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Letter

Site-Selective Double and Tetracyclization Routes to Fused Polyheterocyclic Structures by Pd-Catalyzed Carbonylation Reactions

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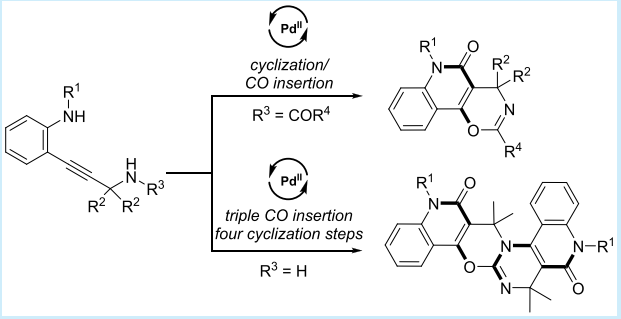
ABSTRACT: In this contribution, we report novel palladium-catalyzed carbonylative cascade approaches to highly functionalized polyheterocyclic structures. The Pd-catalyzed carbonylative process involves the regioselective insertion of one to three CO molecules and the sequential ordered formation of up to eight new bonds (one C−O, two C−C, five C−N). The exclusive formation of six-membered heterocycles is elucidated by detailed modeling studies.



Transition metal-catalyzed carbonylation reactions continue to play a leading role in the synthesis of carbonyl-containing chemicals both on laboratory and industrial scales.[1] Palladium-based carbonylative methodologies feature high versatility and functional group tolerance and may enable the construction of structurally elaborated molecules by elegant reaction sequences.[2] An impressive example that mimics the natural biosynthesis of tetracyclic lanosterol from squalene is the Pd-catalyzed carbonylative pentacyclization reaction reported by Negishi and co-workers as early as 1994 (Figure 1).[3] In this case, the simultaneous presence of multiple competing functionalities, when properly controlled, can lead to an outstanding level of molecular sophistication. More recently, Jiang and co-workers have disclosed a successful ligand-controlled palladium-catalyzed cyclization and carbonylation reaction sequence for the regioselective syntheses of indolo[3,2-*c*]coumarins and benzofuro[3,2-*c*]quinolinones starting from substrates containing both OH and NHR nucleophilic moieties.[4] Not surprisingly, good chemo-, regio-, and stereoselectivities are generally hard to achieve, and an efficient catalytic control of the reaction outcome remains a formidable challenge.[5]

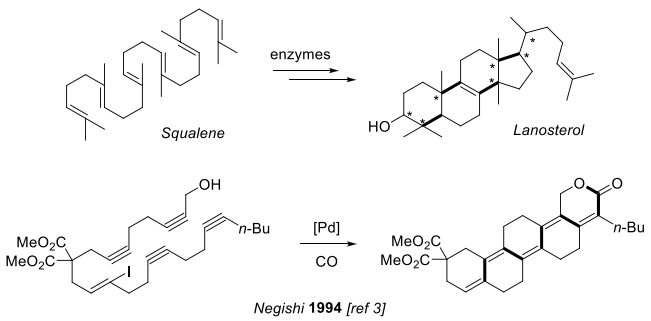


Figure 1. Biosynthesis of lanosterol and bioinspired Pd-catalyzed carbonylation cascade by Negishi.

We have recently reported efficient palladium-catalyzed syntheses of indole-fused furanones[6] and furofuranone derivatives[7] as examples of successful carbonylative cascade double-cyclization processes from easy accessible multifunctional precursors to complex molecular structures.[8] In particular, anilines bearing propargyl alcohol moieties in the *ortho* position delivered a variety of polycyclic furo[3,4-*b*]indol-1-ones through a sequence of indolization (**I-1**), carbonylation (**I-2**), and lactonization reactions in the presence of PdI_2/KI as a stable and highly efficient catalytic system[2a] (Scheme 1a).[6] On the basis of these results, we envisioned that with an NHR moiety in place of the OH group intermediate **I-2′** would be formed. Therefore, the subsequent reductive elimination would have produced the analogous indole-fused γ-lactam product (Scheme 1b).

