



Copper- and phosphine-free Sonogashira coupling reactions of aryl iodides catalyzed by an *N,N*-bis(naphthylideneimino)diethylenetriamine-functionalized polystyrene resin supported Pd(II) complex under aerobic conditions

Mohammad Bakherad*, Amir H. Amin, Ali Keivanloo, Bahram Bahramian, Mersad Raeissi

School of Chemistry, Shahrood University of Technology, Shahrood, Iran

ARTICLE INFO

Article history:

Received 12 April 2010

Revised 16 June 2010

Accepted 2 July 2010

Available online 7 July 2010

Keywords:

Copper- and phosphine-free

Sonogashira reaction

Supported catalyst

Aryl iodides

ABSTRACT

A polymer-supported palladium(II) *N,N*-bis(naphthylideneimino)diethylenetriamine complex is found to be a highly active catalyst for Sonogashira coupling reactions. The reactions are performed under copper- and phosphine-free conditions in an air atmosphere. The palladium catalyst is easily separated, and can be reused several times without significant loss in catalytic activity.

© 2010 Elsevier Ltd. All rights reserved.

The Pd–Cu-catalyzed coupling reaction of terminal alkynes with aryl and vinyl halides to give enynes (Sonogashira cross-coupling), has become an extremely powerful tool for constructing conjugated acetylenes.¹ Conventionally, the reaction is performed using catalytic amounts of a palladium–phosphine complex and CuI in the presence of a large excess of a secondary or tertiary amine or various bases such as alkali-metal carbonates.² However, many Pd–phosphine complexes are sensitive to both air and moisture, and their cost and toxicity limit large scale industrial applications. Also, a major problem with Sonogashira reactions is the use of a copper reagent (co-catalyst), which is frequently required to promote the reaction, and which results in contamination of the coupling products with metal residues.

It has been well-documented that the Sonogashira coupling often suffers from Glaser-type oxidative dimerization of the alkyne substrate,³ as a side-reaction in the presence of a Cu(I) co-catalyst. In recent years, numerous modifications have been reported for the Sonogashira coupling, these include reactions in ionic liquids,⁴ reaction as a microemulsion,⁵ a zeolite-supported reaction system,⁶ a fluoros biphasic system (FBS) using fluoros palladium catalysts,⁷ phase-transfer catalytic reaction conditions,⁸ various copper-free conditions,⁹ non-phosphine Sonogashira coupling,¹⁰ the use of a variety of promoters¹¹ such as Zn, Mg and Sn, and microwave irradiation.¹²

Initially, a soluble palladium complex $[(\text{PdCl}_2(\text{PPh}_3)_2)]$ was used as the catalyst for the Sonogashira coupling reaction. However, it was later found that palladium metal can also catalyze the reaction. The main advantage of using palladium in the form of a heterogeneous catalyst is the easy separation of the catalyst from the reaction mixture. Moreover, from the standpoint of environmentally benign organic synthesis, the development of highly active and easily reusable immobilized catalysts is of significant interest to chemists.¹³ To date, research on polymer-supported catalysts suggests that these catalytic systems are promising alternatives.¹⁴

Despite numerous reports on the use of the Sonogashira reactions in organic synthesis, polymer-supported palladium catalysts have not been widely applied for this reaction.¹⁵ Polymer-supported palladium complex catalysts derived from chloromethyl polystyrene resin have been employed in both the Heck¹⁶ and Suzuki¹⁷ reactions, and have shown lower levels of palladium leaching during cross-coupling.

We previously reported on the Sonogashira coupling reactions of aryl iodides with terminal alkynes using a water-soluble palladium–N,O complex (Pd–salen complex) as a homogenous catalyst.¹⁸

Our continuing interest in the catalytic utility of polystyrene-resin-supported palladium complexes¹⁹ led us to examine Sonogashira coupling reactions with the aforementioned palladium–N,O complex as a heterogeneous catalyst. Herein, we report the facile copper- and phosphine-free Sonogashira reactions of aryl iodides with terminal alkynes catalyzed by an *N,N*-bis

* Corresponding author. Fax: +98 2733395441.

E-mail address: m.bakherad@yahoo.com (M. Bakherad).

