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Cationic Pd(II)-Catalyzed Reductive Cyclization of Alkyne-Tethered Ketones or Aldehydes Using Ethanol as Hydrogen Source

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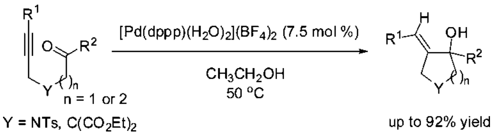
ABSTRACT



A cationic Pd(II)-catalyzed reductive cyclization of alkyne-tethered ketones or aldehydes using ethanol as hydrogen source under mild conditions was developed. The reaction is an environmentally benign synthetic method and proceeds efficiently to give useful *N*-heterocycles or carbocycles bearing an exocyclic double bond and a hydroxyl group in high yield.

Carbon−carbon coupling reactions are the most useful synthetic methods in organic chemistry. Among them, transition-metal-catalyzed alkyne−carbonyl reductive coupling has been established for the synthesis of allylic alcohols. Due to the easy further transformation of functional groups of the products, this reaction becomes a powerful method in synthetic chemistry. In the early stage, a stoichiometric amount of organometallic compounds such as Si, Zn, Sn, Cr, and B were used as the reducing agents, producing equivalent amounts of byproducts.[1] Since the pioneering work by Krische, who developed an atom-economical alkyne−carbonyl reductive coupling using the rhodium- and iridium-catalyzed hydrogenation,[2,3] reactions using different hydrogen sources were reported.[4,5] For example, ruthenium was reported to catalyze reductive alkyne−carbonyl coupling using formic acid as the hydrogen source leading to allylic alcohols.[5]

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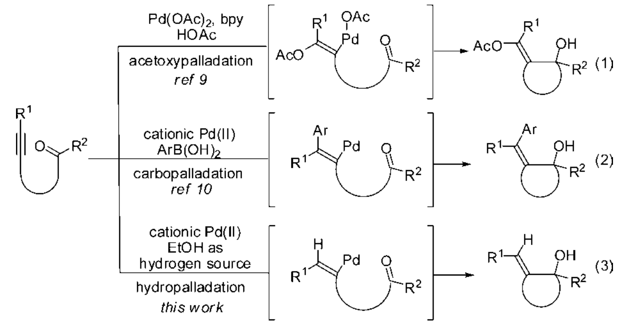
10.1021/ol400531a

Scheme 1. Pd(II)-Catalyzed Alkyne−Carbonyl Coupling

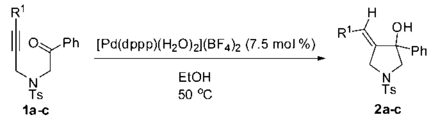


Alcohol is an environmentally benign solvent and hydrogen source that has been utilized in many C−C bond-forming reactions via transition-metal-catalyzed transfer hydrogenation.[6,7] However, only limited examples were reported on alkyne−carbonyl reductive coupling using alcohol as hydrogen source for the reason of low conversions.[5a,b] Sodeoka recently reported an asymmtric conjugate reduction of enones by the Pd−H species generated from a cationic palladium complex and ethanol.[8] This is another example of using alcohol as the hydrogen source.

In our previous work, Pd(II)-catalyzed intramolecular alkyne−carbonyl couplings initiated by acetoxypalladation[9] or carbopalladation[10] of alkynes were reported (Scheme 1, eqs 1 and 2). We wondered if the Pd−H species generated from Sodeoka's strategy would be used to accomplish an intramolecular alkyne−carbonyl reductive coupling reaction initiated by hydropalladation of alkynes (Scheme 1, eq 3). As far as we know, palladium-catalyzed C−C bond-forming reactions initiated by hydropalladation of alkynes using alcohol as the hydrogen source have not been reported in the literature.

In our initial study, the substrate alkyne-tethered ketone **1a** was reacted in the presence of 7.5 mol % of $[Pd(dppp)(H_2O)_2](BF_4)_2$ in ethanol (0.1 M) at 50 °C for 24 h (Table 1, entry 1). The reductive cyclized product **2a** was isolated in 39% yield together with a mixture of dimerized products, the formation of which could not be suppressed after screening many reaction conditions. In order to inhibit the formation of the dimerized products, substrates with bulky group substituted alkynes were employed (Table 1, entries 2 and 3). Using phenyl-substituted alkyne-tethered ketone **1b**, a slightly higher yield was obtained, but a mixture of dimerized products was still formed in addition to **2b** (Table 1, entry 2). To our delight, the reaction went smoothly without the formation of any dimerized product for substrate **1c** with a trimethylsilyl substituent, indicating that substrates with sterically hindered alkynes gave much better results for this reaction (Table 1, entry 3). The stereochemistry of the exocyclic double bond in the products was assigned as *E* as confirmed by the X-ray crystallography of **2c** (see the Supporting Information). Owing to the easy further transformation of the silicon moiety, alkyne-tethered ketone **1c** was chosen as the model substrate for reaction condition screening.

