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Ru-Catalyzed Ring-Opening and Substitution Reactions of Heteroaromatic Compounds Using Propargylic Carboxylates as Precursors of Vinylcarbenoids

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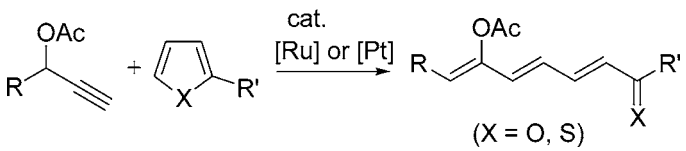
ABSTRACT



The reaction of heteroaromatic compounds with propargylic carboxylates in the presence of a catalytic amount of $[RuCl_2(CO)_3]_2$ or $PtCl_2$ gives trienes in good yields. The key intermediate is an electrophilic (1-acetoxylvinyl)carbene complex generated from the activated propargylic acetates with transition metals.

The in situ generation of transient electrophilic carbenoids from α-diazocarbonyl compounds with various transition-metal complexes is well-investigated for various inter- or intramolecular carbene transfer reactions.[1] The reaction of electrophilic carbenoids generated from diazoalkanes with furans has been found to serve as one of the most convenient routes to 1,6-dioxo-2,4-hexadiene derivatives,[2,3] which have been applied to the synthesis of various natural products[4] and heterocyclic systems.[5] However, unfavorable side reactions such as diazo dimerization and azine formation limited the availability of furans as carbene acceptors with high efficiency.

We have demonstrated the diazoalkane-free in situ generation of vinylcarbenoids **A** from propargylic carboxylates and their application to catalytic carbene transfer reactions (Scheme 1).[6,7] Using this carbenoid formation protocol, we acheived the Ru- or Pt-catalyzed ring-opening and substitution reactions of heteroaromatic compounds via (1-acetoxyvinyl)carbene complexes.

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(1) (a) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Mill Valley, CA, 1999; p 143. (b) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, 1999.

(2) (a) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. *J. Org. Chem.* **1977**, *42*, 3945. (b) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem.* **1990**, *55*, 6203. (c) Wenkert, E.; Khatuya, H. *Helv. Chim. Acta* **1999**, *82*, 551. (d) Shieh, P. C.; Ong, C. W. *Tetrahedron* **2001**, *57*, 7303. (e) Hahn, N. D.; Nieger, M.; Dötz, K. H. *J. Organomet. Chem.* **2004**, *689*, 2662 and references therein.

(3) Padwa, A.; Krumpe, K. E.; Kassir, J. M. *J. Org. Chem.* **1992**, *57*, 4940.

(4) For recent reports for total synthesis of triene-containing natural products, see: (a) Nakatani, Y.; Oshita, J.; Ishigami, K.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2006**, *62*, 160. (b) Mitchell, I. S.; Pattenden, G.; Stonehouse, J. *Org. Biomol. Chem.* **2005**, *3*, 4412. (c) Mehta, G.; Kundu, U. K. *Org. Lett.* **2005**, *7*, 5569. (d) Bialy, L.; Waldmann, H. *Chem.−Eur. J.* **2004**, *10*, 2759.

(5) Burk, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.

(6) For recent reviews, see: (a) Miki, K.; Ohe, K.; Uemura, S. *Chem. Lett.* **2005**, *34*, 1068. (b) Bruneau, C. *Angew. Chem., Int Ed.* **2005**, *44*, 2328. (c) Ohe, K.; Miki, K.; Uemura, S. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 978. (d) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431.

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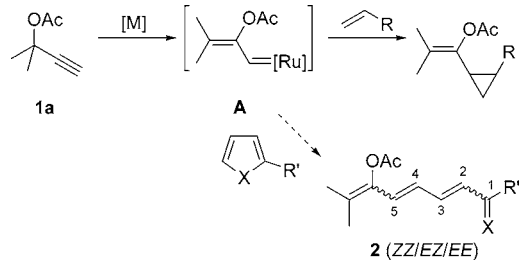
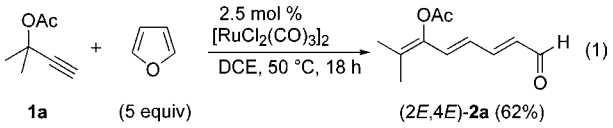
Scheme 1