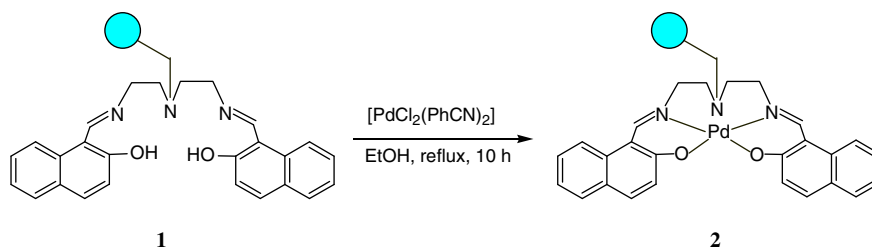
(naphthylideneimino)diethylenetriamine-functionalized polystyrene resin-supported palladium(II) complex [PS-nap-Pd(II)] under aerobic conditions.

The ease of preparation of the complex, its long shelf-life, stability toward air, and compatibility with a wide variety of aryl iodides and alkynes make it ideal for the above mentioned reactions.

The immobilized Schiff base palladium [PS-nap-Pd(II)] can be prepared easily from a commercially available polymer. We used chloromethylated polystyrene (2% divinylbenzene) as the catalyst support because it is a popular polymeric material due to its low cost, ready availability, mechanical robustness, and ease of functionalization. In this approach, the Schiff base palladium complex is attached, via a covalent bond, to a pendant chloromethyl group on the surface of the polymer resin particles.

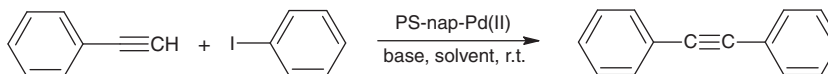
Reaction of polystyrene-*N,N*-bis(naphthylideneimino)diethylenetriamine (PS-nap) (**1**)²⁰ with a solution of [PdCl₂(PhCN)₂] in ethanol under reflux resulted in covalent attachment of the palladium complex to give the polymer-supported palladium(II) complex catalyst [PS-nap-Pd(II)] (**2**) (Scheme 1).

The extent of immobilization was confirmed by IR spectroscopy (Pd–N ≈ 550 cm⁻¹). The metal loading of the polymer-supported palladium complex, determined by neutron activation analysis (NAA), was found to be 3.85% (0.36 mmol/g).



Scheme 1.

Table 1
Optimization of the conditions for the copper- and phosphine-free Sonogashira reaction of iodobenzene with phenylacetylene^a



Entry	Solvent	Base	PS-nap-Pd(II) (mol %)	Time (h)	Yield ^b (%)
1	1,4-Dioxane	Et ₃ N	1.0	4	80
2	1,4-Dioxane	DIEA ^c	1.0	5	78
3	1,4-Dioxane	Pyridine	1.0	4	82
4	1,4-Dioxane	Pyrrolidine	1.0	6	81
5	DMF	Et ₃ N	1.0	3	95
6	DMF	DIEA	1.0	3	91
7	DMF	Pyridine	1.0	4	90
8	DMF	Pyrrolidine	1.0	4	92
9	DMAC ^d	Et ₃ N	1.0	3	92
10	DMAC	DIEA	1.0	5	88
11	DMAC	Pyridine	1.0	4	90
12	DMAC	Pyrrolidine	1.0	4	93
13	NMP ^e	Et ₃ N	1.0	5	90
14	NMP	DIEA	1.0	7	86
15	NMP	Pyridine	1.0	5	91
16	NMP	Pyrrolidine	1.0	6	87
17	THF	Et ₃ N	1.0	6	82
18	THF	DIEA	1.0	8	80
19	THF	Pyridine	1.0	7	84
20	THF	Pyrrolidine	1.0	7	81
21	DMF	Et ₃ N	2.0	2	95
22	DMF	Et ₃ N	0.5	6	85

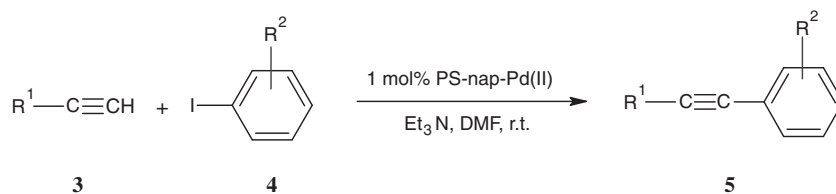
^a Reaction conditions: iodobenzene (1.0 mmol), phenylacetylene (1.5 mmol), base (2.0 mmol), solvent (2 mL), room temperature, aerobic conditions.

