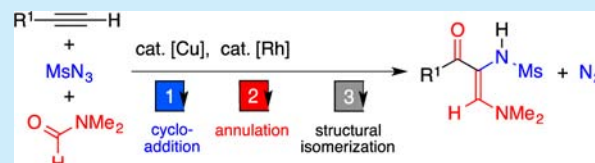


Direct Production of Enaminones from Terminal Alkynes via Rhodium-Catalyzed Reaction of Formamides with *N*-Sulfonyl-1,2,3-triazolesTomoya Miura,* Yuuta Funakoshi,[†] Takamasa Tanaka,[†] and Masahiro Murakami*

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S Supporting Information

ABSTRACT: A rhodium-catalyzed reaction of formamides with *N*-sulfonyl-1,2,3-triazoles is developed to formulate a new one-pot procedure for the direct synthesis of α -amino enaminones from terminal alkynes.



Enaminones serve as versatile intermediates for the synthesis of a wide variety of heterocycles contained in biologically active compounds,¹ and their synthesis from readily available starting materials has been an area of active research.^{2–4} Now, we report a simple method for the synthesis of enaminones from terminal alkynes, *N*-sulfonyl azides, and formamides. Of note is that three different bonds, *i.e.*, a C–N single bond, a C=O double bond, and a C=C double bond are installed regioselectively across the C≡C triple bond in one pot (Figure 1).

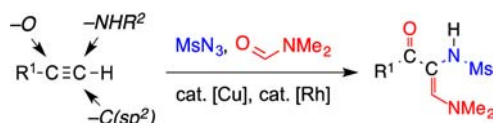
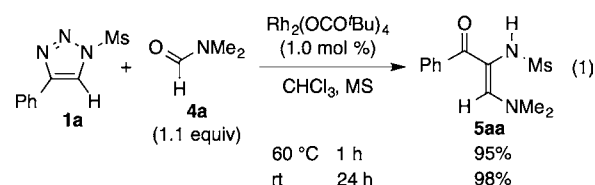


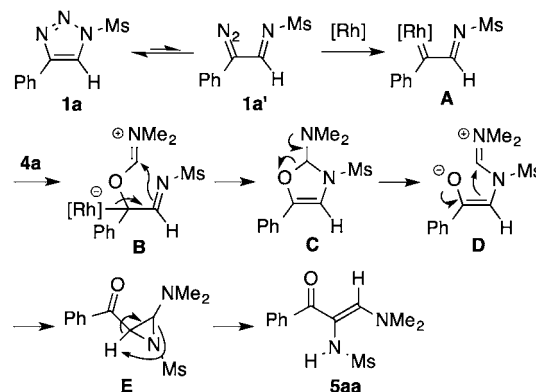
Figure 1. Construction of enaminones from terminal alkynes by introducing three different bonds.

N-Sulfonyl-1,2,3-triazoles react with transition metal complexes to generate α -imino metal carbene complexes,⁵ which react with various compounds of nucleophilic character.⁶ Even formyl groups are nucleophilic enough to add to the carbenoid carbon. For example, a reaction with simple aldehydes produces 4-oxazolines.⁷ On the other hand, α,β -unsaturated aldehydes give rise to 2,3-dihydropyrroles.⁸ Fokin et al. recently reported that ketones were formed with the use of relatively stereo-demanding secondary amides.⁹ These studies led us to examine the use of tertiary formamides as the nucleophilic partner¹⁰ with the expectation of the production of the corresponding 2-amino-4-oxazolines. Thus, 1-mesy-4-phenyl-1,2,3-triazole (**1a**) was prepared from phenylethyne (**2a**) and mesyl azide (**3a**) according to the authentic procedure using copper(I) thiophene-2-carboxylate (CuTC).¹¹ Then, the triazole **1a** (0.20 mmol) was mixed with *N,N*-dimethylformamide (DMF; **4a**, 1.1 equiv), a rhodium pivalate dimer (1.0 mol %), and 4 Å molecular sieves (MS) in chloroform (2 mL), and the mixture was heated at 60 °C for 1 h (eq 1). Much to our surprise, not



the expected 2-amino-4-oxazoline but α -amino-substituted enaminone **5aa** was formed exclusively and isolated in 95% yield after chromatographic purification.¹² The reaction proceeded even at room temperature. The formal metathesis of a C≡C triple bond and a C=O double bond occurs with the simultaneous incorporation of an amino substituent.

