

Amide-Directed Alkenylation of sp^2 C–H Bonds Catalyzed by a Cationic Rh(I)/BIPHEP Complex Under Mild Conditions: Dramatic Rate Acceleration by a 1-Pyrrolidinecarbonyl Group

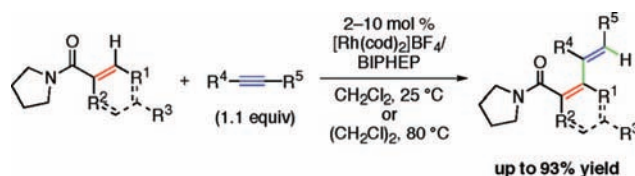
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ABSTRACT



A cationic rhodium(I)/BIPHEP complex catalyzes amide-directed regioselective alkenylations of olefinic or aromatic sp^2 C–H bonds in good yields under mild reaction conditions. The use of a 1-pyrrolidinecarbonyl group as a directing group dramatically accelerates the reaction.

The chelation-assisted alkenylation of olefinic or aromatic sp^2 C–H bonds with alkynes catalyzed by transition-metal complexes is a useful transformation in organic synthesis.¹ Murai and co-workers reported the first carbonyl-directed *ortho*-alkenylation of aryl ketones with alkynes by using a ruthenium catalyst.² After this pioneering work, a number of chelation-assisted alkenylations of sp^2 C–H bonds with alkynes have been reported by using various chelation groups and transition-metal catalysts.^{3–5} However, carbonyl-directed alkenylations of sp^2 C–H bonds with alkynes have been

reported in a limited number.^{2a,3,4,6–9} In particular, the use of amide carbonyl groups as a chelation group is scarce.^{6–9} In this paper, we describe cationic rhodium(I)/BIPHEP complex-catalyzed regioselective alkenylations of olefinic or aromatic sp^2 C–H bonds under mild reaction conditions by a 1-pyrrolidinecarbonyl group as a directing group.

Recently, we have reported that a cationic rhodium(I)/H₈-BINAP complex catalyzes a codimerization of acrylate **1a** and diphenylacetylene (**2a**) leading to 1,3-diene **3aa** at 80 °C presumably through the formation of a rhodacyclopentene intermediate followed by β -hydride elimination (eq 1).¹⁰ However, no conversion was observed in the reaction between crotonate **1b** and **2a** under the same reaction conditions (eq 2).

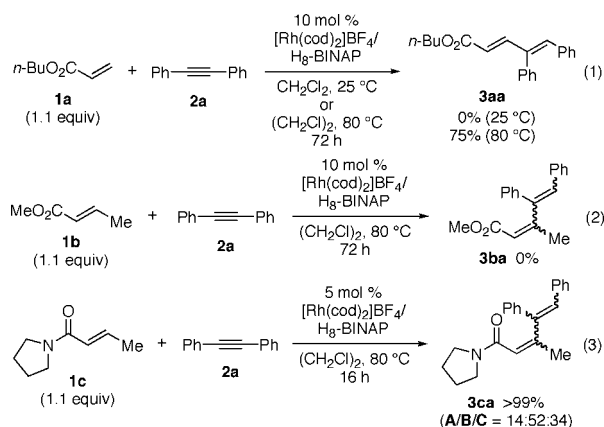
(1) For recent reviews, see: (a) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, 451, 417. (c) Campos, K. R. *Chem. Soc. Rev.* **2007**, 36, 1069. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, 107, 174. (e) Godula, K.; Sames, D. *Science* **2006**, 312, 67. (f) Dyker, G., Ed. *Handbook of C–H Transformations*; Wiley-VCH: Weinheim, Germany, 2005. (g) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, 345, 1077. (h) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, 219, 211. (i) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, 102, 1731. (j) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, 38, 1698.

(2) (a) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681. For the pioneering work on carbonyl-directed alkenylations of aryl ketones with alkenes by using a Ru catalyst, see: (b) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, 366, 529.

(3) For ketone carbonyl-directed alkenylations of sp^2 C–H bonds with alkynes, see: (a) Kakiuchi, F.; Uetsuhara, T.; Tanaka, Y.; Chatani, N.; Murai, S. *J. Mol. Catal. A: Chem.* **2002**, 511, 182. (b) Harris, P. W. R.; Rickard, C. E. F.; Woodgate, P. D. *J. Organomet. Chem.* **1999**, 589, 168. (c) Kakiuchi, F.; Sato, T.; Tsujimoto, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1998**, 27, 1053. (d) Londergan, T. M.; You, Y.; Thompson, M. E.; Weber, W. P. *Macromolecules* **1998**, 31, 2784.

