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Rhenium-Catalyzed Hydroamidation of Unactivated Terminal Alkynes: Synthesis of (*E*)-Enamides

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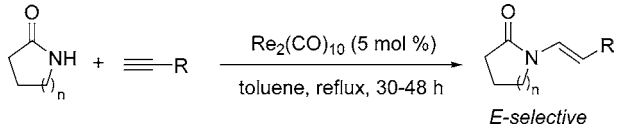
ABSTRACT



Reactions of cyclic amides with unactivated terminal alkynes in the presence of a catalytic amount of a rhenium complex provided (*E*)-enamides in high regio- and stereoselectivity (*E*:*Z* = >99:<1).

Transformations that employ substrates with a readily available N−H bond to provide access to *N*-heteroatom-containing compounds are highly desirable.[1] Enamide is one of the important structures that is often found in natural products and synthetic drugs.[2,3] Therefore, a variety of methods for its synthesis have emerged. In general, enamides are accessed via dehydrative condensation between aldehydes and amides.[3] There have been numerous protocols for synthesizing enamides catalyzed by transition metal complexes, such as isomerization of *N*-allylamides,[4] oxidative amidation of alkenes,[5] coupling reactions of vinylamides with 1,3-butadiene,[6] and co-oligomerization of *N*-vinylamides with alkynes and alkenes.[7] Recently, intermolecular hydroamidation of terminal alkynes has received much attention.

Reported catalytic systems are limited to ruthenium catalysts, and the presence of a ligand is necessary to control the stereoselectivity.[8] Therefore, there still remains a significant need for more efficient methods to afford enamides stereoselectively. Previous work in our laboratory and by other groups show that rhenium complexes are highly effective catalysts for C−C bond-forming reactions to afford useful compounds.[9,10] On the other hand, there have only been a few examples of rhenium catalysts that promote C−N bond-forming reactions; two studies have reported on rhenium-catalyzed C−N bond-forming reactions via hydroamination of alkynes in intramolecular fashion.[11] Direct formation of a new C−N bond by addition of an amine or amide to a C−C triple bond could be of great significance. We

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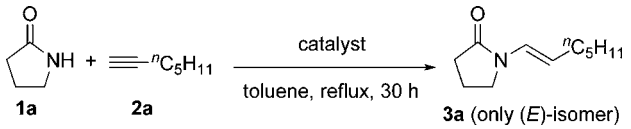
report herein the development of regio- and stereoselective hydroamidation of alkynes to afford enamides.

Preliminary studies were carried out by reaction between pyrrolidinone (**1a**) and 1-heptyne (**2a**) using a series of rhenium and manganase catalysts (5 mol %). The results are summarized in Table 1. Initially, the reaction was carried

Table 1. Transition-Metal-Catalyzed Synthesis of **3a**[a]



1a **2a** **3a** (only (*E*)-isomer)

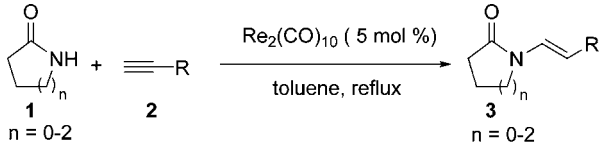
entry	catalyst	mol %	yield (%)[b]
1	$[ReBr(CO)_3(thf)]_2$	5	15
2	$ReBr(CO)_5$	10	19
3	$Re_2(CO)_{10}$	5	80
4	$Re_2(CO)_{10}$	2.5	58
5	$Re_2(CO)_{10}$[c]	5	20
6	$MnBr(CO)_5$	10	0
7	$Mn_2(CO)_{10}$	6	0

[a] **1a** (1 equiv), **2a** (2 equiv). [b] Isolated yield. [c] 1,4-Dioxane was used as a solvent.

out using the $[ReBr(CO)_3(thf)]_2$ catalyst that was used for the C−C bond-forming reactions (entry 1).[9] Fortunately, the catalyst was also suitable for C−N bond-forming reactions to afford an *anti*-Markovnikov adduct in 15% yield, and only the *E*-isomer was formed at the end of the reaction. After examination of several rhenium and manganese complexes, we found that a commercially available rhenium complex, $Re_2(CO)_{10}$, was active without an additive and could catalyze the C−N bond formation to afford enamide **3a** in 80% yield and high stereoselectivity (entry 3). The yield of **3a** decreased when the amount of catalyst was reduced to 2.5 mol % (entry 4). Manganese complexes were ineffective for this transformation (entries 6 and 7).[12]

To elucidate the generality of this reaction, we next examined several alkynes and amides. Representative results are summarized in Table 2. The reaction of *tert*-butyl acetylene (**2b**) proceeded smoothly to afford the corresponding product **3b** in 71% yield (entry 1). Upon treatment with 3-phenyl-1-propyne (**2c**), the pyrrolidinone **1a** gave enamide **3c** in 77% yield (entry 2). When pyrrolidinone (**1a**) was treated with **2d** and **2e**, the corresponding enamides were obtained in 70% and 62% yields, respectively (entries 3 and 4).[13] These results show that carbonyl groups did not inhibit the reactions. By employing a larger-sized cyclic amide such as piperidinone (**1b**) as a substrate, the reaction with **2a** and **2c** proceeded sluggishly to give enamides **3f** and **3g** in 35%

