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Ruthenium-Catalyzed Cycloisomerization of 2-Alkynylanilides: Synthesis of 3-Substituted Indoles by 1,2-Carbon Migration

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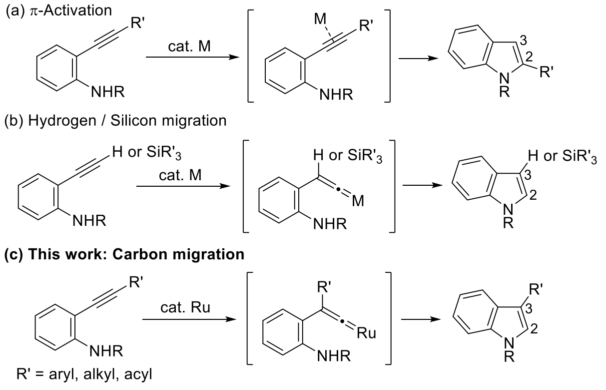
Supporting Information Placeholder

ABSTRACT: We developed ruthenium-catalyzed cycloisomerization of alkynylanilides which gave 3-substituted indoles in high yields. The reaction proceeded via the disubstituted vinylidene ruthenium complex which was formed by the 1,2-carbon migration.

Indole skeleton is found in a large number of natural products and many of them have unique biological activity. Consequently, the indole synthesis has been a very important issue in organic chemistry.[1] The cycloisomerization of 2-alkynylanilines is an efficient method for the synthesis of 2-substituted indoles.[2,3] In the Lewis acid-catalyzed reaction, the cyclization proceeded by the nucleophilic attack of the amino group to the activated alkynyl moiety (Scheme 1a). Alternatively, the formation of the indole skeleton was achieved via the vinylidene intermediate (Scheme 1b).[4,5] In the reaction, the migrating group was limited to hydrogen atom or a silyl group, and no catalytic process which involve the formation of the vinylidene intermediate by the 1,2-carbon migration has been reported. Since the heterolytic cleavage of the C-C bond occurs less readily than the C-Si bond,[6] the 1,2-carbon migration has been considered as a more challenging process.

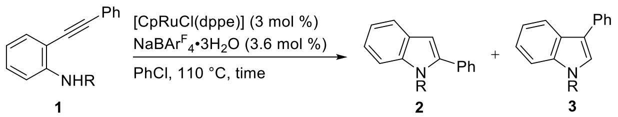
The formation of the vinylidene complex from an alkyne by the alkyne-to-vinylidene rearrangement is a well-known reaction in organometallic chemistry.[7-9] The migration of aryl, alkyl, and acyl group, however, has been far less explored.[10] Herein we report the first ruthenium-catalyzed cycloisomerization of alkynylanilides which gave 3-substituted indoles by 1,2-carbon migration (Scheme 1c).[11]

Scheme 1. Metal-Catalyzed Cycloisomerization of 2-Alkynylanilines



When a solution of **1a**, [CpRuCl(dppe)] (3 mol %), and $NaBAr^F_4 \cdot 3H_2O$ (3.6 mol %) was heated at 110 °C for 4 h in chlorobenzene, two indoles (**2a** and **3a**) were formed in 11% and 20% yields, respectively (Table 1, entry 1). The yields of the products increased when the reaction time was extended to 24 h (entry 2). We assumed that the formation of **2a** was accelerated by the high nucleophilicity of the amino group. When we examined the reaction of a benzoylated substrate (**1b**), the selective formation of the 3-substituted indole was observed (entry 3). We screened the reaction of a series of protected anilines and found that the acetylated substrate (**1c**) was selectively converted to the 3-substituted indole in high yield (entry 4).[12,13]

Table 1. Ruthenium-Catalyzed Cycloisomerization of 2-Aminodiphenylacetylene Derivatives[a]



entry	substrate	time (h)	product (yield, %)
1	**1a** (R = H)	4	**2a** (11), **3a** (20)[a]
2	**1a** (R = H)	24	**2a** (26), **3a** (63)
3	**1b** (R = Bz)	4	**3b** (34)[b]
4	**1c** (R = Ac)	4	**3c** (97)

[a]The yield of **2a** and the recovery of **1a** (62%) were determined by the ^1H NMR analysis. [b]The recovery of **1b** (59%) was observed.

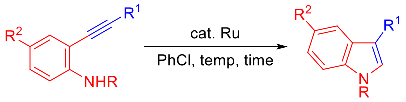
We studied the scope and limitation of this reaction (Table 2). The reaction of a substrate with 4'-methoxy group (**1d**) completed in 2 h and **2d** was isolated in 96% yield (entry 2). The reaction of 4'-bromo derivative (**1e**) gave **3e** (83% yield, entry 3). Compared to these substrates, the reaction of 4'-ethoxycarbonyl derivative (**1f**) was sluggish (entry 4).

