J|A|C|S COMMUNICATIONS

Published on Web 11/11/2004

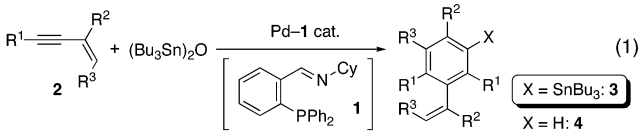
Stannylative Cycloaddition of Enynes Catalyzed by Palladium−Iminophosphine

Yoshiaki Nakao,*,† Yasuhiro Hirata,† Shinjiro Ishihara,† Shinichi Oda,† Tomoya Yukawa,† Eiji Shirakawa,*,‡ and Tamejiro Hiyama*,†

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510 Japan, and Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502 Japan

Received September 14, 2004; E-mail: nakao@npc05.kuic.kyoto-u.ac.jp; shirakawa@kuchem.kyoto-u.ac.jp; thiyama@npc05.kuic.kyoto-u.ac.jp

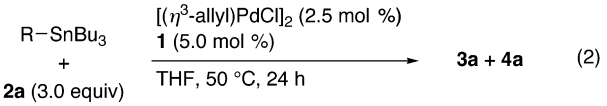
Transition metal-catalyzed regioselective cycloaddition reaction of unsaturated compounds is a powerful tool for one-step construction of substituted benzene.[1] Metalative versions of the reaction would broaden its synthetic versatility as the resulting aromatic organometallics should enjoy a variety of transformations. However, such a reaction has been limited to titanative cyclotrimerization of alkynes.[2] Although the reaction provides variously substituted phenyl- and benzyltitanium compounds with perfect chemo- and regioselectivities, it involves multistep procedures and requires a leaving group, such as sulfonyl or bromo, in an alkyne molecule. Herein, we report the regioselective stannylative cycloaddition of conjugated enynes catalyzed by a palladium complex having *N*-(2-diphenylphosphinobenzylidene)cyclohexylamine (**1**) as a ligand to give variously substituted 3-alkenylphenylstannanes **3** (eq 1). The synthetic potential of the reaction is successfully demonstrated by a concise synthesis of alcyopterosin N, which has been isolated recently from sub-Antarctic soft coral, *Alcyonium paessleri*.[3,4] The nonstannylative version of the present reaction has been studied extensively by Yamamoto and co-workers.[5,6]



(1)

2a, **3a**, **4a**: R^1, R^3 = H; R^2 = Me
2b, **3b**, **4b**: R^1, R^3 = H; R^2 = C_7H_{15}
2c, **3c**, **4c**: R^1, R^3 = H; R^2 = $(CH_2)_2Ph$
2d, **3d**, **4d**: R^1, R^3 = H; R^2 = $(CH_2)_3CH{=}CH_2$
2e, **3e**, **4e**: R^1, R^3 = H; R^2 = $(CH_2)_2C{\equiv}CSiMe_3$
2f, **3f**, **4f**: R^1, R^3 = H; R^2 = $(CH_2)_3OSi(t\text{-}Bu)Me_2$
2g, **3g**, **4g**: R^1, R^2 = H; R^3 = CO_2Et
2h, **3h**, **4h**: R^1 = Me; R^2, R^3 = H
2i, **3i**, **4i**: R^1 = Hex; R^2, R^3 = H
2j, **3j**, **4j**: R^1 = CH_2OMe; R^2, R^3 = H
2k, **3k**, **4k**: R^1 = $(CH_2)_3CN$; R^2, R^3 = H

During our investigation of the alkynylstannylation of 2-methyl-1-buten-3-yne (**2a**) with tributyl(phenylethynyl)tin using a Pd−**1** catalyst,[7] we obtained unexpectedly 2-methyl-5-(propen-2-yl)-1-(tributylstannyl)benzene (**3a**) in 57% yield, as estimated by ^{119}Sn NMR analysis of the crude products (eq 2).[8] None of the expected alkynylstannylation products or the regioisomers of **3a** were detected. GC analysis of the products showed the coproduction of nonstannylated product **4a** in 11% yield.[9] As the phenylethynyl moiety in the stannane reagent was lost, we surveyed various stannane donors[10] to find that hexabutyldistannoxane was the optimum to give **3a** in 74% yield by ^{119}Sn NMR. It is worthy to note that both of the stannyl groups in the stannoxane participate in the reaction. We further optimized reaction conditions and found that a combination of (η^5-cylcopentadienyl)(η^3-allyl)palladium [Cp(allyl)Pd], **1**, and maleic anhydride (1:1:1.5, 5 mol % Pd, with respect to the Bu_3Sn group) was the best to give **3a** in 81% isolated yield. The use of the other derivatives of **1** gave inferior results,



(2)

R−SnBu$_3$	**3a**	**4a**
Ph−≡−SnBu$_3$ (1.0 equiv)	57%[a]	11%[b]
$(Bu_3Sn)_2O$ (0.5 equiv)	74%[a]	11%[b]
$(Bu_3Sn)_2O$ (0.5 equiv)[c]	81%[a] (81%)[d]	14%[b]

