Efficient synthesis of triarylamines catalyzed by palladium/*N*-heterocyclic carbene

Chen Chen [a,b], Ying-Feng Li [a,b], Lian-Ming Yang [a,*]

[a] *Beijing National Laboratory for Molecular Sciences (BNLMS), Laboratory of New Materials, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China*
[b] *Graduate School of Chinese Academy of Sciences, Beijing 100049, China*

Abstract

A palladium(0)/imidazolium salt system as catalyst precursor proved to be effective, under the appropriately selected reaction conditions, for *N*-arylation of diarylamines and anilines with non-activated aryl bromides or chlorides to afford triarylamine derivatives. In most cases, excellent yields were achieved.
© 2007 Elsevier B.V. All rights reserved.

1. Introduction

Triarylamine compounds are attractive targets for chemical synthesis because of their importance as building blocks for organic materials with electronic, photoelectric and magnetic properties [1–5]. There is thus a considerable interest in developing efficient, particularly practical and scalable, protocols for the synthesis of triarylamines. Pd-catalyzed aromatic amination (the Buchwald–Hartwig reaction) has proven to be a powerful tool for the C–N bond formation including the construction of triarylamines [6–8]. With regard to the existing catalyst systems in this methodology, bulky and electron-rich phosphine species have been the most commonly utilized ancillary ligands. Particularly in triarylamine synthesis, specific phosphine-based ligands (usually expensive and/or highly air-sensitive) are necessary for the successful reactions [3,9–11]. The use of such ligands has limitations in the convenience of manipulation and the large-scale preparation. Therefore, it is desirable to search for possible alternatives to those phosphine-based ligands in the Buchwald–Hartwig reaction. During the past decade, a new family of ligands, *N*-heterocyclic carbenes (NHCs), received considerable attention after free *N*-heterocyclic car-

benes became available through the important work of Arduengo et al. [12–15]. NHCs possess advantages of strongly σ-donating ability, air- and thermal stability, and easy tuning of steric and electronic properties as well as easy preparation. The nucleophilic NHCs as ancillary ligands found numerous applications in transition metal-catalyzed cross-coupling reactions [16–22]. In the utility of NHCs as ligands in catalyst systems for the C–N coupling processes, great advances have been made in very recent years. Pd/imidazolium salt systems [23–26] and the well-defined Pd–NHCs complexes [25,27–31] were revealed to be highly efficient for *N*-arylation of a wide range of nitrogen-containing substrates. However, all studies have not yet demonstrated that these systems are effective in the cross-couplings of aryl halides with amines for the synthesis of the more sterically crowded triarylamines. Another closely related example regarding NHCs as ligand was Ni/NHCs system-catalyzed *N*-arylation of amines, and but an attempt to use this catalyst system for the preparation of triarylamines remained unsuccessful [32]. We were strongly interested in efficacy of NHCs ligand in the catalytic C–N coupling reaction and wondered if Pd/NHCs system-catalyzed *N*-arylation for triaryamine synthesis could be realized with the help of properly selected reaction conditions. From academic and practical viewpoints, completion of this task is of value. Here we want to report on the Pd-catalyzed *N*-arylation of diarylamines and anilines to form triarylamines using *N*-heterocyclic carbenes, derived in situ

---

from deprotonation of the corresponding imidazolium chloride precursor, as supporting ligand. To the best of our knowledge, this is the first report on the Pd/NHC system-catalyzed synthesis of triarylamines.

2. Experimental

2.1. General considerations

All reactions were carried out under nitrogen atmosphere with oven-dried glassware and heated in an oil bath. THF, dioxane and toluene were distilled from sodium/benzophenone before use. Aniline, *m*-toluidine and 2,3-xylidine were distilled prior to use. Diaylamines, and aryl halides were commercially available and used without further purification. Potassium *tert*-butoxide (anhydrous, Aldrich) was stored in a desiccator over anhydrous calcium carbonate, and weighted out rapidly in air to minimize their exposure to air. Column chromatography was performed on silica gel (200–300 mesh). Tris(dibenzylideneacetone)dipalladium(0)-chloroform complex [Pd$_2$(dba)$_3$·CHCl$_3$] [33], 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) [34] and 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydro-imidazolium chloride (SIPr·HCl) [35] were prepared according to the literature procedures. All yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR. The known compounds were identified by ^{1}H NMR and MS and compared to authentic samples or the literature data. New compounds were characterized by ^{1}H and ^{13}C NMR, MS, and elemental analysis.

