Full Paper

Applied Organometallic Chemistry

Received: 30 April 2013 Revised: 19 June 2013 Accepted: 19 July 2013 Published online in Wiley Online Library: 24 September 2013

(wileyonlinelibrary.com) DOI 10.1002/aoc.3044

Synthesis of tertiary aryl amines of various aryl halides and secondary amines using *ortho*-palladated complex of tribenzylamine

Abdol R. Hajipour[a,b]*, Fatemeh Dordahan[a] and Fatemeh Rafiee[a]

The activity of dimeric $[Pd\{C_6H_4(CH_2N(CH_2Ph)_2)\}(\mu\text{-}Br)]_2$ complex as an efficient, air- and moisture-tolerant catalyst was investigated in amination reactions of various aryl halides with secondary amines. Substituted tertiary aryl amines were produced in excellent yields and short reaction times using catalytic amounts of this dimeric complex in DMSO at 120°C. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: palladium catalyst; *ortho*-palladated complex; C—N cross-coupling reaction

Introduction

The synthesis of *N*-arylamines and *N*-arylheterocycles is an active area in organic synthesis because of the occurrence of these moieties in biologically important natural products and pharmaceuticals, and their applications in materials research. In addition, these compounds are important for the preparation of new ligands, artificial dyes, polymers, electronic materials and xerographic materials.[1] The palladium-catalyzed cross-coupling of amines with aryl halides has become a principal method for the formation of C—N bonds in aromatic systems.[2–10] Generally, the combination of palladium catalysts with various phosphine ligands and also *N*-heterocyclic carbenes results in excellent yields and high efficiency in cross-coupling reactions. However, most phosphine ligands are air and moisture sensitive, and economically and environmentally undesirable due to difficulties with their recovery and the formation of toxic phosphines as by-products in these reactions. Carbene-type Pd catalysts are in several cases more stable than phosphine Pd catalysts, but they must often be synthesized in multistep procedures.[11] Thus development of new and efficient palladium catalytic systems remains a potentially promising field in organic synthesis.[12] Among new methods, palladacycle catalysts are important classes of catalysts that are very efficient at very low concentration in organic synthesis,[13] biologically active compounds[14] and macromolecular chemistry.[15] The high productivity of the palladacycle catalysts is due to the slow generation of low ligated Pd(0) complexes from a stable palladium(II) pre-catalyst.[16]

Results and Discussion

In continuation of our recent investigations on the synthesis and applications of palladacycle catalysts in cross-coupling reactions,[17–24] we now report the extension of dimeric $[Pd\{C6H_4(CH_2N(CH_2Ph)_2)\}(\mu\text{-}Br)]_2$ homogeneous complex as a thermally stable and oxygen-insensitive catalyst in the C—N cross-coupling reaction. In this paper, the efficiency of this dimeric complex of palladium and tribenzylamine was investigated in an amination reaction with various aryl halides and secondary amines (Scheme 1).

The efficiency of *ortho*-palladated complex (**A**) in the amination reaction was examined by optimizing the reaction conditions in the cross-coupling reaction between iodobenzene with *N*-benzyl-*N*-methylamine as a model reaction. The results are summarized in Table 1. Among the tested conditions, DMSO as solvent, KOH as base and 0.2 mol% of catalyst gave the best result.

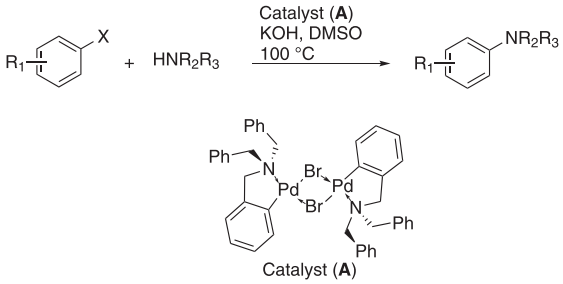
The optimized reaction conditions were applied to the cross-coupling reactions of various aryl halides with different secondary amines using the dimeric *ortho*-palladated catalyst (**A**) (Table 2). As this catalyst is thermally stable and not sensitive to oxygen and moisture, the reactions were carried out under air atmosphere.

