Tetrahedron Letters 55 (2014) 2101–2103

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Hydrazinoaminocarbene–palladium complexes as easily accessible and convenient catalysts for copper-free Sonogashira reactions

Elizaveta A. Savicheva [a,b,*], Daria V. Kurandina [a], Vladimir A. Nikiforov [b], Vadim P. Boyarskiy [a]

[a] *Department of Chemistry, Saint-Petersburg State University, Universitetskiy pr. 26, 198504 Saint-Petersburg, Russia*
[b] *Scientific Research Center for Ecological Safety of Russian Academy of Sciences, Korpusnaya st. 18, 197110 Saint-Petersburg, Russia*

ARTICLE INFO

Article history:
Received 12 October 2013
Revised 30 January 2014
Accepted 13 February 2014
Available online 22 February 2014

Keywords:
Copper-free Sonogashira reaction
Cross-coupling
Acyclic diaminocarbene palladium complexes
Aryl hydrazines
Isocyanides

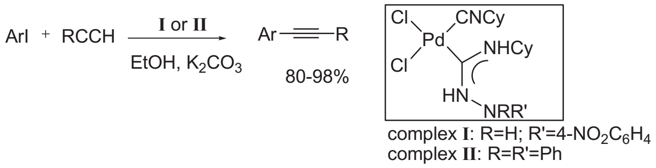
ABSTRACT

Two easily accessible hydrazinoaminocarbene complexes of Pd(II) are shown to be efficient catalysts for copper-free Sonogashira cross-couplings of a variety of aryl iodides with aryl- and alkylalkynes under mild conditions, in ethanol as the solvent and using potassium carbonate as the base. The reactions were carried out with 0.05 mol % of the catalysts which demonstrated exceptional stability in the solid state and in ethanol. Protection from air is not needed. Disubstituted acetylenes were synthesized by the general procedure on up to a gram scale and the yields were 80–98%.

Sonogashira cross-coupling of monosubstituted acetylenes and aryl halides catalyzed by palladium and copper species is a common route to disubstituted acetylenes.[1–3] However, the presence of a copper co-catalyst may lead to unwanted side reactions such as the formation of diynes[2–4] or further cyclization of the target products.[5] Also, it is worth noting that copper is not environmentally friendly and the use of relatively large amounts of copper should be avoided.[6] Copper-free Sonogashira reactions have been known for a long time,[7] but initially required harsh conditions and large amounts of palladium catalysts. The development of more active catalysts has allowed copper-free Sonogashira reactions to be performed under milder conditions.[8–13]

An impressive advance was the use of just 0.001 mol % of a catalyst for copper- and amine-free Sonogashira coupling of aryl iodides, bromides, and chlorides with unsubstituted phenylacetylene. This was achieved with specialized five- or seven-membered palladacycles based on phosphine-ylide ligands.[8b,c]

More typical and simple are Pd–NHC complexes (NHC = N-heterocyclic carbene). They show good activity in classic[9] and copper-free[9,10] Sonogashira reactions between aryl, heteroaryl, or alkyl halides with various acetylenes, but their preparation is often a laborious task.



Scheme 1. Copper-free Sonogashira reaction.

An attractive alternative to Pd–NHCs with equal or superior catalytic activity in cross-coupling reactions is palladium(II) complexes with acyclic diaminocarbenes (Pd–ADC).[11–15] There is only one report in the literature on the use of a Pd–ADC as a catalyst for the copper-free Sonogashira reaction.[12] However, the catalyst was prepared by a rather complicated method involving pretreatment of a specially synthesized formamidinium salt with LDA.

We earlier reported the acyclic hydrazinoaminocarbene palladium complex **I** and demonstrated its good catalytic activity in a variety of classic cross-coupling reactions.[13–15] This complex was synthesized easily by the reaction of a known palladium(II) isocyanide complex (*cis*-$[PdCl_2(C{\equiv}NCy)_2]$) with 4-$NO_2C_6H_4NHNH_2$. Herein, we report a convenient method for the copper-free Sonogashira cross-coupling of aryl iodides with various terminal acetylenes under mild conditions, catalyzed by complex **I**, as well as by another hydrazinoaminocarbene complex, **II** (Scheme 1).

