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Rhodium-Catalyzed Cyclopropanation Using Ene-yne-imino Ether Compounds as Precursors of (2-Pyrrolyl)carbenoids

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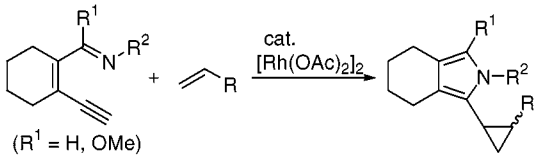
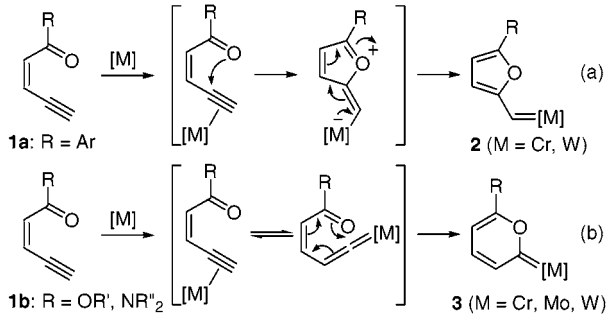
ABSTRACT



The reaction of alkenes with conjugated ene-yne-imino ether or ene-yne-aldimine in the presence of a catalytic amount of $[Rh(OAc)_2]_2$ gives (2-pyrrolyl)cyclopropanes in good yields. The key intermediate of this cyclopropanation is a (2-pyrrolyl)carbenoid generated by the nucleophilic attack of imine nitrogen atom at an internal alkyne carbon activated by rhodium complex. The intramolecular reaction also proceeds to afford a polycyclic pyrrole.

We have previously reported the formation of (2-furyl)-carbene complexes **2** from ene-yne-ketones **1a** promoted by group 6 transition metal complexes[1] and its application to catalytic cyclopropanation of alkenes[2] and the Doyle−Kirmse reaction of allylic sulfides[3] using **1a** as (2-furyl)carbenoid precursors (Scheme 1a). However, similar cyclopropanation

Scheme 1



reactions with ene-yne-esters and -amides **1b** were unsuccessful as a result of the fact that group 6 transition metals underwent pericyclic or pseudopericyclic reactions with vinylidene intermediates generated from **1b** to produce stable 2-pyranylidene-complexes **3** (Scheme 1b).[4] To investigate the new reactivity of these π-conjugated systems with transition metal complexes, we next attempted to elucidate the reactivity of nitrogen analogues **4** such as an ene-yne-imino ether (R^1 = OR) and an ene-yne-imine (R^1 = H) toward transition metal complexes (Scheme 2). These efforts led us to find a novel rhodium-catalyzed cyclopropanation reactions via the formation of (2-pyrrolyl)carbenoid **5** as a nitrogen analogue of (2-furyl)carbenoid **2**. Because pyrroles are found in naturally occurring and biologically important molecules[5,6] and this major class of heterocycles is broadly

(1) (a) Miki, K.; Yokoi, T.; Nishino, F.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2002**, *645*, 228. For 6-*endo-dig* cyclization of 2-ethynylacylbenzene with $W(CO)_5$(THF) complex, see: (b) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814.

(2) Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 5260.

(3) See also the preceding Letter: Kato, Y.; Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *Org. Lett.* **2003**, *5*, 2619.

(4) (a) Ohe, K.; Miki, K.; Yokoi, T.; Nishino, F.; Uemura, S. *Organometallics* **2000**, *19*, 5525. (b) Ohe, K.; Yokoi, T.; Miki, K.; Nishino, F.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 526. For benzopyranylidene complexes, see: Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226.

