# Selective 7-*endo*-Cyclization of 3-Aza-5-alkenols through Oxidative Pd(II)-Catalyzed Olefin Oxyarylation


Silvia Gazzola[a]
Egle M. Beccalli[b]
Tea Borelli[a]
Carlo Castellano[c]
Daria Diamante[a]
Gianluigi Broggini*[a]

[a] Dipartimento di Scienza e Alta Tecnologia, Università dell'Insubria, via Valleggio 11, 22100, Como, Italy
Fax: (+39)-031-238-6449; phone: (+39)-031-238-6443.

[b] DISFARM, Sezione di Chimica Generale e Organica "A. Marchesini" Università degli Studi di Milano, via Venezian 21, 20133 Milano, Italy

[c] Dipartimento di Chimica, Università degli Studi di Milano, via Golgi 19, 20133 Milano, Italy

e-mail_ gianluigi.broggini@uninsubria.it


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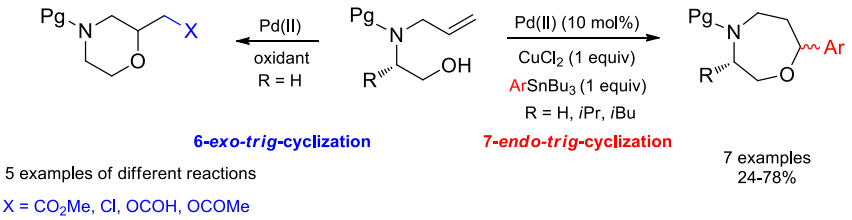



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**Abstract** 3-Aza-5-alkenols undergo selectively 7-*endo-trig* cyclization when treated with a catalytic Pd(II) species, $CuCl_2$ and $ArSnBu_3$ giving 7-aryl-substituted oxazepanes. The intramolecular alkoxylation occurs with formation of a seven-membered ring only when associated to an arylating step. Otherwise, 6-*exo-trig* reactions providing morpholine derivatives were observed.



**Key words** palladium, heterocycles, domino reactions, Wacker reaction, homogeneous catalysis, cyclization, oxyarylation


Transition metal-catalyzed reactions involving C-H bond functionalization can provide a variety of cyclic scaffolds, not easily obtained by conventional synthetic methods, from readily available starting materials.[1] In this field, oxidative palladium-catalyzed reactions were proven to be fruitful to access a wide range of compounds with various molecular architectures.[2] Indeed, the obtainment of molecular complexity through the formation of more than one bond in a single step can represent a powerful tool for organic chemists.[3] To this purpose, the couple palladium(II)/copper(II) as catalyst and oxidizing agent was demonstrated to be highly efficient to promote new procedures for the synthesis of functionalized (poly)heterocyclic systems.[4] In this context, intramolecular Pd-catalyzed processes involving a C-O bond formation starting from alcohols, phenols or carboxylic acids as well as from secondary amides, ureas and carbamates to build oxygen-containing heterocycles are known in the literature.[5] The formation of a C-O bond as one step of domino processes can be successfully combined to C-C, C-N or to another C-O bond in reactions with alkenes, alkynes or allenes.[6] Herein we describe the development of oxidative palladium-catalyzed procedures for the cyclization of 3-aza-5-alkenols in the presence of various nucleophiles, mainly focused on the oxyarylation reactions.

As a continuing interest in intramolecular transition metal-catalyzed reactions providing heterocyclic systems,[7] we reported a molecular oxygen-promoted 6-*exo-trig* Pd(II)-catalyzed cyclization that affords 1,4-oxazine derivatives from 3-aza-5-alkenols in mild conditions with molecular oxygen as sole oxidant (Figure 1, path a).[8] During our investigation, we observed that the 7-*endo*-cyclization was preferred to the most common 6-*exo* one when $R_3SnAr$ was used as the arene source (Figure 1, path b).

