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Pd/C–Cu mediated direct and one-pot synthesis of γ-ylidene butenolides

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ABSTRACT

10% Pd/C in combination with CuI, PPh_3, and Et_3N has been identified as an effective catalyst system for the coupling of (*Z*)-3-iodoacrylic acid with terminal alkynes in 1,4-dioxane leading to the one-pot synthesis of γ-ylidene butenolides. The methodology showed remarkable regio- and stereoselectivity as only the five-membered lactone ring products were formed with an exocyclic double bond possessing *Z*-geometry.

The growing requirements of chemical and pharmaceutical industries have prompted synthetic chemists to devote their continuing efforts in the development of more efficient, effective, and safer chemical reactions or methodologies. The heterogeneous catalysis has attracted particular attention for this purpose as the catalyst used can be separated easily and potentially be recovered and recycled several times thereby enhancing the efficiency and effectiveness of the reaction.

The γ-(alkyl/aryl)idene butenolides belonging to the lactone family are common structural frameworks found in many naturally occurring compounds and possess a wide range of pharmacological activities.[1] For example, Freelingyne (**A**, Fig. 1), a sesquiterpene from *Eremophila freelingii*,[1c] or dihydroxerulin (**B**, Fig. 1),[1d] an inhibitor of cholesterol biosynthesis or the carotinoid peridinin[1d] which plays a dominant role in marine photosynthesis or anti-inflammatory lupeol acetate[1e] belongs to this class. Due to our interest in butenolides as potential anti-inflammatory agents[2] we planned to construct a library of diversity based small molecules **C** (Fig. 1) based on γ-(alkyl/aryl)idene butenolide framework for their pharmacological evaluation. We anticipated that depending on the nature of γ-substituent present these simple lactones may show promising pharmacological properties.

Due to their enormous importance in chemical and pharmaceutical research several methods leading to **C** have been reported.[3] However, over the past decade transition metal-mediated cyclization of alkynes possessing a carboxylic acid moiety in close proximity to the triple bond has become a common method for the construction of γ-butenolide structures. For example, lactonization of 4-alkynoic acids (**D**) afforded γ-ylidene butenolide (**E**) following a 5-exo cyclization (Fig. 2). However, in addition to **E** formation of six-membered δ-lactone (**F**) was also observed in these cases as a result of 6-endo cyclization (Fig. 2). A wide range of transition metal based catalysts (e.g., Ag, Hg, Rh, Pd, Zn, Au, etc.) have shown to promote the intramolecular addition of carboxylic acids to alkynes.[4,5] Generally, β-iodopropenoic acid has been used as a key precursor and the synthesis of γ-butenolides via the reaction of β-iodopropenoic acid and terminal alkynes has been carried out in two separate steps, for example, (i) Sonogashira type coupling leading to the 4-alkynoic acid derivatives followed by (ii) cyclization mediated by metal complexes,[6] bases,[7] and halogen.[8] Thus, synthesis of γ-alkylidene butenolides has been reported via the palladium-mediated cross coupling of alkynylzinc with β-haloacrylic acid followed by lactonization catalyzed by Ag_2CO_3.[9] This methodology though involved two-steps, was found to be a superior alternative to the one pot method reported earlier.[10] While these reactions were found to be quite effective the methodology, however, involved the use of relatively expensive palladium catalysts, that is, $(PPh_3)_4Pd$ and $(PPh_3)_2PdCl_2$ that were not recoverable due to their decomposition during the aqueous workup. Recently, γ-alkylidene butenolides and isocoumarins have been synthesized by using Cu(I)-salt under a palladium-free condition.[11] The methodology, however, involved the use of relatively high catalyst loading, that is, 20 mol % of CuI. Over the years our group has

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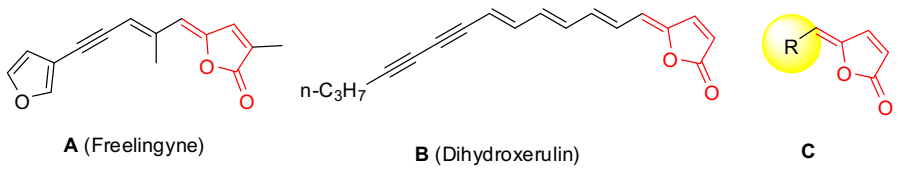


Figure 1. Biologically active γ-alkylidene butenolides (**A** & **B**) and our target compounds **C**.

