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Synthesis of C4-Substituted Indoles via a Catellani and C−N Bond Activation Strategy

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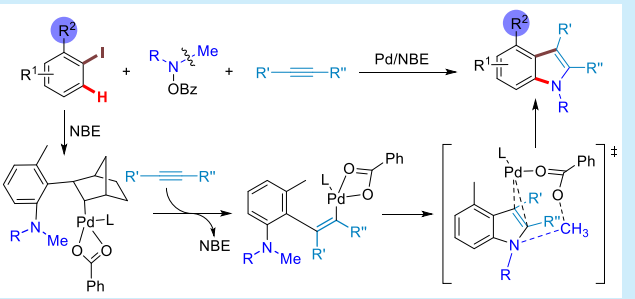
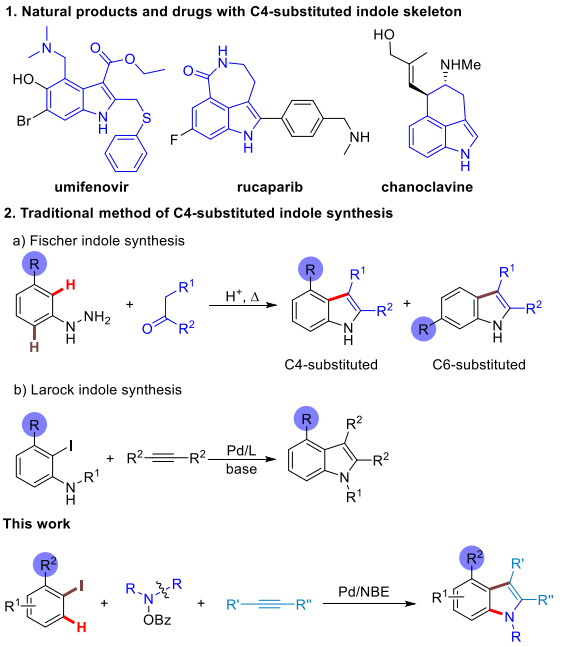
ABSTRACT: This paper describes the case of a cross study between the C−N bond cleavage reaction field and the Catellani−Lautens reaction system. A series of highly functionalized C4-substituted indoles were synthesized using this strategy. By screening the alkyl groups of amines, the energy barrier of C−N bond cleavage reaction was reduced and the corresponding allenization products were avoided. Finally, the density functional theory calculation shows that the inert C−N bond activation reaction is not a concerted process; on the contrary, the coupling reaction first generates indole quaternary ammonium salt, and then C−N bond cleavage occurs via an S_N2 process.



Indole is one of the most popular heterocyclic frameworks in natural products and pharmaceutical chemistry.[1] Among them, C4-substituted indoles are widely studied by pharmaceutical chemists, because of their unique biological activities.[2] For instance, Umifenovir is a C4-dimethylaminomethane-substituted indole with hydrophobicity. Umifenovir is widely used to treat and prevent influenza and other respiratory infections, and it is currently being studied as a potential prophylactic agent and treatment for COVID-19.[3] Rucaparib is "the world's first PARP inhibitor for the third line treatment of ovarian cancer".[4] In addition, C4-substituted indoles are also common in the field of natural products, such as chanoclavine.[5]

Traditional synthesis methods have some limitations in the synthesis of C4-substituted indoles. Fischer indole synthesis is one of the most practical methods for indole synthesis.[6] The corresponding indole products can be directly synthesized from phenylhydrazine through one-step conversion. To synthesize C4-substituted indoles, *m*-substituted phenylhydrazine should be used as the substrate. The method has no regioselectivity, so the product is a mixture of isomers. In particular, the steric hindrance of C4-substituted indoles is greater than that of C6-substituted indoles, which makes the formation of C4 products more difficult. Among the transition-metal catalysts, Larock indole synthesis is the most widely used method in the synthesis of indole, and it has the advantages of mild reaction conditions, high yield, and good selectivity.[7] This method can effectively synthesize C4-substituted indoles, but it needs 3-substituent-*o*-haloaniline, which is relatively expensive and difficult to synthesize, as a substrate (Scheme 1). The use of nitrenes as amination reagents provides a new method for the synthesis of indole. However, other types of C−H amination for indole synthesis have not been developed.[8b−g]

Scheme 1. Synthesis of C4-Substituted Indoles via a Catellani−Lautens and C−N Bond Activation Strategy



