Carbonylative Cross-Coupling Reaction of Ethynylstibane with Aryl Iodides

Naoki Kakusawa and Jyoji Kurita*

Faculty of Pharmaceutical Sciences, Hokuriku University; Kanagawa-machi, Kanazawa 920–1181, Japan.
Received October 19, 2005; accepted February 1, 2006; published online February 6, 2006

Palladium-catalyzed carbonylative cross-coupling reaction of ethynylstibane (Ph$-\equiv-$SbPh$_2$) and aryl iodides (Ar-I) is described. The reaction of the stibanes and the halides under 1 atm of carbon monoxide in *N,N*-dimethylacetamide using a combination of 5 mol% Pd(OAc)$_2$ and 4 equivalents (20 mol%) of PPh$_3$ brought about carbonylative cross-coupling reaction to afford arylethynylketones [ArC(O)$-\equiv-$Ph] in good yields along with a small amount of directly coupled products, aryl acetylens (Ar$-\equiv-$Ph). Formation of the side product was completely suppressed by conducting the reaction under high CO pressure (20 atm) conditions. The present method provides a variety of carbonylated products in good yield even with electron-deficient aryl iodides which usually give inferior results due to their tendency to undergo decarbonylation in the cross-coupling reaction of ethynylstibanes and acyl halides.

Key words   carbonylative cross-coupling; ethynylstibane; aryl iodide; palladium catalyst

Recent remarkable development of novel transmetallating agents for cross-coupling reactions has been fascinating to many synthetic chemists because of its high reliability and wide applicability for C–C, C–O and C–N bond forming reaction.[1,2] Especially, investigations on novel coupling agents involving typical heavier elements such as In,[3,4] Si,[5—7] Bi,[8,9] and Ge[10,11] attract much attention not only of heteroatom chemists, but also of synthetic chemists. These transmetallating agents can easily be activated and coupled with various organic halides under mild condition, based on a hypervalent strategy.[12,13] One useful application of these transmetallating agents is carbonylative cross-coupling reaction which leads to the formation of unsymmetrical ketones in one-pot operation from an appropriate transmetallating agent and organic halides under carbon monoxide (CO) atmosphere.[14—21]

The organoantimony(III) [Sb(III)] compounds are relatively stable and can be prepared easily compared to organoantimony(V) and hypervalent antimony compounds. The facile access of Sb(III) compounds stimulated us to employ them as practical organic reagents. We have recently explored the palladium-catalyzed cross-coupling reaction of Sb(III) compounds with organic halides and their versatile applicability, *e.g.* ethynylstibanes (**1**) were coupled with acyl chlorides, vinyl iodides and aryl iodides to give ethynylketones, 1,3-enynes, and arylacetylens, respectively.[22,23] We also demonstrated that these reactions were accelerated with microwave irradiation.[24] A mild and efficient Sb(III)-mediated cross-coupling reaction was also achieved with ethynyl- and ary-1,5-azastibocienes bearing an intramolecular N···Sb non-bonding interaction.[25,26]

As an extension of the versatility of Sb(III) compounds as a transmetallating agent, we investigated the cross-coupling reaction of ethynylstibanes with aryl iodides under CO atmosphere. In the present reaction, the yield of the carbonylated coupling products is sensitive to the nature of the Pd catalyst, and superior results were obtained by using a monodentate phosphine-ligated Pd catalyst. It also appeared that a variety of unsymmetrical ethynyl ketones could be synthesized in excellent yield under high pressure condition (CO, 20 atm) even in the reactions with electron-deficient aryl iodides

which usually gave inferior results due to their tendency to undergo decarbonylation.

