DOI: 10.1002/adsc.202001342

Advanced Synthesis & Catalysis

A Catalytic Construction of Indoles via Formation of Ruthenium Vinylidene Species from *N*-Arylynamides

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Manuscript received: October 30, 2020; Revised manuscript received: December 22, 2020;
Version of record online: December 30, 2020

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202001342

Abstract: Treatment of ynamides with a catalytic amount of $TpRuCl(PPh_3)_2$ resulted in the construction of indole scaffolds known as privileged structure motifs. This reaction involved a cascade of 1,2-rearrangement and cyclization carrying out C–C bond formation via a ruthenium vinylidene intermediate, as revealed by a deuterium-labeling experiments. Furthermore, the transformation of multifunctionalized ynamide, derived from a practical drug molecule, showed a high functional group tolerance of this reaction.

Keywords: Ynamide; Ruthenium; Vinylidene; Indole; Cyclization

Since the indole scaffold is present as a "privileged structure" in many biologically active compounds including a large number of natural products and pharmaceutics, the development of new methods for the synthesis of an indole scaffold remains a subject of considerable interests in the field of organic chemistry.[1]

Metal vinylidene species are key intermediates in many synthetically important transformations of alkynes.[2] In many studies on the reactions of metal vinylidene species and their applications to synthetic organic chemistry, significant ring formations have been developed with a substrate that has a pendant nucleophilic part in the structure.[3] As an example of cyclization by the pendant carbon nucleus, the synthesis of naphthalenes and polyaromatics has been developed by cyclization with an internal alkene moiety on a vinylidene intermediate generated from *o*-alkynylstyrenes and *o*-alkynylbiphenyls.[3a,d] The use of alkynes bearing a heteroatom nucleus instead of the carbon nucleus afforded heteroaromatics[4] such as benzofuran, which was provided from *o*-alkynylphenol by cyclization of hydroxyl group via the vinylidene intermediate.[4b,d,e,g] Syntheses of indole from *o*-alkynylaniline were realized via C–N bond formation triggered by an intramolecular attack of an amine moiety on vinylidene carbon.[4b,e–i] Tanaka[4g] and Saito[4h] independently developed a method for the synthesis of 3-substituted indoles by 1,2-rearrangement of silyl, aryl, alkyl, and acyl groups (Figure 1, Previous works).

Ynamide has been investigated intensely as a versatile building block because it contains a carbon-carbon triple bond directly substituted to a nitrogen atom of the amide group.[5] The electron-donating ability of the nitrogen atom polarizes the triple bond to give more intriguing reactivity than that of classical alkynes. The utilization of ynamide as a starting material for the synthesis of nitrogen-containing heterocycles has had a dramatic impact in heterocyclic chemistry. Various reactions have been developed for the formation of heterocycles[6–12] such as pyridines,[6] pyrroles,[7] oxazoles,[8] pyrimidines,[9] carbazoles,[10]

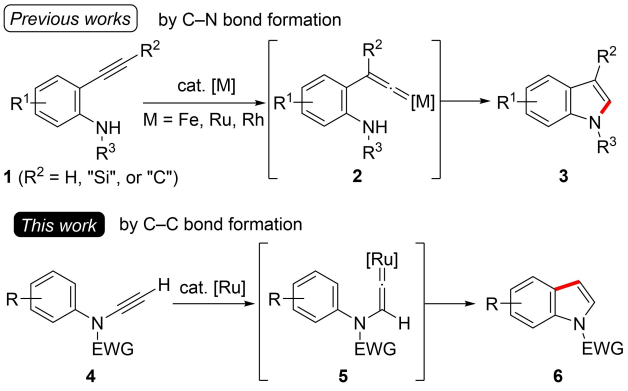


Figure 1. Synthetic methods for indole via a metal vinylidene intermediate by C–N bond and C–C bond formations.

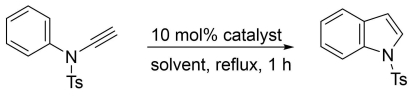
and other heterocycles.[11] Furthermore, applications to natural product synthesis have also been reported.[12] We have also developed a number of molecular transformation of ynamide with a transition metal catalyst to elaborate valuable molecules.[13]

Although there have been many studies on ynamide and metal vinylidene chemistries, the investigation of metal vinylidene generated from ynamide has still been left as an unexplored area. Following our own interests in ynamide chemistry, we envisioned that a new method for the synthesis of an indole scaffold would be realized with metal vinylidene generated from ynamide. Treatment of *N*-arylynamide **4** with a transition metal complex would generate metal vinylidene intermediate **5** by a 1,2-rearrangement. Consecutive cyclization by intramolecular attack of the benzene ring on vinylidene carbon could take place a C–C bond formation to provide the indole scaffold **6** (Figure 1, This work). Here we describe the expedient synthesis of indoles involving C–C bond formation performed by 1,2-rearrangement/cyclization cascade and the investigation of details of the reaction mechanism by deuterium-labeling experiments.

