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Counterion Effects Enable Divergent Pd-Catalyzed Carbonylative Cyclization of Amide-Tethered o-Alkynylphenols

Aleksandr Voronov[1] | Filippo Sacchelli[1] | Diego Olivieri[2] | Ana Maria Constantin[1] | Paolo Pio Mazzeo[3] | Raffaella Mancuso[4] | Bartolo Gabriele[4] | Carla Carfagna[5] | Riccardo Tarroni[5] | Luca Capaldo[1,6] | Valerio Morlacci[1] | Nicola Della Ca'[1,6]

[1]SynCat Lab, Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma (PR), Italy | [2]Department of Biomolecular Sciences, University of Urbino "Carlo Bo" (Campus Scientifico E. Mattei), Urbino, Italy | [3]Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma (PR), Italy | [4]Laboratory of Industrial and Synthetic Organic Chemistry (LISOC), Department of Chemistry and Chemical Technologies, University of Calabria, Arcavacata di Rende (CS), Italy | [5]Department of Industrial Chemistry "Toso Montanari", University of Bologna, Bologna, Italy | [6]CIRCC (Interuniversity Consortium Chemical Reactivity and Catalysis), Bari, Italy

Correspondence: Valerio Morlacci (valerio.morlacci@unipr.it) | Nicola Della Ca' (nicola.dellaca@unipr.it)

Received: 17 March 2026 | **Revised:** 22 April 2026 | **Accepted:** 27 April 2026

ABSTRACT

The catalytic carbonylation of alkynes is a powerful route to heteroaromatic scaffolds, yet achieving regioselectivity remains challenging. Herein, we report a divergent carbonylative cyclization of 2-alkynylphenol derivatives that affords either coumarins (6-*endo-dig*) or 2-coumaranones (5-*exo-dig*) by tuning the palladium-based catalytic system. $Pd(OAc)_2$ in combination with TFA favored coumarins formation with high yield and selectivity (>15:1), whereas electron-deficient species such as $Pd(MeCN)_4(BF_4)_2$ promoted 2-coumaranones with up to 84% yield and >25:1 selectivity. While many approaches exploit ligand design to steer selectivity, these results highlight counterion effects as a powerful tool to control regioselectivity in palladium-catalyzed carbonylative cyclization, expanding the utility of alkyne carbonylation for the synthesis of biologically relevant heterocycles.

1 | Introduction

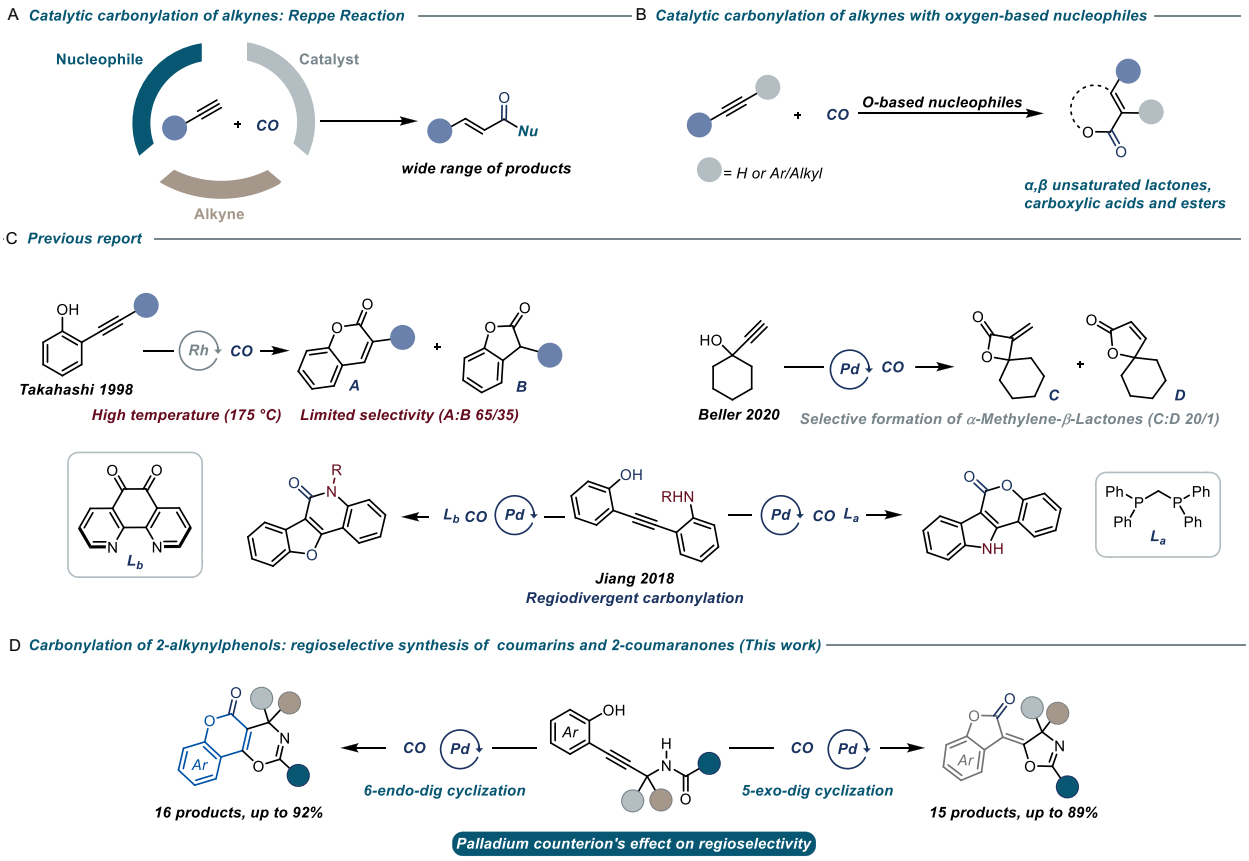
Alkynes have proved to be strategic building blocks for the synthesis of biologically active molecules [1, 2]. As an example, the catalytic carbonylation of alkynes [3] has developed into a powerful and flexible methodology, with the reaction outcome dictated by the catalyst, the operative manifold (i.e., oxidative, additive, etc.), and the nucleophile involved (Scheme 1A) [4]. Notably, oxygen-based nucleophiles provide efficient access to a wide array of α,β-unsaturated lactones, carboxylic acids, and esters (Scheme 1B) [5–11]. Within this framework, coumarin- and 2-coumaranone-derived scaffolds can be readily synthesized. Coumarins represent ubiquitous structural motifs found in a wide variety of natural products [12] as well as in bioactive compounds exhibiting anticoagulant, antibiotic, and anticancer properties [13–16]. By contrast, 2-coumaranones featuring an *exo*-cyclic double bond in the C-*3* position are less common. Nevertheless, some examples are found in natural and biologically active molecules that display notable anti-inflammatory and antibiotic activities [17–20].

