Discovery of A Novel Palladium Catalyst for the Preparation of Enynes with a Copper- and Ligand-Free Sonogashira Reaction

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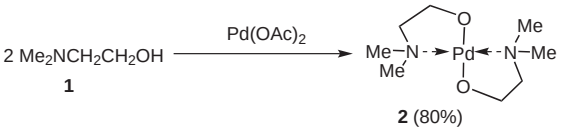
Abstract: A new palladium(II) complex based on *N*,*N*-dimethylethanolamine, (*SP*-4-1′)-bis[*N*,*N*-dimethylaminoethoxy-κ*N*,*O*]palladium(II) which coordinates with two moles of AcOH, has been synthesized. The structure of the complex has been established by X-ray diffraction analysis. Using this complex as a catalyst, a series of conjugated enynes were successfully synthesized by Sonogashira cross-coupling reaction in the absence of co-catalyst CuX and any ligand at room temperature during 20 hours affording the corresponding products in moderate to excellent yields. The optimized catalytic systems are tolerant in the presence of a broad variety of functional groups in the substrates. The catalytic system was found to be ineffective for vinyl chloride. Moreover, it was found that (*Z*)-β-bromostyrene reacts with terminal alkynes with retention of the steric configuration and the transformation of most of the *Z*-isomer did not occur in this reaction.

Key words: *N*,*N*-dimethylethanolamine, copper-free, ligand-free, Sonogashira reaction, enyne, β-bromostyrene, stereochemistry

The palladium-catalyzed Sonogashira reaction is an important method in organic synthesis.[1] In particular, enynes – the main products of this reaction – can be used to synthesize heterocyclic compounds[2] and conjugated alkenes.[3] In addition, the conjugated enyne is a structure of high interest owing to its presence in many natural products and biologically active compounds.[4] For example, this structure is present in *trans*-kumausyne, calicheamycin and terbinafine.[5] The Sonogashira coupling reaction usually requires co-catalyst CuX(I) and other activator.[6] Moreover, there have been a large number of publications concerning Sonogashira reaction catalyzed by other metal complexes, e.g. Ni,[7] Cu(I)[8] and Cu(II)[9] complexes, but the reactions usually proceed under severe reaction conditions or with phosphorus-containing additives.[10] In the last decade, copper- and ligand-free palladium-catalyzed Sonogashira coupling reaction has been a novel independent research direction.Therefore, design and synthesis of novel and active catalysts are at the core of our research. Recently, only one paper has reported that alkoxypalladium complex $[(HOCH_2CH_2)_2NCH_2CH_2O]_2Pd$ has been used as an effective catalyst in Suzuki[11] reaction. But there is no report concerning the catalytic activity in the reaction of β-bromostyrene with terminal alkynes. In our continuous research[12] on this reaction, we intend to study the preparation method for alkoxypalladium complex based on *N*,*N*-dimethylethanolamine, X-ray diffraction analysis of bis[*N*,*N*-dimethylaminoethoxy-κ*N*,*O*]palladium(II) (**2**), and its catalytic activities in copper- and ligand-free Sonogashira reaction for preparation of the enynes.

The di(aminoalkoxy)palladium complex **2** can be obtained with the reaction between $Pd(OAc)_2$ and *N*,*N*-dimethylethanolamine by elimination of two equivalents of acetic acid to give a good yield (Scheme 1).



Scheme 1 Synthesis of palladium complex **2**

Complex **2** was adequately characterized by NMR spectroscopy, mass spectrometry, and elemental analysis. NMR data revealed that in spite of the presence of two moles of AcOH, the Pd–O bonds did not cleave even in a solution. The structure of **2** in crystalline state was established by X-ray diffraction analysis (Figure 1).[13]