[a] ^{119}Sn NMR yields based on the Bu_3Sn group using Me_4Sn as an internal standard. [b] GC yields based on **2a** using tridecane as an internal standard. [c] Cp(allyl)Pd (5.0 mol %), **1** (5.0 mol %), and maleic anhydride (7.5 mol %) were used as a catalyst. [d] Isolated yield based on the Bu_3Sn group.

and typical ligands, such as PPh_3 and dppp, or ligandless conditions retarded the reaction.[11,12]

With the optimized conditions in hand, we studied the scope of the reaction and found that a wide variety of functional groups tolerated the reaction conditions (Table 1). Thus, 2-substituted

Table 1. Stannylative Cycloaddition of Enynes Catalyzed by Pd−**1**[a]

entry	enyne	products	yield of **3** (%)[b]	yield of **4** (%)[c]
1	**2b**	**3b**, **4b**	65	20
2	**2c**	**3c**, **4c**	71	23 (26)[d]
3	**2d**	**3d**, **4d**	64	22
4	**2e**	**3e**, **4e**	52	12
5	**2f**	**3f**, **4f**	65	27
6	**2g**	**3g**, **4g**	67	<5[e]
7[f]	**2h**	**3h**, **4h**	71	4[d]
8[f]	**2i**	**3i**, **4i**	67	20
9[f]	**2j**	**3j**, **4j**	66	10
10[f]	**2k**	**3k**, **4k**	67	30

[a] The reaction was carried out using an enyne (0.90 mmol), $(Bu_3Sn)_2O$ (0.15 mmol), Cp(allyl)Pd (15 μmol), **1** (15 μmol), and maleic anhydride (23 μmol) in THF at 50 °C for 24 h. [b] Isolated yields based on the Bu_3Sn group. [c] Isolated yields based on the enyne. [d] Determined by GC based on the enyne. [e] Determined by ^{1}H NMR. [f] The reaction was carried out using 60 μmol of Pd−**1** catalyst and 90 μmol of maleic anhydride at 80 °C.

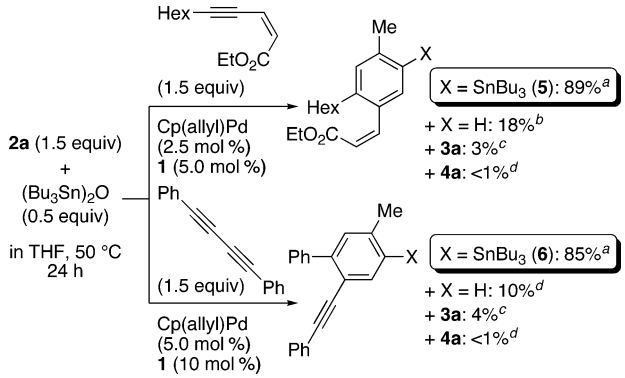
1-buten-3-ynes (**2b**−**2f**) having an alkenyl, alkynyl, or siloxy group reacted to give arylstannanes **3b**−**3f** in good yields (entries 1−5). Ethyl (*Z*)-2-penten-3-ynoate (**2g**) also gave the corresponding arylstannane **3g** in 67% yield, together with only a trace amount of nonstannylated product **4g** (entry 6). Enynes having an internal triple bond and a methoxy or cyano group underwent the reaction under conditions that employed more catalyst (20 mol %) at 80 °C, and various 2,6-disubstituted 3-stannylstyrenes were produced in good yields (entries 7−10). However, 1,2- and 2,4-disubstituted 1-buten-3-ynes, such as 1-ethynylcyclohexene and 2-methyl-1-decen-4-yne, failed to give the corresponding products.

The reaction was also applicable to cross-cycloaddition reactions between different enynes or between enynes and diynes.[13] For

† Graduate School of Engineering.
‡ Graduate School of Science.

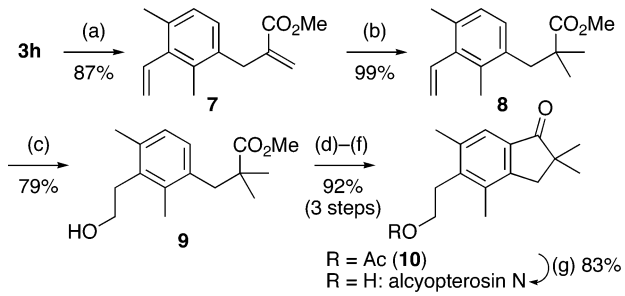
10.1021/ja044429s CCC: $27.50

Scheme 1. Stannylative Cross-Cycloaddition of Enynes



[a] Isolated yields based on the Bu_3Sn group. [b] Determined by ^1H NMR based on **2a**. [c] Determined by ^{119}Sn NMR based on the Bu_3Sn group. [d] Determined by GC based on **2a**.