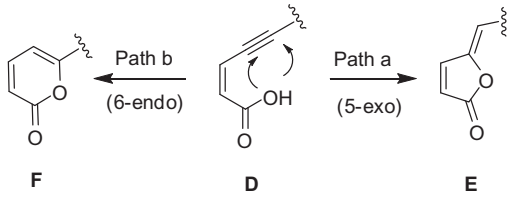
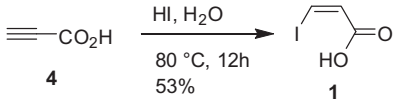


Figure 2. Lactonization of 4-alkynoic acids.

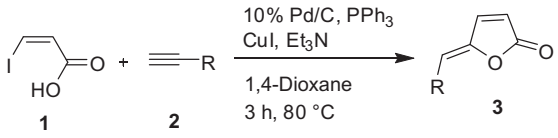


Scheme 2. Preparation of (*Z*)-3-iodoacrylic acid (**1**).

focused on the use of Pd/C as an efficient and effective catalyst for various C–C bond forming reactions either in pure water or other organic solvents.[12] The advantages of Pd/C is that it is stable, easy to handle, and separable from the product. Additionally, the catalyst can be recovered and recycled. Its industrial application in hydrogenation reaction is well documented and being practiced over several decades. All these features prompted us to explore the use of commercially available 10% Pd/C as an alternative catalyst in the direct, one-pot, and regioselective synthesis of γ-ylidene butenolides. Herein we report our initial findings on Pd/C–Cu mediated coupling of terminal alkynes with (*Z*)-3-iodoacrylic acid leading to the practical synthesis of γ-ylidene butenolides (Scheme 1). To the best of our knowledge, such a Pd/C–Cu mediated coupling-cyclization strategy for the synthesis of this class of lactones has not been explored earlier.

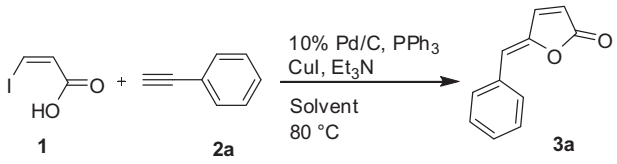
The key starting material, that is, (*Z*)-3-iodoacrylic acid (**1**) required for our synthesis was conveniently prepared[13] via the reaction of propiolic acid (**4**) with HI in water (Scheme 2). Initially, the coupling reaction of (*Z*)-3-iodoacrylic acid (**1**) with phenyl acetylene (**2a**) was examined in the presence of 10% Pd/C (0.026 equiv), PPh_3 (0.20 equiv), CuI (0.05 equiv), and triethylamine (3.0 equiv) in various solvents (Table 1). The (*Z*)-5-benzylidenefuran-2(5*H*)-one (**3c**) was isolated in 84% yield (Table 1, entry 1) when the reaction was performed in 1,4-dioxane for 3 h. The formation of corresponding six-membered lactone was not detected in this case. The increase of reaction time did not improve the product yield further (Table 1, entry 2). To test the recyclability of Pd/C, the catalyst was recovered and reused for additional three runs when the product **3a** was isolated in 75%, 71%, and 67% yields respectively.[14a] The use of other solvents such as MeOH, EtOH, MeCN, and DMF was examined but found to be less effective in terms of product yields (Table 1, entries 3–6). Indeed, the product **3c** was isolated only in 58% yield when the reaction was performed in MeCN even after 10 h (Table 1, entry 5). The yields were marginally improved when MeOH or EtOH was used (Table 1, entries 3 and 4). It is worthy to mention that while we recovered the starting materials mostly in these cases the formation of traces of other regioisomer cannot be ruled out completely in these solvents. However, since the best result was achieved by using 1,4-dioxane as a solvent, all other studies were carried out using 1,4-dioxane. The role of catalyst, co-catalyst, and ligand was also examined. The yield of **3a** was decreased significantly when the reaction was performed in the absence of any one of Pd/C, CuI, and PPh_3 (Table 1, entries 7–9) indicating the key role played by the combined form of these catalysts. We also examined the role of Et_3N in the present coupling-cyclization reaction in the absence of which the reaction did not proceed. All these reactions were performed under a nitrogen atmosphere. An attempt to perform the reaction under air led to the formation of 1,4-diphenylbuta-1,3-diyne as a major product due to the dimerization of **2a** in the presence of aerial oxygen. Overall, the reaction conditions presented in the entry 1 of Table 1 were found to be optimum for the preparation of **3a**.