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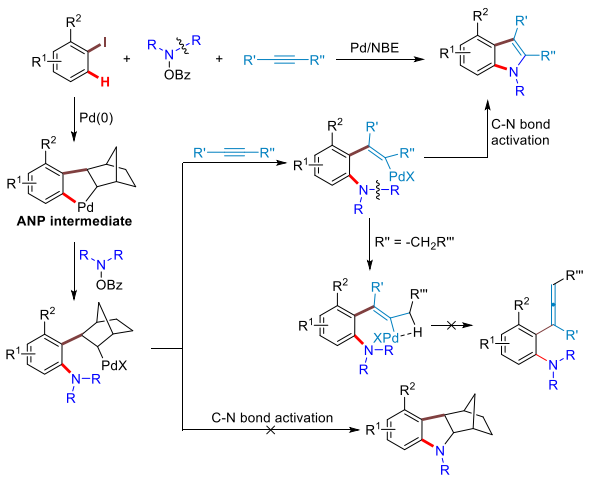
To synthesize indole directly from iodobenzene, C−H amination must be realized first. One of the most remarkable methods in the *o*−C-H amination of aryl halides[8] is realized by the Pd/norbornene (NBE) cocatalysis strategy.[9] In recent years, this reaction has been proven to be a widely applicable and convenient method for the synthesis of highly functionalized aromatics.[10] However, this reaction is only suitable for C−H amination of secondary amines, so the corresponding indole products cannot be obtained by the reaction in series with the Larock indole synthesis method. At present, transition-metal-catalyzed C−N bond activation has developed rapidly and has become a powerful tool for the synthesis of amines, amides, and other nitrogen-containing molecules.[11] Therefore, we assume that if the C−N bond activation reaction is connected with the termination step of the Catellani−Lautens reaction, the C4-substituted indole derivatives can be synthesized effectively in one step.

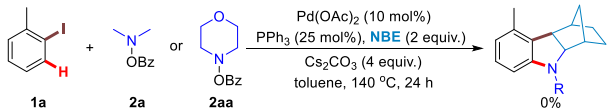
After a preliminary exploration, the main difficulties of this series of reaction are as follows. First, whether arylnorbornenylpalladium can cleave C−N bond directly after C−H amination must be determined. If the C−N bond cannot be cleaved directly, then the *β*-carbon elimination process of norbornene should occur smoothly to obtain the corresponding aromatic Pd(II) intermediate. Second, the energy barrier of the C−N bond cleavage reaction should not be too high after the migration and insertion reaction occurs between the alkyne and the Pd (II) intermediate; otherwise, the alkenyl palladium intermediate will undergo *β*-hydrogen elimination or the concerted metalation deprotonation (CMD) process to form allene compounds.[10h] Therefore, it is a challenge to realize the series reaction of C−N cleavage and the Catellani−Lautens reaction (see Scheme 2).

Scheme 2. Challenges for Overcoming the Compatibility between C−N Bond Activation and Catellani−Lautens Reaction



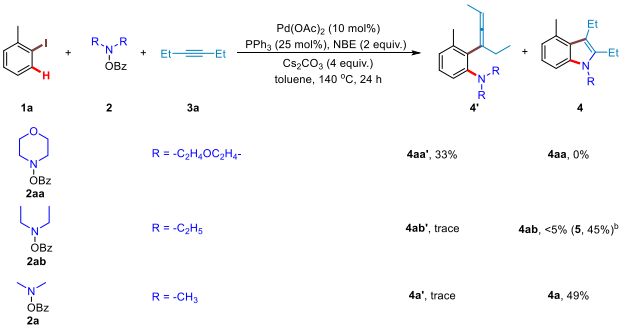
Initially, the following compounds were used to begin the experiment: *o*-iodotoluene (**1a**), which is used as a substrate; *O*-benzoyl-*N*,*N*-dimethylhydramine or morpholino benzoate, which is used as an electrophilic amination reagent; and palladium acetate, which is used as a catalyst. After a series of screening conditions, there was no expected C−N cleavage product (see Scheme 3). Therefore, we added alkynes to the reaction system and hoped that the denorbornene process will occur through the *β*-carbon elimination after C−H amination to generate the corresponding palladium intermediate, and then, transfer and insertion with alkynes. Finally, the C−N bond activation reaction occurs between alkynes and dimethylamine to form the C4-methyl-indole target product.

