J|A|C|S
COMMUNICATIONS

Published on Web 01/11/2006

Palladium(0)-Catalyzed Alkylative Cyclization of Alkynals and Alkynones: Remarkable *trans*-Addition of Organoboronic Reagents

Hirokazu Tsukamoto,* Tatsuhiko Ueno, and Yoshinori Kondo

Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Aoba-ku, Sendai 980-8578, Japan

Received September 20, 2005; E-mail: hirokazu@mail.pharm.tohoku.ac.jp

Transition metal-catalyzed, *cis*-addition specific coupling reactions between alkynes, carbonyls, and organometallic reagents[1−4] serve as a powerful one-step method to prepare synthetically useful allylic alcohols.[5] Particularly interesting are intramolecular versions of this process using less nucleophilic organometallics **5** containing B, Zn, and Zr, which transforms simple precursors **1** into complex, cyclic allylic alcohols **2** that contain *exo*-tetrasubstituted olefin groups (Scheme 1).[1,2,6] Despite their desirability in terms of diversity-oriented synthesis,[7] catalysts that promote the corresponding *trans*-addition[8] process leading to geometrically related cyclic allylic alcohols **4** or cycloalkenols **3** have not been reported. Below, we describe newly discovered *palladium/monophosphine*[9]-catalyzed *trans*-selective alkylative, arylative, and alkenylative cyclization reactions of alkynals **1** with organoboron reagents **6**, in which alkyne substituents and phosphine ligands govern the ratios of the *endo*- and *exo*-cyclic allylic alcohol products (**3** and **4**).

This effort began by developing reaction conditions for the arylative cyclization reaction of terminal alkyne−aldehyde **1a**. Upon heating at 65 °C in the presence of an excess of phenylboronic acid (**6A**) and a catalytic amount of $Pd(PPh_3)_4$, **1a** undergoes phenylative cyclization to afford a single cyclized product **3aA**[10] along with **7**, the product of hydroarylation.[11] The yield of **3aA** is dramatically affected by solvent, with reaction in MeOH leading to exclusive formation of **3aA** (Table 1, entries 1−3 vs 4). Importantly, no reaction takes place in the absence of the palladium catalyst.

Arylboronic acids with electron-donating (entries 5−8) or -withdrawing (entries 9−12) groups serve as nucleophiles in this process, which leads to formation of cyclized products **3aB**−**I** in high yields. Generally, electron-rich boronic acids require shorter reaction times and give higher yields than their electron-deficient counterparts. These cyclization reactions also occur with heteroarylboronic acids **6J**−**K** (entries 13 and 14). Retention of stereochemistry attends reactions of **1a** with alkenylboronic acids **6L**−**M** that afford 2,4-dien-1-ols **3aL**−**M** (entries 15 and 16). Trialkylboranes possessing β-hydrogens participate in this process without undergoing competitive β-hydride elimination (entries 17 and 18).[12]

Arylative cyclization reactions of alkynones **1b**−**c** require higher temperatures and longer times but provide tertiary allylic alcohols **3b**−**cA** in excellent yields (Table 1, entries 19 and 20). While alkynals **1d**−**f** and **1h**, containing Boc-protected nitrogen, tertiary carbon, and aryl tethers, also undergo efficient cyclization reactions (entries 21−23, 25), the conformationally more flexible methylene-tethered substrate **1g** does not cyclize under these conditions (entry 24).

Arylative cyclization reactions of the internal alkyne containing aldehydes **1i**−**k** were also explored (Table 2, entries 1−3). $Pd(PPh_3)_4$ does not promote these processes. A ligand screening effort revealed that palladium ligated with the more σ-donating tricyclohexylphosphine effectively catalyzes cyclization reactions of these substrates to yield mixtures of *trans*-addition products **3** and **4**.[10]

Scheme 1. Transition Metal-Catalyzed Alkylative Alkynal Cyclizations

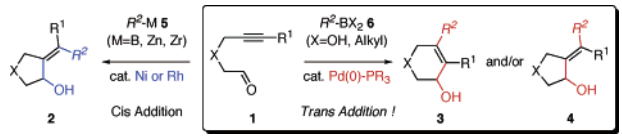
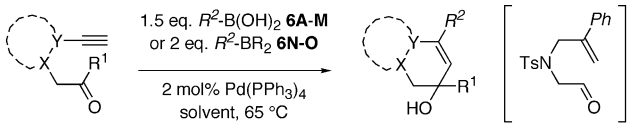


Table 1. $Pd(PPh_3)_4$-Catalyzed Aryl-, Alkenyl-, and Alkylative Cyclizations of **1a**−**h**



a: X=NTs, Y=CH_2, R^1=H **b**: X=NTs, Y=CH_2, R^1=Me **c**: X=NTs, Y=CH_2, R^1=Ph **d**: X=NBoc, Y=CH_2, R^1=H **e**: X=$C(CO_2Et)_2$, Y=CH_2, R^1=H **f**: X=CMe_2, Y=CH_2, R^1=H **g**: X=Y=CH_2, R^1=H **h**: X, Y=C_6H_4, R^1=H

