ORGANIC LETTERS

2000
Vol. 2, No. 19
2927−2930

Pd-Catalyzed Selective Addition of Heteroaromatic C–H Bonds to C–C Triple Bonds under Mild Conditions

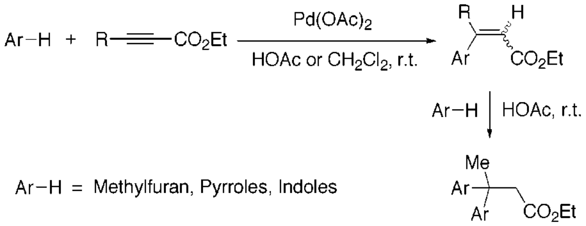
Wenjun Lu, Chengguo Jia, Tsugio Kitamura, and Yuzo Fujiwara*

Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, Hakozaki, Fukuoka, 812-858, Japan

yfujitcf@mbox.nc.kyushu-u.ac.jp

Received June 3, 2000

ABSTRACT



Simple heteroarenes such as pyrroles and indoles undergo addition reactions to C–C triple bonds in the presence of a catalytic amount of Pd(OAc)$_2$ under very mild conditions, affording *cis*-heteroarylalkenes in most cases. The cleavage of aromatic C–H bonds is the possible rate-determining step in CH$_2$Cl$_2$, and the addition of heteroaromatic C–H bonds to C–C triple bonds is in a *trans*-fashion.

The catalytic activation of aromatic C−H bonds leading to useful organic reactions, such as C−C bond formation, is of broad interest because of heightened importance in green chemistry and remains a challenge to organic and organometallic chemists.[1,2] The success of such processes would provide convenient, clean, and economic methodologies to aryl-substituted compounds directly from simple arenes without arene prefunctionalization such as halogenation. The coupling of arenes with olefins with the cleavage of aromatic C−H bonds in the presence of Pd compounds stoichiometrically or catalytically is one of the earliest such examples.[2a,b] The σ-aryl−Pd(II) complexes formed via electrophilic metalation of aromatic C−H bonds have been isolated as the intermediates.[2d] Recently, we reported novel Pd(II)- or Pt(II)-catalyzed inter- and intramolecular addition reaction of electron-rich benzenoid arenes to C−C multiple bonds at room temperature in a mixed solvent containing trifluoroacetic acid.[2g] Similarly, the reaction may involve electrophilic cleavage of aromatic C−H bonds by Pd(II) cationic species.

The heteroaromatic ring systems of pyrrole, indole, and furan constitute the key structural units in many natural products and biologically active compounds.[2,4] Extensive research has been carried out in DNA recognition using pyrrole derivatives,[4a−c] such as pyrrylalkenes.[4b] Simple and efficient functionalization of these ring systems, especially nitrogen-containing heterocycles, would be of great interest

---

[1] (a) Shilov, E.; Shul'pin, G. B. *Chem. Rev.* **1997**, 97, 2879. (b) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: 1999; pp 47−79. (c) Fujiwara, Y.; Jintoku, T.; Takaki, K. *CHEMTECH* **1990**, 636. (d) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (e) Trost, B. M. *Science* **1991**, 1471.

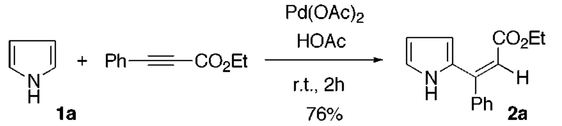
[2] (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 1119. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. (c) Fujiwara, Y.; Asano, R.; Moritani, I.; Teranishi, S. J. *J. Org. Chem.* **1976**, *41*, 1681. (d) Fujita, Y.; Hiraki, K.; Kamogawa, Y.; Suenaga, M.; Toggoh, F.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1081. (e) Fujiwara, Y.; Takaki, K.; Taniguchi, Y. *Synlett* **1996**, 591. (f) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097. (g) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992.