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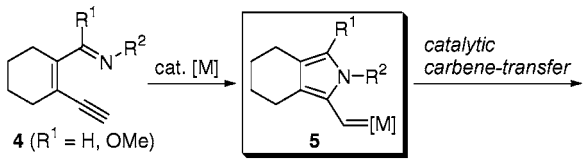
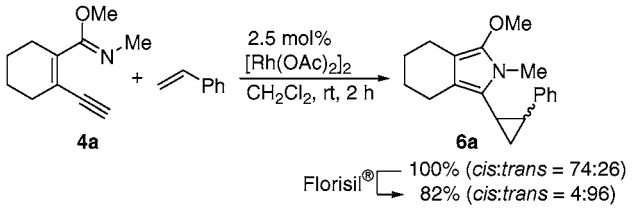
Scheme 2



used in organic synthesis and material science, this approach would provide additional leverage to introduce a diverse array of pyrrole structures into organic molecules. Here, we wish to report a new entry to pyrrole ring construction from ene-yne-imino compounds **4** via transition-metal-induced 5-*exo*-*dig* cyclization, followed by catalytic cyclopropanation of alkenes, which leads to (2-pyrrolyl)cyclopropanes.[7−10]

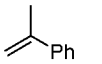
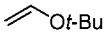
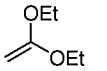
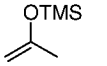
At first, when the reaction of ene-yne-imino ether **4a** with styrene (2 equiv) was carried out in the presence of [Rh(OAc)$_2$]$_2$ (2.5 mol %) in CH_2Cl_2 at room temperature for 2 h, 1-phenyl-2-(2-pyrrolyl)cyclopropane **6a** was obtained quantitatively as a mixture of *cis* and *trans* isomers (*cis*:*trans* = 74:26) (Scheme 3).[11] The product is somewhat labile

Scheme 3



on silica gel, but Florisil column chromatography allows its isolation with isomerization of *cis* to *trans* isomer [from 100% yield (*cis*:*trans* = 74:26) to 82% yield (*cis*:*trans* = 4:96)].[12] Next, we examined cyclopropanation of several alkenes with ene-yne-imino ether **4a** in the presence of [Rh(OAc)$_2$]$_2$ catalyst. These results are summarized in Table 1.

Table 1. Rhodium-Catalyzed Cyclopropanation of Alkenes with **4a**[a]

entry	alkene	product	yield (%)[b]	d.r.[b]
1		**7a**	98	59:41[c]
2		**8a**	90	10:90
3		**9a**	100	N. A.[d]
4		**10a**	88	76:24[c]

[a] Reactions of **4a** (0.20 mmol) with alkene (0.40 mmol) in CH_2Cl_2 (2.0 mL) were carried out in the presence of [Rh(OAc)$_2$]$_2$ (0.005 mmol) at room temperature under N_2. All reactions were complete within 2 h. [b] Without purification. [c] Configuration is not yet clear. [d] N. A. = not applicable.

The reaction of **4a** with α-methylstyrene also gave the cyclopropanated product **7a** in 98% yield with a 59:41 diastereomeric ratio (entry 1). Reactions of **4a** with *tert*-butyl vinyl ether and ketene diethyl acetal proceeded quite smoothly to give cyclopropanes **8a** (90%, *cis*:*trans* = 10:90) and **9a** (100%), respectively (entries 2 and 3). Enol silyl ether also reacted with **4a** to give the corresponding product **10a** in 88% yield with a 76:24 diastereomeric ratio (entry 4).

We then examined cyclopropanations of styrene with other ene-yne-imino ethers **4** in the presence of rhodium catalyst (Table 2). An ene-yne-imino ether **4b** bearing an allyl group on nitrogen reacted with styrene to give the cyclopropanated product **6b** in 99% yield (*cis*:*trans* = 64:36) (entry 1). The reaction of **4c** having a phenyl group proceeded quite smoothly to give the corresponding product **6c** in 99% yield (dr = 55:45) (entry 2). A cyclopentenyl imino ether **4d** reacted with styrene to give cyclopropane **6d** (93%, *cis*:*trans* = 93:7) (entry 3). A *trans* isomer of cyclopropanes was a major product after purification with Florisil in each case. Cyclopropanation between an aldimine **4e** and styrene also gave the cyclopropanated product **6e**, although its yield was lower (18%) (entry 4).