Scheme 3. Testing the Participation of Norbornenylpalladium Species in the C−N Bond Cleavage



Morpholino benzoate was used as an electrophilic amination reagent. When 3-hexyne was added, the corresponding C−N bond cleavage product was not obtained, but the allene product was obtained (see Scheme 4). Through the screening of electrophilic amination reagents, surprisingly, the strategy worked, and we achieved the desired product with an isolated yield of 49%. Note that the C−H amination process of the diethylamine electrophilic amination reagent (**2ab**) was not smooth, and a large amount of norbornene product **5** was obtained. After the temperature was reduced to 120 °C, the phosphorus ligands were screened. Tri(2-furyl)phosphine (TFP) was found to be the best ligand and could effectively inhibit the formation of 4-membered products **5** of aryl norbornene and dehalogenation product **6**, and the target product was obtained in a 61% yield (see Table S1, entries 1−6, in the Supporting Information). Subsequently, we screened the reaction temperature and norbornene derivative and found no better reaction conditions (Table S1, entries 7−12). Note that a small amount of direct allenization product was formed when the **N2** amide-substituted norbornene was used as a co-catalyst. This may be due to the relatively slow migration and insertion reaction occurring between the norbornene and palladium aryl intermediate. According to our previous studies, electron-donating benzoyl hydroxamine (**2a′**) may promote the C−H amination reaction, but the actual effect is not ideal (Table S1, entry 13). Finally, we selected other solvents, but the reaction results were not as good as those obtained with toluene.

Scheme 4. Variations on Electrophilic Amination Reagent[a]



[a]Reaction conditions: substrate **1a** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv), **3a** (0.4 mmol, 2.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), norbornene (0.4 mmol, 2.0 equiv), Cs_2CO_3 (0.8 mmol, 4.0 equiv), toluene (3.0 mL), 140 °C, 24 h. Isolated yields.[b]The yield of the compound was estimated using gas chromatography−mass spectroscopy (GC-MS).

After the optimum reaction conditions were obtained, the substrate scope of iodobenzene was investigated (Scheme 5). The C4-ester and methoxy-indoles were synthesized smoothly from iodobenzenes, whose *ortho*-substitute was an electron-

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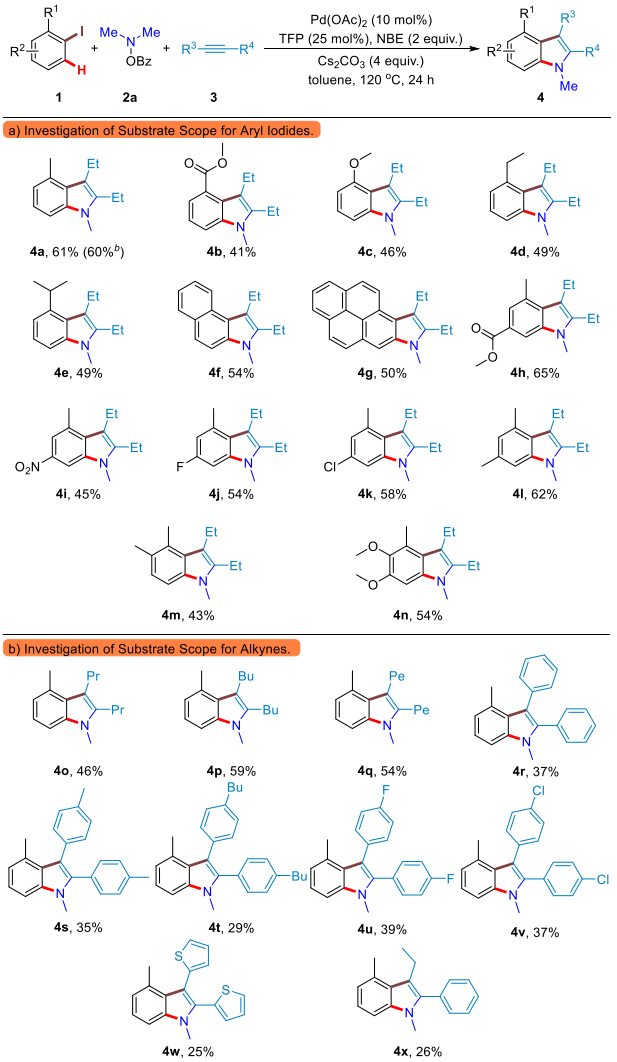
Scheme 5. Investigation of Substrate Scope for Iodobenzenes and Alkynes[a]

