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Dimethylaminoalkyl chalcogenolate palladium(II) complexes as an efficient copper- and phosphine-free catalyst for Sonogashira reaction

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ABSTRACT

N,*N*-Dimethylaminoalkyl chalcogenolate Pd(II) complexes $[PdCl(E^{\cap}NMe_2)]_n$ has been investigated as a moisture/air-stable and robust catalyst for Sonogashira cross-coupling reaction in the absence of copper and phosphine ligand. The dimeric palladium(II) complex of selenium containing ligand shows the best catalytic activity as compared with monomeric and trimeric complexes. The variety of functional groups are tolerated under optimized catalytic systems and provide excellent yields of the products.

The Sonogashira cross-coupling[1] reaction is well-known as being one of the most important reactions for the construction of internal alkynes in the presence of phosphine ligand and copper reagent under inert conditions. The formation of internal alkynes using Sonogashira reaction finds wide applications in various areas such as synthesis of natural products, pharmaceuticals, and advanced materials.[2] Since its discovery by Sonogashira in 1975, a number of modifications have been made including ligand variation, Pd sources, solvents, and the amount of catalyst loading in order to promote the C–C bond formation. The most common catalytic systems used for this transformations which include $PdCl_2(PPh_3)_2$, $PdCl_2/PPh_3$, and $Pd(PPh_3)_4$ together with copper as the co-catalyst. On the other hand, the presence of copper can also induce a Glaser-type oxidative homocoupling of the terminal acetylene to yield a diyne,[3] which cannot be avoided in copper-mediated reactions. These diaryldiacetylene byproducts are generally difficult to separate from the desired products and in situ formed copper acetylide is a potentially explosive reagent. But limiting aspects of these reported methods are the use of air or moisture-sensitive phosphine ligands. Considering both environmental and economic issues, there is an urge to develop copper- and phosphine-free palladium catalysts. In the last decade, copper- and ligand-free palladium-catalyzed Sonogashira coupling reactions have been evolved as efficient routes for achieving these products.[4]

It is well known that the sulfur containing catalysts have been neglected for a long time due to rapid catalyst poisoning.[5] Recently a number of palladium complexes derived from chalcogenoether linkages (C–E–C; E=S or Se) have been shown to be efficient catalysts in C–C coupling reactions.[6] In Heck coupling reaction, the cyclopalladated selenium complex $[Pd(\mu\text{-}OAc)(C_6H_4CH_2SeBu^t)_2]$ has shown excellent activity than its sulfur counterpart as well as Herrmann–Beller palladacycle.[7] The palladium chalcogenolate complexes may offer an attractive way for C–C bond forming reactions owing to a strong Pd-ER linkage.[8] However their utility as a catalyst in C–C bond forming reactions remained relatively unexplored due to their tendency to polymerize which leads to insolubility/sparing solubility in organic solvents.[6]

In this Letter we have explored the catalytic activity of palladium containing dimeric and trimeric complexes of hemi-labile *N*,*N*-dimethyl alkyl chalcogenolate ligands. The dimeric or trimeric structures comprise of two or three palladium atoms bridged through chalcogen atoms of the chelating chalcogenolate ligand forming a four- or six-membered Pd_2E_2 or Pd_3E_3 ring, respectively.[9] The chloro-ligand acts in a monodentate fashion. These complexes have excellent air/moisture and thermal stability. In view of the above perspective it was considered useful to examine their catalytic activity in Sonogashira reaction. Herein we report a phosphine- and copper-free Sonogashira reaction catalyzed by dimethylaminoalkyl chalcogenolate complexes of palladium(II)

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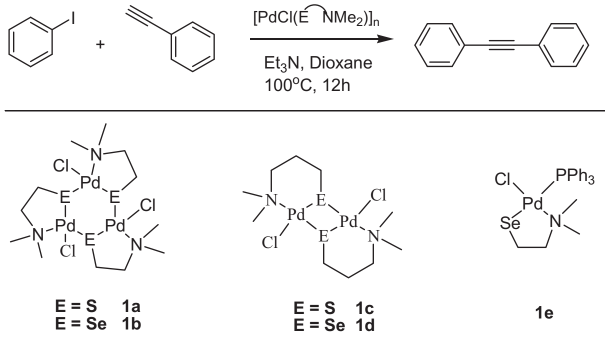


Scheme 1. Chalcogenolate ligated Pd(II) complexes $[PdCl(E^{\frown}NMe_2)]_n$ used as catalysts in Sonogashira reaction.

