Ring Expansion

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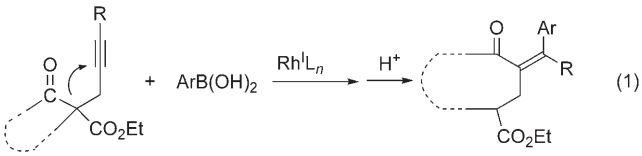
Acyl 1,3-Migration in Rhodium-Catalyzed Reactions of Acetylenic β-Ketoesters with Aryl Boronic Acids: Application to Two-Carbon-Atom Ring Expansions**

*Tomoya Miura, Masahiko Shimada, and Masahiro Murakami**

Rhodium(I)-catalyzed carbon–carbon bond-forming reactions with organometallic reagents have recently attracted significant attention in organic chemistry.[1] We report herein a new acyl 1,3-migration catalyzed by rhodium(I) and its extension to a two-carbon-atom ring-expansion reaction [Eq. (1)].



(1)

We recently reported that a cyclopentanol derivative can be synthesized from a 5-alkyn-1-one by intramolecular nucleophilic addition of an intermediate organorhodium(I) species to the ketone carbonyl group in a 5-*exo*-trig cyclization.[2] We next examined the possibility of an equivalent 4-*exo*-trig cyclization, although such a four-membered-ring formation would suffer from developing ring strain.[3] The desired 4-alkyn-1-one substructure was incorporated into the model substrate **1a**, which was readily synthesized by the alkylation reaction of a β-ketoester with 1-bromo-2-butyne. The 4-alkyn-1-one **1a** was treated with phenylboronic acid (**2a**, 2.0 equiv) in the presence of [{Rh(OH)(cod)}$_2$] (0.05 equiv of Rh) in dioxane/H_2O (100:1) at room temperature under a nitrogen atmosphere. The substrate **1a** was consumed in 16 h, and subsequent chromatographic isolation on silica gel afforded not the expected cyclobutanol derivative **3**, but rather the α,β-unsaturated ketone **4aa** in 69% yield (Scheme 1).

The following mechanism explains the production of **4aa**: A phenylrhodium(I) species is initially generated by trans-

[*] Dr. T. Miura, M. Shimada, Prof. Dr. M. Murakami
Department of Synthetic Chemistry and Biological Chemistry
Kyoto University
Katsura, Kyoto 615-8510 (Japan)
Fax: (+81) 75-383-2748
E-mail: murakami@sbchem.kyoto-u.ac.jp

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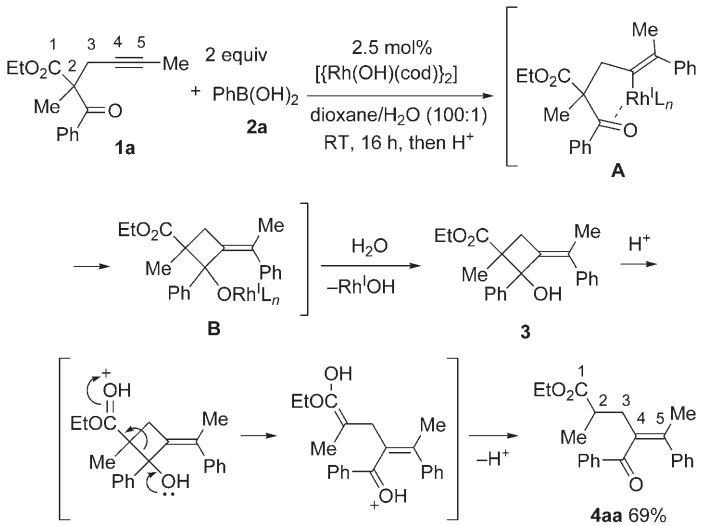
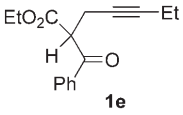


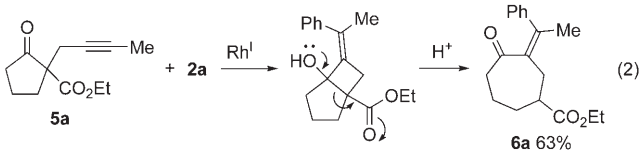
Scheme 1. Rhodium(I)-catalyzed reaction of acetylenic β-ketoester **1a** with phenylboronic acid (**2a**).