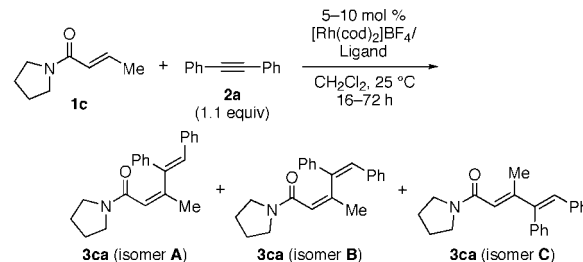
(4) For ester carbonyl-directed alkenylations of sp^2 C–H bonds with alkynes, see: Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, 117, 5371.

Interestingly, the reaction between crotonamide **1c** and **2a** proceeded in quantitative yield, although a mixture of stereoisomers **A**, **B**, and **C** shown in Table 1 was generated (eq 3).

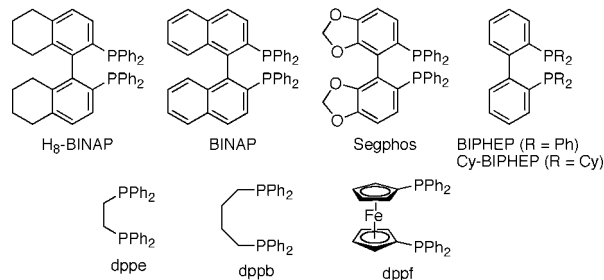


To improve the stereoselectivity, the reaction of **1c** and **2a** was examined at ambient temperature as shown in Table 1. After screening of various diphosphine ligands (entries 1–8), we were pleased to find that the use of BIPHEP furnished the desired diene **3ca** in moderate yield (entry 4). As the reaction proceeds at ambient temperature and isomer **A** was obtained as a predominant stereoisomer, the reaction may proceed through an amide carbonyl-directed C–H bond activation pathway. The yields of **3ca** are highly dependent on dihedral angles of biaryldiphosphine ligands [dihedral angle: $\text{H}_8\text{-BINAP}$ (entry 1) > BINAP (entry 2) > Segphos (entry 3) > BIPHEP (entry 4),¹¹ yield of **3ca**: entry 1 < entry 2 < entry 3 < entry 4]. The electronic nature of the substituents on the phosphorus was also examined, which revealed that the use of electron-rich Cy-BIPHEP completely

Table 1. Screening of Reaction Conditions for Rh-Catalyzed Alkenylation of Alkenylamide **1c** with Monoyne **2a**^a



entry	ligand	catalyst (mol %)	time (h)	conc ^c 1c (M)	convn (%)	% yield ^b (A/B/C)
1	$\text{H}_8\text{-BINAP}$	10	16	0.1	0	0
2	BINAP	10	16	0.1	<2	<2
3	Segphos	10	16	0.1	16	14 (57:0:43)
4	BIPHEP	10	16	0.1	53	41 (100:0:0)
5	Cy-BIPHEP	10	16	0.1	0	0
6	dppe	10	16	0.1	0	0
7	dppb	10	16	0.1	0	0
8	dppf	10	16	0.1	0	0
9	BIPHEP	10	72	0.1	100	92 (84:3:13)
10	BIPHEP	5	72	0.1	81	81 (96:4:0)
11 ^c	BIPHEP	5	72	0.5	100	94 (88:4:8)

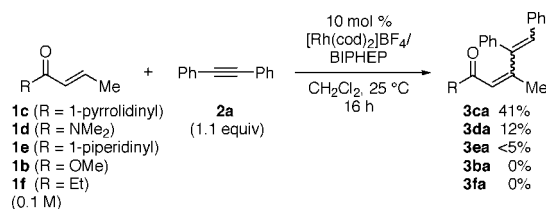


^a $[\text{Rh}(\text{cod})_2]\text{BF}_4/\text{ligand}$ (0.0075 or 0.015 mmol), **1c** (0.150 mmol), **2a** (0.165 mmol), and CH_2Cl_2 (1.5 mL) were used. ^b NMR yield. ^c $[\text{Rh}(\text{cod})_2]\text{BF}_4/\text{ligand}$ (0.025 mmol), **1c** (0.500 mmol), **2a** (0.550 mmol), and CH_2Cl_2 (1.0 mL) were used.

shut down the reaction (entry 5). Prolonged reaction time and high concentration improved the yield of **3ca** to 94% and lowered the catalyst loading to 5 mol% (entry 11).

