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Synthesis of Isotopically Labeled Tri-*p*-tolylamine

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Summary

Three isotopically labeled tri-*p*-tolylamines, ^{15}N, $^{15}N^{2}D_{27}$, and mono-$^{13}CH_3$ have been prepared using zeolite mediated bromination or nitration of toluenes as one of the key steps. The obtained 4-nitrotoluenes were reduced to 4-aminotoluenes, and coupled, *via* a palladium catalyzed amination reaction, with 4-bromotoluenes to afford di- and tri-*p*-tolylamines. The di-*p*-tolylamines were readily transformed into tri-*p*-tolylamines using the same palladium catalyzed methodology.

Keywords

Tri-*p*-tolylamine, zeolite, nitration, bromination, palladium, amination.

Introduction

Molecularly doped polymers prepared with charge-transporting molecules are widely used in xerography because of their photoconducting properties. Charge transport occurs by a hopping process of the charge carriers (either holes or electrons) and is influenced by the spatial relationship between neighboring charge-transporting molecules. The polymer host serves mostly as a binder, but may play a role in determining the relative orientation between the dopant molecules. However, there is little information regarding the structural aspects of molecularly doped polymers because of the difficulties associated with characterizing amorphous materials.

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Certain amines blended with various polycarbonates are good photoconductors. Tri-*p*-tolylamine[3] (*N,N*-bis(4-methylphenyl)-4-methylbenzenamine, Figure 1) is a particularly attractive charge-transporting molecule to study since it has a relatively simple molecular structure with the three carbon-nitrogen bonds of tri-*p*-tolylamine being nearly in the same plane. The photoconducting properties of blends of tri-*p*-tolylamine with various polymers have been studied extensively. Unfortunately, there is little data regarding the structural relationship of the tri-*p*-tolylamine molecules in the polymers, and most models of charge transport for the blends assume a simple model of uniform dispersion of tri-*p*-tolylamine within the polymer host. Because of the amorphous nature of these materials, there is little experimental information about the organization of tri-*p*-tolylamine in polymers.

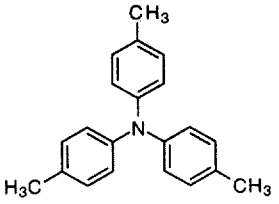


Figure 1. Tri-*p*-tolylamine

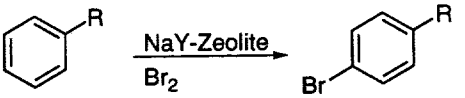
New high-resolution, solid-state NMR experiments have the ability to provide structural information in complex solids. By combining solid-state NMR with site-specific ^{13}C, ^{2}D, and ^{15}N isotopic labeling, accurate internuclear distances between the isotopic labels can be measured. The NMR experiments that we use to measure internuclear distances are rotational-echo, adiabatic-passage, double-resonance (REAPDOR), and rotational-echo, double-resonance (REDOR). Our NMR experiments are designed to probe internuclear separations by monitoring ^{13}C-^{14}N, ^{13}C-^{15}N, and ^{13}C–^{2}D dipolar interactions, and these NMR experiments can measure internuclear separations up to approximately 6 Å. We have examined blends of isotopically labeled tri-*p*-tolylamine and bisphenol-A-polycarbonate with solid-state NMR in an effort to obtain information regarding the organization of tri-*p*-tolylamine in polycarbonate. For our

experiments it was necessary to perform specific ^{13}C, ^{2}D, and ^{15}N isotopic labeling of tri-*p*-tolylamine. The efficient isotopic labeling of tri-*p*-tolylamine is presented herein.

Results and Discussion

Commercially available carbon-13 ($^{13}CH_3$) and deuterium ($^{2}D_8$) labeled toluenes were utilized as starting materials for the synthesis of tri-*p*-tolylamines. The toluenes were smoothly brominated employing the zeolite mediated, regioselective, bromination protocol developed by Smith and Bahzad.[4] In the event, reaction of toluene-$^{2}D_8$ with bromine, in the presence of NaY zeolite, gave 4-bromotoluene-$^{2}D_7$ (**1**) in 81% yield (Table 1). The *ortho/para* ratio was determined by ^{13}C NMR to be in excess of 15:1. Similar reaction of toluene-$^{13}CH_3$ gave the 4-bromotoluene **2** in 74% yield. In the case of **2**, a 12:1 mixture was observed by ^{1}H NMR of the crude reaction mixture. However, only one isomer was obtained after purification.

