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Synergistic Effect of Palladium and Copper Catalysts: Catalytic Cyclizative Dimerization of *ortho*-(1-Alkynyl)benzamides Leading to Axially Chiral 1,3-Butadienes

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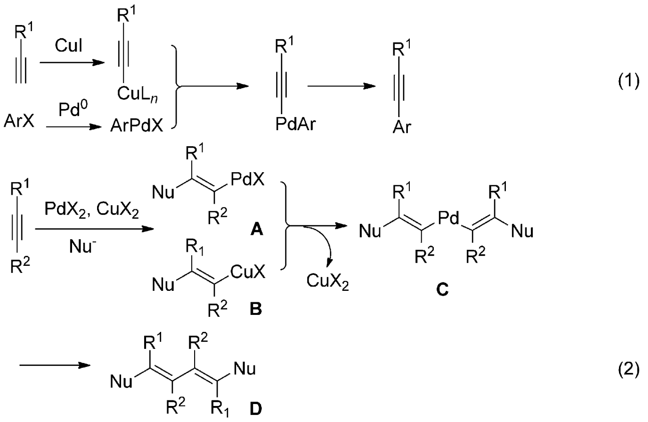
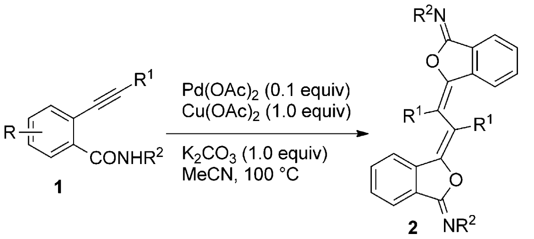
The synergistic effect of two metals in catalytic transformations[1] is well known and is the key to the success of the Sonogashira reaction (reaction (1) in Scheme 1)[2] and of the Wacker oxidation.[3] In connection with our ongoing project on the development of Pd- and Cu-catalyzed domino[4] and multicomponent reactions,[5] we were interested in developing a novel dimerization strategy by combining the use of Pd and Cu catalysts. The underline principle is shown in reaction (2) in Scheme 1. We hypothesized that the introduction of both Pd^{II} and Cu^{II} salts into a solution of alkyne in the presence of a suitable nucleophile could afford concurrently both the vinylpalladium (**A**) and the vinylcopper (**B**) species. While both of them could further evolve to products independently, we thought that transmetalation between **A** and **B** could be kinetically competent relative to other possible pathways to afford divinylpalladium intermediate **C**, which upon reductive elimination would provide the 1,3-diene.[6–8] The palladium-catalyzed coupling of vinyl cuprate with vinyl halide and the CuI-accelerated Stille cross-coupling discovered by Alexakis[9] and Liebeskind,[10] respectively, provided the foundation of our working hypothesis. The development of such a dimerization process is of interest as a number of dimeric natural products having an axially chiral 1,3-diene unit exist in nature.[11] The propensity of *o*-(1-alkynyl)benzamides **1** to undergo Lewis acid or metal-catalyzed cyclization made them ideal candidates to evaluate the feasibility of our concept.[12] We report herein that the combined use of $Pd(OAc)_2$ and $Cu(OAc)_2$ indeed changed profoundly the reaction outcome. The synergistic effect of these two metals led to the formation of the till now unknown axially chiral dimeric imino benzoisofurans **2** from *o*-(1-alkynyl)benzamides **1** by way of a cyclizative dimerization process (Scheme 2).



Scheme 1. Hypothesized synergistic effect of palladium and copper salts in catalytic transformations.



Scheme 2. Cyclizative dimerization of *o*-(1-alkynyl)benzamides leading to axially chiral bis-iminobenzoisofurans.

Keeping in mind the synergistic effect of the two metals, the conditions for the cyclizative dimerization was surveyed using *N*-benzyl-2-(phenylethynyl)benzamide **1a** as a test substrate. After having varied the Pd and the Cu sources, the bases, and the solvents (for details, see the Supporting Information), the optimum conditions found consisted of performing the reaction in MeCN under air atmosphere at 100 °C for 2 h in the presence of $Pd(OAc)_2$ (0.1 equiv), $Cu(OAc)_2$ (1.0 equiv), and K_2CO_3 (1.0 equiv). Under these conditions, cyclizative dimerization took place smoothly to afford the dimer **2a** with an interesting 1,3-diene unit in 72 % isolated yield as a single stereoisomer. The diene geometry was assigned to be *E*,*E*, while that of imine *Z* by X-ray diffraction analysis (Figure 2 and the Supporting Information). It is worth noting that the reaction worked in the presence of a catalytic amount of $Cu(OAc)_2$ (0.2 equiv) under otherwise identical conditions to provide **2a** albeit with a slightly lower isolated yield (60 %).

