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# Palladium-Catalyzed Intermolecular Addition of Formamides to Alkynes

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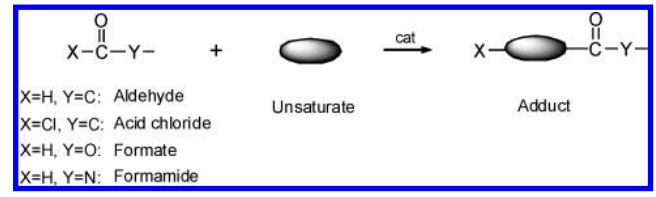
***Abstract:*** A novel palladium system for an intermolecular addition of formamides to alkynes has been developed. The reaction of formamides with internal alkynes in the presence of a palladium catalyst with acid chloride as an additive afforded (*E*)-α,*β*-unsaturated amides regio- and stereoselectively. The same catalyst system realized the first example of the addition of formamides to terminal alkynes giving the corresponding α,*β*-unsaturated amides bearing a terminal methylene moiety as major products. The present reaction was widely applicable to substrates with various functionalities. This method also could be applied to the reaction of *N*,*N*-disubstituted formamides with norbornene. A hydridopalladium species would be formed as a key intermediate with in situ generated HCl under the reaction conditions.

## Introduction

Highly atom-efficient[1] intermolecular addition of carbonyl functionalities to unsaturated compounds must be extremely promising to realize valuable and environmentally benign organic transformation. Among them, addition of aldehydes (X = H and Y = C in Scheme 1) to unsaturates such as alkenes or alkynes has been intensively studied (hydroacylation).[2] However, the reaction frequently suffered from decarbonylation[3] and appropriate directing groups were often indispensable for successful reactions.[2b,4] We recently reported an iridium-catalyzed addition of acid chlorides (X = Cl, Y = C) to alkynes.[5] The reaction proceeds highly atom-efficiently without decarbonylation and affords *β*-chloro-α,*β*-unsaturated ketones in high yields.

On the other hand, addition of formamides (X = H, Y = N) to unsaturated substrates should provide efficient atom-economic synthetic methods, while similar addition of formates (X = H, Y = O) was not fully developed.[6] Previously, we have found the first addition of formamides to alkenes in the presence of $Ru_3(CO)_{12}$ as a catalyst.[7a] However, in spite of many efforts[7b−d] after this finding, the addition of formamides to alkenes was not so efficient. As for the addition of formamides to alkynes, there have been only two precedents to date.[8,9a] The first example of the addition to alkynes was realized as an intramolecular reaction with a Rh catalyst.[8] Very recently, the first intermolecular addition to alkynes was reported by Nakao and Hiyama et al. in the presence of a Ni(0) catalyst combined with $AlMe_3$.[9a] This publication prompted us to report our independent studies on Pd-catalyzed intermolecular addition of formamides to alkynes.[9b] Distinct features of our finding from the Ni(0)/$AlMe_3$ catalyst[9a] are as follows: (1) *Terminal* alkynes were successfully utilized and afforded adducts for the first time. (2) Carbonyl functionalities susceptible to $AlMe_3$ could be tolerated.

***Scheme 1***

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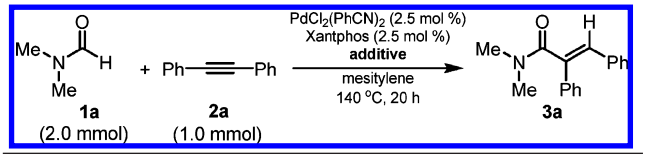
**10.1021/ja910038p** 

***Table 1.*** Effect of Additives on the Palladium-Catalyzed Addition of *N,N*-Dimethylformamide to Diphenylacetylenes[a]




| entry | additive (20 mol %) | yield (%)[b] |
|---|---|---|
| 1 | none | 0 |
| 2 | HCl (in dioxane, 50 mol %) | 82 |
| 3 | $n$-$C_5H_{11}COCl$ | 99 |
| 4 | PhCOCl | 99 (96, $E/Z$ = 99/1)[c] |
| 5 | PhCOBr | 26 |
| 6 | $Me_3SiCl$ | 18 |
| 7 | $Ph_2POCl$ | 31 |
| 8 | HCl aq. | 8 |
| 9 | $CF_3COOH$ | 1 |
| 10 | $CF_3SO_3H$ | 1 |

