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Rh-Catalyzed Cyclization of Diynes and Enynes Initiated by Carbonyl-Directed Activation of Aromatic and Vinylic C–H Bonds

Kyoji Tsuchikama, Yusuke Kuwata, Yu-ki Tahara, Yusuke Yoshinami, and Takanori Shibata*

Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, Okubo, Shinjuku, Tokyo, 169-8555, Japan

tshibata@waseda.jp

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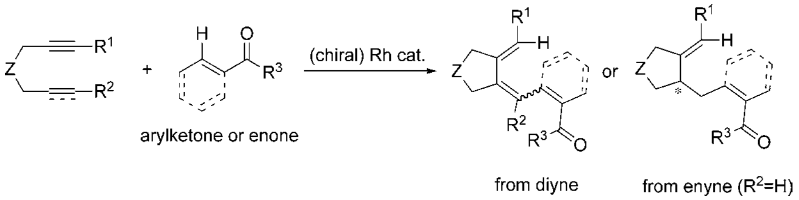
ABSTRACT



The Rh-catalyzed hydroarylative and hydrovinylative cyclization of diynes with aryl ketones or enones gave monocyclic 1,3-dienes. Enynes also underwent the same reaction and chiral products were obtained with high ee using a chiral Rh catalyst. Carbonyl-directed activation of aromatic and vinylic C–H bonds is likely the initial step in the present transformation.

Direct functionalization of unreactive C−H bonds is a valuable and challenging topic in organic synthesis. In particular, many researchers have focused on transition metal-catalyzed C−H activation along with C−C bond formation.[1] Jordan reported a catalytic direct addition of a C−H bond in α-picoline to olefins using a Zr complex.[2] Subsequently, Moore reported a Ru-catalyzed C−H activation in pyridine, which was accompanied by coupling of carbon monoxide and olefin.[3] Murai's report of the Ru-catalyzed addition of a C−H bond in aromatic ketones to vinylsilane is recognized as a monumental work in catalytic C−H activation and has led to a new area of C−C bond formation initiated by heteroatom-directed C−H activation.[4] Various types of catalytic Csp^2−H activation, such as enones,[5] aldimines,[6] and phenols,[7] have been reported since then.[8]

We report here a Rh-catalyzed hydroarylative and hydrovinylative cyclization of diynes and enynes with aryl ketones and enones, including an enantioselective variant.[9,10] We consider that carbonyl-directed Csp^2−H bond activation of aryl ketones and enones is likely to be the initial step in the present reaction.

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(1) For C−H activation reviews, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Kakiuchi, F.; Murai, S. *Activation of Unreactive Bonds and Organic Synthesis*; Springer: Berlin, 1999. (d) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699. (e) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047.

(2) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778.

(3) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888.

(4) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(5) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371.

(6) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440.

(7) (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (b) Oi, S.; Watanabe, S.-i.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665.

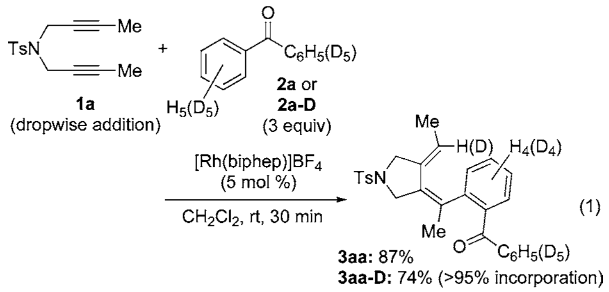
(8) Recently, heteroatom-directed Csp^3−H bond activation along with the C−C bond formation was also reported, see: Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510 and references cited therein.

(9) Rh-catalyzed highly enantioselective cyclization initiated by directed C−H bond activation of aromatic imines, see: Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192.

(10) During the preparation of this manuscript, Tanaka, and coworkers reported the Rh-catalyzed, hydroarylative cyclization of diynes with aryl ketones, and they proposed a metallacyclopentadiene as an intermediate without direct proof, see: Tanaka, K.; Otake, Y.; Wada, A.; Noguchi, K.; Hirano, M. *Org. Lett.* **2007**, *9*, 2203.

