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A Catalytic Reaction of Alkynes via Multiple-Site Functionalization

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The study of transition metal-catalyzed addition reactions of alkenes and alkynes, particularly those involving amino functionalities, has been an important topic in organic chemistry because these reactions can convert common unsaturated petroleum products into chemically and biologically important precursors.[1−4] Unfortunately, a multiple-site activation of alkynes by using amino and halogen moieties has not been discovered thus far. Over the past few years, we have been actively involved in the development of new aminohalogenation and diamination reactions of alkenes. These reactions have resulted in versatile building blocks such as haloamines,[5] α,β-differentiated diamines and imidazolines.[6] In this communication, we report our preliminary results on the regioselective activation of nonsymmetric alkynes and simultaneous halogenation on their adjacent alkyl position (Scheme 1).[7−11] To the best of our knowledge, this reaction serves as the first example of a three-site activation of alkynes with important amine/halogen functionalities.

The reaction takes place only in nitrile-containing solvents such as acetonitrile and propionitrile. Several palladium catalysts such as $Pd(PPh_3)_4$, $Pd(dba)_2$, and $Pd(OAc)_2$ were found to be effective for this catalytic reaction.[12,13] Among these catalysts, palladium acetate gave the best yields. It is crucial to generate palladium (0) prior to the reaction by mixing the palladium acetate with the alkyne in acetonitrile over 1 h. During this period the reaction mixture turned black, which indicates the in situ reduction of palladium (II) to palladium (0). However, other palladium (II) salts such as $PdCl_2$ and $Pd(CF_3COO)_2$ failed to give any products, which is probably due to the fact that they cannot be easily reduced to the palladium (0) state under the current condition.

The reaction was carried out by stirring the pretreated solution containing the catalyst and alkyne with *N*,*N*-dichlorobenzenesulfonamide at 82 °C over a period of 24 h. The crude product was subjected to purification via flash column chromatography without quenching. Among the three halogen/nitrogen sources we examined, *N*,*N*-dichlorobenzenesulfonamide, *N*,*N*-dichloro-*p*-toluenesulfonamide, and *N*,*N*-dibromo-*p*-toluenesulfonamide, the first one gave the best yields. A slight excess amount of *N*,*N*-dichlorobenzenesulfonamide (1.1 equiv) was necessary to achieve optimal yields. Interestingly, increasing the amount of halogen/nitrogen source led to lower yields due to the *N*-chlorination of the product which decomposes on silica gel during column chromatography.

The structure of the product (**1** of Table 1) was unambiguously determined by X-ray structural analysis (Figure 1). The crystals were obtained by slow evaporation of a methanol solution of the pure product, **1**. The results of this new reaction are listed in Table 1. A good scope was observed for the phenyl-substituted aromatic propynes we examined except for entry 7 where a low yield was obtained. Different substituents on aromatic rings have no effect on both regio- and stereoselectivity. Two terminal extended substrates, 1-phenyl-1-hexyne and 1-(4-nitrophenyl)-1-hexyne, have been examined. Interestingly, the reaction was found to stop at the stage of 1,2-addition adducts which are also very useful in organic synthesis. Much work is needed to search for new conditions, catalysts, and halogen/nitrogen sources to improve yields and the scope of this multiple-site activation.

Scheme 1

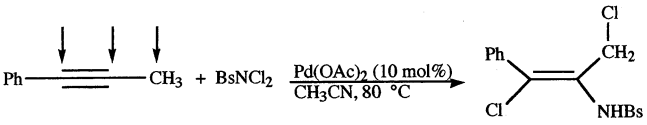
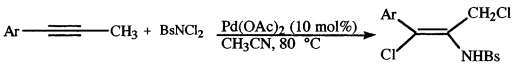


Table 1. Results of the Regio- and Stereoselective Reaction of $BsNCl_2$ with arylalkynes[a]



entry	substrates	product[b]		mp (°C)	yield (%)[c]
1	Ph—≡—CH_3	Ph, CH_2Cl, Cl, NHBs	**1**[d]	117-120	61
2	4-BrPh—≡—CH_3	4-BrPh, CH_2Cl, Cl, NHBs	**2**	145-147	70
3	4-FPh—≡—CH_3	4-FPh, CH_2Cl, Cl, NHBs	**3**	99-101	66
4	4-MePh—≡—CH_3	4-MePh, CH_2Cl, Cl, NHBs	**4**	oil	53
5	4-C_5H_{11}Ph—≡—CH_3	4-C_5H_{11}Ph, CH_2Cl, Cl, NHBs	**5**	67-70	59
6	3-ClPh—≡—CH_3	3-ClPh, CH_2Cl, Cl, NHBs	**6**	118-120	55
7	3-CF_3Ph—≡—CH_3	3-CF_3Ph, CH_2Cl, Cl, NHBs	**7**	99-100	37

