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Palladium-Catalyzed Regioselective Hydroarylation of Ynamides with Aryl Iodides: Easy Synthesis of Various Substituted Enamides Containing Stilbene Derivatives

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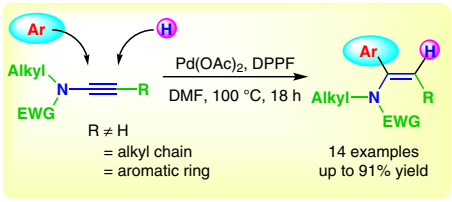

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Abstract Palladium-catalyzed hydroarylation of ynamides has been developed. The desired coupling products were obtained in good yields and with high regioselectivities. Various aryl iodides can be used in this reaction, permitting the syntheses of many different kinds of enamides from ynamides.

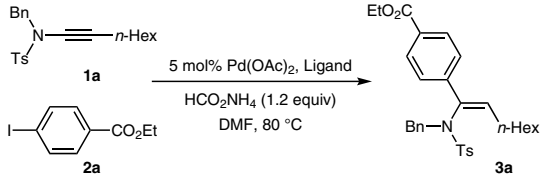
Key words ynamides, hydroarylation, palladium catalysis, cross-coupling, enamides, arylation

Over the past 20 years, the ynamide group has begun to be recognized as a functional group that participates in a new C–C bond-forming reaction.[1] The useful C–C bond-forming reaction of ynamides has been reported by several research groups, who described the different π-orbital electron density in these compounds compared with that in other C≡C triple bonds.[2] We have also become interested in the reactions of ynamides with transition-metal complexes. A ring-closing metathesis (RCM) of ene–ynamides[3] and a copper-free Sonogashira coupling of unsubstituted ynamides[4] have already been reported by our research group. Our continuing interests have focused on developing additional transition-metal-catalyzed C–C bond-formation reactions of ynamides. The hydroarylation of C≡C triple bonds is known to be a useful method for the construction of carbon frameworks.[5–7] These reactions have been successfully used for the synthesis of heterocycles.[8] Here, we describe a palladium-catalyzed regioselective hydroarylation reaction of substituted ynamides.

When the reaction of ynamide **1a**[9] and aryl iodide **2a** in the presence of a catalytic amount of $Pd(OAc)_2$ and Ph_3P in the presence of HCO_2NH_4 as a reducing agent was performed in *N*,*N*-dimethylformamide (DMF) at 80 °C for 20 hours, the desired coupling product **3a** was obtained in 10% yield, together with recovered **1a** in 44% yield (Table 1, entry 1). Several phosphine ligands were tested for this reaction (entries 2–5). Tricyclohexylphosphine did not work, and **1a** was recovered in 59% yield (entry 2). When 1,2-bis(diphenylphosphino)ethane (DPPE), a typical bidentate ligand, was used, a similar result was obtained to that with Ph_3P (entry 3). The use of 1,4-bis(diphenylphosphino)butane (DPPB) slightly improved the chemical yield of **3a** (entry 4), but the best result was obtained when 1,1′-bis(diphenylphosphino)ferrocene (DPPF) was used (entry 5).

The stereochemistry of the enamide **3a** was determined by an NOE experiment, as shown in Figure 1.

Table 1 Palladium-Catalyzed Hydroarylation of Ynamide **1a** and Screening of Ligands[a]



Entry	Ligand	Time (h)	Yield (%) of **3a**	Recovery (%) of **1a**
1	Ph_3P[b]	20	10	44
2	PCy_3[b]	18	–	59
3	DPPE	18	12	63
4	DPPB	18	23	30
5	DPPF	18	24	45

[a] Reaction conditions: **2a** (1.2 equiv), ligand (5 mol%), HCO_2NH_4 (1.2 equiv).
[b] 10 mol% of the ligand was used.