metalation of hydroxorhodium(I) with phenylboronic acid (**2a**), which then undergoes *cis*-1,2-addition to the carbon–carbon triple bond[4] in a regioselective manner directed by the ketone carbonyl group.[5] We propose that the resulting alkenyl rhodium(I) intermediate **A** undergoes intramolecular nucleophilic addition to the benzoyl group[6] in a 4-*exo* mode despite the development of ring strain. As a result, the four-membered ring carbocycle **B** is furnished as a rhodium(I) alkoxide. Hydrolysis produces the cyclobutanol **3** with regeneration of the catalytically active hydroxorhodium(I). Cleavage of the cyclobutane ring through a retro-aldol reaction is promoted by the acidic nature of silica gel during purification[7,8] to afford acyl 1,3-migration product **4aa**.

During the transformation of **1a** into **4aa**, a phenyl group was introduced at C5 of **1a**, and the resulting alkenyl rhodium intermediate facilitated migration of the benzoyl group from C2 to C4.[9] This 1,3-migration reaction was generally applicable to a variety of combinations of acetylenic β-ketoesters **1** and aryl boronic acids **2** (Table 1). Both electron-rich and -deficient aryl boronic acids were suitably reactive (Table 1, entries 1–4). *o*-Tolylboronic acid, however, failed in the acyl 1,3-migration reaction probably owing to steric reasons.[10] A better yield was obtained with 1b having an ethyl-substituted alkyne than with 1a (Table 1, entry 5).[5,6c] Methyl ketone **1c** also underwent acetyl 1,3-migration (Table 1, entry 6). The reaction of trimethylsilyl-substituted alkyne **1d** suffered from lower regioselectivity of the initial 1,2-addition and gave the product **4da** in only 25% yield (Table 1, entry 7).[11] Acetylenic β-ketoester **1e** without an α-substituent failed to undergo the cyclization reaction, probably because of the presence of a stable enol tautomer.

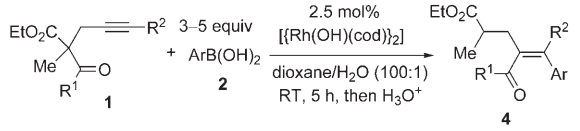


We next envisioned that if a β-ketoester moiety was installed in a cyclic skeleton, an analogous acyl 1,3-migration process would expand the ring by two carbon atoms to serve as a synthetic method for the preparation of medium-sized-ring carbocyclic skeletons.[12,13] Thus, we prepared the cyclopentanone substrate **5a** by the reaction of 2-(ethoxycarbonyl)cyclopentanone with 1-bromo-2-butyne. The cyclic substrate **5a** was treated with phenylboronic acid (**2a**) in the presence of [{Rh(OH)(cod)}$_2$] (0.05 equiv of Rh) in dioxane/H$_2$O (100:1) at room temperature for 6 h under a nitrogen atmosphere, and the resulting reaction mixture was then treated with aqueous NH$_4$Cl for 24 h to promote the retro-aldol process. As expected, the cycloheptanone **6a** was produced in 63% yield through phenyl addition and ring expansion [Eq. (2)].



(2)

Table 1: Rhodium(I)-catalyzed acyl 1,3-migration in the reaction of **1** with **2**.[a]



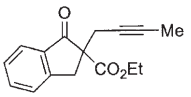
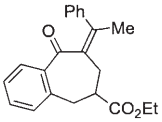
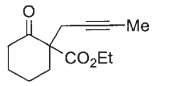
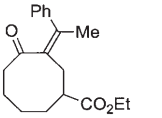
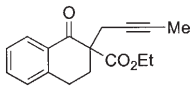
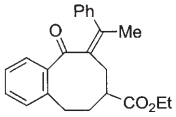
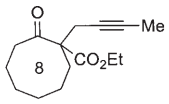
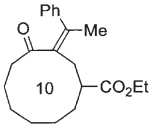
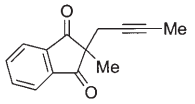
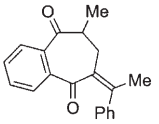
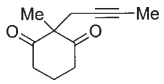
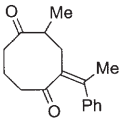
Entry	**1**	R^1	R^2	**2**	Ar	**4**	Yield [%][b]
1	**1a**	Ph	Me	**2b**	4-FC_6H_4	**4ab**	63
2	**1a**	Ph	Me	**2c**	4-MeC_6H_4	**4ac**	75
3	**1a**	Ph	Me	**2d**	3-ClC_6H_4	**4ad**	66
4	**1a**	Ph	Me	**2e**	3-$MeOC_6H_4$	**4ae**	77
5	**1b**	Ph	Et	**2a**	Ph	**4ba**	92
6	**1c**	Me	Et	**2a**	Ph	**4ca**	67
7	**1d**	Ph	TMS	**2a**	Ph	**4da**	25

