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Palladium-Catalyzed Difunctionalization of Alkynes via C−N and S−N Cleavages: A Versatile Approach to Highly Functional Indoles

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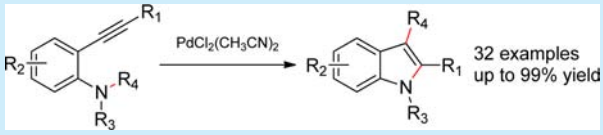
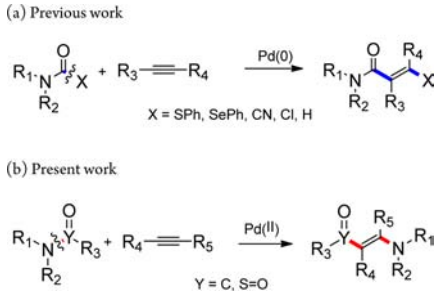
Supporting Information

ABSTRACT: Palladium-catalyzed intramolecular addition of C−N and S−N bond to alkynes with the migration of functional groups has been achieved. A wide range of functional groups including acyl, pyruvoyl, amide, and sulfonyl groups can migrate smoothly and be conveniently introduced at the C-3 postion of indoles in our catalytic system. The operational simplicity and broad substrate scope demonstrate the great potential of this method for the synthesis of highly functional indoles.



Transition-metal-catalyzed addition of alkynes has become an important strategy for the functionalization of carbon−carbon triple bonds.[1] Among the reported synthetic methods, palladium-catalyzed addition of carbamoyl derivatives to alkynes, constituting an important synthetic route to functionalized alkenes, has captured wide attention (Scheme 1a). Generally, the

Scheme 1. Pd-Catalyzed Addition of Carbamoyl Derivatives to Alkynes



transformation involves the initial oxidative addition of the labile C−X bonds, such as the C−S,[2] C−Se,[2] C−CN,[3] C−Cl,[4] and C−H[5] bond, to the Pd(0) center to form the Pd(II) species as a π-acidic catalyst, which coordinates with the alkynes with subsequent simultaneous construction of C−C and C−X bonds through reductive elimination. Despite the remarkable achievements made, however, it is still a great challenge to realize the addition of carbamoyl C−N bond to alkynes using palladium as the catalyst, which prompts us to investigate the new disconnection catalyzed by palladium (Scheme 1b). Although pioneering works reported by Yamamoto[6] realized the intramolecular aminoacylation of alkynes using $PtCl_2$ through the migration of the acyl group, this reaction suffered from the disadvantage of deacylation. Subsequent intramolecular aminosulfonylation of alkynes was also achieved by using a Au catalyst by Yamamoto.[7] Li[8] also achieved the annulation of alkynes with amides employing a Ru(II) catalyst, but with limited substrate scope, especially with regard to the limited kinds of migrating groups. In addition, one obvious disadvantage of these two methods is that one specific metal only catalyzed the migration of one kind of functional group.

Palladium complexes exhibited no sufficient catalytic activity compared to platinum catalysts in the aminoacylation of alkynes according to Yamamoto's results.[6] This reflects the significant challenges that exist for these transformations using palladium as the catalyst. Since the previous palladium-catalyzed addition of carbamoyl derivatives to alkynes relies on the activation of alkynes by the Pd(II) species as a π-acidic catalyst generated from Pd(0) in situ, we expect an appropriate Pd(II) catalyst can directly activate the alkyne moiety followed by the migration of functional groups, thus forging a new catalytic system for the difunctionalization of the carbon−carbon triple bonds. Herein, we present our efforts on palladium-catalyzed difunctionalization of alkynes via C−N and S−N cleavages (Scheme 2). In our new

Scheme 2. Palladium-Catalyzed Difunctionalization of Alkynes via C−N and S−N Cleavages

catalytic system, the migration of a series of functional groups, including acyl, pyruvoyl, amide, and sulfonyl, can smoothly take place, and various substituents (R_3) on the nitrogen atom are well tolerated, thus affording a versatile approach to highly functional indoles.