Given the remarkable significance and practical relevance of these heterocyclic scaffolds, considerable efforts have been devoted to developing efficient strategies for their synthesis. In 1998, Takahashi and coworkers reported the rhodium-catalyzed carbonylative cyclization of alkynylphenols, providing access to coumarins and 2-coumaranones [21]. Although this pioneering contribution opened an important avenue in the field, the results

Aleksandr Voronov and Filippo Sacchelli contributed equally to this work.

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SCHEME 1 | (A) Catalytic carbonylation reaction of alkynes with CO; (B) carbonylation of alkynes using *O*-based nucleophiles; (C) previous reports; and (D) regioselective carbonylation of 2-alkynylphenols for the preparation of coumarin and 2-coumaranone derivatives (This work).

were still limited, particularly in terms of regioselectivity between the 6-*endo* and 5-*exo* cyclization pathways (Scheme 1C). Advances in controlling regioselectivity were later achieved in palladium-catalyzed cyclizations. In 2006, Uchiyama and coworkers reported a seminal study demonstrating that the selective formation of either the 6-*endo* or the 5-*exo* product in the intramolecular cyclization of carboxylic acids could be finely tuned by employing acidic or basic conditions [22]. Building on this concept, Jiang and coworkers recently developed a regiodivergent strategy for the synthesis of indolo[3,2-*c*]coumarins and benzofuro[3,2-*c*]quinolinones [23]. In this case, the regioselectivity was controlled by the choice of ligand: electron-deficient ligands promoted *O*-nucleophilic attack and subsequent *N*-carbonylative cyclization, whereas sterically hindered, electron-rich ligands favored the alternative pathway (Scheme 1C). Similarly, Beller and coworkers reported the selective formation of α-methylene-β-lactones [24] using a sterically demanding *N*-arylated imidazole-based phosphine ligand (Scheme 1C) [25].

In this work, we report a divergent carbonylative reactivity of 2-alkynylphenol substrates, enabling access to isomeric coumarins and 2-coumaranones, featuring *endo*- and *exo*-double bonds, respectively (Scheme 1D). Rather than relying on ligand selection to control the regioselectivity of the process [26, 27], this study examines the role of the palladium counterion and reveals its decisive influence in directing the regioselectivity of the final products [28–33]. The development of two complementary protocols, in which the outcome of the carbonylative cyclization domino reaction is dictated solely by the choice of catalyst counterion and its intrinsics properties, underscores the potential of this strategy to broaden the scope and versatility of carbonylative methodologies.