Table 1. Preliminary Examination of the Reductive Cyclization Reaction[a]



entry	substrate	time (h)	product	yield[b] (%)
1	**1a**, R^1 = Me	24	**2a**	39[c]
2	**1b**, R^1 = Ph	24	**2b**	47[c]
3	**1c**, R^1 = TMS	2	**2c**	65[d]

[a] Conditions: Reactions were carried out with **1** (0.10 mmol) and catalyst (7.5 mol %) in EtOH (1 mL) at 50 °C. [b] Isolated yield. [c] A mixture of dimerized products was observed. [d] Pyrrole **3c** was also formed without the generation of any dimer (see Table 2, entry 1).

The model substrate alkyne-tethered ketone **1c** was completely consumed within 2 h with 7.5 mol % of $[Pd(dppp)(H_2O)_2](BF_4)_2$ as the catalyst, affording **2c** in 65% yield together with pyrrole **3c** in 31% yield (Table 2, entry 1). This byproduct was formed in almost quantitative yield with prolonged reaction time, indicating that **3c** might be generated from **2c** (Table 2, entry 2). When **1c** was reacted in the presence of 7.5 mol % of [Pd(*rac*-binap)$(H_2O)_2](BF_4)_2$ in ethanol (0.1 M) at 50 °C for 24 h, the reductive cyclized product **2c** was isolated in 54% yield with a 38% recovery of **1c** (Table 2, entry 3). A similar result was obtained when the reaction was catalyzed by [Pd(*rac*-binap)$(H_2O)_2](OTf)_2$ (52% yield, Table 2, entry 4). No reaction occurred when $Pd(OAc)_2$ or $Pd(CF_3COO)_2$ was used as the catalyst (Table 2, entries 5 and 6). Efforts to suppress the generation of **3c** by using some weak bases as additives failed (Table 2, entries 7 and 8). Although a trace amount of **3c** was formed when 1 equiv of $BaCO_3$ was added into the reaction, another byproduct **2c′** was isolated in 30% yield together with **2c** in 58% yield (Table 2, entry 7). Substrate **1c** was destroyed after addition of 1 equiv of K_3PO_4 (Table 2, entry 8). The transfomation of **1c** was much slower when the reaction was performed in *i*-PrOH, giving **2c** in 50% yield accompanied by **3c** in 36% yield after 5 h (Table 2, entry 9). Finally, a good yield (82%) was achieved when the reaction was carried out at room temperature for 48 h using 1,2-dichloroethane (DCE) as a cosolvent, although there was still 15% of **3c** isolated (Table 2, entry 10). On the basis of the above investigation, the optimal condition for this reductive

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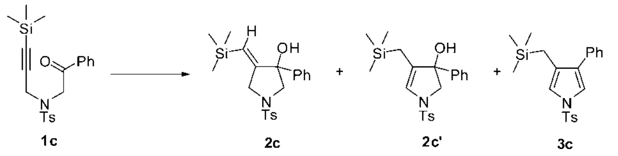
Table 2. Screening of Reaction Conditions[a]



			yield[b] (%)		
entry	catalyst	time (h)	**2c**	**2c′**	**3c**
1	$[Pd(dppp)(H_2O)_2](BF_4)_2$	2	65	0	31
2	$[Pd(dppp)(H_2O)_2](BF_4)_2$	8	trace	0	94
3	$[Pd(\mathit{rac}\text{-binap})(H_2O)_2](BF_4)_2$	24	54	0	trace
4	$[Pd(\mathit{rac}\text{-binap})(H_2O)_2](OTf)_2$	24	52	0	trace
5	$Pd(OAc)_2$ + dppp	24	0	0	0
6	$Pd(CF_3COO)_2$ + dppp	24	0	0	0
7[c]	$[Pd(dppp)(H_2O)_2](BF_4)_2$	2	58	30	trace
8[d]	$[Pd(dppp)(H_2O)_2](BF_4)_2$	2	disordered		
9[e]	$[Pd(dppp)(H_2O)_2](BF_4)_2$	5	50	0	36
10[f,g]	$[Pd(dppp)(H_2O)_2](BF_4)_2$	48	82	0	15

[a] Conditions: Reactions were carried out with **1c** (0.10 mmol) and catalyst (7.5 mol %) in EtOH (1 mL) at 50 °C, unless otherwise noted. [b] Isolated yield. [c] $BaCO_3$ (1 equiv) was added. [d] K_3PO_4 (1 equiv) was added. [e] *i*-PrOH was used as solvent. [f] The reaction was performed at room temperature. [g] $ClCH_2CH_2Cl$ (0.2 mL) was added as a cosolvent to make **1c** soluable.

