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A convenient synthesis of (*E*)-α-alkylidene-γ-lactams and (*E*)-3-alkylideneoxindoles by rhodium-catalyzed intramolecular hydroamidation

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Abstract—Rhodium-catalyzed carbonylative cyclization without carbon monoxide was investigated. Cyclization of various formamides having alkynyl groups proceeded smoothly in the presence of $Rh_4(CO)_{12}$ to provide α-alkylidene-γ-lactams or 3-alkylideneoxindoles in moderate to good yields with high (*E*)-selectivity.
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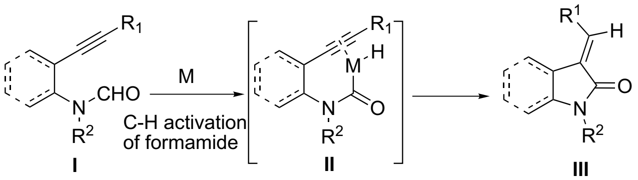
Transition-metal-catalyzed cyclocarbonylation of unsaturated ketones,[1] aldehydes,[2] alcohols and amines[3,4] using carbon monoxide as a powerful tool for the synthesis of cyclic ketones, lactones, lactams, and various heterocyclic compounds.[5] However, the method using carbon monoxide suffers from some disadvantages in terms of toxicity and difficulty of its handling, storage, and transport. Recently, several efficient methods for the cyclization without the use of carbon monoxide have been explored. Although formic acid and its derivatives, aldehydes, and metal carbonyls are used as carbonyl sources in these reactions,[6] there are few reports on the use of formamides as a carbonyl source.[7] This prompted us to utilize the hydroamidation as a novel synthetic tool of various *N*-heterocyclic compounds such as lactams or oxindoles. For this purpose, we first planned to synthesize alkylidenelactams and alkylideneoxindoles **III** by the transition metal-catalyzed C–H bond activation of formamide **I** having an alkynyl group via a presumed intermediate **II** (Scheme 1).



Scheme 1. Synthetic strategy of 3-alkylidene-γ-lactams **III** from alkynylformamides **I**.

Furthermore, the obtained α-alkylidene-γ-lactams and 3-alkylideneoxindoles not only show significant activities against PK-Cs[8] and tyrosine kinase receptors,[9] respectively, but also are recognized to be versatile synthetic intermediates for a variety of natural products such as isopilocarpine,[10] lactacystin, and TMC-95A.[11] So far, various methods for the preparation of **III** have been developed, but only a few methods can be applied to the stereoselective synthesis of (*E*)-**III** and (*Z*)-**III**, respectively.[8–12] Now, we report herein a novel procedure for the synthesis of (*E*)-α-alkylidene-γ-lactams and (*E*)-3-alkylideneoxindoles by $Rh_4(CO)_{12}$-catalyzed intramolecular hydroamidation. To the best of our knowledge, this is the first report of transition metal-catalyzed carbonylative cyclization using the C–H activation[13] of a formamide group.

We first investigated the reaction conditions of the intramolecular hydroamidation of **1a**. Representative results are summarized in Table 1. Although we carried out the reactions of **1a** with $Ru_3(CO)_{12}$ at 135 °C[7c] and with

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Keywords: Rhodium catalyst; Carbonylative cyclization; C–H activation; Formamides; Hydroamidation.

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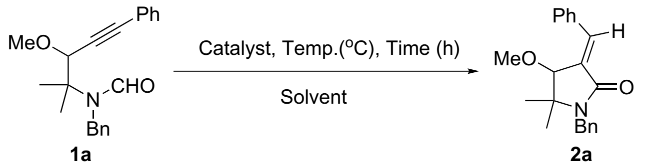
Table 1. Survey of reaction conditions for the cyclization of **1a** to **2a**



Entry	Catalyst[a]	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	$Ru_3(CO)_{12}$	MeCN	135	5	4
2	$Ru_3(CO)_{12}/PCy_3$	Toluene	180	5	Trace
3	$Rh(PPh_3)_2Cl$	Toluene	130	5	0
4	$Pd(PPh_3)_4$	Toluene	130	5	0
5	$Rh_4(CO)_{12}$	Toluene	130	5	50
6[c]	$Rh_4(CO)_{12}$	Xylene	130	10	70
7[c]	$Rh_4(CO)_{12}$	DMF	130	10	56
8[d]	$Rh_4(CO)_{12}$	Xylene	130	10	0

[a] 10 mol % of the catalyst was used under Ar.

[b] Isolated yield.

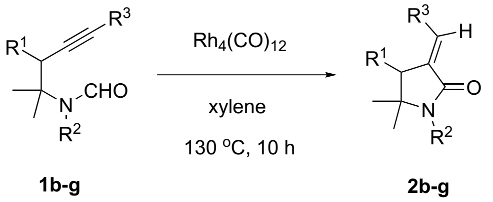
[c] 20 mol % of the catalyst was used under Ar.

[d] Under CO.

