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Palladium-catalyzed aerobic oxidative cross-coupling of arylhydrazines with terminal alkynes

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A palladium-catalyzed Sonogashira-type aerobic oxidative coupling of arylhydrazines with terminal alkynes via C-N bond cleavage has been developed; internal alkynes were afforded with a broad substrate scope. This reaction proceeds under copper- and base-free conditions with molecular oxygen as the sole oxidant and nitrogen and water as the only byproducts.

Palladium-catalyzed cross-coupling of terminal alkynes with aryl electrophiles, widely known as Sonogashira reaction, has become the most important method to prepare internal arylalkynes or enynes, which are precursors for natural products, pharmaceuticals, and molecular organic materials. Aryl iodides, bromides, triflates, and tosylates are commonly used electrophilic counterparts which undergo oxidative addition to the Pd(0) species smoothly. Although they are successfully applied substrates, the requirement of equivalents of inorganic or organic base leads to the generation of salt waste which could not be avoided (Scheme 1). Also, use of a copper salt as cocatalyst is commonly required. Thus, the development of more economic and environmentally benign arylation reagents and milder reaction conditions are still highly desirable. Arylhydrazines could be a class of ideal candidates due to their good reactivity in generating aryl segments via oxidative C-N bond cleavage for coupling reactions, with nitrogen gas as the byproduct. Meanwhile, they are inexpensive and commercially available, which is important to broaden the application scope. In the past decades, elegant examples have been developed by employing arylhydrazines as an aryl synthon in organic reactions commonly through the formation of free aryl radical or aryl-transition metal complex under oxidative conditions. Early reports showed that stoichiometric amount of high valent metal oxidant such as lead(IV) acetate, manganese(III) acetate, and barium ferrate, or hypervalent iodine(V) reagent could oxidatively decompose phenylhydrazine to produce the phenyl radical. The drawback of these oxidants is obvious. Molecular oxygen is an ideal oxidant to replace the above reagents owing to its abundance, readily availability and sustainability. Recently, some attention has been paid to apply dioxygen as the oxidant in some transition-metal-catalyzed coupling reactions using arylhydrazines as the starting material. Herein, we describe our successful aerobic oxidative cross-coupling of arylhydrazines in Sonogashira reactions under copper- and base-free conditions with a broad substrate scope, including the approach of Br-substituted diarylacetylenes which could not be readily obtained in traditional Sonogashira couplings.

We began our study with the selection of phenylhydrazine (1a) and phenylacetylene (2a) as model substrates to optimize the reaction conditions (Table 1). Initially in the presence of Pd(OAc)$_2$ or PdCl$_2$ catalyst, PPh$_3$ ligand and 3 equivalents of pivalic acid additive, the desired product diphenylacetylene (3aa) was obtained in low yield when the reaction was carried out in DMF at room temperature for 12 h under air atmosphere (entries 1 and 3). When CuI was used as cocatalyst, a large amount of Glaser-type oxidative homocoupling product (1,4-diphenylbuta-1,3-diyne) of phenylacetylene was obtained (entry 2). To our delight, when the reaction was performed under 1 atm of oxygen, the yield of 3aa was increased to 43% in the absence of a copper salt (entry 4), only a trace amount of homocoupling products and diphenylethylene were detected on GC. Raising the reaction temperature to 50 °C and using acetic acid instead of pivalic acid led to a satisfactory result (entry 6). We then examined the role of different ligands. It was shown that only PPh$_3$ was effective, and other ligands such as 1,10-phen, bidentate or bulky phosphanes did not promote this reaction efficiently (entries 7-11). Also, higher or lower loading of PPh$_3$ ligand led to a decrease in product yield (entries 12 and 13). Next, we found that solvent played an important role for the success of this reaction. In addition to DMF, only DMA gave a modest yield of the desired product. Other solvents severely inhibited the catalytic activity.
Having identified the optimized reaction conditions, we next explored the scope and generality of this process (Scheme 2). First, a variety of substituted aryl acetylenes were allowed to react with phenylhydrazine (1a). It could be seen that 4-alkylsubstituted phenylacetylenes were transformed to the corresponding diarylacetylenes in high yields (3ab and 3ae). Good yields could be obtained when other electron-donating groups such as phenyl and alkoxyl were on the phenyl ring (3ad and 3ae). The electron-deficient aryl acetylenes also exhibited good reactivity (3af-3ak).

This reaction was also compatible with a larger scale (5 mmol of alkyne substrate 2ai) under the optimized condition. (Scheme 3). The desired product 3ai was obtained in 52% yield.

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Based on the above studies and discussions on palladium complexes containing N-N multiple bonds in previous reports,11 and the detailed study on the reaction of PdII complex with phenyldiazirine (1a) carried out by Loh et al.,1e a general mechanism is illustrated in Scheme 4. Initially, ligand exchange of the PdII precursor by phenyldiazirine affords the palladadiaziridine (I), which allows the oxidative addition with Pd0 to afford the two PdII-centered complex II. Protonolysis of II releases the arylpalladium complex III and the palladadiaziridine complex IV, which collapses to give Pd0, nitrogen gas, and water in the presence of oxygen. The reaction of palladium complex III with terminal alkyne 2a might experience a typical complexation-dehydropalladation-reductive elimination to afford the product 3aa. The anionic ligand X (OAc) might play the role of internal base.12 However, a carbpalladation-β-hydride elimination step is also feasible, which could be found in many base-free cases.13 Finally, the catalytic cycle is closed upon reoxidation of Pd0 by oxygen with the assistance of acetic acid.

Conclusions

In summary, we have developed a new type of Sonogashira cross coupling reaction by using commercially available arylhydrazines as the arylation reagents to prepare internal alkynes. This reaction is performed under mild conditions without the addition of copper salt or base. The substrate scope is broad and also, the utilization of 1 atm of O2 without the addition of copper salt or base. The substrate scope also includes arylhydrazines as the arylation reagents to prepare internal alkynes. This reaction is performed under mild conditions without the addition of copper salt or base. The substrate scope is broad and also, the utilization of 1 atm of O2 without the addition of copper salt or base.

Notes and references


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