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Regio- and Stereoselective Synthesis of 2-Amino-1,3-diene Derivatives by Ruthenium-Catalyzed Coupling of Ynamides and Ethylene

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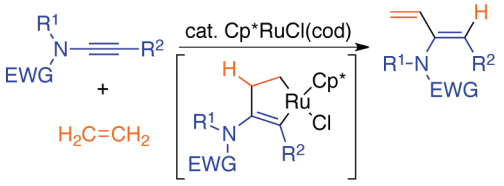
ABSTRACT



A ruthenium-catalyzed hydrovinylation-type cross-coupling of ynamides and ethylene proceeds via ruthenacyclopentene to give 2-aminobuta-1,3-diene derivatives in a highly regioselective manner. It was also demonstrated that 2-aminobuta-1,3-diene derivatives reacted with various dienophiles or singlet oxygen to give a cyclic enamide derivative.

Amino-1,3-diene derivatives have been recognized as versatile units in synthetic organic chemistry, and many methods for the preparation of amino-1,3-dienes have been reported.[1] Recently, amino-1,3-diene derivatives were synthesized by the transition-metal-mediated transformation of ynamides.[2−6]

Transition-metal-catalyzed hydrovinylation of alkynes is an attractive and efficient strategy for the stereoselective synthesis of 1,3-dienes from the standpoint of atom economy.[7] It is known that several ruthenium complexes show high catalytic activity for such hydrovinylation-type direct cross-couplings of alkynes and alkenes.[8,9]

With this background, we planned to investigate the intermolecular coupling of ynamides and ethylene mediated by a low-valent ruthenium catalyst with the focus of introducing a new protocol for the stereoselective synthesis of amino-1,3-dienes (Scheme 1). Based on our previous investigations of the intramolecular reaction of

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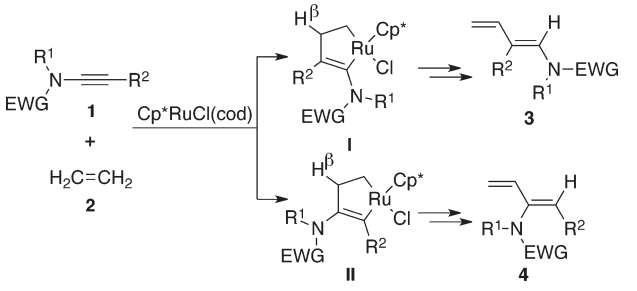
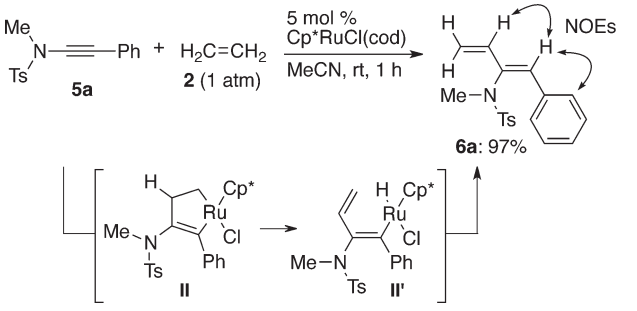
ene-ynes[10a–d] and allene-ynes[10e,f] catalyzed by Cp*RuCl(cod), the oxidative cycloaddition of ynamides **1** and ethylene **2** to a low-valent ruthenium complex could give the ruthenacyclopentene **I** or **II**. β-Hydride elimination from **I** or **II** followed by reductive elimination would afford the corresponding 1-amino-1,3-diene derivative **3** or 2-amino-1,3-diene derivative **4**.

Scheme 1. Strategy for the Synthesis of Amino-1,3-dienes



To examine the feasibility of this strategy, tosylamide-derived ynamide **5a** was reacted with ethylene (**2**, 1 atm) in the presence of Cp*RuCl(cod) (5 mol %) in MeCN. As a result, the desired 2-amino-1,3-diene derivative **6a** was obtained in 97% yield as a single isomer, whose regio- and stereochemistries were determined by NOE experiments (Scheme 2). This result indicated that the oxidative cycloaddition of **5a** and ethylene to the ruthenium complex occurred regioselectively to give the ruthenacyclopentene **II**. β-Hydride elimination then gave the intermediate **II′** from which reductive elimination proceeded to afford **6a** in a regio- and stereoselective manner.[11,12]

Scheme 2. Ruthenium-Catalyzed Regioselective Coupling of Ynamide **5a** and Ethylene