Table 1. 4-Bromination of Toluenes



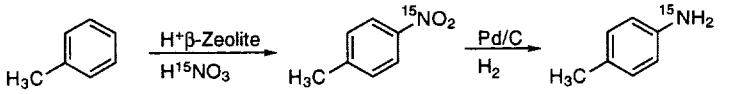
R = $^{2}D_7$ (**1**, 81%); R = $^{13}CH_3$ (**2**, 74%); R = $C^{2}D_3$ (**3**,74%)

In order to compare the present route to labeled 4-bromotoluenes, toluene-$C^{2}D_3$ was reacted with bromine producing **3**. (This compound was not used to prepare tri-*p*-tolylamines.) 4-Bromotoluene-$^{2}D_3$ (**3**) has previously been prepared by reduction of methyl 4-bromobenzoate[5] or 4-bromobenzaldehyde[6] with $LiEt_3BD$ and $LiAlD_4$, respectively. The resulting ($C^{2}D_2$)-4-bromobenzyl alcohol was transformed into a benzyl chloride (or bromide) and reduced to **3** employing the same two hydride reducing reagents. Thus, the present method offers a more direct, one step entry to this compound.

The ^{15}N label was introduced by nitration of either toluene or toluene-$^{2}D_8$, using ^{15}N labeled nitric acid, according to Smith, Musson, and

DeBoss.[7] The use of H⁺ß zeolite made it possible to employ commercially available 40% $H^{15}NO_3$ (Scheme 1). ^{15}N-4-nitrotoluene[8] has previously been prepared by trifluoroacetoxythallation of toluene followed by reaction with $Na^{15}NO_2$. A three-fold excess of sodium nitrate was used. In our case, $H^{15}NO_3$ was used either as the limiting reagent when reacted with toluene or in a slight excess (1.4 equiv.) for the reaction with toluene-$^2D_8$. A *ca.* 3:1 ratio of *para/ortho* nitration was observed by NMR of the crude reaction mixtures. Pure, labeled, 4-nitrotoluenes **5** and **6** were obtained by a single recrystallization from ethanol-water. The 4-nitrotoluenes were reduced to the corresponding 4-aminotoluenes **7** and **8** using palladium on charcoal (10%-Pd) (Scheme 1).

Scheme 1

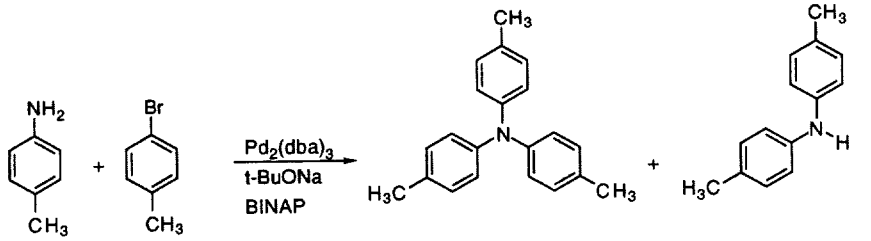


no label — **5** (51%) — **7** (41%)

$^2D_8$ — **6** ($^2D_7$, 51%) — **8** ($^2D_7$, 53%)

As the final step in the synthesis of labeled tri-*p*-tolylamines, the palladium catalyzed Buchwald-Hartwig type amination was employed.[9] A number of triarylamines have previously been prepared using this methodology.[10] Reaction of ^{15}N labeled aminotoluene **7** with 2.3 equivalents of 4-bromotoluene, in the presence of sodium t-butoxide, tris(dibenzylidene)dipalladium(0) ($Pd_2(dba)_3$), and (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) gave a readily separable mixture of the expected ^{15}N labeled tri-*p*-tolylamine **9** together with the monoaminated di-*p*-tolylamine **10**, in 21% and 54% yield, respectively (Scheme 2). It should be noted that no solvent was used in the amination reaction. Reaction of **10** under the same conditions gave **9** in good isolated yield (Scheme 3). The doubly labeled ($^{15}N^2D_{21}$) compound **11** was prepared from **8** and **1** in a similar manner. Monoamination was again observed, affording **12** as the major product. Finally, singly labeled ($^{13}CH_3$)-tri-p-tolylamine (**13**) was obtained by reaction of ($^{13}CH_3$)-4-bromotoluene **2** with commercially available di-*p*-tolylamine.