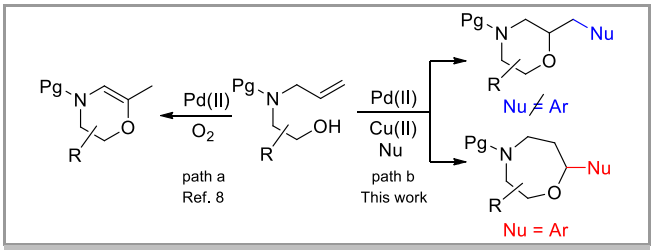
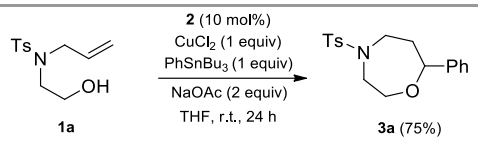



**Figure 1** Possible Pd-catalyzed *exo* and *endo* cyclization of 3-aza-5-alkenols

Optimal oxyarylation conditions were explored using a Pd(II)-catalyst, copper(II)-salt as oxidant and an aryl-organometallic compound as the aryl source. Taking ideas from the procedure for the alkene arylation by coupling with aryl stannanes,[9] the 3-aza-5-alkenol **1a** was treated with 10 mol% of $PdCl_2(MeCN)_2$ (**2**), a stoichiometric amount of $Bu_3SnPh$, an excess of $CuCl_2$ and NaOAc in tetrahydrofuran at room temperature for 24 hours. The complete conversion of the substrate led to the 4-tosyl-7-phenyl-oxazepane **3a**, isolated in 75% yield as the sole product (Scheme 1). COSY experiment was essential to confirm the structure, allowing to exclude the possible formation of a 6-benzyl-morpholine arising from a 6-*exo-trig* cyclization process.

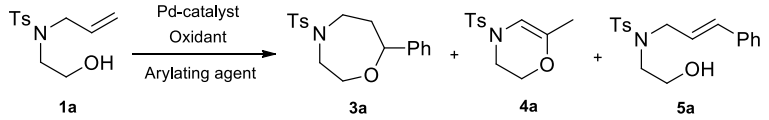



**Scheme 1** Oxyarylation reaction of 3-aza-5-alkenol **1a**

To improve the yield of the reaction, we tested further conditions by changing catalyst, oxidant, solvent, and temperature (Table 1). First of all, the cyclization also proceeded with the mentioned catalytic system in absence of base giving the oxazepane **3a** in 78% yield (Entry 2). The same seven-membered ring was isolated when a smaller amount of **2** was used, although in lower yield (Entry 3). Palladium catalyst was essential for the outcome of the reaction (Entry 4). However, the oxyarylation process can be promoted either by $Pd(OAc)_2$ or $Pd(TFA)_2$ even if in less effective manner (Entries 5-6). In addition to THF as the solvent of choice, DMF and dioxane were likewise suitable as reaction solvents, whereas the process remained incomplete after 24 hours working in $CH_2Cl_2$ (Entries 7-9). An improvement of the conversion was achieved when the reaction was carried out in DMF at 100 °C, which afforded the product in 86% yield (Entry 10). The use of $Cu(OAc)_2$ or catalytic $CuCl_2$ in oxygen atmosphere as oxidant agents supplied the exclusive or prevalent formation of the 6-methyl-4-tosyl-3,4-dihydro-2*H*-1,4-oxazine (**4a**), arising from an alkoxylation reaction followed by migration of the first-formed *exo*-cyclic C-C double bond inside the ring (Entries 11 and 12). Taking literature data on the Pd-catalyzed coupling of organoboron reagents and olefin in oxidative conditions as the model, we envisaged to test organoboron compounds as aryl source.[10] Firstly, we use **2** as catalyst, $CuCl_2$ as oxidant and phenylboronic acid or 4-tolylboronic acid as arylating agent at room temperature, but in both cases only unreacted starting material was recovered (Entries 13 and 14). Also performing the reaction at reflux failed to provide the desired oxyarylation product (Entry 15). Following the conditions successfully employed for the functionalization of alkenes reported by Mori and co-workers,[10c] we treated the substrate **1a** with 4-tolylboronic acid in the presence of $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2$ and LiOAc in DMF at 100 °C (Entry 16). After 18 h, the crude mixture revealed only the arylation product **5a**, isolated in 36% yield. The same outcome of reaction was observed using **2** as catalyst instead of $Pd(OAc)_2$ (Entry 17). Finally, we tested the conditions usefully exploited for the arylating cyclization of alkenyl amines, which involve **2** as catalyst with $Cu(OAc)_2$, 4-tolylboronic acid and $Et_3N$ as additive in MeCN at reflux (Entry 18).[11] However, despite the complete conversion of the substrate, only the compound **5a** was isolated in 44% yield from the crude mixture.