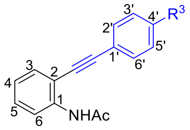
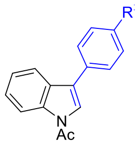
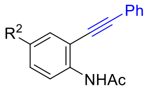
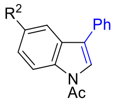
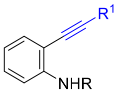
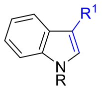
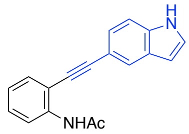
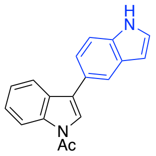
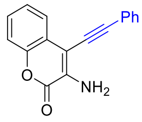
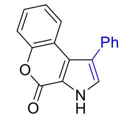
Next, we examined the effect of the substituent introduced to the benzene ring bound to the *N*-acetylamino group (entries 5-7). The reaction of a substrate with 4-methoxy group (**1g**) was sluggish compared to that of **1c**, and **3g**, together with the 2-substituted indole (**2g**), was isolated (entry 5). The reactivity of the chloride (**1h**) was similar to that of **1g** (entry 6). Though the reactivity of the ethoxycarbonyl derivative (**1i**) was very low, the product (**3i**) was obtained in high yield (entry 7).

The scope of this reaction was further explored using sterically congested alkynes. Compared to the reaction of **1c**, harsh conditions (145 °C, 10 mol % of the Ru complex) were required for the reaction of 2'-methylphenyl derivative (**1j,** entry 8). The reaction of 2',6'-dimethylphenyl derivative (**1k**) gave the 3-xylylindole (**3k**) together with **1k** (entry 9).

We next studied the reactions of the substrates with non-aromatic groups bound to the alkynyl group. Though the reaction of a 2-hexynyl derivative (**1l**) completed in the presence of 10 mol % of [CpRuCl(dppbz)] (145 °C, 2 h), the selectivity of the reaction was low (entry 10). The reaction proceeded selectively when an *N*-benzoylaniline (**1m**) was employed as the substrate (entry 11). The reaction of the cyclopentyl derivative (**1n**) gave the corresponding 3-substituted indole (**3n**), while the reaction of *t*-butyl derivative (**1o**) failed (entries 12 and 13). The 2-benzoylethynyl derivative (**1p**) was highly reactive (entry 14). The reaction of an ester (**1q**) gave the corresponding 3-substituted indole (**3q**) in 79% yield (entry 15).

Table 2. Synthesis of 3-Substituted Indoles through 1,2-Carbon Migration[a]



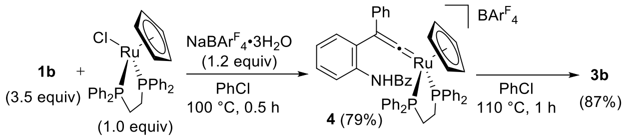
entry	substrate	temp, time	product (yield, %)[b]
			
1	**1c** (R^3 = H)	110 °C, 4 h	**3c** (97)
2	**1d** (R^3 = OMe)	110 °C, 2 h	**3d** (96)
3	**1e** (R^3 = Br)	110 °C, 6 h	**3e** (83)
4	**1f** (R^3 = CO_2Et)	110 °C, 12 h	**3f** (91)
			
5	**1g** (R^2 = OMe)	110 °C, 8.5 h	**3g** (84)[c]
6	**1h** (R^2 = Cl)	110 °C, 8.5 h	**3h** (88)
7	**1i** (R^2 = CO_2Et)	145 °C, 9.5 h	**3i** (90)
			
8[d]	**1j** (R^1, R = 2'-MeC_6H_4, Ac)	145 °C, 2.5 h	**3j** (93)
9[d]	**1k** (R^1, R = 2',6'-$Me_2C_6H_3$, Ac)	145 °C, 24 h	**3k** (54)[e]
10[f]	**1l** (R^1, R = *n*-Bu, Ac)	145 °C, 2.5 h	**3l** (60)[g]
11[f]	**1m** (R^1, R = *n*-Bu, Bz)	145 °C, 2 h	**3m** (87)
12[f]	**1n** (R^1, R = cyclopentyl, Bz)	145 °C, 2.5 h	**3n** (92)
13[f]	**1o** (R^1, R = *t*-Bu, Bz)	145 °C, 6 h	no reaction
14	**1p** (R^1, R = COPh, Ac)	110 °C, 1.5 h	**3p** (93)
15[h]	**1q** (R^1, R = CO_2Et, Ac)	145 °C, 1 h	**3q** (79)
			
16[i]	**1r**	90 °C, 1.5 h	**3r** (92)
			
17[h]	**1s**	145 °C, 2.5 h	**3s** (95)