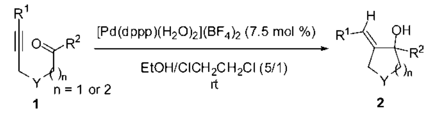
cyclization reaction was as follows: **1c** (0.1 mmol) and $[Pd(dppp)(H_2O)_2](BF_4)_2$ (7.5 mol %) in EtOH/DCE (1 mL/0.2 mL) at room temperature.

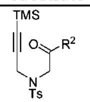
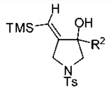
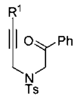
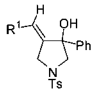
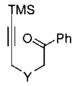
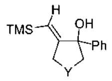
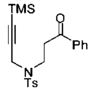
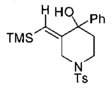
With optimal reaction conditions in hand, we studied the scope of the reductive cyclization of a variety of alkyne-tethered ketones or aldehydes (Table 3). Generally, the reaction worked well with trimethylsilyl-substituted NTs-tethered substrates to give tetrahydropyrroles bearing an exocyclic double bond (Table 3, entries 1–10). Aryl ketones having electron-donating groups such as methyl or methoxy were suitable for the reductive cyclization to give the corresponding products in good yields (Table 3, entries 2 and 6). Substrates with halogen-substituted aryl ketones, which offered opportunities for further transformations of the products, were compatible in this reaction (Table 3, entries 4 and 5). Alkynyl aldehyde **1j** worked well in this reaction, affording secondary alcohol **2j** in moderate yield (Table 3, entry 8). Alkyl ketones (**1k** and **1l**) could also be transformed to the desired products without the formation of pyrroles (Table 3, entries 9 and 10). Substrates bearing other bulky substituents on alkynes show a similar reactivity with **1c** without the observation of any dimer (Table 3, entries 11 and 12). Furthermore, five-membered carbocycles and six-membered N-heterocycles could be synthesized using this method successfully (Table 3, entries 13 and 15). However, NBn-tethered substrate **1p** did not react at all in this reductive cyclizations (Table 3, entry 14).

Subsequently, the asymmetric version of this reductive cyclization reaction was studied (Scheme 2). Our preliminary results showed that the reaction of **1c** in the presence of $[Pd(\mathit{S,S}\text{-bdpp})(H_2O)_2](BF_4)_2$ in EtOH at room temperature can give **2c** in 63% yield with 82% ee.

To gain mechanism insights, the reaction was then conducted in deuteriated ethanol. Subjecting **1l** to the reductive cyclization reaction conditions in CH_3CH_2OD gave **2l** in 97% yield with no deuterium incorporation into the product (Scheme 3, eq 1). However, the use of CH_3CD_2OH afforded *d*-**2l** with a deuterium at the vinyl position in 92% yield (Scheme 3, eq 2).

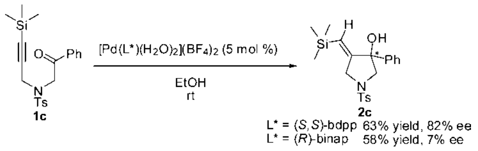
Table 3. Reaction Scope of Alkyne-Tethered Ketones or Aldehydes[a]



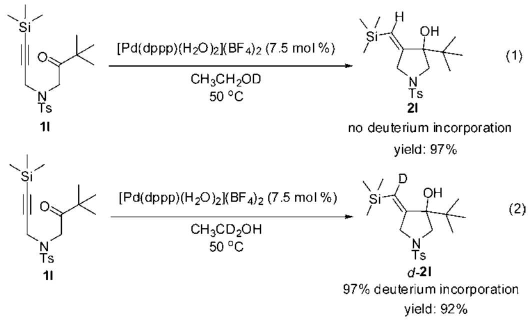
entry	substrate	product	time (h)	yield (%)[b]
				