^b GC yield.

^c Diisopropylethylamine.

^d Dimethylacetamide.

^e *N*-Methylpyrrolidone.



Scheme 2.

Table 2
Copper-free Sonogashira reactions of various terminal alkynes and aryl iodides (see Scheme 2)^a

Entry	R ¹	R ²	Time (h)	Product	Yield ^b (%)
1	Ph	H	3	5a	95 (90)
2	Ph	4-COCH ₃	3	5b	97 (93)
3	Ph	4-OCH ₃	4	5c	90
4	Ph	4-NO ₂	3	5d	99 (95)
5	Ph	3-NO ₂	3	5e	93
6	Ph	4-Cl	3	5f	92
7	Ph	4-Br	3	5g	92
8	<i>n</i> -C ₄ H ₉	H	4	5h	93
9	<i>n</i> -C ₄ H ₉	4-NO ₂	3	5i	98 (93)
10	<i>n</i> -C ₄ H ₉	4-COCH ₃	3	5j	96 (90)
11	<i>n</i> -C ₄ H ₉	4-OCH ₃	4	5k	92
12	Me ₃ Si	H	4	5l	91
13	Me ₃ Si	4-Cl	3	5m	88
14	Me ₃ Si	4-OCH ₃	4	5n	85
15	<i>n</i> -C ₆ H ₁₃	H	5	5o	87
16	<i>n</i> -C ₆ H ₁₃	4-NO ₂	3	5p	95 (91)
17	<i>n</i> -C ₆ H ₁₃	4-COCH ₃	3	5q	93 (88)

^a Reaction conditions: **3** (1.5 mmol), **4** (1.0 mmol), PS-nap-Pd(II) (0.01 mmol), Et₃N (2 mmol), DMF (2 mL), room temperature, aerobic conditions.

^b GC yield. Numbers in parentheses are isolated yields.

Unsurprisingly, *p*-nitroiodobenzene was found to be the most reactive among the aryl iodides studied (entries 4, 9, and 17). As expected, aryl iodides with electron-withdrawing groups reacted faster than aryl iodides possessing electron-donating groups to give the desired products in high yields.

The recyclability of the PS-nap-Pd(II) catalyst **2** was examined in the Sonogashira coupling of iodobenzene and phenylacetylene. The catalyst was separated from the reaction mixture by filtration after each experiment, washed with water and acetonitrile, and dried carefully before use in subsequent runs. Thus after the first reaction, which gave a quantitative yield of the coupling product **5a** (Table 3, entry 1), the catalyst beads were recovered and successively subjected to nine further runs under the same conditions to afford **5a** in 93–85% yields (Table 3).

In conclusion, we have developed a protocol for the copper- and phosphine-free Sonogashira coupling reactions of aryl iodides with terminal acetylenes using a [PS-nap-Pd(II)] complex to give various biaryl acetylene derivatives. The catalyst was recovered and reused 10 times with only marginal loss in catalytic activity.

Table 3
Copper-free Sonogashira reaction of iodobenzene with phenylacetylene catalyzed by the recycled catalyst^a

Entry	Cycle	Yield ^b (%)
1	1	95
2	2	93
3	5	90
4	8	88
5	10	85

^a Reaction conditions: phenylacetylene (1.5 mmol), iodobenzene (1.0 mmol), PS-nap-Pd(II) (0.01 mmol), DMF (2 mL), Et₃N (2 mmol), room temperature, aerobic conditions.

^b GC yield.

1. *N,N*-Bis(naphthylideneimino)diethylenetriamine-function-alyzed polystyrene resin-supported Pd(II) complex **2**

A mixture of polystyrene-*N,N*-bis(naphthylideneimino)diethylenetriamine (**1**) (3.0 g) and [PdCl₂(PhCN)₂] (0.25 g) in EtOH (50 mL) was heated under reflux for 10 h. The resulting bright-yellow colored polymer, impregnated with the metal complex, was filtered, washed with EtOH, and dried at 50 °C to give [PS-nap-Pd(II)] (**2**) (Scheme 1).