2.2. General procedure for the catalytic N-arylation of diarylamines

An oven-dried 100-mL three-necked flask was charged with KO^{t}Bu (5 mmol, 560 mg) and dried with flame under vacuum.

Then Pd$_2$(dba)$_3$·CHCl$_3$ (2 mol% relative to diarylamine, 60 mg), IPr·HCl (8 mol% relative to diarylamine, 106 mg) and diarylamine (3 mmol) were added. Aryl halide (3.6 mmol) was added at this time if it is solid. The flask was evacuated and backfilled with nitrogen, with the operation being repeated two times. The dried toluene (20 mL) was added via a syringe. Aryl halide (3.6 mmol) was added at this time via a syringe if it is liquid. The reaction mixture was thermally treated at 105–110 °C for 6 h (for aryl bromides) or 12 h (for aryl chlorides). The reaction mixture was allowed to cool to room temperature and filtered through a pad of silica. The silica pad was washed with toluene (3× 15 mL). Then the combined toluene was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (60–90 °C petroleum) to give the desired product.

2.3. General procedure for the catalytic N-diarylation of anilines

An oven-dried 50-mL three-necked flask was charged with KO^{t}Bu (8 mmol, 898 mg) and dried with flame under vacuum. Then Pd$_2$(dba)$_3$·CHCl$_3$ (2 mol% relative to aniline, 20 mg) and IPr·HCl (8 mol% relative to aniline, 35 mg) were added. Aniline (1 mmol) and aryl halide (2.4 mmol) were added at this time if they are solid. The flask was evacuated and backfilled with nitrogen, with the operation being repeated two times. The dried toluene (10 mL) was added via a syringe. Aniline (1 mmol) and aryl halide (2.4 mmol) were added at this time via a syringe if they are liquid. The reaction mixture was thermally treated at 105–110 °C for 8 h (for aryl bromides) or 16 h (for aryl chlorides). The reaction mixture was allowed to cool to room temperature and filtered through a pad of silica. The silica pad was washed with toluene (3× 15 mL). Then the combined toluene was evaporated under reduced pressure, and the residue was purified by column chromatog-

Table 1

Screening of reaction conditions for the coupling of diphenylamine with bromobenzene catalyzed by Pd(0)/imidazolium salt system
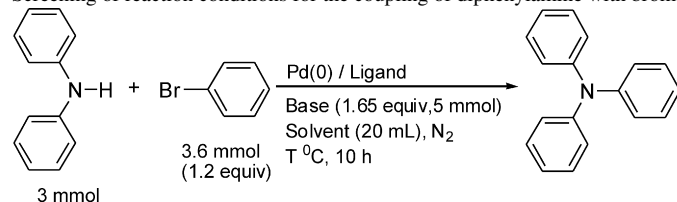
Entry	Pd$_2$(dba)$_3$·CHCl$_3$ (mol%)	Ligand	Ligand/Pd (molar ratio)	Base	Solvent	T (°C)	Isolated yield (%)
1	2	IPr·HCl	2	KO^{t}Bu	Toluene	105	98
2	2	IPr·HCl	0	KO^{t}Bu	Toluene	105	NR
3	2	IPr·HCl	2	KO^{t}Bu	THF	75	NR
4	2	IPr·HCl	2	KO^{t}Bu	Dioxane	105	78
5	2	IPr·HCl	1	KO^{t}Bu	Toluene	105	82
6	1	IPr·HCl	2	KO^{t}Bu	Toluene	105	86
7	2	IPr·HCl	2	NaO^{t}Bu	Toluene	105	72
8	2	SIPr·HCl	2	KO^{t}Bu	THF	75	NR
9	2	SIPr·HCl	2	KO^{t}Bu	Dioxane	105	62
10	2	SIPr·HCl	2	KO^{t}Bu	Toluene	105	70
11	2	SIPr·HCl	2	NaO^{t}Bu	Toluene	105	55

raphy on silica gel (60–90 °C petroleum) to give the desired product.

3. Results and discussion

Two sterically hindered NHCs precursors, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) and the corresponding saturated analogue 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (SIPr·HCl) (Fig. 1), are chosen as supporting ligand since the catalytic process could be facilitated by sterically demanding ligands.