Encouraged by these results, the effects of substituents on the alkyne part or nitrogen atom were investigated (Table 1). The coupling reactions of ynamides **5b** and **5c**, with an aromatic group on the alkyne, were studied with ethylene (**2**) and gave the 2-amino-1,3-dienes **6b** and **6c**, respectively, in high yield (runs 1 and 2). When ynamides **5d–f**, bearing an alkyl group on the alkyne moiety, were reacted with ethylene (**2**), the desired coupling products **6d–f** were stereoselectively produced in low to high yield (runs 3–5). On the other hand, the ethylene coupling reaction of the terminal ynamide **5g** or the ynamide having a TMS group on the alkyne part **5h** did not proceed and the starting ynamides were recovered (runs 6 and 7). Ynamides with an *N*-isopropyl group **5i** and an *N*-phenyl group **5j** also reacted with ethylene (**2**) in the presence of a ruthenium catalyst, giving the corresponding 2-amino-1,3-diene derivatives **6i** and **6j** in 48% and 85% yield, respectively (runs 8 and 9).

(4) For our approach to regio- and stereoselective synthesis of enamide derivatives by Ni(0)-catalyzed multicomponent coupling of ynamide, aldehyde, and silane, see: (a) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829. (b) Saito, N.; Katayama, T.; Sato, Y. *Heterocycles.* **2011**, *82*, 1181.

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(7) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(8) For ene-yne coupling via ruthenacyclopentene formation, see: (a) Mitsudo, T.; Zhang, S.-W.; Nagao, M.; Watanabe, Y. *Chem. Commun.* **1991**, 598. (b) Trost, B. M.; Martos-Redruejo, A. *Org. Lett.* **2009**, *11*, 1071. For ene-yne coupling via hydroruthenation of alkynes, see: (c) Yi, C. S.; Lee, D. W.; Chen, Y. *Organometallics* **1999**, *18*, 2043. (d) Nishimura, T.; Washitake, Y.; Uemura, S. *Adv. Synth. Catal.* **2007**, *349*, 2563. For ene-yne coupling via the formation of ruthenium viynylidene complex, see: (e) Murakami, M.; Ubukata, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 7361. For ene-yne coupling via C–H activation process, see:(f) Kakiuchi, F.; Uetsuhara, T.; Tanaka, Y.; Chatani, N.; Murai, S. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 511. (g) Neisius, N. M.; Plietker, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5752. 1-Amino-1,3-diene derivatives were synthesized by ruthenium-catalyzed direct cross-coupling of alkynes and *N*-vinylamides; see: (h) Tsujita, H.; Ura, Y.; Matsuki, S.; Wada, K.; Mitsudo, T.; Kondo, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5160.

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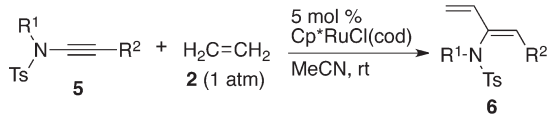
(10) (a) Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5606. (b) Mori, M.; Tanaka, D.; Saito, N.; Sato, Y. *Organometallics* **2008**, *27*, 6313. (c) Tanaka, D.; Sato, Y.; Mori, M. *Organometallics* **2006**, *25*, 799. (d) Tanaka, D.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2007**, *129*, 7730. (e) Saito, N.; Tanaka, Y.; Sato, Y. *Organometallics* **2009**, *28*, 669. (f) Saito, N.; Tanaka, Y.; Sato, Y. *Org. Lett.* **2009**, *11*, 4124.

(11) In acetonitrile, a cationic ruthenium species would be generated from Cp*RuCl(cod) accompanied by dissociation of chloride ligands. See: Davies, S. G.; McNally, J. P.; Smallridge, A. J. *Adv. Organomet. Chem.* **1990**, *30*, 1. At the ruthenacycle formation stage, the reaction proceeded as such cationic ruthenium complex would interact with β-carbon atom of the ynamide which has a partial negative charge (see ref 4a). Consequently, ruthenacyclopentene **II** would be formed in a regioselective manner. In this context, when the reaction of **5a** and **2** was carried out in the presence of $[Cp^*Ru(MeCN)_3]PF_6$ (5 mol %) in MeCN at room temperature, 2-amino-1,3-diene **6a** was produced in 63% yield as a single isomer, and no regioisomer of **6a** was observed.

(12) Recently Hsung reported the synthesis of 2-amino-1,3-diene derivatives via isomerization of allenamide; see: (a) Hayashi, R.; Hsung, R. P.; Feltenberger, J. B.; Lohse, A. G. *Org. Lett.* **2009**, *11*, 2125. (a) Hayashi, R.; Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2010**, *12*, 1152.