10.1021/ol0711669 CCC: $37.00

After the enantioselective [2 + 2 + 2] cycloaddition of diynes with alkenes,[11a] we recently reported a Rh-catalyzed hetero-[2 + 2 + 2] cycloaddition of diynes with carbonyl compounds.[11b] During the course of our study, we examined the reaction of diyne **1a** with benzophenone: hetero-[2 + 2 + 2] cycloaddition did not proceed but hydroarylative cyclization proceeded to give cyclic 1,3-diene **3aa**, whose structure was determined by X-ray measurements (eq 1, Figure 1). Diyne **1a** was promptly consumed at room temperature using [Rh(cod)(biphep)]BF_4 (BIPHEP: 2,2′-bis-(diphenylphosphino)-1,1′-biphenyl), which was treated in situ with hydrogen gas to exclude 1,5-cyclooctadiene (COD) before use.[12] We ascertained cleavage of the aromatic C−H bond adjacent to the carbonyl group and the almost perfect transfer of hydrogen by a labeling experiment using benzophenone-d_{10} (**2a-D**).



3aa: 87%
3aa-D: 74% (>95% incorporation)

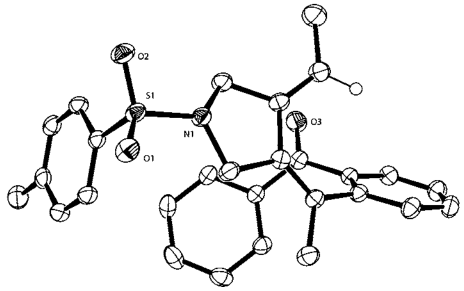
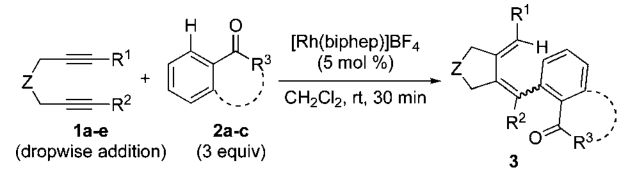


Figure 1. ORTEP diagram of **3aa**

We further examined hydroarylative cyclization using several aryl ketones and diynes (Table 1). Aromatic C−H bonds of acetophenone (**2b**) and tetralone (**2c**) were also activated and reacted with diyne **1a**; however, partial double-bond isomerization was observed in product **3ac** (entries 1, 2). Even phenyl-substituted diyne **1b** could be used in this reaction, but double-bond isomerization proceeded further and the *Z* isomer of **3ba** was a major product (entry 3). When unsymmetrical diyne **1c** was used, a regioselective reaction proceeded to give diene **3ca**, and the *E/Z* ratio was low (entry 4). Intriguingly, Rh-BINAP catalyst suppressed isomerization completely (entry 5).[13] Carbon-tethered 1,6-diyne **1d** and 1,7-diyne **1e** also underwent C−H bond-cleaved hydroarylative cyclization to give 1,3-diene **3da** and **3ea** in high to quantitative yield (entries 6, 7).

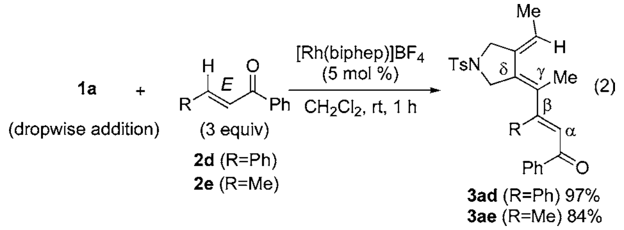
Table 1. Cyclization of Various Diynes and Aryl Ketones



entry	Z	R^1, R^2	diyne	R^3	ketone	yield (%)	*E/Z*[a]
1	NTs	Me, Me	**1a**	Me	**2b**	55 (**3ab**)	>20/1
2	NTs	Me, Me	**1a**	$(CH_2)_3$	**2c**	87 (**3ac**)	4/1
3	NTs	Ph, Ph	**1b**	Ph	**2a**[b]	73 (**3ba**)	1/2
4	NTs	Me, Ph	**1c**	Ph	**2a**	86 (**3ca**)	1/1
5[c]	NTs	Me, Ph	**1c**	Ph	**2a**	63 (**3ca**)	>20/1
6	$C(CO_2Bn)_2$	Me, Me	**1d**	Ph	**2a**	78 (**3da**)	1/>20[d]
7	$\{C(CO_2Et)_2\}_2$	Me, Me	**1e**	Ph	**2a**	>99 (**3ea**)	1/16[d]

[a] See Supporting Information. [b] Reaction run using 10 equiv. [c] *rac*-BINAP was used as a ligand. [d] From the nomenclature rule, *E/Z* ratio is opposite but the major geometry is the same as entries 1, 2, and 5.