Results and Discussion

Pd-Catalyzed Carbonylative Cross-Coupling Reaction of Ethynylstibane with Aryl Iodides under CO Atmosphere   In order to optimize the reaction conditions, we initially attempted the reaction of ethynyldiphenylstibane (**1**) and iodobezene (**2a**) under atmospheric CO pressure using a variety of solvents in the presence of 5 mol% of various palladium (Pd) catalysts (Table 1). The reaction did not proceed in THF or benzene which was often employed for carbonylative cross-coupling with a variety of organometallic compounds.[2,14—16,18,21] For direct cross-coupling reaction of **1** and aryl iodides giving rise to diaryl acetylenes, polar aprotic solvents such as hexamethylphosphramide (HMPA), 1-methyl-2-pyrrolidone (NMP) or amine have been reported to give rather superior result.[23] However, in amine solvents such as morpholine and triethylamine, insertion of CO did not take place smoothly and direct coupled diphenylacetylene (**4a**) was formed as a main product. When the reaction was performed in *N,N*-dimethylacetamide (DMA), the expected carbonylated ethynylphenylketone (**3a**) was obtained in 45% yield and direct coupled product (**4a**) was reduced to 8% even under 1 atm of CO. Search for a suitable Pd catalyst using DMA as a solvent revealed that phosphine-ligated Pd catalysts were superior to ligandless Pd(OAc)$_2$ in the present reaction. For instance, addition of PPh$_3$ in the Pd(OAc)$_2$ catalytic system improved the yield of carbonylated product (**3a**) and suppressed the formation of the cross-coupling (**4a**) and homo-coupling (**5**) products. Consequently, the best results were obtained when the reaction was carried out by use of 5 mol% of Pd(OAc)$_2$ with 4 eq of PPh$_3$ (entry 10). This result suggests that one role of the phosphine ligand is to block undesirable oxidative addition of **1** to Pd(0) for intermediate (E) (Route II in Fig. 1), which eventually leads to the formation of the homo-coupled product (**5**).[27,28] Bidentate phosphine ligands such as dppe and dppf were found to be inappropriate for this carbonylation (entries 11, 12). As expected, the yield of **4a** was increased from 45 to 87% in the presence

Table 1. Solvent and Catalyst for Carbonylative Cross-Coupling Reaction of Ethynylstibane (**1**) and Iodobenzene (**2a**)

$$Ph_2Sb-\!\!\!\equiv\!\!\!-Ph + Ph-I \xrightarrow[\text{CO, 1 atm / 80℃}]{\text{Pd Cat. 5 mol\%}} \underset{\mathbf{3a}}{Ph\overset{O}{\underset{}{C}}\!\!\!\equiv\!\!\!Ph} + \underset{\mathbf{4a}}{Ph-\!\!\!\equiv\!\!\!-Ph} + \underset{\mathbf{5}}{Ph-\!\!\!\equiv\!\!\!\equiv\!\!\!-Ph}$$

Entry	Solvent	Pd catalyst	CO/atm	Time/h	Yield/%[a,b]		
					3a	4a	5
1	Tetrahydrofuran	PdCl$_2$(PPh$_3$)$_2$	1	3.5	20	3	15
2	Benzene		1	3.5	5	9	24
3	1,2-Dichloroethane		1	3.5	7	11	29
4	Morpholine		1	3.5	—	31	3
5	Triethylamine		1	3.5	7	24	36
6	1-Methyl-2-pyrrolidinone		1	1	36	12	20
7	Dimethylacetamide		1	1	4	8	21
8	Dimethylacetamide	Pd(OAc)$_2$	1	1	36	15	25
9		Pd(OAc)$_2$+2PPh$_3$	1	1	58	2	9
10		Pd(OAc)$_2$+4PPh$_3$	1	1	71	1	9
11		Pd(OAc)$_2$+dppe	1	1	—	1	31
12		Pd(OAc)$_2$+dppf	1	1	6	10	62
13		Pd(PPh$_3$)$_4$	1	1	42	12	11
14		Pd(OAc)$_2$+4PPh$_3$	20	1	43	—	5
15		PdCl$_2$(PPh$_3$)$_2$	20	1	87	—	13

a) Isolated yield. *b*) The yields of **3**, **4** and **5** were determined by GLC analysis when they were inseparable by silica gel column chromatography.
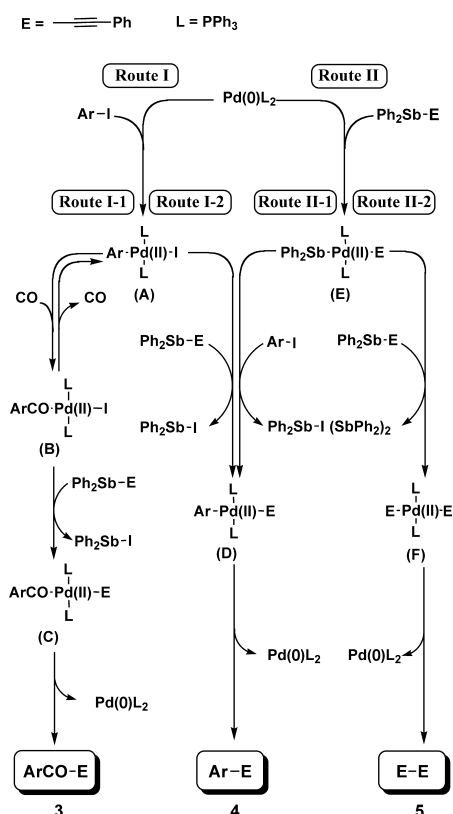