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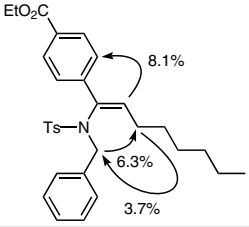
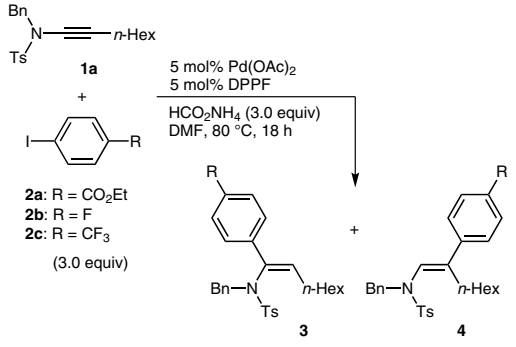


Figure 1 NOE experiment for enamide product **3a**

When the reaction of **1a** with three equivalents each of **2a** and HCO_2NH_4 was carried out at 80 °C for 18 hours, the yield of the coupling product **3a** increased to 56% (Table 2, entry 1). At this point, we recovered **2a** together with a deiodination product. Hydroarylation was restricted by the reduction of **2a**, as in the case shown in Table 1, entry 5. Encouraged by these results, we decided to examine the reactions of various aryl iodides. However, this required further optimization of the reaction conditions, because decreased coupling product yields were obtained in the cases of 1-fluoro-4-iodobenzene (**2b**) and 1-iodo-4-(trifluoromethyl)benzene (**2c**) (entries 2 and 3). The yields were slightly improved on prolonging the reaction time (entry 4). Finally, a satisfactory result in terms of regioselectivity was obtained when the reaction was carried out at 100 °C; the major isomer **3a** was obtained in 76% yield together with a 15% yield of **4a** (entry 5).[10]

Next, we examined the reactions of various aryl iodides with ynamide **1a** (Table 3). When the reactions of **2b** and **2c** were repeated, the yields increased to 73% and 59%, respectively (Table 3, entries 1 and 2). 4-Iodobenzonitrile (**2d**), which contains an additional electron-withdrawing group, gave a satisfactory yield (entry 3). The C–C bond-forming reaction proceeded smoothly to introduce the aryl substituent at the α-position of the ynamide in the case of iodide **2e**, which has a *p*-methoxy substituent as an electron-donating group (entry 4). Aryl iodide **2f**, with a methoxycarbonyl group in the *ortho* position, did not give a satisfactory reaction (entry 5).

Table 2 Optimization of the Reaction Temperature and Time



Entry	2	Yield (%) of **3**	Yield (%) of **4**	Recovery (%) of **1a**
1	**2a**	56	7	22
2	**2b**	30	–	48
3	**2c**	38	4	52
4[a]	**2a**	59	9	18
5[b]	**2a**	76	15	4

[a] Reaction was carried out for 24 h.
[b] At 100 °C.

Table 3 Reactivity of Various Aryl Iodides to Hydroarylation of Ynamide **1a**

Entry	Substrate	Ar	Yield (%) of **3**	Yield (%) of **4**	Recovery (%) of **1a**
1	**2b**	4-FC_6H_4	73	12	3
2	**2c**	4-$F_3CC_6H_4$	59	2	–
3	**2d**	4-NCC_6H_4	57	13	2
4	**2e**	4-$MeOC_6H_4$	77	5	–
5	**2f**	2-$MeO_2CC_6H_4$	10	9	–

At this point, we designed new substrates with the aim of improving the regioselectivity. We surmised that if a functional group was introduced onto the carbon substituent of the ynamide, it might coordinate with the palladium to provide the palladacycle intermediate **III**, with suppression of the intermediate **IV**. Consequently, we predicted that the yield of product **V** might be improved (Scheme 1).

When the reaction of ynamide **1b**, having a benzoyloxymethyl group at the terminal position of the alkyne, was performed under the standard conditions, the desired product was not obtained (Table 4, entry 1), and a complex mixture was obtained on introduction of an ethoxycarbonyl group (entry 2). When ynamide **1d**, in which a siloxy group was introduced at the end of the carbon chain, was exposed to the standard reaction conditions, a good yield and high regioselectivity were obtained (entry 3). Unfortunately, the regioselectivity completely disappeared when the carboxy amide **1e** was used (entry 4). These results showed that an improvement in the regioselectivity was difficult to achieve through coordination of the functional group to the palladium metal. Because the regioselectivity disappeared on changing the 4-toluenesulfonamide group on the alkyne to a carboxy amide group, the reaction of **1** should proceed re-

