Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 7515–7517
Tetrahedron Letters

Selective *cis*-addition of C–H bonds of pyrroles and thiophenes to alkynes catalyzed by a dinuclear palladium complex

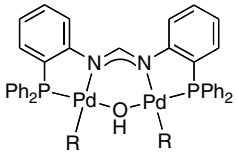
Naofumi Tsukada,* Kazuko Murata and Yoshio Inoue

Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Sendai 980-8579, Japan

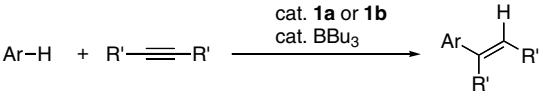
Received 20 August 2005; revised 31 August 2005; accepted 1 September 2005
Available online 16 September 2005

Abstract—Pyrroles and thiophenes reacted with alkynes in the presence of dinuclear palladium complexes with high stereoselectivity (*cis*-addition) in almost all cases. While regioselectivity in the reaction with pyrroles depended on substituents on the nitrogen atom and alkynes, all reactions of thiophenes afforded 2-alkenylthiophenes.

Heteroarenes are important units for a wide range of useful organic compounds, such as fluorescent dyes, natural products, and pharmaceuticals. Development of methods for their functionalization is important for the efficient synthesis of their derivatives. Direct functionalization of their C–H bonds is one of the attractive methods because the transformation would eliminate the need for preactivation, such as halogenation and stoichiometric metalation, and lead to a more efficient process.[1,2] Whereas the addition of C–H bonds to an alkyne is a simple, accessible, and atom-economical process for the synthesis of alkenyl heteroarenes, the alkyne used in the reaction was limited to ynoates and ynone, and the stereoselectivity for products was low.[3] Transition metal catalysts enable the addition of C–H bonds of heteroarenes to unactivated alkynes.[4–7] Heteroarenes having directing groups react with silylalkynes in the presence of $Ru(H)_2(CO)(PPh_3)_3$.[4] The addition to diphenylacetylene proceeds in the presence of $Rh_4(CO)_{12}$ under pressure of carbon monoxide.[5] Stereoselective *trans*-addition reactions to alkynoates are catalyzed by palladium[6] and gold[7] complexes. During the course of our study on the reactivity of novel bimetallic complexes,[8] we found that the dinuclear palladium complexes, $Pd_2R_2(\mu\text{-OH})(\mu\text{-dpfam})$ (dpfam = *N*,*N*′-bis[2-(diphenylphosphino)phenyl]formamidinate, R = *p*-Tol (**1a**), Me (**1b**)) catalyzed *cis*-hydroarylation of alkynes with unactivated arenes in the presence of trialkylborane (Eq. 1).[8c] We report herein that these catalysts can also be efficient for the addition reaction of heteroarene C–H bonds to alkynes.



1a (R = *p*-Tol)
1b (R = Me)



(1)

Reaction conditions were optimized for the reaction of *N*-methylpyrrole with 3-hexyne (Eq. 2, Table 1). The reaction proceeded at 100 °C in the presence of 2 mol % of **1b** and 30 mol % of $B(n\text{-Bu})_3$ to afford *E*-alkenylpyrroles **2** with high stereoselectivity, although the regioselectivity was not high.[9] The products were obtained in higher yields in hydrocarbon solvents (runs 3–5) than in 1,4-dioxane and *p*-xylene (runs 1 and 2), while the solvents did not affect the ratio of **2a** and **2b**. The reaction did not take place in 1,2-dichloroethane, acetonitrile, and nitromethane. When the reaction was carried out without solvent, the products **2a** and **2b** were obtained in 55% yield (run 7). Optimization of a reaction time showed that the yield was highest after 5 h (run 8) and a prolonged reaction time decreased the yield, while the yield was much lower after 5 h in the reaction in cyclohexane (run 6). Tri-*sec*-butylborane was also efficient as additive as well as $B(n\text{-Bu})_3$, although the reaction with BEt_3 and BPh_3 gave poorer results.[10]