[3] (a)Jackson, A. H. In *Comprehensive Organic Chemistry*, Vol. 4; Sammes, P. G., Ed.; Pergamon: Oxford, 1979; pp 282−290. (b) Brown, R. T.; Joule, J. A. In *Comprehensive Organic Chemistry*, Vol. 4; Sammes, P. G., Ed.; Pergamon: Oxford, 1979; pp 418−434. (c) Baxier, R. L.; Scott, A. I. In *Comprehensive Heterocyclic Chemistry*, Vol. 1; Katritsky, A. R., Ress, C. W., Eds.; Pergamon: Oxford, 1984; pp 85−172. (d) Gibble, G. W. In *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A. R., Ress, C. W., Servien, E. F. V., Eds.; Pergamon: Oxford, 1996; pp 207−258.

10.1021/ol006156l CCC: $19.00

to pharmaceutical industries. On the other hand, the electrophilic substitution is the most characteristic reaction for these electron-rich heteroarenes, and Michael addition of indoles to electron-deficient olefins is a very useful reaction.[3] More recently, transition metal catalyzed hydrocarbonation of C−C multiple bonds through activation of various C−H bonds has drawn much attention.[1,2,5] However, few reports are available on the addition of heteroarenes to C−C triple bonds.[1] Herein, we report that heteroaromatic compounds such as methylfuran, pyrroles, and indoles readily undergo addition reactions to alkynoates at room temperature in the presence of a catalytic amount of $Pd(OAc)_2$ in acetic acid or CH_2Cl_2, affording *cis*-heteroarylalkenes in most cases. This reaction provides a synthetic protocol to heteroarylalkenes, especially *cis*-alkenes, from simple heteroarenes. The evidence from isotope experiments reveals that the activation of heteroaromatic C−H bonds is the possible rate-determining step in a neutral solvent such as CH_2Cl_2 and the heteroaromatic C−H bonds add to C−C triple bonds in a *trans*-fashion.

Initially, we investigated the reaction of pyrrole (**1a**)with ethyl phenylpropiolate to optimize the reaction conditions [eq 1 and Table 1]. The reaction gave ethyl (2*Z*)-3-(2-pyrryl)-phenylpropenoate (**2a**) in 76% yield as the only isolated product in the presence of 5% $Pd(OAc)_2$ as the catalyst in acetic acid in 2 h,[3] while no reaction occurred in the absence of $Pd(OAc)_2$. The olefin geometry was established unambiguously by differential NOE ^1H NMR experiments. The *Z*-isomer **2a** was obtained exclusively, and no *E*-isomer could be detected by analysis of the reaction mixture. The reaction was apparently slowed when the quantity of the catalyst was reduced to 1% (entry 3, Table 1). From investigation of various solvents, we found that the reaction proceeded more smoothly in acetic acid than in other solvents such as ether and CH_2Cl_2 (entries 2, 4, 5, 6, 7, and 8 in Table 1). The $Pd(OAc)_2$ is the best catalyst among the transition metal catalysts investigated. The reaction was very slow with $PtCl_2$ as the catalyst (entry 9), and almost no reaction occurred with $Ni(OAc)_2$ or $Cu(OAc)_2$ (entries 10 and 11).



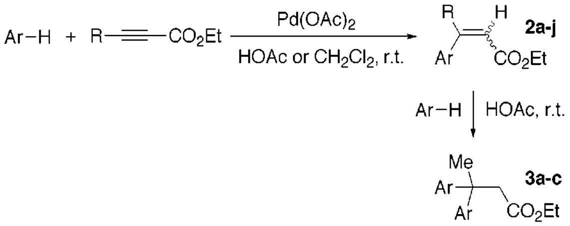
(1)

Table 1. Pd-Catalyzed Reaction of Pyrrole (**1a**) with Ethyl Phenylpropiolate

entry	catalyst (mol %)	solvent	time (h)	yield (%)[a]
1	none	HOAc	48	no reaction
2	$Pd(OAc)_2$ (5)	HOAc	2	86 (76)
3	$Pd(OAc)_2$ (1)	HOAc	8	91
4	$Pd(OAc)_2$ (5)	HOAc	2	60[b]
5	$Pd(OAc)_2$ (5)	H_2O	40	78
6	$Pd(OAc)_2$ (5)	CH_2Cl_2	48	40
7	$Pd(OAc)_2$ (5)	ether	96	42
8	$Pd(OAc)_2$ (5)	none	24	91
9	$PtCl_2$ (5)	HOAc	24	8
10	$Ni(OAc)_2$ (5)	HOAc	48	no reaction
11	$Cu(OAc)_2$ (5)	HOAc	48	no reaction

[a] The GC yield of **2a** in the reaction of **1a** (3 mmol) with ethyl phenyppropiolate (1 mmol) in a solvent (1 mL) at rt. The isolated yield is given in parentheses. [b] **1a** (1 mmol).

