RESEARCH ARTICLE

Synthesis of 2,3-Disubstituted Indoles by Nickel(0)-Catalyzed Migratory Cycloisomerization of *o*-Alkynylanilides

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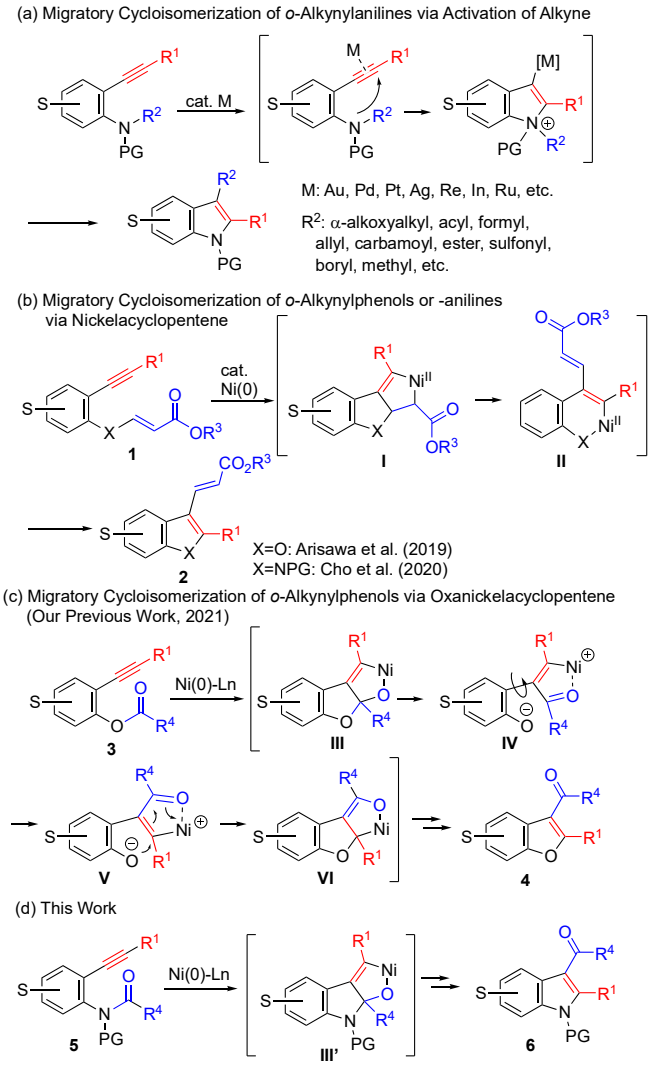
Abstract: We herein report a nickel-catalyzed migratory cycloisomerization of *o*-alkynylanilides, giving 2,3-disubstituted indoles in good yields. The cyclization proceeded via acyl transfer on the nitrogen atom of the substrate to C3-position in the product, and an N-heterocyclic carbene (NHC) ligand such as ICy or SICy was found to be suitable in this reaction. It was thought that the reaction proceeds via an aza-nickelcyclepentene intermediate formed from alkyne and the C=O bond of the amide moiety in *o*-alkynylanilides.

Introduction

Indoles are one of the most privileged structures found in a variety of biologically active substances including naturally occurring alkaloids and a pharmaceutically important motif.[1] Therefore, development of methodology for synthesis of indoles has a long history, and various reactions have been reported.[2] Among them, transition metal-catalyzed migratory cycloisomerizations of *o*-alkynylaniline derivatives are one of the promising methodologies for synthesis of a 2,3-disubstituted indole structure (Scheme 1). This type of reaction usually starts from activation of the alkyne moiety of the substrate by a metal catalyst. There is a large variety of reactions using combinations of transition metal catalysts and migratory groups of the substrates (Scheme 1-(a)).[3] On the other hand, another type of migratory cycloisomerization of *o*-alkynylaniline or *o*-alkynylphenol derivatives has recently been reported (Scheme 1-(b)). In 2019, Arisawa reported a nickel(0)-catalyzed migratory cycloisomerization of 3-phenoxyl acrylate **1** (X=O), giving 2,3-disubstituted benzofuran **2** (X=O) accompanied by C−O bond cleavage and migration of the acrylic ester moiety at the C3 position of the product.[4a] Cho et al. reported in 2020 that a similar reaction of *o*-alkynylaniline derivative **1** (X=NPG, PG=protecting group) proceeded by using a Ni(0) complex to give the corresponding 2,3-disubstituted indole **2** (X=NPG).[4b]



