Full Paper

Applied Organometallic Chemistry

Received: 30 April 2012 Revised: 30 July 2012 Accepted: 6 August 2012 Published online in Wiley Online Library: 3 October 2012

(wileyonlinelibrary.com) DOI 10.1002/aoc.2920

Dimeric *ortho*-palladated homoveratrylamine as an efficient homogeneous catalyst for copper-free Sonogashira cross-coupling reaction

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

The catalytic activity of *ortho*-palladated [Pd{C6H2(CH2CH2NH2)-(OMe)2,3,4}(m-Br)]2, a complex of homoveratrylamine in the copper-free Sonogashira coupling reaction has been investigated. This complex is a catalyst that is efficient, stable and non-sensitive to air and moisture in the Sonogashira reaction. In this homogeneous catalytic system, various aryl halides were efficiently coupled with phenylacetylene in mostly moderate to good yields in *N*-methylpyrrolidone at 100 °C under copper-free conditions. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: Sonogashira reaction; catalyst; *ortho*-palladated complex; internal alkynes

Introduction

Palladium-catalyzed transformations are among the most potent and convenient tools of modern organic synthesis for C-C bond formation.[1,2] There are various cross-coupling reactions, and among them Sonogashira coupling reactions of acetylenes with aryl or alkenyl halides or triflates have been developed in organic chemistry and material science for the production of internal alkyne and enynes.[3–6] Alkynes are the building blocks of a wide range of pharmaceuticals, natural products, biologically active molecules, conducting polymers, nonlinear, optical and liquid-crystal materials.[7–12] The Sonogashira cross-coupling reactions are usually mediated by phosphane-based palladium complexes. Generally, sterically hindered phosphine ligands showed high activities in cross-coupling reactions such as Sonogashira couplings.[13–15] Most research has developed to obtain high catalytic activity with efficient catalytic systems. Moreover, a number of important studies have focused on the development of phosphine-free ligands such as *N*-heterocyclic carbenes.[16–18] Phosphine ligands suffer some drawbacks such as sensitivity to air or moisture and the requirement for an inert environment and large amounts of palladium source for carrying out the reaction. Although carbene-type ligands are more stable than alkyl phosphines, they must be synthesized through multiple steps.

Among the advanced catalysts, the palladacycles are the most important class of organometallic catalyst precursors and are used for highly efficient catalysis at very low concentration for C-C bond formation in organic synthesis, material science, biologically active compounds and macromolecular chemistry.[19–22] Oxime[23] and ferrocenylimine[24] palladacycles as effective catalysts were found to promote the Sonogashira reaction. The high productivity of palladacycle catalysts is due to the slow generation of paltry ligated Pd(0) complexes from a stable palladium(II) pre-catalyst that undergoes an activation process.[25]

In continuation of our recent investigations on the synthesis and applications of the palladacycle catalysts in cross-coupling reactions,[26–33] we now wish to report the extension of dimeric [Pd{$C_6H_2(CH_2CH_2NH_2)$–$(OMe)_2$,3,4}(μ-Br)]$_2$ homogeneous complex as thermally stable and oxygen insensitive catalysts for the Sonogashira cross coupling reaction.

Results and Discussion

The *ortho*-palladated complex [Pd{$C_6H_2(CH_2CH_2NH_2)$–$(OMe)_2$,3,4}(μ-Br)]$_2$ was prepared according to our previous work.[32] The acetate-bridged *ortho*-palladated complex was obtained from homoveratrylamine by addition of $Pd(OAc)_2$ in acetonitrile as a binuclear complex. The halogen-bridged *ortho*-palladated complex was prepared by the addition of NaBr to a solution of the acetate-bridged complex in acetone.

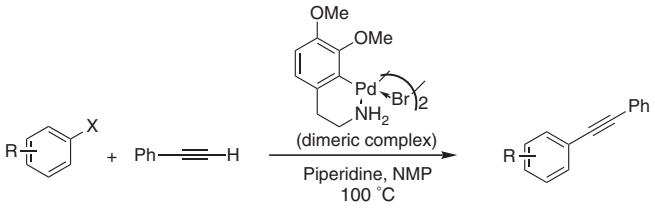
A suitable chemical production process via palladium catalysis requires high catalyst productivity and activity. Furthermore, the availability and cost of catalysts and the price of the organic starting materials are of great importance for industrial processes. Homoveratrylamine is an available and inexpensive amine. The *ortho*-palladation reaction of this substrate is simple and leads to an efficient catalyst for coupling reactions even with unreactive aryl chlorides, which are readily available and inexpensive substrates. Herein, the efficiency of this catalyst is evaluated in the Sonogashira reaction of various types of aryl halides with phenylacetylene (Scheme 1).