To expand the scope of the present Pd/C–Cu mediated synthesis of γ-ylidene butenolide, a variety of terminal alkynes (**2**) were re-



Scheme 1. Pd/C–Cu mediated synthesis of γ-ylidene butenolides.

Table 1
Effect of reaction conditions on Pd/C-mediated reaction of (*Z*)-3-iodoacrylic acid (**1a**) with phenyl acetylene (**2a**)[a]



Entry	Solvent	Time (h)	% Yield[b]
1	1,4-Dioxane	3	84
2	1,4-Dioxane	6	85
3	MeOH	6	63[c]
4	EtOH	3	77
5	MeCN	10	58
6	DMF	3	60
7	1,4-Dioxane	3	17[d]
8	1,4-Dioxane	3	36[e]
9	1,4-Dioxane	3	35[f]
10	1,4-Dioxane	3	0[g]

[a] All the reactions were carried out by using **1** (0.89 mmol), **2a** (1.33 mmol), 10% Pd/C (0.023 mmol), PPh_3 (0.092 mmol), CuI (0.046 mmol), and Et_3N (2.67 mmol) in a solvent under a nitrogen atmosphere.
[b] Isolated yields.
[c] The reaction was performed at 60 °C.
[d] The reaction was performed in the absence of CuI.
[e] The reaction was performed in the absence of 10% Pd/C.
[f] The reaction was performed in the absence of PPh_3.
[g] The reaction was performed in the absence of Et_3N.

Table 2
Pd/C-mediated preparation of γ-alkylidene butenolides (Scheme 1)[a]

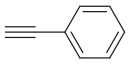
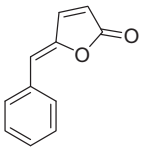
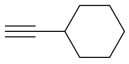
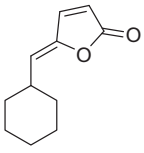
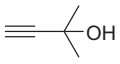
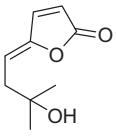
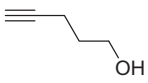
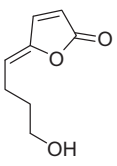
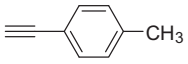
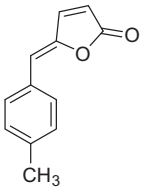
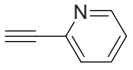
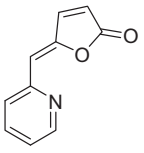
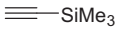
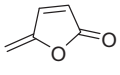
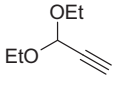
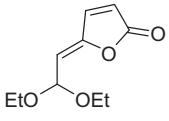
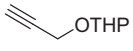
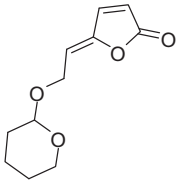
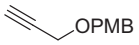
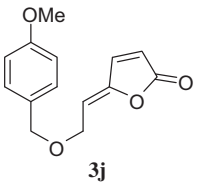
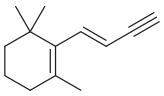
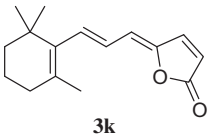
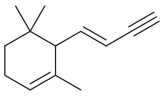
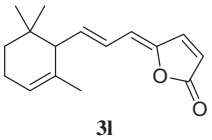
Entry	Substrate (**2**)	Products[b] (**3**)	% Yield[c]
1	 **2a**	 **3a**	72
2	 **2b**	 **3b**	75
3	 **2c**	 **3c**	84
4	 **2d**	 **3d**	80
5	 **2e**	 **3e**	82
6	 **2f**	 **3f**	72
7	 **2g**	 **3g**	15
8	 **2h**	 **3h**	75
9	 **2i**	 **3i**	72