Scheme 1. Metal-Catalyzed Migratory Cycloisomerization of *o*-Alkynylaniline or *o*-Alkynylphenol derivatives

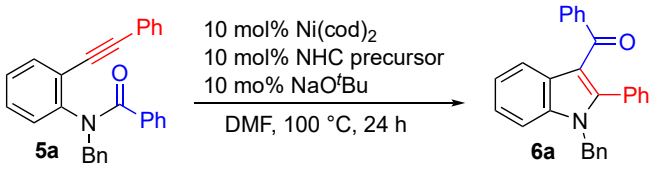
In these reactions, nickelacyclopentene intermediate **I** was initially formed by oxidative cycloaddition of alkyne and alkene in **1** to a nickel(0) catalyst, and intermediate **I** was isomerized to oxa- or azanickelacycle intermediate **II**, finally giving the product **2**. In 2021, we reported nickel(0)-catalyzed migratory cycloisomerization of *o*-alkynylphenyl ester **3**, giving 2,3-disubstituted benzofuran **4** (Scheme 1-(c)).[5] DFT calculation revealed that the reaction proceeded via oxanickelacyclopentene **III** formed by oxidative cycloaddition of alkyne and C=O bond of the ester moiety in **3** to a nickel(0) catalyst, which was successively isomerized to the intermediates **IV**, **V**, and **VI**, finally giving the product **4**. Oxidative cycloaddition involving the C=O bond of an ester is uncommon compared with oxidative cycloaddition involving the C=O bond of aldehyde or ketone, and we therefore decided to investigate migratory cycloisomerization of *o*-alkynylanilide **5** as the substrate instead of **3**. If migratory cycloisomerization of **5** proceeds in a manner similar to that of migratory cycloisomerization of **3**, 2,3-disubstituted indoles **6** would be obtained via oxanickelacyclopentene **III'**, which is a very rare case of the formation of oxanickelacyclopentene intermediates from alkyne and the C=O bond of amide.

Results and Discussion

We started our study on migratory cycloisomerization of *o*-alkynylanilide by using the model substrate **5a**. By reference to the optimized conditions of the above-mentioned reaction of **3**, the reaction of **5a** was carried out by using 10 mol% $Ni(cod)_2$ and an equivalent of IAd as the ligand in DMF at 100 °C for 24 hours. Unexpectedly, the desired product **6a** was obtained in only 4% yield along with recovery of **5a** in 66% yield (Table 1, Entry 1). Thus, screening of ligands was conducted with a focus on N-heterocyclic carbene ligands (NHCs). The use of I^{t}Bu, IPr, SIPr, IMes, and SIMes did not affect the yield of **6a** (Entries 2-6). On the other hand, the use of IMe was only slightly effective in this reaction, giving **6a** in 56% yield (Entry 7). Furthermore, we found that the use of ICy, SICy, or I^{i}Pr was very effective for improving the yield of **6a**, with 97%, 90%, and 88% yields, respectively (Entries 8-10). According to the screening, Ni(0)-ICy catalyst system found to be most effective in the reaction of **5a**.