At first, when the reaction of 2-methyl-3-butyn-2-yl acetate (**1a**) with 5 equiv of furan in dichloroethane (DCE) was carried out in the presence of $[RuCl_2(CO)_3]_2$ (2.5 mol %) under the effective conditions for catalytic cyclopropanation via vinylcarbene complexes,[7a,b] triene (2*E*,4*E*)-**2a** was obtained in 62% yield (eq 1). Next, we carefully examined the



reaction of 2-methoxyfuran with propargylic acetate **1a** to find optimized reaction conditions. The results are summarized in Table 1. In contrast with the reaction of furan shown in eq 1, the reaction of 2-methoxyfuran gave a mixture of trienes (2*Z*,4*E*)-**3a** and (2*Z*,4*Z*)-**4a** in high yields (entry 1).[8] Under the storage conditions, the (2*Z*,4*E*) and (2*Z*,4*Z*) isomers obtained completely isomerized into a single (2*E*,4*E*) isomer, which is more thermodynamically stable.[9] It was found that the ring-opening reaction took place with good chemical yield by heating a solution of **1a** and 2-methoxyfuran (1.5 equiv) in DCE (2.5 mL) at 50 °C in the presence of 2.5 mol % of ruthenium catalyst (entry 3). When **1a** was reacted with 2-methoxyfuran in the presence of $PtCl_2$ instead of $[RuCl_2(CO)_3]_2$, the corresponding product was also obtained in 76% yield (entry 7).[10]

Using the optimized reaction conditions described in entry 3 (Table 1), we examined the reactions of 2-methoxyfuran

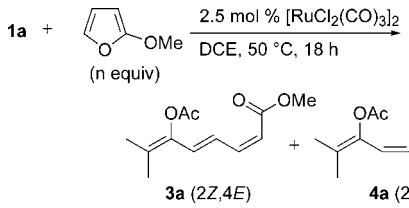
(7) (a) Miki, K.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **2003**, *44*, 2019. (b) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505. For recent examples reported by other groups, see: (c) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (d) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (e) Prasad, B. A. B.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468. (f) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *Organometallics* **2005**, *24*, 3182. (g) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546. (h) Blaszykowski, C.; Harrak, Y.; Gonçalves, M.-H.; Cloarec, J.-M.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 3771. (i) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (j) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656. (k) Bartels, A.; Mahrwald, R.; Müller, K. *Adv. Synth. Catal.* **2004**, *346*, 483.

(8) The configuration and ratios of (2*Z*,4*E*)-**3a** and (2*Z*,4*Z*)-**4a** were determined by ^{1}H NMR spectra; see Supporting Information.

(9) In the case of eq 1 (the recation of **1a** with furan), we suppose that the (2*Z*,4*E*) and (2*Z*,4*Z*) isomers were quickly converted to the thermodynamically stable (2*E*,4*E*)-**2a** isomer under the reaction conditions or the column chromatographic conditions.

(10) $PtCl_2$ is also an efficient catalyst for in situ carbenoid generation and carbene transfer recations. See ref 7.

Table 1. Optimization of the Ru-Catalyzed Ring-Opening Reaction of 2-Methoxyfuran[a]

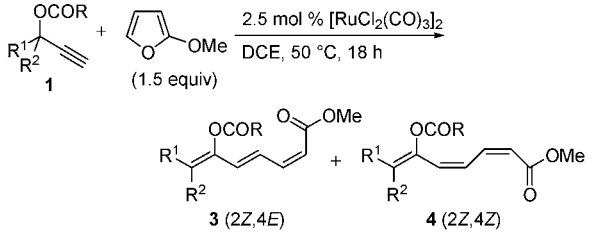


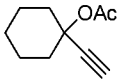
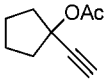
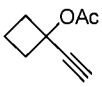
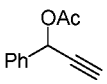
entry	*n* (equiv)	isolated yield	ratio (**3a**/**4a**)
1	5.0	82%	38:62
2	2.0	85%	41:59
3	1.5	86%	42:58
4	1.2	80%	44:56
5[b]	1.5	62%	38:62
6[c]	1.5	84%	41:59
7[d]	1.5	76%	37:63

