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Intramolecular Pd(II)-Catalyzed Cyclization of Propargylamides: Straightforward Synthesis of 5-Oxazolecarbaldehydes

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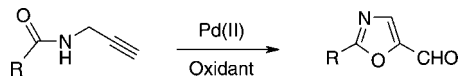
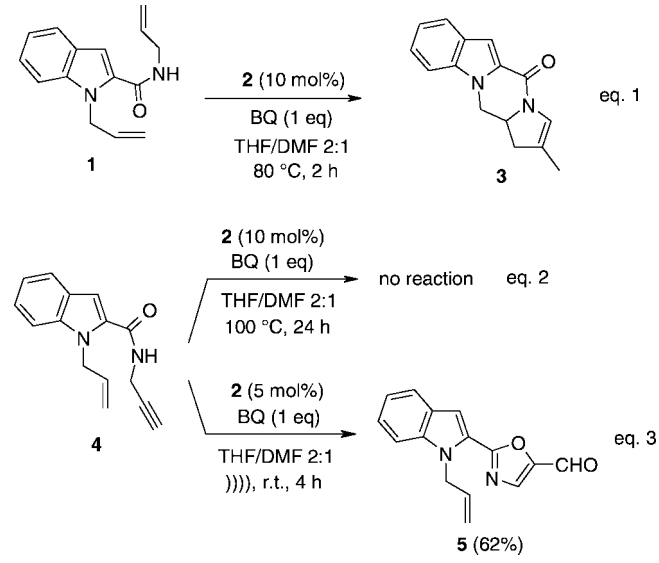


Direct synthesis of 2-substituted 5-oxazolecarbaldehydes was performed by intramolecular reaction of propargylamides through treatment with a catalytic amount of Pd(II) salts in the presence of a stoichiometric amount of reoxidant agent. The heterocyclization process was well-tolerated by a wide range of aryl, heteroaryl, and alkyl propargylamides. This protocol constitutes a valuable synthetic pathway to 5-oxazolecarbaldehydes, alternative to the formylation on oxazole rings, often unsatisfactory in term of regioselectivity and yields.

Intramolecular palladium-promoted cyclizations have became a milestone also in heterocyclic synthesis.[1] A widespread array of hetero(poly)cycles have been achieved by different methodologies, using a catalytic amount of palladium.[2] Among the most used reaction typologies, including the well-known Heck, Buchwald−Hartwig, and cross-coupling reactions, the Pd(II)-catalyzed oxidative reactions (i.e., Wacker-type reactions) play a prominent role due to the simplified requirements of the starting material.[3,4]

Our previous contribution in this area was concerned with intramolecular cyclizations of alkenyl systems bearing a nucleophilic moiety under conditions which require Pd(II) catalysis in the presence of a stoichiometric amount of an oxidant agent.[5] In particular, we recently found that *N*-allyl 1-allyl-2-indolecarboxyamide **1** undergoes an intramolecular Pd(II)-catalyzed process to give the tetracyclic structure **3** when treated with $PdCl_2(MeCN)_2$ (**2**) and 1,4-benzoquinone (BQ) as reoxidant (Scheme 1, eq 1).[5e] This result prompted us to investigate the behavior of the related *N*-propargyl 1-allyl-2-indolecarboxyamide **4** toward Pd(II) complexes to achieve reaction conditions suitable for a tandem reaction. When submitted to the conditions which successfully promoted the cyclization of **1**, compound **4** was recovered unchanged (Scheme 1, eq 2), while it reacted only by exposition to ultrasound irradiations. However, the reaction provided a product in 62% yield, whose analytical and spectroscopic data accorded to the unexpected 5-oxazolecarbaldehyde structure **5**, arising from 5-*exodig* cyclization of the propargylamide moiety without involving the allylindole portion of the starting molecule (Scheme 1, eq 3).