The coupling of diphenylamine with bromobenzene was selected as a model reaction and a set of experiments was performed to determine the optimal reaction conditions (Table 1). The added base initially deprotonates the imidazolium chloride to in situ form the free carbene ligand coordinating to Pd(0), and then serves as a strong base to neutralize the HX formed in the course of the coupling reaction. As shown in Table 1, a catalyst system with 2:1 molar ratio of IPr to Pd(0) was found to be the most effective for this coupling reaction at an elevated temperature in toluene with KO^{t}Bu as base, leading to the desired product in a 98% isolated yield (entry 1). Indeed, the coupling reaction did not proceed without the imidazolium chloride as ligand precursor (entry 2). Ethereal solvents were inferior to toluene: the desired product was given in lower yield with dioxane as solvent (entries 4 and 9) and no reaction occurred in THF (entries 3 and 8). NaO^{t}Bu, which is the most widely used base in Pd-catalyzed amination reaction, appeared less effective than KO^{t}Bu in this reaction (entry 7 versus entry 1; and entry 11 versus entry 10). Changing the molar ratio of IPr to palladium from 2:1 to 1:1 (entry 5) or decreasing the catalyst loading from 4 mol% Pd to 2 mol% (entry 6) led to relative low yields. Generally, the activity of SIPr in this coupling was far lower than that of IPr under similar reaction conditions (entry 10 versus entry 1; entry 9 versus entry 4; and entry 11 versus entry 7).

Under the optimized conditions, the coupling of representative diarylamines with a range of non-activated aryl halides was firstly examined (Table 2). It is very satisfying that this coupling process was effective with inexpensive and readily available aryl chlorides. The use of aryl chlorides in the coupling chemistry has proven to be difficult but would be favorable economically for the large-scale production process [36,37], and great efforts have been made to perform amination reactions with aryl chlorides as coupling partner [19–32]. Table 2 shows that the N-arylation of diarylaimes proceeded in good to excellent isolated yields (entries 1–7, and 9–14). Though the
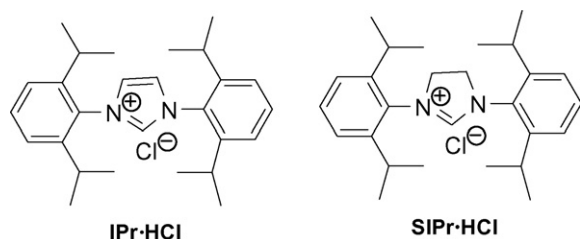
Fig. 1. Two imidazolium salts used in this study.

Table 2
N-arylation of diarylamines catalyzed by Pd(0)/IPr·HCl catalyst system

Entry	Diarylamines	Aryl halides	Product	Isolated yields (%)[a]
1				98
2				92
3				91
4				97
5				97
6				95
7				85
8				71
9				98
10				96
11				98
12				99
13				96
14				94
15				71

[a] Reaction conditions: diarylamines (1.0 equiv.), aryl halides (1.2 equiv.), Pd$_2$(dba)$_3$·CHCl$_3$ (2 mol%), IPr·HCl (8 mol%), KO^{t}Bu (1.65 equiv.), toluene (20 mL), reaction times (6–12 h, not optimized).

bromides generally reacted more quickly (the conversion was completed within 6 h) than the chlorides in a rough comparison by TLC monitoring, the chlorides could finally provide the yields similar to their bromide counterparts. Interestingly, *ortho*-substituted aryl halides, albeit with the factor of steric hindrance, were coupled smoothly with diarylaimnes, resulting in excellent yields (entries 2, 5, 7 and 12). Exceptionally, in the coupling combination of diphenylamine and the aryl halide bearing electron-donating substituents at the *para* position, an unexpected side-reaction occurred substantially. Our experiments revealed that diphenylamine reacted with *p*-bromotoluene, *p*-bromoanisole, *p*-chlorotoluene and *p*-chloroanisole to furnish only 25%, trace, 31% and 10% yield of the corresponding triary-
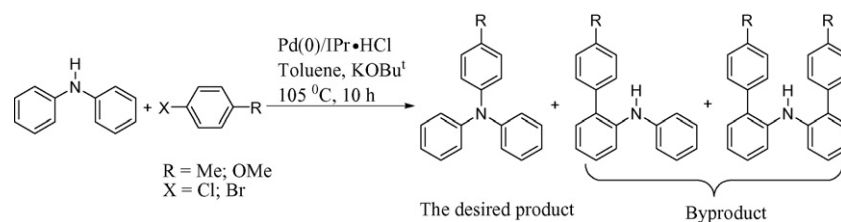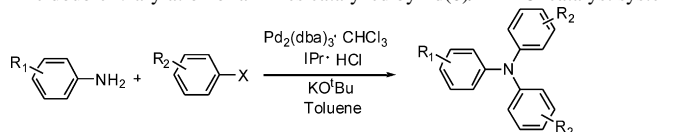
Scheme 1. The coupling of diphenylamine with electron-rich aryl halides.