However, with a secondary amino group (R = alkyl) the reaction led to a complex mixture of unidentified compounds

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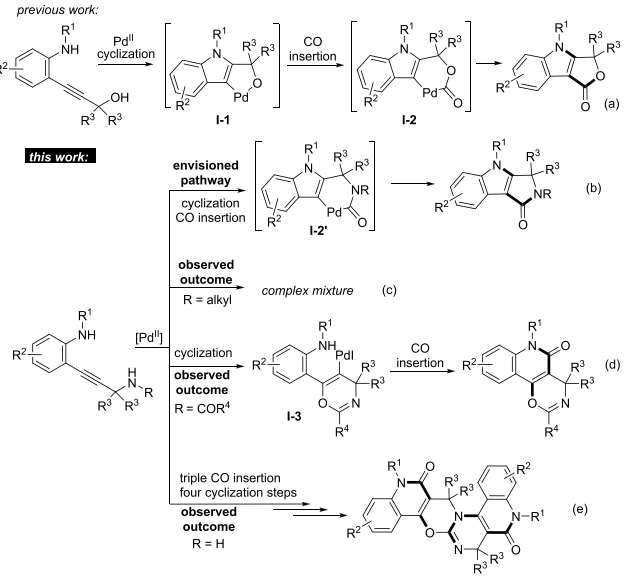
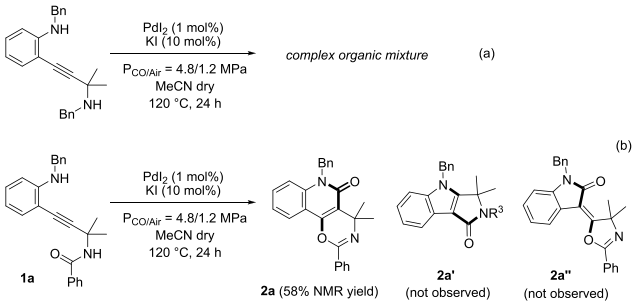
Scheme 1. Site-Selective Pd-Catalyzed Carbonylative Cyclizations to Fused 5-Membered (Previous Work) and 6-Membered Rings (This Work)



(Scheme 1c), while surprisingly, it took very different pathways when R = COR[4] (selectively leading to oxazino[5,6-*c*]quinolin-5-ones, Scheme 1d) and when R = H (leading in one step to nonsymmetrical fused polyheterocyclic structures, Scheme 1e). Remarkably, both (d) and (e) routes are selective toward 6-membered cyclization products with high molecular complexity achieved in a single reaction sequence. This allowed us to access quinolinone-based polyheterocyclic structures, which are useful in medicinal chemistry and material science.[8,9]

Initially, we assessed the reactivity of *N*-benzyl-2-(3-(benzylamino)-3-methylbut-1-yn-1-yl)aniline bearing a secondary amino group (R = Bn, Scheme 2a). Under the same

Scheme 2. Preliminary Results under Palladium-Catalyzed Carbonylative Conditions



conditions employed in the synthesis of indole-fused furanones (PdI_2 (1 mol %), KI (10 mol %) in the presence of CO (1.2 MPa) and air (4.8 MPa) in MeCN at 120 °C for 24 h),[6] the expected indole-fused γ-lactam product was not observed, and a complex mixture of unidentified organic compounds was instead formed. The same result was observed for other *N*-alkyl-substituted substrates.[10]

In sharp contrast, however, a substrate bearing a propargylic amido group, such as *N*-(4-(2-(benzylamino)phenyl)-2-methylbut-3-yn-2-yl)benzamide**1a** (R = COPh) followed a selective reaction pathway, which led to the formation of oxazino[5,6-*c*]quinolin-5-one **2a** in 58% yield (as determined by ^{1}H NMR analysis) (Scheme 2b). As suggested by DFT calculations, the initial step is the nucleophilic attack of the carbonyl oxygen of the amide moiety to the triple bond activated by Pd(II) species leading to intermediate **I-3** (Scheme 1d). This pathway was clearly preferred with respect to the sequential indolization and CO insertion to give **2a′** (Schemes 2b and 1b), but more importantly, the process was highly selective toward the 6-*endo-dig* cyclization mode, as the compound **2a′′**, deriving from 5-*exo-dig* annulation, was not detected at all. As a result, the tricyclic fused 6-membered heterocycle **2a** was produced by further CO insertion and subsequent intramolecular nucleophilic amine displacement. Interestingly, although (a) Baldwin's rules could allow for both cyclization types[11] and (b) several examples strongly call for a 5-*exo-dig* pathway[12] over the 6-*endo-dig* one,[13] especially when indole/indolones are generated,[6,14] a complete selectivity toward the 6-membered ring was observed in our reaction.

