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Ruthenium-Catalyzed Hydrocarbamoylative Cyclization of 1,6-Diynes with Formamides

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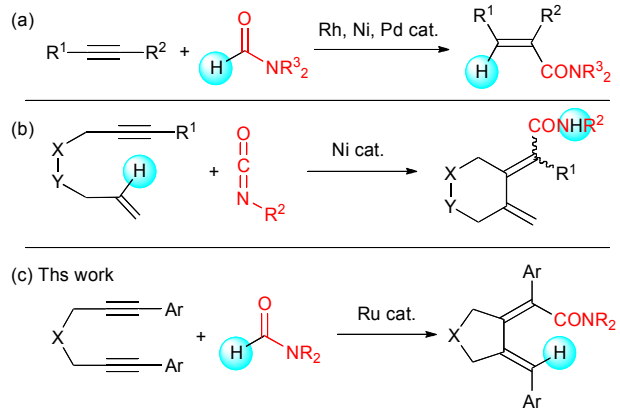
The ruthenium-catalyzed hydrocarbamoylative cyclization of 1,6-diynes with formamides afforded exocyclic-diene-type α,β,γ,δ-unsaturated amides with complete stereoselectivity. A plausible mechanism involving ruthenium hydride species is proposed to explain experimental results. Some control experiments performed using DMF-d_7 and/or D_2O corroborate the proposed mechanism.

Acrylamide is an important raw material that is used for the industrial production of polyacrylamides.[1] Although the parent acrylamide is manufactured by the catalytic hydration of acrylonitrile at an industrial scale,[2] an efficient and selective access to multi-substituted acrylamides has been sought in laboratory settings.[3] One of the most atom-efficient approaches is the hydrocarbamoylation of substituted alkynes. To this aim, the stoichiometric and catalytic carbonylative coupling of alkynes with amines has been developed, although such coupling requires harmful carbon monoxide.[3,4] To avoid the use of carbon monoxide, the transition-metal-catalyzed hydrocarbamoylation of alkynes with formamides has been recently developed to produce cyclic and acyclic α,β-unsaturated amides (Scheme 1a).[5] Despite these breakthroughs, a relevant hydrocarbamoylative coupling of formamides with two molecules of alkynes that yields α,β,γ,δ-unsaturated amides has not yet been realized.

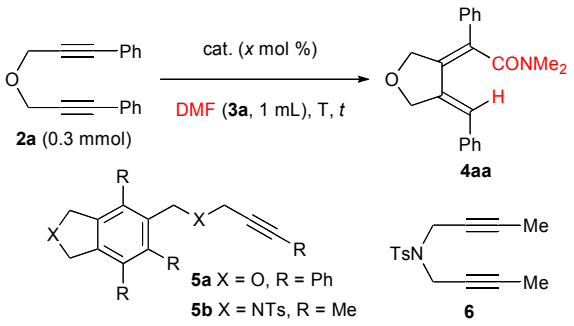


Scheme 1 (a) Hydrocarbamoylation of alkynes with formamides, (b) cyclocoupling of α,ω-enynes with isocyanates, and (c) hydrocarbamoylative cyclization of 1,6-diynes (This work).

Further, α,β,γ,δ-unsaturated amides are important synthetic targets as they are found in various natural products, showing significant biological activities.[6] Nevertheless, the atom-efficient synthesis of α,β,γ,δ-unsaturated amides is still scarce.[7] Notably, D'Souza and Louie reported that the nickel-catalyzed cyclocoupling of α,ω-enynes with isocyanates produced exocyclic-diene-type α,β,γ,δ-unsaturated amides with high atom efficiency (Scheme 1b).[7b] However, the drawbacks of this method is that it requires moisture-sensitive isocyanates and stereoselectivity is imperfect owing to the isomerization of the acrylamide moiety under catalytic conditions.