lamine, respectively. This side reaction is attributed tentatively to the *C*-arylation at the *ortho* position of diphenylamine (herein called *C*2-arylation, shown in Scheme 1) [38]. This *C*2-arylation side-reaction cannot yet be explained clearly and further investigation is required. Perhaps the mechanistic information about the Pd-catalyzed intramolecular direct arylation reactions with aryl chlorides [39,40] as well as the *C*-arylation of phenol with aryl halides [41–43] might be referred to. On the other hand, it was found that 4,4′-dimethyldiphenylamine functions well in this coupling reaction (entries 9–14), and that the desired product was obtained in acceptable yield even when reacting with the electron-rich *p*-chloroanisole (entry 15). Presumably, the *C*2-arylation side-reaction could be restrained to the most degree in the case of 4,4′-dimethyldiphenylamine because its *ortho* C–H

Table 3
The double *N*-arylation of anilines catalyzed by Pd(0)/IPr·HCl catalyst system

Entry	Arylamines	Aryl halides	Product	Isolated yields (%)[a]
1				92
2				85
3				91
4				80
5				85
6				84
7				80
8				68
9				90
10				95

[a] Reaction conditions: arylamines (1.0 equiv.), aryl halides (2.4 equiv.), Pd₂(dba)₃·CHCl₃ (2 mol%), IPr·HCl (8 mol%), KO^{t}Bu (8 equiv.), toluene (10 mL), reaction time (8–16 h).

bond is less activated than that of relatively electron-deficient diphenylamine.

Next, our interest turned to extending the scope of this protocol to the double *N*-arylation of anilines for the preparation of triarylamines. Initially, the coupling reaction was performed under the standard conditions where aniline (1 equiv.) coupled bromobenzene (2.4 equiv.) with 2.6 equiv. of KO^{t}Bu as base in the presence of Pd₂(dba)₃·CHCl₃ (2 mol%) and IPr·HCl (8 mol%), but it was found that the reaction proceeded only to *N*-monoarylation and gave diphenylamine in a high yield of 95%. After some experiments, we found that the used amount of KO^{t}Bu is crucial for the successful double *N*-arylation. When a large excess of base (8 equiv. of KO^{t}Bu relative to aniline) was added, the coupling of aniline with bromobenzene gave a satisfactory result with 92% yield of triphenylamine. Under the modified standard conditions, anilines were *N*-diarylated with a range of non-activated aryl bromides or chlorides to afford the desired products in good to excellent yields (Table 3).

4. Conclusion

In conclusion, an efficient and convenient method for the synthesis of triarylamines has been developed through *N*-arylation of secondary and primary arylamines catalyzed by the Pd(0)/IPr·HCl catalyst system. This work represents an integral part of the application of palladium/*N*-heterocyclic carbene systems in the catalytic C–N coupling reactions. The current catalyst system is more economical and convenient for handling than the Pd/phosphine systems [3,9–11], and compared to Cu catalyst systems, this catalytic system is far more effective for a wide scope of substrates with high efficiency and mild reaction conditions [44]. The mechanism of this coupling should follow a general catalytic cycle for the palladium-catalyzed *N*-arylation [6–8,26]. Despite the fact that the reaction of diphenylamine and aryl halides with *p*-donating groups gave unsatisfactory results, this relative drawback can be overcome by changing the combination pattern of amines and aryl halides as the coupling partner. In addition, the *N*-arylation degree of anilines seems to be base amount-controlled under the reaction conditions, which may provide an easy route to mono- or diarylation of anilines.

