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Palladium(0)-catalyzed cis-selective alkylative and arylative cyclization of alkynyl enones with organoboron reagents

Hirokazu Tsukamoto *, Takamichi Suzuki, Tomomi Uchiyama, Yoshinori Kondo

Graduate School of Pharmaceutical Sciences, Tohoku University, Aramai-aza aoba 6-3, Aoba-ku, Sendai 980-8578, Japan

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ABSTRACT

A palladium(0)-tricyclohexylphosphine catalyzes cis-selective alkylative and arylative cyclization of alkyne-containing electron-deficient alkenes with organoboron reagents to provide five- or six-membered rings with *exo* tri- or tetra-substituted alkenes. The opposite stereoselectivity to that for the alkyne–aldehyde cyclization using the same reagents would result from palladacycle-forming oxidative addition of the substrates to the Pd^0 catalyst followed by transmetalation with the boron reagents, protonation, and reductive elimination. The functional group compatibility, availability, stability, and non-toxicity of the reagents, and the fact that no additives are needed make the process more practical than the Ni^0-catalyzed cyclization with organozinc reagents.

Organoboron reagents are generally non-toxic, commercially available, stable, and compatible with various functional groups, and often employed for a wide variety of Pd^0-catalyzed carbon–carbon bond formations such as cross-coupling reactions,[1] arylations of unsaturated carbon–carbon bonds,[2–4] and alkylative cyclization reaction of functionalized unsaturated carbon–carbon bonds.[5–7] Our recent interest has been focused on base-free transformations of substrates containing no halogens because they are atom-economical and does not form inorganic salts.[4a,5]

Recently, we discovered the palladium(0)/monophosphine-catalyzed trans-selective alkylative cyclization of alkyne–aldehyde **1** with organoboron reagents to provide structurally complex cyclic allylic alcohols **2a** and **2b** (Scheme 1).[5a,b] The trans selectivity is in striking contrast to for the Ni^0-catalyzed cis-selective one with organozinc reagents.[8] The opposite selectivity in these cyclization reactions would originate from the different oxidative addition mode of alkynal **1** to these catalysts. Whereas 'anti-Wacker'-type oxidative addition to the Pd^0 catalyst and concomitant transmetalation with the boron reagents would occur in the former cyclization, metallacycle-forming one to the Ni^0 catalyst and subsequent transmetalation with the zinc reagents would occur in the latter cyclization. The different oxidative addition mode to the same group VIII metals would imply that the Pd^0 catalyst has lower tendency to form π-complex with the carbonyl group than the Ni^0 catalyst. Herein, we have investigated whether α,β-unsaturated carbonyls in **4** as an electrophile change the oxidative addition mode to the Pd^0 catalyst.[9] The alkyne–enones **4** were reported to undergo cis-selective alkylative cyclization under the Ni^0 catalysis.[10]

The arylative cyclization of (2*E*)-1-phenyl-2-octen-7-yn-1-one (**4a**) with a slight excess of phenylboronic acid and its anhydride mixture in a ratio of 2 to 1[11] proceeds in the presence of 5 mol % of $PdCp(\eta^3\text{–}C_3H_5)$[12] and 15 mol % of PCy_3, and provides *cis*-addition product **5aA** in good yield (Scheme 2, Table 1, entry 1).[13] In contrast to the cyclization of alkynal **1**, methanol is not an essential solvent for the cyclization of **4a** and 1,4-dioxane turns out to be better. The yield of **5aA** is dramatically decreased as the ratio of phenylboronic anhydride in the mixture increases (entry 1 vs entries 2 and 3). These results indicate that Brønsted acidity of the boronic acid is important for the cyclization. Importantly, a Pd^0 catalyst ligated with less σ-donating PPh_3 is less effective for the cyclization than the one with more σ-donating PCy_3 (entry 2 vs entry 4).[14]

Arylboronic acids with electron-donating (Table 1, entries 5 and 6) or -withdrawing (entries 7 and 8) groups serve as nucleophiles in this process, which leads to formation of cyclized products **5aB–E** in moderate to good yields. Generally, electron-rich boronic acids give higher yields than their electron-deficient counterparts. Trialkylborane possessing β-hydrogens participates in this process without undergoing competitive β-hydride elimination only when reaction is conducted in methanol (entries 9 and 10).