[a] Diphenylacetylene (1.0 mmol), *N,N*-dimethylformamide (2.0 mmol), $PdCl_2(PhCN)_2$ (0.025 mmol, 2.5 mol %), Xantphos (0.025 mmol, 2.5 mol %), additive (20 mol %), mesitylene (1.0 mL) at 140 °C for 20 h. [b] Yield based on the GC internal standard technique. [c] Yield of isolated product. *E/Z* ratio (99/1) of the product was determined by the GC analysis.

(3) Adducts with diarylacetylenes did not undergo *E/Z* isomerization.

## Results and Discussion

**Optimization of the Reaction Conditions.** First, the reaction of *N,N*-dimethylformamide (**1a**) with diphenylacetylene (**2a**) was carried out in the presence of a catalytic amount (2.5 mol %) of $PdCl_2(PhCN)_2$ and Xantphos[10] (Table 1). Without an additive, no adducts were obtained at all (entry 1). In contrast, when anhydrous HCl (50 mol %) was added to the catalyst system, an adduct (**3a**) was obtained in 82% yield. It is well-known that reaction of HCl with Pd compounds provides Pd−H species.[11] However, the use of anhydrous HCl is not expedient in a laboratory and yield of **3a** decreased to 67% with a smaller (20 mol %) amount of HCl. Recently, Skrydstrup reported that in a Pd catalyzed reaction, acid chlorides were useful additives to generate Pd−H species in situ.[12] Actually, hexanoyl chloride and benzoyl chloride[13] as an additive (20 mol %) afforded **3a** in both >99% yields (entries 3 and 4). Thus, Pd−H species might play an important role in the reaction. Benzoyl bromide (entry 5) and other chloride sources such as $Me_3SiCl$ and $Ph_2P(O)Cl$ (entries 6 and 7) were less effective as the additive. Addition of Brønsted acids such as conc. HCl aq, trifluoroacetic acid, and trifluoromethanesulfonic acid only afforded a trace amount of **3a** (entries 8−10). As the ligand, Xantphos was the most effective. Under the same reaction conditions as in Table 1, other phosphines such as $PPh_3$, P(*o*-Tol)$_3$. $PCy_3$, dppp, dppf, and *rac*-BINAP[10] did not afford **3a** at all. The reaction proceeds smoothly at 140 °C, but yields decreased at a lower temperature. The reaction is perfectly stereoselective to afford only the (*E*)-isomer as determined by X-ray crystallography (Figure 1). On the contrary, in the Ni(0)/$AlMe_3$ catalyzed reaction,[9a] initially formed (*E*)-product was readily isomerized to (*Z*)-isomer (*E/Z* = 3:7 even after 30 min). Thus, the present Pd catalyst system realizes highly stereoselective reaction.