With this initial result in hand, we set out to optimize the reaction conditions (see Table S1). First we noticed that decreasing the temperature was beneficial to this transformation. The yield of **2a** improved up to 86% at 80 °C, using 1.6/0.4 MPa of the CO/air mixture. Among the examined solvents, MeCN clearly emerged as a suitable reaction medium in which product **2a** was produced with higher selectivity. The amount of KI, PdI_2, and the optimal substrate concentration were further considered, and eventually, the use of PdI_2 (1 mol %), KI (10 mol %), CO (1.6 MPa), and air (0.4 MPa) in anhydrous MeCN at 80 °C was defined as the standard reaction conditions for exploring the reaction scope. Therefore, substituted alkynyl anilines **1a−r** bearing the amide moiety were reacted with CO under the optimized conditions (Figure 2).[15] The benzyl group and the more readily removable *p*-OMe benzyl substituent were found to be excellent substituents on the nitrogen bonded to the aromatic ring (R^1), providing compounds **2a** and **2b** in 83 and 80% isolated yield, respectively. A range of electron-releasing (ER) and electron-withdrawing (EW) groups on the aromatic ring in the *para* position to the N (R^2, Figure 2), including alkyl, chloro, bromo, fluoro and ester, were nicely tolerated in this transformation. *Ortho* and *meta* substitutions were also possible (**2j**, 62% and **2l**, 84%), even though some limitations were present (**2k**, 12%). Alkyl groups in propargylic position, as in **2a−m**, were found to promote the sequential carbonylative cyclization, probably owing to the reactive rotamer effect.[16] However, the absence of substituents in this position also afforded the corresponding product in satisfactory yield (**2n**, 58%). The R^4 group of the amide moiety was then studied. *Para*-substituted aryl groups gave good results (**2o−q**, 63−82%), while a lower yield was observed when R^4 was an alkyl group, such as Me (**2r**, 38%). The structures of representative products **2g** and **2o** were unambiguously confirmed by single crystal X-ray diffraction analysis.[10]

The reactivity of substrates **1t−x** bearing a free amino group on the carbon α to the triple bond was next investigated (Figure 3). To our surprise, a totally different product arising from a completely unexpected reaction pathway was in this case observed. Under the same standard conditions employed for the synthesis of compounds **2** (see Table S2), the condensed polyheterocyclic structure **3** was formed. Eight new bonds and four condensed heterocycles were formed during this triple carbonylative cascade reaction in a single operation, and good yields were obtained with both EW and

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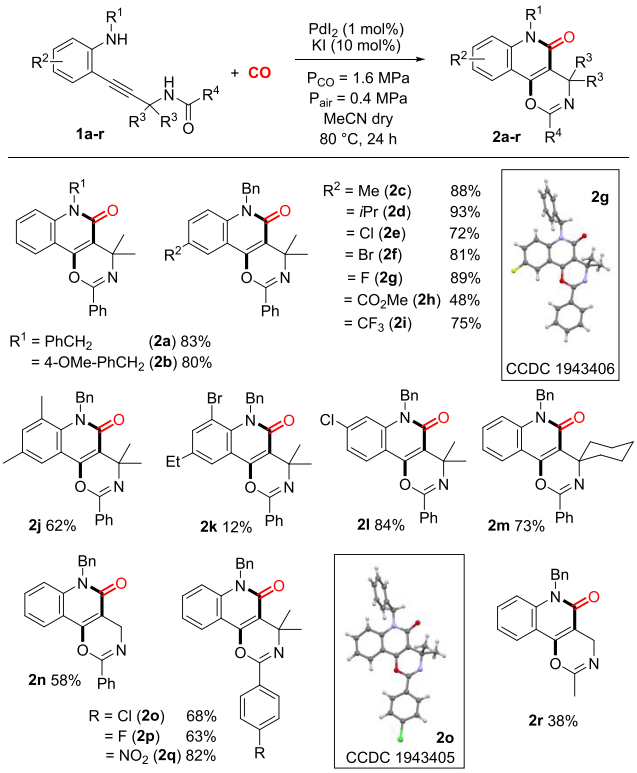


Figure 2. Carbonylation of *ortho*-alkynylanilines bearing the amide moiety (**1a−r**) to oxazino[5,6-*c*]quinolin-5-ones **2a−r**. Reactions were performed in an autoclave with **1** (0.5 mmol), PdI_2 (1 mol %), KI (10 mol %), P_{CO} (1.6 MPa), P_{air} (0.4 MPa), in dry MeCN (5 mL) at 80 °C for 24 h. Yield of isolated product after flash chromatography.