During our study on the ruthenium-catalyzed hydrofunctionalization/cyclization of α,ω-diynes,[8] we discovered that in the presence of a ruthenium catalyst, hydrocarbamoylative cyclization of 1,6-diynes proceeded in DMF to afford similar cyclic α,β,γ,δ-unsaturated amides (Scheme 1c). The advantage of this method is that the carbamoyl group can be directly introduced from readily available and bench-top stable formamides with the formal cleavage of a formyl C–H bond, and the exocyclic diene moiety is constructed with complete stereoselectivity. Herein, we report the preliminary results of our study on the ruthenium-catalyzed hydrocarbamoylative cyclization of 1,6-diynes using formamides.

In order to optimize the reaction conditions, the hydrocarbamoylative cyclization of a representative diyne substrate (**2a**) was investigated using DMF (**3a**) as a solvent (Scheme 2 and Table 1). In the presence of 10 mol % cationic ruthenium complex $[CpRu(MeCN)_3]PF_6$ (**1a**, Cp = η^5-C_5H_5), **2a** was heated in DMF at 100 °C under Ar. The reaction completed in 1 h, affording amide **4aa** in 57% yield (Table 1, entry 1). Notably, the stereochemistry of both alkylidene moieties was completely controlled (*vide infra*).



Scheme 2 Hydrocarbamoylative cyclization of diyne **2a** in DMF.

When more electron-rich catalyst $[Cp^*Ru(MeCN)_3]PF_6$ (**1b**, Cp* = η^5-Me_5C_5) was used, the reaction completed in a shorter reaction time (20 min) and the yield of **4aa** increased to 72% (entry 2). On the other hand, the neutral catalyst Cp*RuCl(cod) (**1c**, cod = 1,5-cyclooctadiene) proved ineffective owing to the yield of an undesired dimerization product **5a** (entry 3). When the reaction was repeated at a lower temperature of 70 °C, **4aa** was obtained in a comparable yield, albeit with a longer reaction time of 2 h (entry 4). However, a further reduction in the reaction

temperature (50 °C) diminished the yield of **4aa** (entry 5). At a decreased loading of **1b** (5 mol %), the reaction did not complete even after stirring at 120 °C for 12 h (entry 6). Therefore, the conditions of entry 2 are optimal. In striking contrast, diyne **6** bearing methyl terminals was treated with **1b** (10 mol %) in DMF at 100 °C for 11 h, affording **5b** in 31% yield. Therefore, terminal aryl groups are essential for this reaction. The use of *n*-propyl formate istead of DMF did not produce the corresponding hydrocarboxylative cyclization product.

Table 1. Optimization of reaction conditions using DMF solvent.

Entry	Cat. (*x*)	*T* (°C)	*t* (h)	Yield (%)[a]
1	**1a** (10)	100	1	57 (59)
2	**1b** (10)	100	1/3	72 (76)
3	**1c** (10)	100	6	—[b]
4	**1b** (10)	70	2	72 (76)
5	**1b** (10)	50	20	(42)[c]
6	**1b** (5)	120	12	(48)[c]

[a]Isolated yields. The yields determined by the NMR analysis of crude materials are indicated in parentheses. [b]Dimer **5a** was obtained in 21% yield (NMR) along with unreacted **2a** (28% NMR). [c]Unreacted **2a** was observed for entries 5 (8% NMR) and 6 (4% NMR).

The scope of diyne substrates in terms of terminal aryl groups was investigated under optimized conditions (Fig. 1). The reaction of diyne **2b** with *p*-tolyl terminals afforded a result similar to that obtained with the reaction of **2a**. Similarly, diynes **2c** and **2d**, possessing *p*-chlorophenyl and *p*-fluorophenyl terminals, afforded the corresponding amides **4ca** and **4da** in higher yields (79% and 86%, respectively). To investigate electronic influence of the aryl terminals, diyne substrates possessing electron-withdrawing or electron-donating substituents on the aryl terminals were subjected to the reaction. The reaction of *p*-ethoxycarbonyl and *p*-acetyl-substituted diyne **2e** and **2f** completed in 6.5 h, affording **4ea** and **4fa** in 64% yields. In contrast, diyne **2g** with *p*-formylphenyl terminals gave the corresponding product **4ga** in a low yield (15%) due to side reaction(s).[9]