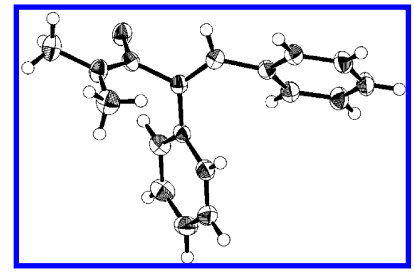


***Figure 1.*** Crystal structure of **3a** with thermal ellipsoids at the 50% probability level.

**Reaction with Internal Alkynes.** The scope of the catalytic reaction was examined by using various internal alkynes **2** and formamides **1** with benzoyl chloride as an additive (Table 2). Di(4-acetylphenyl)acetylene (**2b**) with **1a** afforded the corresponding product (**3b**) stereoselectively in 72% yield (entry 1). The reaction did not suffer from the *E/Z* isomerization at all (vide supra). Furthermore, the acetyl functionality susceptible to $AlMe_3$[9a] could be tolerated in the reaction. An alkyne bearing thiophene rings (**2c**) smoothly afforded the corresponding product (**3c**) in 90% yield stereoselectively (entry 2). 5-Decyne (**2d**) also provided the corresponding (*E*)-adduct (**3d**) in high stereoselectivity and in high yield (entry 3). Symmetrical aliphatic alkynes bearing ether (**2e**) and acetate (**2f**) functionalities could be employed in the reaction and gave the addition products in good yields (entries 4 and 5). As for unsymmetrical alkynes, even the reaction with a simple hydrocarbon alkyne such as **2g** proceeded with good regioselectivity, and **3g** and **3g′** were isolated in pure form in 77 and 6% yields, respectively (entry 6). Alkynes with ester functionality (**2h** and **2i**) provided the corresponding adducts (**3h** and **3i**) highly regio- and stereoselectively (entries 7 and 8). Furthermore, a substrate having both olefin and ester functionalities (**2j**) afforded the corresponding product in good yield (entry 9). In all these products (entries 7−9), the ester moieties were located away from the carbamoyl group with (*E*)-configuration. Gratifyingly, a boronic acid ester functionality, which will be highly useful in a further derivatization, was compatible and provided the corresponding product (**3k**) in good yield with high selectivity (entry 10). The reaction of other formamide derivatives (**1b−d**)

(10) Abbreviations: Xantphos, 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene; P(*o*-Tol)$_3$, tri-*ortho*-tolylphosphine; $PCy_3$, tricyclohexylphosphine; dppp, 1,3-bis(diphenylphosphino)propane; dppf, 1,1′-bis(diphenylphosphino)ferrocene; *rac*-BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

(11) (a) Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011–2033. (b) Kudo, K.; Hidai, M.; Murayama, T.; Uchida, Y. *J. Chem. Soc. D: Chem. Commun.* **1970**, 1701–1702. (c) Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178–13179.

(12) Lindhardt, A. T.; Mantel, M. L. H.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2668–2672.

(13) In the case of hexanoyl chloride, HCl may be afforded by a sequence of oxidative addition, decarbonylation. and $\beta$-hydrogen elimination as postulated in the literature.[12] However, in the case of benzoyl chloride, $\beta$-hydrogen elimination from the resulting phenyl-palladium intermediate is not possible. Thus, the material balance after the reaction (entry 3 in Table 2) was analyzed by GC (eq i). As a result, 0.18 mmol of *N,N*-dimethylbenzamide was found as well as **3d** (0.92 mmol, 92% yield) in the reaction mixture. Therefore, HCl was most likely generated by the reaction of benzoyl chloride (0.2 mmol) with **1a** with concomitant formation of CO (detected by GC). After the reaction, 0.76 mmol of **1a** still remained, indicating further decommission of **1a** did not occur substantially.