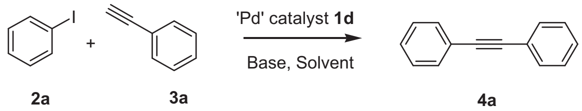
Table 1
Effect of catalyst screening and loading on Sonogashira reaction[a]

Entry	‘Pd’ catalyst	‘Pd’ (mol %)	Yield[b] (%)
1	$[PdCl(SCH_2CH_2NMe_2)]_3$ **1a**	4	56
2	$[PdCl(SeCH_2CH_2NMe_2)]_3$ **1b**	4	64
3	$[PdCl(SCH_2CH_2CH_2NMe_2)]_2$ **1c**	4	78
4	$[PdCl(SeCH_2CH_2CH_2NMe_2)]_2$ **1d**	4	97
5	$[PdCl(SeCH_2CH_2NMe_2)(PPh_3)]$ **1e**	4	76
6	$[PdCl(SeCH_2CH_2CH_2NMe_2)]_2$ **1d**	3	96
7	$[PdCl(SeCH_2CH_2CH_2NMe_2)]_2$ **1d**	2	84

[a] Reaction conditions: Iodobenzene (1 mmol), phenyl acetylene (1.2 mmol), triethyl amine (2 mmol), solvent-1,4-dioxane (4 ml), 100 °C, 12 h.

[b] GC yield.

Table 2
Optimization of reaction parameters[a]



Entry	Solvent	Base	Temp (°C)	Time (h)	Yield[b] (%)
Effect of solvent:					
1	Toluene	Et_3N	100	12	48
2	DMF	Et_3N	100	12	26
3	DMSO	Et_3N	100	12	Trace
4	Dioxane	Et_3N	100	12	96
Effect of base:					
5	Dioxane	K_2CO_3	100	12	76
6	Dioxane	$NaHCO_3$	100	12	82
7	Dioxane	K_3PO_4	100	12	80
8	Dioxane	^{t}BuOK	100	12	68
9	Dioxane	Pyrolidine	100	12	90
10[c]	Dioxane	Et_3N	100	12	78
Effect of temperature and time:					
11	Dioxane	Et_3N	90	12	82
12	Dioxane	Et_3N	90	15	86
13	Dioxane	Et_3N	100	10	88
14	Dioxane	Et_3N	110	12	96

[a] Reaction conditions: Iodobenzene (1 mmol), phenyl acetylene (1.2 mmol), base (2 mmol), ‘Pd’ catalyst **1d** (3 mol %).

[b] GC yield.

[c] Base (1 mmol).

which gives moderate to good yields under aerobic conditions (Scheme 1).

At the onset of the research, we made a conscious effort to develop a catalytic system that would address the limitations of the previously reported palladium catalyzed Sonogashira reaction. During preliminary studies, iodobenzene **2a** was reacted with phenyl acetylene **3a** and used as the model system. A series of experiments were performed to optimize various reaction parameters, such as the nature of the catalyst, effect of catalyst loading, base, solvent, temperature, and time. Initially we screened various *N*,*N*-dimethylalkyl chalcogenolate ligands chelated palladium catalyst such as $[PdCl(SCH_2CH_2NMe_2)]_3$ **1a**, $[PdCl(SeCH_2CH_2NMe_2)]_3$ **1b**, $[PdCl(SCH_2CH_2CH_2NMe_2)]_2$ **1c**, $[PdCl(SeCH_2CH_2CH_2NMe_2)]_2$ **1d**, and $[PdCl(SeCH_2CH_2NMe_2)(PPh_3)]$ **1e** (Table 1, entries 1–5) for the present Sonogashira protocol. The complex **1d** was the best catalyst giving excellent yield of the desired product **4a** (Table 1, entry 4). We further studied catalyst loading ranging from 2 to 4 mol %, wherein increasing catalyst concentration from 2 to 3 mol % showed increase in the yield of the desired product and further increase in catalyst concentration has no profound effect on the yield of the product (Table 1, entries 4, 6 and 7).

As the nature of the base is assumed to have a marked impact on the overall process the effect of different bases such as, K_2CO_3, K_3PO_4, $NaHCO_3$, ^{t}BuOK, pyrolidine, and Et_3N were examined. The best results were obtained with Et_3N affording **4a** in excellent yield (Table 2, entries 4–10). We studied the effect of different solvents in the standard reaction. It was found that 1,4-dioxane was a better solvent to yield the desired product in good yield (Table 2, entries 1–4). While studying the effect of temperature, the yield of the desired product increased with increasing the reaction temperature from 90 °C to 100 °C. The latter appears to be the optimum temperature for the reaction. The reaction time is also optimized and maximum yield of the desired product was obtained after 12 h (Table 2, entries 4, 11–14).