The total selective 7-*endo-trig* cyclization, which allows easy access to the oxazepane ring, prompted us to extend the oxyarylating conditions to other 3-aza-5-alkenols in order to have evidences for a general behaviour of this catalytic system (Scheme 2).[12] The reactions on the *O*-allyl derivatives **1b-e** were carried out using 10 mol% of **2**, 1 equivalent of $CuCl_2$ and $Bu_3SnPh$ in THF. Similarly to **1a**, all the substrates gave 7-membered ring products. In this case milder conditions were proven to be enough for the cyclization because reactions were

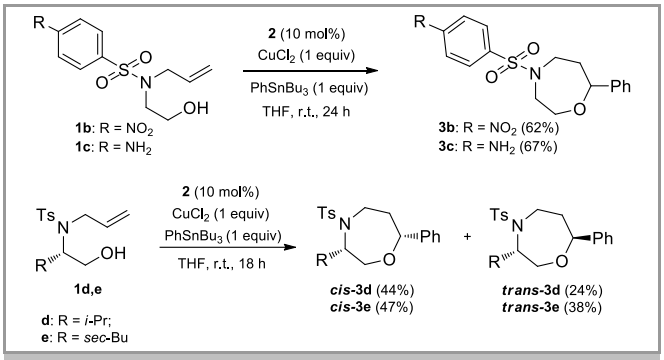
**Table 1** Optimization conditions for 7-*endo-trig* oxyarylation reaction[a]




| Entry | Catalyst | Oxidant | Arylating agent | Solvent | Temp (°C) | Product (%)[b] |
|---|---|---|---|---|---|---|
| 1[c] | **2** | $CuCl_2$ | $Bu_3SnPh$ | THF | 25 | **3a** (75) |
| 2 | **2** | $CuCl_2$ | $Bu_3SnPh$ | THF | 25 | **3a** (78) |
| 3[d] | **2** | $CuCl_2$ | $Bu_3SnPh$ | THF | 25 | **3a** (62) |
| 4 | - | $CuCl_2$ | $Bu_3SnPh$ | THF | 25 | SM |
| 5 | $Pd(OAc)_2$ | $CuCl_2$ | $Bu_3SnPh$ | THF | 25 | **3a** (64) |
| 6 | $Pd(O_2CCF_3)_2$ | $CuCl_2$ | $Bu_3SnPh$ | THF | 25 | **3a** (67) |
| 7 | **2** | $CuCl_2$ | $Bu_3SnPh$ | DMF | 25 | **3a** (61) |
| 8 | **2** | $CuCl_2$ | $Bu_3SnPh$ | Dioxane | 25 | **3a** (49) |
| 9 | **2** | $CuCl_2$ | $Bu_3SnPh$ | $CH_2Cl_2$ | 25 | **3a** (13) |
| 10[e] | **2** | $CuCl_2$ | $Bu_3SnPh$ | DMF | 100 | **3a** (86) |
| 11 | **2** | $Cu(OAc)_2$ | $Bu_3SnPh$ | THF | 25 | **4a** (47) |
| 12[f] | **2** | $CuCl_2/O_2$ | $Bu_3SnPh$ | THF | 25 | **3a** (8) + **4a** (42) |
| 13 | **2** | $CuCl_2$ | $PhB(OH)_2$ | THF | 25 | SM |
| 14 | **2** | $CuCl_2$ | 4-tolylB$(OH)_2$ | THF | 25 | SM |
| 15 | **2** | $CuCl_2$ | $PhB(OH)_2$ | THF | Reflux | -[g] |
| 16[h] | $Pd(OAc)_2$ | $Cu(OAc)_2$ | 4-tolylB$(OH)_2$ | DMF | 100 | **5a** (36) |
| 17[i] | **2** | $Cu(OAc)_2$ | 4-tolylB$(OH)_2$ | DMF | 100 | **5a** (40) |
| 18[j] | **2** | $Cu(OAc)_2$ | 4-tolylB$(OH)_2$ | MeCN | Reflux | **5a** (44) |