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The synergistic effect of Pd and Cu is evidenced from the results of our control experiments. As it is shown in Table 1, monomeric isoindolinone **3** (Figure 1) was isolated as the only product in 92 % yield in the presence of K_2CO_3 alone (Table 1, entry 1).[13] Treatment of **1a** with K_2CO_3/$Cu(OAc)_2$ or with K_2CO_3/$Pd(OAc)_2$ afforded **2a** in less than 10 % yield together with isoindolinone **3** as a major product (Table 1, entries 2 and 3).[14] On the other hand, using $Cu(OAc)_2$ (1.0 equiv) or $Pd(OAc)_2$ (0.1 equiv) alone in the absence of K_2CO_3 provided iminoisocoumarins **4** as a major product resulting from the 6-*endo-dig* cyclization with amide oxygen as nucleophile (Table 1, entries 4 and 5).[15] Only when both $Cu(OAc)_2$ and $Pd(OAc)_2$ were introduced together with K_2CO_3, the cyclizative dimerization took place as a major pathway to afford diene **2a** (Table 1, entries 6 and 7). When benzoquinone instead of $Cu(OAc)_2$ was used as oxidant under otherwise identical conditions, the dimer **2a** was isolated in only 10 % yield together with 64 % yield of isoindolinone **3** (Table 1, entry 8). It is noteworthy that the tandem catalytic system not only allowed the occurrence of the dimerization pathway, but also diverted the cyclization mode. In fact, under the optimized conditions, the amide oxygen instead of the amide nitrogen was implicated in the 5-*exo-dig* cyclization leading to iminobenzoisofuran subunit at the expense of the isoindolinone and iminoisocoumarin. This cyclization mode has been rarely reported with *o*-(1-alkynyl)benzamides[16] and only few alternative methods existed in the literature for the synthesis of iminobenzoisofuran.[17]

Table 1. Control experiments.[a]

Entry	$Pd(OAc)_2$ [equiv]	$Cu(OAc)_2$ [equiv]	K_2CO_3 [equiv]	Yield **2a** [%]
1	–	–	1.0	–[b]
2	–	1.0	1.0	< 10[c]
3	0.1	–	1.0	< 10[d]
4	–	1.0	–	12[e]
5	0.1	–	–	11[f]
6	0.2	1.0	–	48
7	0.1	1.0	1.0	72
8	0.1	–[g]	1.0	10[h]

[a] Reaction conditions: **1a** (0.1 mmol) in CH_3CN (2.0 mL) was heated at 100 °C under air atmosphere for 2 h. [b] **3** was isolated in 92 % yield. [c] **3** was isolated in 53 % yield. [d] **3** was isolated in 63 % yield. [e] **4** was isolated in 43 % yield. [f] **4** was isolated in 35 % yield. [g] 1.0 equiv of benzoquinone was used instead of $Cu(OAc)_2$. [h] **3** was isolated in 64 % yield.

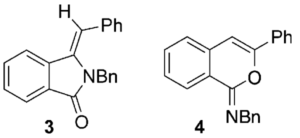
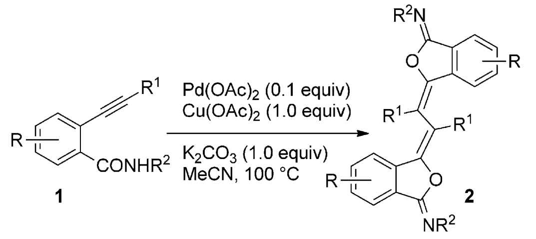


Figure 1. Isoindolinone (**3**) and imino-isocoumarin (**4**) formed in initial survey of reaction conditions.

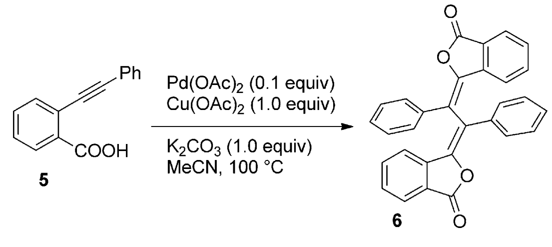
With optimum conditions in hand, the scope of this cyclizative dimerization was evaluated (Table 2). A variety of substituents (R, R^1, and R^2) whether electron-donating or electron-withdrawing in *o*-(1-alkynyl)benzamides **1** were tolerated. As expected, the chlorine atom was survived under these reaction conditions providing therefore a handle for further functionalization. However, incorporation of a methyl group at the C3 position of the benzamide **1** inhibited the cyclization completely presumably due to the steric hindrance (Table 2, entry 13). Finally, while *o*-(1-alkynyl)benzoic ester was inactive towards the cyclization under our conditions,[18] the *o*-(1-alkynyl)benzoic acid **5** underwent the cyclizative dimerization smoothly to furnish the dimer **6** in 52 % yield (Scheme 3).[19] The structure of **6** was determined by X-ray analysis (see the Supporting Information). We were also able to convert the bis-iminobenzoisofuran **2a** into bisbenzolactone **6** under acidic conditions (1N HCl), thus confirming the dimeric nature and the *E*,*E*-stereochemistry of the 1,3-diene unit of compound **2a**.