Having optimized the reaction conditions in hand, we next set out to explore the substrate scope of **1d** catalyzed Sonogashira reaction.[10]

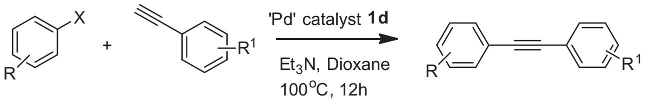
Various aryl halides containing different functional groups were investigated (Table 3). We observed that electron donating (Table 3, entries 2–4) as well as electron withdrawing (Table 3, entries 5–9) substituents provided remarkable yield of products. Gratifyingly this protocol tolerated a variety of common functional groups such as alkyl, ether, halogen, and nitro groups regardless of the positions. We also found that the heteroaryl halides also gave moderate to good yields of the desired products (Table 3, entries 10–14). Next we attempted to widen the scope of chalcogenolate Pd catalyst for aryl bromide and aryl chloride; among these, aryl bromides were well tolerated (Table 3, entries 1, 2 and 8) and gave good yields. It should be noted that the coupling reactions of the aryl chlorides also took place under similar copper- and phosphine-free conditions, after increasing the catalyst loading up to 5 mol % and increasing the reaction temperature to 120 °C for 15 h, though the reactivity was much lower than their iodo and bromo counterparts (Table 3, entries 1 and 8).

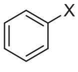
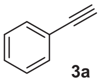
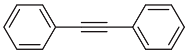
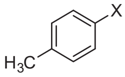
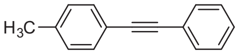
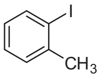
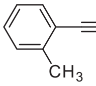
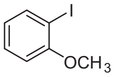
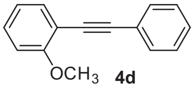
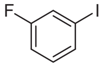
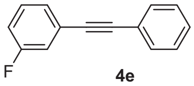
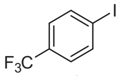
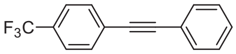
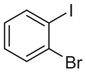
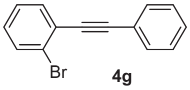
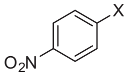
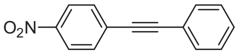
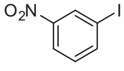
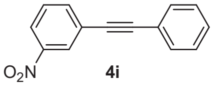
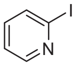
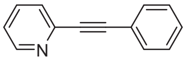
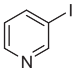
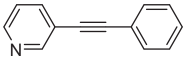
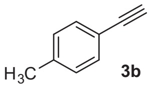
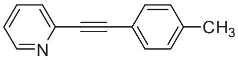
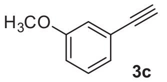
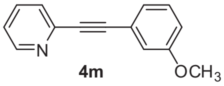
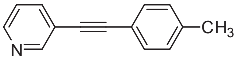
A small library of heteroaryl halides and substituted aryl acetylenes was tested and the provided corresponding products were obtained in good yields (Table 3, entries 12–14).

In conclusion, we have developed a protocol for the Sonogashira coupling using *N*,*N*-dimethylaminoalkyl chalcogenolate palladium(II) complexes as catalyst to give various biarylacetylene derivatives. The reactions work under copper- and phosphine-free conditions in air. It was found that the catalyst exhibited good activity and selectivity for the Sonogashira reaction.

The activity of chalcogenolate Pd-complexes, $[PdCl(E^{\frown}NMe_2)]_n$ is influenced by the nature and number of $(E^{\frown}N)$ group and follows

Table 3
Substrate study for Sonogashira reaction[a]



Entry	Aryl halide	Alkyne	Product	Yield (%)[b]
1	 **2a**	 **3a**	 **4a**	X = I, 92 Br, 58 Cl, 14[c]
2	 **2b**	**3a**	 **4b**	X = I, 89 Br, 48
3	 **2c**	**3a**	 **4c**	78
4	 **2d**	**3a**	 **4d**	76
5	 **2e**	**3a**	 **4e**	82
6	 **2f**	**3a**	 **4f**	88
7	 **2g**	**3a**	 **4g**	67
8	 **2h**	**3a**	 **4h**	X = I, 93 Br, 64 Cl, 18[c]
9	 **2i**	**3a**	 **4i**	81
10	 **2j**	**3a**	 **4j**	80
11	 **2k**	**3a**	 **4k**	78
12	**2j**	 **3b**	 **4l**	76
13	**2j**	 **3c**	 **4m**	63
14	**2k**	3b	 **4n**	74

[a] Reaction conditions: Aryl halide (1 mmol), aryl acetelyne (1.2 mmol), Pd catalyst **1d** (3 mol %), triethyl amine (2 mmol), 100 °C, 12 h.
[b] Isolated yield.
[c] Reaction conditions for chloro-substrate 120 °C, 15 h.

the trend: E = Se > S and dimeric > trimeric in Sonogashira cross coupling reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.004.