[a] Reaction conditions: **1a** (0.4 mmol), catalyst (10 mol%), oxidant (1.0 equiv), arylating agent (1 equiv), solvent (5 mL) for 24 h, unless otherwise noted.
[b] Yield of isolated products.
[c] Reaction performed in the presence of NaOAc (2 equiv).
[d] 5 mol% of **2** instead of 10 mol%.
[e] The reaction was completed after 8 h.
[f] $CuCl_2$ (10 mol%).
[g] A complex mixture of tarry products was obtained.
[h] **1a** (0.4 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2 equiv), 4-tolylB$(OH)_2$ (1 equiv), LiOAc (3 equiv), DMF (10 mL) at 100 °C for 18 h.
[i] Conditions (h) with **2** (10 mol%) as catalyst.
[j] **1a** (0.4 mmol), **2** (10 mol%), $Cu(OAc)_2$ (3 equiv), 4-tolylB$(OH)_2$ (0.6 mmol), $Et_3N$ (2 equiv), MeCN (5 mL) at reflux for 24 h.

fruitfully accomplished at room temperature in shorter timeframes (see, Table 1, Entry 10). For instance, 3-aza-5-alkenols **1b,c** provided the oxazepanes **3b**[13] and **3c** in similarly good yields, excluding any issues arising from different protecting groups. Compounds **1d,e**, deriving from (+)-valinol and (+)-isoleucinol respectively, also underwent cyclization process affording two diastereoisomeric 7-membered ring products (*cis/trans* **3d** and *cis/trans* **3e**). Thus, although the reaction resulted ineffective from the stereochemical point of view, also with the enantiopure chiral alkenols the 7-*endo* approach was solely operating. The X-ray crystal structure analysis of the compounds *trans*-**3e** allowed to confirm the oxazepane structure with two independent molecules in the asymmetric unit as well as to assign the *S*-configuration to the new stereocenter (Figure 2).[14] Assignment of the absolute configuration to all the products was then possible through a direct comparison between the similar $^{1}H$ and $^{13}C$ NMR spectra.




**Scheme 2** Oxyarylation process on 3-aza-5-alkenols **1b-d**

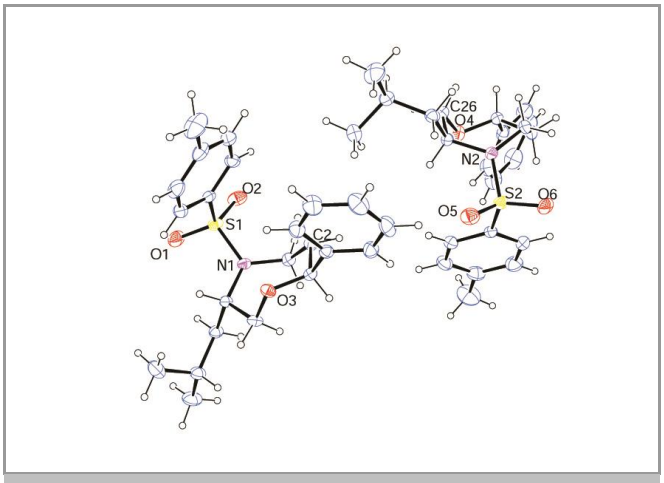
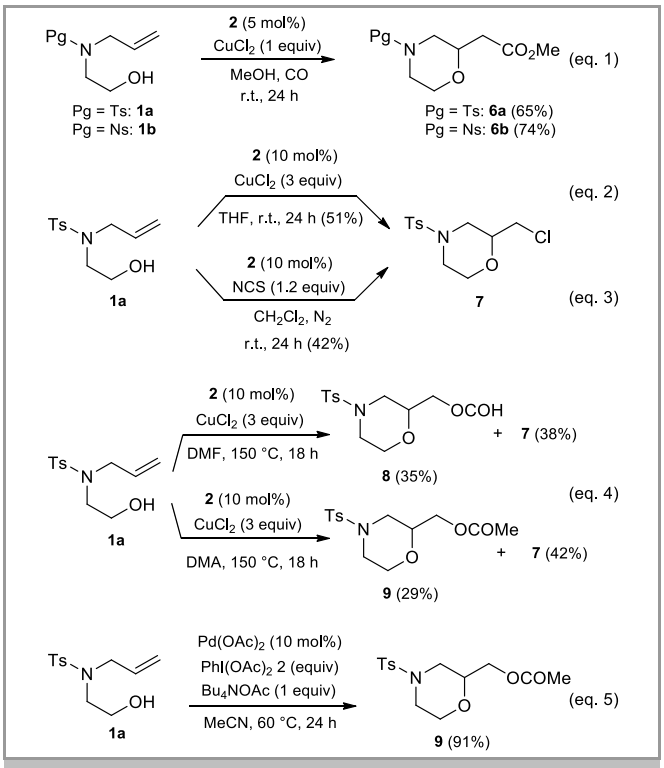