---

[*] Corresponding author. Tel./fax: +7 812 499 64 55.
E-mail address: savicheva90@gmail.com (E.A. Savicheva).

http://dx.doi.org/10.1016/j.tetlet.2014.02.044

Catalysts **I** and **II** were prepared by the procedure described previously for complex **I** (Scheme 2).[13–15] The reaction between equimolar amounts of *cis*-$[PdCl_2(C{\equiv}NCy)_2]$ and the corresponding hydrazine proceeded to completion in four hours in 1,2-dichloroethane at reflux, and subsequent work-up provided complexes **I** and **II** in yields of 95% and 85%, respectively.[16] Both complexes are air- and moisture-stable in the 20–80 °C temperature range, and are also stable as ethanol solutions for at least four months.

To study the catalytic activity of complexes **I** and **II** we chose the reaction of phenylacetylene with 4-iodotoluene.[17] Cheap and environment-friendly ethanol and potassium carbonate were used as the solvent and base, respectively, in order to find a catalytic system operating under mild conditions. The reaction conditions were optimized in a standard manner (the variables were temperature, reaction time and amount of catalyst). The reactions were carried out in screw-capped vials with rapid stirring. No special measures were used to protect the reactions from air. The results are presented in Table 1.

At room temperature, the reaction proceeded too slowly (entries 1 and 2). At 80 °C, full conversion of 4-iodotoluene was achieved in two hours and the yield of the product, as determined by GC, was 97% (entry 3). It was possible to reduce the amount of the catalyst to 0.05 mol % (entry 4) without decreasing the yield. Further reduction of the amount of catalyst led to longer reaction times in order to reach 100% conversion of the aryl iodide (entry 6). In addition, long reaction times affected the selectivity of the reaction and a decrease in the yield of the desired product was detected (entries 6 and 8). The following conditions were found to be optimum for catalyst **I**: 0.05 mol % of catalyst, ethanol at 80 °C, and excess potassium carbonate (entry 4). Similar results were obtained with catalyst **II** (entries 9–13) and the optimum conditions were the same as for catalyst **I** (entry 10).

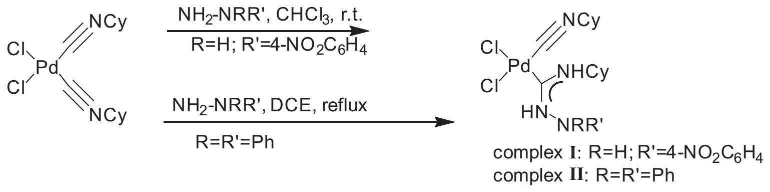
Next, the scope of the reaction was studied with catalyst **I** and eight different aryl iodides and four terminal acetylenes under optimized conditions, until 100% conversions (of ArI) were attained (Table 2).[18] We also tested two aryl bromides (4-bromotoluene and 4-nitrobromobenzene) with phenylacetylene using 1 mol % of the palladium catalyst and carried out the reaction for 72 h (Table 2, entries 21 and 22). The products were obtained in yields of 12% and 62% (conversions were 15% and 62%), respectively. In all cases (except for entries 6 and 11), full conversions of the aryl iodides were achieved.

The reaction was found to be applicable to a variety of aryl iodides with electron-donating (entries 2–4, 6, 10, 11, and 14) or electron-withdrawing (entries 5, 7, 8, 12, 13, 16, 17, 19, and 20) groups, and with one or even two *ortho*-substituents (entries 2, 4, 5, and 11). Terminal acetylenes with aryl-(entries 1–14) and alkyl (entries 15–20) substituents could be employed.

The mass spectrum of the mixture after coupling iodobenzene with 2-methylbut-3-yn-2-ol (entry 18) showed fragments with m/z values of 162, 144, and 142. These data proved the presence of by-products formed via dehydration and reduction of the target product. Such by-products were not detected in the other Sonogashira reactions that we carried out.

