

# Regio- and Stereoselective Synthesis of Enamides and Dienamides by Ruthenium-Catalyzed Co-Oligomerization of *N*-Vinylamides with Alkenes or Alkynes\*\*

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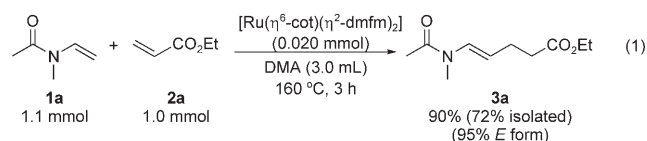
In memory of Yoshihiko Ito

Enamides are contained in many natural products such as salicylhalamide<sup>[1]</sup> and lobatamide,<sup>[2]</sup> and have recently been synthesized using transition-metal catalysts, as represented by a) the vinylation of amides,<sup>[3]</sup> b) the chelation-assisted coupling reaction of *N*-vinylamides with 1,3-butadiene,<sup>[4]</sup> c) the addition of amides to alkynes,<sup>[5]</sup> d) the oxidative amidation of alkenes,<sup>[6]</sup> and e) the isomerization of *N*-allylamides.<sup>[7]</sup> Dienamides are also important building blocks for preparing several alkaloids by the Diels–Alder reaction.<sup>[8]</sup> However, there are still few examples of transition-metal-mediated or -catalyzed synthesis of dienamides.<sup>[9]</sup>

In considering potential new methods for the synthesis of enamides and dienamides, we have focused our efforts on ruthenium-catalyzed regio- and stereoselective codimerization reactions. Many examples of transition-metal-catalyzed codimerization reactions of alkenes with alkynes have been reported.<sup>[10]</sup> We also have already developed and reported the reactions of [2+2] cycloaddition<sup>[11]</sup> and linear codimerization reactions<sup>[12]</sup> of alkenes with alkynes. In sharp contrast, a codimerization reaction of “different alkenes” is still quite difficult except for hydrovinylation<sup>[13]</sup> and a challenging subject in modern organic and organometallic chemistry.<sup>[14]</sup> Herein we report zero-valent ruthenium-catalyzed codimerization reaction of different alkenes, that is, a codimerization reaction of *N*-vinylamides with alkenes as well as a co-oligomerization reaction of *N*-vinylamides, acrylates, and ethylene, which offer novel and atom-economical methods for

the synthesis of enamides with high regio- and stereoselectivity in one step.<sup>[15,16]</sup> As expected, the present catalyst system can be applied to the codimerization of *N*-vinylamides with alkynes, which enables the selective synthesis of dienamides.

Treatment of *N*-methyl-*N*-vinylacetamide (**1a**, 1.1 mmol) with ethyl acrylate (**2a**, 1.0 mmol) in the presence of a catalytic amount of [Ru( $\eta^6$ -cot)( $\eta^2$ -dmfm)<sub>2</sub>] (0.020 mmol; cot = 1,3,5-cyclooctatriene, dmfm = dimethyl fumarate) in *N,N*-dimethylacetamide (DMA, 3.0 mL)<sup>[14b,17]</sup> at 160 °C for 3 h gave the linear codimer, ethyl 5-(*N*-methylacetylaminopent-4-enoate (**3a**), in 90 % yield with 95 % *E* selectivity [Eq. (1)].



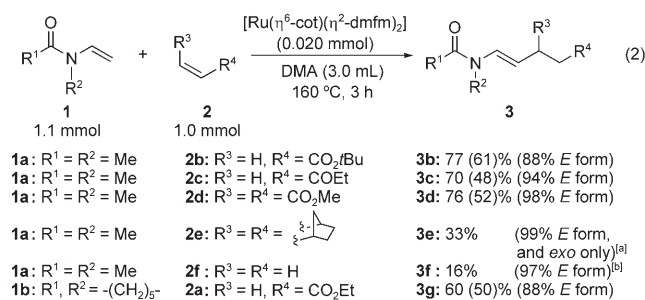
First, the catalytic activity of several low-valent ruthenium complexes for the codimerization of **1a** with **2a** was examined. Besides [Ru( $\eta^6$ -cot)( $\eta^2$ -dmfm)<sub>2</sub>], [Ru( $\eta^5$ -cyclooctadienyl)<sub>2</sub>] (**3a**, 81 %), and [Ru( $\eta^4$ -cod)( $\eta^6$ -cot)] (**3a**, 78 %; cod = 1,5-cyclooctadiene) showed high catalytic activity, while other zero-valent ruthenium complexes, such as [Ru<sub>3</sub>(CO)<sub>12</sub>] (**3a**, 6 %) and [Ru(CO)<sub>3</sub>(PPh<sub>3</sub>)<sub>2</sub>], and divalent ruthenium complexes, such as [Cp\*RuCl( $\eta^4$ -cod)] (Cp\* = pentamethylcyclopentadienyl), [(RuCl<sub>2</sub>(CO)<sub>3</sub>)<sub>2</sub>], [RuH<sub>2</sub>(PPh<sub>3</sub>)<sub>4</sub>], and [RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub>], were almost ineffective for the reaction in this study.