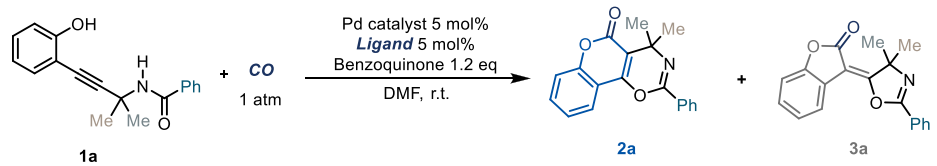
2 | Results and Discussion

Drawing on our recent studies [34–36], we selected 2-alkynylphenols bearing an *ortho*-propargylamide as model substrates to promote an intramolecular cyclization cascade with carbon monoxide. In contrast to the efficient transformations observed with 2-alkynylanilines [34], the reaction of phenol derivative **1a** under previously optimized conditions afforded only a low-yielding mixture of 6-*endo-dig* and 5-*exo-dig* products (**2a** and **3a**), with poor selectivity. Guided by precedents on phenolic hydroxyl carbonylation [37–43], we initiated a new optimization study employing diverse palladium catalysts at room temperature under 1 atm of CO in the presence of benzoquinone (BQ) as oxidant (Table 1, for the full optimization study see supporting information Table S1).

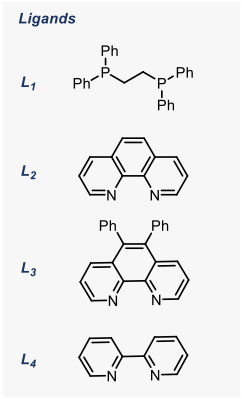
When palladium acetate was employed as a catalyst together with bis-1,2-(diphenylphosphino)ethane (dppe, $\boldsymbol{L_1}$) as ligand, the product **2a** was obtained in 65% yield, while the 5-*exo-dig* isomer was formed only in 10% yield (Table 1, **Entry 4**). In contrast, replacing the palladium counterion with halide completely

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TABLE 1 | Optimization study for the carbonylative double cyclization of **1a**.



Entry	Pd catalyst	Ligand	Time (h)	Conv. **1a** (%)[a]	Yield **2a** (%)[a]	Yield **3a** (%)[a]
1	$PdCl_2$	L_1	24	-	n.d.	
2	$Pd(OPiv)_2$	L_1	24	<10	n.d.	
3	$Pd(TFA)_2$	L_1	24	<10	n.d.	9
4	$Pd(OAc)_2$	L_1	8	100	65	10
5[c]	$Pd(OAc)_2$	L_1	6	100	73	19
6[d]	$Pd(OAc)_2$	L_1	6	100	77	19
7[e]	$Pd(OAc)_2$	L_1	6	100	80 (78)[b]	16
8[e]	$Pd(OAc)_2$	L_2	2	100	91 (89)[b]	6
9	$Pd(MeCN)_2Cl_2$	L_2	2	-	n.d.	
10	$Pd(MeCN)_4(BF_4)_2$	L_2	2	100	8	65
11	$Pd(MeCN)_4(BF_4)_2$	L_3	2	100	4	68
12	$Pd(MeCN)_4(BF_4)_2$	L_4	2	100	5	84[b]



Note: **Reaction conditions**: **1a** (0.2 mmol, 1 equiv.), **palladium salt** (0.01 mmol, 5.0 mol%), **ligand** (0.01 mmol, 5.0 mol%), **1,4-benzoquinone** (0.24 mmol, 1.2 equiv.) in DMF (1 mL) with CO balloon at r.t.
[a]NMR Yield.
[b]Yield of the isolated compound.
[c]With TFA (5.0 mol%).
[d]$Pd(OAc)_2$ 2.5 mol% + $Pd(TFA)_2$ 2.5 mol%.
[e]With TFA (2.5 mol%). For additional control experiments see supporting information.

suppressed the reactivity of the catalytic system (Table 1, **Entry 1**), and the use of either pivalate or triflate salts afforded less than 10% conversion of the starting material (Table 1, **Entries 2–3**). Consistent with prior mechanistic studies showing that mixed salts such as Pd(OTf)(OAc) or Pd(TFA)(OAc) exhibit distinct catalytic activity [44–46], the addition of trifluoroacetic acid (5.0 mol%, equimolar to Pd) significantly accelerated the reaction and improved selectivity toward **2a**, affording a **2a**/**3a** ratio of 3.8 (Table 1, **Entry 5**). To exclude the possibility that this effect simply arose from pH variations in the medium, we performed a control experiment with a 1:1 mixture of $Pd(OAc)_2$ and $Pd(TFA)_2$ (5 mol%), which gave comparable results (Table 1, **Entry 6**). Lowering the TFA loading to 2.5 mol% further improved the outcome, increasing the selectivity toward the *6-endo-dig* product and affording **2a** in 78% isolated yield (Table 1, **Entry 7**). Finally, further optimization identified 1,10-phenanthroline (L_2) as the most effective ligand, enabling the selective formation of **2a**, with only small amounts of **3a** detected, in 89% isolated yield after 2 h (Table 1, **Entry 8**).