In order to optimize the reaction conditions, we first carried out the cross-coupling reaction between 4-bromobenzonitrile with phenylacetylene as a model reaction. We examined the effect of various reaction parameters such as solvent, base and temperature on yields of the coupling products as shown in Table 1. The data showed that the best results were obtained

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

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

b *Department of Neuroscience, University of Wisconsin Medical School, Madison, WI, 53706-1532, USA*



Scheme 1. The Sonogashira cross-coupling reaction of various aryl halides by dimeric *ortho*-palladated complex.

Table 1. Optimization of reaction conditions for the Sonogashira cross-coupling reaction[a]

Entry	Solvent	Base	Temperature (°C)	Yield (%)[b]
1	NMP	NaOAc	100	45
2	NMP	NEt_3	100	50
3	NMP	Pyrrolidine	100	55
4	NMP	K_2CO_3	100	70
5	NMP	Cs_2CO_3	100	75
6	NMP	Piperidine	100	90
7	—	Piperidine	100	60
8	DMAc	Piperidine	100	88
9	DMAc	Piperidine	80	75
10	DMF	Piperidine	100	75
11	CH_3CN	Piperidine	80	65
12	EtOH	Piperidine	r.t.	0
13	EtOH	Piperidine	70	45

[a]Reaction conditions: 4-bromobenzonitrile (0.5 mmol), phenylacetylene (0.5 mmol), base (1 mmol), *ortho*-palladated catalyst (1 mol%), 2 h.
[b]GC yield.

using *N*-methylpyrrolidone (NMP) as solvent and piperidine as a base at 100 °C. Under these conditions 4-cyanodiphenylacetylene was obtained as the desired product in 90% yield and 1, 4-diphenylbuta-1,3-diyne was formed as a by-product in 3% yield via the homo-coupling of phenylacetylene.

Furthermore, we optimized the percentage of catalyst used, employing various amounts of catalyst for this cross-coupling using piperidine as a base and NMP as solvent. The results are summarized in Table 2. A low palladium concentration usually led to a longer period of reaction, as increasing the amount of palladium catalyst shortened the reaction time, but did not increase the yield of cross-coupled product. The best result was obtained when the cross-coupling reaction was carried out with 0.8 mol% of dimeric complex (Table 2, entry 5).

Table 2. Optimization of the catalyst concentration on the Sonogashira cross-coupling reaction[a]

Entry	Catalyst (mol%)	Time (h:min)	Conversion (%)[b]
1	None	12	0
2	0.2	5	50
3	0.5	5	65
4	0.6	5	75
5	0.8	2:30	90
6	1	2:30	90
7	2	2	90

[a]Reactions conditions: 4-bromobenzonitrile (0.5 mmol), phenylacetylene (0.5 mmol), piperidine (1 mmol), NMP (3 ml), *ortho*-palladated catalyst.
[b]GC yield.

The optimized reaction conditions were applied to the Sonogashira cross-coupling reaction of various aryl halides with phenylacetylene (Table 3).

We examined the electronic and steric effects on the resulting yields and conversion times of the reactions. Aryl halides substituted with electron-withdrawing groups in comparison to electron-donating substituent gave better conversions in shorter reaction times. The effects of steric hindrance and chemo-selectivity of the procedure were examined using 2-, 3- and 4-chlorobromobenzene (Table 3, entries 12–14). An increasing hindrance in the vicinity of the leaving group results in a decrease in the conversion. In these reactions, Br acted as a better leaving group. In some of these cross-coupling reactions 1,4-diphenylbuta-1,3-diyne was formed as a by-product (3–15%).