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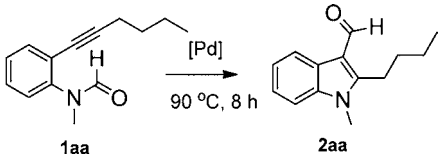
Initial screening experiments were performed employing **1aa** as the model substrate to optimize the reaction conditions (Table 1). As we expected Pd(II) catalysts could directly activate the

Table 1. Optimization of the Reaction Conditions[a]



1aa **2aa**

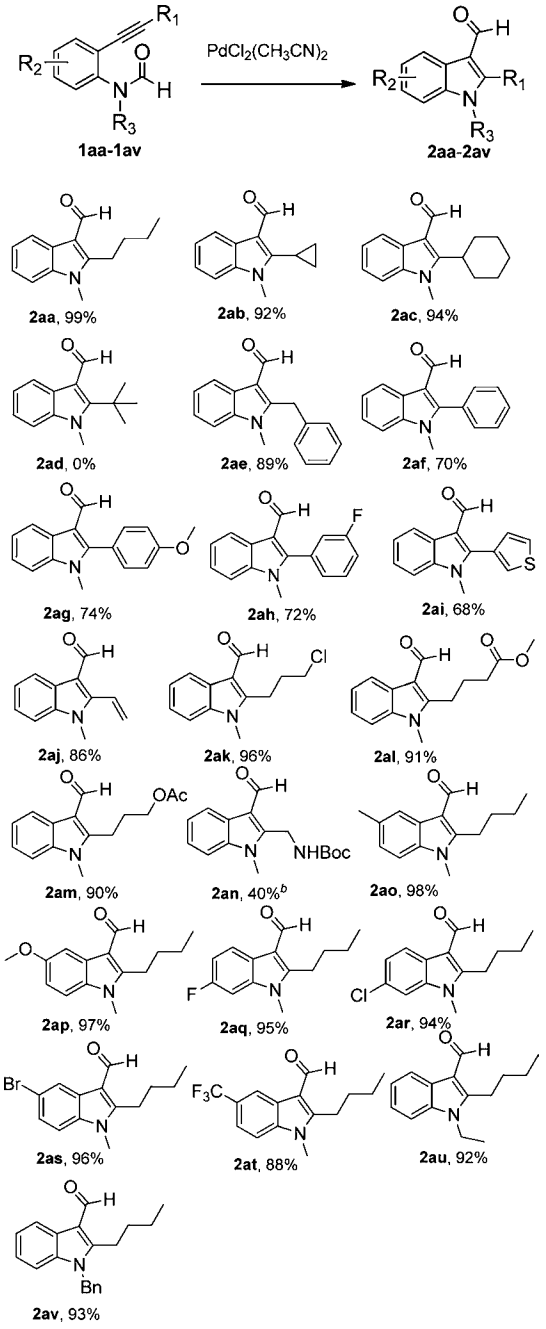
entry	[Pd]	solvent	yield (%)[b]
1	$PdCl_2(dppf)_2$	toluene	0[c]
2	$Pd(OAc)_2$	toluene	0[c]
3	$Pd_2Cl_2C_6H_{10}$	toluene	11[c]
4	$PdCl_2(dppe)_2$	toluene	72
5	Na_2PdCl_4	toluene	82
6	$PdCl_2(PhCN)_2$	toluene	85
7	$PdCl_2(CH_3CN)_2$	toluene	92
8	$Pd(PPh_3)_4$	toluene	0[c]
9	$Pd_2(dba)_3$	toluene	0[c]
10	$PdCl_2(CH_3CN)_2$	THF	64
11	$PdCl_2(CH_3CN)_2$	1,2-dichloroethane	88
12	$PdCl_2(CH_3CN)_2$	1,4-dioxane	74
13	$PdCl_2(CH_3CN)_2$	CH_3CN	99
14	$PdCl_2(CH_3CN)_2$	EtOH	5[c]
15	$PdCl_2(CH_3CN)_2$	DMF	12

[a]Reaction conditions: **1aa** (0.5 mmol), [Pd] (0.025 mmol), and solvent (2.0 mL) under an argon atmosphere at 90 °C for 8 h. [b]Isolated yield. [c]**1aa** was recovered.

alkyne moiety followed by the migration of functional groups, various Pd(II) catalysts were chosen to test the hypothesis. Treatment of **1aa** with Pd(II) catalysts such as $PdCl_2(dppf)_2$ and $Pd(OAc)_2$ did not afford the desired product (entries 1 and 2). Pleasingly, **2aa** was achieved when an allylpalladium(II) chloride dimer was used as the catalyst, albeit with a low yield (entry 3). Encouraged by this result, an investigation of other Pd(II) sources was carried out (entries 4−7). Among them, $PdCl_2(CH_3CN)_2$ displayed the highest catalytic reactivity, providing product **2aa** in 92% yield (entry 7). As we anticipated, treatment of **1aa** with Pd(0) catalysts such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ in toluene at 80 °C for 8 h did not give the desired product at all (entries 8 and 9). The screening of solvents revealed the transformation was strongly influenced by the solvents used (entries 10−15), and CH_3CN turned out to be the most suitable solvent for this reaction resulting in almost quantitative yield (entry 13).

