Tetrahedron Letters 50 (2009) 1557–1559

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper-free Sonogashira coupling reactions catalyzed by a water-soluble Pd–salen complex under aerobic conditions

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A R T I C L E I N F O

Article history:
Received 23 October 2008
Revised 23 December 2008
Accepted 13 January 2009
Available online 19 January 2009

Keywords:
Water
Copper-free
Sonogashira reaction
Pd–salen
Aryl iodides

A B S T R A C T

The water-soluble Pd–salen complex, palladium(II) *N,N′*-bis{[5-(triphenylphosphonium)methyl]salicylidene}-1,2-ethanediamine chloride, is a highly active catalyst for the copper-free Sonogashira coupling of aryl iodides with terminal alkynes in water under aerobic conditions.

1. Introduction

The Sonogashira cross-coupling reaction[1] is a powerful method for C(sp)–C(sp^2) bond formation. It can be used for the synthesis of a variety of compounds,[2] including heterocycles,[3] natural products, and pharmaceuticals.[4] In addition, oligomers and polymers have also been prepared via the Sonogashira reaction.[5]

The reaction is generally carried out in an organic solvent such as an amine, benzene, THF, or DMF with a palladium catalyst in conjunction with copper(I) iodide as a co-catalyst, and in the presence of a stoichiometric amount of base.[6]

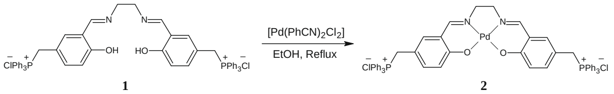
In recent years, a variety of modifications have been reported for this reaction and great progress has been made.[7] The most important modification is elimination of the copper salt,[8] since it can induce Glaser-type homocoupling of the terminal alkynes in the presence of oxidative agents or air.[9]

The use of aqueous media in palladium-catalyzed reactions has become popular[10] because water-based synthetic processes are inherently safer (water is non-toxic and non-flammable) as well as being inexpensive. Moreover, the products can be isolated easily by extraction. Its use is particularly beneficial in the cross-coupling reaction of peptides with alkyne ligands for the construction of biomolecule-based systems, where the poor solubility of the reactants often prevents the reaction being performed in common organic solvents. Thus, the use of water-soluble catalysts[10g] and water-soluble phosphine ligands, for example, sulfonated phosphines[10f] has been investigated. Moreover, the original Sonogashira reaction conditions require degassed organic solvents, and have to be carried out under an inert atmosphere. This is particularly inconvenient when the reactions are carried out in multiple vessels for library generation. Therefore, the development of convenient methods for Sonogashira reactions is an important objective. Thus, we decided to concentrate on developing a novel palladium catalyst that is highly active and air stable.

As part of our ongoing project on palladium-catalyzed reactions,[11] herein, we report the synthesis of water-soluble palladium(II) *N,N′*-bis{[5-(triphenylphosphonium)methyl]salicylidene}-1,2-ethanediamine chloride **2** and its catalytic activity in the copper-free Sonogashira coupling reaction of aryl iodides with terminal alkynes in water under aerobic conditions.

The palladium(II) salen complex **2** was synthesized by the reaction of the salen ligand *N,N′*-bis{[5-(triphenylphosphonium)methyl]salicylidene}-1,2-ethanediamine chloride **1**[12] with bis(benzonitrile)palladium(II) chloride for 12 h in refluxing ethanol (Scheme 1).

The catalytic activity of complex **2** (1 mol %) was studied in the copper-free Sonogashira reaction using aryl iodides and terminal alkynes, in the presence of Cs_2CO_3 as base in water at 60 °C under aerobic conditions.



Scheme 1.

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doi:10.1016/j.tetlet.2009.01.053

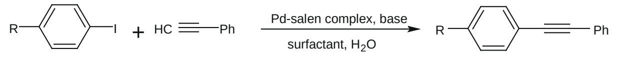
For optimization of the reaction conditions, we chose the cross-coupling of iodobenzene or 4-iodoanisole with phenylacetylene as model reactions, and the effects of the base, surfactant, and catalyst were examined. We first investigated the influence of various bases on the copper-free Sonogashira reaction of electron-neutral iodobenzene and electron-rich 4-iodoanisole with phenylacetylene using 1 mol % of **2** in water under aerobic conditions. We found that the reaction was highly dependent on the amount of base as well as its nature. According to the results obtained (Table 1), Cs_2CO_3 gave an excellent yield (entry 2, 95%) in the reaction of electron-neutral iodobenzene with phenylacetylene; K_2CO_3 also gave a similar yield (entry 3, 90%).