The reaction in Equation (1) required a temperature of over 150 °C for complete conversion of both substrates, and the best result was obtained at 160 °C (**3a**, 90 %). However, at 170 °C, the reaction became sluggish, and the yield of **3a** decreased to 65 %.

Several enamides were prepared by this method in good to high yields with high *E* selectivity [Eq. (2)]. Electron-deficient alkenes are suitable for this reaction; for example, codimerization of *N*-methyl-*N*-vinylacetamide (**1a**) with ethyl vinyl ketone (**2c**) or dimethyl maleate (**2d**) gave **3c** and **3d** in respective yields of 70 % and 76 %. Although 2-norbornene (**2e**) and ethylene (**2f**) could also be used, the yields of the codimers, **3e** (*exo* only) and **3f**, were rather low. For the

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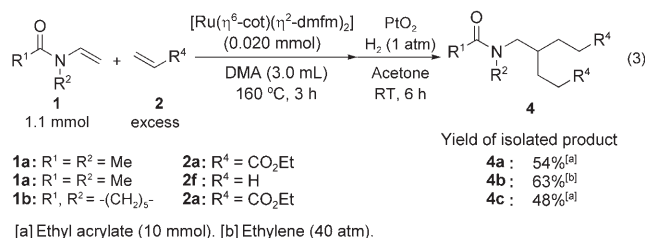
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Yield was determined by GLC. Figures in parentheses are yields of isolated product. [a] 2-Norbornene (5.0 mmol). [b] Ethylene (10 atm).

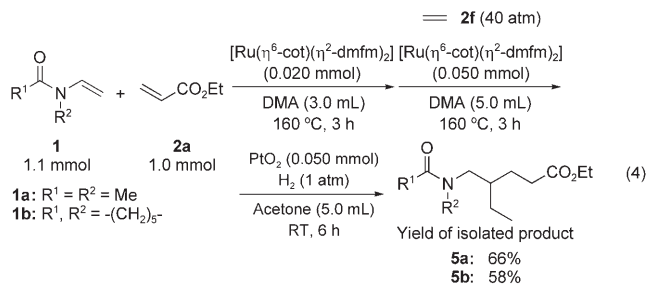
synthesis of **3f**, higher ethylene pressure promoted 1:2 co-oligomerization of **1a** with **2f** (see Eq. (3)). *N*-Vinylcaprolactam (**1b**) also reacted with ethyl acrylate (**2a**) to give the desired enamide, ethyl 5-(2-oxoazaperhydroepinyl)pent-4-enoate (**3g**), in 60% yield.

In this study, only *N*-vinylamides worked well and no codimerization occurred between other vinylamide derivatives, such as 3-vinyl-2-oxazolidinone (**1c**) or *N*-methyl-*N*-vinyl-*p*-toluenesulfonamide (**1d**), and ethyl acrylate (**2a**) even under the optimum reaction conditions. A chelating effect of *N*-vinylamides toward an active ruthenium species should play an important role in the catalytic cycle (see Scheme 1). On the other hand, treatment of *N*-vinylamides **1** with a large excess of alkenes **2** under the same catalytic reaction conditions and subsequent hydrogenation gave 1:2 co-oligomers **4** in up to 63% yield [Eq. (3)].

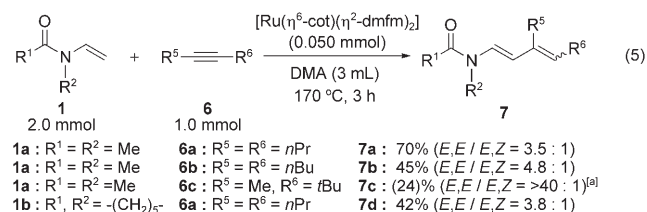


This result means that double C–C bond formation proceeded selectively at the β position of a vinyl group in *N*-vinylamides **1**. Furthermore, codimerization reaction of the isolated enamide **3a** with **2a** proceeded with the same catalyst system to give **4a** in a yield of 56% (isolated product) after hydrogenation. This result strongly suggests that the co-oligomerization proceeds stepwise and substituted *N*-vinylamides would be generally applicable to the reaction.