We propose the following mechanism for the unexpected formation of the enaminone **5aa** from triazole **1a** and DMF (**4a**) (Scheme 1). Initially, reversible ring–chain tautomerization of the triazole **1a** generates α -diazo imine **1a'**, which reacts with rhodium(II) to afford α -imino rhodium carbene complex

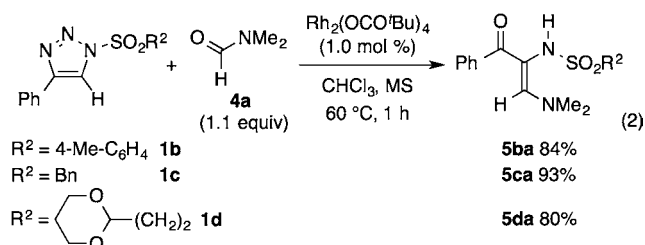
Scheme 1. Proposed Mechanism for the Formation of Enaminones 5aa

Received: April 14, 2014

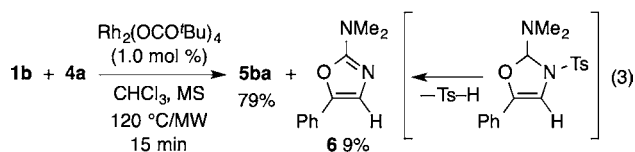
Published: April 28, 2014

A with extrusion of molecular nitrogen. Nucleophilic addition of the formyl group of **4a** to the electrophilic carbene center gives zwitterionic intermediate B. The anionic rhodium releases an electron pair, which induces the imino nitrogen to attack the carbon of the iminium ion, producing 4-oxazoline intermediate C.⁷ The C–O bond of the *N,O*-hemiaminal moiety is cleaved, and the resulting zwitterionic species D recyclizes to aziridine intermediate E. Finally, the aziridine ring is opened to rearrange into the enaminone **5aa**.¹³

With respect to the substituent on the sulfonyl group, *p*-tolyl, benzyl, and 2-(1,3-dioxan-2-yl)ethyl¹⁴ groups are all suitable (eq 2). The product **5ba** was a crystalline compound, and its structure was confirmed by a single-crystal X-ray analysis.



When the reaction of **1b** was carried out at 120 °C under microwave irradiation, 2-amino-oxazole **6** was isolated in 9% yield in addition to the enaminone **5ba** (eq 3). The formation of **6** is consistent with elimination of *p*-toluenesulfonic acid from the 4-oxazoline intermediate corresponding to C, which supports the mechanism shown in Scheme 1.



Various triazoles **1** were subjected to the reaction with DMF at 60 °C (Table 1). Triazoles **1e–i** possessing an aryl group at the 4-position all reacted well to afford the corresponding products **5ea–ia** in high yields ranging from 92% to 97%

Table 1. Rh(II)-Catalyzed Reaction of Various Triazoles **1e–m** with DMF (**4a**)^a

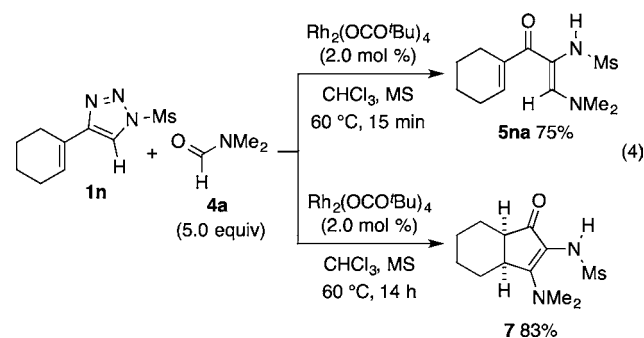
Reaction scheme showing the synthesis of product **5** from triazole **1** and compound **4a** (N,N-dimethyl-2-oxoethanimine) using $\text{Rh}_2(\text{OCOtBu})_4$ (1.0 mol %) in CHCl_3 with MS at 60°C for 1 h.

triazole 1	entry	R ¹	product 5	yield (%)
1	4-Me-C ₆ H ₄	1e	5ea	97
2	4-MeO-C ₆ H ₄	1f	5fa	93
3	4-MeO ₂ C-C ₆ H ₄	1g	5ga	94 ^b
4	4-CF ₃ -C ₆ H ₄	1h	5ha	92
5	3-thienyl	1i	5ia	93
6	ⁿ Hex	1j	5ja	91 ^c
7	BzO(CH ₂) ₄	1k	5ka	91 ^c
8	(phth)N(CH ₂) ₄	1l	5la	92 ^c
9	EtO	1m	5ma	56 ^c