Not only BIPHEP as a ligand but also a 1-pyrrolidinecarbonyl group as a directing group are essential for this transformation. Dimethylcarbamoyl (**1d**) and 1-piperidinecarbonyl (**1e**) groups significantly decreased the reaction rate, and ester (**1b**) and ketone (**1f**) carbonyl groups completely shut down the reaction (Scheme 1). This observation may correlated with electron densities of carbonyl oxygens (electron density: 1-pyrrolidinyl

Scheme 1



(5) For chelation-assisted alkenylations of sp^2 C–H bonds with alkynes, see: (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (b) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309. (c) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2452. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (e) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (f) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362. (g) Kuninobu, K.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (h) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146. (i) Kuninobu, K.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498. (j) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J. B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759. (k) Lim, Y.-G.; Lee, K.-H.; Koo, B. T.; Kang, J.-B. *Tetrahedron Lett.* **2001**, *42*, 7609. (l) Satoh, T.; Nishinaka, Y.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 615. (m) Dürr, U.; Kisch, H. *Synlett* **1997**, 1335. (n) Halbritter, G.; Knoch, F.; Wolski, A.; Kisch, H. *Angew. Chem., Int. Ed. Engl.* **1994**, 331603.

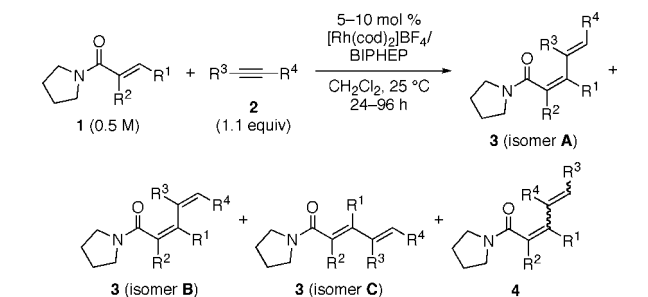
(6) Ru-catalyzed codimerizations of *N,N*-dimethylacrylamide and alkynes at 80 °C were reported, and a mechanism, the formation of a ruthenacyclopentene intermediate followed by β -hydride elimination, is proposed; see: Mitsudo, T.; Zhang, S.-W.; Nagao, M.; Watanabe, Y. *Chem. Commun.* **1991**, 598.

(7) Ru-catalyzed intramolecular alkenylations of crotonates and crotonamide derivatives with alkynes at 110 °C were reported, although the mechanism is not clear; see: Mori, M.; Kozawa, Y.; Nishida, M.; Kanamaru, M.; Onozuka, K.; Takimoto, M. *Org. Lett.* **2000**, *2*, 3245.

(8) Pd-catalyzed codimerizations of acrylate and acrylamide derivatives with internal aryl alkynes at 100 °C were reported, and a mechanism, the formation of a Pd hydride species followed by hydropalladation with the alkyne, is proposed; see: Lindhardt, A. T.; Mantel, M. L. H.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2668.

(9) Ru-catalyzed co-oligomerizations of *N*-vinylamides with alkenes or alkynes at 160–170 °C were reported, and a mechanism, the formation of a Ru hydride species by activation of sp^2 C–H bonds in alkenes or a ligand, is proposed; see: Tsujita, H.; Ura, Y.; Matsuki, S.; Wada, K.; Mitsudo, T.; Kondo, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5160.

Table 2. Cationic Rhodium(I)/BIPHEP Complex-Catalyzed Alkenylation of Alkenylamides **1** with Monoynes **2**^a



entry	1 (R ¹ , R ²)	2 (R ³ , R ⁴)	3 /% yield ^b (A/B/C)	4 /% yield ^b
1 ^c	1c (Me, H)	2a (Ph, Ph)	88 (89:8:3)	
2 ^c	1g (<i>n</i> -Pr, H)	2a (Ph, Ph)	64 (>98:<1:<1) ^d	
3	1h (H, Me)	2a (Ph, Ph)	0 (–)	
4	1i (H, H)	2a (Ph, Ph)	0 (–)	
5	1j [–(CH ₂) ₄ –]	2a (Ph, Ph)	80 (>99:<1:–)	
6	1c (Me, H)	2b [Ph, (CH ₂) ₃ Me]	74 (>98:<1:<1)	<5
7	1c (Me, H)	2c [Ph, (CH ₂) ₃ OTs]	80 (>98:<1:<1)	<5
8	1c (Me, H)	2d [Ph, (CH ₂) ₃ Br]	73 (>98:<1:<1)	<5
9	1c (Me, H)	2e [Me, (CH ₂) ₄ Me]	75 (>98:<1:<1) ^e	10 ^e
10	1c (Me, H)	2f (<i>n</i> -PrC≡C, <i>n</i> -Pr)	35 (>98:<1:<1) ^d	0