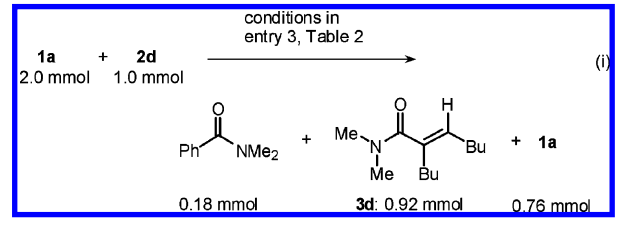
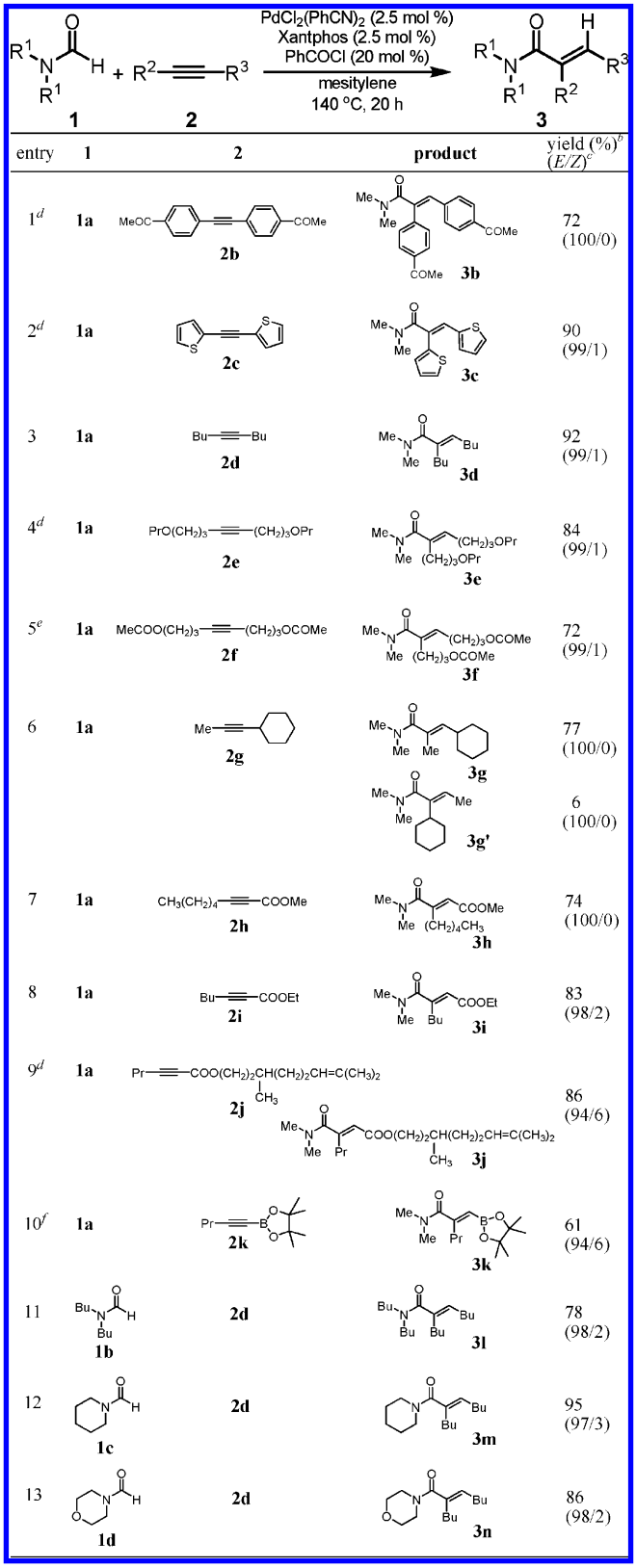
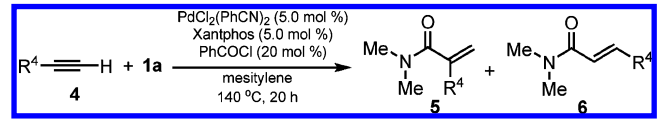


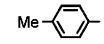
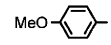
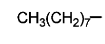
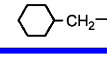
***Table 2.*** Addition of Formamides **1** to Internal Alkynes **2**[a]




[a] Alkyne (1.0 mmol), formamide derivative (2.0 mmol), $PdCl_2(PhCN)_2$ (0.025 mmol, 2.5 mol %), Xantphos (0.025 mmol, 2.5 mol %), PhCOCl (20 mol %), mesitylene (1.0 mL), 140 °C, 20 h. [b] Isolated yield. [c] Determined by GC analysis. [d] $PdCl_2(PhCN)_2$ (0.050 mmol, 5.0 mol %, Pd/Xantphos/PhCOCl = 1/1/4) and **1a** (6.0 mmol). [e] $PdCl_2(PhCN)_2$ (0.10 mmol, 10 mol %, Pd/Xantphos/PhCOCl = 1/1/1) and **1a** (12 mmol). [f] $PdCl_2(PhCN)_2$ (0.050 mmol, 5.0 mol %, Pd/Xantphos/PhCOCl = 1/1/4) and **1a** (10 mmol).

***Table 3.*** Addition of **1a** to Terminal Alkynes **4**[a]




| entry | 4: $R^4$ | yield of 5+6 (%)[b] | yield of 5 (%)[c] |
|---|---|---|---|
| 1 | **4a**:  | **5a+6a**: 96 (89/11) | **5a**: 78 |
| 2 | **4b**:  | **5b+6b**: 94 (92/8) | **5b**: 85 |
| 3 | **4c**:  | **5c+6c**: 87 (95/5) | **5c**: 81 |
| 4 | **4d**:  | **5d+6d**: 93 (87/13) | **5d**: 77 |
| 5 | **4e**:  | **5e+6e**: 74 (84/16) | **5e**: 58 |
| 6 | **4f**:  | **5f+6f**: 67 (84/16) | **5f**: 45 |
| 7 | **4g**:  | **5g+6g**: 69 (87/13[d]) | **5g**: 59 |
| 8 | **4h**:  | **5h+6h**: 69 (81/19[d]) | **5h**: 49 |