The substituent effects on the aryl iodides proved to be less significant than in the aryl bromides and the reactivity of aryl bromides with electron-withdrawing substituent was higher than that of aryl bromides with electron-donating substituent. Because of the inexpensiveness and availability of aryl chlorides, they are the best substrates for coupling reactions in comparison with the corresponding bromide or iodide compounds. This method can be used for the C—N cross-coupling reaction of even less reactive aryl chloride derivatives with longer reaction

* *Correspondence to: Abdol R. Hajipour, Pharmaceutical Research Laboratory, Department of Chemistry, Isfahan University of Technology, Isfahan 84156, IR Iran. Email: haji@cc.iut.ac.ir*

a *Pharmaceutical Research Laboratory, Department of Chemistry, Isfahan University of Technology, Isfahan 84156IR, Iran*

b *Department of Pharmacology, University of Wisconsin, Medical School, 1300 University Avenue, Madison, WI, 53706-1532, USA*



Scheme 1. Amination reaction using *ortho*-palladated complex (**A**).

times. Aromatic and also aliphatic secondary amines containing *N*-benzyl-*N*-methylamine, diphenylamine, morpholine, indole, dicyclohexylamine and *N*-methylcyclohexanamine were coupled with various aryl halides in excellent yields and acceptable reaction times. This catalytic system was also applied to primary amines such as aniline, but in these reactions secondary and tertiary amines were obtained in 70:30 ratios.

Conclusions

In this work, a general protocol was applied to the C—N cross-coupling reaction of various aryl halides with secondary amines using *ortho*-palladated complex of tribenzylamine. The catalytic amounts of this efficient dimeric complex converted various aryl halides to the corresponding substituted tertiary aryl amines in excellent yields and acceptable reaction times.

Experimental

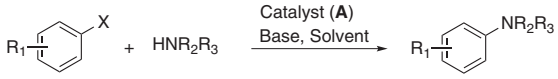
General

^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ solution at room temperature (tetramethylsilane was used as an internal standard) on a Bruker Avance 500 instrument (Rheinstetten, Germany) and Varian 400 NMR. FT-IR spectra were recorded on a spectrophotometer (Jasco-680, Japan). Spectra of solids were carried out using KBr pellets. Vibrational transition frequencies are reported as wavenumber (cm^{-1}). We used gas chromatography (GC; BEIFIN 3420 gas chromatograph equipped a Varian CP SIL 5CB column: 30 m, 0.32 mm, 0.25 μm) for examination of reaction completion and yields. Palladium acetate, aryl halides and all chemicals were purchased from Merck and Aldrich and were used as received.

General Procedure for C—N Cross-Coupling Reaction of Aryl Halides

A mixture of aryl halide (1 mmol), amine (1.2 mmol), KOH (3 mmol) and *ortho*-palladated catalyst (**A**) (0.2 mol%) in DMSO (2 mL) in a round-bottom flask equipped with a condenser was placed in an oil bath at 120°C. The mixture was stirred continuously using an appropriate magnet during the reaction. After the reaction was complete, the mixture was cooled to room temperature and diluted with H_2O (30 ml) and Et_2O (30 ml). The organic phase was dried over $MgSO_4$. The solution was filtered and the solvent evaporated using a rotary evaporator. The residue was purified by silica gel column chromatography (*n*-hexane or *n*-hexane/EtOAc (9:1)).

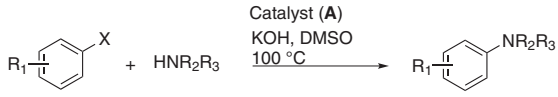
Table 1. Optimization of reaction conditions for the amination coupling reaction[a]



Entry	Solvent	Base	Catalyst (mol%)	Temp (°C)	Time (min)	Conversion (%)[b]
1	NMP	KOH	0.1	120	120	25
2	DMF	KOH	1	120	180	20
3	DMSO	KOH	0.1	120	105	100
4[c]	DMSO	KOH	0.1	100	50	100
5	CH_3CN	KOH	0.1	80	180	—
6	Dioxane	KOH	0.1	90	120	70
7	H_2O	KOH	0.1	100	180	—
8	DMSO	K_2CO_3	0.1	120	120	75
9	DMSO	Na_2CO_3	0.1	120	180	50
10	DMSO	NaOAc	0.1	120	180	10
11	DMSO	$NaHCO_3$	0.1	120	180	30
12	DMSO	KOH	0.05	120	200	53
13[c]	DMSO	KOH	0.2	120	10	100
14	DMSO	KOH	0.3	120	10	100
15	DMSO	KOH	0.2	140	10	100

[a]Reaction conditions: iodobenzene (1 mmol), *N*-benzyl-*N*-methylamine (1.2 mmol), base (2 mmol), solvent (2 ml), catalyst (**A**).
[b]GC yield.
[c]Base (3 mmol).

