Switchable Oxidative Reactions of N-allyl-2-Aminophenols: Palladium-Catalyzed Alkoxyacyloxylation vs an Intramolecular Diels–Alder Reaction

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ABSTRACT: The Pd(II)-catalyzed reaction of N-allyl-2-aminophenols in the presence of PhI(OCOR)₂ as the oxidant resulted in an alkoxyacyloxylation process, with the formation of functionalized dihydro-1,4-benzoxazines. The reaction performed in the absence of palladium catalyst switched to an intramolecular Diels–Alder reaction (IMDA) pathway, which was the result of an oxidative dearomatization of the 2-aminophenol, nucleophilic addition, and Diels–Alder reaction cascade, highlighting the role of the oxidant as both a nucleophilic donor and an oxidizing agent.

The construction of functionalized heteropolycyclic molecules in one step, with the advantage to avoid isolation of intermediates is an attractive goal compared to traditional stepwise synthesis.¹ Moreover, the formation of several bonds combined in one pot complies with the concept of green chemistry in terms of timesaving and due to the reduced waste production.² The interest of a domino processes may be increased by using transition metal catalysis;³ in particular, the use of palladium(II) catalyst in oxidative conditions offers the possibility to use unactivated substrates as the unsaturated systems. In this case, in addition to the catalyst and the solvent, the oxidant may also have a crucial role in the outcome of the reaction. The synthetic strategies for the construction of oxygen-containing heterocycles applying the palladium(II)-catalyzed reactions through the formation of the intramolecular C–O bond, starting from alcohols, phenols, or carboxylic acids, are known in the literature,⁴ while the domino processes are less explored as the alkoxyacyloxylation.⁵ Continuing our studies on the C–O bond formation exploiting Pd-catalyzed intramolecular reactions in oxidative conditions,⁶ we set out to study the reactivity of phenols bearing an unsaturated pendant, to investigate the regioselectivity and the stereoselectivity in the cyclization step. Different regioselective pathways are dependent on the exo- or endo-cyclization processes arising from the length and rigidity of the linking alkyl chain. Moreover, the choice of a substrate that is easily oxidizable, such as a phenol, in oxidative conditions, represented a challenge due to the different possible pathways that the reaction can follow.

In particular, in the present study the reported oxidative reactions allowed the construction of two different heteropolycyclic systems starting from the same substrates but mild tuning the reaction conditions (Scheme 1.1). In both cases, the
reported processes showed easy synthetic pathways to achieve important building blocks for bioactive compounds and natural products endowed with cytotoxic activity as clavenone and gambogenic acid (Scheme 1.2).8

The study started using N-allyl-N-tosyl 2-aminophenol 1a as a substrate to test different reaction conditions. The use of Pd(OAc)2 in the presence of PIDA as oxidant in CH3CN as solvent at room temperature (RT) afforded dihydro-1,4-benzoxazine 3 as the result of the alkoxyacetoxylolation process (Table 1, entry 1).

Table 1. Alkoxyacyloxylation Reaction on N-Allyl-N-Ts-2aminophenol 1a

| entry | R1             | solvent | time (h) | 3 (%) |
|-------|----------------|---------|----------|-------|
| 1a    | Me (PIDA)      | CH3CN   | 24 h     | 32%   |
| 2a    | Me (PIDA)      | DCM     | 24 h     | 30%   |
| 3a    | Me (PIDA)      | THF     | 24 h     | 26%   |
| 4a    | m-Cl-(C6H4) (2a)| CH3CN   | 24 h     | 82%   |
| 5a    | o-F-(C6H4) (2b)| CH3CN   | 3 h      | 86%   |
| 6b    | PhI(mcbA) (2c) | CH3CN   | 24 h     | -     |
| 7c    | NAc            | DCM     | 24 h     | 62%   |

“Reaction conditions: 10 mol % Pd(OAc)2, 1.2 equiv of 2a or 2b in CH3CN at RT.”9 Reaction conditions: 10 mol % Pd(OAc)2, 1.2 equiv of 2c in CH3CN at RT. “Reaction conditions: 10 mol % Pd(OAc)2, 1.2 equiv of 2c in DCM at 40 °C.”