[a] Reaction conditions: reactions of propargylic acetate **1a** (0.5 mmol) with 2-methoxyfuran (0.6−2.5 mmol) in DCE (2.5 mL) were carried out under N_2 in the presence of 2.5 mol % of $[RuCl_2(CO)_3]_2$ unless otherwise noted. [b] 1.0 mol % of $[RuCl_2(CO)_3]_2$ was used. [c] 1.0 mL of DCE was used. [d] 2.5 mol % of $PtCl_2$ was used instead of $[RuCl_2(CO)_3]_2$.

with other propargylic carboxylates. The results are summarized in Table 2. The reaction of propargylic benzoate **1b** with 2-methoxyfuran also gave a mixture of trienes, (2*Z*,4*E*)-**3b** and (2*Z*,4*Z*)-**4b**, in 86% total yield (**3b**/**4b** = 43:57) (entry 1). From cyclic acetates **1c**, **1d**, and **1e**, the cor-

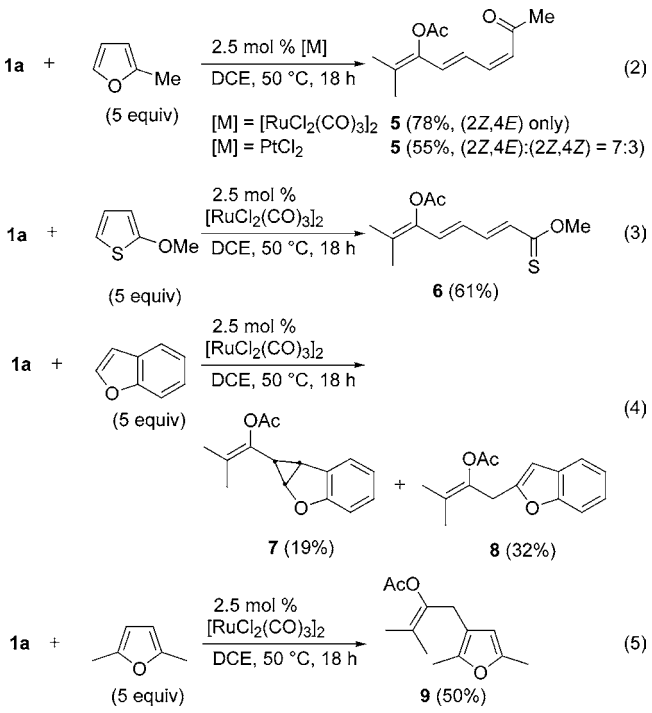
Table 2. Ru-Catalyzed Ring-Opening Reaction of 2-Methoxyfuran with Propargylic Carboxylates[a]



entry	**1**		isolated yield (ratio (**3**:**4**))
1		**1b**	86% (**3b**/**4b** = 43/57)
2		**1c**	83% (**3c**/**4c** = 39/61)
3		**1d**	86% (**3d**/**4d** = 62/38)
4		**1e**	89% (**3e**/**4e** = 50/50)
5		**1f**	44% (**3f**/**4f** = 57/43) (R^1 = Ph, R^2 = H)

[a] Reaction conditions: reactions of propargylic carboxylate **1** (0.5 mmol) with 2-methoxyfuran (0.75 mmol) in DCE (2.5 mL) were carried out under N_2 in the presence of 2.5 mol % of $[RuCl_2(CO)_3]_2$.