Then, we attempted to develop a three-component coupling reaction of different alkenes. After many trials, we realized this reaction through the combination of *N*-vinylamides **1**, ethyl acrylate (**2a**), and ethylene (**2f**; 40 atm). Hydrogenation of the generated isomeric cotrimers gave **5** as a single product in up to 66% yield [Eq. (4)]. To the best of our knowledge, the selective cotrimerization reaction of two or three different alkenes had never been accomplished before.



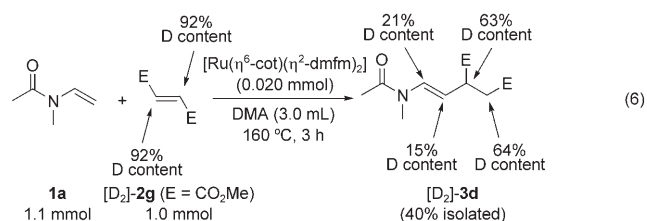
The same catalyst system can be applied to the codimerization of *N*-vinylamides **1** with alkynes **6**, which enables the selective synthesis of dienamides **7** [Eq. (5)]. Both symmetri-



Yield was determined by GLC. Figures in parentheses are yields of isolated product. [a] For 24 h.

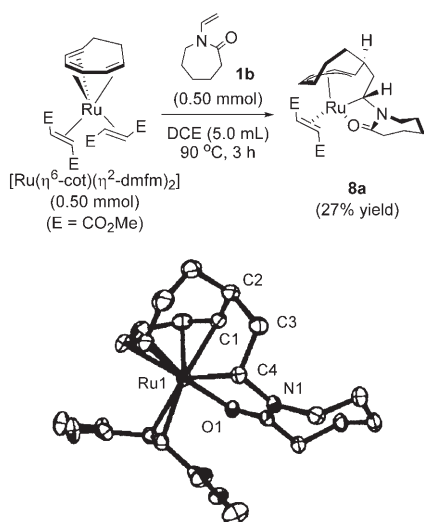
cally and unsymmetrically substituted internal alkynes, such as 4-octyne (**6a**), 5-decyne (**6b**), and 4,4-dimethyl-2-pentyne (**6c**), reacted smoothly with *N*-vinylamides **1a** and **1b** to give the corresponding dienamides in good yields with high *E,E* selectivity.

To investigate the mechanism, the reaction of **1a** with [D<sub>2</sub>]dimethyl fumarate ([D<sub>2</sub>]-**2g**) was carried out in the presence of the [Ru(η<sup>6</sup>-cot)(η<sup>2</sup>-dmfm)<sub>2</sub>] catalyst in DMA at 160 °C for 3 h to give the deuterium-scrambled enamide ([D<sub>2</sub>]-**3d**) in a yield of 40% isolated product [Eq. (6)]. This



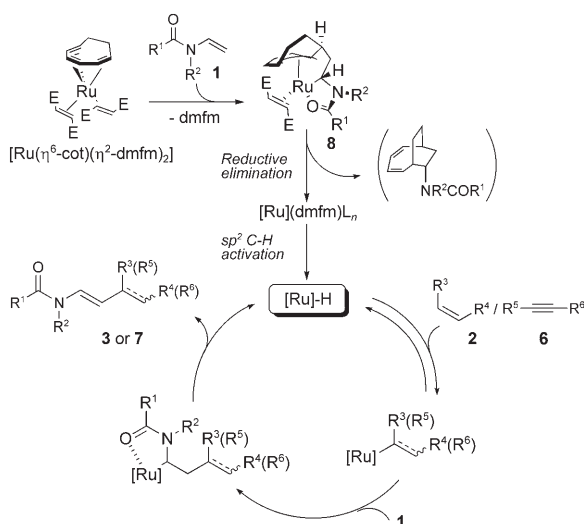
deuterium scrambling could be explained by the formation of a ruthenium hydride species at an early stage in the catalytic cycle (see below).

A stoichiometric reaction of [Ru(η<sup>6</sup>-cot)(η<sup>2</sup>-dmfm)<sub>2</sub>] with *N*-vinylcaprolactam in 1,2-dichloroethane (DCE) at 90 °C for 3 h under an argon atmosphere gave a new complex **8a** (27% yield of isolated product; Figure 1).<sup>[18]</sup> This complex could be obtained by a ligand-exchange reaction of one molecule of dmfm with *N*-vinylcaprolactam and subsequent oxidative cyclization between a cot ligand with a vinyl group of *N*-vinylcaprolactam. Complex **8a** also showed good catalytic activity for the codimerization of **1b** with **2a** to give **3g** in 56% yield.