References

[1] P. Strohriegl, J.V. Grazulevicius, Adv. Mater. 14 (2002) 1439.
[2] Y. Shirota, J. Mater. Chem. 10 (2000) 1.
[3] J. Louie, J.F. Hartwig, J. Am. Chem. Soc. 119 (1997) 11695.
[4] M.-Y. Chou, M.-K. Leung, Y.-O. Su, C.-L. Chiang, C.-C. Lin, J.-H. Liu, C.-K. Kuo, C.-Y. Mou, Chem. Mater. 16 (2004) 654.

[5] L. Porrés, O. Mongin, C. Katan, M. Charlot, T. Pons, J. Mertz, M. Blanchard-Desce, Org. Lett. 6 (2004) 47.

[6] J. Tsuji, Palladium Reagents and Catalysts: New Perspectives for the 21st Century, Wiley, New York, 2004, pp. 373–391.

[7] A.R. Muci, S.L. Buchwald, in: N. Miyaura (Ed.), Topics in Current Chemistry, vol. 219, Springer-Verlag, Berlin, 2002, pp. 131–209.

[8] J.F. Hartwig, Angew. Chem., Int. Ed. 37 (1998) 2046.

[9] M.H. Ali, S.L. Buchwald, J. Org. Chem. 66 (2001) 2560.

[10] J. Louie, J.F. Hartwig, Macromolecules 31 (1998) 6737.

[11] Pd/N-heroarylphosphines: F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen, M. Beller, Chem. Eur. J. 10 (2004) 2983.

[12] A.J. Arduengo III, R.L. Harlow, M. Kline, J. Am. Chem. Soc. 113 (1991) 361.

[13] A.J. Arduengo III, H.V.R. Dias, M. Kline, J. Am. Chem. Soc. 114 (1992) 5530.

[14] A.J. Arduengo, III, US Patent 5,182,405 (1993).

[15] A.J. Arduengo III, Acc. Chem. Res. 32 (1999) 913.

[16] M. Regitz, Angew. Chem., Int. Ed. Engl. 35 (1996) 725.

[17] W.A. Herrmann, Angew. Chem. Int. Ed. 41 (2002) 1290.

[18] A.C. Hillier, G.A. Grasa, M.S. Viciu, H.M. Lee, C. Yang, S.P. Nolan, J. Organomet. Chem. 653 (2002) 69.

[19] N. Hadei, E.A.B. Kantchev, C.J. O'Brien, M.G. Organ, Org. Lett. 7 (2005) 1991.

[20] N. Hadei, E.A.B. Kantchev, C.J. O'Brien, M.G. Organ, J. Org. Chem. 70 (2005) 8503.

[21] V.P.W. Böhm, T. Weskamp, C.W.K. Gstöttmayr, W.A. Herrmann, Angew. Chem. Int. Ed. 39 (2000) 1602.

[22] V.P.W. Böhm, C.W.K. Gstöttmayr, T. Weskamp, W.A. Herrmann, Angew. Chem. Int. Ed. 39 (2001) 3387.

[23] J. Huang, G.A. Grasa, S.P. Nolan, Org. Lett. 1 (1999) 1307.

[24] G.A. Grasa, M.S. Viciu, J. Huang, S.P. Nolan, J. Org. Chem. 66 (2001) 7729.

[25] M.S. Viciu, R.M. Kissling, E.D. Stevens, S.P. Nolan, Org. Lett. 4 (2002) 2229.

[26] S.R. Stauffer, S. Lee, J.P. Stambuli, S.I. Hauck, J.F. Hartwig, Org. Lett. 2 (2000) 1423.

[27] M.S. Viciu, R.A. Kelly III, E.D. Stevens, F. Naud, M. Studer, S.P. Nolan, Org. Lett. 5 (2003) 1479.

[28] O. Navarro, N. Marion, N.M. Scott, J. Gonzalez, D. Amoroso, A. Bell, S.P. Nolan, Tetrahedron 61 (2005) 9716.

[29] M.S. Viciu, R.F. Germaneau, O. Navarro-Fernadez, E.D. Stevens, S.P. Nolan, Organometallics 21 (2002) 5470.

[30] O. Navarro, H. Kaur, P. Mahjoor, S.P. Nolan, J. Org. Chem. 69 (2004) 3173.

[31] N. Marion, O. Navarro, J. Mei, E.D. Stevens, N.M. Scott, S.P. Nolan, J. Am. Chem. Soc. 128 (2006) 4101.

[32] C. Desmarets, R. Schneider, Y. Fort, J. Org. Chem. 67 (2002) 3029.