Initially, we studied the reaction of *N*-arylynamide and a catalytic amount of a ruthenium complex (Table 1). The reaction of *N*-phenyl-*N*-tosylynamide **4a** in THF with 10 mol% $[RuCl_2(p\text{-cymene})]_2$ produced the expected *N*-tosylindole **6a** in 11% yield (entry 1). Although the use of the cationic complex $[Cp^*Ru(MeCN)_3]PF_6$ did not give **6a** (entry 2), the neutral complex $CpRuCl(PPh_3)_2$ gave **6a** in the yield of 17% (entry 3). The use of $TpRuCl(PPh_3)_2$ afforded **6a** in an excellent yield (93%; entry 4). Next, solvent effects were investigated (entries 5–7). When the reaction of **4a** was carried out in toluene, **6a** was obtained in 72% yield (entry 5). On the other hand, the reaction did not occur in acetonitrile, and **4a** was recovered in 98% yield (entry 6). The use of ethanol afforded **6a** in 13% yield and resulted in the recovery of **4a** in 28% yield accompanying the generation of dealkynylated tosylanilide in 51% yield (entry 7).

With the optimized conditions in hand, we then studied the application of this reaction to several other ynamide derivatives (Table 2). In the case of *N*-carbamate ynamides such as *N*-methoxycarbonyl and *N*-*tert*-butoxycarbonylynamides **4b** and **4c**, the reactions proceeded smoothly to produce the *N*-methoxycarbonyl and *N*-*tert*-butoxycarbonylindoles **6b** and **6c** in 97% and 84% yields, respectively (entries 1 and 2). When *N*-acetylynamide **4d** was used, the corresponding *N*-acetylindole (**6d**) was obtained in 88% yield (entry 3). The reaction of *p*-methylphenyl, *p*-methoxyphenyl, and *p*-*N*,*N*-dimethylaminophenylynamides **4e**–**4g** afforded the corresponding 5-substituted indoles **6e**–**6g** in good yields (entries 4–6). The structure of **6g** was elucidated by X-ray crystallographic analysis (Figure 2).[14] The use of electron-withdrawing groups bearing ynamides **4h** and **4i** furnished the corresponding indoles **6h** and **6i** in good yields as well (entries 7 and 8). The reaction with

Table 1. Optimization of the reaction conditions.

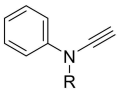
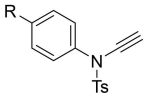
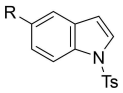
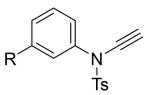
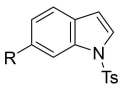
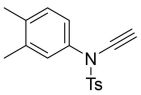
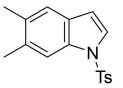


4a **6a**

Entry	Catalyst	Solvent	Yield (%)
1	$[RuCl_2(p\text{-cymene})]_2$	THF	11
2	$[Cp^*Ru(MeCN)_3]PF_6$	THF	-[a]
3	$CpRuCl(PPh_3)_2$	THF	17
4	$TpRuCl(PPh_3)_2$	THF	93
5	$TpRuCl(PPh_3)_2$	toluene	72
6	$TpRuCl(PPh_3)_2$	MeCN	-[b]
7	$TpRuCl(PPh_3)_2$	EtOH	13[c]

[a] 96% recovery of **4a**.
[b] 98% recovery of **4a**.
[c] *p*-tosylanilide was obtained in 51% yield.

Table 2. Ruthenium-catalyzed cyclization of various ynamides.[a]

Entry	Substrate **4**	Product **6** (%)
		
1	**4b** (R = CO_2Me)	**6b**: 97
2	**4c** (R = Boc)	**6c**: 84
3	**4d** (R = Ac)	**6d**: 88
		
4	**4e** (R = Me)	**6e**: 88
5	**4f** (R = OMe)	**6f**: 92
6	**4g** (R = NMe_2)	**6g**: 73
7	**4h** (R = CF_3)	**6h**: 60
8	**4i** (R = Cl)	**6i**: 89
		
9	**4j** (R = Me)	**6j**: 95
10	**4k** (R = OMe)	**6k**: quant
11	**4l** (R = CF_3)	**6l**: 82
12	**4m** (R = F)	**6m**: 83
		
13	**4n**	**6n**: 95

[a] The reaction was carried out in the presence of $TpRuCl(PPh_3)_2$ (10 mol%) in THF under reflux conditions for 1 hour.