Enones **4b–d** containing aryl, alkyl, and methoxycarbonyl group-substituted internal alkynes also undergo the cis-selective cyclization with reaction in methanol (Scheme 3, Table 2, entries 1–3). Tertiary carbon, oxygen, and nitrogen-tethered alkynyl enones **4e–g** also cyclize and provide five-membered carbo- and heterocycles **5e–gB** (entries 4–6). Alkynyl enone **4h** as a homologue of **4g** is successfully converted to six-membered cyclized compound **5hB** (entry 7).

Next, cyclization reactions of terminal alkynes **4i–m** containing various electron-deficient alkenes were explored (Scheme 4, Table

* Corresponding author. Tel./fax: +81 22 795 3906.
E-mail address: hirokazu@mail.pharm.tohoku.ac.jp (H. Tsukamoto).

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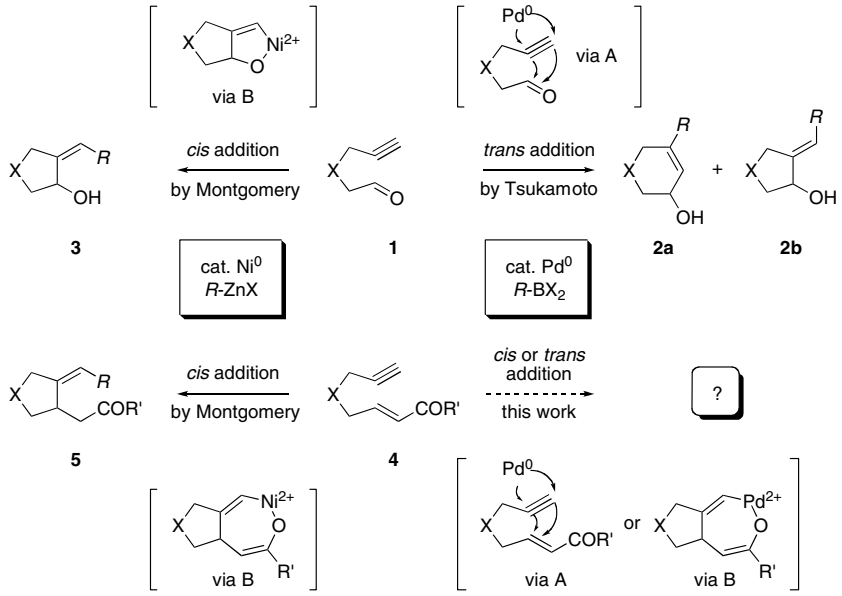
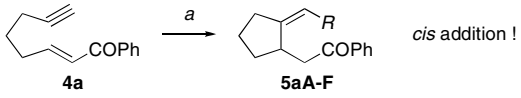


A: 'anti-Wacker'-type oxidative addition. B: metallacycle-forming oxidative addition.

Scheme 1. Ni^0- and Pd^0-catalyzed alkylative cyclization reactions of alkyne–aldehyde **1** and –enone **4**.

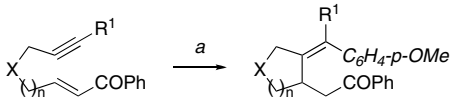


Scheme 2. Pd-catalyzed arylative and alkylative cyclization of **4a**. Reagents and conditions: (a) 1.2 equiv [*R*-B] **6A–F**, 5 mol % $PdCp(\eta^3\text{-}C_3H_5)$, 15 mol % PCy_3, 1,4-dioxane, 80 °C, 30 min.

Table 1
Effects of boron reagents on the arylative and alkylative cyclization of **4a**

Entry	[*R*-B] **6**	**5a**	Yield (%)
1	$PhB(OH)_2/(PhBO)_3$ (2:1) **6A**	**5aA**	77
2	$PhB(OH)_2/(PhBO)_3$ (1:1)	**5aA**	65
3	$PhB(OH)_2/(PhBO)_3$ (2:3)	**5aA**	23
4[a]	$PhB(OH)_2/(PhBO)_3$ (1:1)	**5aA**	5
5	*p*-MeO–$C_6H_4B(OH)_2$ **6B**[b]	**5aB**	70
6	*p*-Me–$C_6H_4B(OH)_2$ **6C**[b]	**5aC**	69
7	*p*-Ac–$C_6H_4B(OH)_2$ **6D**[b]	**5aD**	56
8	*m*-NO_2–$C_6H_4B(OH)_2$ **6E**[b]	**5aE**	43
9[c]	Et_3B **6F**	**5aF**	nd[d]
10[c,e]	Et_3B **6F**	**5aF**	85

[a] Reaction with 5 mol % of $Pd(PPh_3)_4$ as a catalyst.
[b] Boronic anhydride is also contained.
[c] 1.6 equiv of nucleophile is used.
[d] Formation of **5aF** was not observed by TLC.
[e] Reaction in MeOH in place of 1,4-dioxane.