The Sonogashira reaction probably proceeds through oxidative addition of the aryl halide to the Pd(0) catalytic species that generates homogeneous Ar-Pd-X species. The coordination of the alkyne to the metal center followed based-assisted H-X elimination gave Ar-Pd-C&tbond;C-Ph, which by reductive elimination yielded the coupling product and Pd(0).[34]

A study on NC palladacycle catalyst cross-coupling showed that palladacycles decompose to liberate catalytic Pd(0) species and show a positive Hg(0) test.[35,36] To evaluate the proposed mechanism, the mercury drop test was utilized, since mercury leads to amalgamation of the surface of a heterogeneous catalyst. In contrast, Hg(0) is not expected to have a poisoning effect on homogeneous palladium complexes.[35,37] When a drop of Hg(0) was added to the reaction mixture of 4-bromobenzonitrile and phenylacetylene under the mentioned optimized conditions and heated using an oil bath, no catalytic activity was observed for the catalyst. The data obtained confirmed the Pd(0):Pd(II) cycle.

Conclusion

We employed dimeric *ortho*-palladated complex [Pd{C_6H_2($CH_2CH_2NH_2$)–$(OMe)_2$,3,4}(μ-Br)]$_2$ as a catalyst that is highly efficient, stable and non-sensitive to air and moisture in the Sonogashira cross-coupling reaction. The catalytic amount of this catalyst led to formation of substituted aromatic alkynes in good to excellent yields under copper-free conditions.

Experimental

Chemicals

All melting points were taken on a Gallenkamp melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ solution at room temperature (tetramethylsilane was used as an internal standard) on a Bruker Avance 500 instrument (Rheinstetten, Germany). 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 wave number (cm^{-1}). We used a Beifin 3420 gas chromatograph equipped with a Varian CP SIL 5CB column (30 m, 0.32 mm, 0.25 μm) for examination of reaction competition and yields. Palladium acetate, aryl halides and all chemicals were purchased from Merck and Aldrich and were used as received.

Table 3. Sonogashira reaction using dimeric *ortho*-palladated complex of homoveratrylamine[a]

Entry	Ar–X	Product[ref.]	Time (h)	Yield (%)[c]
1	Ph-I	Ph-C&tbond;C-Ph[24]	1	88
2	*p*-O_2N-C_6H_4-I	*p*-O_2N-C_6H_4-C&tbond;C-Ph[39]	0.35	97
3	*m*-O_2N-C_6H_4-I	*m*-O_2N-C_6H_4-C&tbond;C-Ph[40]	0.6	94
4	*p*-MeO-C_6H_4-I	*p*-MeO-C_6H_4-C&tbond;C-Ph[38]	2.5	70
5	Ph-Br	Ph-C&tbond;C-Ph[24]	10	50
6	*p*-MeO-C_6H_4-Br	*p*-MeO-C_6H_4-C&tbond;C-Ph[38]	18	43
7	*p*-NC-C_6H_4-Br	*p*-NC-C_6H_4-C&tbond;C-Ph[24]	2.5	90
8	*o*-O_2N-C_6H_4-Br	*o*-O_2N-C_6H_4-C&tbond;C-Ph[24]	10	66
9	*p*-OHC-C_6H_4-Br	*p*-OHC-C_6H_4-C&tbond;C-Ph[39]	5	60
10	*p*-MeOC-C_6H_4-Br	*p*-MeOC-C_6H_4-C&tbond;C-Ph[24]	10	55
11	*p*-Cl-C_6H_4-Br	*p*-Cl-C_6H_4-C&tbond;C-Ph[38]	0.8	79
12	*m*-Cl-C_6H_4-Br	*m*-Cl-C_6H_4-C&tbond;C-Ph[41]	1	66
13	*o*-Cl-C_6H_4-Br	*o*-Cl-C_6H_4-C&tbond;C-Ph[41]	1.2	50
14	1-Br-naphthalene	1-Ph-C&tbond;C-naphthalene[38]	5	56
15	9-Br-phenanthrene	9-Ph-C&tbond;C-phenanthrene[42]	;5	67
16	*p*-O_2N-C_6H_4-Cl	*p*-O_2N-C_6H_4-C&tbond;C-Ph[24]	18	38
17	2-Br-pyridine	2-Ph-C&tbond;C-pyridine[24]	24	35

[a]Reaction conditions: arylhalide (0.5 mmol), phenylacetylene (0.5 mmol), piperidine (1 mmol), NMP (3 ml), *ortho*-palladated catalyst (0.8 mol%).
[b]Isolated yield.