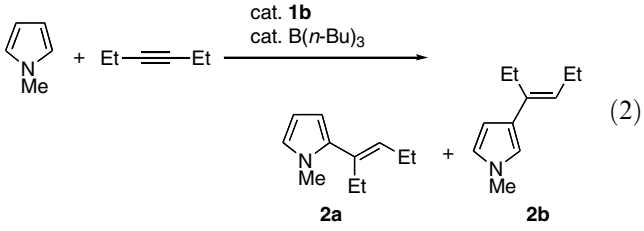
Keywords: Heteroarene; C–H activation; Palladium; Dinuclear complexes; Alkyne; Catalysis.
* Corresponding author. Tel.: +81 22 795 5874; fax: +81 22 795 5876; e-mail: tsukada@aporg.che.tohoku.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.09.001

Table 1. Reaction of *N*-methylpyrrole with 3-hexyne[a]

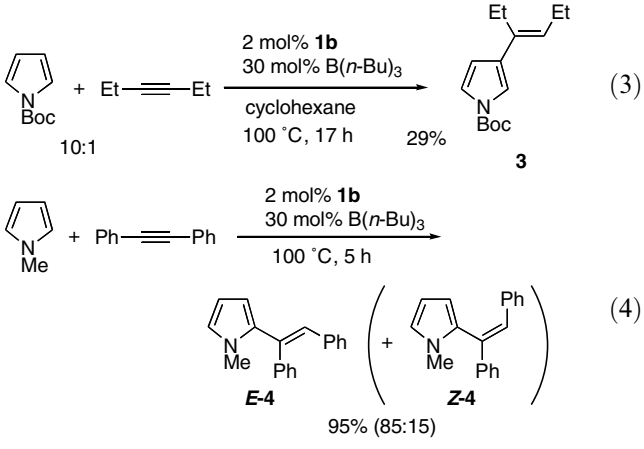
Run	Solvent	Yield (%)[b]	**2a**:**2b**[c]
1	1,4-Dioxane	32	79:21
2	*p*-Xylene	29	74:26
3	*n*-Octane	34	83:17
4	Isooctane	45	77:23
5	Cyclohexane	41	78:22
6	Cyclohexane[d]	9	82:18
7	—[e]	55	63:37
8	—[d,e]	69	62:38

[a] A mixture of 3-hexyne (0.50 mmol), *N*-methylpyrrole (5.0 mmol), **1b** (0.010 mmol), and B(*n*-Bu)$_3$ (0.15 mmol) in solvent (1.0 ml) was heated at 100 °C, for 17 h.
[b] Isolated yields.
[c] Determined by ^{1}H NMR analysis.
[d] 5 h.
[e] *N*-Methylpyrrole (1.0 ml) was used as solvent.



(2)

The reaction of *N*-(*tert*-butoxycarbonyl)pyrrole proceeded with high regioselectivity to give 3-alkenylpyrrole **3**, although the yield was low (Eq. 3). Bulkiness of substituents on nitrogen could affect the regioselectivity. Unfortunately, no product was obtained in the reaction of *N*-unsubstituted pyrroles. The reaction of *N*-methylpyrrole with diphenylacetylene gave 2-alkenylpyrrole **4** with high regioselectivity (Eq. 4). In this reaction, however, the *Z*-isomer was also generated along with the *E*-isomer. The ratio of *E*-**4** and *Z*-**4** was not improved even at lower temperature, and it was constant from the beginning to the end of the reaction.



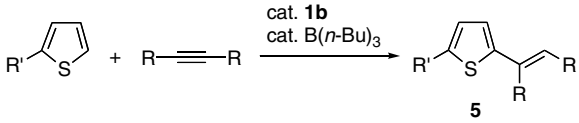
(3)
(4)

Although the reaction of furanes with 3-hexyne and diphenylacetylene did not give any products, thiophenes reacted with alkynes under the similar conditions to give products[9,11] in moderate to high yields (Eq. 5, Table 2). Complex **1a** can also be used as a catalyst (entry 6). In contrast to the reactions of *N*-methylpyrrole, *E*-2-alkenylthiophenes were selectively generated in all reactions. The reaction is tolerant to ketone and ester groups, although the reaction with 2-thiophenecarboxaldehyde afforded no product.