When the reaction of diyne **2h** with *p*-methoxyphenyl terminals was carried out at 100 °C for 20 h, **4ha** was obtained in a low yield (27%) along with the recovered substrate (16%). Therefore, electron-donating aryl terminals are detrimental to hydrocarbamoylative cyclization. Nevertheless, diyne **2i** with 1,3-benzodioxol-5-yl terminals was allowed to react with DMF at 100 °C for 5.5 h, affording amide **4ia** in a moderate yield (47%). Moreover, diynes **2j** and **2k** with 3,5-dimethoxyphenyl or 3,4,5-trimethoxyphenyl terminal groups were converted to the corresponding amides **4ja** and **4ka**, respectively, over a shorter period, and their yields were higher (74% and 73%, respectively). In these cases, polyoxygenated aryl terminals are presumably less electron-donating, because the resonance of the ether-oxygen lone pairs with the π-system of the terminal phenyl rings is inefficient owing to the restricted conformations. Then, the reaction of unsymmetrical diyne **2l**, possessing both *p*-methoxyphenyl and *p*-fluorophenyl terminals, was carried out to investigate the influence of the terminal groups on regioselectivity. As a result, amide **4la** and **4la'** were formed in 63% combined yield with a ratio of **4la**/**4la'** = 2:1. This result suggests that carbamoylation preferably occurs at the more electron-rich terminal.

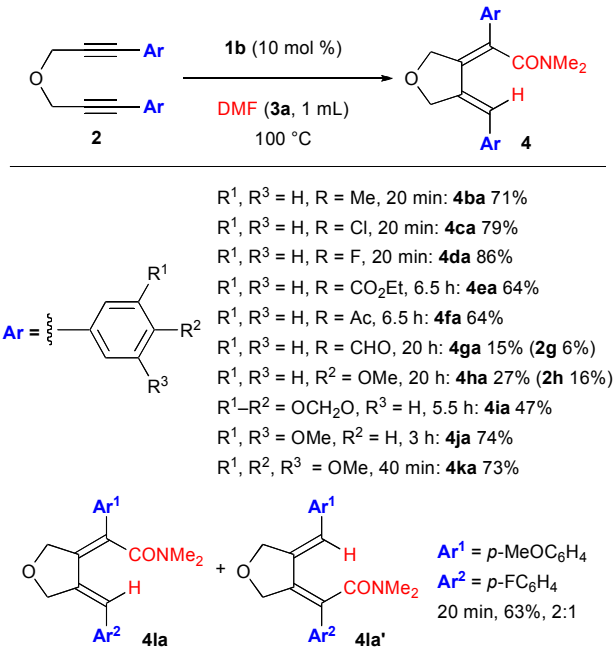


Figure 1 Reactions of diynes **2b–l** in DMF.