Then, we examined the generality of the process as summarized in Scheme 3. Substrates with alkyl groups at R_1 furnished the corresponding products in excellent yields (**2aa**−**2ac**), while the reaction of **1ad** bearing a bulky *tert*-butyl group did not give the desired product (**2ad**). A high yield (89%) was also achieved from **1ae** with a benzyl group at R_1 (**2ae**). The reactions of **1af**−**1ai** carrying aromatic rings at the alkynyl moiety afforded the corresponding products **2af**−**2ai** in moderate yields (68−74%) because of the formation of 3-deformylated indole byproducts. To our delight, various functional groups such as alkenyl, halide, ester, and BocNH at the alkynyl moiety were well tolerated with moderate to high yields (**2aj**−**2an**). The protocol was also compatible with substrates bearing electron-donating substituents (MeO, Me), halides (F, Cl, Br), and an electron-

Scheme 3. Substrate Scope of Pd-Catalyzed Intramolecular Aminoacylation of Alkynes[a]



[a]Reaction conditions: **1** (0.5 mmol), $PdCl_2(CH_3CN)_2$ (0.025 mmol), and CH_3CN (2.0 mL) under an argon atmosphere at 90 °C for 8 h. [b]The reaction was performed in toluene at 110 °C.

withdrawing substituent (CF_3) at R_2, which produced the corresponding products in excellent yields (**2ao**−**2at**). It is worth noting that various functional groups were well tolerated in this transformation, which makes this method very useful for synthesizing highly functional indole skeletons. In addition, different substituents at R_3 were also briefly investigated. The reaction of **1au** having an ethyl group at R_3 proceeded smoothly, providing **2au** in 92% yield. In particular, **2av** was also obtained in high yield (93%) from **1av** bearing a benzyl group at R_3 under our catalytic system, while only a poor yield was achieved from **1av** using a Ru catalyst.[8]

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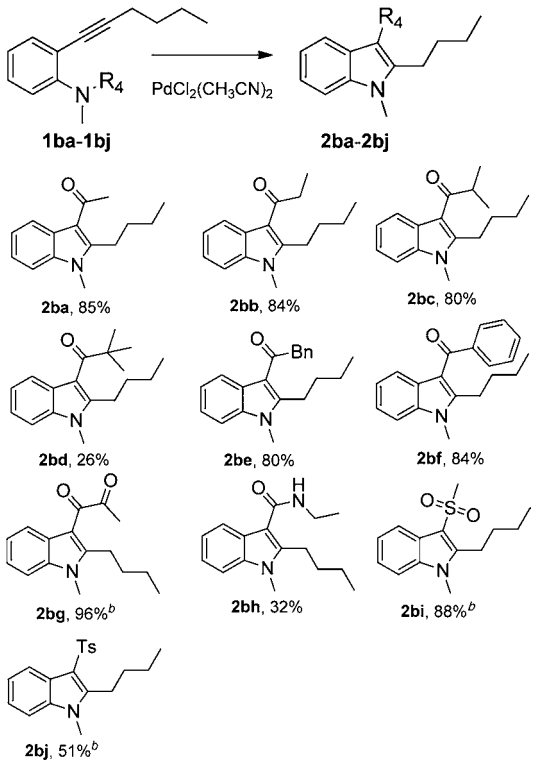
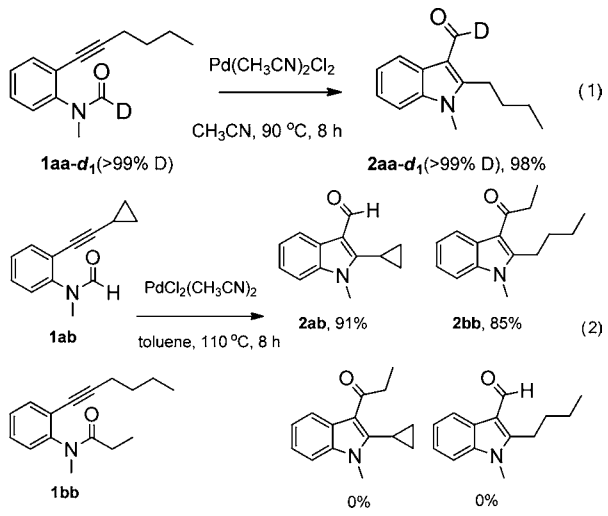
Next, various migrating groups on the nitrogen were explored (Scheme 4). Compared to the formyl migration, the bulky acyl migration was sluggish under the standard conditions. The use of toluene instead of acetonitrile and elevation of the reaction temperature successfully addressed the problem. The acetyl migration of substrate **1ba** took place smoothly and gave the corresponding product in 85% yield. The migration of more bulky propionyl, isobutyryl, phenylacetyl, and benzoyl groups also proceeded very well (**2bb**–**2bf**). Even the sterically congested pivaloyl group could migrate successfully and afforded the desired product (**2bd**). Particularly, we first proved that a pyruvoyl group can be used as the migrating group and gave the desired product in excellent yield (**2bg**). It should be emphasized that this new method allows ready installation of the amide and sulfonyl groups at the C-3 position of indoles, which is difficult to achieve by traditional electrophilic substitution (**2bh**–**2bj**). In addition, when the substrates were secondary amines with the formyl/acyl/amide/sulfonyl group, the amines did react with carbon–carbon triple bonds to produce indoles but the formyl/acyl/amide/sulfonyl group did not migrate to the 3-position of the indoles under our catalytic system.[9]