[a] Alkyne (1.0 mmol), **1a** (1.0 mL, 13 mmol), $PdCl_2(PhCN)_2$ (0.050 mmol, 5.0 mol %), Xantphos (0.050 mmol, 5.0 mol %), PhCOCl (20 mol %), mesitylene (1.5 mL), 140 °C, 20 h. [b] Isolated yield of a mixture of **5** and **6**. Parentheses shows a ratio of **5**/**6** determined by GC analysis. [c] Isolated yield of pure **5**. [d] **6** contains some olefin isomers.

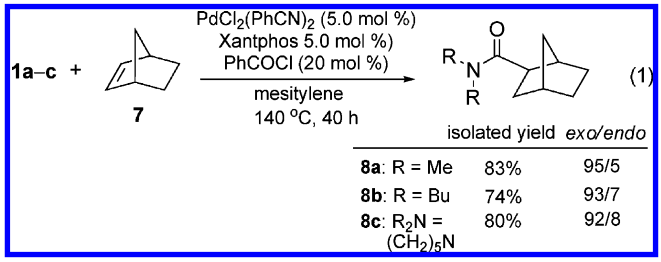
with **2d** also gave the corresponding adducts (**3l**, **3m**, and **3n**) selectively in 78, 95, and 86% yields, respectively (entries 11−13). Thus, these results indicate that the present reaction can be widely applicable to substrates with various functionalities.

**Reaction with Terminal Alkynes.** To date, terminal alkynes have not been successfully utilized in the addition of formamide, possibly due to very high catalytic activity of Ni(0)[9a] for the trimerization of terminal alkynes.[14] In Table 3, various terminal alkynes **4** afforded the adducts in high yields with an excess **1a** by employing the same Pd catalyst system. In the reaction of phenylacetylene (**4a**) with **1a**, the adducts were isolated in 96% yield as a mixture of two regioisomers **5a** and **6a** in a 89/11 ratio (entry 1). From 2-ethynyltoluene (**4b**) or 1-ethynylnaphthalene (**4c**), the products (**5** and **6**) were obtained in 94 or 87% yields with 92 and 95% regioselectivity for **5**, respectively (entries 2 and 3). Various aromatic (**4d**−**f**) and aliphatic (**4g**−**h**) terminal alkynes also afforded the corresponding adducts as mixtures of two regioisomers in 67−93% yields with 81−87% regioselectivities. Major regioisomers (**5a**−**h**) were easily and efficiently isolated in analytically pure form by a column chromatography in high to moderate yields as shown in Table 3.

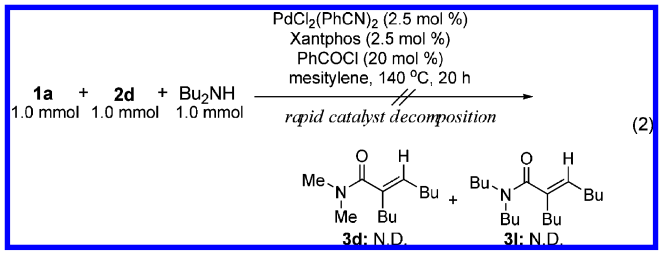
**Addition of Formamides with Norbornene.** Besides alkynes, the addition reaction of **1a**−**c** with norbornene (**7**) also proceeded in the presence of the same palladium catalyst system. The corresponding adducts (**8a**−**c**) were isolated in good yields with high stereoselectivity (eq 1). In the reaction, without the addition of benzoyl chloride, no additions occurred. Unfortunately, 1,3-dienes and 1,2-dienes cannot be utilized as substrates in the present reaction. To date, in all the reported intermolecular additions of formamides to alkenes, there were severe limitations with respect to formamides: *N*,*N*-disubstituted formamides could

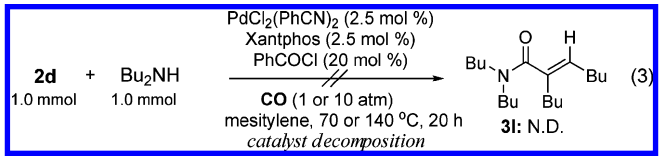
(14) Keim, W.; Behr, A.; Roper, M. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: New York, 1982; Vol. 8, pp 410−413.

not be employed.[7] As for the Ni(0) catalyzed reaction,[9a] only intramolecular addition of formamides to alkenes proceeded and no intermolecular reactions occurred.