Table 2. Substrate scope.[a]



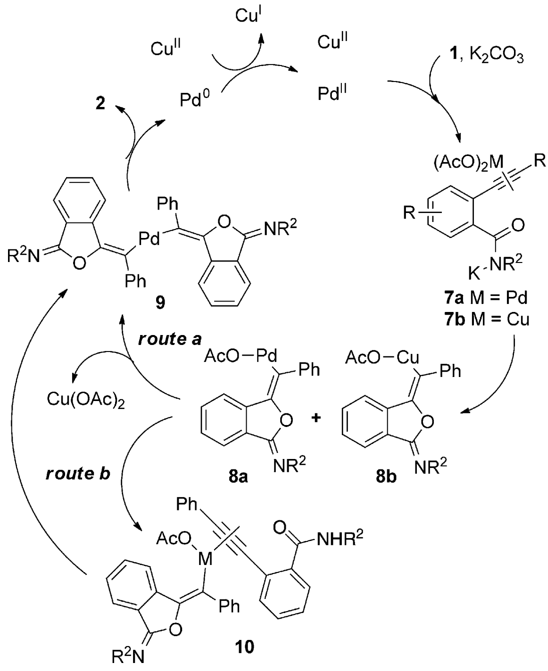
Entry	1	R^1	R^2	R	Yield [%][b]
1	**1a**	Ph	Bn	H	72
2	**1b**	4-MeC_6H_5	Ph	H	79
3	**1c**	Ph	Ph	H	65
4	**1d**	Ph	4-MeC_6H_5	H	76
5	**1e**	Ph	4-ClC_6H_5	H	55
6	**1f**	Ph	3-ClC_6H_5	H	42
7	**1g**	Ph	4-$OMeC_6H_5$	H	70
8	**1h**	4-$OMeC_6H_5$	4-$OMeC_6H_5$	H	46
9	**1i**	4-MeC_6H_5	4-$OMeC_6H_5$	H	61
10	**1j**	4-FC_6H_5	4-$OMeC_6H_5$	H	72
11	**1k**	4-FC_6H_5	4-$OMeC_6H_5$	6-Me	52
12	**1l**	4-FC_6H_5	4-$OMeC_6H_5$	4-OMe	52
13	**1o**	Ph	Ph	3-Me	–[c]

[a] Reaction conditions: A mixture of **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol, 10 mol %), $Cu(OAc)_2$ (0.1 mmol, 1.0 equiv), and K_2CO_3 (0.1 mmol, 1.0 equiv) in CH_3CN (2.0 mL) was heated at 100 °C (sealed tube, air atmosphere) for 2 h. [b] Yield of isolated product. [c] No corresponding dimer was isolated.



Scheme 3. Cyclizative dimerization of *o*-(1-alkynyl)benzoic acid **5**.

A plausible reaction scenario that could account for the formation of cyclic dimer is illustrated in Scheme 4. It is known that both nucleopalladation and nucleocupration of **1a** can take place under appropriate conditions in line with earlier reports.[12–15] and our own observations (Table 1). We therefore hypothesized that under our reaction conditions, both oxypalladation and oxycupration could occur concurrently to provide vinylpalladium (**8a**) and vinylcopper (**8b**) intermediates, via alkyne–metal complexes **7a** and **7b**, respectively. While disproportionation of **8a** could provide bis-vinylpalladium species **9**, it was considered as a thermodynamically unfavorable process.[20] On the other hand, transmetalation between **8a** and **8b** should be kinetically more viable to afford **9**, which upon reductive elimination would afford the cyclizative dimer **2** and Pd^0 (***route a*** in Scheme 4). Oxidation of Pd^0 by Cu^{II} would regenerate Pd^{II}, therefore closing the catalytic cycle. According to this mechanism, Cu^{II} has two distinct roles: as catalyst participating in the processes that form C–O and C–C bonds and as oxidant to regenerate the Pd^{II} species.[21]



Scheme 4. Plausible reaction pathways.