The results with the deactivated electron-rich substrate 4-iodoanisole were similar. The best result was obtained in the case of cesium carbonate as the base (Table 1, entry 10). The influence of the amount of surfactant and catalyst was investigated using the reaction of iodobenzene with phenylacetylene, Table 2. Increasing the amount of the palladium catalyst reduced the reaction time but did not increase the yield (entry 1). A low palladium concentration prolonged the reaction time and decreased the yield (entry 2). The use of a surfactant was also critical for the success of the reaction: without a surfactant/phase-transfer reagent, the yield dropped from 95% to 30% (compare entries 3 and 6); however, increasing the amount of the surfactant did not improve the yield (entry 5). A low surfactant concentration decreased the yield (entry 4).

Using the optimized reaction conditions (0.01 mmol of **2**, 0.07 mmol of sodium lauryl sulfate, 2.0 mmol of Cs_2CO_3), we explored the general applicability of the Pd–salen complex **2** as a catalyst for coupling different alkynes **3** and aryl iodides **4** containing electron-withdrawing or donating substituents, and the results are shown in Table 3. Alkynes reacted with aryl iodides such as iodobenzene, nitroiodobenzene, *p*-iodoacetophenone, and *p*-iodoanisole, delivering the corresponding products in good to excellent yields. Unsurprisingly, *p*-nitroiodobenzene was found to be the most reactive amongst the aryl iodides studied (entries 2, 6, and 12). 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.

In summary, we have shown that the water-soluble palladium–salen complex **2** efficiently catalyzes the copper-free Sonogashira coupling reaction of aryl iodides with terminal alkynes in water using sodium lauryl sulfate as the surfactant and Cs_2CO_3 as base under aerobic conditions.

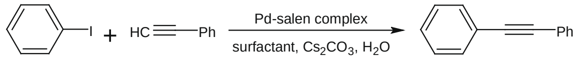
Table 1
Effect of base on the Sonogashira reactions of aryl iodides with phenylacetylene in water[a]



Entry	R	Base	Yield[b] (%)
1	H	KOH	40
2	H	Cs_2CO_3	95
3	H	K_2CO_3	90
4	H	Et_3N	45
5	H	DIEA	35
6	H	Pyrrolidine	48
7	H	Piperidine	55
8	MeO	KOH	22
9	MeO	K_2CO_3	65
10	MeO	Cs_2CO_3	85
11	MeO	Et_3N	20
12	MeO	DIEA	25
13	MeO	Pyrrolidine	34
14	MeO	Piperidine	30

[a] Reaction conditions: aryl iodide (1.0 mmol), phenylacetylene (1.5 mmol), Pd–salen complex (0.01 mmol), sodium lauryl sulfate (0.07 mmol), base (2.0 mmol), water (5 mL), 60 °C, 12 h under aerobic conditions.
[b] GC yields.

Table 2
Effect of catalyst and surfactant on the Sonogashira reaction of iodobenzene with phenylacetylene in water[a]



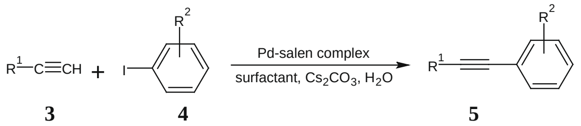
Entry	Pd–salen complex (mol %)	Sodium lauryl sulfate (mol %)	Time (h)	Yield[b] (%)
1	2	7	7	92
2	0.5	7	12	80
3	1	7	9	95
4	1	3	12	62
5	1	10	12	30
6	1	–	12	30

[a] Reaction conditions: iodobenzene (1.0 mmol), phenylacetylene (1.5 mmol), cesium carbonate (2.0 mmol), water (5 mL) at 60 °C under aerobic conditions.
[b] GC yields.