Various heteroarenes and alkynoates were tested in the present reaction at room temperature [eq 2], and the results are shown in Table 2. The reaction either gave monoaddtion products, 3-arylpropenoates (**2a**−**j**) and in *Z*-configuration in most cases, or diaddition products, 3-diarylpropanoates (**3a**−**c**), depending on the substituents (R) in alkynoates and the solvent.



(2)

With small R groups such as Me or *n*-C_5H_{11} in alkynoates, the reaction in HOAc mainly afforded diaddition products (**3a**−**c**) (entries 3, 4, and 13), while the reaction gave monoaddition products (**2a, 2e**−**j**) with a relatively bulky R group such as Ph under the same conditions (entries 1 and 7−12). It has been confirmed that the diaddition products were produced by further addition of arenes to the arylalkenes in acetic acid. Even with small R substituents such as Me and H in alkynoates, the reaction can be controlled to stop at the monoaddition step to give arylalkene when CH_2Cl_2 was used as the solvent (entries 2 and 6), although the reactions in CH_2Cl_2 were slow. All the reactions listed in Table 2 gave fair to good yield of adducts.

For pyrrole, 1-methylpyrrole, and 2-methylfuran, the substitution of aromatic C−H bonds occurred exclusively at the 2- or 5-position of the arenes, characteristic of electrophilic substitution. For indole and 1-methylindole, the reaction occurred at the 3-position predominantly while very small amounts (<3%) of 2-substituted adducts could be detected by analysis of the reaction mixture by ^1H and ^{13}C NMR spectra. However, when the 3-position of indole was substituted by a methyl group, the reaction could proceed smoothly at the 2-position (entry 10 in Table 2) although it is not a favorable position for the electrophilic substitution.[3]

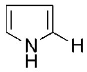
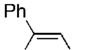
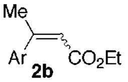
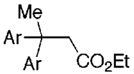
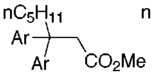
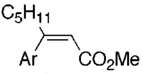
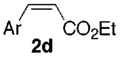
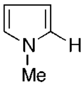
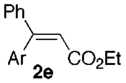
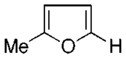
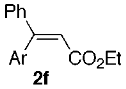
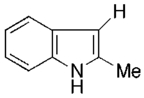
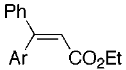
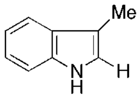
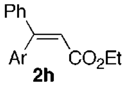
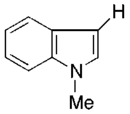
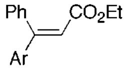
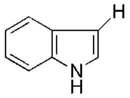
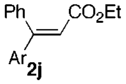
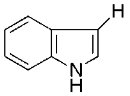
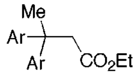
To investigate the possible mechanism of this reaction, several isotope experiments were carried out using either DOAc as a solvent or d_5-pyrrole as an arene. When the reaction of pyrrole with ethyl phenylpropiolate was run in

---

(4) (a) Faust, R.; Garratt, P. J.; Jones, R.; Yeh, L.; Tsotinis, A.; Panoussopoulou, M.; Calogeropoulou, T.; Teh, M.; Sugden, D. *J. Med. Chem.* **2000**, *43*, 1050 and references cited in. (b) Tao, Z.; Saito, I.; Sugiyama H. *J. Am. Chem. Soc.* **2000**, *122*, 1602. (c) White, S.; Turner, J. M.; Szewczyk, J. W.; Baird, E. E.; Dervan, P. B. *J. Am. Chem. Soc.* **1999**, *121*, 260 (d) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *3*, 44.

(5) Pd-catalyzed intramolecular *trans*-hydrocarbonation of C−C triple bonds has been reported. Tsukada, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.Engl.* **1997**, *36*, 2477.