2. General procedure for the Sonogashira coupling reaction

A round-bottomed flask was charged with aryl iodide (1.0 mmol), terminal alkyne (1.5 mmol), [PS-nap-Pd(II)] (0.01 mmol), Et₃N (2 mmol), and DMF (2 mL). The mixture was stirred at room temperature for 3–5 h under aerobic conditions. Upon completion of the reaction, the solution was concentrated in vacuo, and the crude product was subjected to silica gel column chromatography using CHCl₃–CH₃OH (97:3) as eluent to afford the pure product.

Acknowledgment

The authors are grateful to the Research Council of Shahrood University of Technology for the financial support of this work.

References and notes

- (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874; (b) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834; (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979; (d) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *44*, 4467.
- (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442; (b) Nájera, C.; Chinchilla, R. *Chem. Rev.* **2007**, *107*, 874; (c) Novák, Z.; Szabo, A.; Répási, J.; Kotschy, A. J. *Org. Chem.* **2003**, *68*, 3327; (d) Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. J. *Org. Chem.* **2004**, *69*, 5082; (e) Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P. *Org. Lett.* **2004**, *6*, 3473; (f) Bedford, R. B. *Chem. Commun.* **2003**, 1787; (g) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Adv. Synth. Catal.* **2003**, *345*, 1146; (h) Consorti, C. S.; Flores, F. R.; Rominger, F.; Dupont, J. *Adv. Synth. Catal.* **2006**, *348*, 133; (i) Yang, F.; Wu, Y. *Eur. J. Org. Chem.* **2007**, 3476; (j) Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056; (k) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993; (l) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173; (m) Heiden, A. M.; Plenio, H. *Chem. Commun.* **2007**, 972; (n) Gil-Moltó, J.; Nájera, C. *Eur. J. Org. Chem.* **2005**, 4073; (o) Park, S. B.; Alper, H. *Chem. Commun.* **2004**, 1306; (p) Bandini, M.; Luque, R.; Budarin, V.; Macquarrie, D. J. *Tetrahedron* **2005**, *61*, 9860; (q) Li, P.-H.; Wang, L. *Adv. Synth. Catal.* **2006**, *348*, 681; (r) Cai, M.; Xu, Q.; Wang, P. *J. Mol. Catal., A: Chem.* **2006**, *250*, 199.
- (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
- Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2004**, *4*, 1691.
- Jiang, J.-Z.; Cai, C. *Colloids Surf., A* **2006**, *287*, 212.
- Corma, A.; García, H.; Primo, A. *J. Catal.* **2006**, *241*, 123.
- (a) Markert, C.; Bannwarth, W. *Helv. Chim. Acta* **2002**, *85*, 1877; (b) Tzschucke, C. C.; Markert, C.; Glatz, H.; Bannwarth, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 4500; (c) Tzschucke, C. C.; Andrusko, V.; Bannwarth, W. *Eur. J. Org. Chem.* **2005**, 5248; (d) Garcia-Bernabé, A.; Tzschucke, C. C.; Bannwarth, W.; Haag, R. *Adv. Synth. Catal.* **2005**, *347*, 1389.
- Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910.
- (a) Cheng, J.; Sun, Y.; Wang, F.; Guo, M.; Xu, J.-H.; Pan, Y.; Zhang, Z. *J. Org. Chem.* **2004**, *69*, 5428; (b) Böhm, V. P. M.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679; (c) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295; (d) Alonso, D. A.;