Pyrrolin-2-ones as well as pyrroles are pharmacologically active materials, and more importantly the former are synthons for γ-amino acid,[13] various alkaloids,[14] and natural products.[15] We next attempted the conversion of 2-methoxypyrroles obtained by the present method to pyrrolin-2-

(5) For a review, see: Gossauer, A. Pyrrole. In *Houben-Weyl*; Thieme: Stuttgart, 1994; E6a/1, p 556.

(6) (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (b) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54. (c) Sayah, B.; Pelloux-Léon, N.; Vallée, Y. *J. Org. Chem.* **2000**, *65*, 2824. (d) Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587.

(7) Synthesis of (2-pyrrolyl)cyclopropanes from a stoichiometric amount of (2-pyrrolyl)carbene complexes with alkenes at high temperature has been reported. See: Barluenga, J.; López, S.; Trabanco, A. A.; Fernández-Acebes, A.; Flórez, J. *J. Am. Chem. Soc.* **2000**, *122*, 8145.

(8) For copper-mediated synthesis of isoindazole derivatives using pseudocoarctate cyclization of (2-ethynylphenyl)triazene compounds, see: (a) Kimball, D. B.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 1572. (b) Kimball, D. B.; Weakley, T. J. R.; Herges, R.; Haley, M. M. *J. Org. Chem.* **2002**, *67*, 6395. (c) Kimball, D. B.; Weakley, T. J. R.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 13463. (d) Kimball, D. B.; Haley, M. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3339.

(9) For generation and reaction of tungsten-containing azomethine ylides, see: Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592.

(10) For recent advance of transition-metal-assisted nucleophilic attack of an imine nitrogen atom to an alkyne carbon via 6-*endo*-*dig* cyclization, see: cat. [Cu] (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553. (b) Roesch K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86. cat. [Pd] (c) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (d) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, 67, 7042. (e) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048.

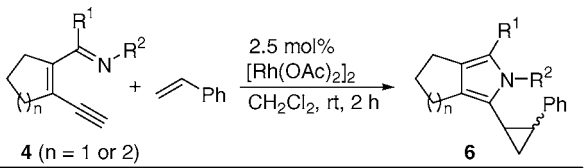
(11) Purity of **6a** (>90%) was confirmed by ^{1}H and ^{13}C NMR spectra.

(12) Florisil (150−250 μm, 60−100 mesh) was purchased from Wako Chemicals USA, Inc. This isomerism is presumably attributed to the basic nature of Florisil.

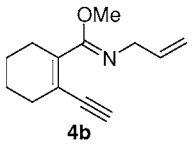
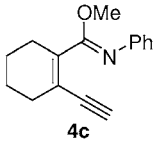
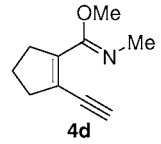
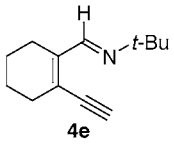
(13) (a) Jouin, P.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177. (b) Ma, D.; Ma, J.; Ding, W.; Dai, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2365.

(14) (a) Klaver, W. J.; Hiemstra, H.; Speckamp, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 2588. (b) Casiraghi, G.; Spanu, P.; Rassu, G.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1994**, *59*, 2906.