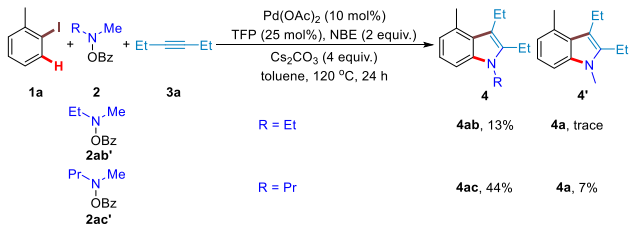


[a]Reaction conditions: substrate **1** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv), **3** (0.4 mmol, 2.0 equiv), $Pd(OAc)_2$ (10 mol %), TFP (25 mol %), norbornene (0.4 mmol, 2.0 equiv), Cs_2CO_3 (0.8 mmol, 4.0 equiv), toluene (3.0 mL), 120 °C, 24 h. Isolated yields. [b]The amount of substrate **1a** was amplified to 2 mmol scale.

drawing or electron-donating group. Furthermore, we also tried to synthesize a series of C4-alkyl indoles by using various types of *o*-alkyl iodobenzenes in one step. Note that this reaction can also be applied to the synthesis of indole derivatives with fused rings, which is difficult to achieve by the previous synthesis methods. This reaction is also suitable for the synthesis of highly functionalized indoles. Various substituted indoles, such as C6- or C5-ester groups, -nitro, -methoxy, -halogen (-F, -Cl), etc., can be obtained in moderate yields. In addition, we also tried some other asymmetric alkynes and electrophilic amination reagents, and the yields were not ideal (see the Supporting Information).

The next step is to investigate the scope of alkynes. All types of alkyl alkynes (4-octyne, 5-alkyne, and 6-dodecyne) can be obtained in high yields. Electron-donating, electron-withdrawing, and halogen (-Cl)-substituted diaryldindoles can be successfully synthesized by using corresponding diphenylacetylene derivatives. In particular, dithienylacetylene can also be successfully applied to the reaction. It is worth mentioning that only one product was obtained, when ethylphenylacetone was used as the substrate. Subsequently, an *N*-alkyl-*N*-methyl electrophilic amination reagent was used to study the reaction, and the results showed that the C−N bond at the methyl end was selectively activated. Because a large amount of norbornene compound **5** was detected by GC-MS, the key reason for the large difference between the yields of **4ab** and **4ac** is the difficulty of the reaction between the ANP intermediates and corresponding electrophilic amination reagents. This problem has always existed in the Catellani reaction, since the researchers have yet to further solve it (see Scheme 6).

Scheme 6. Investigation of Substrate Scope for *N*-Alkyl-*N*-Methyl Electrophilic Amination Reagent



After the completion of the substrate scope study, the mechanism of C−N bond activation was studied by density functional theory (DFT) calculations. Three possible mechanisms of the C−N bond cleavage reaction are proposed (see Figure S2 in the Supporting Information). The first mechanism is derived from the CMD process of C−H bond activation, and we infer that the cleavage of the C−N bond was directly realized through the concerted metallization process promoted by benzoic acid. The second mechanism we speculate is that the intramolecular coupling reaction between N and alkyne is the first step to form indole quaternary ammonium salt, and then the target product was obtained by the S_N2 process occurring between benzoic acid and methyl. At this point, we realize that palladium in the intermediate of indole quaternary ammonium salt is tricoordinated. Therefore, we left a ligand to investigate the reaction in the presumed third mechanism. After confirming the mechanism of C−N bond cleavage, we hope to explain the reason why norbornene cannot cleave the C−N bond.

According to the above ideas and our previous mechanism research work,[10h] we first constructed intermediate **A** via alkyne coordination with palladium (Figure 1). Intermediate **B** was obtained by the migration and insertion process of intermediate **A**, and the energy barrier of this process was only 13.0 kcal/mol.

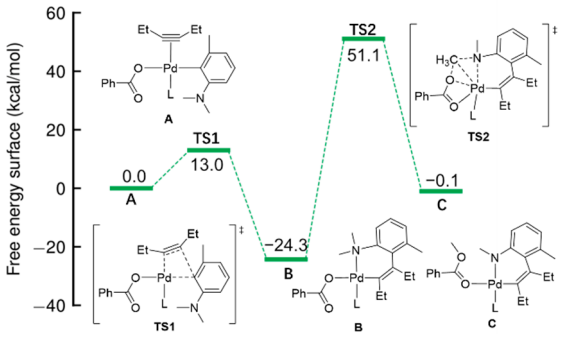


Figure 1. Mechanism of C−N bond cleavage (concerted metallization).