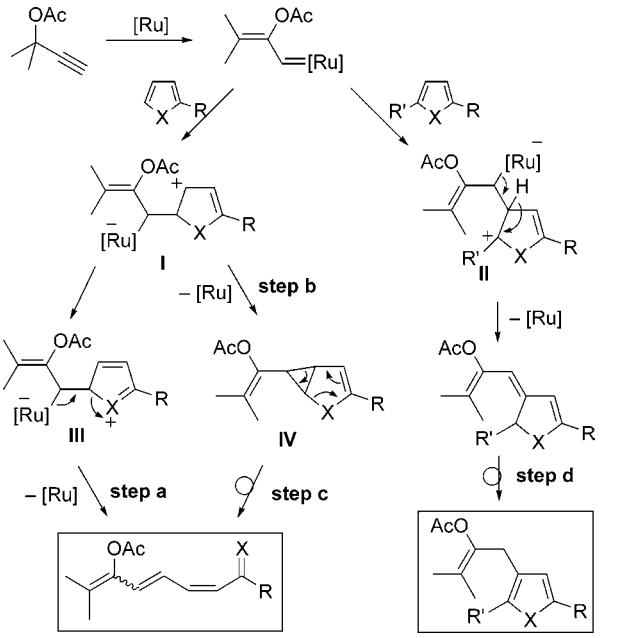
responding products **3c**/**4c**, **3d**/**4d**, and **3e**/**4e** were obtained in 83%, 86%, and 89% total yields, respectively (entries 2−4). In the case of the reaction of secondary propargylic acetate **1f**, a mixture of **3f** and **4f** was obtained in 44% total yield with a 57:43 diastereomeric ratio. Primary propargylic benzoate was less reactive, and the formation of the corresponding product was scarcely detected even after 48 h.



We also investigated the catalytic ring-opening reaction of other heterocyclic compounds. The reaction of **1a** with 2-methylfuran gave triene (2*Z*,4*E*)-**5** exclusively in 78% yield (eq 2). $PtCl_2$ also showed a similar catalytic activity to give the same product in 55% yield. 2-Methoxythiophene could be used for this ring-opening reaction to afford the corresponding triene thioesters in good yields (eq 3). On the other hand, when the reaction with benzofuran was carried out, tricyclic cyclopropane **7**[11] and 2-substituted benzofuran derivative **8** were obtained in 19% and 32% yields, respectively, without ring-opening products (eq 4).[12] The reaction of **1a** with 2,5-dimethylfuran gave 3-substituted 2,5-dimethylfuran **9** in 50% yield selectively (eq 5).

Plausible reaction pathways to account for the formation of products involving trienes, cyclopropanes, and substituted products are shown in Scheme 2. A ruthenium- or platinum-carbenoid formation is the first step which is followed by nucleophilic attack of a heteroaromatic compound to the carbenoid carbon. The bond formation at the 2- or 3-position of a heteroaromatic compound gives cationic intermediates **I** and/or **II**. The charge-separated intermediate **I** successively undergoes ring opening (step a) or cyclopropanation (step b) leading to trienes and cyclopropanes **IV**, respectively. Sigmatropic rearrangement of cyclopropanes **IV** (step c) might also be responsible for the triene formation.[13] At both steps of a and c, it appears reasonable that the *Z*-configuration of $\Delta_{2,3}$ stems from the possible bond cleavage in a five-membered cyclic structure such as an intermediate **III** or an initially formed cyclopropane **IV**.[14] Both *E*- and *Z*-configurations at $\Delta_{4,5}$ might be determined by the anti- and syn-elimination of the ruthenium moiety from intermediate **III** or ring opening of cyclopropane **IV**. On the other hand, the charge-separated intermediate **II** allows mainly hydride shift and aromatization (step d) to produce 3-substituted products. Reactions of 2,5-dimethylfuran favor the intermediary of **II** probably because of the stability of the carbocation and the sterical preference.

Scheme 2



In conclusion, we have demonstrated the ruthenium- or platinum-catalyzed ring-opening and substitution reactions of heteroaromatic compounds using in situ vinylcarbenoid generation. This vinylcarbenoid formation protocol using simple propargylic carboxylates as substrates might find more synthetic applications for π-extended materials in the near future. These approaches are under investigation in our laboratory.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org/.

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(11) In the case of the cyclopropanation reaction of cyclopentadiene with propargylic carboxylates as vinylcarbenoid precursors, syn-cyclopropanated products are exclusively obtained; see ref 7b.

(12) When the reaction of **1a** with *N*-phenylpyrrole was carried out, a 2-substituted pyrrole derivative-like compound **8** was obtained in ca. 10% yield via vinylcarbene insertion at the 2-position. No ring-opened products were observed.

(13) Davies, H. M. L.; Clark, D. M.; Alligood, D. B.; Eiband, G. R. *Tetrahedron* **1987**, *43*, 4265.

(14) Catalysts used for eq 2 might alter the route and the intermediary.