2. Preparation of palladium(II) *N,N′*-bis{[5-(triphenylphosphonium)methyl]salicylidene}-1,2-ethanediamine chloride 2

A mixture of *N,N′*-bis{[5-(triphenylphosphonium)methyl]salicylidene}-1,2-ethanediamine dichloride **1**[12] (1.8 g, 2 mmol) and $[PdCl_2(C_6H_5CN)_2]$ (0.76 g, 2 mmol) in absolute ethanol (10 mL) was heated under reflux for 12 h. The resulting precipitate was filtered off and recrystallized from ethanol to afford the title compound. Yield, 80%; mp 195–196 °C; IR, ν (KBr disc): 3415 (s), 3055 (m), 3038 (m), 2915 (m), 2854 (m), 1624 (vs), 1583 (s), 1555 (s), 1530 (s), 1463 (s),1433 (s), 1382 (s), 1326 (m), 1212 (w), 1148 (m), 1105 (s), 1040 (m), 810 (s), 745 (s), 730 (m), 710 (s), 688 (sh), 620 (w), 595 (w), 540 (m), 520 (w), 510 (s), 490 (m), 475(m), 445 (w), 439 (w) cm^{-1}; UV–vis, (MeOH) λ_{max} (nm): 406 (sh), 315 (sh), 285 (sh).

Table 3
Copper-free Sonogashira reaction of terminal alkynes with aryl iodides[a]



Entry	R^1	R^2	Time (h)	Product	Yield[b] (%)
1	n-C_4H_9	H	8	**5a**	92
2	n-C_4H_9	4-NO_2	6	**5b**	98
3	n-C_4H_9	4-$COCH_3$	7	**5c**	90
4	n-C_4H_9	4-OCH_3	12	**5d**	82
5	Ph	H	9	**5e**	95
6	Ph	4-NO_2	6	**5f**	98
7	Ph	3-NO_2	6	**5g**	94
8	Ph	2-NO_2	7	**5h**	95
9	Ph	4-$COCH_3$	8	**5i**	92
10	Ph	4-OCH_3	11	**5j**	85
11	Me_3Si	H	10	**5k**	94
12	Me_3Si	4-NO_2	7	**5l**	97
13	Me_3Si	3-NO_2	7	**5m**	95
14	Me_3Si	2-NO_2	8	**5n**	96
15	Me_3Si	4-OCH_3	12	**5o**	80
16	CH_2OH	H	10	**5p**	86
17	CH_2OH	3-NO_2	8	**5q**	90
18	CH_2OH	4-OCH_3	12	**5r**	78

[a] Reaction conditions: **3** (1.5 mmol), **4** (1.0 mmol), Pd–salen complex (0.01 mmol), sodium lauryl sulfate (0.07 mmol), Cs_2CO_3 (2.0 mmol), water (5 mL) at 60 °C under aerobic conditions.
[b] GC yields.

3. General procedure for the Sonogashira coupling reaction

A round-bottomed flask was charged with aryl iodide (1.0 mmol), alkyne (1.5 mmol), palladium(II) *N*,*N*′-bis{[5-(triphenylphosphonium)methyl]salicylidene}-1,2-ethanediamine dichloride (0.01 mmol), sodium lauryl sulfate (0.07 mmol), and cesium carbonate (2.0 mmol), with stirring under aerobic conditions in 5 mL of water. The mixture was heated at 60 °C for 6–12 h. After completion of the reaction, the resulting solution was concentrated in vacuo, and the crude product was subjected to silica gel column chromatography using $CHCl_3$–CH_3OH (98:2) as eluent to afford the pure product (Table 3).

Acknowledgment

The authors are thankful to Shahrood University of Technology for financial support.