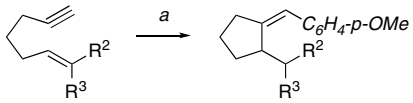


Scheme 3. Effects of alkyne substituents and tethers on the arylative cyclization. Reagents and conditions: (a) 1.2 equiv **6B**, 5 mol % $PdCp(\eta^3\text{-}C_3H_5)$, 15 mol % PCy_3, 1,4-dioxane or MeOH, 80 °C, 30 min.

Table 2
Effects of alkyne substituents and tethers on the arylative cyclization[a]

Entry	**4**	R^1	X	*n*	**5**	Yield (%)
1	**4b**	Ph	CH_2	1	**5bB**	92
2	**4c**	Me	CH_2	1	**5cB**	73
3	**4d**	CO_2Me	CH_2	1	**5dB**	82
4	**4e**	H	CMe_2	1	**5eB**	84
5	**4f**	H	O	1	**5fB**	38
6	**4g**	H	NTs	1	**5gB**	69
7	**4h**	H	NTs	2	**5hB**	71

[a] Reaction in MeOH (entries 1–3, 5 and 7) and 1,4-dioxane (entries 4 and 6).



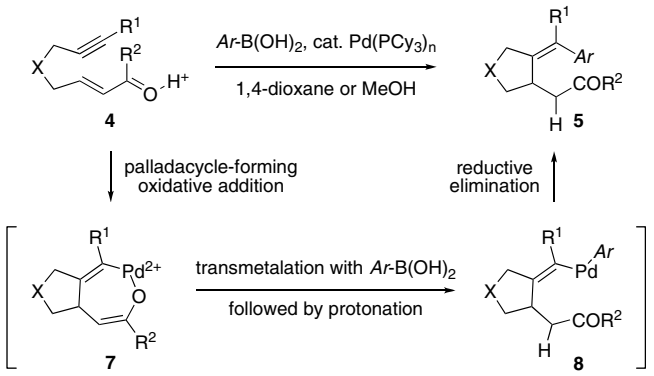
Scheme 4. Effect of electron-deficient alkenes on the arylative cyclization. Reagents and conditions: (a) 1.2 equiv **6B**, 5 mol % $PdCp(\eta^3\text{-}C_3H_5)$, 15 mol % PCy_3, 1,4-dioxane or MeOH, 80 °C, 30 min.

Table 3
Effect of electron-deficient alkenes on the arylative cyclization[a]

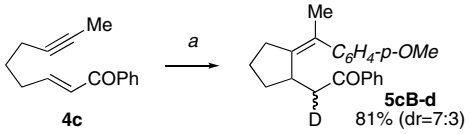
Entry	**4**	R^2	R^3	**5**	Yield (%)
1	**4i**	CHO	H	**5iB**	64
2	**4j**	COMe	H	**5jB**	39
3	**4j**	COMe	H	**5jB**	57
4	**4k**	CO_2Et	H	**5kB**	nd[b]
5	**4k**	CO_2Et	H	**5kB**	36
6	**4l**	CO_2Et	CO_2Et	**5lB**	49
7	**4m**	NO_2	H	**5mB**	40

[a] Reaction in 1,4-dioxane (entries 1, 2, 4, 6 and 7) and MeOH (entries 3 and 5).
[b] Hydroarylation of the alkyne instead of cyclization occurred.

3). More electron-deficient alkenes such as enal, alkylidene malonate, and nitroalkene make the cyclization in 1,4-dioxane smoother than less electron-deficient ones such as methyl vinyl ketone and enoate (entries 1, 6 and 7 vs entries 2 and 4). Methanol as a solvent increases the yield of the cyclization reaction of the substrates containing the latter alkenes, again (entries 2 vs 3 and 4 vs 5).



Scheme 5. Possible mechanism of the arylative cyclization of **4**.