[a] Reaction conditions: **1** (0.5 mmol, [**1**] = 0.2 M, in PhCl), [CpRuCl(dppe)] (3.0 mol %), $NaBAr^F_4 \cdot 3H_2O$ (3.6 mol %). [b] Isolated yields. A trace amount of **2** was detected in the crude mixture in some reactions. [c] 2-Substituted indole (**2g**) was isolated in 13% yield. [d] [CpRuCl(dppe)] (10 mol %), $NaBAr^F_4 \cdot 3H_2O$ (12 mol %). [e] The recovery of **1k** (35%) was observed. [f] [CpRuCl(dppbz)] (10 mol %), $NaBAr^F_4 \cdot 3H_2O$ (12 mol %). [g] *N*-Acetyl-2-butylindole (**2l**) was isolated in 33% yield. [h] [CpRuCl(dppe)] (5 mol %), $NaBAr^F_4 \cdot 3H_2O$ (6 mol %). [i] [**1r**] = 0.13 M. dppbz = 1,2-bis(diphenylphosphino)benzene.

We further studied the reactions of the substrates bearing a heterocyclic component. The reaction of the 5-indolyl derivative (**1r**) gave **3r** (entry 16). Unexpectedly, the reaction of an aminocoumarin derivative (**1s**) proceeded selectively and a pyrrolocoumarin derivative (**3s**) was isolated (entry 17).

To gain a mechanistic insight, we studied the stoichiometric reaction of **1b** (Scheme 2). When a mixture of **1b**, [CpRuCl(dppe)], and $NaBAr^F_4 \cdot 3H_2O$ was heated at 100 °C for 0.5 h, the vinylidene complex **4** was isolated in 79% yield.[10d,14] When a solution of **4** was heated at 110 °C for 1 h, **3b** was isolated in 87% yield. The formation of **3b** from **4** supports the idea that the vinylidene complex **4** would be the key intermediate.

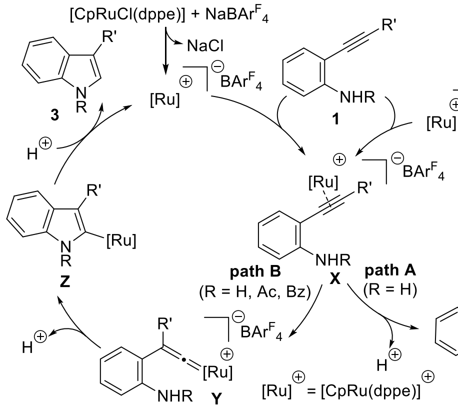
Scheme 2. Synthesis and Reaction of Vinylidene Complex 4



The proposed catalytic cycle of this reaction is shown in Scheme 3. A cationic ruthenium complex would react with **1** to yield π-alkyne complex **X**. The cyclization reaction would proceed when the amino group was bound to the benzene ring, and the 2-substituted indole **2** would be isolated (path A). Alternatively, the 1,2-carbon migration[10c,f,g,i] would yield the vinylidene complex **Y**, which would undergo cyclization (path B). When a less nucleophilic *N*-acylamino group was present, the reaction would proceed preferentially via path B. Finally, 3-substituted indole **3** would be isolated by the protonolysis of **Z.**

In summary, we developed a new ruthenium-catalyzed cycloisomerization of internal alkynes. This reaction is the first example of the catalytic process which proceeded via the ruthenium vinylidene intermediate formed by 1,2-carbon migration. Further development of the reactions which involve the carbon migration is on going.

Scheme 3. Proposed Catalytic Cycle



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and characterization data (PDF)
Crystallographic data for **3g, 3k, 3p,** and **3s** (CIF)

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Notes

The authors declare no competing financial interest.

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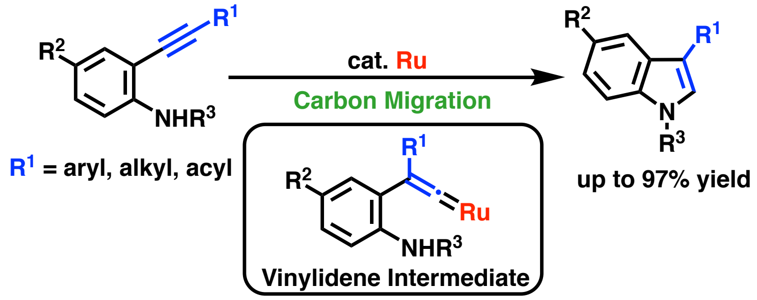
(14) We assume that compound **4** was isolated because the introduction of the benzoyl group reduced the rate of the cyclization of **4**.


R2
R1
NHR3
R1 = aryl, alkyl, acyl
cat. Ru
Carbon Migration
R1
R2
Ru
NHR3
Vinylidene Intermediate
R2
R1
N
R3
up to 97% yield