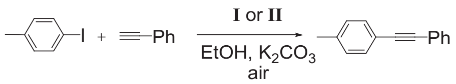
To demonstrate the synthetic abilities of the catalytic system, we performed two experiments on a gram scale with PhI and $4\text{-}NO_2C_6H_4I$ and phenylacetylene. Based on 20 mmol of ArI, we obtained the corresponding coupling products in good (84%, $PhC{\equiv}CPh$) or excellent (95%, $4\text{-}NO_2C_6H_4C{\equiv}CPh$) preparative yields (entries 1 and 8).[19,20]

In conclusion, we have reported a general and efficient method to obtain disubstituted acetylenes. Two catalysts **I** and **II** belonging to the family of ADC palladium complexes were shown to be active in copper-free Sonogashira reactions under mild conditions. No protection from air was needed. The catalysts can be prepared easily and are stable as ethanol solutions for at least four months. Environment-friendly ethanol proved to be a suitable solvent for the reaction. The method allowed Sonogashira cross-coupling products to be obtained in good to excellent preparative yields (up to 95%) on gram scale.



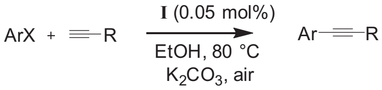
Scheme 2. Synthesis of the catalysts.

Table 1
Optimization of the reaction conditions (optimal conditions are in bold)[17]



Entry	Catalyst (mol %)	T (°C)	Time (h)	Conversion of $4\text{-}MeC_6H_4I$ (%)	Yield of $4\text{-}MeC_6H_4C{\equiv}CPh$ (%)
1	**I** (0.1)	21	24	12	10
2	**I** (0.1)	21	96	28	25
3	**I** (0.1)	80	2	100	97
4	**I (0.05)**	**80**	**2**	**100**	**96**
5	**I** (0.02)	80	2	61	58
6	**I** (0.02)	80	4	100	82
7	**I** (0.01)	80	4	45	39
8	**I** (0.01)	80	24	84	65
9	**II** (0.1)	80	2	100	92
10	**II (0.05)**	**80**	**2**	**100**	**94**
11	**II** (0.02)	80	4	100	81
12	**II** (0.01)	80	4	47	43
13	**II** (0.01)	80	24	70	53

Table 2
Reactions of aryl iodides and bromides with terminal acetylenes[18]



Entry	Ar-X	R-C$\equiv$CH	Yield of Ar-C$\equiv$C-R (%)
1	Ph-I	Ph-C$\equiv$CH	95 (84[a])
2	2-MeC$_6$H$_4$-I	Ph-C$\equiv$CH	96
3	4-MeC$_6$H$_4$-I	Ph-C$\equiv$CH	96
4	2,6-Me$_2$C$_6$H$_3$-I	Ph-C$\equiv$CH	94
5	2,4,6-Cl$_3$C$_6$H$_2$-I	Ph-C$\equiv$CH	95
6	4-MeOC$_6$H$_4$-I	Ph-C$\equiv$CH	90[b]
7	4-OHCC$_6$H$_4$-I	Ph-C$\equiv$CH	96
8	4-NO$_2$C$_6$H$_4$-I	Ph-C$\equiv$CH	98 (95[a])
9	Ph-I	4-MeOC$_6$H$_4$-C$\equiv$CH	94
10	4-MeC$_6$H$_4$-I	4-MeOC$_6$H$_4$-C$\equiv$CH	94
11	2,6-Me$_2$C$_6$H$_3$-I	4-MeOC$_6$H$_4$-C$\equiv$CH	90[b]
12	4-NO$_2$C$_6$H$_4$-I	4-MeOC$_6$H$_4$-C$\equiv$CH	98
13	4-OHCC$_6$H$_4$-I	4-MeOC$_6$H$_4$-C$\equiv$CH	98
14	4-MeOC$_6$H$_4$-I	4-MeOC$_6$H$_4$-C$\equiv$CH	95
15	Ph-I	*n*-C$_6$H$_{13}$-C$\equiv$CH	89
16	4-OHCC$_6$H$_4$-I	*n*-C$_6$H$_{13}$-C$\equiv$CH	85
17	4-NO$_2$C$_6$H$_4$-I	*n*-C$_6$H$_{13}$-C$\equiv$CH	97
18	Ph-I	Me$_2$(HO)C-C$\equiv$CH	80
19	4-OHCC$_6$H$_4$-I	Me$_2$(HO)C-C$\equiv$CH	98
20	4-NO$_2$C$_6$H$_4$-I	Me$_2$(HO)C-C$\equiv$CH	96
21	4-MeC$_6$H$_4$-Br	Ph-C$\equiv$CH	12[c]
22	4-NO$_2$C$_6$H$_4$-Br	Ph-C$\equiv$CH	62[c]

[a] Isolated yield on 20 mmol scale.[19,20]
[b] Conversion of ArI was 94%.
[c] 1 mol % of the catalyst was used.