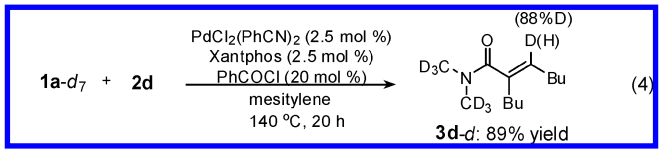



**Reaction Mechanisms.** To gain insight into the reaction mechanisms, some control experiments were carried out. The reaction might proceed via decomposition of a formamide derivative into CO and the corresponding amine; that is, aminocarbonylation[15] of alkyne with CO and the amine. When one equivalent of dibutylamine was added into the reaction mixture of **1a** and **2d**, a rapid catalyst decomposition to palladium black occurred, and neither **3d** nor **3l** were obtained (eq 2). In addition, under the aminocarbonylation reaction conditions at 70 and 140 °C employing dibutylamine and CO (1 or 10 atm), the palladium catalyst was decomposed even at 70 °C and the corresponding product **3l** was not obtained at all (eq 3). Thus, in the catalytic reaction, the formamides would directly react with the alkynes, not via CO and the corresponding amine.




Next deuterium labeling reactions were carried out. In the reaction of **1a**-$d_7$ (99.5 atom % D) with **2d**, the adduct **3d**-*d* was obtained in 89% yield with 88% D incorporation at the vinyl position (eq 4). Furthermore, the reaction of **1a**-$d_7$, **1c**, and **2d** afforded the two products **3d**-*d* and **3m**-*d* in 65 and 35% yields, respectively (eq 5). The deuterium of the formyl moiety of **1a**-$d_7$ was scrambled at the olefin positions of **3d**-*d* and **3m**-*d* (47 and 45% D incorporation, respectively). Here, H/D exchange between **1a**-$d_7$ and **1e**[16] did not occur (**1e**-*d* < 5%, if any) under various reaction conditions as shown in Table 4. Such scrambling shown in eq 5 was not observed in the Ni(0) catalyzed reaction,[9a] suggesting that the mechanisms of the Pd and Ni(0) catalyzed reaction may be distinct.



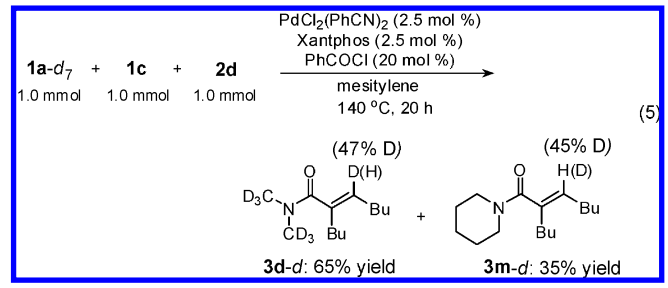
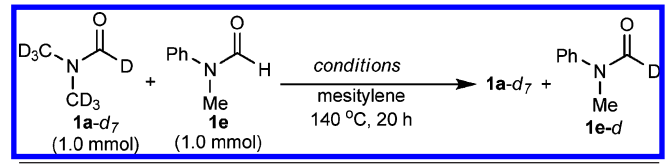




***Table 4.*** H/D Exchange between **1a**-$d_7$ and **1e** under Various Conditions[a]




| entry | conditions | **1a**-$d_7$ (mmol)[b] | **1e**-*d* (mmol)[b] |
|---|---|---|---|
| 1 | none | 0.98 | 0 |
| 2 | PhCOCl (20 mol %) | 0.89 | 0.02 |
| 3 | $PdCl_2(PhCN)_2$, Xantphos (2.5 mol %) | 0.98 | 0 |
| 4 | $PdCl_2(PhCN)_2$, Xantphos (2.5 mol %), PhCOCl (20 mol %) | 0.86 | 0.05 |

[a] **1a** (1.0 mmol), **1e** (1.0 mmol), mesitylene (1.0 mL) at 140 °C for 20 h. [b] Amounts of **1a**-$d_7$ and **1e**-*d* were determined by $^1$H and $^2$H NMR measurements.