We next examined the reaction using *trans*-chalcone as a carbonyl compound (eq 2). Vinylic C−H activation preceded aromatic C−H activation, and monocyclic trienone **3ad** was obtained exclusively in excellent yield. Moreover, two alkene moieties (α,*β*- and *γ*,*δ*-positions), which were derived from the C−C double-bond of *trans*-chalcone and an alkyne moiety of the diyne, respectively, were completely isomerized into the (*Z*,*Z*)-isomer. Also, in the case of phenyl 1-propenyl ketone (**2e**), the vinylic C−H activation proceeded predominantly along with the complete isomerization of two C−C double bonds.



The present hydroarylative and hydrovinylative cyclization also proceeded with enynes and α,*β*-unsaturated ketones: the reaction of nitrogen-tethered enyne **4a** with benzophenone gave monocyclic product **5aa**, where hydrogen added to the alkyne moiety and the aryl group added to the alkene moiety of the enyne, and another pattern of hydroarylative product **6aa** could not be detected. These results indicate the reaction

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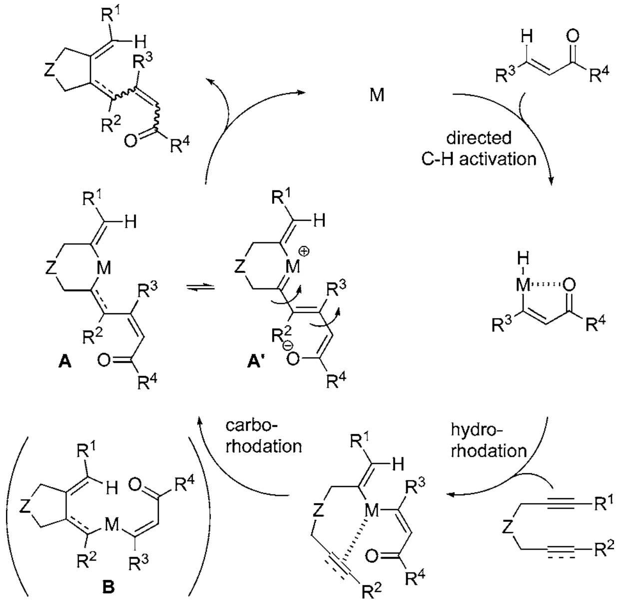
(11) (a) Tsuchikama, K.; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc.* **2006**, *128*, 13686. (b) Tsuchikama, K.; Yoshinami, Y.; Shibata, T. *Synlett* **2007**, 1395.

(12) A typical experimental procedure (eq 1): CH_2Cl_2 (1 mL) was added to [Rh(cod)(biphep)]BF_4 (3.8 mg, 0.005 mmol) in the Ar-filled flask, and the solution was stirred at ambient temperature for 5 min. After the flask was purged with hydrogen gas, the solution was stirred for 30 min. Both the solvent and hydrogen gas were removed under reduced pressure. Then argon gas was introdued to the flask, and the CH_2Cl_2 solution (0.3 mL) of benzophenone (**2a**) (54.0 mg, 0.30 mmol) was added. Diyne **1a** (27.6 mg, 0.10 mmol) in CH_2Cl_2 (0.7 mL) was added dropwise over 30 min at room temperature, and the mixture was stirred for 5 min. After completion of the reaction, the solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography (hexane/AcOEt = 4/1) to give pure **3aa** (40.0 mg, 87%).

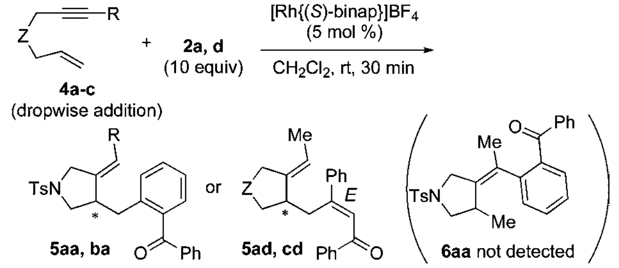
(13) These compounds were primary products because the *E/Z* ratios were not changed if they were heated in 1,2-dichloroethane at 40 °C for 24 h.