Scheme 2

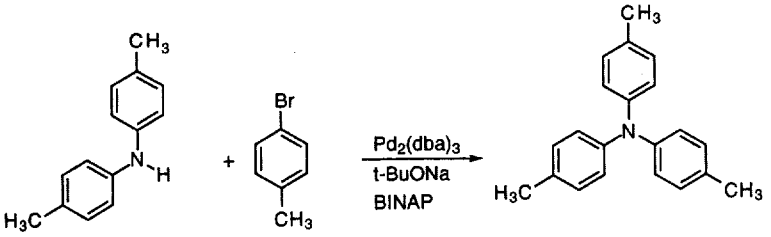


7 (^{15}N) no label
8 (^{15}N^{2}D$_7$) **1** (^{2}D$_7$)

9 (^{15}N, 21%)
11 (^{15}N^{2}D$_7$, 11%)

10 (^{15}N, 54%)
12 (^{15}N^{2}D$_7$, 54%)

Scheme 3



10 (^{15}N) no label **9** (^{15}N, 71%)
12 (^{15}N^{2}D$_7$) **1** (^{2}D$_7$) **11** (^{15}N^{2}D$_7$, 60%)
no label **3** (^{13}CH$_3$) **13** (^{13}CH$_3$, 67%)

Experimental Section

General Procedures. All NMR spectra were obtained in $CDCl_3$ at 270 MHz (^{1}H NMR) and 67.5 MHz (^{13}C NMR). The chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. Spin-spin coupling constants are reported as calculated from spectra; thus a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained.

NH_4^+β zeolite was obtained from Zeolyst international and converted to the H^+ form by heating to 600 °C overnight, refluxing twice in 1 M aqueous ammonium acetate (10 mL/g zeolite), and reheating to 600 °C overnight. It was reheated to 400 °C for two hours immediately prior to use. NaY zeolite was also obtained from Zeolyst International and dried at 100 °C

under vacuum for twelve hours prior to use. All other reagents were obtained from commercial sources and used as received. The reactions were carried out in oven dried glassware, and solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure. Column chromatography was performed on silica gel (200-400 mesh, Natland International Corporation). Melting points were determined using a Mettler Toledo DSC30.

($^2D_7$)-4-Bromotoluene (1). A solution of bromine (0.65 mL, 12.6 mmol) in dichloromethane (4 mL) was added dropwise to a flask, wrapped with aluminum foil, containing NaY zeolite (6 g), dichloromethane (45 mL), and ($^2D_8$)-toluene (1.0 g, 9.98 mmol). The mixture was allowed to stir at ambient temperature for 6 h. The zeolite was removed by filtration, and the filtrate was treated with sodium hydrogen bisulfite (10 mL, sat. aqueous) to destroy excess bromine. The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed at reduced pressure (40 °C, 2 h) affording **1** (1.44 g, 8.10 mmol, 81%) as colorless crystals. mp 16 °C; ^{13}C NMR δ 136.3, 130.7 (t, J = 25.2 Hz), 130.3 (t, J = 26.8 Hz), 118.7, 19.9 (apparent septet, J = 18.5 Hz).

($^{13}CH_3$)-4-Bromotoluene (2). Bromine (0.31 mL, 6.01 mmol) in dichloromethane (4 mL) was reacted (6 h) with NaY zeolite (4 g) and ($^{13}CH_3$)-toluene (500 mg, 5.37 mmol) in dichloromethane (45 mL), and purified as described above, affording **2** (687 mg, 3.99 mmol, 74%) as colorless crystals. mp 16 °C, ^1H NMR δ 7.36 (d, J = 8.3 Hz, 2H), 7.05 (dd, J = 8.1 and 4.3 Hz, 2H), 2.29 (d, J = 126.8 Hz, 3H); ^{13}C NMR δ 136.7 (d, J = 44.2 Hz), 131.3, 130.9 (d, J = 3.1 Hz), 119.1, 21.0.