A possible catalytic cycle is shown in Scheme 2. A Pd−H species (**A**) generated in situ by the reaction with HCl[11,12] might be a key catalytic intermediate. Hydropalladation[11a,17] of an alkyne (**2**) with **A** may initiate the catalytic cycle to afford an alkenyl Pd intermediate (**B**) (step 1). Then, insertion of C═O bond of a formamide (**1**) might take place to form a corresponding alkoxypalladium intermediate (**C**) (step 2 in cycle I). Finally, $\beta$-hydride elimination of **C** could provide the desired product (**3**) and the Pd−H species (**A**) regenerates (step 3). Alternatively, a cycle involving an oxidative addition of a formyl C−H bond of **1** to afford a Pd(IV)[18] intermediate (**D**) (step 4) might be possible. A reductive elimination from **D** could provide **3**, and the Pd−H species (**A**) would regenerate (cycle II).

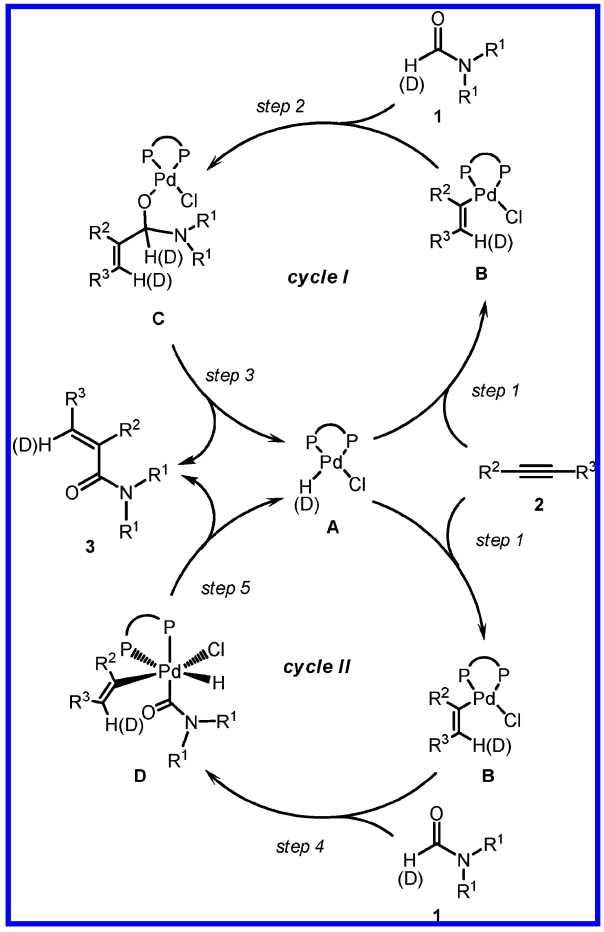
## Conclusion

Formamides are successfully added to internal alkynes to afford (*E*)-$\alpha,\beta$-unsaturated amides regio- and stereoselectively in the presence of a palladium catalyst with acid chloride as an additive. Furthermore, the same catalyst system realized the first example of the addition of formamides to terminal alkynes. Further studies on the reaction mechanism and the application of the catalysis are now in progress.

## Experimental Section

**General Procedures.** All manipulations were performed under an argon atmosphere using standard Schlenk-type glasswares on a dual-manifold Schlenk line. Mesitylene was dried and purified by usual procedures.[19] Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Xantphos was purchased from Wako. $PdCl_2(PhCN)_2$ was prepared according to literature.[20] Substrates **2b**,[21] **2c**,[21] **2d**,[22] and **4f**[22] were prepared according to literatures. IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. $^1$H, $^2$H and $^{13}$C{$^1$H} NMR spectra were measured with a JEOL ECX-400P spectrometer. The $^1$H NMR chemical shifts are reported relative to tetramethylsilane (TMS, 0.00 ppm). The