[33] T. Ukai, H. Kawazura, Y. Ishii, J.J. Bonnet, J.A. Ibers, J. Organomet. Chem. 65 (1974) 253.

[34] L. Jafarpour, E.D. Steven, S.P. Nolan, J. Organomet. Chem. 606 (2000) 9.

[35] A.J. Arduengo III, R. Krafczyk, R. Schmutzler, Tetrahedron 55 (1999) 14523.

[36] B. Cornils, W.A. Herrmann (Eds.), Applied Homogenous Catalysis with Organometallic Compounds, VCH, Weinheim, 1996.

[37] C.G. Fu, A.F. Littke, Angew. Chem. Int. Ed. 41 (2002) 4176.

[38] This side reaction generally gave a mixture of by-products (*C*-mono- and diarylated). The pure by-products could be obtained by column chromatography, and were then identified by the Mass and NMR spectroscopies. 2-(*p*-Tolyl)diphenylamine: EI-MS (*m/z*): 259 (M^+, 100%). ^{1}H NMR (acetone-d_6, 400 MHz): 2.32 (s, 3H), 5.90 (s, 1H), 6.78 (t, J = 7.32 Hz, 1H), 6.97 (d, J = 7.9 Hz, 2H), 7.02 (t, J = 7.4 Hz, 1H), 7.13-7.27 (m, 6H), 7.29 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H). ^{13}C NMR (acetone-d_6, 100 MHz): 20.4, 116.9, 119.8, 120.0, 122.0, 128.0, 129.1, 129.2, 129.4, 131.0, 133.2, 136.7, 136.8, 140.3, 144.8. 2,2′-Di(*p*-tolyl)diphenylamine: EI-MS (*m/z*): 349 (M^+, 100%). ^{1}H NMR (acetone-d_6, 400 MHz): 2.32 (s, 6H), 5.90 (s, 1H), 6.93 (t, J = 7.4 Hz, 2H), 7.06 (d, J = 8.0 Hz, 4H), 7.09-7.16 (m, 6H), 7.22 (t, J = 7.7 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H). ^{13}C NMR (acetone-d_6, 100 MHz): 20.4, 117.1, 121.0, 128.2, 128.8, 129.5, 130.7, 132.1, 136.1, 137.0, 140.4. 2-(*p*-Anisyl)diphenylamine: EI-MS (*m/z*): 275 (M^+, 100%). ^{1}H NMR (acetone-d_6, 400 MHz): 3.81 (s, 3H), 6.43 (s, 1H), 6.80 (t, J = 7.3 Hz, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.97–7.04 (m, 3H), 7.18 (t, J = 7.7 Hz, 2H), 7.21–7.26 (m, 2H), 7.34 (d, J = 8.4 Hz, 3H). ^{13}C NMR (acetone-d_6, 100 MHz): 52.2, 114.0, 116.8, 119.7, 121.8, 127.7, 129.1, 130.2, 130.9, 131.6, 133.0, 140.3, 141.4, 144.8, 159.1. 2,2′-Di(*p*-anisyl)diphenylamine: EI-MS (*m/z*): 381 (M^+, 100%). ^{1}H NMR (acetone-d_6, 400 MHz): 3.81 (s, 6H), 5.89 (s, 1H), 6.88 (d, J = 8.5 Hz, 4H), 6.93 (t, J = 7.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 6H), 7.22 (t, J = 7.7 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H). ^{13}C NMR (acetone-d_6, 100 MHz): 54.7, 114.1, 116.9, 120.8, 127.9, 130.0, 130.6, 131.0, 131.7, 140.5, 159.1.

[39] L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, J. Am. Chem. Soc. 128 (2006) 581.

[40] L.-C. Campeau, P. Thansandote, K. Fagnou, Org. Lett. 7 (2005) 1857.

[41] Y. Kawamura, T. Satoh, M. Miura, M. Nomura, Chem. Lett. (1999) 961.

[42] T. Satoh, Y. Kawamura, M. Miura, M. Nomura, Angew. Chem. Int. Ed. Engl. 36 (1997) 1740.

[43] J. Tsuji, Palladium Reagents and Catalysts: New Perspectives for the 21st Century, Wiley, New York, 2004, pp. 184–190.

[44] A.V. Cheprakov, Coord. Chem. Rev. 248 (2004) 2337.