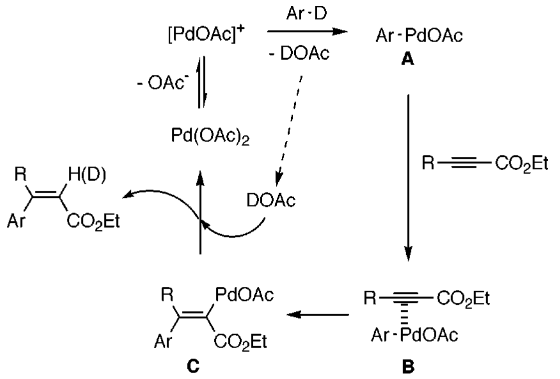
Table 2. Pd-Catalyzed Addition of Heteroarenes to Alkynoates

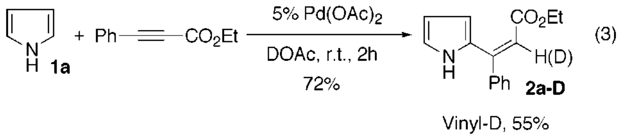
Entry	Ar–H	R	Time (h)	Adduct and Yield (%)[a]	
1	 **1a**	Ph	2	 **2a**	78
2	**1a**	Me	48	 **2b**	64[b] (*Z* / *E* = 2)
3	**1a**	Me	24	 **3a**	57
4	**1a**	*n*-C_5H_{11}	24	 **3b**  **2c**	40 5
5	**1a**	H	5	 **2d**	18[b]
6	**1a**	H	20	**2d**	52[c]
7		Ph	24	 **2e**	83
8		Ph	48	 **2f**	72
9		Ph	24	 **2g**	82
10		Ph	48	 **2h**	69
11		Ph	24	 **2i**	80
12		Ph	24	 **2j**	78
13		Me	72	 **3c**	45

[a] Isolated yield of adducts from reaction of heteroarenes (2 mmol) with alkynoates (1 mmol) in HOAc (1 mL) at rt. [b] CH_2Cl_2 (1 mL) as the solvent. [c] Ethyl propiolate (3 mmol) and **1a** (1 mmol) were used, and CH_2Cl_2 (1 mL) was used as the solvent.

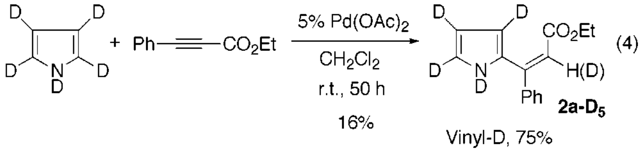
DOAc [eq 3], D atoms incorporated into the adduct (**2a-D**) at a rate of 55% at the 2-vinyl position. This suggests the possible formation of a vinyl–palladium complex (**C**) in Scheme 1; the protonation of **C** by DOAc affords the product.[2g] It may also explain why the reaction in acetic acid is the fastest compared with the reaction in other solvents. In addition to this protonation step, the formation of aryl–palladium complex (**A**) may also be facilitated by an acid.

Scheme 1. Possible Mechanism for the Addition of Heteroarenes to Alkynoates





On the other hand, D atoms incorporated into the adduct (**2a-D$_5$**) at a rate of 75% at the 2-vinyl position when the reaction of *d*$_5$-pyrrole with ethyl phenylpropiolate was carried out in dichloromethane [eq 4]. This suggests that the vinyl-D



atoms of the adduct **2a-D$_5$** may result from the protonation of **C** by DOAc, and DOAc itself may be formed from metalation of pyrryl C-H by Pd(II) species.

Unfortunately, the attempt to establish the isotope effect in a reaction of pyrrole and *d*$_5$-pyrrole (1:1 molar ratio) with ethyl phenylpropiolate was thwarted by a rapid pyrryl H/D exchange between pyrrole and *d*$_5$-pyrrole. However, we have noticed that in two separate reactions the initial rate of the reaction of pyrrole with ethyl phenylpropiolate in dichloromethane was three times faster than that of *d*$_5$-pyrrole with ethyl phenylpropiolate, $K_H/K_D = 3$ (Figure 1), indicating that the cleavage of the pyrryl C–H bonds is the possible rate-determining step in the present reaction.