SCHEME 1. Pd(II)-Catalyzed Oxidative Cyclization of 1-Allyl-2-indolecarboxyamides 1 and 4



From this preliminary result, we envisioned the possible development of a general method for producing 2-substituted oxazoles directly formylated in the 5-position by using prop-

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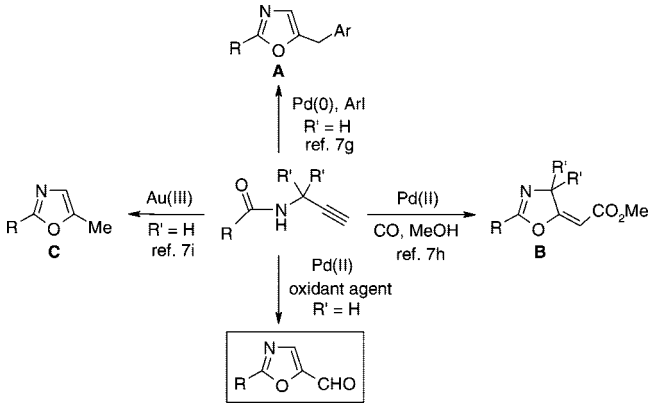

FIGURE 1. Behavior of propargylamides as tools for the transition metal-catalyzed synthesis of oxazole derivatives.

argylamides as starting material and working in the presence of Pd(II) catalysis with a reoxidant agent.

It is worthwhile to mention that the oxazole nucleus is present as a key structural moiety in a wide number of natural and unnatural biologically active products,[6] among which there are antitumor, antiviral, and antileukemia agents, as well as herpes simplex virus inhibitors, serine-threonine phosphatase inhibitors, antibacterials, antialgicidals, and peripheral analgesics. Consequently, a new efficient synthesis of functionalized oxazoles may well be a valuable goal. Some protocols for the construction of the oxazole nucleus starting from propargylamides are already known in the literature[7] and three of them are based on transition metal catalyzed cyclization (Figure 1).[7g–i] The first represents an effective access to 2,5-disubstituted oxazoles **A** by a tandem process with use of propargylamides and aryl iodides in the presence of catalytic Pd(0) species.[7g] The second concerns the synthesis of 4,4-disubstituted 4*H*-oxazol-5-ylidenacetic acid methyl esters **B** by Pd(II)-catalyzed oxidative carbonylation.[7h] The third involves $AuCl_3$ as catalyst affording to 5-methyloxazoles **C**.[7i] Following the oxidative Pd-catalyzed process observed for compound **4**, a new methodology to furnish directly 5-oxazolecarbaldehydes would be desirable.

On the basis of the above considerations, we aimed to evaluate the generality of the envisioned reaction and first we tested the behavior of the simple *N*-propargylbenzamide **6** under the previous successful reaction conditions. The experiment was accomplished by either ultrasound activation or heating at 60 °C and in both cases afforded the 2-phenyloxazole-5-carbaldehyde (**7**), which was isolated in 28% and 37% yields, respectively, besides degradation materials (Scheme 2).