Fig. 1. Possible Reaction Mechanisms for the Formation of the Coupling Products (**3**, **4**, **5**)

Table 2. Carbonylative Cross-Coupling Reaction of Ethynylstibane (**1**) with Aryl Iodides (**2a—e**)

$$Ph_2Sb-\!\!\!\equiv\!\!\!-Ph + Ar-I \xrightarrow[\text{Condition B (CO, 20 atm)}]{\text{Condition A (CO, 1atm)}}$$

$$\underset{\mathbf{3a-e}}{Ar\overset{O}{\underset{}{C}}\!\!\!\equiv\!\!\!Ph} + \underset{\mathbf{4a-e}}{Ar-\!\!\!\equiv\!\!\!-Ph} + \underset{\mathbf{5}}{Ph-\!\!\!\equiv\!\!\!\equiv\!\!\!-Ph}$$

	Aryl iodide (**2**)	Yield/%, Condition A (Condition B)		
		3	4	5
a:	Phenyl	71 (87)	1 (—)	9 (13)
b:	*p*-Tolyl	67 (75)	11 (—)	14 (19)
c:	*p*-Anisyl	52 (55)	14 (—)	30 (16)
d:	*p*-Acetylphenyl	78 (85)	4 (—)	10 (12)
e:	*p*-Nitrophenyl	75 (81)	6 (—)	8 (16)

Condition A: A mixture of **1** (1.0 mmol), **2** (1.5 mmol), Pd(OAc)$_2$ (0.05 mmol), PPh$_3$ (0.2 mmol) in DMA (20 ml) was heated at 80 °C for 1 h under 1 atm of CO. Condition B: A mixture of **1** (1.0 mmol), **2** (1.5 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.05 mmol) in DMA (20 ml) was heated at 80 °C for 1 h under 20 atm of CO.

Table 2, the reactions under atmospheric pressure of CO were proved to be enough to get the carbonylated products (**3**) in moderate to good yield, along with small amounts of the direct cross-coupling products (**4**) and homo-coupling products (**5**) (Condition A in Table 2). Under 20 atm of CO, carbonylation was facilitated effectively and the ethynyl ketones (**3**) were produced in satisfactory yield, and no direct coupled products (**4**) were found from all the reaction mixtures (Condition B in Table 2).

Reaction Mechanisms Possible reaction mechanisms for the formation of these coupling products (**3**, **4**, **5**) in the present reaction are depicted in Fig. 1. The ethynylketones (**3**) were produced through Route I-1. The Ar-Pd(II)-I complex (**A**) was formed by oxidative addition of aryl iodide to Pd(0)L$_2$ generated *in situ* from Pd(II)L$_2$ with PPh$_3$, CO or

of PdCl$_2$(PPh$_3$)$_2$ when the pressure of CO was raised from 1 to 20 atm. Although the reason was not clear at present, inferior result was obtained by use of the Pd(OAc)$_2$–4(PPh$_3$) catalytic system under 20 atm of CO.

Finally, we demonstrated the reaction of ethynylstibane (**1a**) with aryl iodides (**2b—e**) to establish the generality of the carbonylative cross-coupling reaction. As can be seen in

ethynylstibane (**1**).[22] Insertion of CO to the complex (**A**) afforded acyl palladium complex (**B**) which was transformed to the intermediate (**C**) by the transmetallation of ethynyl group on the stibane. Following reductive elimination furnished **3** (Route I-1). The direct cross-coupling product (**4**) was produced from Ar-Pd(II)-E complex (**D**) which may be originated from the intermediate (**A**) (Route I-2). When aryl iodides with an electron-donating substituent (MeO, Me) were employed as a coupling partner, a considerable amount of homo-coupled 1,3-diynes (**5**) was formed (30% and 14%, respectively). Slow oxidative addition of aryl iodides to the Pd(0) species will facilitate the formation of Sb-Pd(II)-E intermediate (**E**) (Route II). These Routes I and II should be a competitive process relying upon the reactivity toward oxidative addition of the aryl halides (**2**) and the stibane (**1**) to Pd(0) species.[26] It has been well established that the reactivity of aryl halides to Pd(0) depends upon the electronic nature of the substituents on the aryl group and the halides bearing an electron-withdrawing substituent are more reactive than those having an electron-donating group.[29,30] Successive transmetallation of the intermediates (**E**) with another ethynylstibane led to the formation of diethynyl-Pd(II) complex (**F**) and the following reductive elimination afforded 1,3-diynes (**5**) (Route II-2). Formation of the direct cross-coupling products (**4**) would be also possible *via* the intermediate (**D**) caused from reaction of the intermediate (**E**) with aryl iodide (Route II-1).