$Ru_3(CO)_{12}/PCy_3$ at 180 °C,[7b] the desired product **2a** was obtained in low yields (entries 1 and 2). We also examined Wilkinson's catalyst and $Pd(PPh_3)_4$, which were found to be effective for intramolecular hydroformylation[13] and selenoacylation,[14] respectively, but no desired product was obtained (entries 3 and 4). After various experiments for the cyclization, we found that $Rh_4(CO)_{12}$ was an effective catalyst for the hydroamidation and the desired lactam **2a** was obtained in 50% yield as a single stereoisomer[15] (entry 5). The use of 20 mol % of the catalyst improved the chemical yield to 70% yield[16] (entry 6). Next, various solvents were examined. Among the solvents examined, xylene was the most suitable for the reaction and the use of other solvents, such as DMF or THF led to decrease of the chemical yields (entry 7). Expecting to diminish the catalyst loading,[7a] we carried out the reaction under 1 atom of carbon monoxide, but the desired product could not be obtained at all (entry 8). In any event, it is noteworthy that the cyclization proceeded with perfect stereoselectivity, giving the (*E*)-adduct **2a** as a single product.

Having established the optimum reaction conditions, we next investigated the carbonylative cyclization of various formamides **1b–g** bearing different alkynes (Table 2). The Rh-catalyzed reaction of alkynes **1b–d**, which have different substituents such as *n*-C_4H_9, CH_2OBn, and CH_2OTBS gave the corresponding (*E*)-lactams **2b–d** in 38–74% yields as the single stereoisomers (entries 1–3). The same reaction of alkynes **1e** and **1f** bearing no substituents as the R^1 group ($R^1 = H$) also occurred smoothly to furnish the corresponding lactams **2e** and **2f** in 56% and 72% yields, respectively (entries 4 and 5). On the other hand, concerning the R^2 group, replacement of benzyl group by methyl group or hydrogen led to a significant decrease of the chemical yield of **2g** (entries 6 and 7). This result suggests that somewhat bulky group is necessary as the *N*-protecting group for this cyclization.

Table 2. The Rh-catalyzed cyclization of alkynyl formamides **1b–g**



Entry[a]	Substrates	Yield[b] (%)
1	**1b** ($R^1 = MeO$, $R^2 = Bn$, $R^3 = Bu$)	74
2[c]	**1c** ($R^1 = MeO$, $R^2 = Bn$, $R^3 = CH_2OBn$)	58
3[c]	**1d** ($R^1 = MeO$, $R^2 = Bn$, $R^3 = CH_2OTBS$)	38
4	**1e** ($R^1 = H$, $R^2 = Bn$, $R^3 = Bu$)	56
5	**1f** ($R^1 = H$, $R^2 = Bn$, $R^3 = Ph$)	72
6	**1g** ($R^1 = H$, $R^2 = Me$, $R^3 = Ph$)	36
7	**1h** ($R^1 = H$, $R^2 = H$, $R^3 = Ph$)	0

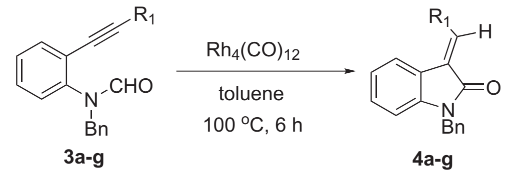
[a] 20 mol % of the catalyst was used under Ar.

[b] Isolated yield.

[c] Dioxane was used as solvent.

The intramolecular hydroamidation protocol was finally applied to a range of alkynes **3a–g** to synthesize 3-alkylideneoxindoles **4a–g** with high stereoselectivity. The results are summarized in Table 3. The reaction of formanilides **3a** and **3b**, bearing different alkyl chains, proceeded under milder reaction conditions (100 °C, 6 h), giving the corresponding oxindoles **4a** and **4b** in 85% and 73% yields, respectively (entries 1 and 2). To our disappointment, however, the products were obtained as mixtures of the stereoisomers ($E/Z = 7.4{:}1$ and 12.5:1).[15] It is noteworthy that the catalyst loading can be diminished to 10 mol % for the cyclization of the formanilides **3**. Similarly, the Rh-catalyzed reaction of alkynes **3c–e** bearing several aromatic groups furnished the corresponding oxindoles **4c–e** in 51–70% yields (entries 3–5). The substituents on the aromatic

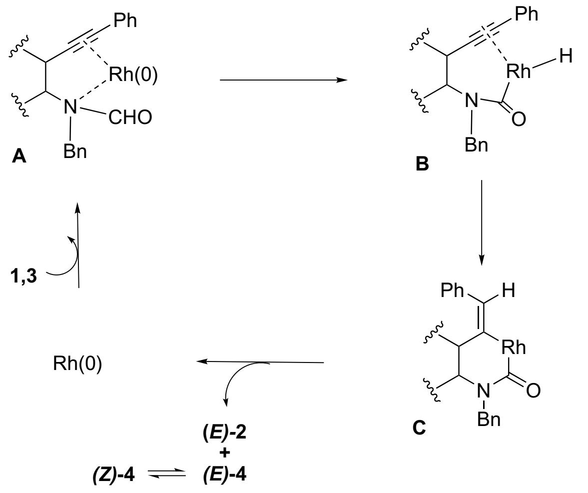
Table 3. The Rh-catalyzed cyclization of alkynyl formanilides **3a**–**g**