SCHEME 2. Palladium-Catalyzed Cyclization of Propargylamide 6

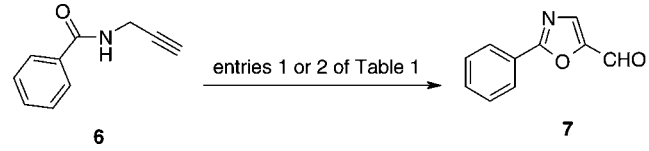

TABLE 1. Optimization of the Palladium-Catalyzed Cyclization of Propargylamide 6

entry	catalyst	oxidant	solvent[a]	*T* (°C)	yields of **7**
1	**2**[b]	BQ[d]	THF/DMF 5:3	rt[g]	28
2	**2**[b]	BQ[d]	THF/DMF 5:3	60	37
3	PTSA[c]	BQ[d]	THF	rt	
4	PTSA[c]	BQ[d]	CH_2Cl_2	rt	
5	PTSA[c]	BQ[d]	THF/DMF 5:3	rt[g]	
6	**2**[b]	BQ[d]	DMF	[h]	11
7	$Pd(OAc)_2$[c]	BQ[d]	THF/DMF 5:3	60	15
8	$Pd(OAc)_2$[c]	BQ[d]	DMF	100	18
9	**2**[b]	BQ[d]	THF/DMF 5:3	r.t.	10
10	**2**[b]	BQ[d]	THF/DMF 5:3	100	23
11	**2**[c]	BQ[e]	THF/DMF 5:3	100	26
12	**2**[c]	MnO_2[f]	THF/DMF 5:3	100	–
13	**2**[b]	BQ,[d] O_2	THF/DMF 5:3[i]	60	29
14	**2**[c]	O_2	THF/DMF 5:3	100	17
15	**2**[b]	$CuCl_2$[c] O_2	DMF[j]	100	46
16	**2**[b]	$CuCl_2$[e]	DMF	100	41
17		$CuCl_2$[c] O_2	DMF[j]	100	

[a] If not differently stated, the reaction time was 3 h. [b] 5 mol %. [c] 10 mol %. [d] 1 equiv. [e] 3 equiv. [f] 2 equiv. [g] Reactions were carried out under ultrasound irradiation. [h] Reactions were carried out under microwave irradiation. [i] 90 min. [j] 2 h.

The effective cyclization of amide **6** prompted us to perform a number of experiments to improve the reaction yield. As summarized in Table 1, some features were clearly evidenced. First, palladium catalyst was essential for a positive outcome of the reaction. The use of an acidic catalyst, more specifically *p*-toluenesulfonic acid (PTSA), was not able to convert the amide **6** in any solvents (entries 3−5).[8] An attempt to carry out the reaction by exposition of microwave irradiation failed because the decomposition of amide **6** was faster than the cyclization process (entry 6). The presence of **2** in the catalyst systems proved to be highly effective for the desired cyclization product (entry 2 vs entry 7). The increase of reaction temperature (entry 10) as well as of BQ amount did not improve significantly the yields (entry 11). The reaction was inhibited working in certain solvents or in the presence of a base. The use of other oxidant systems gave rise to different results. While MnO_2 totally inhibits the conversion of **6** (entry 12), the environmentally friendly molecular oxygen showed a different behavior depending on reaction conditions. In particular, when combined with BQ or employed as sole oxidant (entries 13 and 14) it slowed the desired reaction, but produced **7** in highest yield when associated with $CuCl_2$ in the role of cocatalyst (entry 15). The oxidative cyclization took place also in the presence of an excess of $CuCl_2$ (entry 16). The role of $CuCl_2$ is only of reoxidant agent and the absence of palladium inhibits the process.

Having established the optimal reaction conditions, we screened a series of propargylamides to generate different 2-substituted oxazole-5-carbaldehydes. The cyclization of substrates **8a**−**j** took place in higher yields working in conditions

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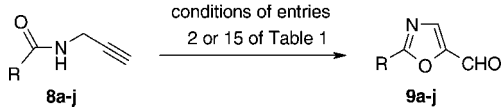
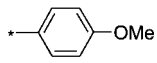
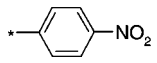
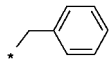
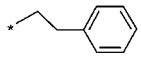
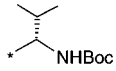
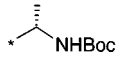
TABLE 2. Cyclization Yields of the Propargylamides 8a−j into the 5-Oxazolecarbaldehydes 9a−j



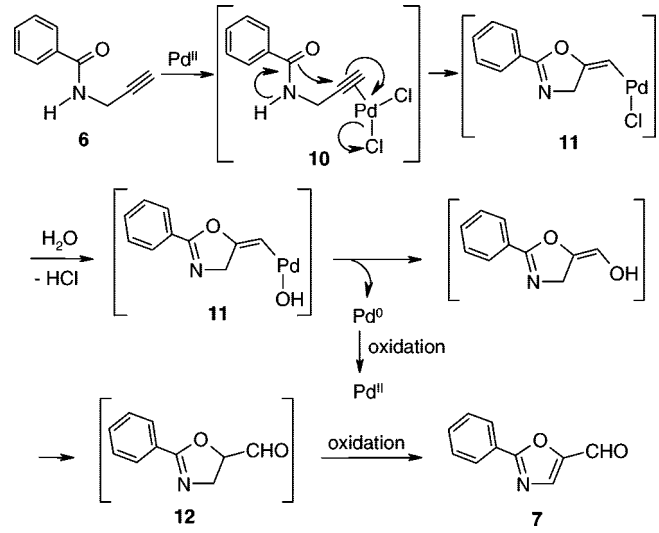
entry	R	condition	yield of **9**
A		entry 15	48
B		entry 2	41
C		entry 2	54
D		entry 15	61
E		entry 15	39
F		entry 15	37
G		entry 15	48
H		entry 15	37
I		entry 15	42
J		entry 15	39