Under 20 atm of CO, carbonylation took place effectively and no direct coupled products (**4**) were found from all the reaction mixtures investigated, because insertion of CO to Ar-Pd(II)-I (**A**) was facilitated to form acyl palladium complex ArCO-Pd(II)-I (**B**). Accordingly, competitive Route I-2 was suppressed under high CO pressure environment, which brought about predominant formation of **3**. No decrease of homo-coupled 1,3-diynes (**5**) under the high-pressure conditions indicates that oxidative addition of the antimony reagent (**1**) with the Pd(0) was not influenced by CO pressure and that insertion of CO to Sb-Pd(II)-E intermediates (**E**) with Route II-1 seemed to be unlikely. Consequently, these results show that the present Sb-mediated carbonylation provides good yield of the unsymmetrical aryl ethynyl ketones (**3**) even with electron-deficient aryl iodides which usually result in inferior yields due to their tendency to undergo decarbonylation.[31—33]

Experimental

General Melting points were taken on a Yanagimoto micro melting point hot-stage apparatus (MP-S3) and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-ECP-500 (500 MHz) spectrometer in CDCl$_3$ using tetramethylsilane as internal standard (δ 0 ppm) unless otherwise stated. Mass spectra (MS) were obtained on a JEOL JMS-SX-102 instrument by electronic impact at 70 eV. IR spectra were recorded on a HORIBA FT-720 instrument in KBr disk. Chromatographic separations were accomplished with Silica Gel 60N (Kanto Chemical Co., Inc.). Thin-layer chromatography (TLC) was performed with Macherey-Nagel pre-coated TLC plates Sil G25 UV$_{254}$. High CO pressure reactions were performed in a stainless steel reactor (100 ml) provided from Taiatsu Techno Corp., Japan. *N,N*-Dimethylacetamide (DMA) was purchased from Wako Pure Chemical Ind. Ltd. Japan, and used without further purification.

Reaction of Ethynylstibane (1) with Iodobenzene (2a) under 1 atm of CO: Condition A General Procedure: A mixture of ethynylstibane (**1**: 1.00 mmol), iodobenzene derivatives (**2a**—**i**: 1.50 mmol), Pd(OAc)$_2$ (0.05 mmol), PPh$_3$ (0.20 mmol) in DMA (20 ml) was heated at 80 °C for 1 h under stream of CO. The reaction mixture was dissolved with ether and the

ether layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was separated on silica gel column chromatography using hexane as an eluent to give ethynylketones (**3a**—**i**), diarylacetylenes (**4a**—**i**), and 1,4-diphenyl-1,3-butadiyne (**5**). The yields of the products (**3**, **4**, **5**) were determined by GLC analysis (SE-30, 5%, 1.6 m, 210 °C) using octadecane as an internal standard when they could not be separated by the chromatography, and the results are collected in Tables 1 and 2. All products except for *p*-acetylphenyl-(phenylethynyl)ketone (**3d**) are known compounds and the structure of them was determined by comparing their melting points and spectral data (MS, NMR, and/or IR) with those of the corresponding authentic samples. **3d**: colorless prisms (mp 103—105 °C, from hexane–benzene). EI-MS *m/z*: 248 (M$^+$, 78%), 220 (100%), 129 (67%). IR (KBr) cm^{-1}: 2199 (C≡C), 1686 (C=O). ^{1}H-NMR (CDCl$_3$) δ: 2.54 (3H, s), 7.41—7.55 (3H, m), 7.70—7.73 (2H, m), 8.03 (2H, d, *J*=8.71 Hz), 8.26 (2H, d, *J*=8.71 Hz).

Reaction of Ethynylstibane (1) with Iodobenzene (2a) under 20 atm of CO: Condition B General Procedure: A mixture of **1** (1.00 mmol), **2a**—**i** (1.50 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.05 mmol) in DMA (20 ml) was heated at 80 °C for 1 h in a stainless steel cylinder (Nippon Taiatsu Kogyo Co. Ltd., 50 ml) under 20 atm of CO. The reaction mixture was dissolved with ether and the ether layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was separated on silica gel column chromatography using hexane as an eluent to give **3** and **5**. The yields of the products for **3** and **5** are collected in Table 2.