Furthermore, the impact of the tether moiety was investigated as shown in Fig. 2. The reaction of tosylamide-derived diyne **2m** efficiently underwent hydrocarbamoylative cyclization under optimized conditions to afford amide **4ma** in 75% yield. Because a single crystal with good quality was obtained, the structure of **4ma** was unambiguously confirmed by X-ray diffraction analysis (Fig. S2). In contrast, the reaction of malonate-derived diyne **2n** was sluggish at 100 °C, and, thus, the reaction was carried out at a higher temperature (140 °C). However, the yield of **4na** (33%) was much lower than the yields of **4aa** and **4ma**. The inefficiency of **2n** can be ascribed to the sterically demanding malonate moiety. Accordingly, diynes **2o**, **2p** and **2q** possessing less-hindered tertiary carbon centers in the tethers, were subjected to hydrocarbamoylative cyclization at 140 °C for 20 h. As a result, the conversions of these substrates improved, and the corresponding products **4oa**, **4pa** and **4qa** were obtained in 40–50% yields. Thus, ester, ketone and acetoxy groups were well tolerated. Although diyne **2r** with an all-methylene tether was completely consumed at 140 °C, an inseparable mixture of the desired product **4ra** and unidentified by-products was formed. Nevertheless, **4ra** was isolated in 43% yield along with the intact **2r** (20%) when the same reaction was carried out at 100 °C for 20 h. In contrast, no corresponding product was observed for the reaction of 1,7-diyne **2s**. Moreover, neither hydrocarbamoylative cyclization nor hydrocarbamoylation occurred from 1,6-enyne **7** or (3-methoxyprop-1-ynyl)benzene (**8**). These results show that a 1,6-diyne moiety is imperative for the present hydrocarbamoylative cyclization.

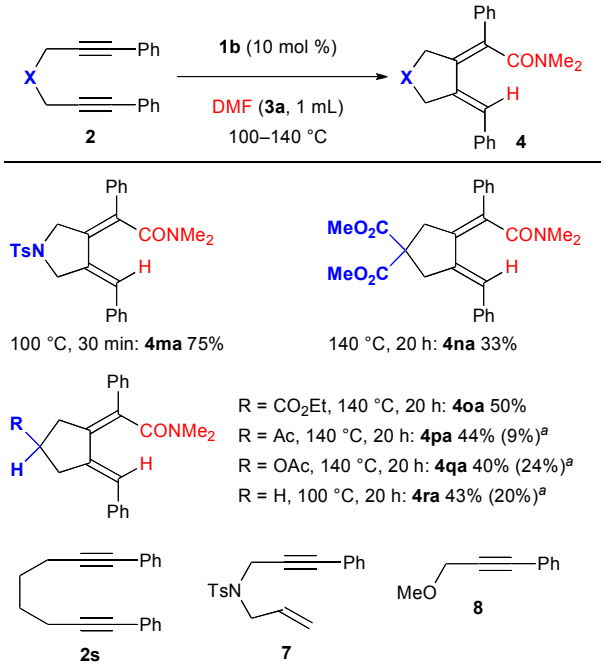


Figure 2 Reactions of diynes **2m**–**s** and enyne **7** in DMF. [a]Yields of unreacted **2** were shown in parenthesis.

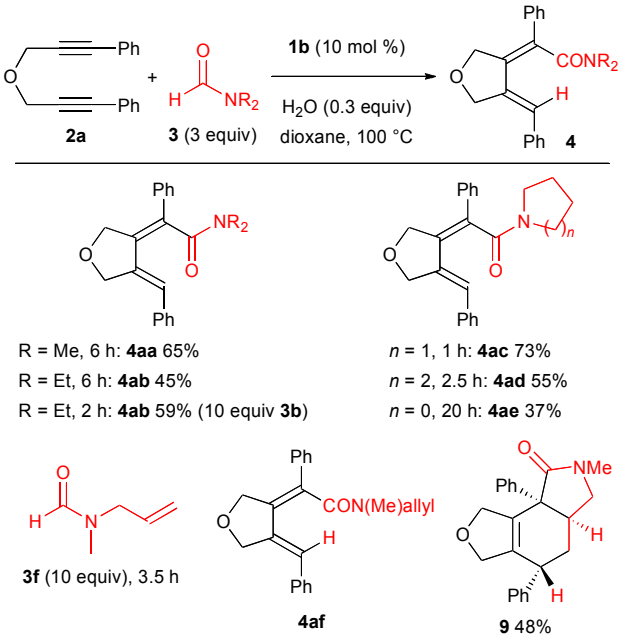
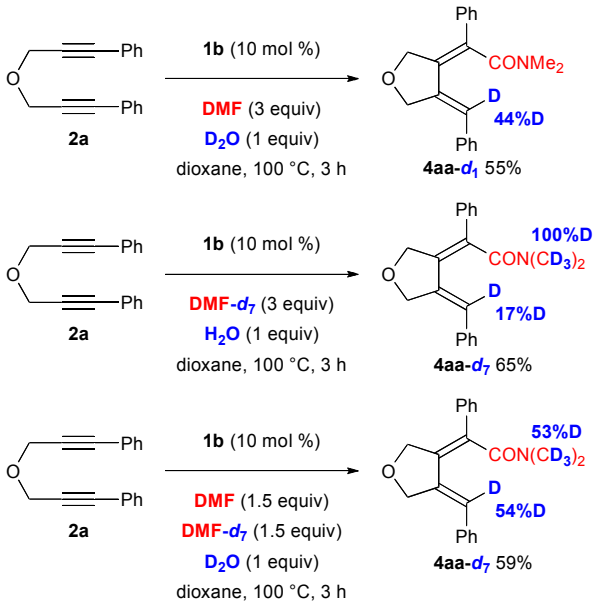