References and notes

1. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470; (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46–49.
2. For application of Sonogashira reaction: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922; (b) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173; (c) Doucet, H.; Hierso, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834–871; (d) Odlo, K.; Klaveness, J.; Rongved, P.; Hansen, T. V. *Tetrahedron Lett.* **2006**, *47*, 1101–1103; (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489; (f) Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem.* **2005**, *70*, 10615–10618.
3. (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424; (b) Arques, A.; Auñon, D.; Molina, P. *Tetrahedron Lett.* **2004**, *45*, 4337–4340; (c) Consorti, C. S.; Flores, F. R.; Rominger, F.; Dupont, J. *Adv. Synth. Catal.* **2006**, *348*, 133–141; (d) Likhar, P. R.; Subhas, M. S.; Roy, M.; Roy, S.; Kantam, M. L. *Helv. Chim. Acta* **2008**, *91*, 259–264; (e) Sawant, D. N.; Tambade, P. J.; Wagh, Y. S.; Bhanage, B. M. *Tetrahedron Lett.* **2010**, *51*, 2758–2761; (f) Wang, X.; Qin, W.; Kakusawa, N.; Yasuike, S.; Kurita, J. *Tetrahedron Lett.* **2009**, *50*, 6293–6297; (g) Yang, F.; Cui, X.; Li, Y.; Zhang, J.; Ren, G.; Wu, Y. *Tetrahedron* **2007**, *63*, 1963–1969.
4. (a) Gladysz, J. A.; Curran, D. P.; Horváth, Y. I. T. *Handbook of Fluorous Chemistry*; Willey: New York, 2004; pp 175–365. Chapter 10; (b) Aggarwarl, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183–7189.
5. Dunleavy, J. K. *Platinum Met. Rev.* **2006**, *50*, 110.
6. (a) Kostas, I. D.; Steele, B. R.; Terzis, A.; Amosova, S. V.; Martynov, A. V.; Makhaeva, N. A. *Eur. J. Inorg. Chem.* **2006**, 2642–2646; (b) Bai, S. Q.; Hor, T. S. A. *Chem. Commun.* **2008**, 3172–3174; (c) Wang, H.; Zhong, R.; Guo, X. Q.; Feng, X. Y.; Hou, X. F. *Eur. J. Inorg. Chem.* **2010**, 174–178; (d) Yuan, D.; Huynh, H. V. *Organometallics* **2010**, *29*, 6020–6027; (e) Rao, G. K.; Kumar, A.; Ahmed, J.; Singh, A. K. *Chem. Commun.* **2010**, 5954–5956; (f) Das, D.; Singh, P.; Singh, M.; Singh, A. K. *Dalton Trans.* **2010**, *39*, 10876–10882; (g) Rao, G. K.; Kumar, A.; Kumar, B.; Kumar, D.; Singh, A. K. *Dalton Trans.* **2012**, *41*, 1931–1937; (h) Chakraborty, T.; Srivastava, K.; Singh, H. B.; Butcher, R. J. *J. Organomet. Chem.* **2011**, *696*, 2559–2564.
7. (a) Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *18*, 2881–2884; (b) Yao, Q.; Kinney, E. P.; Zheng, C. *Org. Lett.* **2004**, *6*, 2997–2999.
8. (a) Paluru, D. K.; Dey, S.; Wadawale, A.; Jain, V. K. *J. Organomet. Chem.* **2013**, *728*, 52–56; (b) Vivekananda, K. V.; Dey, S.; Wadawale, A.; Bhuvanesh, N.; Jain, V. K. *Dalton Trans.* **2013**, *42*, 14158–14167.
9. (a) Dey, S.; Jain, V. K.; Chaudhury, S.; Knoedler, A.; Lissner, F.; Kaim, W. *J. Chem. Soc., Dalton Trans.* **2001**, 723–728; (b) Dey, S.; Jain, V. K.; Varghese, B.; Schurr, T.; Niemeyer, M.; Kaim, W.; Butcher, R. J. *Inorg. Chim. Acta* **2006**, *359*, 1449–1457.
10. *Typical experimental procedure:* In an oven dried 25 ml Schlenk tube was added a mixture of aryl halide (1 mmol), arylacetylene (1.2 mmol), Pd catalyst **1d** (3 mol %), and triethyl amine (2 mmol) in 4 ml of dioxane. The reaction mixture was heated in an oil bath at 100 °C for 12 h with continuous stirring. After 12 h the reaction mixture was cooled to room temperature and the product was extracted into ethyl acetate (3×10 ml). After drying over anhydrous Na_2SO_4, the combined ethyl acetate layer was concentrated by rotary evaporation. All the prepared compounds were characterized by by GC–MS and NMR techniques.