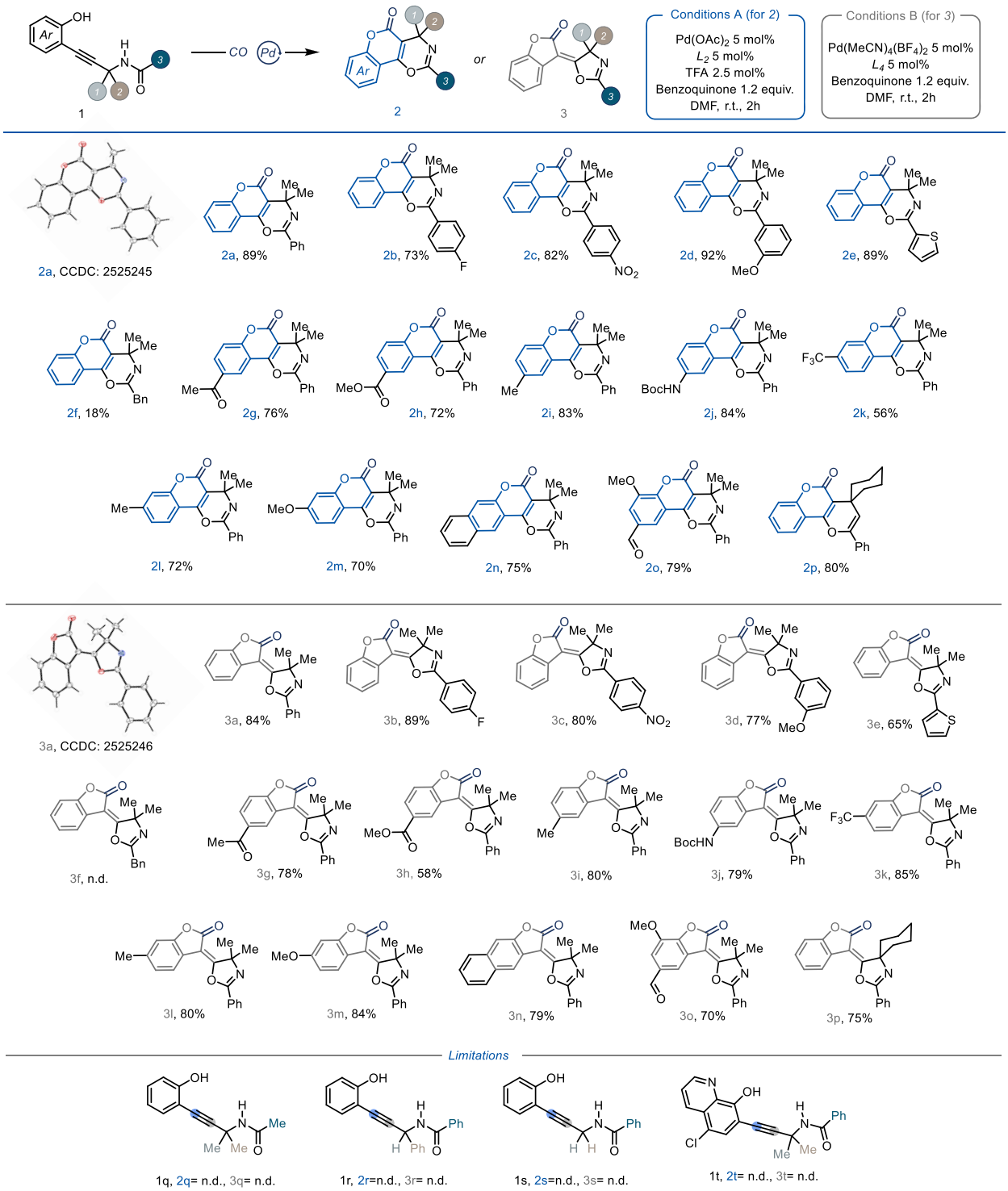
Having established optimal conditions for the selective synthesis of **2a**, we next investigated whether the regioselectivity of the methodology could be reversed to favor the formation of the corresponding *5-exo-dig* products. The use of $Pd(MeCN)_2Cl_2$ as the catalyst (Table 1, **Entry 9**) did not afford the desired products. In contrast, $Pd(MeCN)_4(BF_4)_2$ proved effective, delivering product **3a** in 65% yield with an 8:1 regioselectivity over **2a** (Table 1, **Entry 10**).

Subsequent ligand screening led to a further improvement in efficiency. In the presence of ligand L_3, product **3a** was obtained in 68% yield (Table 1, **Entry 11**), while replacement with 2,2′-bipyridine (bpy, L_4) further increased the yield to 84% (Table 1, **Entry 12**).

With the selective optimized conditions in hand, we next evaluated the scope and functional group tolerance of the transformation of phenol derivatives **1** into the corresponding **2** and **3** products. The results are summarized in Scheme 2.