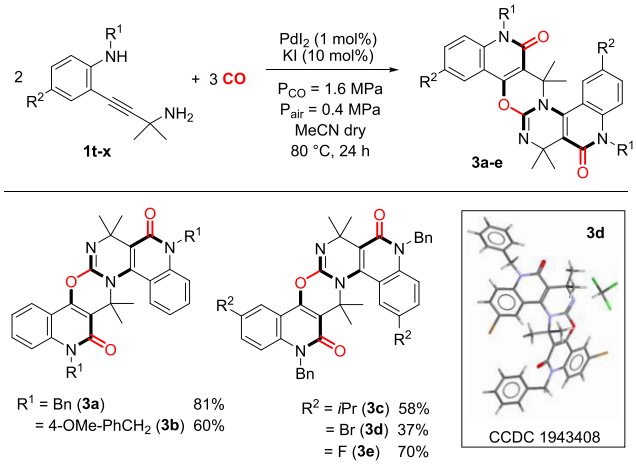


Figure 3. Carbonylation of *o*-alkynylanilines bearing the NH_2 moiety (**1t−x**) to condensed heterocycles **3a−e**. For reaction conditions, see Figure 2. Yield of isolated product after flash chromatography.

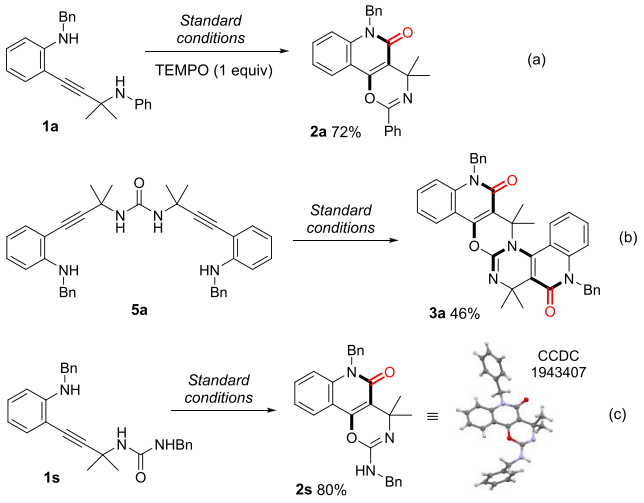
ER groups (**3c−e**). The structure of **3d** was unequivocally assigned by SC-XRD.[10]

Based on control experiments (Scheme 3) and DFT calculations, pathways to compounds **2** and **3** are proposed (Scheme 4). The process seemed to have a nonradical nature (see the reaction carried out in the presence of TEMPO, Scheme 3a); therefore, we excluded radical intermediates from the catalytic cycle. At the beginning, the triple bond of amide **1** can easily coordinate Pd(II) to give complex **II** (Scheme 4, pathway a).[17] In accordance with the experimental observations, the most favorable predicted route consists of the chemoselective nucleophilic attack of the oxygen of the amide group on the activated triple bond following a 6-*endo-dig* cyclization mode, affording the *σ*-vinylpalladium complex **III**. The 5-*exo-dig* route was proved to be unfavorable (TS^1_{2-3} = 29.8 kcal/mol, Figure S5) if compared with the 6-*endo-dig* one (TS^1_{2-3} = 16.7 kcal/mol).