Acknowledgments

The authors thank the Russian Foundation for Basic Research (Grant 14-03-00297a) and St. Petersburg State University (Grant 12.38.195.2014) for financial support of this work. NMR studies were performed at the Research Resources Center for Magnetic Resonance of Saint Petersburg State University. GC and GC–MS analyses were performed at the Educational Resource Center of Chemistry of Saint-Petersburg State University.

References and notes

1. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
2. Chinchilla, R.; Najera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.
3. Pu, X.; Li, H.; Colacot, T. J. *J. Org. Chem.* **2013**, *78*, 568.
4. Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422.
5. (a) Heravi, M. M.; Sadjadi, S. *Tetrahedron* **2009**, *65*, 7761; (b) Yoo, E. J.; Chang, S. *Org. Lett.* **2008**, *10*, 342; (c) Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Aldrichimica Acta* **2010**, *43*, 37.
6. Beletskaya, I. P.; Kustov, L. M. *Russ. Chem. Rev.* **2010**, *79*, 441.
7. (a) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259; (b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253.
8. (a) Kritchenkov, A. S.; Luzyanin, K. V.; Bokach, N. A.; Kuznetsov, M. L.; Gurzhiy, V. V.; Kukushkin, V. Yu. *Organometallics* **2013**, *1979*, 32; (b) Sabounchei, S. J.; Ahmadi, M. *Catal. Commun.* **2013**, *37*, 114; (c) Sabounchei, S. J.; Ahmadi, M.; Nasri, Z.; Shams, E.; Panahimehr, M. *Tetrahedron Lett.* **2013**, *54*, 4656; (d) Marziale, A. N.; Johannes, S.; Eppinger, J. *Tetrahedron Lett.* **2011**, *52*, 6355; (e) Bakherad, M.; Keivanloo, A.; Bahramian, B.; Hashemi, M. *Tetrahedron Lett.* **2009**, *50*, 1557.
9. (a) Yus, M.; Pastor, I. M. *Chem. Lett.* **2013**, *42*, 94; (b) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151.
10. (a) Dash, C.; Shaikh, M. M.; Ghosh, P. *Eur. J. Inorg. Chem.* **2009**, 1608; (b) Samantaray, M. K.; Shaikh, M. M.; Ghosh, P. *J. Organomet. Chem.* **2009**, *694*, 3477; (c) John, A.; Modak, S.; Madasu, M.; Katari, M.; Ghosh, P. *Polyhedron* **2013**, *64*, 20.
11. (a) Slaughter, L. G. M. *ACS Catal.* **2012**, *1802*, 2; (b) Boyarskiy, V. P.; Luzyanin, K. V.; Kukushkin, V. Yu. *Coord. Chem. Rev.* **2012**, *256*, 2029.
12. Dhudshia, B.; Thadani, A. N. *Chem. Commun.* **2006**, 668.
13. Khaibulova, T. S.; Boyarskaya, I. A.; Boyarskii, V. P. *Russ. J. Org. Chem.* **2013**, *49*, 360.
14. Miltsov, S.; Karavan, V.; Boyarsky, V.; Gomez-de Pedro, S.; Alonso-Chamarro, J.; Puyol, M. *Tetrahedron Lett.* **2013**, *54*, 1202.
15. Ryabukhin, D. S.; Sorokoumov, V. N.; Savicheva, E. A.; Boyarskiy, V. P.; Balova, I. A.; Vasilyev, A. V. *Tetrahedron Lett.* **2013**, *54*, 2369.