of entries 2 or 15 of Table 1. The better results are collected in Table 2. The access to the oxazole compounds **9** was accomplished on propargylamides of aromatic, heteroaromatic, and aliphatic carboxyacids as well as of natural α-aminoacids. The crucial feature of this approach lies in its ability to access to 5-oxazolecarbaldehydes bearing an electron-rich heterocycle in position 2 (entries e−h). In fact, direct formylation of oxazoles substituted in position 2 with a pyrrolyl, furyl, or thienyl ring provides for a competitive functionalization involving both heterocyclic rings.

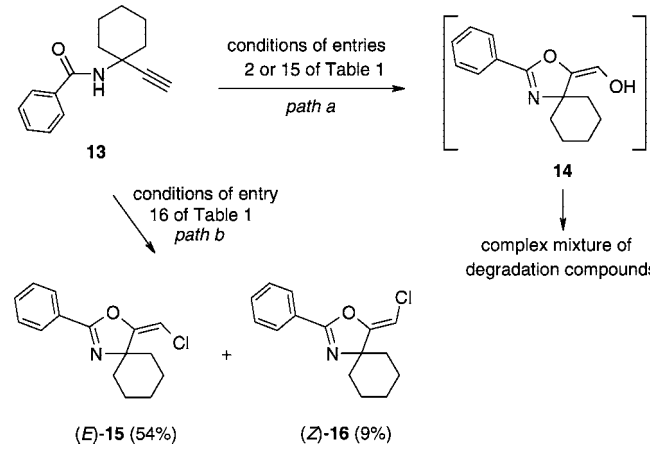
Despite several investigations in different reaction conditions, we have not found clear-cut evidence for determining the Pd mechanistic role. Although highly speculative, we propose the outcome of oxidative heterocyclization depicted in Scheme 3. The complexation of amide **6** with Pd(II) salts takes place on the C−C triple bond (intermediate **10**) making it susceptible to nucleophilic attack. The role of the nucleophile is covered by the oxygen atom of the amide group, which gives rise to 5-*exodig* cyclization to produce the oxazole skeleton by formation of the σ-alkenylpalladium complex **11**. The intervention of water provided, through its enol form, the 4,5-dihydrooxazole-5-carbaldehyde **12**, neither isolated nor detected in the reaction mixture (NMR). At this level the oxidizing system intervenes with a double role, namely (i) to reoxidize the Pd(0) species, formed at the end of the catalytic cycle, to the active Pd(II) and (ii) to promote the dehydrogenation of **12** giving **7**.[9]

In the search for evidence to support the proposed mechanism, we applied our protocol to the α,α-disubstituted propargylamide

SCHEME 3. Mechanism Proposed for Conversion of the Amide 6 on the 5-Oxazolecarbaldehyde 7



SCHEME 4. Outcome of Pd(II)-Catalyzed Cyclization of α,α-Disubstituted Propargylamide 13



13 foreseeing the impossibility of the 4,5-dihydrooxazole-5-carbaldehyde intermediate to undergo the dehydrogenation step. Accordingly, amide **13** was submitted to the conditions of entries 2 and 15 (Scheme 4, path a). In both conditions, the ^{1}H NMR spectrum of the crude mixture revealed only signals arising from degradation of the starting material, plausibly because the lack of hydrogen in the 4-position of the 4,5-dihydrooxazole precluded the oxidative aromatization of the putative intermediate **14**. On the other hand, the treatment of the amide **13** with **2** (10 mol %) and $CuCl_2$ (3 equiv) in DMF gave a mixture (63% yield) of compounds **15** and **16** (*E*/*Z* 6:1 ratio) (Scheme 4, path b).[10] This finding indicates that the presence of chloride ions as potential nucleophiles warrants the formation of the stable vinyl chlorides **15** and **16** instead of **14**.