A possible mechanism is shown in Scheme 1. The electrophilic substitution of the aromatic C–H bond by cationic Pd(II) species would result in the formation of a σ-arylpalladium complex (**A**) which is followed by coordination of alkyne to give **B**. *trans*-Insertion of C–C triple bonds to the σ-aryl–Pd bond would afford vinyl–Pd complexes

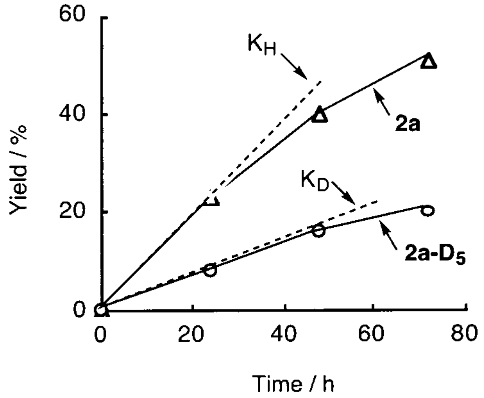


Figure 1. The time dependence of the yields of the adducts **2a** and **2a−D$_5$** in two separate reactions of pyrrole (3 equiv) or d_5-pyrrole (3 equiv) with ethyl phenylpropiolate in CH_2Cl_2 in the presence of 5% $Pd(OAc)_2$ at room temperature.

(**C**),[5,7] and upon protonation of **C**, a 1/1 arene/alkyne adduct would be released from the Pd(II) species. The presence of the acid would facilitate both the formation of cationic Pd(II) species and the protonation of the vinyl−Pd complexes. The possible involvement of Pd(II)−vinylidene and Pd(II)−allenyl complexes could be excluded.[8−10]

Further investigation of the scope, mechanism, and synthetic application of this reaction is under way.

Acknowledgment. C.J. thanks the Japan Society for the Promotion of Science for a research fellowship (No. P98430).

Supporting Information Available: The detailed spectroscopic data for characterization of compounds **2a−j** and **3a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006156L

---

(6) **Representative procedure for the addtion reaction. Synthesis of Ethyl (2*Z*)-3-(2-Pyrryl)phenylpropenoate (2a) from the Reaction of Pyrrole (1a) with Ethyl Phenylpropiolate.** To a magnetic stirred solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and pyrrole (0.20 g, 3.0 mmol) in acetic acid (1.0 mL) was added ethyl phenylpropiolate (0.18 g, 1.0 mmol). The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by GC or TLC. After 2 h, ethyl phenylpropiolate was completely consumed, and the reaction mixture was poured into a saturated NaCl solution and extracted with ether. The ethereal layer was dried over Na_2SO_4 and concentrated, and column chromatography over silica gel with hexane/EtOAc (6:1) afforded pure **2a** as light yellow oil in 76% yield (0.19 g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21 (t, $J = 7.2$ Hz, 3H, CH_3), 4.12 (q, $J = 7.2$ Hz, 2H, CH_2), 5.48 (s, 1H, vinyl), 5.99 (m, 1H, aryl), 6.10 (m, 1H, aryl), 6.95 (m, 1H, aryl), 7.24−7.32 (m, 5H, aryl), 12.7 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.17, 60.53, 109.63, 109.70, 118.97, 122.77, 127.73, 128.11, 128.81, 130.25, 142.46, 149.15, 168.82. IR (neat, cm^{-1}) 3192 (N−H), 1675 (C═O). Anal. Calcd for $C_{15}H_{15}O_2N$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.66; H, 6.39; N, 5.62.

(7) *trans*-Additions of M−H or M−R across C−C triple bonds and Pd(II)-catalyzed inter- and intramolecular *trans*-hydroacetoxylation of alkynes have been reported, and in some cases *trans*-additions is the preferred addition mode. (a) Zeijden, A.; Bosch, H. W.; Berke, H. *Organometallics* **1992**, *11*, 563. (b) Lu, X.; Zhu, G.; Ma, S. *Tetrahedron Lett.* **1992**, *33*, 7205. (c) Zargarrian, D.; Alper, H. *Organometallics*, **1993**, *12*, 712.

(8) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311.

(9) Chen, J. T.; Hsu, R. H.; Chen, A. J. *J. Am. Chem. Soc.* **1998,** *120*, 3243.

(10) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995.