**Figure 1.** Formation and molecular structure of **8a**. Thermal ellipsoids are shown at 50% probability.

Considering all of the results described above, we postulated the following mechanism for the codimerization of *N*-vinylamides **1** with alkenes **2** or alkynes **6** (Scheme 1).



**Scheme 1.** A possible mechanism for the codimerization of *N*-vinylamides **1** with alkenes **2** or alkynes **6**.

The reaction starts with the removal of a cot ligand in  $[\text{Ru}(\eta^6\text{-cot})(\eta^2\text{-dmfm})_2]$  by *N*-vinylamides **1** through metallacycle formation of **8** and reductive elimination<sup>[19]</sup> to give coordinatively unsaturated zero-valent ruthenium species, which is effective for the formation of a ruthenium hydride species through activation of  $\text{sp}^2$  C–H bonds in alkenes or a dmfm ligand.<sup>[20]</sup> Alkenes **2** or alkynes **6** are then inserted into a Ru–H bond, followed by the successive chelation-assisted insertion of *N*-vinylamides into a Ru–C bond (see above). Subsequent  $\beta$ -hydride elimination gives the products, **3** and **7**, with regeneration of an active ruthenium hydride species. At this stage, a mechanism that involves oxidative cyclization of *N*-vinylamides with alkenes (or alkynes) to give a

ruthenacyclopentane (or ruthenacyclopentene) intermediate could not be completely excluded; however, the result of deuterium scrambling shown in Equation (6) can be reasonably explained by a mechanism that involves the formation of a ruthenium hydride species.

In conclusion, we have succeeded in developing novel ruthenium-catalyzed regio- and stereoselective codimerization and co-oligomerization of *N*-vinylamides with alkenes or alkynes. This process provides a rapid and atom-economical method for the synthesis of biologically and synthetically important enamides and dienamides. Isolation of organometallic intermediates as well as DFT calculations are currently under investigation.

## Experimental Section

Representative procedure for the synthesis of **3a** from **1a** and **2a**: A mixture of *N*-vinylacetamide (**1a**; 108 mg, 1.1 mmol), ethyl acrylate (**2a**; 100 mg, 1.0 mmol),  $[\text{Ru}(\eta^6\text{-cot})(\eta^2\text{-dmfm})_2]$  (9.9 mg, 0.020 mmol), and *N,N*-dimethylacetamide (DMA, 3.0 mL) was placed in a two-neck 20-mL pyrex flask equipped with a magnetic stirring bar and a reflux condenser under a flow of argon. The reaction was carried out at 160 °C for 3 h with stirring under an argon atmosphere (balloon). After the reaction mixture was cooled, the products were analyzed by GLC and isolated by Kugelrohr distillation as a pale yellow oil (143 mg, 0.72 mmol, 72 % yield); b.p. 150 °C (6.0 torr, Kugelrohr); IR (neat): 2980, 1735, 1677, 1648, 1391  $\text{cm}^{-1}$ . Major rotamer:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 6.68 (d,  $J$  = 13.6 Hz, 1 H), 5.02–4.92 (m, 1 H), 4.14 (q,  $J$  = 7.2 Hz, 2 H), 3.04 (s, 3 H), 2.41 (br, 4 H), 2.20 (s, 3 H), 1.26 ppm (t,  $J$  = 7.2 Hz, 3 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 172.8, 169.0, 129.9, 109.2, 60.3, 34.9, 29.4, 25.8, 21.9, 14.2 ppm. Minor rotamer:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 7.36 (d,  $J$  = 14.5 Hz, 1 H), 5.02–4.92 (m, 1 H), 4.13 (q,  $J$  = 7.2 Hz, 2 H), 3.08 (s, 3 H), 2.39 (brs, 4 H), 2.19 (s, 3 H), 1.26 ppm (t,  $J$  = 7.2 Hz, 3 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 172.9, 168.8, 127.9, 108.9, 60.3, 35.1, 33.0, 25.7, 22.5, 14.2 ppm; MS (EI):  $m/z$ : 199 [ $M^+$ ]. Elemental analysis (%) calcd for  $\text{C}_{10}\text{H}_{17}\text{NO}_3$ : C 60.28, H 8.60, N 7.03; found: C 60.04, H 8.31, N 6.76.

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