***Scheme 2.*** Plausible Reaction Mechanisms




$^{13}C\{^1H\}$ NMR chemical shifts are reported relative to $CDCl_3$ (77.0 ppm). HSQC, HMBC, and NOESY were also measured with a JEOL ECX-400P spectrometer. EI-MS were recorded on a Shimadzu GCMS-QP5050A with a direct inlet. HR-FAB and HR-EI mass spectra were measured with a JEOL JMS-HX110A and a JEOL JMS-SX102A, respectively. Elemental analysis was carried out at Center for Organic Elemental Microanalysis, Graduate School of Pharmaceutical Science, Kyoto University. GC analysis was carried out using Shimadzu GC-17A equipped with an integrator (C-R8A) with a capillary column (CBP-5, 0.25 mm i.d. × 25 m). Melting points were measured on a Yanako MP-J3 apparatus. Column chromatography was carried out on silica gel (Kanto N60, spherical, neutral, 63-210 $\mu$m). TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck silica gel 60F254.

**General Procedure of Palladium-Catalyzed Addition of Formamides (1) to Internal Alkynes (2) (Tables 1 and 2).** To a 10-mL Schlenk flask with a reflux condenser were added $PdCl_2(PhCN)_2$ (9.6 mg, 0.025 mmol) and Xantphos (14.5 mg, 0.025 mmol). The flask was evacuated and backfilled with argon three times. A degassed mesitylene (1.0 mL) and a formamide (**1**) (2.0 mmol) were added to the flask and the resultant solution was stirred at room temperature for 10 min. Then, additive (0.2 mmol, 20 mol %) was added to the flask. After stirring for 5 min, an internal alkyne (**2**) (1.0 mmol) was added to the flask and the mixture was stirred for additional 10 min. The reaction mixture was heated (bath temp. 140 °C) for 20 h under an argon atmosphere. After cooling to room temperature, the mixture was evaporated and the product (**3**) was isolated by silica gel chromatography using hexane-AcOEt as an eluent.

**General Procedure of Palladium-Catalyzed Addition of *N*,*N*-Dimethylformamide (1a) to Terminal Alkynes (4) (Table 3).** To a 10-mL Schlenk flask with a reflux condenser were added $PdCl_2(PhCN)_2$ (19.2 mg, 0.05 mmol) and Xantphos (29 mg, 0.05 mmol). The flask was evacuated and backfilled with argon three times. After a degassed mesitylene (1.5 mL) and **1a** (1.0 mL, 13 mmol) were added to the flask, the resultant solution was stirred at room temperature for 10 min. Then, benzoyl chloride (24 $\mu$L, 0.2 mmol) was added to the flask. After stirring for 5 min, a terminal alkyne (**4**) (1.0 mmol) was added to the flask and the mixture was stirred for additional 10 min. The reaction mixture was heated (bath temp. 140 °C) for 20 h under an argon atmosphere. After cooling to room temperature, the mixture was evaporated and the products (**5** and **6**) were isolated by silica gel chromatography using hexane-AcOEt as the eluent.

**X-ray Crystallographic Analysis of 3a.** Single crystal of **3a** was obtained by recrystallization from hot hexane solution. Data were collected on a Rigaku/Saturn70 CCD diffractometer using graphite-monochromated Mo Kα radiation ($\lambda = 0.71070$ Å) at 153 K, and processed using CrystalClear[23] (Rigaku). The structure was solved by direct methods (SIR97)[24] and refined by full-matrix least-squares refinement on $F^2$. The non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located on the calculated positions and not refined. All calculations were performed using the CrystalStructure[25] crystallographic software package. Crystal data for **3a**: $C_{17}H_{17}NO$, $M = 252.34$, monoclinic, space group = *C*2/*c* (#15), $a = 25.137(17)$ Å, $b = 6.351(4)$ Å, $c = 19.808(13)$ Å, $\beta = 116.975(8)$ °, $V = 2818(3)$ Å$^3$, $Z = 8$, density (calc.) = 1.189, total reflections collected = 10016, unique reflections = 3150 ($R_{int} = 0.067$), GOF = 1.003. The final *R*1 factor was 0.0659 ($I > 2\sigma(I)$) ($wR2 = 0.1528$ for all data).

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

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