An alternative pathway from **8a** to **9** would involve the coordination of vinylpalladium (**8a**) to the alkyne function of the remaining starting material followed by a second oxypalladation via intermediate **10** (***route b*** in Scheme 4). To gain mechanistic information, the following control experiments were carried out. Cyclization of **1a** in the presence of an excess of dimethyl acetylenedicarboxylate (DMAD) or 1,2-diphenylacetylene under otherwise identical conditions provided cleanly **2a** in a yield comparable to the standard conditions. If ***route b*** was the major reaction pathway, the competitive coordination of **8a** to these additional alkynes would lead to the formation of by-products, hence side reactions should be expected. Indeed, Pd-catalyzed cyclization of alkynamides followed by trapping of the resulting vinylpalladium by an external double bond is known.[22] However, detailed studies will be required to determine the exact mechanism and the role of $Cu(OAc)_2$ in this reaction. Nonetheless, the spectacular modification of the reaction pathway catalyzed by the Pd^{II}/Cu^{II} couple versus that catalyzed by a single metal (Pd, or Cu) is truly remarkable. With bulky substituents, 1,3-butadienes show properties of axial chirality due to the hindered rotation around the central C2–C3 σ bond.[23] We obtained a single crystal of **2j** suitable for X-ray diffraction analysis (Figure 2). The crystal structure revealed that the torsion angle between the two planes of the double bonds was 75.08° and two enantiomers were seen in the crystal. Separation of the two enantiomers by SFC and HPLC with different enantio-discriminating columns turned out to be challenging presumably due to the low energy barrier of the racemization. After a number of trials, the two enantiomers of **2a** were finally separated using analytical Chiralcel OJ-RH column (eluent: acetonitrile/$H_2O = 4{:}1$, see the Supporting Information) indicating the existence of the atropisomerism for this series of compounds.

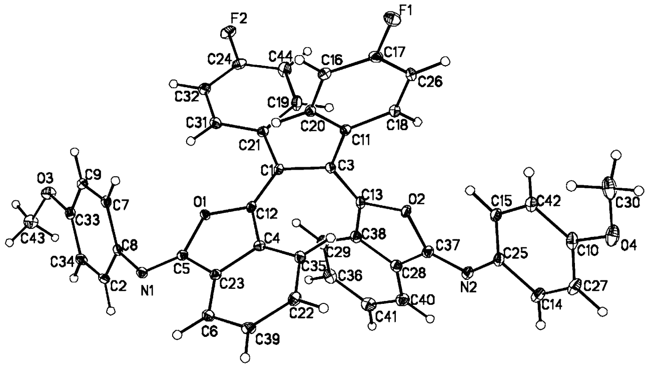


Figure 2. X-ray structure of compound **2j**. Thermal ellipsoids are drawn at 30% probability.

In summary, we developed a $Pd(OAc)_2/Cu(OAc)_2$ co-catalyzed cyclizative dimerization of *o*-(1-alkynyl)benzamides leading to axially chiral *E*,*E*-1,3-diene. The concurrent formation of vinylpalladium and vinylcopper species followed by transmetalation is key to our reaction design. Experimental evidences have been gathered demonstrating that $Cu(OAc)_2$ was not simply acting as an oxidant. It might also participate in the process forming C–C and C–O bonds in concert with the Pd catalyst.[24] Further studies on the asymmetric synthesis of axially chiral *E*,*E*-1,3-diene of type **2** are ongoing.

Experimental Section

General procedure: A mixture of *N*-benzyl-2-(phenylethynyl)benzamide **1a** (31.1 mg, 0.1 mmol), $Pd(OAc)_2$ (2.24 mg, 0.1 equiv), $Cu(OAc)_2$

(18.1 mg, 1 equiv), and K_2CO_3 (13.8 mg, 1 equiv) in CH_3CN (2.0 mL) was heated at 100 °C for 2 h. The reaction mixture was diluted with water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to give the product **2a** (22.3 mg, 72 %). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.91–7.82$ (m, 6H), 7.57–7.48 (m, 6H), 7.44–7.29 (m, 12H), 7.29–7.22 (m, 4H), 5.00 ppm (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 155.5, 148.6, 140.3, 136.5, 135.7, 132.4, 130.6, 130.0, 129.5, 128.7, 128.6, 128.1, 128.1, 128.0, 127.0, 123.6, 123.3, 114.0, 52.4 ppm; FTIR: $\tilde{\nu} = 2987$, 1770, 1697, 1616, 1494, 1247, 1094, 1022, 989, 761, 729, 687 cm^{-1}; HRMS (ESI): m/z calcd for $C_{44}H_{33}N_2O_2$: 621.2542, $[M+H]^+$; found: 621.2538.

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Keywords: atropisomerism · copper · palladium · synergistic effects · tandem catalysis

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