Scheme 4. Investigation of Migrating Groups[a]



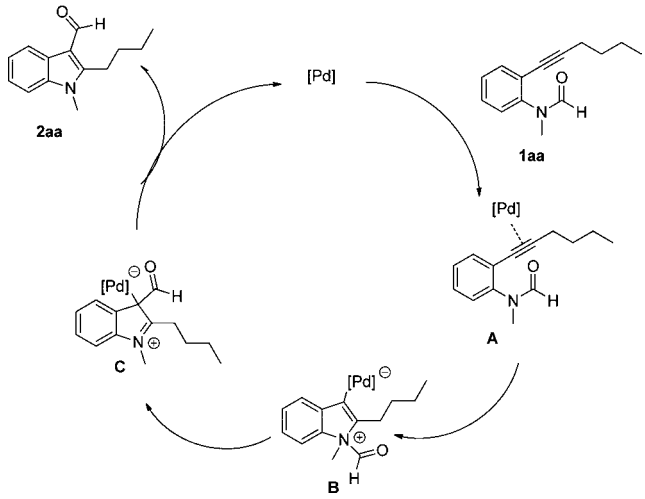
[a]Reaction conditions: **1** (0.5 mmol), $PdCl_2(CH_3CN)_2$ (0.025 mmol), and toluene (2.0 mL) under an argon atmosphere at 110 °C for 8 h. [b]The reaction was performed in CH_3CN at 90 °C for 8 h.

Mechanistic studies were also carried out with the deuterium-labeling experiments. As shown in eq 1, the reaction of the deuterium-labeled substrate **1aa**-d_1 afforded the corresponding deuterium-labeled product **2aa**-d_1 in 98% yield. Addtionally, no crossover products of the acyl group were observed when we mixed equimolar **1ab** and **1bb** under the standard reaction conditions (eq 2), indicating that this palladium-catalyzed addition of the C–N bond to alkynes proceeds in an intramolecular manner.



Based on the above results, a plausible mechanism was proposed as shown in Scheme 5. Coordination of alkyne to $PdCl_2(CH_3CN)_2$ yields intermediate **A**, followed by nucleophilic attack of nitrogen to the alkyne, affording the intermediate **B**. An intramolecular [1,3]-migration of the formyl group then gives intermediate **C**, which affords the product and regenerates the catalyst.

Scheme 5. Proposed Reaction Mechanism



In conclusion, we have developed an efficient approach to construct highly functional indoles by palladium-catalyzed intramolecular C–N and S–N bond addition to alkynes. The new protocol features a low catalyst loading, operational simplicity, and excellent functional tolerability. Particularly, a wide range of fuctional groups such as acyl, pyruvoyl, amide, and sulfonyl can migrate smoothly and be conveniently introduced at the C-3 postion of indoles in our catalytic system. We believe that this new synthetic method will find wide applications in the future.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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