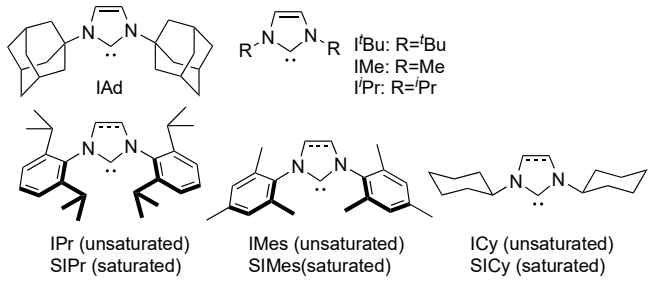
With the optimal conditions in hand, we next examined the reactions of various substrates (Figure 1). When the protecting group on a nitrogen atom in the substrate was changed from a benzyl group, only the substrate **5b** having a methyl group gave the corresponding product **6b** in 96% yield, and other substrates having a free amine **5c**, *tert*-butoxycarbonyl (Boc) group **5d**, and *p*-toluenesulfonyl (Ts) group **5e** afforded no cyclized products. In the case with **5c**, the reaction gave messy reaction mixtures. With respect to the acyl group functionality, an electron-withdrawing group at the *p*-position on the benzamide moiety such as a trifluoromethyl group (CF_3) or a methoxycarbonyl group (CO_2Me) was tolerated in this reaction. Namely, **6f** was obtained in an excellent yield from **5f** under the optimized conditions, while an increase in the reaction temperature to 130 °C was necessary in the case of the reaction of **5g**, but **6g** was obtained in high yield. In contrast, an electron-donating group such as a methoxy group (OMe) was not suitable for this reaction, giving no cyclized product **6h**. The reaction of *m*-toluamide **5i** and 2-naphthamide **5j** proceeded to give **6i** and **6j**, respectively, in high yields. The substrate **5k** having a cyclobutyl group as the R^4 substituent was also found to be a suitable substrate for the reaction, giving the corresponding indole **6k** in high yield, while analogous *n*-butyl-substituted substrate **5l** showed poor reactivity.