**Figure 2** ORTEP drawing of compound *trans*-**3e** at 25% probability level

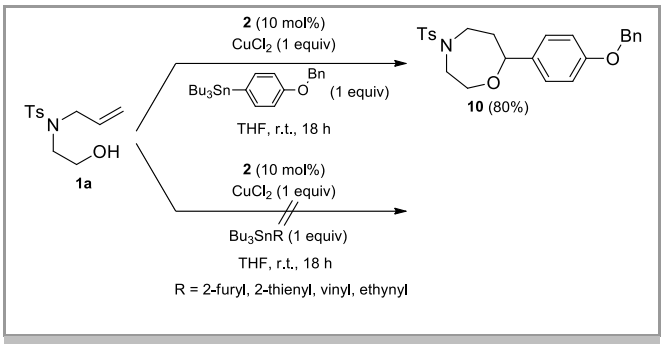
This general oxyarylation outcome affording only the 7-*endo* product with total selectivity, is intriguing and, in one sense, unexpected. Wondering whether this regioselectivity depends on the substrate or on the reaction conditions, we decided to investigate other palladium-catalyzed procedures typically occurring by *exo*-cyclization. First of all, we tried carbonylative conditions on the alkenols **1a,b** with a catalytic amount of **2** (5 mol%) and a stoichiometric amount of $CuCl_2$ in methanol under CO (1 atm) at room temperature for 24 h.[15] In both cases, the reactions led to the 2-[(methoxycarbonyl)methyl]-morpholines (**6a** and **6b**) as the sole products, isolated in 65% and 74% yield, respectively, confirming that those conditions are able to promote an alkoxylation/carboalkoxylation reaction (Scheme 3, equation 1). An alkoxychlorination process was subsequently investigated under two different conditions based on the presence of **2** as catalyst (Scheme 3, equations 2 and 3).[16,17] Working either with an excess of $CuCl_2$ in THF at room temperature or NCS as the chlorine source in $CH_2Cl_2$ at room temperature, the cyclization occurred with formation of the 5-chloromethyl-morpholine **7**. We also tried to achieve an alkoxylation/esterification sequence on substrate **1a** using analogue conditions of our previous work focused on an arylation/esterification procedure of indolyl allylamides.[18] The best result was obtained by use of **2** as catalyst and 3 equivalents of $CuCl_2$ in DMF as well as DMA at 150 °C, which furnished formic and acetic esters (**8** and **9**, respectively) beside the chloro-derivative **7** (Scheme 3, equation 4). Worthy of note, despite the low selectivity, the outcome of the reaction also in this case supplied only 6-membered ring products. Finally, the established conditions to carry out the Pd-catalyzed amino- or oxyacetoxylation of alkenes in the presence of $PhI(OAc)_2$ as oxidant agent *via* Pd(IV)-intermediates were tested.[19] The treatment of **1a** with $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2 equiv), $Bu_4NOAc$ (1 equiv) in acetonitrile at 60 °C for 24 h, selectively yielded the 5-acetoxymethyl-morpholine **9** (Scheme 3, equation 5). On the whole, all the Pd-catalyzed reactions collected in Scheme 3 resulted in the 6-*exo-trig* cyclization, confirming that the oxyarylation is the sole procedure which occurs with 7-*endo-trig* cyclization.