Figure 3 Reactions of **2a** with formamides **3a**–**f** in dioxane.

In order to reduce the amount of formamides, we screened several reaction parameters and found that in the presence of **1b** (10 mol %), **2a** was heated with DMF (**3a**, 3 equiv) and H_2O (0.3 equiv) in dioxane at 100 °C for 6 h to afford **4aa** in 65% yield. Although the use of THF as a solvent (70 °C, 8 h) afforded a similar result, other solvents such as chlorobenzene, *N*,*N*-dimethylacetamide, acetonitrile, and 1,2-dichloroethane proved ineffective. The reaction was sluggish in the absence of H_2O; however, its increased loading resulted in a negative impact on the yield of **4aa** because undesired hydrative cyclization proceeded.[10] The reactions of diyne **2a** with other formamides were investigated under the conditions referred above (Fig. 3). *N*,*N*-Diethylformamide (**3b**) afforded the corresponding amide **4ab** in a lower yield (45%). The same reaction was repeated with an increased loading of **3b** (10 equiv) in a shorter reaction time (2 h), affording **4ab** in an improved yield (59%). These results show that relatively bulky formamide reduced the reaction efficiency. In fact, the reaction of *N*-formylpyrrolidine **3c** afforded amide **4ac** in a good yield of 73%, whereas the yield of the corresponding piperidine derivative **4ad** was moderate (55%). However, the reaction was sluggish using much smaller *N*-formylazetidine **3e** and **4ae** was obtained in a lower yield (37%). Moreover, the reaction of diyne **2a** with *N*-allylformamide **3f** (10 equiv), was also examined as a synthetic application. Interestingly, the expected hydrocarbamoylative cyclization product **4af** underwent *exo*-selective intramolecular Diels–Alder reaction (IMDA) to afford tricyclic lactam **9** as a single stereoisomer in 48% yield. The relative stereochemistry of **9** was elucidated by NOE measurements (Fig. S1). The density functional theory calculations suggest that the second IMDA step is a thermally feasible process, which proceeds with an activation energy of $\Delta G^{\ddagger}$ = +28.5 kcal/mol and is exergonic by ΔG = 25.4 kcal/mol (Fig. S3).