16. PdCl$_2${$\underline{C}$(N(H)-NPh$_2$)=N(H)Cy}(C$\equiv$NCy), complex **II**. PdCl$_2$(CyNC)$_2$ (200 mg, 0.50 mmol) and 1,1-diphenylhydrazine (97 mg, 0.54 mmol) were dissolved in 1,2-dichloroethane (10 mL) and refluxed at 84 °C for 4 h. The mixture was cooled and *n*-hexane (30 mL) was added. The white precipitate was filtered off, washed with Et$_2$O (2 × 30 mL) and dried under air. Yield 244 mg (85%). ^{1}H NMR (300 MHz, CDCl$_3$): 10.34 s (1H, C=NHN), 7.29–7.35 m (8H, H$_{Ar}$), 7.08–7.14 m (3H, 2H$_{Ar}$ + NH), 4.47–4.62 m (1H, CH), 3.98–4.05 m (1H, CH), 1.28–2.17 m (20H, 10CH$_2$). IR (KBr, selected bands, cm^{-1}): ν (C-H) 2933–2830, ν(C$\equiv$N) 2227, δ (N-C$_{carbene}$-N) 1560, ν(C$_{Ar}$–N) 1360. ESI$^+$-MS: found: 545.1421 [M–Cl]$^+$; calcd for C$_{26}$H$_{34}$ClN$_4$Pd: 545.1490. Elemental analysis: found, %: C 53.95; H 5.81; N 9.48; calcd for C$_{26}$H$_{34}$Cl$_2$N$_4$Pd, %: C 53.81; H 5.90; N 9.46.
17. Optimization of the reaction parameters. A vial was charged with 4-iodotoluene (0.1 mmol), phenylacetylene (0.11 mmol), biphenyl (0.03 mmol, internal standard), K$_2$CO$_3$ (0.15 mmol) and EtOH (2 mL). Complex **I** or **II** (an aliquot of an ethanol solution) was added. The mixture was stirred for the selected amount of time at room temperature or at reflux. The mixture was cooled and CH$_2$Cl$_2$–*n*-hexane (1:2, 2 mL) and H$_2$O (2 mL) were added. The organic layer was separated, filtered through a small amount of silica gel and analyzed by GC.
18. General procedure for the coupling of aryl halides with terminal acetylenes. A vial was charged with an aryl halide (0.1 mmol), an aryl or alkylacetylene (0.11 mmol), K$_2$CO$_3$ (0.15 mmol), palladium catalyst (0.05 mol %), and EtOH (2 mL). The mixture was refluxed with stirring for 2 h. After this time, the mixture was cooled and CH$_2$Cl$_2$–*n*-hexane (1:2, 2 mL) and H$_2$O (2 mL) were added. The organic layer was separated, filtered through a small amount of silica gel and analyzed by GC–MS. The solvent was removed and the residue weighed and analyzed by ^{1}H NMR.
19. 1,2-Diphenylacetylene.[8c] A 100 mL round-bottom flask was charged with iodobenzene (4.1 g, 20 mmol), phenylacetylene (2.2 g, 22 mmol), K$_2$CO$_3$ (4.2 g, 30 mmol), complex **I** (5.5 mg, 0.01 mmol), and EtOH (35 mL). The mixture was refluxed with stirring for 2 h. After this time, the mixture was cooled and diluted with H$_2$O. The organic compounds were extracted with *n*-hexane (2 × 50 mL), the solvent evaporated and the crude residue purified by column chromatography (*n*-hexane) to afford 3.0 g of pure diphenylacetylene (84%, white solid, mp = 60 °C).
20. 1-(4-Nitrophenyl)-2-phenylacetylene.[8c] A 100 mL round-bottom flask was charged with 4-nitroiodobenzene (4.9 g, 20 mmol), phenylacetylene (2.2 g, 22 mmol), K$_2$CO$_3$ (4.2 g, 30 mmol), complex **I** (5.5 mg, 0.01 mmol), and EtOH (35 mL). The mixture was refluxed with stirring for 2 h. After this time, the mixture was cooled and diluted with H$_2$O. The organic compounds were extracted with EtOAc (2 × 50 mL). The solvent was evaporated and the crude residue purified by recrystallization (MeOH) to afford 4.2 g of pure 1-(4-nitrophenyl)-2-phenylacetylene (95%, yellow solid, mp = 120 °C).