Reactions bearing either electron-withdrawing (**1b–c**) or electron-donating (**1d**) substituents on the benzene ring of the amide moiety (R_3) were well tolerated under both cyclization conditions, affording the desired products in good to excellent yields. Introduction of a thiophene ring at the same position was also effective, providing 89% yield for the *6-endo-dig* cyclization and 65% for the *5-exo-dig* pathway. By contrast, benzylic substitution at R_3 led to poor reactivity, delivering product **2f** in only 18% yield, while the corresponding product **3f** was not observed. Substituent effects on the phenolic aromatic ring were further investigated, resulting in moderate to high yields depending on the electronic properties of the substituent. For example, the Boc-protected aniline derivative (**1j**) afforded products **2j** and **3j** in 84% and 79% yields, respectively, whereas the trifluoromethyl-substituted analog (**1k**) gave the corresponding coumarin in 56% yield and the coumaranone derivative in an excellent 85% yield. Cyclization of a naphthyl-substituted phenol proceeded smoothly, furnishing products **2n** and **3n** in 75% and 79% yield. Replacement of the R_1 and R_2 methyl groups with a cyclohexyl unit was also compatible with the reaction, leading to the spirocyclic derivatives **2p** and **3p** in 80% and 75% yield. Nonetheless, some limitations were identified. In addition to the poor performance of benzylic substitution at R_3 or the use

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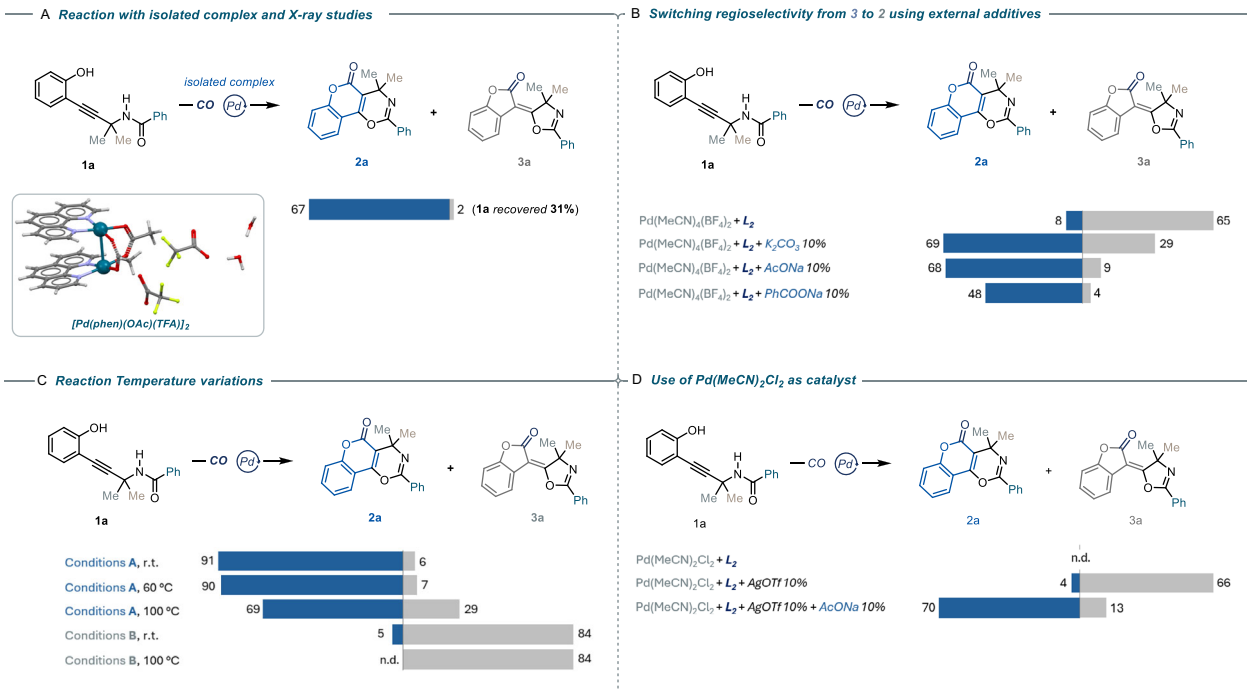


SCHEME 2 | Substrate scope of 6-*endo-dig* and *5-exo-dig* cyclization starting from **1**. **Conditions A: 1** (0.2 mmol, 1 equiv.), **$Pd(OAc)_2$** (0.01 mmol, 5.0 mol%), **L_2** (0.01 mmol, 5.0 mol%), **1,4 benzoquinone** (0.24 mmol, 1.2 equiv.) in DMF (1 mL) with CO balloon at 25°C. **Conditions B**: **1** (0.2 mmol, 1 equiv.), **$Pd(MeCN)_4(BF_4)_2$** (0.01 mmol, 5.0 mol%), **L_4** (0.01 mmol, 5.0 mol%), **1,4 benzoquinone** (0.24 mmol, 1.2 equiv.) in DMF (1 mL) with CO balloon at 25°C.

of the quinolinol moiety (**1t**), the replacement of the aryl group on the amide nitrogen with a methyl substituent (**1q**), as well as alternative substitution patterns at R_1/R_2, failed to deliver the desired products. These observations indicate that the reactive rotamer and *gem*-dialkyl effects [47–49] are crucial for promoting the double cyclization process under mild conditions.