Scheme 1. A Possible Mechanism of the Present Cyclization



mechanism described later (Scheme 1). When a chiral catalyst (Rh-(*S*)-BINAP complex) was used, highly enantioselective induction was observed (Table 2, entry 1). Phenyl-substituted enyne **4b** was sluggish to react with **2a** and the yield was moderate, but the ee of the product **5ba** remained high (entry 2). The vinylic C−H activation of chalcone along with enantioselective cyclization was also possible, and dienone **5ad** was obtained (entry 3).[14] Carbon-tethered enyne **4c** was a good substrate and the corresponding product **5cd** was obtained in excellent ee (entry 4).[15]

Table 2. Enantioselective Cyclization of Enynes



entry	Z	R	enyne	ketone	yield (%)	ee (%)
1	NTs	Me	**4a**	**2a**	69 (**5aa**)	92
2[a]	NTs	Ph	**4b**	**2a**	45 (**5ba**)	91
3	NTs	Me	**4a**	**2d**	37 (**5ad**)	97
4	$C(CO_2Bn)_2$	Me	**4c**	**2d**	76 (**5cd**)	96

[a] The reaction was carried out for 2.5 h.

On the basis of the above results, we can now speculate a reaction mechanism (Scheme 1), where an enone is depicted as a representative reactant. The oxidative addition of Rh(I) to vinylic C−H bond is initiated by the directing effect of a carbonyl group,[16] and this is followed by hydrorhodation to the alkyne moiety of the diyne or enyne.[17] A carborhodation pathway can be ruled out because the reaction of enyne, where an alkyne moiety is more reactive than an alkene moiety, did not give a benzylidene product such as **6aa**. Subsequent intramolecular carborhodation would give metallacyclohexane **A**. In the case of diynes, an equilibrium would exist between metallacycle **A** and zwitterionic carbene complex **A′**, and the most thermodynamically favored geometry is obtained by double-bond isomerizations.[18] This is a good explanation for complete isomerization in the case of diyne **1a** and enones. Another pattern of carborhodation, which gives **B**, would be less likely because double-bond isomerization would also occur in the hydroarylative product **3ab**, which was derived from benzophenone, as with product **3ad** from chalcone (entry 1 in Table 1 and eq 2).[19]

In summary, we have developed the hydroarylative and hydrovinylative cyclizations, which would be initiated by carbonyl-directed C−H activation. The reaction of diynes with aryl ketones or enones gave 1,3-dienes, and the enantioselective reaction of enynes gave chiral compounds with high ee. Although we provide a possible mechanism, further study is in progress.

Acknowledgment. We thank Prof. Nobuharu Iwasawa (Tokyo Institute of Technology, Japan) for his helpful discussion and Ai Kawachi (Waseda University, Japan) for her experimental assistance. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Spectral data for products and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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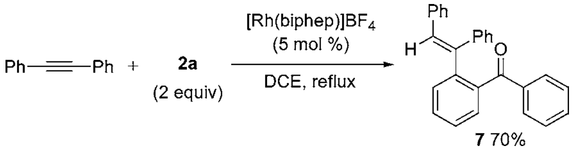
(14) Even using Rh-BIPHEP catalyst, no isomerization of C−C double bond, derived from C−C double bond of chalcone, was observed in product **5ad**.

(15) Under the same reaction conditions, the [2 + 2 + 2] cycloaddition of carbon-tethered enyne **4c** with methyl acrylate or methyl pyruvate did not proceed, where metallacyclopentene would be an intermediate. These results indicate that the metallacyclopentene would not be an intermediate for the formation of present hydroarylative cycloadduct **5cd**.

(16) In place of diynes, tolan as a monoyne also reacted with benzophenone using the same catalyst at higher temperature to give the hydroarylated product **7** in good yield. This result shows that C−H bond cleavage surely occurred without the formation of metallacyclopentadiene intermediate.



7 70%

(17) An example of hydrorhodation of arylrhodium hydride complex to an alkyne: Jones, W. D.; Chandler, V. L.; Feher, F. J. *Organometallics* **1990**, *9*, 164.

(18) This isomerization mechanism via carbene complex was already reported, see: (a) Tanke, R. S.; Crabtree, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 7984. (b) Ojima, I.; Clos, N.; Donovan, R. J.; Ingallina, P. *Organometallics* **1990**, *9*, 3127.

(19) The reaction mechanism involving the oxidative coupling of diynes or enynes could not be wholly ruled out but it cannot give reasonable explanations for the C−C double bond isomerization, which depends on the substrates.