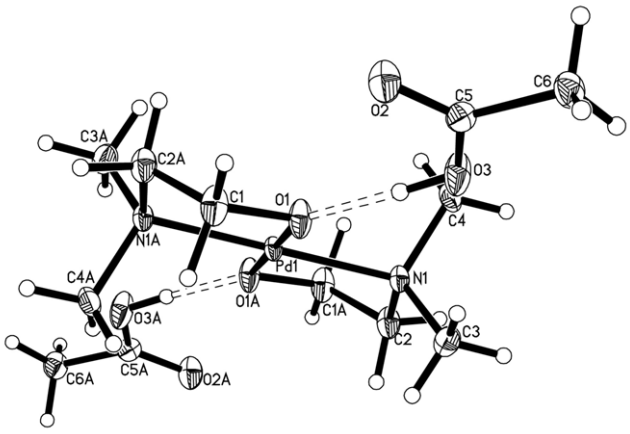


Figure 1 Molecular structure of complex **2**. Displacement ellipsoids are shown at the 50% probability level. Hydrogen bonds are depicted as dashed open lines.

We examined the catalytic activity of the complex 2 in the modified Sonogashira reaction between (*E*/*Z*)-β-bromostyrene **3a** (*E*/*Z* = 85:15) and phenylacetylene (**4a**; Table

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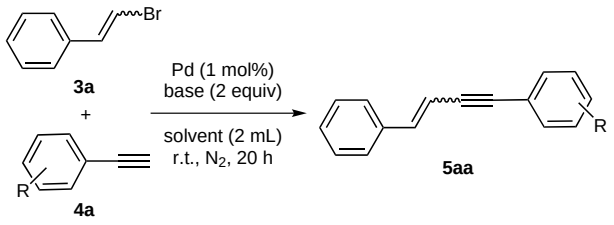
1). The results indicate that the reaction of **3a** with **4a** proceeds smoothly at room temperature in the presence of Cs_2CO_3 in polar solvents DMF or DMSO (Table 1, entries 4 and 7). An increase in the polarity of the aprotic solvent resulted in an impressive increase of the yield (Table 1, entries 7–10). When using the relative strong or weak base in this reaction, the desired product **5aa** was only obtained in middle yield (Table 1, entries 1–3, 5 and 6). In addition, the obtained product **5aa** was obtained as a mixture of (*E*)- and (*Z*)-1,4-diphenylbut-1-en-3-yne (*E*/*Z* = 93:7). The result indicates that a part of the *Z*-isomeric product transformed into the *E*-isomer.

Table 1 Screening Bases and Solvents for the Coupling of (*E*)-β-Bromostyrene and Phenylacetylene[a]

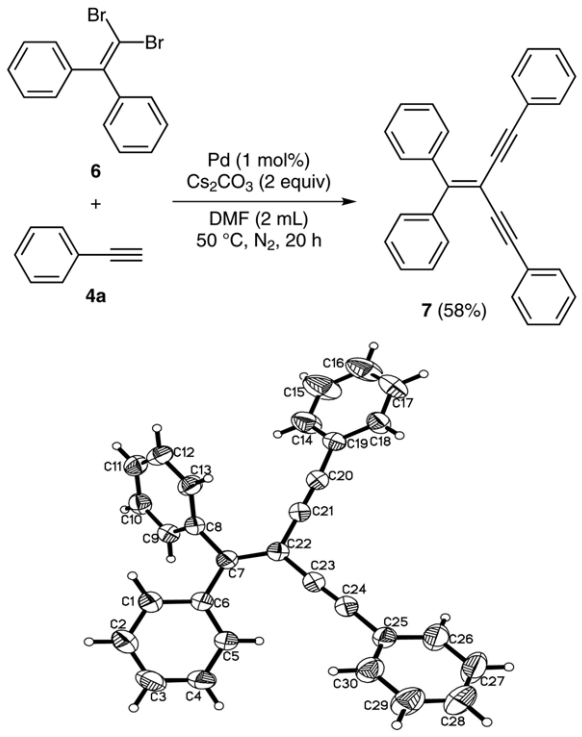


Entry	Base	Solvent	Yield (%)[b]
1	Et_3N	DMF	57
2	K_2CO_3	DMF	69
3	KOAc	DMF	47
4	Cs_2CO_3	DMF	99
5	KOH	DMF	77
6	K_3PO_4	DMF	76
7	Cs_2CO_3	DMSO	99
8	Cs_2CO_3	THF	88
9	Cs_2CO_3	1,4-dioxane	68
10	Cs_2CO_3	toluene	11