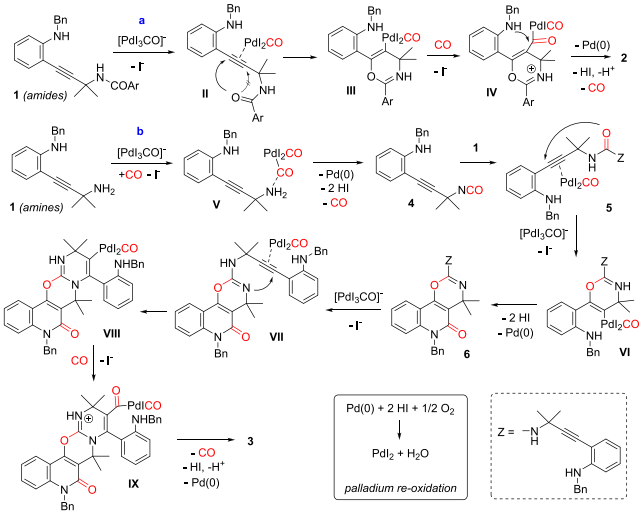
In a similar manner, the routes leading to indolone or quinolinone frameworks required higher activation free energies (Figure S5). It is worthy to note that, looking at the electrostatic potential map of complex **II** (Figure 4), the sp carbon *α* to the aromatic ring features a deeper blue color than the other, indicating a more positive environment. Therefore, the asymmetric aryl-alkyl substitution on the triple bond may orient the Pd to bind to the *β*-C relative to the phenyl ring making the *α* carbon more prone to undergo nucleophilic substitution.[18] Then, after CO insertion and formation of **IV**, the second cyclization takes place, delivering product **2** and Pd(0), which is reoxidized in a highly exergonic process.[19,20]

In a different way, when a primary amino group is present on **1** (R = H in Scheme 1e; Scheme 4, pathway b), the

Scheme 3. Experimental Findings



Scheme 4. Most Favorable Modeled Pathways to Compounds 2 and 3



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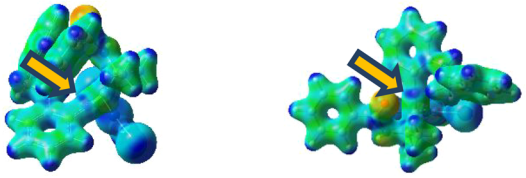

Figure 4. Molecular electrostatic potential projected onto the VdW surface of two modeled conformations of intermediate **II**. Yellow arrows indicate the sp carbon α to the aromatic ring, featuring a deeper blue color than the β carbon.

symmetrical urea **5** is likely generated by palladium catalysis, through isocyanate intermediate **4** (Figure S2), as we have also previously reported.[21] Multifunctional urea **5** is supposed to be highly reactive under standard conditions and can undergo sequential 6-*endo-dig* *O*-cyclization to **VI**, CO insertion, and reductive elimination to organic compound **6**. As we have seen for substrates **1a−r** containing the amide group (Scheme 4, pathway a), the oxo tautomer is the active form also for urea **5**, since the enol formation is more energy demanding (Figure S5). Then a nucleophilic attack on the other triple bond by the imino N of the isourea function yields palladium complex **VIII**, again in a 6-*endo-dig* fashion. The sequential insertion of the third CO molecule leads to the final cyclization step, delivering compound **3** and palladium(0). Several factors are likely at work to control the site-selectivity of the reaction, including the preorganization of the starting material, the nature of the active catalytic species as well as the reaction medium. In particular, the electronic nature of the Pd(II) species can affect the most favorable pathway. On the basis of the computed free energies, the $[PdI_3CO]^-$ species is the active form of the catalyst for both pathways a and b, as compared to the stabilities of $[PdI_4]^{2-}$ and $PdI_2(CO)_2$ (Figure S6).[22]

In order to gain further evidence of the described pathway, intermediate **5a** was independently prepared and caused to react under the standard conditions (Scheme 3b). To our delight, dipropargylic urea **5a** delivered the desired compound **3a** in good yield, giving strong support for the intermediacy of symmetrical urea **5** in the reaction sequence. In addition, we also demonstrated that the nonsymmetrical urea **1s**, gave exclusively the usual *O*-cyclization product **2s** in high yield (80%), and no products arising from a *N*-cyclization process were detected (Scheme 3c). The structure of **2s** was again confirmed by SC-XRD.

In conclusion, the present study provides new attractive routes to quinolinone-fused and more complex polyheterocyclic structures by means of PdI_2/KI-catalyzed oxidative carbonylation methodology. The described transformations are extremely selective toward 6-membered cyclization products, with two to four sequential 6-*endo-dig* cyclization steps and three to eight new bonds realized in a one-pot manner. A detailed computational study revealed the origin of the complete site selectivity toward the 6-*endo-dig* cyclization mode. It is noteworthy that both amides and ureas exhibited the same type of chemoselectivity (O-cyclization). This can pave the way for even more prolonged site-selective reaction sequences leading to bioinspired molecular architectures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00171.

Experimental procedures, characterization of reagents and products and spectroscopic data (PDF)

Accession Codes

CCDC 1943405−1943408 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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