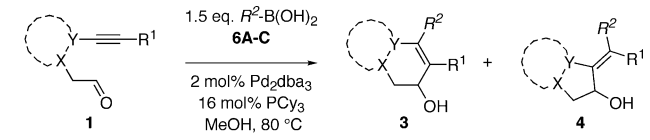
entry[a]	1	6	3	time (h)	yield (%)
1	**1a**	C_6H_5 **6A**	**3aA**	6	17 (8)[b]
2	**1a**	**6A**	**3aA**	6	23 (25)[b]
3	**1a**	**6A**	**3aA**	6	53 (15)[b]
4	**1a**	**6A**	**3aA**	6	92
5	**1a**	*p*-MeO−C_6H_4 **6B**	**3aB**	3.5	85
6	**1a**	*p*-Me−C_6H_4 **6C**	**3aC**	3.5	86
7	**1a**	*o*-Me−C_6H_4 **6D**	**3aD**	3.5	79
8	**1a**	*m*-Me−C_6H_4 **6E**	**3aE**	3.5	85
9	**1a**	*p*-Cl−C_6H_4 **6F**	**3aF**	6	88
10	**1a**	*p*-F_3C−C_6H_4 **6G**	**3aG**	6	80
11	**1a**	*p*-OHC−C_6H_4 **6H**	**3aH**	12	73
12	**1a**	*p*-NC−C_6H_4 **6I**	**3aI**	18	75
13	**1a**	3-thiophene **6J**	**3aJ**	12	89
14	**1a**	2-thiophene **6K**	**3aK**	24	96
15	**1a**	*trans*-propenyl **6L**	**3aL**	6	90
16	**1a**	*cis*-propenyl **6M**	**3aM**	6	83
17	**1a**	Et_3B **6N**	**3aN**	9	100
18	**1a**	octyl-9-BBN **6O**	**3aO**	9	67
19[c]	**1b**	**6A**	**3bA**	30	85
20[c]	**1c**	**6A**	**3cA**	18	97
21	**1d**	**6A**	**3dA**	12	81
22	**1e**	**6A**	**3eA**	6	68
23	**1f**	**6A**	**3fA**	12	80
24[c]	**1g**	**6A**	**3gA**	24	0
25	**1h**	**6C**	**3hC**	24	46

[a] Reactions in CH_2Cl_2 (entry 1), toluene (entry 2), THF (entry 3), and MeOH (entries 4−25). [b] Hydrophenylated product **7** is also obtained in the yields shown in parentheses. [c] Reaction at 80 °C.

The **3**:**4** ratios depend on both steric and electronic requirements of substituents R^1 on the alkyne carbon. Large primary alkyl groups lower the reaction rate and lead to preferences for formation of **3** (entries 1, 2, and 4), while electron-withdrawing aryl substituents at this position facilitate cyclization and again favor formation of **3** (entry 3). These results contrast to those coming from the $Pd(PPh_3)_4$-catalyzed reactions of alkynals **1a** and **1h** with terminal

10.1021/ja056458o CCC: $33.50

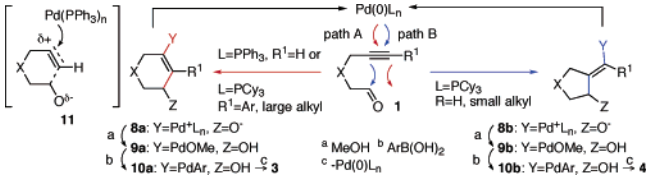
Table 2. Pd_2dba_3/PCy_3-Catalyzed Arylative Alkynal Cyclizations



entry	1	R^1	product	time (h)	yield (%)	3:4
1[a]	**1i**	Me	**iA**	2	90	61:39[d]
2[a]	**1j**	Bu	**jA**	8	66	83:17[d]
3[b]	**1k**	*p*-Me−C_6H_4	**kB**	1	97	93:7[d]
4[a]	**1a**	H	**aA**	0.2	78	32:68[e]
5[c]	**1h**	H	**hC**	0.5	41	**4** only[e]

[a] **6A** is the nucleophile. [b] **6B** is the nucleophile. [c] **6C** is the nucleophile. [d] The ratio is determined from isolated yields. [e] The ratio is determined by ^{1}H NMR analysis.

Scheme 2. Possible Mechanism for the Arylative Alkynal Cyclization Process

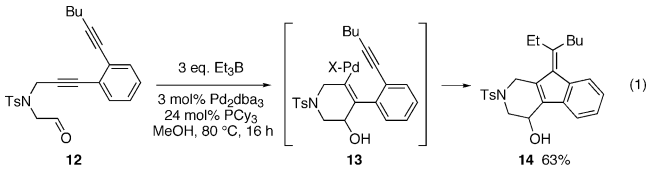


alkyne groups, which yield **4aA** and **4hC** predominantly (Table 2, entries 4 and 5).