[a] Reaction conditions: (*E*)-β-bromostyrene (1 mmol), phenylacetylene (1.5 mmol), complex **2** (1 mol%), base (2 mmol) in solvent (2 mL) at 25 °C for 20 h, N_2.
[b] GC yield.

On the basis of the abovementioned results, the scope and limitation of the coupling reaction were explored by using various bromostyrenes and terminal alkynes, and the results are summarized in Table 2. It was found that this coupling reaction can be applied to all aryl terminal alkynes, affording the corresponding products in moderate to excellent yields. Generally, electron-donating terminal alkynes give higher yields (Table 2, entries 1 and 2). Compared to phenylacetylene, the terminal alkyne **4f** bearing an electron-withdrawing group *o*-CF_3 gave a considerably lower yield owing to the steric hindrance (Table 2, entry 6). But this catalytic system was found to be ineffective for vinyl chloride (Table 2, entry 11). Besides that, we found that the functional group of terminal alkynes did not have an influence on the steric ratio of their corresponding products (Table 2, entries 1–6). This ratio remained constant (*E*/*Z* = 97:3). In addition, it was found that (*Z*)-β-bromostyrene (*Z*/*E* = 86:14)[14] could react smoothly with terminal alkynes, and the product yields were higher than those of the analogous *E*-isomers (Table 2, entries 9 and 10). The transformation of some of the *Z*-isomeric product to *E*-isomer was also obtained from the reaction of (*Z*)-bromostyrene with terminal alkynes (Table 2, entries 9 and 10). The same catalytic system also gives excellent results in case of aliphatic alkyne **4h** (Table 2, entry 8). However, in the presence of a proton-donating group in a substrate (propargyl-type alcohol **4g**), the examined catalyst lost the catalytic ability (Table 2, entry 7). In addition, this catalyst could be used in the reaction of aliphatic vinyl bromide with phenylacetylene, but the product yield was only 28% (Table 2, entry 12).

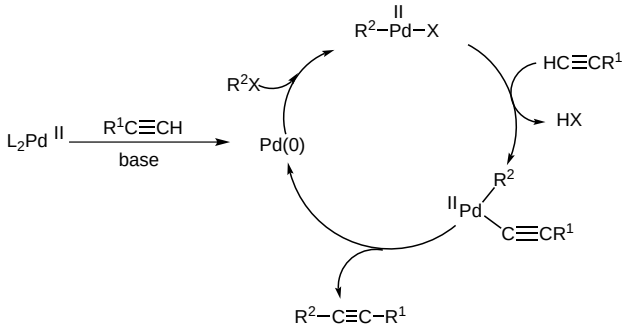
In addition, we examined the reaction of 1,1-dibromo-2,2-diphenylethene (**6**)[15] with phenylacetylene (**4a**). While at the room temperature there was no sign of the reaction, at 50 °C the expected product **7** was formed and could be isolated in a 58% yield. The molecular structure of the compound **7** was established by X-ray diffraction analysis (Scheme 2).[16]



Scheme 2 Molecular structure of compound **7**

We surmise that the mechanism of the complex **2** catalyzed Sonogashira reaction is similar to that of the reaction using $Pd(OAc)_2$ as a catalyst. The proposed mechanism is shown in Scheme 3. In the process, we found that under reaction conditions using 1 mol% Pd $(OAc)_2$ as a catalyst and 4 mol% $Me_2NCH_2CH_2OH$ as a li-

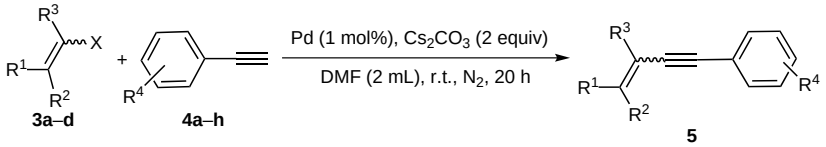
gand, the yield reduced to 90%. After $Pd(OAc)_2$ is reduced to Pd(0), Pd(0) cannot easily coordinate with the ligand, which results in the deactivation of the Pd(0) species. Thus, the above results demonstrated that the complex **2** was an efficient catalyst for the coupling reaction.