Scheme 2. Synthesis of Alcyopterosin N[a]



[a] Reagents and Conditions: (a) $BrCH_2CH(CO_2Me)=CH_2$ (1.1 equiv), $Pd_2(dba)_3$ (5 mol %), PPh_3 (20 mol %), NMP, 100 °C, 3 h; (b) DIBAL-H (3.0 equiv), CuMe (10 mol %), THF−HMPA, −50 °C, 1 h, then MeI (20 equiv), −10 °C, 25 h; (c) $Me_2CHCMe_2BH_2$ (5.0 equiv), THF, 0 °C, 3 h, then H_2O_2, NaOH aq., rt, 3 h; (d) LiOH (10 equiv), H_2O−MeOH (9:1), 50 °C, 12 h; (e) Ac_2O (10 equiv), pyridine (5.0 equiv), CH_2Cl_2, rt, 9 h; (f) $SOCl_2$ (10 equiv), CH_2Cl_2, rt to 40 °C, 4 h, then $AlCl_3$ (1.2 equiv), CH_2Cl_2, 40 °C, 3 h; (g) K_2CO_3 (5.0 equiv), H_2O−MeOH (1:1), rt, 1 h.

example, the reaction of **2a** with ethyl (*Z*)-2-undecen-4-ynoate or 1,4-diphenylbutadiyne under similar conditions[14] afforded the corresponding arylstannane **5** or **6**, respectively, in good yield (Scheme 1).

The synthetic potential of the reaction is demonstrated by synthesis of alcyopterosin N starting with 2,6-dimethyl-3-(tributylstannyl)styrene (**3h**) (Scheme 2). Thus, Pd-catalyzed cross-coupling reaction of **3h** with ethyl α-bromomethylacrylate gave **7** in 87% yield. Copper-catalyzed 1,4-reduction[15] of **7** followed by α-methylation yielded **8**, which was subjected to hydroboration−oxidation sequence to provide the alcohol **9**. Acetylation of the hydroxyl group in **9** was followed by the intramolecular Friedel−Clafts acylation and deacetylation to give alcyopterosin N.

In conclusion, we have demonstrated regioselective stannylative cycloaddition of enynes catalyzed by Pd−**1**. Highly substituted 3-alkenylphenylstannanes obtained by this reaction are demonstrated to be synthetically useful by the concise synthesis of alcyopterosin N. Efforts directed toward expansion of the reaction scope and elaboration of the detailed mechanism[16] are currently underway in our laboratories.

Acknowledgment. The authors acknowledge Professor Koichiro Oshima for allowing us to use 500 MHz NMR. This work has been supported financially by Grant-in-Aids for Creative Scientific Research (16GS0209), COE Research on "Elements Science" and on "United Approach to New Material Science", and Encouragement for Young Scientists (B) from MEXT. Y.N. also thanks The Japan Science Society for the Sasakawa Scientific Research Grant.

Supporting Information Available: Detailed experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at http:/pubs.acs.org.

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(8) The structure of the products was determined unambiguously by a combination of NOE experiments, J_{H-H} and J_{H-Sn} values, and protodestannylation. For details, see Supporting Information.

(9) Under the reaction conditions, **4a** and hexabutylstannoxane did not give **3a**.

(10) For detailed results, see Supporting Information.

(11) As the reaction generates water, we also examined the effect of molecular sieves 4A (100 mg) under the optimized conditions and found that the yield of **3a** was unchanged (81% by ^{119}Sn NMR), whereas that of **4a** was slightly lowered (8% by GC). On the other hand, addition of water (3.0 equiv with respect to the Bu_3Sn group) to the reaction mixture diminished the yield of **3a** (43% by ^{119}Sn NMR) and increased that of **4a** (25% by GC). Thus, the formation of **4a** might be derived partially from hydrolysis of **3a** and/or **12** (see ref 16).

(12) Use of $[(\eta^3\text{-allyl})PdCl]_2$ or $Pd_2(dba)_3$ for the reaction of enynes **2b**−**f** caused isomerization of the alkenyl moieties of **3b**−**f**. For detailed results, see Supporting Information. Maleic anhydride might affect the rapid reductive elimination of Cp and allyl from Cp(allyl)Pd due presumably to its strong π-accepting character, generating active Pd(0)−**1** effectively. For the acceleration of reductive elimination by maleic anhydride, see: Yamamoto, T.; Yamamoto, A.; Ikeda, S. *J. Am. Chem. Soc.* **1971**, *93*, 3350−3359.

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(14) Although the reason remains yet to be clarified, a catalyst derived from a 1:1 molar ratio of Pd and **1** gave slightly lower yields of **5** (74%) and **6** (67%), as estimated by ^{119}Sn NMR. Maleic anhydride is not essential in these cases.

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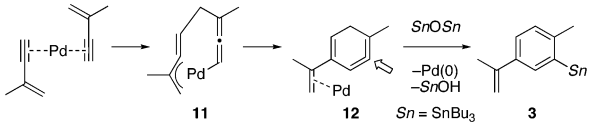
(16) The mechanism of the present reaction is totally unclear at the present stage. A referee suggests a mechanism involving interception of a strained cyclic allene intermediate **12**, which is formed via **11** (see ref 5c), with the Bu_3Sn group to give a stannylated product **3**. Analogous reactions of a strained allene intermediate with a chlorine radical or proton has been reported: Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2003**, *68*, 1938−1946, and ref 6a.



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