^a [Rh(cod)₂]BF₄/BIPHEP (0.050 mmol, 10 mol %), **1** (0.500 mmol), **2** (0.550 mmol), and CH₂Cl₂ (entries 1–5) or (CH₂Cl)₂ (entries 6–10) (1.0 mL) were used. ^b Isolated yield. ^c Catalyst: 5 mol %. ^d Conversion of **1g**: 71% (entry 2). Conversion of **1c**: 38% (entry 10). ^e Isolated as a mixture of **3ce** and **4ce**.

> NMe₂ > 1-piperidinyl ≫ OMe or Et,¹² yield of **3**: 1-pyrrolidinyl > NMe₂ > 1-piperidinyl ≫ OMe or Et).

The scope of both alkenylamides **1** and monoynes **2** was examined as shown in Table 2. Not only crotonamide (**1c**, entry 1) but also 2-hexenylamide (**1g**, entry 2) and cyclic alkenylamide (**1j**, entry 5) could participate in this reaction.¹³ However, methacrylamide **1h** and acrylamide **1i** could not participate in this reaction (entries 3 and 4). With respect to monoynes, the reactions of phenyl, alkyl, and functionalized alkyl substituted unsymmetrical monoynes **2b–e** with **1c** proceeded in good yields with high regioselectivity (entries 6–9). The reaction of **1c** with 1,3-diyn **2f** proceeded with complete regioselectivity although it was sluggish (entry 10).¹⁴ Importantly, the present alkenylation is highly stereoselective and isomer **A** was obtained as a predominant isomer.

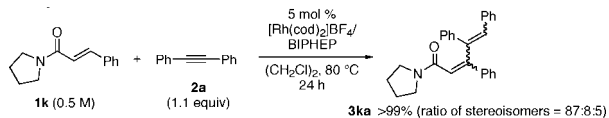
If the present rhodium-catalyzed alkenylations of olefinic sp² C–H bonds with alkynes proceed through an amide

(10) Shibata, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2829.

(11) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

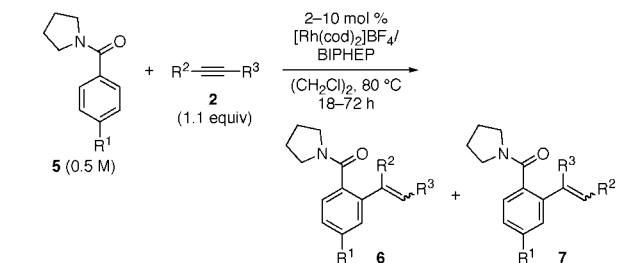
(12) Kanner, C. B.; Pandit, U. K. *Tetrahedron* **1982**, *38*, 3597.

(13) The reaction of phenyl-substituted alkenylamide **1k** with **2a** proceeded at 80 °C in quantitative yield, while the stereochemistry of the product **3ka** has not been determined.



(14) Ru-catalyzed Alder ene reactions of di- and triynes were reported; see: Cho, E. J.; Lee, D. J. *Am. Chem. Soc.* **2007**, *129*, 6692.

Table 3. Cationic Rhodium(I)/BIPHEP Complex-Catalyzed Alkenylation of Benzamides **5** with Monoynes **2**^a