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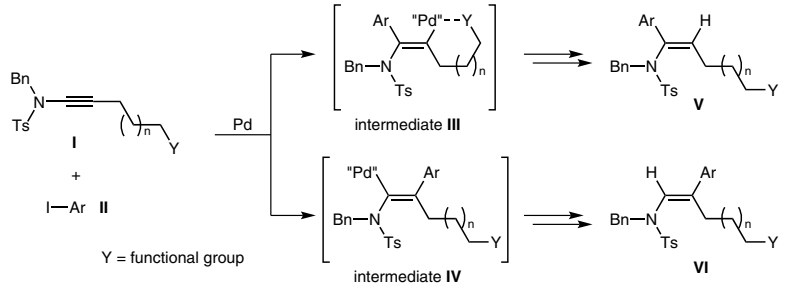
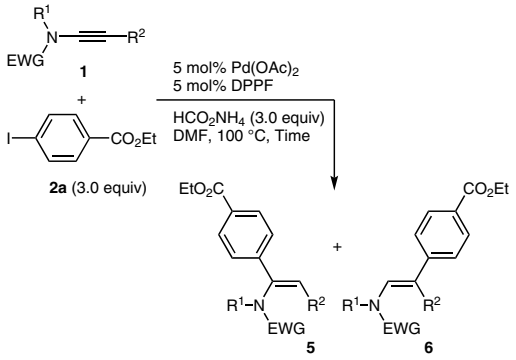
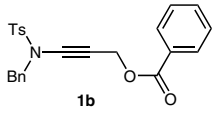
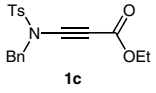
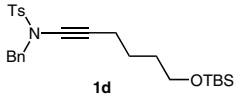
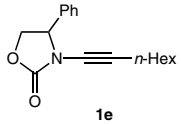


Scheme 1 Our hypothesis for the improvement of the regioselectivity

Table 4 Hydroarylation of Various Ynamides



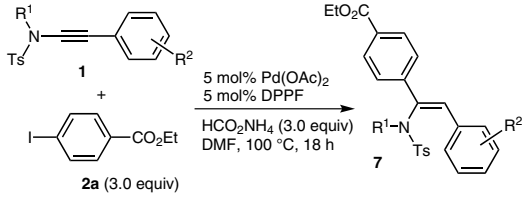
Entry	Ynamide	Time (h)	Yield (%) of **5**	Yield (%) of **6**
1	 **1b**	18	–	–
2	 **1c**	18	–	–
3	 **1d**	24	57	13
4	 **1e**	18	30	31

[a] *n*-Hex = $(CH_2)_5Me$.

gioselectively to provide compound **5** through steric repulsion between the *N*-benzyl-*N*-(4-toluene)sulfonamide group and the palladium metal.

Next, we attempted to synthesize various stilbene derivatives by introducing a phenyl group onto the terminal carbon atom of the alkyne part of the ynamide (Table 5). Under the optimized conditions, the reaction of ynamide **1f**, substituted by a methyl group on the nitrogen atom and a phenyl group on the terminal carbon of the alkyne, gave the desired enamide **7f** in 43% yield, together with a 25% recovery of substrate **1f** (entry 1). An improved chemical yield of **7g** compared with that of **7f** was observed on changing the phenyl group to an electron-donating anisyl group (entry 2). The alkyl substituent on the nitrogen did not appear to affect the product yield when the *N*-benzyl ynamide **1h** was used as a substrate (entry 3). However, we found that the benzyl group had a slightly positive effect on the product yield compared with that of the methyl group, and improved yields were obtained when an anisyl group was present on the terminal carbon atom of the alkyne (entry 4).