Table 1. Screening of Conditions for Reaction of **5a**

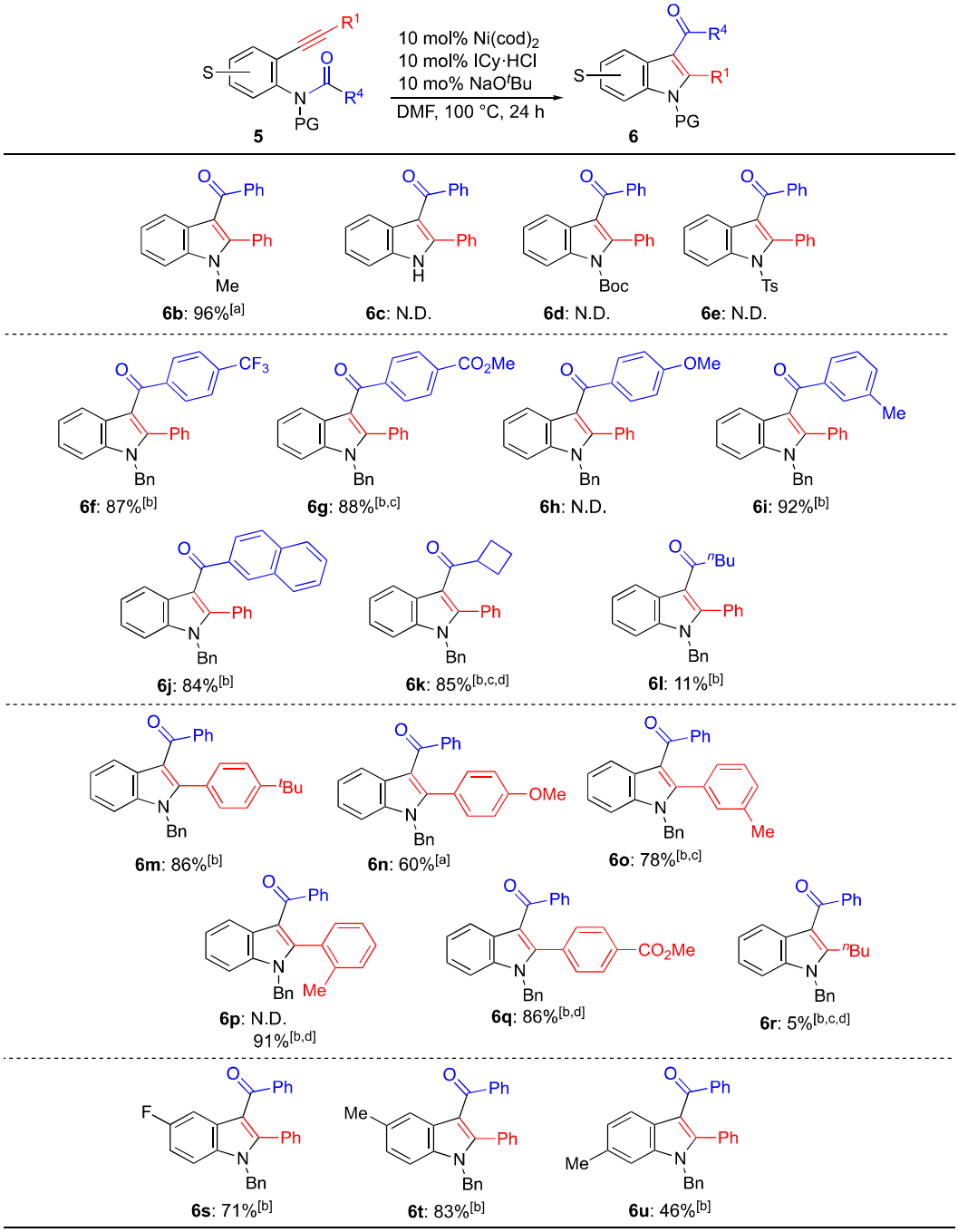


Entry	NHC Precursor[a]	Yield of **6a**[b]	SM[b]
1	IAd·HBF_4	4%	66%
2	I^{t}Bu·HCl	9%	66%
3	IPr·HCl	–	74%
4	SIPr·HCl	–	76%
5	IMes·HCl	–	59%
6	SIMes·HCl	–	77%
7	IMe·HCl	56%	41%
8	ICy·HCl	97%[c]	–
9	SICy·HCl	90%	–
10	I^{i}Pr·HCl	88%	–

Structures of NHC Ligands



[a] NHC ligands were prepared *in situ* by treatment of the precursors with an equivalent of NaO^{t}Bu. [b] Yields and recoveries of the starting material were determined by ^{1}H-NMR using 1,1,2,2-tetrachloroethane as an internal standard unless otherwise noted. [c] Isolated yield.



[a] ^{1}H-NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. [b] Isolated yield. [c] Reaction was carried out at 130 °C. [d] Reaction was carried out using SICy as a ligand at 130 °C.

Figure 1. Scope and limitations of the reaction.

Next, substrates having various aromatic rings on the terminus of the alkyne moiety were investigated. Substrates **5m** and **5n** having an electron-donating group at the *para*-position on the benzene ring gave the corresponding products **6m** and **6n**, respectively, in good yields. In the case of the substrate **5o** having a methyl group at the *m*-position of the benzene ring, the desired product **6o** was not obtained under standard conditions, but the reaction at 130 °C provided the product **6o** in 78% yield. Similarly, the reaction of **5p** having a methyl group at the *o*-position of the benzene ring did not afford the desired product **6p** under standard conditions probably due to the steric hindrance by the methyl group. In this case, however, we found that the use of SICy instead of ICy as the ligand was fairly effective, **6p** being obtained in 91% yield from the reaction at 130 °C. In the reaction of **5q** having an electron-withdrawing CO_2Me group at the *p*-position, the use of SICy was effective, giving **6q** in 86% yield under conditions similar to those in the case of **5p**. The substrate with alkyl-substituted alkyne **5r** showed decreased reactivity to give the corresponding product **6r** in 5% yield, even at 130 °C. Finally, substrates having a substituent such as a fluoride or a methyl group on the aniline moiety, **5s**-**5u**, were investigated, and it was

found that they afforded **6s**-**6u**, respectively, in good yields under standard conditions.

The plausible mechanism of this migratory cycloisomerization is depicted in Figure 2. Speculation of the plausible mechanism was based on the mechanism for benzofuran formation previously reported by us (cf. Scheme 1-(c)).[5] Initially, the oxidative cycloaddition of alkyne and the amide C=O bond in **5** to a nickel(0) catalyst would occur to produce the oxanickelacyclopentene intermediate **III'**. The intermediate **III'** would be reorganized into another oxanickelacyclopentene intermediate **VI'** via the intermediates **IV'** and **V'**. From the intermediate **VI'**, aromatization and reductive elimination would take place at the same time, giving the product **6** along with regeneration of the nickel(0) catalyst. Oxidative cycloaddition involving the C=O bond of amide is very rare; however, Cho et al. very recently proposed the formation of a similar intermediate from *o*-alkynylanilide and a nickel(0) complex in their nickel(0)-catalyzed reductive coupling of alkynes and amides,[6] which supports our proposed mechanism.