(C^2D_3)-4-Bromotoluene (3). Bromine (0.31 mL, 6.01 mmol) in dichloromethane (4 mL), was reacted (6 h) with NaY zeolite (4 g) and (C^2D_3)-toluene (500 mg, 5.25 mmol) in dichloromethane (45 mL), and purified as described above, affording **3** (679 mg, 3.88 mmol, 74%) as colorless crystals. mp 16 °C; ^1H NMR δ 7.36 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 136.6, 131.2, 130.8, 119.0, 20.0 (apparent pentet, J = 24.7 Hz).

(^{15}N)-4-Nitrotoluene (5). To an oven-dried round bottom flask, equipped with a stir bar, was added $H^+\beta$ zeolite (1.00 g) and $H^{15}NO_3$ (1.0 g, 15.6 mmol, 40% $H^{15}NO_3$ by weight). The mixture was cooled (ice bath), and acetic anhydride (13 mL, 137 mmol) was added dropwise. After stirring for 30 minutes, toluene (1.90 mL, 17.8 mmol) was added dropwise *via* pipette. The resulting reaction mixture was stirred at 0-5 °C for 30 min., and at ambient temperature for 1.5 h. The zeolite was removed by filtration and washed with chloroform. The filtrate was placed in a separatory funnel, and washed with water (10 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed at reduced pressure. The crude product was purified by chromatography (hexanes:chloroform, 3:2) to give a mixture of (^{15}N)-4-nitrotoluene (**5**) and (^{15}N)-2-nitrotoluene. Recrystallization from ethanol-water gave (^{15}N)-4-nitrotoluene (**5**) (1.11 g, 8.04 mmol, 52%) as faint yellow crystals. mp 48 °C; ^{1}H NMR δ 8.10 (dd, J = 8.7 and 2.0 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR δ 146.3, 145.9, 129.3 (d, J = 2.1 Hz), 123.4, 21.5.

(^{15}N, $^2D_7$)-4-Nitrotoluene (6). A slurry of $H^+\beta$ zeolite (1.00 g), $H^{15}NO_3$ (1.0 g, 15.6 mmol), acetic anhydride (13 mL, 137 mmol), and ($^2D_8$)-toluene (2.00 g, 21.7 mmol) was reacted (2 h) as described above. Extraction and purification yielded **6** (1.154 g, 7.95 mmol, 51 %) as faint yellow crystals. mp 48 °C; ^{13}C NMR δ 145.9 (d, J = 15.4 Hz), 145.6, 129.3 (t, J = 24.2 Hz), 123.0 (t, J = 25.2 Hz), 20.6 (apparent pentet, J = 19.6 Hz).

(^{15}N)-4-Aminotoluene (7). To an oven-dried hydrogenation flask was added (^{15}N)-4-nitrotoluene (**5**) (1.105 g, 8.00 mmol), absolute ethanol (200 mL), and palladium on carbon (10%, 400 mg). The vessel was sealed, pressurized to 3 atm of H_2, and stirred (2.5 h). The catalyst was removed by filtration through Celite and the filtrate was evaporated to dryness at reduced pressure. The crude product was purified by chromatography (hexanes-chloroform, 1:7) to give **7** (353 mg, 3.26 mmol, 41%) as colorless crystals. mp 42 °C; ^{1}H NMR δ 6.96 (d, J = 8.1 Hz, 2H), 6.61

(dd, J = 8.3 and 2.0 Hz, 2H), 3.42 (br s , 2H), 2.24 (s, 3H); ^{13}C NMR δ 143.7 (d, J = 10.8 Hz), 129.7, 127.7, 115.2 (d, J = 2.6 Hz), 20.4.