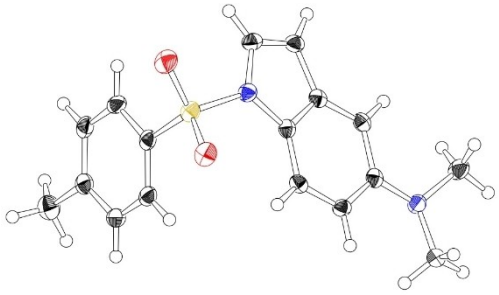


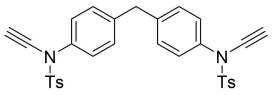
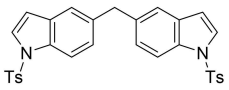
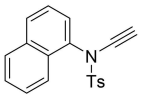
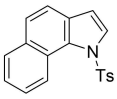
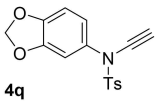
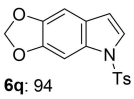
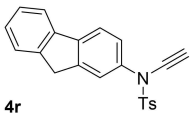
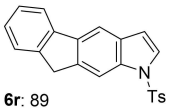
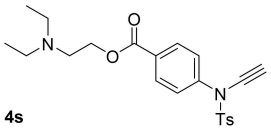
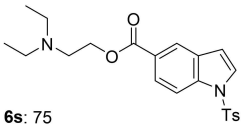
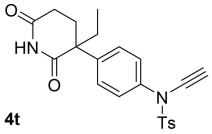
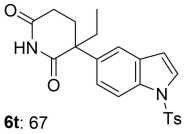
Figure 2. X-Ray crystal structure of **6g** (ellipsoids are shown at 50% probability).

meta-substituted ynamides possessing electron-donating or electron-withdrawing groups **4j**–**4m** gave 6-substituted indoles **6j**–**6m** in high yields because the cyclization proceeded with avoiding the steric hindrance (entries 9–12). When disubstituted ynamide **4n** was subjected to the same reaction conditions, 5,6-dimethylindole **6n** was obtained in 95% yield (entry 13).

We then turned our attention to the challenge of constructing an indole moiety in more complex structures to verify the synthetic utility of this reaction (Table 3). First, ynamides **4o** and **4p** were used for this transformation, and the expected methylene-bridged bisindole **6o** and benzoindole **6p** were obtained in good yields (entries 1 and 2). They are the key structures in a monoamine reuptake inhibitor[15] and a Keap1-Nrf2 protein-protein interaction inhibitor,[16] respectively. When methylenedioxyphenylynamide **4q** was used, the corresponding methylenedioxyindole **6q** was obtained in 94% yield, and it had the core structure of an HIV-1 reverse transcriptase inhibitor[17] and oxidative burst inhibitor[18] (entry 3). In the case of fluorenylynamide **4r**, the corresponding indenoindole **6r**, consisting of a substantial scaffold of organic transistors,[19] was produced in 89% yield (entry 4). Next, to realize the synthesis of indole from multi-functionalized ynamide, the reaction was performed with ynamides **4s** and **4t** derived from the anesthetic drug procaine and the anticancer drug aminoglutethimide, and the desired indoles **6s** and **6t** were obtained in good yields (entries 5 and 6).

To gain an insight into the reaction mechanism, we carried out deuterium-labeling experiments and a cross-over experiment (Scheme 1). The reaction of deuterated ynamide **4a**–d_1 was carried out under the same reaction conditions as those shown in Table 1 to provide 2-deuterated indole **6a**–d_1 in 86% yield with a D-content of more than 95% (Scheme 1a). This result indicated that the reaction proceeded through a vinylidene intermediate generated by 1,2-rearrangement. Next, we used deuterated ynamide **4a**–d_5 as the substrate to clarify the proton source on the C3

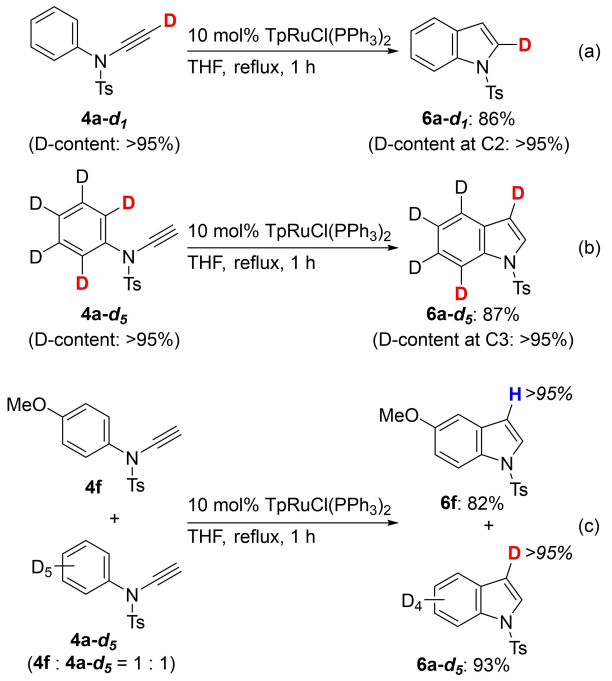
Table 3. Synthesis of indole from complex ynamides.[a]