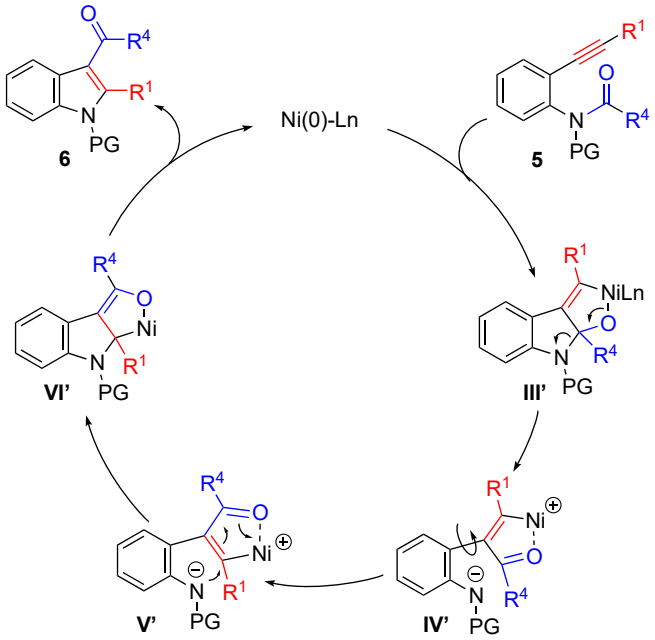


Figure 2. Plausible Mechanism.

Conclusion

In conclusion, we have developed a nickel(0)-catalyzed migratory cycloisomerization of *o*-alkynlyanilide to produce 2,3-disubstituted indoles. In this reaction, an NHC ligand such as ICy or SICy was found to be effective, and various substituents as an acyl group functionality on the terminus of the alkyne and on the aniline benzene ring are tolerated to give the products accompanied by acyl group migration. The reaction would proceed via an oxanickelacyclopentene intermediate formed by oxidative cycloaddition of the alkyne and the C=O bond of amide in the substrate to a nickel(0) catalyst. Further studies on the mechanism as well as application to the synthesis of natural products are in progress.

Experimental Section

General procedure for Ni(0)-catalyzed migratory cycloisomerization: In a nitrogen-filled glove box, a clean oven-dried vial equipped with a stirring bar was loaded with $Ni(cod)_2$ (10 mol% to the substrate), NHC precursor (10 mol%), NaO^tBu (10 mol%), and DMF (1.5 mL). The mixture was stirred at room temperature for several minutes. The substrate (0.30 mmol) was added to the mixture, and the vial was tightly sealed with a screwcap and removed from the glove box. The mixture was heated in a pre-heated metal bath at 100 °C for 24 h. The reaction mixture was diluted with brine, and the mixture was extracted with an appropriate organic solvent. The combined organic layer was dried over Na_2SO_4. After removal of the solvent, the residue was used as an NMR sample for determination of the NMR yield by using 1,1,2,2-tetrachloroethane as an internal standard or was purified by slica gel column chromatography to isolate the product.

Acknowledgements

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Keywords: Cycloisomerization • Indole • Migration • NHC • Nickel

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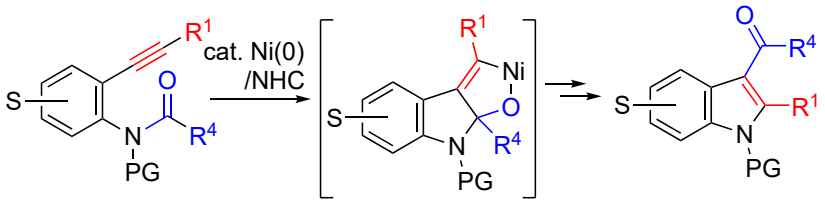

A nickel-catalyzed migratory cycloisomerization of *o*-alkynylanilides was investigated, and it was found to give 2,3-disubstituted indoles. The cyclization was thought to proceed via an aza-nickelcyclepentene intermediate formed from alkyne and the C=O bond amide moiety in the substrate, accompanied by acyl transfer on the nitrogen atom to the C3 position in the product.

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