To gain further insight into the catalytic species, we first investigated the reaction of **1a** under the conditions optimized for the selective cyclization to **2a**, employing the isolated mixed complex. As shown in Scheme 3A, the use of the $[Pd(phen)(OAc)(TFA)]_2$ preisolated complex (see Supporting Information for X-ray analysis), employed in 2.5 mol%, resulted in the formation of **2a** in 67%

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SCHEME 3 | Further investigations. (A) Reaction with isolated complex. (B) Experiments using different basic additives. (C) Temperature variations. (D) $Pd(MeCN)_2Cl_2$ used as catalyst for the formation of product **2a** and **3a**. Yields reported in the Scheme have been calculated via ^{1}H-NMR analysis, using CH_2Br_2 as internal standard.

yield (with 31% of **1a** unconverted). Subsequently, a series of control experiments was then conducted to elucidate how different counterions influence the regioselectivity of cyclization, favoring either the *6-endo-dig* or the *5-exo-dig* pathway. Based on the hypothesis that the basicity of acetate may play a key role in directing selectivity, reactions were performed under **conditions B**—typically selective for the *5-exo-dig* product **3a**—in the presence of added bases. As shown in Scheme 3B, the addition of K_2CO_3 (10 mol%) resulted in a complete reversal of selectivity, affording the *6-endo-dig* product **2a** in 69% yield. Even higher selectivity was achieved using NaOAc (10 mol%) as the additive, providing a comparable yield with an improved **2a**/**3a** ratio. Similarly, the use of sodium benzoate led to preferential formation of **2a**, which was obtained as the major product in 48% yield. These results clearly demonstrate that the formation of the *6-endo-dig* product **2a** can be promoted by the presence of a base, which under standard **conditions A** is intrinsically provided by the acetate counterion of the palladium catalyst.

The effect of temperature was subsequently evaluated under both standard **conditions A** and **B**. Under **conditions A**, increasing the temperature to 60°C had no significant impact on regioselectivity, giving results comparable to those obtained at room temperature. However, further heating to 100°C led to a marked decrease in selectivity for **2a**, with the *5-exo-dig* product **3a** being formed in 29% yield. In contrast, reactions performed under **conditions B** at 100°C showed no appreciable change in product distribution relative to room temperature (Scheme 3C).

These observations suggest that the formation of the *6-endo-dig* product **2** is likely governed by kinetic control, whereas the generation of the 2-cumarone **3** occurs under thermodynamic control. However, the possibility that the formation of compounds **2** and **3** proceeds via two distinct competitive mechanisms cannot be ruled out.

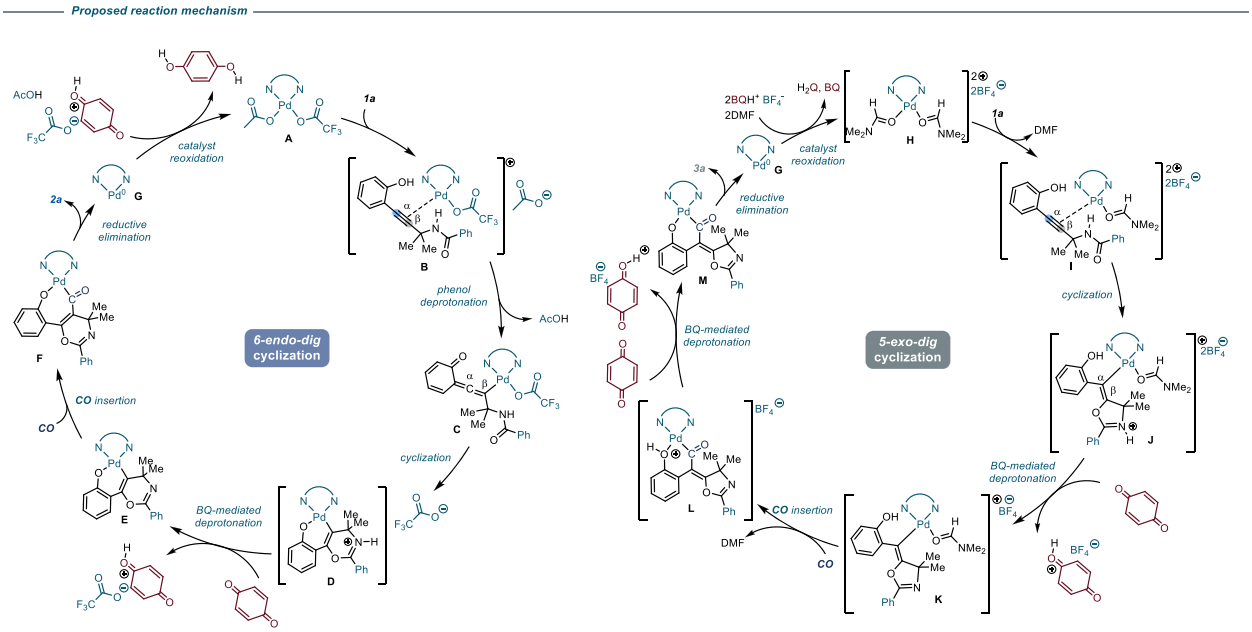
Finally, to verify that strong Pd–halide interactions significantly suppress catalytic reactivity, a series of experiments was conducted using $Pd(MeCN)_2Cl_2$ in the presence of AgOTf, thereby generating less strongly coordinated palladium species through halide abstraction. Notably, when the reaction was performed with a $Pd(MeCN)_2Cl_2$/AgOTf (10 mol%) system in combination with ligand $\boldsymbol{L_2}$, catalytic performance comparable to that obtained with $Pd(MeCN)_4(BF_4)_2$ (**Entry 10**, Table 1) was achieved (Scheme 3D). In contrast, consistent with the results discussed above, the addition of NaOAc (10 mol%) to this system led to a complete reversal of regioselectivity, affording product **2a** in 70% yield with a remarkable **2a/3a** molar ratio of 5.4.