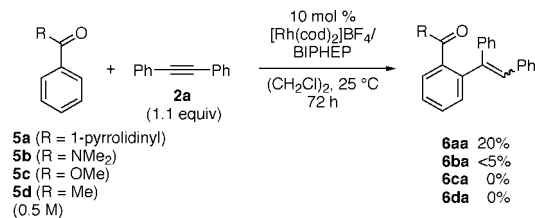


entry	5 (R ¹)	2 (R ² , R ³)	6 /% yield ^b (E/Z)	7 /% yield ^b
1	5a (H)	2a (Ph, Ph)	78 (>99:1)	
2	5e (CF ₃)	2a (Ph, Ph)	79 (>99:1)	
3	5f (OMe)	2a (Ph, Ph)	93 (>99:1)	
4 ^c	5f (OMe)	2a (Ph, Ph)	92 (>99:1)	
5 ^d	5f (OMe)	2a (Ph, Ph)	76 (>99:1) ^f	
6 ^e	5f (OMe)	2a (Ph, Ph)	60 (>99:1) ^f	
7	5f (OMe)	2b [Ph, (CH ₂) ₃ Me]	81 (>99:1)	0
8	5f (OMe)	2c [Ph, (CH ₂) ₃ OTs]	40 (>99:1) ^f	<2
9	5f (OMe)	2d [Ph, (CH ₂) ₃ Br]	45 (>99:1) ^f	<2
10	5f (OMe)	2e [Me, (CH ₂) ₄ Me]	36 (87:13) ^f	0
11	5f (OMe)	2f (<i>n</i> -PrC≡C, <i>n</i> -Pr)	20 (>99:1) ^f	0

^a [Rh(cod)₂]BF₄/BIPHEP (0.050 mmol, 10 mol %), **5** (0.500 mmol), **2** (0.550 mmol), and (CH₂Cl)₂ (1.0 mL) were used. ^b Isolated yield. ^c Catalyst: 5 mol %. ^d Catalyst: 2 mol %. ^e At 25 °C. ^f Conversion of **5f**: 76% (entry 5), 60% (entry 6), 50% (entry 8), 46% (entry 9), 37% (entry 10), 32% (entry 11).

carbonyl-directed C–H bond activation pathway, the reaction between benzamide **5a** and monoyne **2a** should proceed in the presence of the same rhodium catalyst. Indeed, the desired alkenylation proceeded at ambient temperature, and the 1-pyrrolidinecarbonyl group is again the best directing group (Scheme 2).^{15,16}

Scheme 2

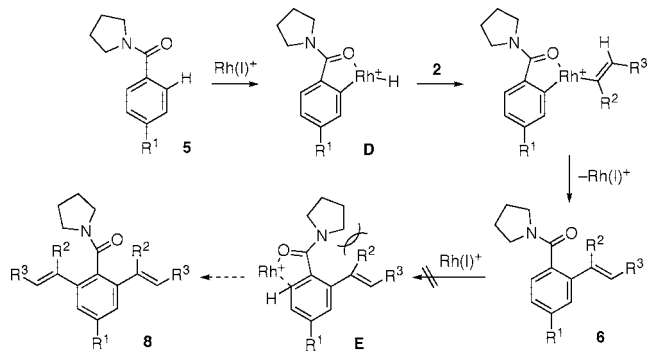


At elevated temperature, the reaction of **5a** and **2a** was accelerated to give the desired alkenylation product **6aa** in

(15) During preparation of this manuscript, ketone carbonyl-directed alkenylations and alkylations of aryl ketones with diphenylacetylene, styrene, and norbornene catalyzed by cationic Ir(I)/biaryldiphosphine complexes were reported; see: (a) Tsuchikama, K.; Kasagawa, M.; Hashimoto, Y.-k.; Endo, K.; Shibata, T. *J. Organomet. Chem.* **2008**, *693*, 3939. Amide carbonyl-directed asymmetric alkylations of a NH₂-benzamide with norbornene catalyzed by a Ir(I)/bisphosphine/Cp complex were reported; see: (b) Aufdenbatten, R.; Diezi, S.; Togni, A. *Monatsh. Chem.* **2000**, *131*, 1345.

(16) The corresponding Ir(I) complexes showed significantly low catalytic activities in the present 1-pyrrolidinecarbonyl-directed sp² C–H bond alkenylations.

Scheme 3



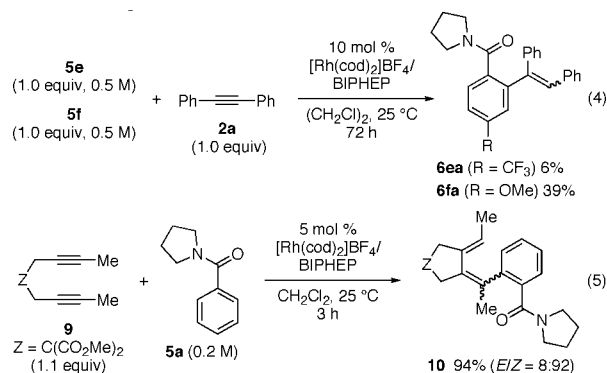
improved yield (Table 3, entry 1). The scope of both benzamides **5** and monoynes **2** was then examined as shown in Table 3. The use of electron-deficient 4-trifluoromethyl-substituted benzamide **5e** did not affect the product yield (entry 2), but that of electron-rich 4-methoxy-substituted benzamide **5f** improved the product yield (entry 3) and allowed the reaction to be conducted at lower catalyst loadings (5 mol %, entry 4; 2 mol %, entry 5) or ambient temperature (25 °C, entry 6). Like the alkenylations of alkenylamide **1c** with unsymmetrical monoynes **2b–f**, those of benzamide **5f** with **2b–f** proceeded with high regio- and stereoselectivity (entries 7–11), although the reactions with **2c–f** were sluggish (entries 8–11).