Entry[a]	Substrates	Yield[b] (%)	Ratio (E/Z)
1	**3a** ($\mathrm{R}^1 = n\text{-}\mathrm{C}_4\mathrm{H}_9$)	85	7.4:1
2	**3b** ($\mathrm{R}^1 = n\text{-}\mathrm{C}_{10}\mathrm{H}_{21}$)	73	12.5:1
3	**3c** ($\mathrm{R}^1 = \mathrm{Ph}$)	70	4.7:1
4	**3d** ($\mathrm{R}^1 = 4\text{-}\mathrm{MeOC}_6\mathrm{H}_4$)	52	9.4:1
5	**3e** ($\mathrm{R}^1 = 4\text{-}\mathrm{NO}_2\mathrm{C}_6\mathrm{H}_4$)	51	3.1:1
6	**3f** ($\mathrm{R}^1 = \mathrm{CH}_2\mathrm{OBn}$)	48	2.4:1
7	**3g** ($\mathrm{R}^1 = \mathrm{CH}_2\mathrm{OTBS}$)	44	5.0:1

[a] 10 mol % of the catalyst was used under Ar.

[b] Isolated yield.

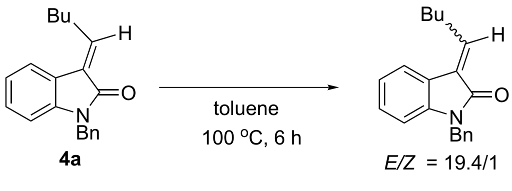


Scheme 3. The plausible reaction mechanism of the intramolecular Rh-catalyzed hydroamidation of **1** and **3**.

rings of **3c**–**e** had only marginal effect on the chemical yield and stereoselectivity. The E/Z ratios of the obtained products were affected by reaction time as well as reaction temperature. Furthermore, oxindoles **4f** and **4g**, possessing the hydroxymethyl moiety, were prepared from alkynes **3f** and **3g** in 44% and 58% yields by the same procedure (entries 6 and 7).

To clarify the applicability of this reaction, we applied the same reaction to the corresponding alkene analogue. However, we could not obtain the desired cyclic product, resulting in the recovery of the starting material. This result suggests that alkyne moieties of the substrates are essential for the Rh-catalyzed intramolecular hydroamidation. In addition, the slow isomerization from (E)-**4** to (Z)-**4** was observed when (E)-**4a** was heated in toluene (100 °C, 6 h: $E/Z = 19.4{:}1$, Scheme 2).[17]

From these results, we proposed the plausible mechanism of the Rh-catalyzed intramolecular hydroamidation as shown in Scheme 3. Although it is not clear at the present stage whether rhodium acts as a mononuclear or as a cluster, the initial coordination of active Rh(0) species to the alkyne moiety of the substrates would promote the oxidative addition of the Rh(0) to the C–H bond (**A** → **B**). The direct insertion of rhodium to the C–H bond cannot be ruled out. Then, the formed Rh–H bond of **B** inserts into the alkyne in a cis-manner to give the intermediate **C**,[18] and subsequent reductive elimination affords (E)-**2** or (E)-**4** exclusively. However, we obtained the products **4** as a mixture of both isomers due to the isomerization of (E)-**4** to (Z)-**4**.[19] An alternative pathway, rhodium-catalyzed decarbonylation of **1** or **3** and subsequent aminocarboxylation of the intramolecular alkyne with the CO released from the substrates or $\mathrm{Rh}_4(\mathrm{CO})_{12}$ could be ruled out from the results of Table 1 (entry 8). The fact that, in the course of the reaction, no decarbonylated products were obtained also suggests a direct hydroamidation.



Scheme 2. Isomerization experiment of **4a**.

In summary, we have developed a novel synthetic method of (E)-α-alkylidene-γ-lactams **2** and (E)-3-alkylidene-oxindoles **4** without using carbon monoxide. The rhodium-catalyzed hydroamidation of formamides **1** and **3** having several alkynyl groups provided the corresponding lactams **2** and **4** with E-selectivity in moderate to good yields. Further detailed investigations into the synthetic and mechanistic aspects of this cyclization are underway.[20]

Acknowledgments

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16. A mixture of **1a**–**g** (0.10 mmol), Rh$_4$(CO)$_{12}$ (0.020 mmol), and xylene (1.0 mL) was placed in a Pyrex flask with a magnetic stirring bar under an argon atmosphere. The mixture was then magnetically stirred at 130 °C (oil bath temp.) for 5–10 h. After cooling to room temperature, column chromatograph on silica gel (eluent: hexane/EtOAc = 10:1–5:1) gave the products **2a**–**g**.
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