl)-N-phenylamine*: white solid, mp 152 °C, IR (neat): ν_{max} 3398, 2964, 2892, 1598, 1482, 1235, 1075, 930, 803, 747, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.15 (t, J = 7.5 Hz, 2H), 6.85 (d, J = 7.5 Hz, 2H), 6.78 (t, J = 7.5 Hz, 1H), 6.69–6.61 (m, 2H), 6.48 (dd, J = 8.3 and 2.2 Hz, 1H), 5.88 (s, 2H), 5.39 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 144.5, 137.1, 129.3, 121.3, 119.9, 116.1, 112.8, 108.5, 102.4, 101.0; ESI-MS: *m/z*: 214 (M+H); HRMS calcd for $C_{13}H_{12}NO_2$: 214.0868, found: 214.0860. Compound **3j**. *N-(1-Naphthyl)-N-phenylamine*: white solid, mp 132 °C, IR(neat): ν_{max} 3391, 3051, 2922, 1595, 1495, 1398, 1303, 774, 741, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.01–7.95 (m, 1H), 7.83–7.78 (m, 1H), 7.54–7.40 (m, 3H), 7.36–7.31 (m, 2H), 7.20 (t, J = 7.5 Hz, 2H), 6.95 (d, J = 7.5 Hz, 2H), 6.85 (t, J = 7.5 Hz, 1H), 5.85 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 138.7, 134.6, 129.3, 128.5, 127.7, 126.1, 125.9, 125.6, 122.9, 121.7, 120.4, 117.3, 115.8; ESI-MS: *m/z*: 220 (M+H); HRMS calcd for $C_{16}H_{14}N$: 220.1126, found: 220.1125. Compound **3b**. *N-(2-Methoxyphenyl)-N-phenylamine*: White solid, mp 102 °C, IR (neat): ν_{max} 3413, 2959, 1593, 1517, 1238, 1026, 714, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.21–6.95 (m, 5H), 6.84–6.66 (m, 4H), 5.97 (br s, 1H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 142.6, 132.9, 129.2, 121.1, 120.7, 119.8, 118.5, 114.6, 110.4, 55.5; ESI-MS: *m/z*: 200 (M+H); HRMS calculated for $C_{13}H_{14}NO$: 200.1075, found: 200.1069. Compound **3i**. *N-Mesityl-N-phenylamine*: White solid, mp 52 °C IR (neat): ν_{max} 3390, 2919, 1600, 1495, 1311, 746, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.06 (t, J = 7.5 Hz, 2H), 6.87 (s, 2H), 6.65 (t, J = 7.5 Hz, 1H), 6.42 (d, J = 7.5 Hz, 2H), 5.00 (br s, 1H), 2.29 (s, 3H), 2.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6, 135.9, 135.4, 135.3, 129.1, 127.0, 117.8, 113.2, 20.9, 18.2; ESI-MS: *m/z*: 212 (M+H); HRMS calcd for $C_{15}H_{18}N$: 212.1439, found: 212.1438.