Table 5 Synthesis of Stilbene Derivatives **7**



Entry	Substrate	R^1	R^2	Yield (%) of **7**	Recovery (%) of **1**
1	**1f**	Me	H	43	25
2	**1g**	Me	4-MeO	55	–
3	**1h**	Bn	H	40	48
4	**1i**	Bn	4-MeO	71	15

In conclusion, we have studied the palladium-catalyzed hydroarylation of ynamides to establish a new method for constructing C–C bonds. When ynamides were exposed to a catalytic amount of $Pd(OAc)_2$ and DPPF in the presence of 3.0 equivalents of an aryl iodide and HCO_2NH_4 in DMF at 100 °C, the reactions proceeded smoothly to provide the desired products in good yields. Regioselective C–C bond

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formation on a carbon atom neighboring a nitrogen atom was achieved by using various ynamides containing a tosyl group as an electron-withdrawing group; however, the regioselectivity was not satisfactory by using ynamides containing a carboxy group as an electron-withdrawing group. Various aryl iodides can be used in this reaction, and many different kinds of enamide can now be synthesized from ynamides. Further studies on this type of reaction and on the possibility of using ynamides for transition-metal-catalyzed reactions are now in progress in our laboratory.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588874.

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(10) **Ethyl 4-[(1*Z*)-1-{Benzyl[(4-tolyl)sulfonyl]amino}oct-1-en-1-yl]benzoate (3a) and Ethyl 4-[(*E*)-2-{Benzyl[(4-tolyl)sulfonyl]amino}-1-hexylvinyl]benzoate (4a); Typical Procedure**
Ethyl 4-iodobenzoate (**2a**; 0.21 mL, 1.23 mmol, 3.0 equiv) was added a solution of ynamide **1a** (150.0 mg, 0.41 mmol), $Pd(OAc)_2$ (4.6 mg, 20.5 µmol, 5 mol%), DPPF (11.4 mg, 20.5 µmol, 5 mol%), and HCO_2NH_4 (77.6 mg, 1.23 mmol, 3.0 equiv) in DMF (20 mL) at 0 °C under argon. The mixture was stirred at 100 °C for 18 h and then cooled to 0 °C. H_2O (22 mL) was added, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The organic phases were combined, washed with brine (1 × 50 mL), and dried (Na_2SO_4). The volatiles were removed under reduce pressure, and the residue was purified by column chromatography [silica gel, hexane–Et_2O (20:1) to hexane–EtOAc (10:1)] to afford **3a**, **4a**, and recovered **1a** (6.0 mg; 4%).
3a: off-white solid; yield: 161.1 mg (76%); mp 71 °C. IR (KBr): 3059, 2921, 1705, 1605 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3 H), 1.04–1.28 (m, 8 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.92 (br s, 2 H), 2.48 (s, 3 H), 4.14 (br s, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 4.71 (br s, 1 H), 6.11 (t, *J* = 7.4 Hz, 1 H), 7.06–7.12 (m, 4 H), 7.21–7.23 (m, 3 H), 7.35 (d, *J* = 7.6 Hz, 2 H), 7.81–7.85 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.3, 21.5, 22.5, 28.7, 29.1, 29.9, 31.6, 52.4, 60.9, 126.4, 127.6, 128.0, 128.2, 129.3, 129.5, 129.5, 129.7, 134.6, 135.5, 137.3, 137.9, 141.7, 143.6, 166.2. EI-LRMS: *m/z* = 519 [M^+], 364, 155, 91. EI-HRMS; *m/z* [M^+] calcd for $C_{31}H_{37}NO_4S$: 519.2443; found: 519.2442.
4a: off-white solid; yield: 31.9 mg (15%); mp 73–74 °C. IR (KBr): 2929, 1716, 1607 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.65–0.75 (m, 2 H), 0.81 (t, *J* = 7.2 Hz, 3 H), 0.97–1.05 (m, 4 H), 1.10–1.18 (m, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 2.42–2.49 (m, 2 H), 2.44 (s, 3 H), 4.25 (s, 2 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 5.32 (s, 1 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.26–7.35 (m, 7 H), 7.70 (d, *J* = 8.2 Hz, 2 H), 7.95 (d, *J* = 8.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.3, 21.5, 22.5, 27.2, 29.3, 29.8, 31.5, 55.2, 60.9, 123.7, 126.8, 127.6, 127.9, 128.4, 129.3, 129.5, 129.7, 129.7, 134.7, 135.5, 143.7, 144.0, 149.2, 166.3. EI-LRMS: *m/z*: 519 [M^+], 364, 155, 91. EI-HRMS: *m/z* [M^+] calcd for $C_{31}H_{37}NO_4S$: 519.2443; found: 519.2423.

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