Table 2. Hydroamidation Reactions of Cyclic Amides with Alkynes[a]



1 **2** **3**

entry	amide	alkyne	time (h)	product	yield (%)[b]
1	**1a**	**2b**	30	**3b**	71
2	**1a**	**2c**	30	**3c**	77
3	**1a**	**2d**	30	**3d**	70
4	**1a**	**2e**	30	**3e**	62
5	**1b**	**2a**	48	**3f**	35
6	**1b**	**2c**	48	**3g**	20
7	**1c**	**2a**	48	**3h**	68[c]

[a] **1** (1 equiv), **2** (2 equiv). [b] Isolated yield. [c] *E*:*Z* = 2:1

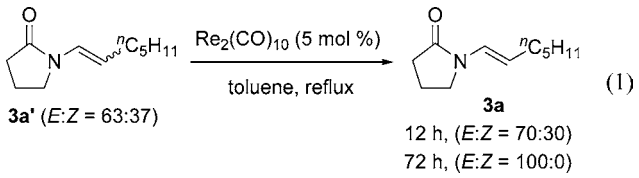
and 20% yields, respectively (entries 5 and 6). When the reaction of azetidinone (**1c**) with 1-heptyne (**2a**) was conducted under the same conditions, a mixture of products was obtained (*E*:Z = 2:1) in 68% yield (entry 7).

Several experiments were carried out to obtain information on the product selectivity. First, we examined the *E*-isomer product **3a** by treatment of **1a** with **2a** under the present conditions but varying the reaction time (2, 4, 6, 8, 10, 12, 24, and 30 h). Interestingly, in all cases the reaction proceeded highly selectively to give only the *E*-isomer product. On the other hand, when a mixture of isomers **3a′** (*E*:*Z* = 63:37)[14] was heated at reflux in toluene in the presence of $Re_2(CO)_{10}$ (5 mol %); the ratio changed to *E*:*Z* = 70:30 after 12 h. The ratio changed to *E*:*Z* = 100:0 after 72 h (eq 1). This result shows that the rhenium complex also catalyzed the isomerization of the *Z*-isomer of **3a** to an *E*-enamide; however, the rate of the isomerization was slow. The above two investigations suggest that the present reaction proceeds in an *E*-stereoselective manner.

(12) For our recent example of manganese catalytic reaction, see: Kuninobu, Y.; Nishina, Y.; Takeuchi, K.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6518−6520 and refererences therein.

(13) When phenylacetylene was used as the reaction partner instead of aliphatic acetylenes, a dimerization reaction of phenylacetylene occurred giving (*E*)-1,4-diphenylbut-1-en-3-yne in 45% yield. On the other hand, when acyclic amides were used instead of cyclic amide, the reaction did not occur and the amide was recovered almost quantitatively.

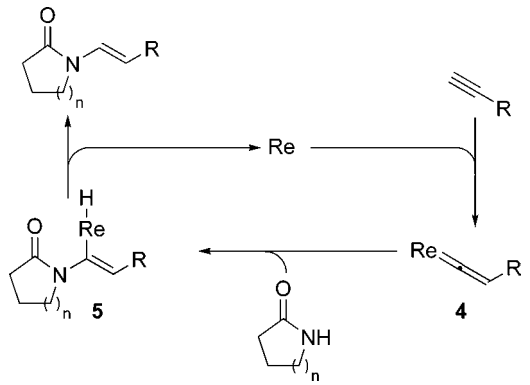
(14) The substrate was synthesized following the procedure in ref 8a.



(1)

Although the mechanism of the reaction remains uncertain, one possibility is that the reaction proceeds via the activation of a C−C triple bond by π-coordination of the alkyne moiety to the metal center.[15] Subsequent formation of a rhenium−vinylidene intermediate **4**, followed by intermolecular nucleophilic attack of the amide group to **4**, gives **5**.[16] Reductive elimination of rhenium from **5** gives enamide and regenerates the rhenium catalyst (Scheme 1). Another possibility is the oxidative addition of the amide group followed by the insertion of the alkyne moiety into the rhenium−amide complex.

Scheme 1. Plausible Mechanism for the Rhenium-Catalyzed Hydroamidation of Alkynes



In summary, we have succeeded in developing novel rhenium-catalyzed regio- and stereoselective hydroamidation reactions to afford enamides in moderate to good yields. To the best of our knowledge, rhenium complexes have not been utilized for such intermolecular hydroamidation of alkynes. This methodology represents a powerful diverse catalytic system for the constructions of enamides.

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Supporting Information Available: Experimental details, characterization data, and copies of both ^{1}H and ^{13}C NMR spectra of all compounds (**3a**−**3h**). This material is available free of charge via the Internet at http://pubs.acs.org.

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