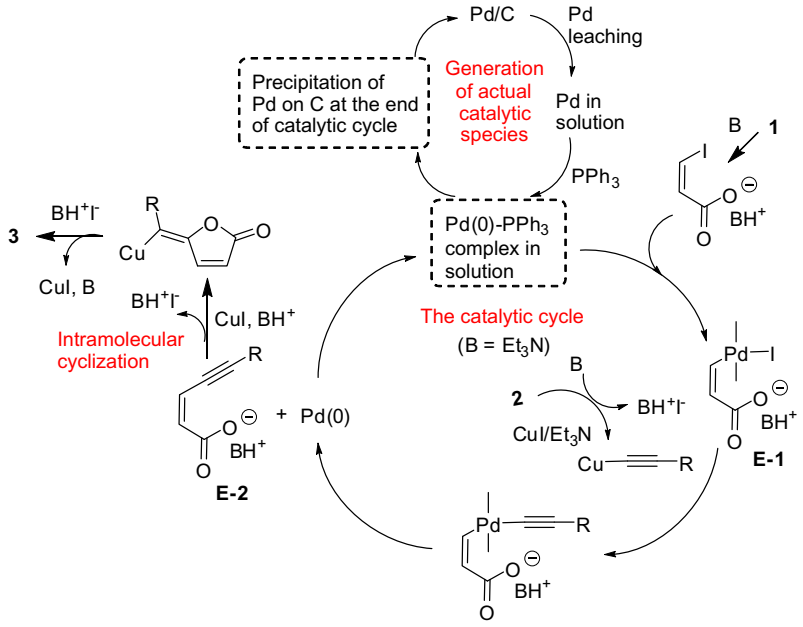
Table 2 (*continued*)

Entry	Substrate (**2**)	Products[b] (**3**)	% Yield[c]
10	 **2j**	 **3j**	70
11	 **2k**	 **3k**	68
12	 **2l**	 **3l**	65

THP = tetrahydro-2*H*-pyran-2-yl; PMB = *p*-methoxybenzyl.
[a] All the reactions were carried out by using **1** (0.89 mmol), **2** (1.33 mmol), 10% Pd/C (0.023 mmol), PPh_3 (0.092 mmol), CuI (0.046 mmol), and Et_3N (2.67 mmol) in 1,4-dioxane (5.0 mL) at 80 °C for 3 h under a nitrogen atmosphere.
[b] Identified by ^1H NMR, IR, mass.
[c] Isolated yield.

acted with **1** under the condition[14b] of entry 1 of Table 1. The results are summarized in Table 2. The presence of aryl (**2a**, **2e**), cycloalkyl (**2b**), hydroxy alkyl (**2c**, **2d**) or their protected form (**2i**, **2j**), heteroaryl (**2f**), and alkenyl moiety (**2k**, **2l**) in the terminal alkynes employed was well tolerated. The use of trimethylsilyl acetylene (**2g**) however afforded 5-methylenefuran-2(5*H*)-one (**3g**) in low yield. Nevertheless, a range of γ-ylidene butenolides (**3**) were synthesized in good yields (except the butenolide **3g**) without formation of the corresponding regioisomeric six-membered lactones. We also examined the coupling-cyclization of (*Z*)-3-bromoacrylic acid[10] with **2a** when the desired product **3a** was isolated in 70% yield after 12 h under the conditions employed. It is worthy to mention that all these reactions were performed using a 1:4:2 ratio of 10% Pd/C, PPh_3, and CuI with a low catalyst loading, that is, 2.6 mol % of 10% Pd/C and 5.2 mol % of CuI for each reaction. Moreover, no significant dimerization of terminal alkynes (i.e., formation of R–≡–≡–R as a result of Glasser coupling) as a side reaction[9] was observed during the present synthesis of **3**. However, the starting material **1** was recovered in some of the cases where the yield of product **3** was not particularly high. The compound **3d** can be converted into the polyene natural product dihydroxerulin (**B**, Fig. 1) via an organocatalytic IBX-mediated dehydrogenation process of simple alcohols to enals as a key step.[15] Though the reaction proceeded well with the alkyl ether **2j**, the use of an arylether, for example, (prop-2-ynyloxy)benzene was not successful as it underwent depropargylation reaction under the conditions employed.[16] Nevertheless, the use of Pd/C–Cu mediated coupling-cyclization strategy in 1,4-dioxane presented here appeared as a useful and faster method for accessing γ-ylidene butenolides. Based on the spectral data[17] and comparing them with that reported in the literature[11] all the compounds synthesized were found to possess *Z*-stereochemistry around the exocyclic double bond. Thus the present approach to γ-ylidene butenolides appeared to be a regio and stereoselective one.