**Scheme 3** Different synthetic transformation performed on alkenols **1a** and **1b**

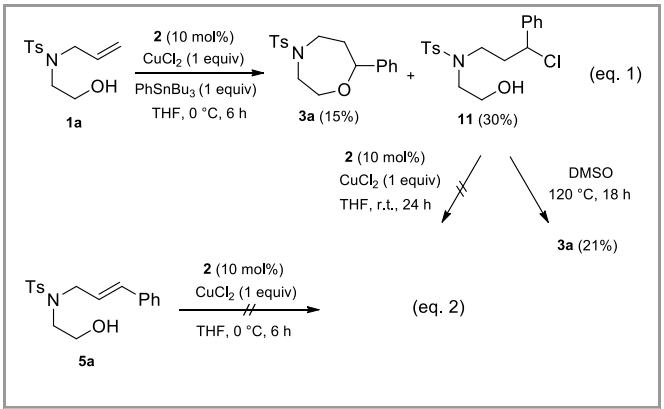
To shed light on the central role of the organotin reagent for the success of the *endo*-cyclization process, other organotin derivatives were tested. The overall results obtained suggest that only arylstannanes are suitable substrates for domino

intramolecular oxylation reactions. Actually, the use of 4-benzyloxyphenyl-(tributyl)stannane was found to be effective for the 7-*endo-trig* process, providing the oxazepane **10**[20] in 80% (Scheme 4). Conversely, heteroaryl substrates such as 2-furyl and 2-thienyl (tributyl)stannanes, vinyl and ethynyl (tributyl)stannanes gave only complex mixtures of degradation compounds.




**Scheme 4** Oxidative alkoxylation reactions of 3-aza-alkenol **1a** with organotin derivatives

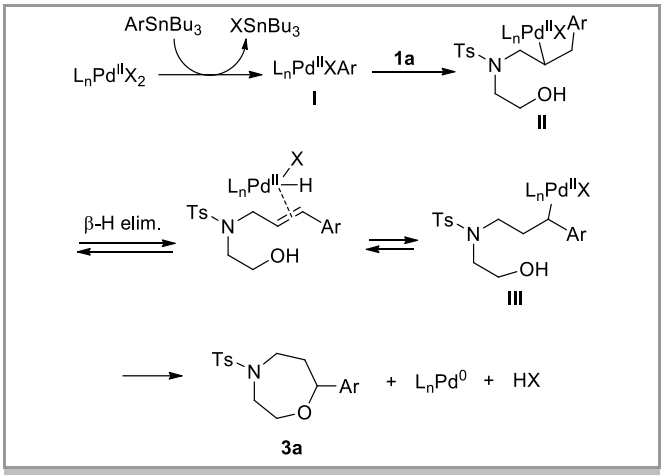
At this point, some experiments were performed in order to elucidate the outcome of the oxyarylation reaction. In order to exclude the participation of a chlorophenyl derivative as possible first-formed reaction product followed by cyclization,[21] we investigated the behavior of compound **11**, obtained carrying out the reaction at 0 °C (Scheme 5, equation 1). In the standard conditions (Entry 2, Table 1) no conversion of the substrate was observed. Effectively, the intramolecular displacement of the chlorine atom of **11** by the hydroxyl group, giving the desired oxazepane ring **3a**, was achieved solely working at 120 °C in DMSO as solvent. On the other hand, an hydroalkoxylation process on the first-formed product of olefin arylation was ruled out due to the unfruitful oxidative Pd(II)-catalyzed cyclization performed on the derivative **5a** (Scheme 5, equation 2).




**Scheme 5** Experimental attempts for mechanism elucidation

The results depicted in Scheme 5 suggest that the formation of the aryl-substituted seven-membered products involves the cyclization step on a palladium intermediate. The proposed mechanism to rationalize the selective 7-*endo-trig* reaction is outlined in Scheme 6. Initially, olefin insertion in the Pd-aryl bond of the Pd(II)-complex **I**, arising from transmetalation with $Bu_3SnAr$,[22] generates the σ-alkyl-Pd(II) intermediate **II**. This latter is susceptible of reversible β-hydride elimination followed by olefin insertion with opposite regiochemistry involving selectively the benzylic position.[23] The resulting favoured Pd-benzyl complex **III** is intramolecularly intercepted by the OH group to give the final product and the Pd(0) species after elimination of HX. The presence of copper chloride is essential to reconvert the Pd(0) to the active Pd(II).