Table 2. C—N cross-coupling reaction of aryl halides using *ortho*-palladated catalyst (**A**)[a]



Entry	Ar-X	Amine substrate		Time (min)	Yield (%)[b]
		R_2	R_3		
1	Ph—I	$PhCH_2$	Me	10	98
	Ph—Br			45	97
	Ph—Cl			480	70
2	*p*-MeO—Ph—I	$PhCH_2$	Me	55	80
	p-MeO—Ph—Br			180	70
3	*p*-O_2N—Ph—I	$PhCH_2$	Me	10	98
	p-O_2N—Ph—Br			30	95
	p-O_2NPh—Cl			360	90
4	*p*-NC—Ph—Br	$PhCH_2$	Me	50	97
5	Ph—I	Ph	Ph	40	96
	Ph—Br			90	94
	Ph—Cl			600	95
6	*p*-MeO—Ph—I	Ph	Ph	180	96
	p-MeO—Ph—Br			300	94
7	*p*-O_2N—Ph—I	Ph	Ph	75	98
	p-O_2N—Ph—Br			120	96
	p-O_2NPh—Cl			300	80
8	*p*-NC—Ph—Br	Ph	Ph	135	94
9	Ph—I	Morpholine		25	97
	Ph—Br			30	95
	Ph—Cl			240	85
10	*p*-MeO—Ph—I	Morpholine		60	96
	p-MeO—Ph—Br			90	94
11	*p*-O_2N—Ph—I	Morpholine		10	98
	p-O_2N—Ph—Br			25	96
12	Ph—I	Indole		10	93
	Ph—Br			15	95
13	Ph—I	Cy-hexyl	Cy-hexyl	20	94
	Ph—Br			25	96
14	Ph—I	Cy-hexyl	Me	30	97
	Ph—Br			45	95

[a]Reaction conditions: aryl halide (1 mmol), amine (1.2 mmol), KOH (3 mmol), DMSO (2 ml), catalyst (**A**) (0.2 mol%), oil bath (120 °C).
[b]Isolated yield.

Acknowledgements

We gratefully acknowledge the funding support received for this project from the Isfahan University of Technology (IUT), IR Iran and Isfahan Science and Technology Town (ISTT), IR, Iran. Further financial support from the Center of Excellence in Sensor and Green Chemistry Research (IUT) is gratefully acknowledged.

References

[1] A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131.
[2] A. J. Belfield, G. R. Brown, A. J. Foubister, P. D. Ratcliffe, *Tetrahedron* **1999**, *55*, 13285.
[3] J. F. Hartwig, Handbook of Organopalladium Chemistry for Organic Synthesis, *Vol. 1*, Wiley, Hoboken, NJ, **2002**, pp. 1051.
[4] Q. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 6586.
[5] B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125.
[6] C. A. Parrish, S. L. Buchwald, *J. Org. Chem.* **2001**, *66*, 3820.
[7] B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 15914.
[8] X. Xie, T. Y. Zhang, Z. Zhang, *J. Org. Chem.* **2006**, *71*, 6522.
[9] O. Navarro, H. Kaur, P. Mahjoor, S. P. Nolan, *J. Org. Chem.* **2004**, *69*, 3173.
[10] C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 4321.
[11] H. Tang, K. Menzel, G. C. Fu, *Angew. Chem. Int. Ed.* **2003**, *42*, 5079.
[12] W. A. Herrmann, *Angew. Chem. Int. Ed.* **2002**, *41*, 1290.
[13] R. B. Bedford, L. T. Pilarski, *Tetrahedron Lett.* **2008**, *49*, 4216.
[14] K. K. Lo, C. Chung, T. K. Lee, L. Lui, K. H. Tang, N. Zhu, *Inorg. Chem.* **2003**, *42*, 6886.
[15] A. Moyano, M. Rosol, R. M. Moreno, C. López, M. A. Maestro, *Angew. Chem. Int. Ed.* **2005**, *44*, 1865.
[16] A. Zapf, M. Beller, *Top. Catal.* **2002**, *19*, 101.
[17] A. R. Hajipour, F. Rafiee, *Appl. Organomet. Chem.* **2011**, *25*, 542.
[18] A. R. Hajipour, F. Rafiee, *J. Organomet. Chem.* **2011**, *696*, 2669.
[19] A. R. Hajipour, F. Rafiee, A. E. Ruoho, *Tetrahedron Lett.* **2012**, *53*, 526.
[20] A. R. Hajipour, K. Karami, F. Rafiee, *Appl. Organomet. Chem.* **2012**, *26*, 27.
[21] A. R. Hajipour, F. Abrisham, G. Tavakoli, *Transition Met. Chem.* **2011**, *36*, 725.
[22] A. R. Hajipour, K. Karami, A. Pirisedigh, *Inorg. Chim. Acta* **2011**, *370*, 531.
[23] A. R. Hajipour, I. Mahboobi Dehbane, F. Rafiee, *Appl. Organomet. Chem.* **2012**, *26*, 743.
[24] A. R. Hajipour, N. Najafi, F. Rafiee, *Appl. Organomet. Chem.* **2013**, *27*, 228.