[a] Into a dry vial was added (4-bromophenyl)-1-propyne (97.5 mg, 0.50 mmol) and freshly distilled acetonitrile (0.80 mL). The mixture was stirred and then loaded with palladium acetate (11.2 mg, 10 mol %) to give a homogeneous brownish solution. This solution was stirred at room temperature for 1 h until the brownish color changed to black before *N*,*N*-dichlorobenzenesulfonamide (124 mg, 0.55 mmol, 1.1 equiv) was added. The resulting mixture was heated to 80−82 °C and stirred at this temperature for 24 h. It was then cooled to room temperature, and the solvent was evaporated at reduced pressure. The crude residue was directly purified by flash column chromatography using ethyl acetate in hexane as the eluent (hexane/EtOAc, 4:1) to give product **2** as a white solid (148 mg, 70% yield). [b] No regio- and stereominor isomers were detected. [c] Yields after purification via column chromatography. [d] X-ray structure of the product was obtained (Figure 1).

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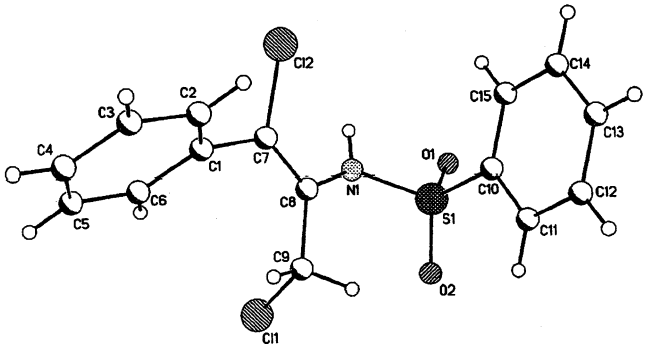
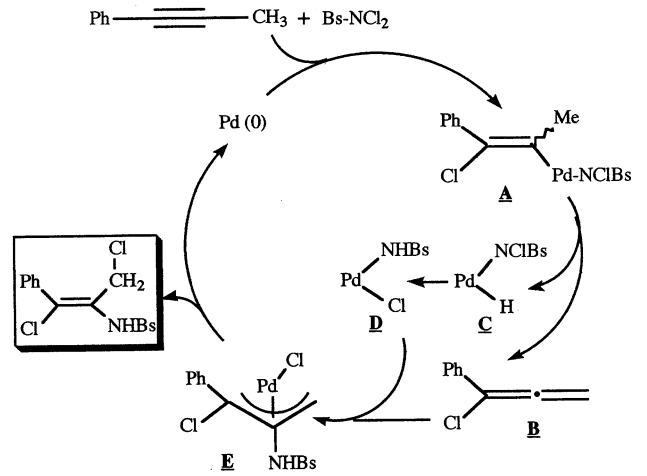


Figure 1. X-ray structure of product **1**.

Scheme 2



Aryl alkyne substrates (entries 2−7 of Table 1) were synthesized by the Sonogashira coupling[14] between propyne gas and aromatic iodides or bromides in piperidine or triethylamine in the presence of catalytic amounts of $Pd(PPh_3)_4$ (1.0 mol %), triphenylphosphine (1.0 mol %), and copper (I) iodide (1.0 mol %). With aromatic iodides, the reaction proceeds smoothly at room temperature, but with bromides the optimal temperature was found to be at 70 °C. For this preparation, the addition of triphenylphosphine was important to ensure that the palladium does not precipitate out of the reaction mixture.

The mechanism hypothesis is described in Scheme 2 which is inspired by similar mechanisms proposed by Trost and Yamamoto.[7,15] The first step involves the formation of β-halovinyl palladium species (**A**). This intermediate could be attributed to the reaction of alkyne and *N*-chloro,*N*-(chloropalladium)benzenesulfonamide or to the oxidative addition of palladium (0) into an initially formed β-chloroenamine by the reaction of the alkyne with *N*,*N*-dichlorobenzenesulfonamide. Intermediate (**A**) undergoes β-hydride elimination to give the following two species, an arylallene (**B**) and Pd(H)NClBs (**C**). Intermediate (**C**) is converted into Pd(Cl)NHBs (**D**) prior to the addition onto phenylallene (**B**) to result in a π-allylpalladium species (**E**). This complex finally decomposes to give the product and to regenerate the Pd(0) catalyst.

This mechanism can explain the observation that both the chlorines of *N*,*N*-dichlorobenzenesulfonamide are consumed during the reaction process. Our preliminary ^{1}H NMR experiments indicated the presence of β-chloroenamine intermediate in the catalytic process. The further study of mechanism will be conducted in our laboratories. More importantly, the use of carbamates to replace sulfonamides for this reaction has been proven to be promising. The first application of this reaction for the synthesis of methyleneaziridine derivatives[16] is currently being studied in our laboratories.

In summary, a novel catalytic stereo- and regioselective multiple-site activation of alkynes has been discovered. A new mechanism was proposed which involves the novel formation of β-halovinyl palladium and π-allylpalladium species. The resulting multiple functionalized haloenamines will find extensive applications in organic chemistry.

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Supporting Information Available: Typical procedure, X-ray data, ^{1}H and ^{13}C NMR spectra of all pure products and CIF data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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