(^{15}N)-4-Amino-($^{2}D_7$)-toluene (8). (^{15}N, $^{2}D_7$)-4-Nitrotoluene (**6**) (887 mg, 6.11 mmol), absolute ethanol (200 mL), and Pd/C (10%, 400 mg) was reacted and purified as described above (2.5 h) affording **8** (370 mg, 3.21 mmol, 53%) as colorless crystals. mp 42 °C; ^{1}H NMR δ 3.42 (br s); ^{13}C NMR δ 143.6 (d, J = 10.3 Hz), 129.2 (t, J = 23.2 Hz), 127.3, 114.8 (t, J = 23.2 Hz), 19.7 (m, J = 18.8 Hz).

(^{15}N)-*N,N*-bis(4-methylphenyl)-4-methylbenzenamine (9) and (^{15}N)-*N*-(4-methylphenyl)-4-methylbenzenamine (10). To an oven dried ACE-Glass pressure tube was added 4-bromotoluene (1.28 g, 7.50 mmol), (^{15}N)-4-aminotoluene (**7**) (353 mg, 3.27 mmol), sodium t-butoxide (432 mg, 4.49 mmol), tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (60 mg, 0.065 mmol), and (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (122 mg, 0.196 mmol). The reaction vessel was flushed with N_2 and sealed with a Teflon screwcap, then heated to 90 °C for four days. The mixture was allowed to cool to ambient temperature, diethyl ether (50 mL) was added, and the mixture was filtered through Celite. Solvent removal and purification by chromatography (hexanes-chloroform, 5:1) gave, in order of elution, **9** (202 mg, 0.70 mmol, 21%) and **10** (350 mg, 1.77 mmol, 54%) both as faint yellow crystals. Analytical data for **9**: mp 114 °C; ^{1}H NMR δ 7.03 (d, J = 8.5 Hz, 6H), 6.95 (d, J = 8.3 Hz, 6H), 2.29 (s, 9H); ^{13}C NMR δ 145.7 (d, J = 15.4 Hz), 131.7, 129.7, 123.8, 20.7. Analytic data for **10**: mp 78 °C; ^{1}H NMR δ 7.05 (d, J = 8.3 Hz, 2H), 6.92 (dd, J = 8.3 and 1.8, 2H), 5.50 (br d, J = 27 Hz, 1H), 2.28 (s, 6H); ^{13}C NMR δ 141.2 (d, J = 14.4 Hz), 130.2, 129.9, 118.0, 20.7.

(^{15}N) *N,N*-bis(4-methylphenyl)-4-methylbenzenamine (9). Reaction of 4-bromotoluene (342 mg, 2.00 mmol), (^{15}N)-*N*-(4-methylphenyl)-4-methylbenzenamine (**10**) (349 mg, 1.77 mmol), sodium t-butoxide (480 mg, 5.00 mmol), $Pd_2(dba)_3$ (32.4 mg, 0.035 mmol), and

BINAP (66.1 mg, 0.106 mmol), as described above (90 °C, 4 days) gave, after chromatography (hexanes-chloroform, 6:1), **9** (361 mg, 1.25 mmol, 71%) as faint yellow crystals.

(^{15}N, $^{2}D_{21}$)-*N*,*N*-bis(4-methylphenyl)-4-methylbenzenamine (11) and (^{15}N, $^{2}D_{14}$) *N*-(4-methylphenyl)-4-methylbenzenamine (12). Reaction of ($^{2}D_7$)-4-bromo-1-toluene (**1**) (641 mg, 3.60 mmol), (^{15}N, $^{2}D_7$)-4-aminotoluene (**8**) (370 mg, 3.42 mmol), sodium t-butoxide (461 mg, 4.80 mmol), $Pd_2(dba)_3$ (62.7 mg, 0.068 mmol), and BINAP (128 g, 0.205 mmol) as described above (90 °C, 4 days) gave, after extraction and purification, **11** (108 mg, 0.37 mmol, 11%) and **12** (367 mg, 1.85 mmol, 54%) both as faint yellow crystals. Analytical data for **11**: mp 114 °C; ^{13}C NMR δ 145.5 (d, J = 16.0 Hz), 131.1, 129.3 (t, J = 23.7 Hz), 123.4 (t, J = 23.2 Hz), 19.9 (apparent sextet, J = 18.5 Hz).
Analytical data for **12**: mp 78 °C; ^{1}H NMR δ 5.55 (br s); ^{13}C NMR δ 140.9 (d, J = 14.9 Hz), 129.6, 129.2 (dd, J = 23.2 and 16.0 Hz), 117.2 (dd, J = 47.3 and 23.2), 19.7 (apparent sextet, J = 19.0 Hz).