Scheme 6. Arylative cyclization of **4c** in methanol-d_4. Reagents and conditions: (a) 1.2 equiv **6B**, 5 mol % PdCp(η^3-C_3H_5), 15 mol % PCy_3, CD_3OD, 80 °C, 30 min.

The plausible mechanism for the arylative cyclization is outlined in Scheme 5. The catalytic cycle would be initiated by oxidative addition of alkynyl enones **4** to Pd^0 with metallacycle formation.[15–17] Transmetalation and protonation with the boronic acid or its reverse sequence followed by reductive elimination reproduces the Pd^0 catalyst along with cis-addition product **5**. The oxidative addition mode is quite different from that of the Pd^0-catalyzed alkylative cyclization of alkynyl aldehydes and would result from much higher tendency for carbon–carbon double bond to form π-complex with the Pd^0 catalyst than that for carbon–heteroatom double bond. The oxidative addition step could be accelerated by use of hydrogen donors such as boronic acids and methanol solvent for the activation of the carbonyl group in **4** as well as the Pd catalyst ligated with more σ-donating PCy_3. Incorporation of a deuterium atom into the α-position of phenyl ketone in **5cB** with reaction in methanol-d_4 was observed (Scheme 6) and would support the formation of palladacycle **7**.

In summary, we have developed the Pd^0-catalyzed arylative and alkylative cyclization reaction of alkynyl enones with organoboron reagents. The functional group compatibility, availability, stability, and non-toxicity of the reagents and the fact that no additives are needed make the process more practical than the Ni^0-catalyzed cyclization with organozinc reagents. Rh^I catalyst is also reported to promote the same type of cyclization via transmetalation with arylboronic acid and sequential carborhodations of alkyne and enones,[18] but it has some limitations including unlikely alkyl group introduction and chemo- and regioselectivity in the cyclization of alkyne–enals and phenyl-substituted alkyne–enones such as **4i** and **4b**. Although the five- and six-membered ring systems containing both *exo*-alkylidene and (carbonyl)methyl groups can also be produced by other Pd^0-catalyzed cyclization of alkyne–allylic alcohols[19] and -allylic geminal diacetate,[20] these require a base additive leading to stoichiometric salt formation, and troublesome substrate preparation and methanolysis of the enolacetate formed by the cyclization, respectively. Further studies on transformation of the functionalized cyclic compounds generated in these reactions are underway.

Acknowledgments

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13. General procedure: To a test tube containing **4a** (20.1 mg, 0.101 mmol), $PhB(OH)_2$ (15.4 mg, 0.126 mmol), PdCp(η^3-C_3H_5) (1.1 mg, 5.2 μmol), and PCy_3 (4.8 mg, 17.1 μmol) was added anhydrous 1,4-dioxane (0.5 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 30 min. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.58 mmol/g, 0.15 g, 0.24 mmol) and THF (2 mL) were added to the mixture. The mixture was agitated at room temperature for 2 h. The mixture was filtered and thoroughly washed with $CHCl_3$. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC eluting with toluene–EtOAc (40:1) to yield **5aA** (21.5 mg, 0.0778 mmol, 77%). Cis-selectivity was determined by NOESY experiments and the spectral data of **5aA** agreed with those of the reported one.[10a]
14. However, $Pd(PPh_3)_4$ turned out to be effective for the cyclization of more reactive alkyne–enones such as **4g**.
15. At this time, it is not possible to rule out a mechanism involving formation of π-allylpalladium via oxidative addition of enone moiety in **4** to the Pd^0 catalyst followed by insertion of the intramolecular alkyne to generate the common intermediates **7** and **8**. However, the cyclization reaction of **9**, which cannot form palladacycle owing to its short tether, did not afford alkyne insertion products **11** or **12**. It is reported that the oxidative addition of enone to the Pd^0

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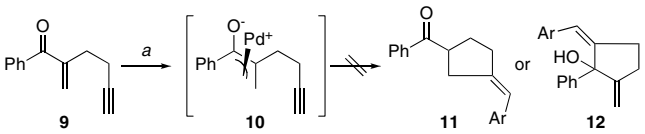

[a] 1.2 equiv **6B**, 5 mol % $PdCp(\eta^3\text{-}C_3H_5)$, 15 mol % PCy_3, 1,4-dioxane or MeOH, 80 °C, 30 min. Ar = C_6H_4-*p*-OMe.

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