General Procedure for the Synthesis of Dimeric *ortho*-Palladated Complex

A 50 ml round-bottom flask was charged with homoveratrylamine (1.1 mmol), $Pd(OAc)_2$ (1.1 mmol) and acetonitrile (20 ml) and refluxed for 4 h. The resulting suspension was filtered through a plug of $MgSO_4$, the solvent was removed under reduced pressure, and then CH_2Cl_2 (2 ml) and *n*-hexane (15 ml) or Et_2O (7 ml) was added to give acetate-bridged *ortho*-palladated complex as a yellow precipitate, which was filtered off, washed with water and air dried. To a solution of this complex (0.2 mmol) in acetone (25 ml) was added NaBr (1.94 mmol) and the suspension was stirred for 8 h; then acetone was evaporated, CH_2Cl_2 (10 ml) was added and the mixture was filtered through a plug of $MgSO_4$. The filtrate was concentrated to 2 ml under reduced pressure using a rotary evaporator and *n*-hexane (15 ml) or Et_2O (7 ml) was added. The produced suspension was filtered off and air dried to afford the halogen-bridged *ortho*-palladated complex as an orange solid. Decomp. 140 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): d, 6.85 (br d, 1 H, C_6H_2), 6.77 (br d, 1 H, C_6H_2), 3.92 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.10 (br m, 2 H, NH_2), 2.88 (m, 2 H, CH_2), 2.65 (m, 2 H, CH_2) ppm. IR (KBr, cm^{-1}): 3250–3268 (N-H). ^{13}C NMR (75 MHz, MeOH, ppm): 148.5 (1C, C_6H_2 (C-OMe)), 148.0 (1C, C_6H_2 (C-OMe)), 129.0 (1C, C_6H_2 (C-$CH_2CH_2NH_2$)), 120.1 (1C, C_6H_2 (C-Pd)), 110.0 (1C, C_6H_2 (-CH)), 112 (1C, C_6H_2 (-CH)) 55.8 (2C, OMe), 41.1 (1C, -CH_2-NH_2), 24.9 (1C, -CH_2). Anal. Calcd for $C_{20}H_{28}Br_2N_2O_4Pd_2$: C, 32.767; H, 3.85; N, 3.82. Found: C, 32.55; H, 4.11; N, 3.80%.

General Procedure for the Sonogashira Cross-Coupling Reaction

A mixture of the aryl halide (0.5 mmol), phenylacetylene (0.5 mmol), piperidine (1 mmol) and *ortho*-palladated catalyst (0.8 mol%) was added to NMP (3 ml) in a round-bottom flask equipped with condenser and was heated at 100 °C in an oil bath. The mixture was stirred continuously during the reaction and monitored by both thin-layer chromatography and gas chromatography (GC). After the reaction was complete, the mixture was cooled to room temperature and diluted with *n*-hexane and water. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure using a rotary evaporator. The residue was purified by silica gel column chromatography. The products were characterized by comparing their m.p., IR and ^{1}H, ^{13}C NMR spectra with those found in the literature.[24,38–42]

Acknowledgments

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] J. Tsuji, Palladium Reagents and Catalysts: Innovations in Organic Synthesis, Wiley, Chichester, **1995**.
[2] A. D. Meijere, F. Diederich, Metal-Catalyzed Cross-Coupling Reactions, *Vol. 1 and 2*, 2nd edn, Wiley-VCH, Weinheim, **2004**.
[3] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *15*, 4467.
[4] K. Sonogashira in Metal-Catalyzed Cross-Coupling Reactions (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, p. 203.
[5] K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46.
[6] K. Sonogashira in Comprehensive Organic Synthesis, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, p. 521.
[7] F. Bohlmann, F. T. Burkhart, C. Zero, Naturally Occurring Acetylenes, Academic Press, London, **1973**.
[8] V. D. Hunstman in The Chemistry of the Carbon–Carbon Triple Bond (Ed.: S. Patai), Wiley-Interscience, London, **1978**, p. 553.
[9] J. K. Young, J. S. Moore in Modern Acetylene Chemistry (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**, p. 415.
[10] U. H. F. Bunz, *Chem. Rev.* **2000**, *100*, 1605.
[11] D. Mujahidin, S. Doye, *Eur. J. Org. Chem.* **2005**, 2689. DOI: 10.1002/ejoc.200500095
[12] A. Hamajima, M. Isobe, *Org. Lett.* **2006**, *8*, 1205.
[13] F. N. Ngassa, E. A. Lindsey, B. E. Haines, *Tetrahedron* **2009**, *65*, 4085.
[14] K. Prabakaran, F. N. Khan, J. S. Jin, *Tetrahedron Lett.* **2011**, *52*, 2566.