We have demonstrated that combination of 10% Pd/C–CuI–PPh_3 in the presence of Et_3N facilitated the coupling-cyclization of (*Z*)-3-



Scheme 3. Proposed mechanism for the one-pot synthesis of γ-alkylidene butenolides (**3**) under the catalysis of Pd/C–CuI–PPh_3.

iodoacrylic acid with terminal alkynes via C–C bond forming reaction as a key step. A proposed mechanism for the one-pot synthesis of γ-alkylidene butenolides (**3**) under the catalysis of Pd/C–CuI–PPh_3 is shown in Scheme 3. The reaction seemed to proceed via three key steps, that is, (a) the generation of actual catalytic species, (b) alkynylation of iodo compound **1** and (c) intramolecular cyclization of the resulting enynoic acid under regio- and stereocontrol conditions. The alkynylation step proceeds via generation of an active Pd(0) species in situ that produces the organo-Pd(II) species **E-1** via oxidative addition with **1**. The active Pd(0) species is generated via a Pd leaching process[18] into the solution [from the minor portion of the bound palladium (Pd/C)] followed by interactions with the phosphine ligands. The dissolved Pd(0)–PPh_3 complex then catalyzes the C–C bond forming reaction in solution via (i) trans organometallation with copper acetylide generated in situ from CuI and terminal alkyne **2** followed by (ii) reductive elimination of Pd(0) to afford the enynoic acid **E-2**. The acid **E-2** thus formed subsequently undergoes Cu-mediated 5-*exo*-*dig* ring closure in an intramolecular fashion to give the five-membered ring product (**3**). It appears that the catalytic cycle works in solution rather than on the surface and at the end of the reaction re-precipitation of Pd occurs on the surface of the charcoal.

In order to gain further evidence in support to this reaction mechanism (*Z*)-5-phenylpent-2-en-4-ynoic acid prepared according to a known method[8a] was treated with CuI in the presence of Et_3N in 1,4-dioxane at 80 °C for 3 h when the corresponding γ-alkylidene butenolide **3a** was isolated in 61% yield. This clearly suggested that the intramolecular cyclization of **E-2** via C–O bond formation was generally aided by the Cu-salt present in the reaction mixture.[19] While the preference of exclusive 5-*exo*-*dig* ring closure of **E-2** over the 6-*endo*-*dig* pathway was not clearly understood perhaps the ease of formation of the five-membered lactone ring over the six-membered one was the reason for this observation under the reaction conditions employed.

In conclusion, the combination of 10% Pd/C–CuI–PPh_3 in the presence of Et_3N allowed coupling of (*Z*)-3-iodoacrylic acid with terminal alkynes in 1,4-dioxane leading to the one-pot synthesis of γ-ylidene butenolides. The present coupling-cyclization based methodology proceeded via a C–C bond forming reaction as a key step and afforded a range of desired products under mild conditions. The merits and demerits of the methodology are presented. The methodology showed remarkable regio- and stereoselectivity as only the five-membered lactone ring products were formed with an exocyclic double bond possessing (*Z*-geometry). Due to its operational simplicity, relatively low catalyst loading, and the use of inexpensive and stable Pd/C the methodology has potential to become a useful alternative to the existing methods for accessing diversity based γ-alkylidene butenolides.