References and notes

1. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467; (b) Sonogashira, K.; Yatake, T.; Tohda, Y.; Takahashi, S.; Hagihara, N. *J. Chem. Soc., Chem. Commun.* **1977**, 291; (c) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.
2. (a) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566; (b) Negishi, E.; Nastasia, L. *Chem. Rev.* **2003**, *103*, 1979.
3. Li, J. J.; Gribble, G. W.. *Palladium in Heterocyclic Chemistry*. In *Tetrahedron Organic Chemistry Series*; Pergamon: Amsterdam, 2000; Vol. 20.
4. (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387; (b) Grissom, J. M.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453; (c) De Kort, M.; Correa, V.; Valentijin, A. R. P. M.; Van der Marel, G. A.; Potter, B. V. L.; Taylor, C. W.; Van Boom, J. H. *J. Med. Chem.* **2000**, *43*, 3295; (d) Lang, P.; Magnin, G.; Mathis, G.; Burger, A.; Biellmann, J.-F. *J. Org. Chem.* **2000**, *65*, 7825; (e) Uenishi, J.-I.; Matsui, K.; Ohmiya, H. *J. Organomet. Chem.* **2002**, *653*, 141.
5. (a) Ziener, U.; Godt, A. *J. Org. Chem.* **1997**, *62*, 6137; (b) Francke, V.; Mangel, T.; Muellen, K. *Macromolecules* **1998**, *31*, 2447; (c) Huang, S.; Tour, J. M. *Tetrahedron Lett.* **1999**, *40*, 3347.
6. Sonogashira, K.. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, p p. 521.
7. (a) Chow, H. F.; Wan, C. W.; Low, K. H.; Yeung, Y. Y. *J. Org. Chem.* **2001**, *66*, 1910; (b) Ruiz, J.; Cutillas, N.; Lopez, F.; Lopez, G.; Bautista, D. *Organometallics* **2006**, *25*, 5768; (c) Consorti, C. S.; Flores, F. R.; Rominger, F.; Dupont, J. *Adv. Synth. Catal.* **2006**, *348*, 133; (d) Dhudshia, B.; Thadani, A. N. *Chem. Commun.* **2006**, 668; (e) Yi, C. Y.; Hua, R. M. *Catal. Commun.* **2006**, *7*, 377; (f) Park, S. B.; Alper, H. *Chem. Commun.* **2004**, 1306; (g) Komáromi, A.; Novák, Z. *Chem. Commun.* **2008**, *40*, 4968.
8. (a) Yi, C. Y.; Hua, R. M. *J. Org. Chem.* **2006**, *71*, 2535; (b) Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191; (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290; (d) Gholap, A. R.; Venkatesan, K.; Pasricha, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2005**, *70*, 4869.
9. (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; (b) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320; (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
10. (a) Lopez-Deber, M. P.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 2823; (b) Pierre Genet, J.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305; (c) Mori, A.; Ahmed, M. S. M.; Sekiguchi, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, 756; (d) Bumagin, N. A.; Sukhomlinova, L. I.; Luzikova, E. V.; Tolstaya, T. P.; Beletskaya, I. P. *Tetrahedron Lett.* **1996**, *37*, 897; (e) Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71; (f) Amatore, C.; Blart, E.; Genet, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829; (g) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324; (h) Dibowski, H.; Schmidtchen, F. P. *Tetrahedron Lett.* **1998**, *39*, 525; (i) Wolf, C.; Lerebours, R. *Org. Biomol. Chem.* **2004**, 2161; (j) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. *J. Org. Chem.* **2004**, *69*, 7919; (k) Li, C. J. *Acc. Chem. Res.* **2002**, *35*, 533; (l) Bong, D. T.; Ghadiri, M. R. *Org. Lett.* **2001**, *3*, 2509; (m) Komáromi, A.; Tolnai, G. L.; Novák, Z. *Tetrahedron Lett.* **2008**, *49*, 7294.
11. (a) Bakherad, M.; Isfahani, H. N.; Keivanloo, A.; Doostmohammadi, N. *Tetrahedron Lett.* **2008**, *49*, 3819; (b) Bakherad, M.; Isfahani, H. N.; Keivanloo, A.; Sang, G. *Tetrahedron Lett.* **2008**, *49*, 6188.
12. (a) Bahramian, B.; Mirkhani, V.; Moghadam, M.; Amin, A. H. *Appl. Catal. A* **2006**, *315*, 52; (b) Bahramian, B.; Mirkhani, V.; Tangestaninejad, S.; Moghadam, M. *J. Mol. Catal. A: Chem.* **2005**, *224*, 139.