The product was obtained with complete regioselectivity through a 6-exo-trig cyclization but in low yield. Different solvents, as DCM and THF, did not improve the yields (entries 2 and 3). With the purpose to increase yields, different functionalized hypervalent iodine reagents 2 were synthesized, due to the greater reactivity shown in the literature in alkene functionalization (Scheme 1.2).9

Regarding the stereocontrol of the cyclization step, few examples are reported in the literature on the difunctionalization of alkenes involving the C–O bond formation.11 Conversely, good enantioselectivity was reported in the aminoacetoxylation process by the crucial use of the pyridine-oxazoline (Pyox) ligands with a sterically bulky group at the C-6 position of the pyridine.12 Starting our investigations with the reported reaction conditions, 10 mol % Pd(OAc)2 PIDA in DCM (0.6 M) and ligand L1,12a the alkoxyacetoxylolated product was not even achieved (entry 1, Table 2). Also, the replacement with the more reactive PhI(mcbA) did not afford the expected results (entries 2 and 3, Table 2). Only when we employed acetonitrile as solvent (entry 4) was expected ester derivative 3aa achieved in excellent yield but with a very low enantiomeric excess. The explanation of this behavior may depend on the acetonitrile properties, through the interaction of the nitrile with the palladium species affecting the formation of the Pd–ligand complex.13 In order to improve the stereoselectivity, the reaction of 1a was performed at −20 °C, with better stereoselectivity but low yield (entry 5). Using a mixture 1:5 of CH3CN/toluene as solvent, in the presence of L2, no product 3aa was formed but a different compound 5aa was observed (entry 6, Table 2). Replacing ligands L1 and L2 with commonly used ligand L3, product 3aa was barely achieved, and compound 5aa was the major product (entry 7). Similar results were obtained with N-oxide ligand L4 (entry 8), known to be able to combine with Lewis acids to catalyze asymmetric difunctionalization of alkenes.14 Remarkably, the use of L5 ligand afforded compound 5aa as the exclusive product (entry 9). The analytical and spectroscopic data revealed the structure of 5aa as a tricyclic product, confirmed by X-ray diffraction analysis.

The use of not suitable Pd(II)-ligands favored a reaction promoted exclusively by the hypervalent iodine. Indeed, under
Table 2. Investigations on the Stereoselective Pd-Catalyzed Alkoxyacyloxylation of N-Allyl-N-Ts-2-aminophenol 1a

| entry | lig | solvent | T(°C) | 3aa (%) | 5aa (%) |
|-------|-----|---------|-------|---------|---------|
| 1a    | L1  | DCM     | RT    |         |         |
| 2     | L1  | DCM     | RT    |         |         |
| 3     | L2  | DCM     | 0°C   |         |         |
| 4     | L2  | CH3CN   | 0°C   | 59% er 55:45 |         |
| 5     | L2  | CH3CN   | −20°C | 23% er 65:35 |         |
| 6     | L2  | CH3CN/CH3Ph 1:5 | 0°C | traces | 29% |
| 7     | L3  | CH3CN   | RT    | 15%    | 49%    |
| 8     | L4  | CH3CN   | RT    | 10%    | 43%    |
| 9     | L5  | CH3CN   | RT    | 64%    |        |
| 10    | b   | CH3CN   | 40°C  | 71%    |        |

"In the presence of Pd-catalyst and L5 (entry 9, Table 2), may be also due to the stabilization of the quinone intermediate C, mediated by the Pd-ligand complex, according to a mechanism proposed by Sigman (Scheme 3)."

In the last years, the intramolecular Diels–Alder reactions in combination with other reactions have been fully investigated in domino/tandem processes, but to the best of our knowledge, no use of oxidant agent as nucleophile was reported. Thus, we described a mild procedure for the achievement of different functionalized tricyclic structures, simply varying the hypervalent iodine species (Scheme 1.b).

The results are reported in Table 3. By using the hypervalent iodine agents, 2a−c, corresponding α-amino-functionalized tricycles 5aa−ac were obtained in good yields (entries 2−5). When a good nucleophile was employed, such as the benzimidazole, the reaction could be carried out by using PhI(OAc)2 and 1.2 equiv of benzimidazole instead of PhI(mcba)2. PhI(OAc)2 (2 equiv) and benzimidazole (1.5 equiv) were used instead of PhI(mcba)2.