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In conclusion, the direct and effective protocol to 2-substituted 5-oxazolecarbaldehydes described in this paper represents a valuable alternative to the formylation on oxazole rings, often unsatisfactory in terms of regioselectivity and yields. Moreover, the protocol can be carried out by using aryl, heteroaryl, and alkyl propargylamides, with tolerance of various functional groups and sensitive heterocycles such as *N*-unsubstituted pyrrole and furan. This protocol increases the versatility of the propargylamides as tools in Pd-catalyzed reactions for the direct synthesis of oxazoles and increases the availability of different functionalized oxazoles accessible by transition metal catalysis.

Experimental Section

General Procedure for the Preparation of 2-Substituted 5-Oxazolecarbaldehydes. Entry 2: A solution of **6** or **8a**−**j** (1.0 mmol), **2** (0.05 mmol), and BQ (1.0 mmol) in 8 mL of DMF/THF (3:5) was heated at 60 °C for 3 h. After being washed with brine, the solution was extracted with Et_2O (2 × 20 mL). The organic layer was dried over Na_2SO_4 and taken to dryness under reduced pressure. The crude mixture was chromatographed on a silica gel column giving **7** or **9a**−**j**. **Entry 15:** A solution of $CuCl_2$ (0.1 mmol) and **2** (0.05 mmol) in DMF (20 mL) was stirred at room temperature for 30 min. A solution of **6** or **8a**−**j** (1.0 mmol) in 15 mL of DMF was added, and then the resulting mixture was warmed at 100 °C for 2 h under oxygen atmosphere. The solution was treated with brine and extracted with Et_2O (2 × 40 mL). The organic layer was dried over Na_2SO_4 and taken to dryness under reduced pressure. The crude mixture was chromatographed on a silica gel column giving **7** or **9a**−**j**.

2-(4-Methoxyphenyl)oxazole-5-carbaldehyde (9a). Yield 48%. Mp 140−142 °C (diisopropyl ether). IR (nujol) 1680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (3H, s), 7.01 (2H, d, J = 8.8 Hz), 7.93 (1H, s), 8.13 (2H, d, J = 8.8 Hz), 9.79 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0 (q), 114.8 (d), 114.9 (d), 118.8 (s), 130.1 (d), 130.5 (d), 140.1 (d), 149.7 (s), 163.4 (s), 166.2 (s), 175.4 (d). MS *m*/*z* 203 (M^+). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.88; H, 4.29; N, 7.16.

2-(2-Phenylethyl)oxazole-5-carbaldehyde (9d). Yield 61%. Oil. IR (nujol) 1683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.15−3.23 (4H, m), 7.21−7.33 (5H, m), 7.78 (1H, s), 9.74 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1 (t), 33.0 (t), 126.8 (d), 128.6 (d), 129.1 (d), 138.3 (d), 139.9 (s), 150.3 (s), 169.3 (s), 176.7 (d). MS *m*/*z* 201 (M^+). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.48; H, 5.79; N, 7.08.

2-(2-Furyl)oxazole-5-carbaldehyde (9h). Yield 37%. Mp 138−140 °C (diisopropyl ether). IR (nujol) 1682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.62−6.63 (1H, m), 7.31 (1H, d, J = 3.5 Hz), 7.68 (1H, s br), 7.94 (1H, s), 9.81 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.0 (d), 116.1 (d), 139.2 (d), 142.0 (s), 146.9 (d), 149.4 (s), 157.9 (s), 176.4 (d). MS *m*/*z* 163 (M^+). Anal. Calcd for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 59.01; H, 2.81; N, 8.35.

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Supporting Information Available: Experimental procedures, characterization data, as well as ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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