Scheme 3 Plausible reaction mechanism

In conclusion, we have synthesized a new cyclopalladated complex based on *N*,*N*-dimethylethanolamine.[17] The structure of the obtained complex was studied by X-ray crystallography. As an effective catalyst it can be used to prepare conjugated enynes by Sonogashira cross-coupling reaction in the absence of co-catalyst CuX and any ligand at room temperature in 20 hours to give the corresponding products in moderate to excellent yields.[18] Moreover, it was found that (*Z*)-β-bromostyrene reacts with terminal alkynes with retention of the steric configuration. The major part of the *Z*-isomer did not transform to the *E*-isomer in this reaction.

Table 2 Modified Sonogashira Cross-Coupling Reaction of Halogenated Alkene with Terminal Alkynes[a]



3a–d **4a–h** **5**

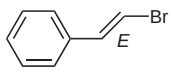
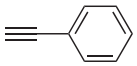
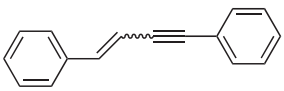
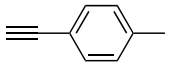
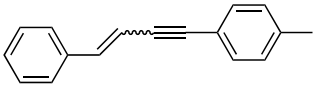
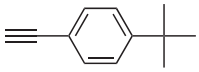
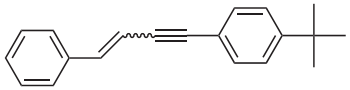
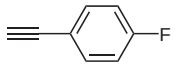
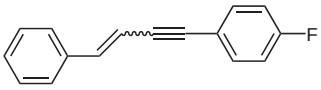
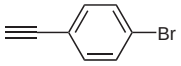
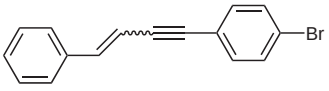
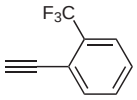
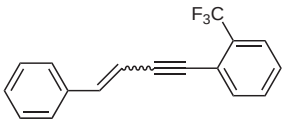
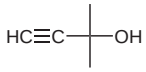
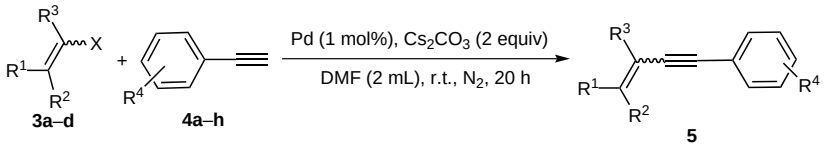
Entry	Halogenated alkene	Terminal alkyne	Product	Yield (%)[b]
1	 **3a**	 **4a**	 **5aa**	97 (*E*/*Z* = 93:7)
2	**3a**	 **4b**	 **5ab**	93 (*E*/*Z* = 93:7)
3	**3a**	 **4c**	 **5ac**	40 (*E*/*Z* = 93:7)
4	**3a**	 **4d**	 **5ad**	92 (*E*/*Z* = 93:7)
5	**3a**	 **4e**	 **5ae**	77 (*E*/*Z* = 93:7)
6	**3a**	 **4f**	 **5af**	12 (*E*/*Z* = 93:7)
7	**3a**	 **4g**	–	NR[c]

Table 2 Modified Sonogashira Cross-Coupling Reaction of Halogenated Alkene with Terminal Alkynes[a] (continued)