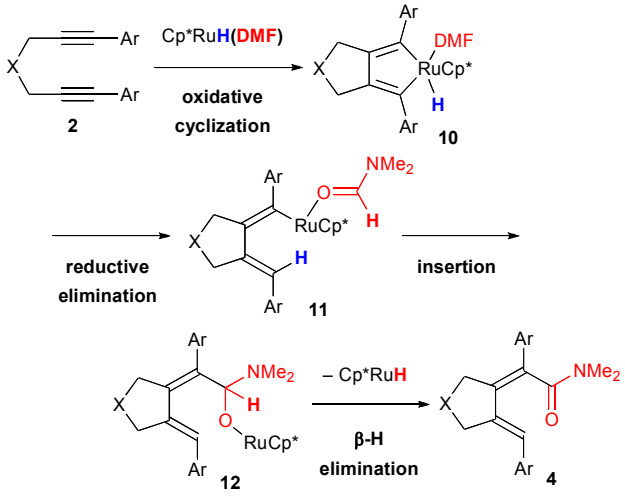
To gain insights into the reaction mechanism, we carried out several control experiments. The reaction of diyne **2a** with 3 equiv of DMF was carried out in the presence of 1 equiv of D_2O in dioxane at 100 °C for 3 h, affording **4aa**-d_1 in 55% yield with a 44% D content at the vinylic position. Therefore, the vinylic proton is derived from both D_2O and DMF. The reaction of **2a** with 3 equiv of DMF-d_7 was also carried out in the presence of 1 equiv of H_2O in dioxane at 100 °C for 3 h, affording **4aa**-d_7 in 65% yield. In this case, the D labels of the *N*-methyl substituents were completely preserved, although the D content of vinylic proton was only 17%. These results indicate that the ruthenium hydride species involved in the catalytic cycle caused H–D exchange, and the vinylic proton was derived from the formyl proton as well as added H_2O.



Scheme 3 Control experiments.

Furthermore, the same reaction was also repeated with DMF/DMF-d_7 (each 1.5 equiv) in dioxane at 100 °C for 3 h, affording **4aa**-d_7 with the D contents of 53% and 54% at the *N*-methyl and vinylic protons, respectively. This result indicates that no KIE was observed ($k_{DMF}/k_{DMF\text{-}d7} \simeq 1$) and, thus, the formyl C–H cleavage is not involved in the rate-determining step. Moreover, *N*-formylpiperidine (**3d**) was treated with 20 mol % **1b** in the presence of D_2O (1 equiv) in dioxane at 100 °C for 8 h; however, the incorporation of deuterium into the formyl proton was negligible. Therefore, the direct cleavage of the formyl C–H bond via oxidative addition can be ruled out.

Tsuji and co-workers previously proposed that the hydrocarbamoylation of internal alkynes was catalyzed by hydropalladium species, which undergo initial hydropalladation of an internal alkyne.[5c] Similarly, it can be envisaged that ruthenium hydride species [Cp*RuH] undergoes sequential hydroruthenation of a diyne.[11] However, this mechanism is less likely to occur because the present reaction is strictly limited to 1,6-diynes with aryl terminals (Fig. 2). Thus, the involvement of ruthenacycle intermediates was inferred from the necessity of a 1,6-diyne moiety. On the basis of the above results, a plausible mechanism is proposed as outlined in Scheme 4. The initial oxidative cyclization of diyne **2** with [Cp*RuH(DMF)] generates ruthenacycle **10**,[12] which undergoes subsequent reductive elimination to generate dienylruthenium intermediate **11**. Next, the insertion of the ligated DMF into the Csp^2–Ru bond produces alkoxyruthenium intermediate **12**, which finally undergoes *β*-H elimination to afford amide **4** with the concomitant restoration of [Cp*RuH].[13] Because this pathway involves ruthenium hydride species, the observed deuterium incorporation from D_2O can be explained by the H–D exchange of the hydride ligands.



Scheme 4 Proposed mechanism for hydrocarbamoylative cyclization.

In conclusion, we discovered that the ruthenium-catalyzed hydrocarbamoylative cyclization of 1,6-diynes proceeded in DMF to afford exocyclic-diene-type α,β,γ,δ-unsaturated amides with complete stereoselectivity. Furthermore, we also found that the same reaction proceeded with 3–10 equiv of formamides by adding H_2O (0.3 equiv) in dioxane. Under these conditions, we could obtain various amides from the combination of 1,6-diynes and formamides. As an synthetic application, tandem hydrocarbamoylative cyclization/intramolecular Diels–Alder reaction was achieaved to obtain a fused lactam as a single stereoisomer.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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