Table 1. Coupling of Tosylamide-Derived Ynamides and Ethylene

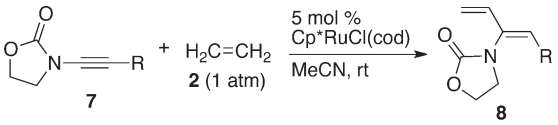


run	ynamide	time (h)	yield (%)[b]
1	**5b** (R^1 = Me, R^2 = 4-$MeO_2CC_6H_4$)	2	**6b**: quant
2	**5c** (R^1 = Me, R^2 = 4-$MeOC_6H_4$)	3	**6c**: 99
3[a]	**5d** (R^1 = Me, R^2 = ^{n}Bu)	19	**6d**: 80
4[a]	**5e** (R^1 = Me, R^2 = CH_2CH_2OTBS)	21	**6e**: 88
5[a]	**5f** (R^1 = Me, R^2 = CH_2OTBS)	20	**6f**: 20 (57)
6[a]	**5g** (R^1 = Me, R^2 = H)	21	**6g**: - (45)
7[a]	**5h** (R^1 = Me, R^2 = TMS)	18	**6h**: - (83)
8[a]	**5i** (R^1 = ^{i}Pr, R^2 = Ph)	22	**6i**: 48 (23)
9	**5j** (R^1 = R^2 = Ph)	4	**6j**: 85

[a] The reaction was carried out at 60 °C. [b] Values in parentheses are the yields of recovered ynamide **5**.

Next, the coupling reaction using oxazolidinone-derived ynamides with ethylene was investigated (Table 2). When ynamides with an aromatic group on the alkyne moiety **7a**–**c** were employed for the coupling with ethylene, 2-amino-1,3-diene derivatives **8a**–**c** were obtained in high yield in a stereoselective manner (runs 1–3). On the other hand, the reaction of an alkyl-group-substituted ynamide **7d** and ethylene (**2**) gave the coupling product in low yield (run 4).

Table 2. Coupling of Oxazolidinone-Derived Ynamides and Ethylene



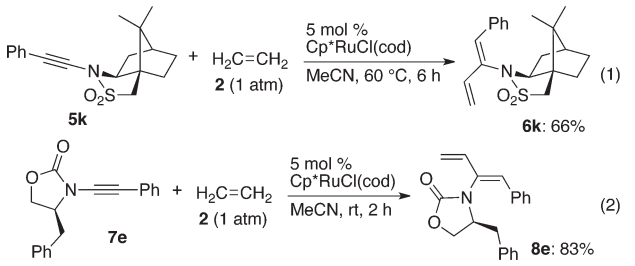
run	ynamide	time (h)	yield (%)[b]
1	**7a** (R = Ph)	2	**8a**: 86
2	**7b** (R = 4-$MeO_2CC_6H_4$)	2	**8b**: 87
3	**7c** (R = 4-$MeOC_6H_4$)	2	**8c**: 92
4[a]	**7d** (R = ^{n}Bu)	25	**8d**: 10 (89)

[a] The reaction was carried out at 60 °C. [b] Values in parentheses are the yields of recovered ynamide **7**.

Furthermore, chiral ynamides **5k** derived from Oppolzer's sultam[13] and **7e**, prepared from L-phenylalanine, could be applied in the coupling with ethylene (**2**), and the corresponding 2-amino-1,3-dienes **6k** and **8e** were obtained in optically active form (Scheme 3).

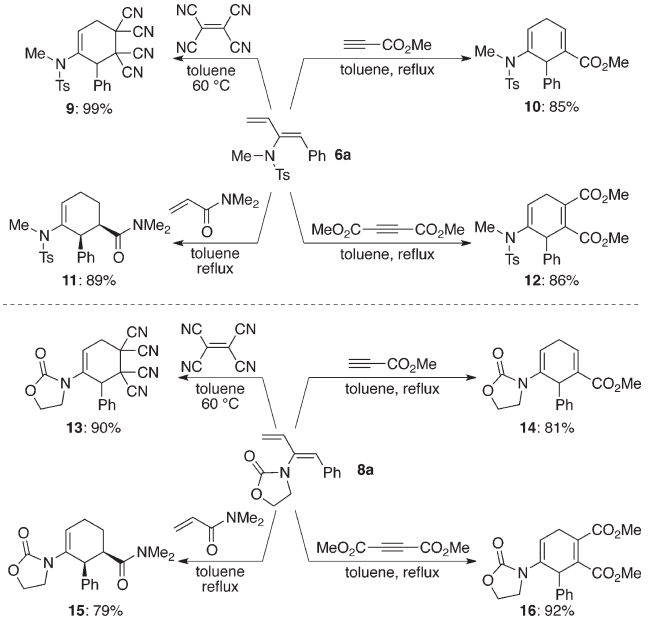
Next, we turned our attention to the utilization of 2-aminobuta-1,3-diene derivatives we had prepared. First, we investigated the Diels–Alder reaction of **6a** and **8a**