From our preliminary calculations, the effect of the acetate ion (and more generally, of a base) is to deprotonate the phenol once the alkyne **1a** is coordinated to the palladium (see Supporting Information). Therefore, the formation of the phenate ion, which accounts for the observed selectivity, can be obtained only under **conditions A**, favoring the formation of **2** over **3**.

Taken together control experiments and theoretical calculations, a plausible mechanism for the two distinct reaction pathways is proposed in Scheme 4.

Under **conditions A**, which favor the formation of the coumarin derivative **2**, the isolated dimeric species $[Pd(Phen)(OAc)(TFA)]_2$ in solution likely exists in equilibrium with complex **A**, in which palladium is coordinated to the phenanthroline $\boldsymbol{L_2}$ and bears both acetate and trifluoroacetate ligands. Ligand exchange

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SCHEME 4 | Proposed reaction mechanism for products **2** and **3**.

between complex **A** and substrate **1a** can lead to the displacement of the acetate ligand, affording intermediate **B**. According to our computational analysis (see Supporting Information), the liberated acetate anion subsequently deprotonates the phenolic moiety of **1a** only when the alkyne is linked to the palladium, generating intermediate **C**, in which palladium is η^1 coordinated to the β-carbon (with respect to the phenolic ring), C_β, of the alkyne unit. In intermediate **C**, the strong electron-donating effect of the phenolate induces a significant polarization of the alkyne, favoring an allene-like electronic structure rather than a classical triple bond. This interpretation is supported by our calculations, which show that intermediate **C** exhibits a C_α–C_β bond order of 2.14 and a C_α–phenol bond order of 1.46. In addition, NPA analysis reveals pronounced charge separation, with atomic charges of −0.19 and +0.28 on the C_β and C_α carbons, respectively (see Supporting Information).

Therefore, this electronic rearrangement increases the electrophilicity of C_α, which can undergo nucleophilic attack by the amide oxygen. Consequently, a 6-*endo-dig* cyclization occurs, leading to the palladium six-membered ring intermediate **D**, in which the nitrogen atom can be subsequently deprotonated by benzoquinone. The ability of benzoquinone to act as a proton acceptor, in addition to its established role as an oxidant, is well documented [50–53], including in palladium-catalyzed carbonylation processes [36, 54]. Subsequent coordination and migratory insertion of carbon monoxide afford intermediate **F**, which undergoes reductive elimination to deliver the desired product **2a**, along with the Pd(0) species **G**. Finally, reoxidation of Pd(0) by benzoquinone regenerates the active palladium catalyst, thereby completing the catalytic cycle. Under **conditions B**, a dicationic palladium(II) intermediate can be proposed, in which the metal center is coordinated only to the bidentate bipyridine ligand ***L*****$_4$**, while the two remaining coordination sites are most plausibly occupied by DMF solvent molecules. Coordination of substrate **1a** to the palladium center occurs under these conditions. However, according to our preliminary calculations, none of the species present in solution (i.e., BF_4^-, benzoquinone, or DMF) is sufficiently basic to promote the phenol deprotonation after the alkyne coordination. In this case, an *anti 5-exo-dig* cyclization of the amide oxygen onto the coordinated alkyne occurs, leading to intermediate **J**. This pathway is intrinsically favored over the competing *6-endo-dig* cyclization, as already observed for similar transformations [55, 56]. Subsequent N–H deprotonation mediated by benzoquinone, followed by carbon monoxide coordination and insertion, affords intermediate **L**. A second benzoquinone-assisted deprotonation generates intermediate **M**, which undergoes reductive elimination to furnish product **3a**, together with a Pd(0) species **G**. The latter is subsequently reoxidized by benzoquinone, thereby regenerating the catalytically active palladium species. Notably, two equivalents of protonated benzoquinone are formally generated along the catalytic cycle; at the end, one functions as the terminal oxidant, while the other acts as a Brønsted acid (analogously to acetic acid in the alternative catalytic pathway), ultimately yielding hydroquinone (H_2Q) and regenerating one equivalent of benzoquinone. Usually, palladium oxidation mediated by benzoquinone is favored in acidic media, as the first step of this process was reported to be BQ protonation [57]. However, in our reaction no acid was necessary, since the BQ, acting as a base, is already protonated during the cycle.