References and Notes

1) Trost B. M., Fleming I., "Comprehensive Organic Synthesis," Vol. 3, Pergamon Press, Oxford, 1991, pp. 413—561.
2) Diederich F., Stang P. J., "Metal-Catalyzed Cross-Coupling Reactions," Wiley-VCH, New York, 1998.
3) Fausett B. W., Liebeskind L. S., *J. Org. Chem.*, **70**, 4851—4853 (2005).
4) Pena M. A., Sestelo J. P., Sarandeses L. A., *Synthesis*, **2005**, 485—492 (2005).
5) Rendler S., Oestreich M., *Synthesis*, **2005**, 1727—1747 (2005).
6) Denmark S. E., Sweis R. F., *Chem. Pharm. Bull.*, **50**, 1531—1541 (2002).
7) Nakao Y., Imanaka, H., Sahoo A. K., Yada A., Hiyama T., *J. Am. Chem. Soc.*, **127**, 6952—6953 (2005).
8) Suzuki H., Ikegami T., Matano Y., *Synthesis*, **1997**, 249—267 (1997).
9) Yamazaki O., Tanaka T., Shimada S., Suzuki Y., Tanaka M., *Synlett*, **2004**, 1921—1924 (2004).
10) Faller J. W., Kultyshev R. G., *Organometallics*, **21**, 5911—5918 (2002).
11) Nakamura T., Kinoshita H., Shinokubo H., Oshima K., *Org. Lett.*, **4**, 3165—3167 (2002).
12) Yamamoto H., Oshima K., "Main Group Metals in Organic Synthesis," Wiley-VCH, Weinheim, 2004.
13) Akiba K.-y., "Chemistry of Hypervalent Compounds," Wiley-VCH, New York, 1999.
14) Lee S. W., Lee K., Seomoon D., Kim S., Kim H., Kim H., Shim E., Lee M., Lee S., Kim M., Lee P. H., *J. Org. Chem.*, **69**, 4852—4855 (2004).
15) Maerten E., Hassouna F., Couve-Bonnaire S., Mortreux A., Carpentier J.-F., Castanet Y., *Synlett*, **2003**, 1874—1876 (2003).
16) Pena M. A., Sestelo J. P., Sarandeses L. A., *Synthesis*, **2003**, 780—784 (2003).
17) Hanamoto T., Hanada K., Mido T., *Bull. Chem. Soc. Jpn.*, **75**, 2497—2502 (2002).
18) Gotov B., Kaufmann J., Schumann H., Schumalz H.-G., *Synlett*, **2002**, 1161—1163 (2002).
19) Kang S.-K., Ryu H.-C., Hong Y. T., *J. Chem. Soc., Perkin Trans. 1,* **2001**, 736—739 (2001).
20) Kang S.-K., Ryu H.-C., Lee S.-W., *J. Organomet. Chem.*, **610**, 38—41 (2000).
21) Ishiyama T., Kizaki H., Hayashi T., Suzuki A., Miyaura N., *J. Org. Chem.*, **63**, 4726—4731 (1998).
22) Kakusawa N., Yamaguchi K., Kurita J., Tsuchiya T., *Tetrahedron Lett.*, **41**, 4143—4146 (2000).

23) Kakusawa N., Yamagichi K., Kurita J., *J. Organomet. Chem.*, **690**, 2956—2966 (2005).

24) Kakusawa N., Kurita J., *Chem. Pharm. Bull.*, **53**, 1369—1371 (2005).

25) Kakusawa N., Tobiyasu Y., Yasuike S., Yamaguchi K., Seki H., Kurita J., *Tetrahedron Lett.*, **44**, 8589—8592 (2003).

26) Kakusawa N., Tobiyasu Y., Yasuike S., Yamaguchi K., Seki H., Kurita J., *J. Organomet. Chem.*, JOM 14083 (2006).

27) Barton D. H. R., Ozbalik N., Ramesh M., *Tetrahedron*, **44**, 5666—5668 (1988).

28) Barton D. H. R., Khamsi J., Ozbalik N., Reibenspies J., *Tetrahedron*, **46**, 3111—3122 (1990).

29) Negishi E., Anastasia L., *Chem. Rev.*, **103**, 1979—2017 (2003).

30) Littke A., Fu G. C., *Angew. Chem.*, *Int. Ed.*, **41**, 4176—4211 (2002).

31) Ohno K., Tsuji J., *J. Am. Chem. Soc.*, **90**, 99—107 (1968).

32) Verbicky J. W., Jr., Dellacoletta B. A., Williams L., *Tetrahedron Lett.*, **23**, 371—372 (1982).

33) A similar reaction of diphenyl(2-*N*,*N*-dimethylaminobenzyl)stibane with aroyl chlorides having electron-withdrawing groups (*p*-XC$_6$H$_4$COCl: X=Cl, CF$_3$, NO$_2$) afforded considerable amount of decarbonylated products (*p*-XC$_6$H$_4$-Ph) along with the normal cross-coupling products (*p*-XC$_6$H$_4$COPh), unpublished results.