Scheme 3. Coupling of Chiral Ynamides and Ethylene



(Scheme 4). Thus, various alkenes and alkynes were employed as dienophiles, giving the corresponding cyclic enamide derivatives **9**–**16** in good yields and in a regio- and stereoselective manner.

Scheme 4. Diels–Alder Reaction of **6a** and **8a** with Various Dienophiles

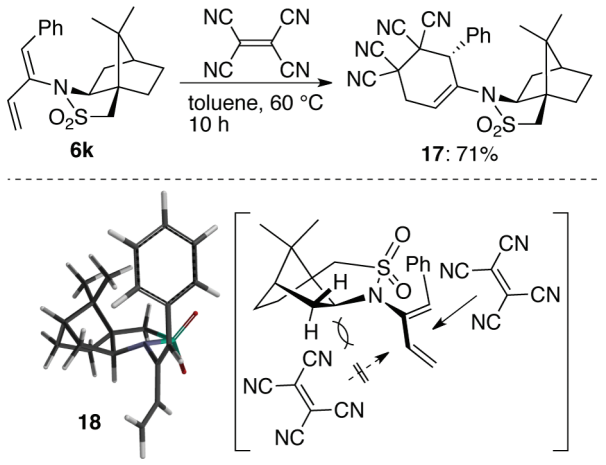


The chiral 2-amino-1,3-diene **6k** was applied to a diastereoselective Diels–Alder reaction with tetracyanoethene (TCNE), and the enamide derivative **17** was obtained as a single diastereomer (Scheme 5).[14] The most stable conformation of **6k** was found by conformational analysis using Spartan'06 (Wavefunction, Inc., Irvine, CA) with the MMFF force field, and the structure was depicted as **18**. Based on this result, it was thought that TCNE would approach the diene part of **6k** to avoid steric repulsion with the camphor ring of **6k**, which might control the stereochemistry of **17**.

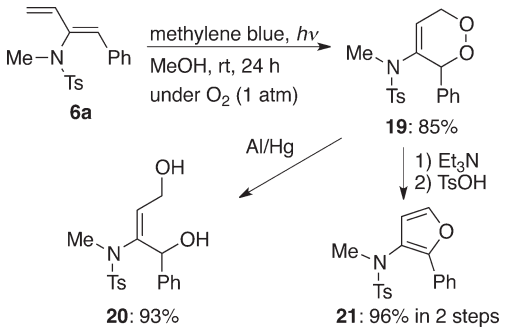
(13) For reviews on the use of Oppolzer's sultam as a chiral auxiliary in asymmetric synthesis, see: (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.

(14) The absolute configuration at the methyne carbon in the cyclohexene ring of **17** was determined by X-ray crystallographic analysis. Crystallographic data of **17** have been deposited at the Cambridge Crystallographic Data Center (CCDC 818816).

Scheme 5. Diels–Alder Reaction of **6k** and TCNE



Scheme 6. Reaction of **6a** and Singlet Oxygen and Transformations of Endoperoxide **19**



Furthermore, the reaction of **6a** and singlet oxygen was examined (Scheme 6). When a solution of **6a** in MeOH was stirred under oxygen gas (1 atm) in the presence of the catalytic amount of methylene blue for 1 day, the six-membered endoperoxide **19** was produced in 85% yield. The endoperoxide was reduced by Al/Hg[15a] to give bis-allylic alcohol derivative **20** in 93% yield. On the other hand, when the endoperoxide **19** was treated with Et_3N followed by TsOH, it gave the 3-aminofuran derivative **21** in high yield.[15b]

In summary, we have succeeded in developing a new method for the synthesis of 2-amino-1,3-diene derivatives by ruthenium-catalyzed regioselective coupling of ynamides and ethylene via the formation of a ruthenacyclopentene intermediate. We have also shown that 2-amino-1,3-dienes are suitable substrates for the preparation of cyclic enamide derivatives by a Diels–Alder reaction or reaction with singlet oxygen.

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Supporting Information Available. Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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