- Nájera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365; (e) Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, *44*, 8653; (f) Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191; (g) Mery, D.; Heuze, K.; Astruc, D. *Chem. Commun.* **2003**, 1934; (h) Heuze, K.; Mery, D.; Gause, D.; Astruc, D. *Chem. Commun.* **2003**, 2274; (i) Park, S.; Kim, M.; Koo, D. H.; Chang, S. *Adv. Synth. Catal.* **2004**, *346*, 1638; (j) Urganonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752; (k) Arques, A.; Aunon, D.; Molina, P. *Tetrahedron Lett.* **2004**, *45*, 4337; (l) Djakovitch, L.; Rollet, P. *Tetrahedron Lett.* **2004**, *45*, 1367; (m) Djakovitch, L.; Rollet, P. *Adv. Synth. Catal.* **2004**, *346*, 1782; (n) Heuze, K.; Mery, D.; Gauss, D.; Blais, J.-C.; Astruc, D. *Eur. J. Org. Chem.* **2004**, 3936; (o) Tyrrell, E.; Al-Saardi, A.; Millet, J. *Synlett* **2005**, 487; (p) Yi, C.; Hua, R. *Catal. Commun.* **2006**, *7*, 377; (q) Cwik, A.; Hell, Z.; Figueras, F. *Tetrahedron Lett.* **2006**, *47*, 3023.
10. (a) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823; (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; Sánchez, G.; López, G.; Serrano, J. J.; García, L.; Pérez, J.; Pérez, E. *Dalton Trans.* **2004**, 3970; (c) Alonso, D. A.; Botella, L.; Nájera, C.; Pacheco, M. C. *Synthesis* **2004**, 1713; (d) Alacid, E.; Alonso, D. A.; Botella, L.; Nájera, C.; Pacheco, M. C. *Chem. Rec.* **2006**, *6*, 117; (e) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239; (f) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290; (g) Herrmann, W. A.; Ófele, K.; Preysing, D. V.; Schneider, S. K. *J. Organomet. Chem.* **2003**, *687*, 229; (h) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247; (i) Dhudshia, B.; Thadani, A. N. *Chem. Commun.* **2006**, 668; (j) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768.
11. (a) Powell, N. A.; Rychnosky, S. D. *Tetrahedron Lett.* **1996**, *37*, 7901; (b) Crisp, G. T.; Turner, P. D.; Stephens, K. A. *J. Organomet. Chem.* **1998**, *570*, 219; (c) Nakamura, K.; Ohubo, H.; Yamaguchi, M. *Synlett* **1999**, 549.
12. Kabalka, G. W.; Wang, L.; Nambodiri, V.; Pagni, R. M. *Tetrahedron Lett.* **2000**, *41*, 5151.
13. (a) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881; (b) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095; (c) Dioso, B. M. L.; Vankelecom, I. F. J.; Jacobs, P. A. *Adv. Synth. Catal.* **2006**, *348*, 1413.
14. Zheng, P.-W.; Zhang, W. Q. *J. Catal.* **2007**, *250*, 324.
15. (a) Leese, M. P.; Williams, J. M. J. *Synlett* **1999**, 1645; (b) Lin, C.-A.; Luo, F.-T. *Tetrahedron Lett.* **2003**, *44*, 7565; (c) Gonthier, E.; Breinbauer, R. *Synlett* **2003**, 1049.
16. Phan, N. T. S.; Brown, D. H.; Adams, H.; Spey, S. E.; Styring, P. *Dalton Trans.* **2004**, 1348.
17. (a) Phan, N. T. S.; Brown, D. H.; Styring, P. *Tetrahedron Lett.* **2004**, *45*, 7915; (b) Byun, J. W.; Lee, Y. S. *Tetrahedron Lett.* **2004**, *45*, 1837; (c) Vassilyev, O.; Chen, J.; Panarello, A. P.; Khinast, J. G. *Tetrahedron Lett.* **2005**, *46*, 6865; (d) Shimizu, K.; Koizumi, S.; Hatamachi, T.; Yoshida, H.; Komai, S.; Kodama, T.; Kitayama, Y. *J. Catal.* **2004**, *228*, 141.
18. Bakherad, M.; Keivanloo, A.; Bahramian, B.; Hashemi, M. *Tetrahedron Lett.* **2009**, *50*, 1557.
19. (a) Bakherad, M.; Bahramian, B.; Isfahani, H. N.; Keivanloo, A.; Doostmohammadi, N. *J. Heterocycl. Chem.* **2009**, *46*, 100; (b) Bakherad, M.; Bahramian, B.; Isfahani, H. N.; Keivanloo, A.; Sang, G. *Chin. J. Chem.* **2009**, *27*, 353; (c) Bakherad, M.; Keivanloo, A.; Bahramian, B.; Mihanparast, S. *Tetrahedron Lett.* **2009**, *50*, 6418; (d) Bakherad, M.; Keivanloo, A.; Bahramian, B.; Kamali, A. T. *J. Brazil. Chem. Soc.* **2009**, *20*, 907.
20. Chamjangali, A. M.; Talebzadeh, F. S.; Bahramian, B. *J. Hazard. Mater.* **2010**, *174*, 843.