Entry	Halogenated alkene	Terminal alkyne	Product	Yield (%)[b]
8	**3a**	$HC{\equiv}C{-}(CH_2)_4Me$ **4h**	$(CH_2)_4Me$ **5ah**	95 (*E*)
9	Z, Br **3b**	**4a**	**5ba**	97 (*E*/*Z* = 22:78)
10	**3b**	**4b**	**5bb**	97 (*E*/*Z* = 19:81)
11	Cl, CHO **3c**	**4a**	–	NR[c]
12	Br **3d**	**4a**	H **5da**	28

[a] Reaction conditions: halogenated alkene (1 mmol), terminal alkyne (1.5 mmol), complex **2** (1 mol%), Cs_2CO_3 (2 mmol) in DMF (2 mL) at 25 °C for 20 h, N_2.
[b] Isolation yield containing *E*- and *Z*-isomers based on **3**.
[c] No reaction.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) CCDC 869934 contains the supplementary crystallographic data of compound **2** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.
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(16) CCDC 869935 contains the supplementary crystallographic data of compound **7** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.
(17) **Synthesis of $(Me_2NCH_2CH_2O)_2Pd·2AcOH$**: A solution of $Me_2NCH_2CH_2OH$ (0.24 g, 2.68 mmol) in toluene (10 mL) was add to a stirred solution of $Pd(OAc)_2$ (0.3 g, 1.34 mmol) in toluene (10 mL), and the mixture was stirred at r.t. After 2 d all volatiles were removed under reduced pressure to give **2** as a yellow crystalline solid. Yield: 0.54 g (80%); mp 93–95 °C. ^{1}H NMR (400 MHz, C_6D_6): δ = 1.92–2.00 (m, 4 H, CH_2N), 2.01 (s, 6 H, CH_3COOH), 2.17 (s, 12 H, CH_3N), 3.37–3.75 (m, 4 H, CH_2O), 11.00–11.15 (br s, 2 H, CH_3COOH). ^{13}C NMR (100 MHz, C_6H_6): δ = 22.08 (CH_3COOH), 49.63 (CH_3N), 63.87 (CH_2N), 68.50 (CH_2O), 174.27 (C=O). Anal. Calcd for $C_8H_{20}N_2O_2Pd·2AcOH$: C, 35.78; H, 7.01; N, 6.96. Found: C, 35.20; H, 6.79; N, 6.88.
(18) **Palladium-Catalyzed Sonogashira Reaction of β-Bromostyrene and Terminal Acetylene (Table 1 and Table 2)**: Table 2, entry 2, is given as an example: β-Bromostyrene (183 mg, 1.0 mmol), *p*-tolyacetylene (174 mg, 1.5 mmol), alkoxypalladium complex (4 mg, 1 mol%), Cs_2CO_3 (652 mg, 2.0 mmol) and DMF (2 mL) were added in Schlenk flask under nitrogen atmosphere. The reaction mixture was stirred at r.t. for 20 h. Then H_2O (50 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over anhyd Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by TLC using petroleum ether as an eluent to give the pure diphenyl acetylene. Yield: 93%; white solid; mp 75–76 °C (lit.[19] 75–76 °C). For *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, Me), 6.41 (d, *J* = 16.1 Hz, 1 H, CH=), 7.04 (d, *J* = 16.1 Hz, 1 H, CH=), 7.16 (d, *J* = 7.8 Hz, 2 H), 7.29–7.46 (2 × m, 7 H, ArH). For *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, Me), 5.93 (d, *J* = 12.2 Hz, 1 H, CH=), 6.70 (d, *J* = 11.7 Hz, 1 H, CH=), 7.29–7.46 (2 × m, 7 H, ArH), 7.94 (d, *J* = 7.3 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.49 (Me), 88.24, 91.97 (C≡ group), 108.31, 120.32, 126.25, 128.50, 128.71, 129.11, 131.40, 136.41, 138.34, 140.85 (CH=CH, ArC). Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.47; H, 6.40.
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