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References and notes

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14. (a) The reaction was performed in a bigger scale using ~100 mg of 10% Pd/C (0.092 mmol), PPh_3 (0.37 mmol), CuI (0.184 mmol), Et_3N (10.68 mmol), compound **1a** (3.56 mmol), and acetylenic compound **2a** (5.32 mmol) in 1,4-dioxane (20.0 mL). After stirring at 80 °C for 3 h under nitrogen the mixture was cooled to room temperature. The Pd/C was filtered off and washed with water (2 × 10 mL), acetone (2 × 10 mL), and EtOAc (2 × 10 mL). Then the catalyst was collected, dried at 100 °C in an oven, and reused for the next run. The co-catalyst CuI along with PPh_3 was added in every repeated run. (b) *General method for the preparation of* ***3****:* A mixture of compound **1** (0.89 mmol), 10% Pd/C (0.023 mmol), PPh_3 (0.092 mmol), CuI (0.046 mmol), and Et_3N (2.67 mmol) in 1,4-dioxane (5.0 mL) was stirred at 25 °C for 30 min under nitrogen. The acetylenic compound **2** (1.33 mmol) was added slowly with stirring. The mixture was then stirred at 80 °C for 3 h, cooled to room temperature, diluted with EtOAc (30 mL), and filtered through celite. The filtrate was collected and concentrated. The residue was purified by column chromatography (2–15% EtOAc/hexane) to afford the desired product.
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17. *Spectral data of selected compounds: compound* ***3a****:* pale yellow solid; mp 87–89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.02 (s, 1H), 6.20 (d, J = 6 Hz, 1H), 7.31–7.48 (m, 5H), 7.78 (d, J = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 114.2, 118.0, 128.7, 129.2, 130.7, 132.8, 145.1, 148.3, 170.1; IR (KBr): 1787, 1762, 1550 cm^{-1}; MS (ESI): m/z ([M+H]$^+$): 173. *Compound* ***3d****:* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.70–1.73 (m, 2H), 2.30 (br, 1H), 2.44–2.46 (m, 2H), 3.61 (t, J = 6.5 Hz, 2H), 5.32 (t, J = 8.0 Hz, 1H), 6.10 (d, J = 5.5 Hz, 1H), 7.32 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.7, 31.5, 61.6, 116.7, 118.8, 143.5, 149.7, 170.0; MS (ESI): m/z ([M+H]$^+$): 154.9. *Compound* ***3f****:* ash colored solid; mp 82–84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.32 (dd, J = 5.5 and 1.7 Hz, 1H), 6.56 (br d, J = 1.2 Hz, 1H), 7.15 (dd, J = 7.6 and 4.5 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.66 (td, J = 7.7 and 1.8 Hz, 1H), 8.60 (br d, J = 4.5 Hz, 1H), 8.78 (dd, J = 5.5 and 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 113.2, 122.1, 123.1, 126.3, 132.5, 137.0, 144.1, 150.3, 153.2, 169.6; IR (KBr): 1787, 1763, 1584, 1550 cm^{-1}; MS (ESI): m/z ([M+H]$^+$): 174. *Compound* ***3h****:* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (t, J = 7.0 Hz, 6H), 3.52–3.61 (m, 2H), 3.66–3.75 (m, 2H), 5.34 (d, J = 7.8 Hz, 1H), 5.47 (d, J = 7.8 Hz, 1H), 5.26 (dd, J = 5.4 and 0.7 Hz, 1H), 7.37 (d, J = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.5, 62.7, 96.8, 112.1, 121.5, 144.0, 150.1, 169.2; MS (ESI): m/z ([M+H]$^+$): 198.9.
18. The leaching of Pd in a Pd/C-mediated coupling reaction has been investigated and confirmed earlier, see: Chen, J.-S.; Vasiliev, A. N.; Panarello, A. P.; Khinast, J. G. *Appl. Catal. A: Gen.* **2007**, *325*, 76; see also Ref. 16. Additionally, in the case of reaction of **1a** with **2a** when Pd/C–CuI–PPh_3 was hot filtered, after 20% conversion, the filtrate continued to react, indicating that some of the palladium was leaching from the surface and catalyzing the reaction. We thank one of the reviewers for his suggestion to perform this hot filtration test which is known to be a strong test for assessing the presence of soluble active palladium in the filtrate.
19. For a similar Ag-catalyzed cyclization, see: (a) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1995**, *41*, 2587; While cyclization of (*Z*)-5-phenylpent-2-en-4-ynoic acid has been reported in the presence of pyridine the reaction however required higher temperature and longer reaction time (13 h), see: (b) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517.