Table 2. Reaction of thiophenes with alkynes[a]

Run	R	R′	Yield (%)[b]
1	Et	H	34
2	Et	Me	94
3	Et	$COCH_3$	52
4	Et	CO_2CH_3	11
5	Ph	H	79
6	Ph	Me	98 (98)[c]
7	Ph	$COCH_3$	76
8	Ph	CO_2CH_3	80

[a] A mixture of an alkyne (0.50 mmol), thiophene (5.0 mmol), **1b** (0.010 mmol), and B(*n*-Bu)$_3$ (0.15 mmol) in cyclohexane (1.0 ml) was heated at 100 °C for 17 h.
[b] Isolated yields.
[c] Complex **1a** was used as catalyst.



(5)

In summary, we demonstrated that C–H bonds of heteroarenes reacted with unactivated alkynes in the presence of dinuclear palladium complexes, and the reaction proceeded with high stereoselectivity (*cis*-addition) except for the reaction of *N*-methylpyrrole with diphenylacetylene. Further application of the present reaction for functionalization of heteroarenes and mechanistic studies is in progress.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research (No. 14550618) from MEXT. N.T. also acknowledges the TEIJIN PHARMA Award in Synthetic Organic Chemistry, Japan, for financial support.

References and notes

1. (a) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; Vol. 3, pp 47–79; (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698–1712; (c) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047–1055; (d) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437–2450; (e) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241; (f) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1769.
2. Recent examples for the direct functionalization catalyzed by transition metal complexes. (a) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700–1701; (b) Godula, K.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 3648–3649; (c) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew.*

Chem., Int. Ed. **2005**, *44*, 3125–3129; (d) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996–4997.
3. (a) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. b. I.; Ushakov, I. A.; Elokhina, V. N. *Synthesis* **2001**, 1878–1882; (b) Trofimov, B. A.; Sobenina, L. N.; Mikhaleva, A. b. I.; Ushakov, I. A.; Vakul'skaya, T. I.; Stepanova, Z. V.; Toryashinova, D. y.-S. D.; Mal'kina, A. G.; Elokhina, V. N. *Synthesis* **2003**, 1272–1278, and references cited therein.
4. (a) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, *24*, 681–682; (b) Kakiuchi, F.; Sato, T.; Igi, K.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, *30*, 386–387.
5. Hong, P.; Cho, B.-R.; Yamazaki, H. *Chem. Lett.* **1980**, *9*, 507–510.
6. (a) Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927–2930; (b) Oyamada, J.; Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Chem. Lett.* **2002**, *31*, 20–21.
7. Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485–3496.
8. (a) Tsukada, N.; Tamura, O.; Inoue, Y. *Organometallics* **2002**, *21*, 2521–2528; (b) Tsukada, N.; Ohba, Y.; Inoue, Y. *J. Organomet. Chem.* **2003**, *687*, 436–443; (c) Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102–12103.
9. The structure of products was confirmed by NOE experiments.
10. The role of trialkylboranes is not clear at the present time. However, we think a hydride-bridged complex generates from the reaction of **1b** and trialkylboranes. See Ref. 8c.
11. Representative procedure for the addition reaction. Synthesis of (*E*)-2-methyl-5-(1,2-diphenylvinyl)thiophene from 2-methylthiophene and diphenylacetylene. To a solution of **1b** (0.01 mmol, 8.2 mg), diphenylacetylene (0.5 mmol, 89 mg), and 2-methylthiophene (5.0 mmol, 0.48 ml) in cyclohexane (1.0 ml) was added a THF solution (1.0 M) of tri(*n*-butyl)borane (0.15 mmol, 0.15 ml) under nitrogen atmosphere in a pressure vial. After heating at 100 °C, for 17 h, the mixture was filtered through a short plug of silica using ether as an eluent. Excess 2-methylthiophene and cyclohexane were removed under reduced pressure. Silica gel column chromatography with hexane/EtOAc (20:1) afforded the product in 98% yield (135 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.47 (d, $J = 1.0$ Hz, 3H), 6.48 (d, $J = 3.5$ Hz, 1H), 6.59 (dd, $J = 1.0$, 3.5 Hz, 1H), 6.98–7.02 (m, 3H), 7.11–7.17 (m, 3H), 7.33–7.37 (m, 2H), 7.41–7.46 (m, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 15.6, 125.2, 125.7, 126.2, 126.6, 127.7, 127.9, 128.7, 129.3, 129.9, 136.5, 136.8, 139.3, 139.6, 145.5. Anal. Calcd for $C_{19}H_{16}S$: C, 82.56; H, 5.83. Found: C, 82.82; H, 6.00.