A plausible mechanism for the alkylative cyclization reactions of alkynals (Scheme 2) starts with a novel intramolecular electrophilic addition of the carbonyl group to the alkyne, promoted by nucleophilic addition of the electron-rich palladium/phosphine complex to the adjacent alkyne carbon (i.e., anti-Wacker-type oxidative addition).[13] The cyclic cationic alkenylpalladium(II) intermediates **8a** or **8b**, generated in this manner, then undergo solvolysis to form (methoxo)palladium(II) complexes **9a** or **9b**, which upon transmetalation with organoboronic acids produce dioorganopalladium complexes **10a** or **10b**.[14] Reductive elimination then gives **3** or **4** and the Pd(0) complex.

This mechanism can be used to explain the regiochemical preferences (**3**:**4** ratio) associated with the cyclization reactions. For example, the σ-donating character of the ligand coordinated to Pd(0) should control whether oxidative addition occurs at the terminal or internal alkyne carbon. Addition of the lower σ-donating PPh_3 coordinated, less nucleophilic Pd(0) to the internal alkyne carbon of **1** (Path A) would require activation of the alkyne by overlap of its π-system with the carbonyl π^*-orbital (transition state **11**). This corresponds to Markovnikov-type selectivity. It is expected that electron-donating alkyl substituents at the terminal alkyne position would hinder nucleophilic addition of this Pd(0) complex. In contrast, the more σ-donating PCy_3 ligated Pd(0) should be sufficiently nucleophilic to undergo unassisted addition to the less hindered alkyne carbon (Paths A and B). Here, electron-withdrawing aryl groups at the terminal carbon or within the tether would guide nucleophilic attack of the Pd(0) complex to the opposite alkyne position.

The existence of alkenylpalladium(II) intermediates **8**−**10a** in this pathway is evidenced by the domino cyclization reaction of diynal **12** (eq 1). Treatment of **12** with triethylborane in the presence of Pd(0)/PCy_3 for 16 h leads to formation of tricyclic 2,4-dien-1-ol **14** (63%) as a single isomer in an anti-Wacker-type oxidative addition−carbopalladation process.



This study has uncovered the first examples of *trans*-selective, alkylative, arylative, and alkenylative cyclization reactions of alkynals and alkynones. The functional group compatibility, availability, stability, and nontoxicity of the organoboronic reagents and the fact that no additives are needed make the process highly practical. The proposed mechanism, involving oxidative addition without oxametallacycle formation, is different from that for the corresponding nickel-catalyzed reaction. Finally, cyclic allylic alcohol products generated in these reactions should be useful intermediates in carbo- and heterocycle synthesis since they contain a rich array of preparatively important functional groups. Studies probing the detailed mechanism and expanding the scope of the cyclization process are underway.

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Ni-catalyzed reaction: (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Ni, Y.; Amarasinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743. (c) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890 and references therein. For the synthesis of allylamines, see: (d) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364. (e) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941.

(2) Rh-catalyzed reaction: (a) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (b) Miura, T.; Shimada, M.; Murakami, M. *Synlett* **2005**, 667.

(3) Fe-catalyzed reaction: Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621.

(4) Mn-catalyzed reaction: (a) Rang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1997**, *53*, 5061. (b) Yorimitsu, H.; Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **1998**, 11.

(5) We recently reported the palladium(0)-catalyzed direct cross-coupling reaction of allyl alcohols with arylboronic acids. Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* **2004**, 1200.

(6) Intramolecular hydroacylation of 5-alkynals followed by reduction would also provide **2** (R^2 = H). Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem.—Eur. J.* **2004**, *10*, 5681 and references therein.

(7) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46 and reference therein.

(8) Some examples of *trans*-selective carbometalation of functionalized alkynes are reported. (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) Fallis, A. G.; Forgoine, P. *Tetrahedron* **2001**, *57*, 5899 and references therein.

(9) Palladium catalysts have not been employed previously because they are less suitable for insertion into carbonyl groups. The limited number of palladium-catalyzed carbonyl alkenylations are based on carbonyl insertions into organopalladium(II) formed in situ. (a) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *J. Organomet. Chem.* **1992**, *436*, C9. (b) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *Organometallics* **1996**, *15*, 3509. (c) Vicente, J.; Abad, J.-A.; Lopez-Pelaez, B.; Martinez-Viviente, E. *Organometallics* **2002**, *21*, 58. (d) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545. (e) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089. (f) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343.

(10) Structure determinations were performed by using NOESY techniques, transformations into the known compounds, and preparations of authentic samples; see Supporting Information.

(11) Oh, C. H.; Jung, H. H.; Kim, K. S.; Kim, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 805.

(12) Alkylboronic acids are not suitable as nucleophiles.

(13) An "anti-Wacker"-type mechanism was proposed for hydroalkoxylation of electron-deficient alkenes and alkynes. See: (a) Camacho, D. H.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 1085. (b) Matsukawa, Y.; Mizukado, J.; Quan, H.; Tamura, M.; Sekiya, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1128.

(14) Miyaura, N.; Yamada, K.; Suginome H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

JA056458O