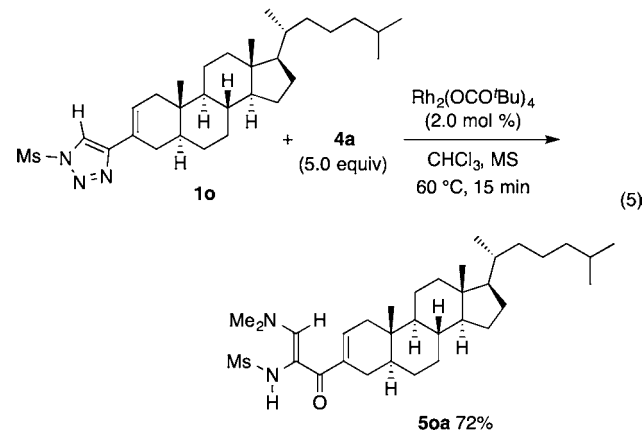
^a**1** (0.20 mmol), **4a** (0.22 mmol), $\text{Rh}_2(\text{OCO}^t\text{Bu})_4$ (2.0 μmol), and MS (40 mg) in CHCl_3 (2 mL). ^b3 h. ^c**4a** (1.0 mmol) in CHCl_3 (0.5 mL).

(entries 1–5). Of note was that even alkyl-substituted triazoles **1j–l** gave the products **5ja–la** in high yields, despite the possibility of a 1,2-hydride shift occurring with the rhodium carbene complex (entries 6–8).¹⁵

Whereas it has been reported that 1-cyclohexenyl-substituted triazole **1n**¹⁶ undergoes an intramolecular cyclization to give 2,3-fused pyrrole in the absence of DMF,¹⁷ it underwent the intermolecular reaction with DMF selectively to give divinyl ketone **5na**, which is suggestive of the relatively strong nucleophilicity of DMF.¹⁸ Interestingly, a prolonged reaction time caused the ensuing Nazarov cyclization to afford 2-cyclopentenone **7**.

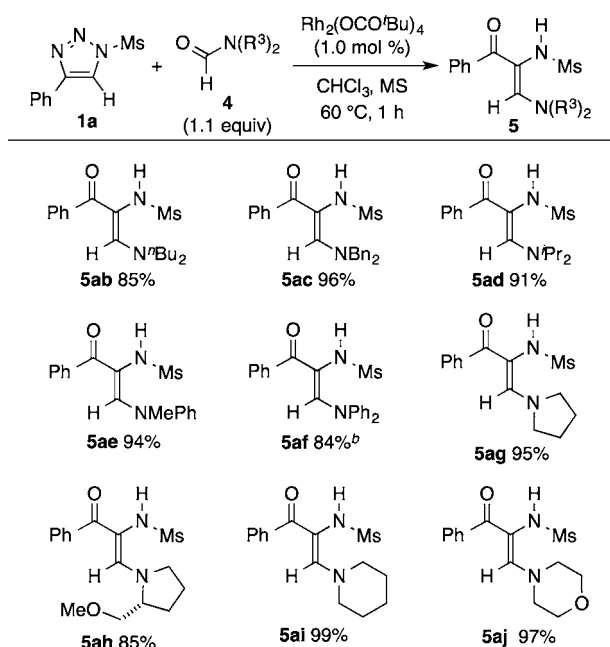


The synthetic applicability of the present reaction was demonstrated by the reaction using the substrate **1o** derived from 5α-cholestan-3-one (eq 5).

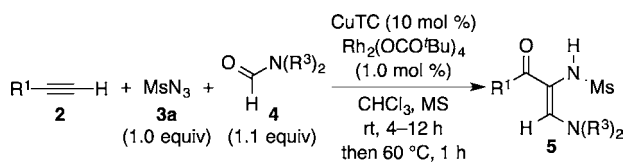


Various tertiary formamides prepared from acyclic and cyclic secondary amines successfully participated in the reaction with the 1-mesityltriazole **1a**, and the corresponding products were obtained in good to high yields (Scheme 2). However, secondary formamides derived from primary amines such as *N*-methylformamide failed to participate in the reaction. This is probably because the –NH group either directly adds to the rhodium carbene complex A or provides the imino nitrogen of intermediate B with a proton.⁹

With the reaction of formamides with triazoles in hand, we next developed an all-in-one-pot synthesis of enaminones starting from terminal alkynes (Table 2). Substrates **2a**, **3a**, and **4a**, copper(I) and rhodium(II) catalysts, and chloroform were put in a reaction vessel, and the mixture was stirred at room temperature. After 6 h, **2a** and **3a** were both consumed to generate triazole **1a**. Then, the reaction mixture was stirred at 60 °C for 1 h, and the following chromatographic purification afforded the enaminone **5aa** in 83% isolated yield based on the

Scheme 2. Rh(II)-Catalyzed Reaction of Triazoles 1a with Various Formamides 4b–j^a

^aThe same reaction conditions with those in Table 1. ^b Toluene (2 mL) at 100 °C.