Table 3. Scope of the Intramolecular Diels–Alder Reaction

| Entry | Substrate | Product |
|-------|-----------|---------|
| Modification nucleophile |
| 1     | R1 = H; R2 = Ts | 1a | Na = OCOCH3 | Sod (23%) |
| 2     | R1 = H; R2 = Ts | 1a | Na = OCOCH3-Cl-(CH2)4 | Sod (71%) |
| 3a    | R1 = H; R2 = Ts | 1a | Na = OCO-Cl-(CH2)4 | Sod (39%) |
| 4     | R1 = H; R2 = Ts | 1a | Na = OCO-Cl-(CH2)4 | Sod (35%) |
| 5     | R1 = H; R2 = Ts | 1a | Na = OCO-Cl-(CH2)4 | Sod (67%) |
| 6     | R1 = H; R2 = Ts | 1a | Na = OCO-Cl-(CH2)4 | Sod (58%) |
| Modification N-protecting group |
| 7     | R1 = H; R2 = Boc | 1b | / | (-%) |
| 8     | R1 = H; R2 = COCl, | 1i | / | (-%) |
| 9     | R1 = H; R2 = (4-methyl)CO | 1j | / | (-%) |
| Substitutions on the aromatic ring |
| 10    | R1 = 4-Me; R2 = Ts | 1c | / | (-%) |
| 11    | R1 = 5-Me; R2 = Ts | 1d | / | (-%) |
| 12    | R1 = 4-CMe; R2 = Ts | 1e | / | (-%) |
| 13    | R1 = 4,5-(CH2)4R2 = Ts | 1f | / | (-%) |
| 14    | R1 = 5-CI; R2 = Ts | 1g | / | (-%) |

"In the presence of Pd-catalyst and L5 (entry 9, Table 2), may be also due to the stabilization of the quinone intermediate C, mediated by the Pd-ligand complex, according to a mechanism proposed by Sigman (Scheme 3)."

The conditions of Table 2, entries 7−9, compound 5aa was achieved as major or exclusive product. Thus, the explanation could rely on the inability of ligands L3−L5 to keep the electrophilicity of Pd(II), kidnapping the palladium and promoting a hypervalent iodine-based reaction. In fact, repeating the reaction in the absence of palladium and in the presence only of hypervalent iodine 2b, compound 5aa was obtained as the exclusive product with 71% yields (entry 10, Table 2). Thus, the mechanism suggested for the formation of functionalized tricyclic system 5aa is reported in Scheme 3.

Scheme 3. Proposed Mechanism for the Formation of Compound 5aa

The first step includes an oxidation/dearomatization of the 2-aminophenol induced by the coordination of the iodine to the phenolic oxygen with the formation of ortho-quinone form B. The subsequent attack of the nucleophile gives intermediate D, followed by the intramolecular Diels–Alder reaction involving the allyl substituent, affording the tricyclic system. The process is fully diastereoselective with the formation of only one diastereoisomer. The good result still achieved the formation of product 5aa in the presence of Pd-catalyst and L5 (entry 9, Table 2), may be also due to the stabilization of the quinone intermediate C, mediated by the Pd-ligand complex, according to a mechanism proposed by Sigman (Scheme 3). In the last years, the intramolecular Diels–Alder reactions in combination with other reactions have been fully investigated in domino/tandem processes, but to the best of our knowledge, no use of oxidant agent as nucleophile was reported. Thus, we described a mild procedure for the achievement of different functionalized tricyclic structures, simply varying the hypervalent iodine species (Scheme 1.b).

The results are reported in Table 3. By using the hypervalent iodine agents, 2a−c, corresponding α-amino-functionalized tricycles 5aa−ac were obtained in good yields (entries 2−5). When a good nucleophile was employed, such as the benzimidazole, the reaction could be carried out by using PhI(OAc)2 and 1.2 equiv of benzimidazole in CH3CN (entry 6). Hence, the reaction was applied on N-allyl-2-aminophenol bearing different N-protecting groups, 1b, 1i, and on different substituted substrates, 1c−g. While the Boc-derivative (1b) was degraded and the trifluoroacetic-group (1i) was not reactive, amide 1j gave good results. Regarding the substitution on the ring, only para-substitution at the amino group was tolerated, affording products Sod and Sga with 52 and 57% yields, respectively. In order to check the need to prefunction-
alize the hypervalent iodine, a control reaction was carried out in the presence of PIDA and m-chlorobenzoic acid as an external nucleophile (entry 3, Table 3). The achievement of a mixture of both functionalized systems, with the m-chlorobenzoate and the acetoxy group, respectively, confirmed the need to preinstalled the nucleophile of interest into the iodine(III).

In conclusion, we described a useful reactivity of N-allyl-2-aminophenols under Pd-catalysis in oxidative conditions, by the use of uncommon hypervalent iodines. By tuning the reaction conditions, it was possible to switch between the two processes, the intra/interdifunctionalization of the double bond resulting in the methacrylicxylated dihydro-1,4-benzoxazin-3-ones and the functionalized tricyclic system achieved through dearomatization of the substrate and intramolecular Diels–Alder reaction (IMDA).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02539.

Experimental procedures, compound characterization data including copies of 1H and 13C NMR spectra (PDF)

Accession Codes

CCDC 2078893 contains 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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