1[c]	**1c** $R^2 = C_6H_5$	**2c**	48	82[d]
2[e]	**1d** R^2 = 2-Me-C_6H_4	**2d**	12	92
3[c]	**1e** R^2 = 4-Ph-C_6H_4	**2e**	48	90
4[c]	**1d** R^2 = 4-Cl-C_6H_4	**2f**	48	80
5[c]	**1g** R^2 = 4-Br-C_6H_4	**2g**	48	82
6[c]	**1h** R^2 = 4-MeO-C_6H_4	**2h**	48	77
7[c]	**1i** R^2 = β-naphthyl	**2i**	48	85
8[e]	**1j** R^2 = H	**2j**	5	65
9[e]	**1k** R^2 = Me	**2k**	12	50
10[e]	**1l** R^2 = ^{t}Bu	**2l**	2	87
				
11[c]	**1m** R^1 = TBDMS	**2m**	24	81
12[c]	**1n** R^1 = ^{t}Bu	**2n**	24	77
				
13[e]	**1o** Y = $C(CO_2Et)_2$	**2o**	5	65
14[e]	**1p** Y = NBn	**2p**	48	0
				
15[e]	**1q**	**2q**	5	71

[a] Conditions: The reaction was carried out with **1** (0.1 mmol) and $[Pd(dppp)(H_2O)_2](BF_4)_2$ (7.5 mol %) in EtOH/$ClCH_2CH_2Cl$ (1 mL/0.2 mL) at room temperature, unless otherwise noted. [b] Isolated yield. [c] Small amounts of pyrroles were also formed. [d] **2c** was isolated in 71% yield with a 24% recovery of **1c** when the reaction was performed on a 0.5 mmol scale. [e] The reaction was performed in EtOH (1 mL) at 50 °C.

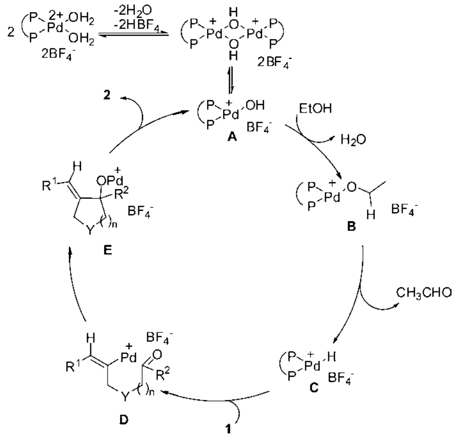
Scheme 2. Asymmetric Reductive Cyclization of **1c**



Scheme 3. Deuterium Labeling Studies

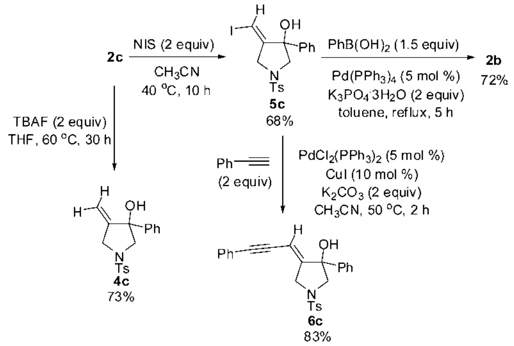


Scheme 4. Proposed Mechanism for the Reductive Cyclization



On the basis of the above results, a possible mechanism of this reductive cyclization reaction is shown in Scheme 4. The Pd hydroxo complex **A** is presumed to be the active catalytic species.[11] The Pd hydroxo complex **A** reacts with ethanol to generate Pd ethoxide complex **B**, which subsequently gives the Pd hydride complex **C** via β-hydride elimination. Hydropalladation to the alkyne of the substrate affords a vinylpalladium intermediate **D** followed by intramolecular addition to the carbonyl group to give the intermediate **E**. The protonolysis of the newly formed intermediate **E** generates the product and the Pd(II) species **A** to complete the catalytic cycle. This proposed mechanism is in accordance with the configuration of the exocyclic double bond of the products and the results of the reaction with deuteriated ethanol.

Scheme 5. Transformations of Product **2c**



Finally, the transformation of the vinylic silane moiety in product **2c** was studied. Treatment of **2c** with TBAF in THF at 60 °C for 30 h gave rise to the desilated product **4c** in 73% yield. The reaction of **2c** with NIS could give **5c** in 68% yield, which could be used for Suzuki or Sonogashira coupling reaction to afford **6c** or **2b**, respectively (Scheme 5).

In conclusion, a cationic Pd(II)-catalyzed intramolecular reductive cyclization of alkyne-tethered ketones or aldehydes using ethanol as the hydrogen source under mild reaction conditions was developed. The reaction is environmentally benign and proceeds efficiently to give synthetically useful hydroxy group substituted N-heterocycles and carbocycles bearing an exocyclic double bond with *E*-configuration. Further studies on the mechanism and an asymmetric version of the reaction are underway in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data of new compounds, copies of NMR spectra, HPLC data of optically active products, and X-ray data of compound **2c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.