Table 2. All-in-One-Pot Synthesis of 5 Starting from Terminal Alkynes 2^a

entry	1-alkynes 2	formamides 4	product 5	yield (%)
	R ¹	N(R ³) ₂		
1	Ph	2a	N(Me) ₂ 4a	5aa 83
2	4-MeO-C ₆ H ₄	2b	N(Me) ₂ 4a	5fa 61 ^b
3	4-CF ₃ -C ₆ H ₄	2c	N(Me) ₂ 4a	5ha 56
4	ⁿ Hex	2d	N(Me) ₂ 4a	5ja 59 ^c
5	Ph	2a	N(Bn) ₂ 4c	5ac 74
6	Ph	2a	N(ⁱ Pr) ₂ 4d	5ad 75
7	Ph	2a	N-pyrrolidinyl 4g	5ag 74
8	Ph	2a	N-piperidinyl 4i	5ai 78
9	Ph	2a	N-morpholinyl 4j	5aj 77

^aOn a 0.20 mmol scale. ^bCH₂ClCH₂Cl (2 mL). ^c4a (0.60 mmol) in CHCl₃ (1 mL).

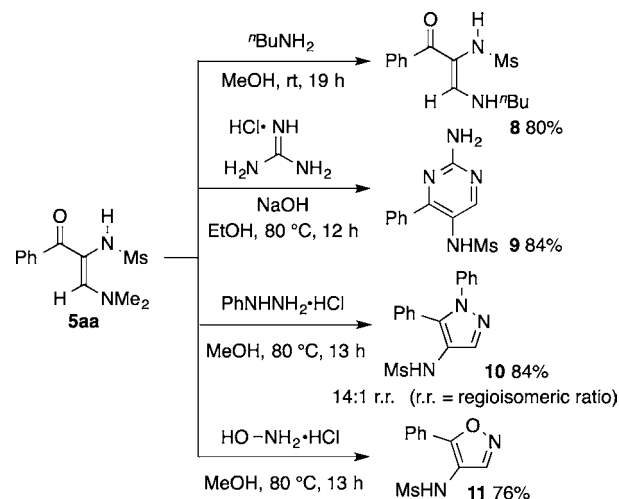
alkyne 2a (entry 1). Similar results were obtained when the reaction of 2a was carried out on a 10 mmol scale or even at room temperature.¹⁹ This one-pot procedure minimizes generation of waste solvents.

Various enaminones 5 were synthesized from other combinations of terminal alkynes 2 and formamides 4 and

isolated in moderate to good yields through a single workup/purification procedure (entries 2–9).

Synthetic utilities unique to the enaminone 5aa were exemplified by further derivatizations shown in Scheme 3. A

Scheme 3. Synthetic Derivatizations of Enaminone 5aa



reaction with butylamine caused replacement of the dimethylamino group at the β-position to furnish secondary amine 8, which was difficult to prepare by using *N*-butylformamide in the present reaction. Various heterocycles such as pyrimidine 9, pyrazole 10, and isoxazole 11 were readily synthesized by treatment with guanidine, phenylhydrazine, and hydroxylamine, respectively.

In summary, we have developed a new method for the synthesis of α-amino enaminones, which serve as useful building blocks for the construction of various nitrogen-containing frameworks. Terminal alkynes can be used as starting materials, and multiple functionalities are regioselectively installed across the C≡C triple bonds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data for the new compounds, details of the X-ray analysis, and CIF file. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Prof. Biing-Jiun Uang (National Tsing Hua University) in celebration of his 60th birthday. We thank Dr. Y. Nagata (Kyoto University) for his kind help in the X-ray analysis. This work was supported by MEXT (Grant-in-Aid for Scientific Research on Innovative Areas Nos. 22105005 and 24106718, Young Scientists (A) No. 23685019, Scientific Research (B) No. 23350041) and JST (ACT-C).

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- (19) See the Supporting Information for details.