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.6–1.0 mmol), [{Rh(OH)(cod)}$_2$] (0.05 equiv of Rh) in dioxane/H$_2$O (2.0 mL/20 μL); then treatment with aqueous NH$_4$Cl. [b] Yields of isolated products. cod = cyclooctadiene.

As listed in Table 2, the catalytic ring-expansion process worked well with substrates of five-, six-, and eight-membered-ring structures to give the seven-, eight-, and ten-membered-ring products, respectively, in yields ranging from 49% to 66%.[14] Cyclic 1,3-diketones **5f** and **5g** also underwent the analogous ring-expansion reaction. The ring opening of intermediate cyclobutanols formed from substrates **5c**, **5d**, and **5f** under the weakly acidic conditions proceeded more slowly than that of **5a** and thus required longer times for completion (see Supporting Information).

In summary, a new rhodium(I)-catalyzed acyl 1,3-migration reaction of acetylenic β-ketoesters was developed in which an intermediate organorhodium(I) species undergoes intramolecular nucleophilic addition to a ketone carbonyl group in a 4-*exo* process, which is followed by cyclobutane cleavage through a retro-aldol reaction. On the basis of this new 1,3-migration reaction, medium-sized carbocyclic rings

Table 2: Rhodium(I)-catalyzed two-carbon-atom ring expansion of **5** with **2a**.[a]

Entry	Substrate **5**	Product **6**	Yield [%][b]
1	 **5b**	 **6b**	51
2	 **5c**	 **6c**	49
3	 **5d**	 **6d**	58
4	 **5e**	 **6e**	54[c]
5	 **5f**	 **6f**	57
6	 **5g**	 **6g**	66

[a] Reaction conditions: **5** (0.2 mmol), **2** (1.0 mmol), [{Rh(OH)(cod)}$_2$] (0.05 equiv of Rh), room temperature, dioxane/H_2O (2.0 mL/20 μL); then treatment with aqueous NH_4Cl. [b] Yields of isolated products. [c] 100 °C

that are otherwise difficult to form were constructed in a simple operation from readily available substrates.

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[1] For reviews, see: a) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169–196; b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844.
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[7] When the ^{1}H NMR spectrum of the crude reaction mixture was measured prior to chromatographic purification, we observed about 50% of **3** and approximately 20% of **4aa**.
[8] Ring opening of a cyclobutanol skeleton by a retro-aldol reaction occurred much more readily than β-carbon elimination of rhodium(I) cyclobutanolates: a) T. Matsuda, M. Makino, M. Murakami, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1528–1533; see also reference [6d]; for a review on β-carbon elimination from palladium(II) cyclobutanolate, see: b) T. Nishimura, S. Uemura, *Synlett* **2004**, 201–216.
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[10] Although *o*-tolylboronic acid underwent 1,2-addition to the carbon–carbon triple bond, the resultant alkenyl rhodium(I) intermediate was not reactive enough for the addition to the benzoyl group.
[11] A 1,2-adduct formed by addition of a phenylrhodium species with the opposite regiochemistry was obtained in 47%.
[12] For examples of ring expansion through intramolecular carbonyl addition/ring opening, see: a) C.-J. Li, D.-L. Chen, Y.-Q. Lu, J. X. Haberman, J. T. Mague, *J. Am. Chem. Soc.* **1996**, *118*, 4216–4217; b) A. E. Imai, Y. Sato, M. Nishida, M. Mori, *J. Am. Chem. Soc.* **1999**, *121*, 1217–1225; c) U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341; for a review, see: d) P. M. Wovkulich in *Comprehensive Organic Synthesis, Vol. 1* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 892–897.
[13] For ring expansion through photochemical [2+2] cycloaddition/ring opening, see: J. D. Winkler, C. M. Bowen, F. Liotta, *Chem. Rev.* **1995**, *95*, 2003–2020, and references therein.
[14] The major by-products were the simple 1,2-adducts formed by addition to the carbon–carbon triple bond.