[15] M. Feuerstein, H. Doucet, M. Santelli, *J. Mol. Catal. A: Chem.* **2006**, *256*, 75.
[16] J. H. Kim, D. H. Lee, B. H. Jun, Y. S. Lee, *Tetrahedron Lett.* **2007**, *48*, 7079.
[17] C. Yang, S. P. Nolan, *Organometallics* **2002**, *21*, 1020.
[18] M. Eckhanlt, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 13642.
[19] R. B. Bedford, L. T. Pilarski, *Tetrahedron Lett.* **2008**, *49*, 4216.
[20] J. Buey, P. Espinet, *J. Organomet. Chem.* **1996**, *507*, 137.
[21] K. K. Lo, C. Chung, T. K. Lee, L. Lui, K. H. Tang, N. Zhu, *Inorg. Chem.* **2003**, *42*, 6886.
[22] C. Lopez, A. Caubet, S. Perez, X. Solans, M. Font-Bardía, *J. Organomet. Chem.* **2003**, *681*, 80.
[23] D. A. Alonso, C. Nájera, M. C. Pacheco, *Tetrahedron Lett.* **2002**, *43*, 9365.
[24] F. Yang, X. Cui, Y. Li, J. Zhang, G. Rena, Y. Wu, *Tetrahedron* **2007**, *63*, 1963.
[25] A. Zapf, M. Beller, *Top. Catal.* **2002**, *19*, 101.
[26] A. R. Hajipour, F. Rafiee, *J. Organomet. Chem.* **2011**, *696*, 2669.
[27] A. R. Hajipour, F. Rafiee, *Appl. Organomet. Chem.* **2011**, *25*, 542.
[28] A. R. Hajipour, K. Karami, A. Pirisedigh, *Inorg. Chim. Acta* **2011**, *370*, 531.
[29] A. R. Hajipour, K. Karami, G. Tavakoli, *J. Organomet. Chem.* **2011**, *696*, 819.
[30] A. R. Hajipour, F. Rafiee, A. E. Ruoho, *Tetrahedron Lett.* **2011**, *52*, 4782.
[31] A. R. Hajipour, K. Karami, F. Rafiee, *Appl. Organomet. Chem.* **2012**, *26*, 27.
[32] A. R. Hajipour, K. Karami, A. Pirisedigh, *Appl. Organomet. Chem.* **2009**, *23*, 504.
[33] A. R. Hajipour, K. Karami, A. Pirisedigh, A. E. Ruoho, *Amino Acids* **2009**, *37*, 537.
[34] C. S. Consorti, F. R. Flores, F. Rominger, J. Dupont, *Adv. Synth. Catal.* **2006**, *348*, 133.
[35] D. E. Bergbreiter, P. L. Osburn, J. D. Frels, *Adv. Synth. Catal.* **2004**, *347*, 172.
[36] M. T. Reetz, E. Westermann, *Angew. Chem. Int. Ed.* **2000**, *39*, 165.
[37] M. R. Eberhard, *Org. Lett.* **2004**, *6*, 2125.
[38] D. A. Alonso, C. Nájera, M. C. Pacheco, *Adv. Synth. Catal.* **2003**, *345*, 1146.
[39] A. Elangovan, Y. H. Wang, T. I. Ho, *Org. Lett.* **2003**, *5*, 1841.
[40] P. Li, L. Wang, H. Li, *Tetrahedron* **2005**, *61*, 8633.
[41] A. N. Marziale, J. Schlüter, J. Eppinger, *Tetrahedron Lett.* **2011**, *52*, 6355.
[42] M. Wu, J. Mao, J. Guo, S. Ji, *Eur. J. Org. Chem.* **2008**, *23*, 4050.