3 | Conclusion

In this work, we have developed a simple and efficient catalytic protocol for the selective synthesis of coumarin and coumarone derivatives, in which product formation is finely controlled by modulation of the palladium counterion. This methodology enables access to distinct products with high regioselectivity and excellent yields in most cases. Mechanistic investigations highlight the crucial role of a basic counterion, such as acetate (AcO^-), in promoting the selective formation of the *6-endo-dig*

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cyclization product. Accordingly, the introduction of basic additives provides a straightforward strategy to switch the regioselectivity of the reaction. Overall, the ability to selectively access two structurally distinct products with high efficiency simply by altering the palladium counterion represents a significant advance in palladium-catalyzed alkyne carbocyclizations. This finding highlights the underexplored role of counterion effects and may stimulate their broader exploitation in palladium-catalyzed reactions where regioselectivity remains a key challenge.

4 | Experimental Section

Starting material **1** has been prepared using already reported procedures (See SI references for further details). All reagents and solvents were bought from Sigma Aldrich, TCI, Fluorochem, and BLDPharm and used as received unless otherwise specified. The solvents employed in this work were purchased from Carlo Erba or Sigma Aldrich and used as received.

4.1 | General Procedure for the Synthesis of Coumarin Derivatives 2a-p

In a 45 mL Schlenk tube under N_2, palladium acetate (0.01 mmol, 2.2 mg) and 1,10-phenanthroline (0.01 mmol, 1.8 mg) were dissolved in 2 mL of a 2.5 μM trifluoroacetic acid solution in dry DMF (0.0076 mmol, 0.58 μL of TFA in 2 mL of DMF). The solution was stirred for 15 min at room temperature and then **1** (0.2 mmol, 1 equiv.) was added, followed by the addition of 1,4-benzoquinone (0.24 mmol, 1.2 equiv.). The reaction was purged with CO for ∼30 s and, finally, a balloon charged with CO (1 atm) was attached to the tube. Full conversion of **1** was observed after 2 h of reaction time. The resulting mixture was filtered through a pad of Celite and concentrated in vacuo. The product **2** was isolated by flash column chromatography on silica gel using mixtures of hexane/DCM or hexane/EtOAc as eluents.

4.2 | General Procedure for the Synthesis of 2-Coumaranone Derivatives 3a-p

In a 45 mL Schlenk tube under N_2, tetrakis(acetonitrile) palladium(II) tetrafluoroborate (0.01 mmol, 4,4 mg) and 2,2′-bipyridine (0.01 mmol, 1,6 mg), were dissolved in 2 mL of dry DMF. The solution was allowed to stir for 5–10 min before adding **1** (0.2 mmol, 1 equiv.) and 1,4-benzoquinone (0.24 mmol, 1.2 equiv.). The reaction was purged with CO for ∼30 s and, finally, a balloon charged with CO (1 atm) was attached to the tube. Full conversion of **1** was observed after 2 h of reaction time. The resulting mixture was filtered through a pad of Celite and concentrated in vacuo. The product **3** was isolated by flash column chromatography on silica gel using mixtures of hexane/DCM or hexane/EtOAc as eluents.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Acknowledgments

This work has benefited from the equipment and framework of the COMP-HUB and COMP-R Initiatives, funded by the "Departments of Excellence" programs of the Italian Ministry for University and Research (MUR, 2018–2027). The authors warmly thank support from the National Recovery and Resilience Plan (NRRP, grant: 0001052), CIRCC (Progetto competitivo CMPT248870), and UNIPR ("Bando di Ateneo 2023 per la ricerca"). The authors also thank Chiesi Farmaceutici for XRD analysis.

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Funding

This study was supported by NRRP (0001052).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in IRIS (Institutional Research Information System) at https://air.unipr.it/.

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