Table 2. Rhodium-Catalyzed Cyclopropanation of Styrene with **4**[a]



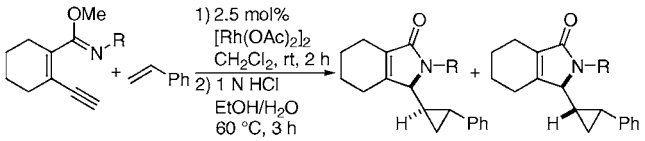
4 (n = 1 or 2) **6**

entry	substrate	product	yield (%)[b]	*cis*:*trans*[b]
1	 **4b**	**6b**	99 (88)	68:32 (3:97)
2	 **4c**	**6c**	99 (81)[c]	55:45[d] (27:73)[c,d]
3	 **4d**	**6d**	93 (47)	93:7 (45:55)
4	 **4e**	**6e**	18[c]	—[d]

[a] Reactions of **4** (0.20 mmol) with alkene (0.40 mmol) in CH_2Cl_2 (2.0 mL) were carried out in the presence of $[Rh(OAc)_2]_2$ (0.005 mmol) at room temperature under N_2. [b] Without purification. Values in parentheses after purification with Florisil. [c] After purification with column chromatography on SiO_2. [d] Configuration is not yet clear.

ones. Thus, when crude products obtained by cyclopropanation reactions of styrene with **4a**, **4b**, and **4c** were directly treated with 1 N HCl solution in EtOH/H_2O at 60 °C for 3 h,[16] the corresponding pyrrolin-2-ones **11a**, **11b**, and **11c** were produced in 81%, 87%, and 96% yields, respectively (Scheme 4). All pyrrolinones obtained could be purified by

Scheme 4



4a: R = Me
4b: R = allyl
4c: R = Ph

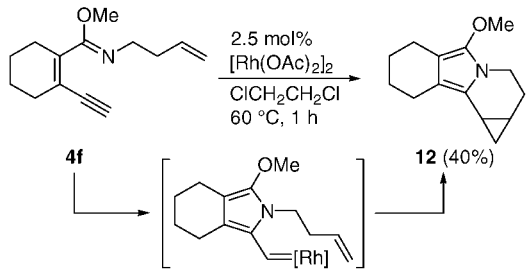
11a: 81% (d.r. = 46:54)
11b: 87% (d.r. = 50:50)
11c: 96% (—)[a]

[a] The diastereomeric ratio is not determined.

column chromatography on silica gel without decomposition. In these cases, the configurations at constructed cyclopropyl rings are only *trans*, and therefore the diastereomeric ratios of **11a** and **11b** would be attributed to the relative configuration between C-1′ of the cyclopropane ring and C-5 of the pyrrolin-2-ones.

Finally, we examined an intramolecular reaction of ene-yne-imino ether **4f** having a homoallyl group on nitrogen as an acceptor for an intermediate carbenoid. Treatment of **4f** in the presence of $[Rh(OAc)_2]_2$ (2.5 mol %) for 1 h afforded the tetracyclic product **12** in 40% yield, although higher reaction temperature (60 °C) and diluted conditions (0.01 M) in $ClCH_2CH_2Cl$ were required (Scheme 5). Formation

Scheme 5



of **12** can be explained by assuming intramolecular cyclopropanation of a (2-pyrrolyl)carbene-rhodium intermediate.

In conclusion, we have developed a new rhodium-catalyzed inter- and intramolecular cyclopropanation of alkenes on the basis of the generation of (2-pyrrolyl)-carbenoids from conjugated ene-yne-imino compounds. Both ene-yne-imino ethers (R^1 = OMe) and an aldimine (R^1 = H) are applicable to the present reaction. These studies have demonstrated the 5-*exo*-*dig* cyclization of ene-yne-imino compounds to (2-pyrrolyl)carbenoids (Scheme 2), which is similar to the transformation of ene-yne-ketone **1a** to (2-furyl)carbenoid (Scheme 1a), providing the new synthetic method for pyrrole and pyrrolinone structures.

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Supporting Information Available: Full experimental details and spectral data for all transformations and compounds are described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845. (b) Iwasawa, N.; Maeyama, K. *J. Org. Chem.* **1997**, *62*, 1918.

(16) Eicher, T.; Stapperfenne, U. *Synthesis* **1987**, 619.