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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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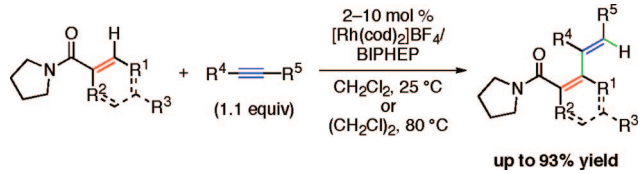
ABSTRACT



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)/H$_8$-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 alkylations 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.

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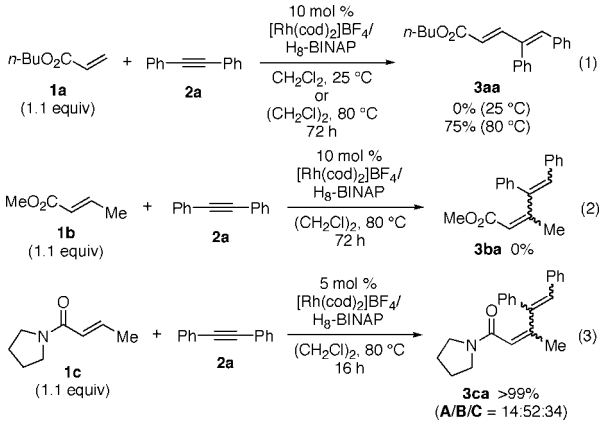
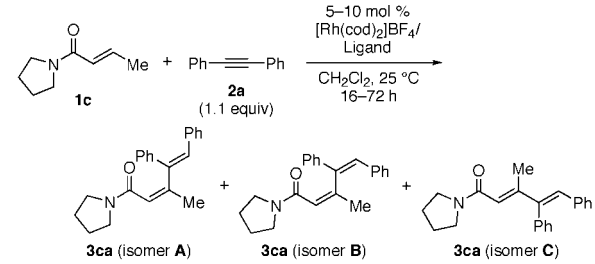
Interestingly, the reaction between crotonamide **1c** and **2a** proceeded in quantitative yield, although a mixture of stereoisomers **A**, **B**, and **C** shown in Table 1 was generated (eq 3).

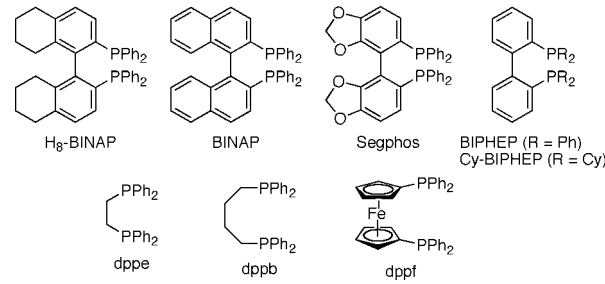


To improve the stereoselectivity, the reaction of **1c** and **2a** was examined at ambient temperature as shown in Table 1. After screening of various diphosphine ligands (entries 1−8), we were pleased to find that the use of BIPHEP furnished the desired diene **3ca** in moderate yield (entry 4). As 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: H_8-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)	concn **1c** (M)	convn (%)	% yield[b] (**A**/**B**/**C**)
1	H_8-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)

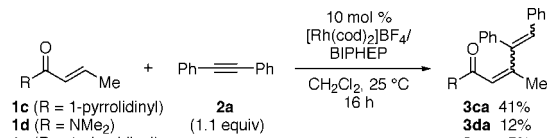


[a] $[Rh(cod)_2]BF_4$/ligand (0.0075 or 0.015 mmol), **1c** (0.150 mmol), **2a** (0.165 mmol), and CH_2Cl_2 (1.5 mL) were used. [b] NMR yield. [c] $[Rh(cod)_2]BF_4$/ligand (0.025 mmol), **1c** (0.500 mmol), **2a** (0.550 mmol), and CH_2Cl_2 (1.0 mL) were used.

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**, *331*603.

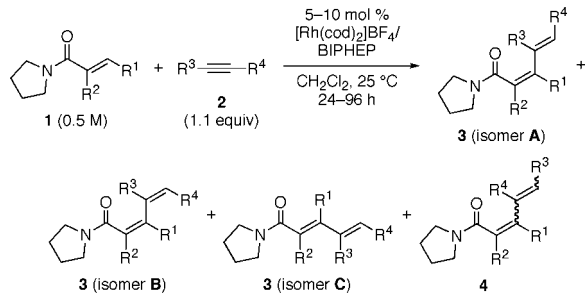
(6) Ru-catalyzed codimerizations of *N*,*N*-dimethylacrylamide and alkynes at 80 °C were reported, and a mechanism, the formation of a ruthenacyclopentene intermediate followed by β-hydride elimination, is proposed; see: Mitsudo, T.; Zhang, S.-W.; Nagao, M.; Watanabe, Y. *Chem. Commun.* **1991**, 598.

(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.