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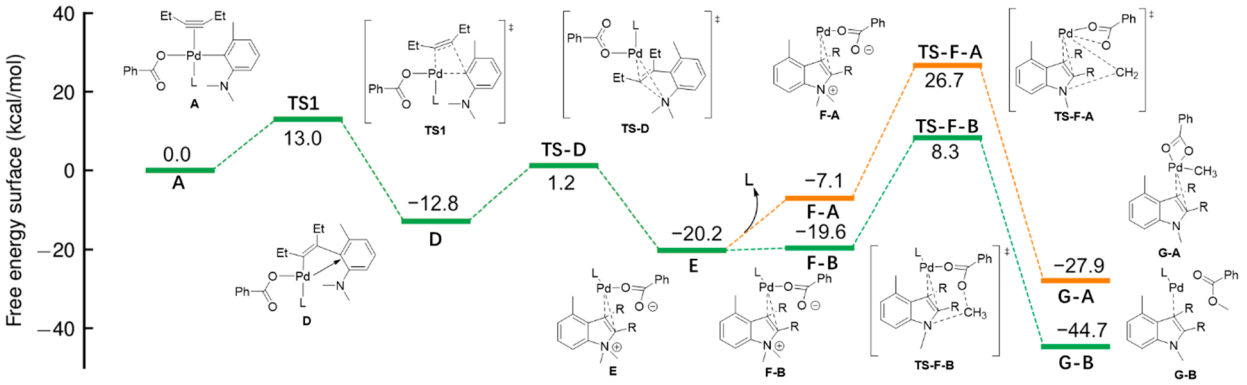

Figure 2. Mechanism of C−N bond cleavage.

We then determined the concerted metallization transition state **TS2**, which has a high energy barrier (75.4 kcal/mol). Therefore, the reaction mechanism was excluded.

The cleavage of the C−N bond by a concerted metallization process is excluded, and we consider that the electron-deficient effect of indole quaternary ammonium salt may weaken the strength of the C−N bond (Figure 2). Intermediate **A** reacted with alkyne to obtain intermediate **D**. The intermediate **E** of indole quaternary ammonium salt then was obtained by the reduction elimination reaction of **D**. Intermediate **E** can be directly attacked by the oxygen of benzoic acid, and the target product **G-B** is obtained by an S_N2 reaction. This is the rate-determining step of the reaction, and the energy barrier is 27.9 kcal/mol (see Figure 3).[12]

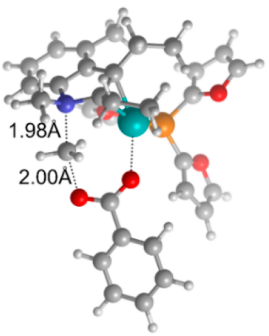

Figure 3. Mechanism of C−N bond cleavage (S_N2 process).

The palladium in intermediate **E** is tricoordinated, so we consider whether the energy barrier of the C−N activation reaction can be reduced by removing a triphosphate. However, the high energy intermediate **F-A** can be obtained by the removal of TFP. Subsequently, the C−N bond cleavage product **G-A** was obtained by metallization. The energy barrier of this process is very high, which is 46.9 kcal/mol. In conclusion, the mechanism of C−N bond cleavage should be a S_N2 process. Finally, we use the above SN2 method to calculate the C−N bond cleavage reaction of norbornene, and the results showed that the process could not happen (see Figure S3 in the Supporting Information).

In conclusion, we have developed the first case of a cross study between the C−N bond cleavage reaction field and Catellani−Lautens reaction system. A series of highly functionalized C4-substituted indoles were synthesized by this strategy. The experimental results showed that norbornene could not cleave the C−N bond directly with an alkyl amine. Therefore, after the elimination of the β-carbon of norbornene, the palladium intermediate reacted with alkynes by migration and insertion, which was followed by the C−N bond activation of the alkyl amine. By screening the alkyl groups of amines, the energy barrier of the C−N bond cleavage reaction was reduced and the corresponding allenization products were avoided. Finally, three possible C−N bond cleavage mechanisms were proposed. The density functional theory (DFT) calculation shows that the inert C−N bond activation reaction is not a concerted process; on the contrary, the coupling reaction first generates indole quaternary ammonium salt, and then C−N bond cleavage occurs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02897.

Experimental details, characterization data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(12) The intermediate **E** and **F-B** are the same compound. In DFT calculation, **F-B** is the relevant minimum of **TS-F-B** in the intrinsic reaction coordinate (IRC) calculations.