The possible alternative and competitive mechanistic pathway based on a first intramolecular formation of the C-O bond followed by transmetalation of the σ-alkyl-Pd(II) intermediate with $Bu_3SnAr$, was reasonably ruled out due to the results of the reactions performed with different nucleophiles than aryls, that afforded 1,4-oxazine derivatives through 6-*exo-trig* cyclization.




**Scheme 6** Proposed mechanism for the 7-*endo-trig* cyclization depicted on substrate **1a**

In conclusion, we have developed a direct oxyarylation of unactivated 3-aza-5-alkenols by oxidative palladium-catalyzed conditions which occurs selectively by a 7-endo-trig process. The ability of the catalytic system to promote this reaction in mild conditions at room temperature open up the possibility to develop a stereoselective procedure using chiral ligands.

## Acknowledgment

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## Supporting Information

YES (this text will be updated with links prior to publication)

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(12) **General procedure for the 7-*endo-trig* oxyarylation process:** A mixture of *N*-allylaminoalcohol **1** (1.0 equiv.), $PdCl_2(CH_3CN)_2$ (0.1 equiv.), $CuCl_2$ (1.0 equiv.), and $PhSnBu_3$ (1.0 equiv.) in THF (0.2 M) was stirred at room temperature for 18-24 h. The solvent was evaporated under reduced pressure and water (10 mL) was added. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL), then the organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding oxazepane **3**.

(13) **Spectroscopic Data of 7-Phenyl-4-(4-nitrobenzenesulfonyl)-1,4-oxazepane (3b):** $^1$H NMR (400 MHz, $CDCl_3$): δ 1.92-2.03 (m, 1H), 2.24-2.31 (m, 1H), 3.27 (ddd, *J* = 13.2, 10.0, 2.8 Hz, 1H), 3.35-3.42 (m, 1H), 3.54-3.59 (m, 1H), 3.67 (dt, *J* = 13.6, 2.8 Hz, 1H), 3.73 (ddd, *J* = 12.4, 7.6, 4.4 Hz, 1H), 4.08 (dt, *J* = 13.2, 3.2 Hz, 1H), 4.62 (dd, *J* = 9.6, 4.4 Hz, 1H), 7.14-7.28 (m, 5H), 7.94 (d, *J* = 8.4, 2H), 8.33 (d, *J* = 8.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 37.9 (t), 46.3 (t), 51.7 (t), 69.9 (t), 81.6 (d), 124.5 (d), 125.5 (d), 127.6 (d), 128.1 (d), 128.5 (d), 142.4 (s), 149.9 (s), 150.0 (s). MS: (m/z) 362 ($M^+$). Anal. Calcd for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73. Found: C, 56.11; H, 5.27; N, 7.48.

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(20) **Spectroscopic Data of 7-[4-(Benzyloxy)phenyl]-4-(4-methylbenzenesulfonyl)-1,4-oxazepane (10):** $^1$H NMR (400 MHz, $CDCl_3$): δ 1.93-1.99 (m, 1H), 2.16-2.21 (m, 1H), 2.37 (s, 3H), 3.15-3.19 (m, 1H), 3.23-3.29 (m, 1H), 3.48-3.54 (m, 1H), 3.58-3.70 (m, 2H), 3.99 (dt, *J* = 12.8, 2.9 Hz, 1H), 4.54 (dd, *J* = 5.6, 9.6 Hz, 1H), 4.97 (s, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.24-7.35 (m, 7H), 7.63 (d, *J* = 8.1 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 21.5 (q), 37.6 (t), 46.2 (t), 51.7 (t), 69.8 (t), 70.0 (t), 81.1 (d), 114.8 (d), 126.9 (d), 127.0 (d), 127.4 (d), 127.9 (d), 128.6 (d), 129.8 (d), 135.3 (s), 135.9 (s), 136.9 (s), 143.4 (s), 158.1 (s). MS: (*m/z*) 437 ($M^+$). Anal. Calcd for $C_{25}H_{27}NO_4S$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.74; H, 5.98; N, 3.47.

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