A possible mechanism for the alkenylation of benzamide **5** with monoyne **2** is shown in Scheme 3. Benzamide **5** reacts with rhodium to give rhodium hydride **D** through 1-pyrrolidinecarbonyl-directed C–H bond activation. Insertion of monoyne **2** followed by reductive elimination of rhodium furnishes alkenylation product **6**. Importantly, double alkenylation products **8** were not generated in the all of entries shown in Table 3. The steric repulsion between the amide group and the alkenyl group may deter the formation of plausible intermediate **E** leading to **8**.

To access the electronic effect on the present alkenylation, a competition experiment was conducted between benzamides **5e** and **5f** at ambient temperature, which revealed that electron-rich amide **5f** preferentially reacted with **2a** (eq 4). According to this observation and a lack of the catalytic activity of electron-rich Cy-BIPHEP as a ligand (Table 1, entry 5), the electrophilic metalation of sp^2 C–H bonds by cationic rhodium(I) species may be involved in the catalytic cycle.¹⁷

We have recently reported the cationic rhodium(I)/Segphos complex-catalyzed *ortho*-dienylation of aryl ketones with 1,6-

diynes.^{18,19} However, slow addition of 1,6-diynes and/or a large excess of aryl ketones were necessary to obtain high product yields. Pleasingly, the use of benzamide **5a** is also effective in the dienylation with 1,6-diyne **9** to give the desired dienylation product **10** in high yield without employing slow addition of **9** and using excess **5a** (eq 5).²⁰



In conclusion, we have demonstrated that a cationic rhodium(I)/BIPHEP complex catalyzes 1-pyrrolidinecarbonyl-directed regioselective alkenylations of olefinic or aromatic sp^2 C–H bonds in good yields under mild reaction conditions. Future studies will focus on further catalyst tuning, expanding the scope, and elucidation of the precise reaction mechanism.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research (Nos. 20675002 and 19028015) from JSPS, Japan. We thank Takasago Int. Co. for the gift of H₈-BINAP and Segphos.

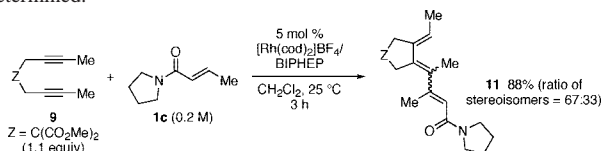
Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) (a) Tanaka, K.; Otake, Y.; Wada, A.; Hirano, M. *Org. Lett.* **2007**, 9, 2203. After our publication, the same reaction was independently reported by another research group, see: (b) Tsuchikama, K.; Kuwata, Y.; Tahara, Y.; Yoshinami, Y.; Shibata, T. *Org. Lett.* **2007**, 9, 3097.

(19) Dienylations of sp^2 C–H bonds with alkynes have been developed by using various transition-metal complexes; see: (a) Aubert, C.; Betschmann, P.; Eichberg, M. J.; Gandon, V.; Heckrodt, T. J.; Lehmann, J.; Malacria, M.; Masjost, B.; Paredes, E.; Vollhardt, K. P. C.; Whitener, G. D. *Chem.–Eur. J.* **2007**, 13, 7443. (b) Aubert, C.; Gandon, V.; Geny, A.; Heckrodt, T. J.; Malacria, M.; Paredes, E.; Vollhardt, K. P. C. *Chem.–Eur. J.* **2007**, 13, 7466, and references cited therein.

(20) The reaction of alkenylamide **1c** with 1,6-diyne **9** also proceeded in high yield, while the stereochemistry of the product **11** has not been determined.



(17) Electron-deficient cationic Rh(I) complexes efficiently catalyze arylation reactions of sp^2 C–H bonds; see: (a) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, 128, 11748. (b) Nambo, M.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2007**, 129, 8080.