(^{15}N, $^{2}D_{21}$) *N*,*N*-bis(4-methylphenyl)-4-methylbenzenamine (11). Reaction of ($^{2}D_7$)-4-bromotoluene (**8**) (391 mg, 2.18 mmol), (^{15}N, $^{2}D_{14}$) *N*-(4-methylphenyl)-4-methylbenzenamine (**12**) (367 mg, 1.79 mmol), sodium t-butoxide (506 mg, 5.26 mmol), $Pd_2(dba)_3$ (34 mg, 0.037 mmol), and BINAP (69.6 mg, 0.112 mmol) as described above (90 °C, 4 days) gave, after extraction and purification, **11** (335 mg, 1.08 mmol, 60%) as faint yellow crystals.

***N*,*N*-bis(4-methylphenyl)-4-($^{13}CH_3$)-methylbenzenamine (13)** Reaction of ($^{13}CH_3$)-4-bromotoluene (**3**) (342 mg, 1.99 mmol), *N*-(4-methylphenyl)-4-methylbenzenamine (473 mg, 2.40 mmol), sodium t-butoxide (269 mg, 2.80 mmol), $Pd_2(dba)_3$ (18.4 mg, 0.037 mmol), and BINAP (37.4 mg, 0.11 mmol) as described above (90 °C, 4 days) gave, after extraction and purification, **13** (467 mg, 1.62 mmol, 67%) as faint

yellow crystals. mp 114 °C; ^{1}H NMR δ 7.02 (d, J = 8.5 Hz, 6H), 6.94 (d, J = 8.5 Hz, 6H), 2.29 (d, J = 126.2 Hz, 3H), 2.29 (s, 6H); ^{13}C NMR δ 145.7, 131.7, 129.7, 123.8, 20.8.

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Footnotes and References

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[3] The trivial name tri-*p*-tolylamine has been used in place of the Chemical Abstract name, *N,N*-bis(4-methylphenyl)-4-methylbenzenamine, in the bulk of the text. The Chemical Abstract names have been used in the Experimental Section.

[4] Smith, K.; Bahzad, D. *J. Chem. Soc., Chem. Commun.* 467-8 (1996)

[5] (a) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **107**: 2046-54 (1985). (b) Pollack, S. K.; Raine, B. C.; Hehre, W. J. *J. Am. Chem. Soc.* **103**: 6308-13 (1981).

[6] Holland, H. L.; Brown, F. M.; Conn, M. *J. Chem. Soc., Perkin Trans. 2* 1651-5 (1990).

[7] Smith, K.; Musson, A.; DeBoos, G. A. *J. Org. Chem.* **63**: 8448-54 (1998).

[8] (a) Bagno, A.; Dorigo, F.; McCrae, P.; Scorrano, G. *J, Chem. Soc., Perkin Trans. 2* 2163-8 (1996). (b) van den Berg, E. M. M.; Baldew, A. U.; De Goede, A. T. J. W.; Raap, J.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **107**: 73-81 (1988).

[9] For recent reviews, see: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **576**: 125-46 (1999). (b) Hartwig, J. F. *Angew Chem., Int Ed.* **37**: 2046-67 (1998). (c) Wolfe, J. P.; Wagaw, S, Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **31**: 805-18 (1998). (d) Hartwig, J. F. *Synlett* 329-40 (1997).

[10] For some recent examples forming triaryl amines, see: (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **64**: 5575-80 (1999). (b) Thayumanavan, S.; Mendez, J.; Marder, S. R. *J. Org. Chem.* **64**: 4289-97 (1999). (c) Thayumanavan, S.; Barlow, S.; Marder, S. R. *Chem. Mater.* **9**: 3231-5 (1997).