Entry	Substrate **4**	Product **6** (%)
1	 **4o**	 **6o**: 80
2	 **4p**	 **6p**: 55
3	 **4q**	 **6q**: 94
4	 **4r**	 **6r**: 89
5[b]	 **4s**	 **6s**: 75
6	 **4t**	 **6t**: 67

[a] The reaction was carried out in the presence of TpRuCl$(PPh_3)_2$ (10 mol%) in THF under reflux conditions for 1 hour.
[b] 30 mol% of TpRuCl$(PPh_3)_2$ was used.

position of the indole core. 3-Deuterated indole **6a**–d_5 was obtained in 87% yield with a D-content of more than 95%. Therefore, the source of C3 proton was shown to be derived from the aromatic ring proton of **4a**–d_5 (Scheme 1b). In order to determine whether the C3 protonation proceeded by an intramolecular or intermolecular reaction, we performed a cross-over experiment with **4f** and **4a**–d_5. The C3 protonation occurred in an intramolecular manner since the indoles **6f** and **6a**–d_5 were produced in 82% (H-content $>95\%$) and 93% (D-content $>95\%$) yields without intermolecular scrambling of hydrogen and deuterium (Scheme 1c).

The plausible reaction mechanism based on the observations in these experiments is shown in Figure 3. First, the coordination of ynamide **4** to the ruthenium complex results in the formation of **I**, which induces 1,2-rearrangement to generate ruthenium vinylidene intermediate **II**. Next, consecutive cyclization of **II** produces iminium intermediate **III** forming a C–C bond. Finally, intramolecular C3 protonation proceeds by aromatization to afford indole **6**.



Scheme 1. Deuterium-labeling and cross-over experiments to reveal the reaction mechanism.

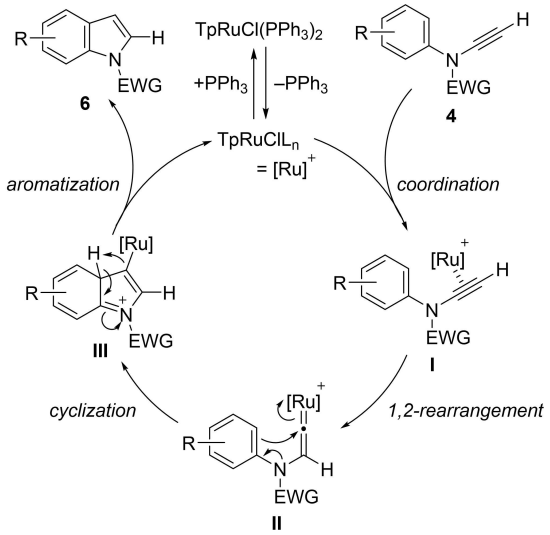


Figure 3. Plausible catalytic cycle of indole synthesis from ynamide.

In summary, we developed a novel ruthenium-catalyzed method for the synthesis of indoles that involves a cascade of 1,2-rearrangement and cyclization to form a C–C bond via a vinylidene intermediate. This method is the first example of the construction of indole scaffolds from ynamides and has high functional group tolerance, as revealed by the reaction with drug molecule-derived multi-functionalized ynamides. Deuterium-labeling and cross-over experiments revealed the detailed mechanism of this reaction. We are currently applying this methodology to internal ynamides and the synthesis of heteroaromatics other than indoles.

Experimental Section

General Procedure: Ruthenium-catalyzed Construction of Indole 6. A solution of ynamide **4** in THF was added to ruthenium catalyst (10 mol% to **4**) by cannulation at ambient temperature. After reflux for 1 h, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give indole **6**.

Acknowledgements

We gratefully acknowledge financial support from JSPS KAKENHI Grant Numbers 17K08226 and 17K15427. We are grateful to Prof. Kazuhiko Takatori for performing X-ray spectroscopy. We also thank Tamami Koseki and Shoko Yamada at the Analytical Center of our university for performing microanalysis, NMR, and mass spectrometry measurements.

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