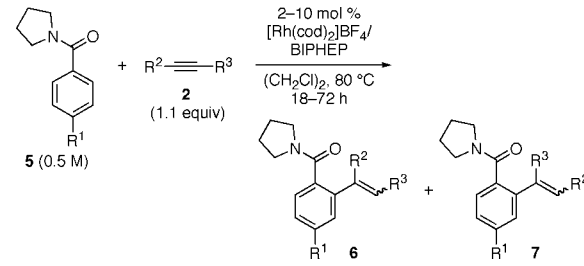
Table 2. Cationic Rhodium(I)/BIPHEP Complex-Catalyzed Alkenylation of Alkenylamides **1** with Monoynes **2**[a]



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** (*n*-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** (*n*-PrC≡C, *n*-Pr)	35 (>98:<1:<1)[d]	0

[a] $[Rh(cod)_2]BF_4$/BIPHEP (0.050 mmol, 10 mol %), **1** (0.500 mmol), **2** (0.550 mmol), and CH_2Cl_2 (entries 1−5) or $(CH_2Cl)_2$ (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**.

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** (*n*-PrC≡C, *n*-Pr)	20 (>99:1)[f]	0

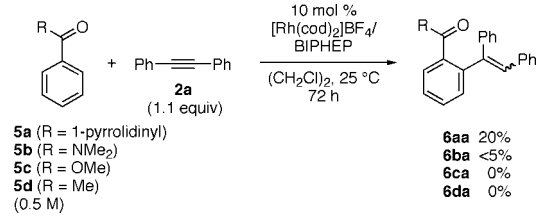
[a] $[Rh(cod)_2]BF_4$/BIPHEP (0.050 mmol, 10 mol %), **5** (0.500 mmol), **2** (0.550 mmol), and $(CH_2Cl)_2$ (1.0 mL) were used. [b] Isolated yield. [c] Catalyst: 5 mol %. [d] Catalyst: 2 mol %. [e] At 25 °C. [f] Conversion of **5f**: 76% (entry 5), 60% (entry 6), 50% (entry 8), 46% (entry 9), 37% (entry 10), 32% (entry 11).

> NMe_2 > 1-piperidinyl ≫ OMe or Et,[12] yield of **3**: 1-pyrrolidinyl > NMe_2 > 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-diyne **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.

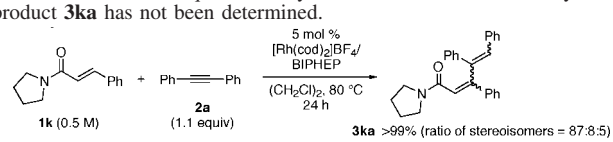
If the present rhodium-catalyzed alkenylations of olefinic sp^2 C−H bonds with alkynes proceed through an amide carbonyl-directed C−H bond activation pathway, the reaction between benzamide **5a** and monoyne **2a** should proceed in the presence of the same rhodium catalyst. Indeed, the desired alkenylation 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

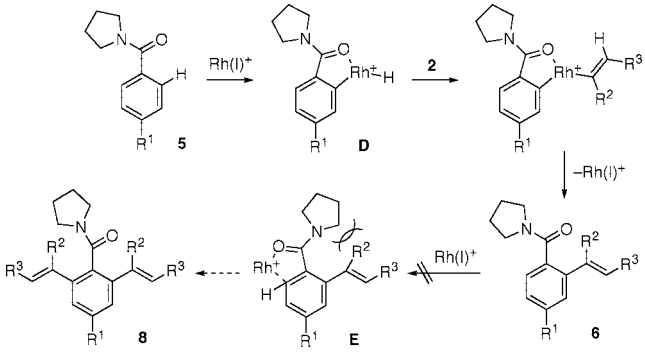
(10) Shibata, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2829.
(11) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.
(12) Kanner, C. B.; Pandit, U. K. *Tetrahedron* **1982**, *38*, 3597.
(13) The reaction of phenyl-substituted alkenylamide **1k** with **2a** proceeded 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.

(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 NH_2-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 sp^2 C−H bond alkenylations.

Scheme 3

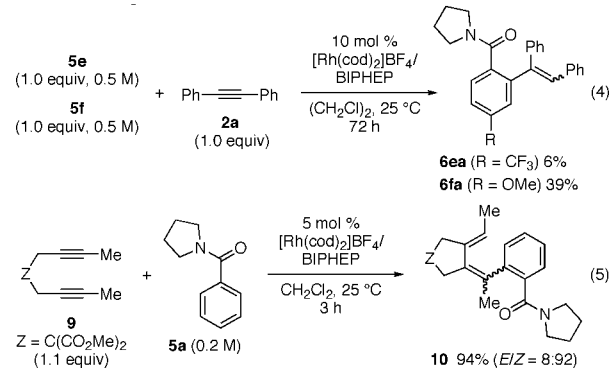


improved yield (Table 3, entry 1). The scope of both benzamides **5** and monoynes **2** was then examined as shown in Table 3. The use of electron-deficient 4-trifluoromethyl-substituted benzamide **5e** did not affect the product yield (entry 2), but that of electron-rich 4-methoxy-substituted benzamide **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.

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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.

OL802767S

(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.

(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.