Synlett S. Gazzola et al. Letter

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

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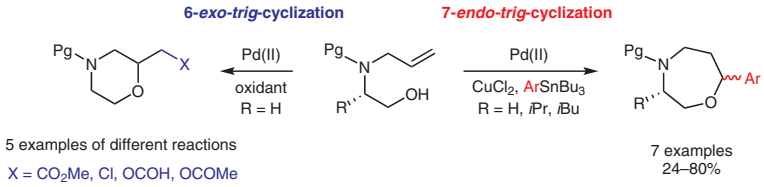


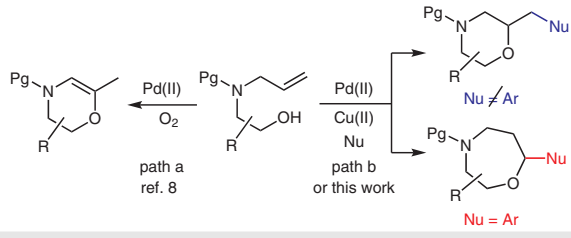
Received: 31.08.2017
Accepted after revision: 04.10.2017
Published online: 08.11.2017
DOI: 10.1055/s-0036-1590939; Art ID: st-2017-d0658-l

Abstract 3-Aza-5-alkenols undergo selective 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 with 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 have proven to be fruitful in accessing a wide range of compounds with a range of molecular architectures.[2] Indeed, obtaining molecular complexity through the formation of more than one bond in a single step presents a powerful synthetic tool.[3] To this purpose, the palladium(II)/copper(II) combination, as catalyst and oxidizing agent respectively, has been demonstrated to be productive in developing 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 with C–C, C–N, or to another C–O bond-forming step in reactions with alkenes, alkynes, or allenes.[6] Herein, we describe the development of an oxidative palladium-catalyzed procedures for the cyclization of 3-aza-5-alkenols in the presence of various nucleophiles, mainly focused on oxyarylation reactions.

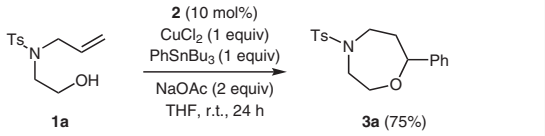
In our continuing interest in intramolecular transition-metal-catalyzed reactions to provide access to heterocyclic systems,[7] we have reported a molecular oxygen-promoted 6-*exo*-*trig* Pd(II)-catalyzed cyclization that affords 1,4-oxazine derivatives from 3-aza-5-alkenols under mild conditions with molecular oxygen as the sole oxidant (Scheme 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 (Scheme 1, path b).



Scheme 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 a lead 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. In this way, com-

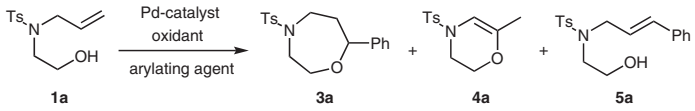
plete conversion of the substrate led to the 4-tosyl-7-phenyl-oxazepane **3a** being isolated in 75% yield as sole product (Scheme 2). A COSY experiment was essential to confirm the structure, allowing us to exclude the possible formation of a 6-benzyl-morpholine arising from a 6-*exo-trig* cyclization process.



Scheme 2 Oxyarylation reaction of 3-aza-5-alkenol **1a**

To improve the yield of the reaction, we examined further conditions by changing catalyst, oxidant, solvent, and temperature (Table 1). The cyclization also proceeded with the above catalytic system in the absence of base giving the oxazepane **3a** in 78% yield (Table 1 entry 2). The same seven-membered ring was isolated when a smaller amount of **2** was used, although in lower yield (Table 1 entry 3). The palladium catalyst was essential for the successful outcome of the reaction (Table 1 entry 4). However, the oxyarylation process could be promoted either by $Pd(OAc)_2$ or $Pd(O_2CCF_3)_2$ even in the less effective manner (Table 1 entries 5 and 6). In addition to THF as solvent of choice, DMF and dioxane were likewise suitable as reaction solvents, whereas the process remained incomplete after 24 hours using CH_2Cl_2 (Table 1 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 (Table 1 entry 10). The use of $Cu(OAc)_2$ or catalytic $CuCl_2$ under oxygen atmosphere as oxidants 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 re-

Table 1 Optimization Conditions for 7-*endo-trig* Oxyarylation Reaction[a]

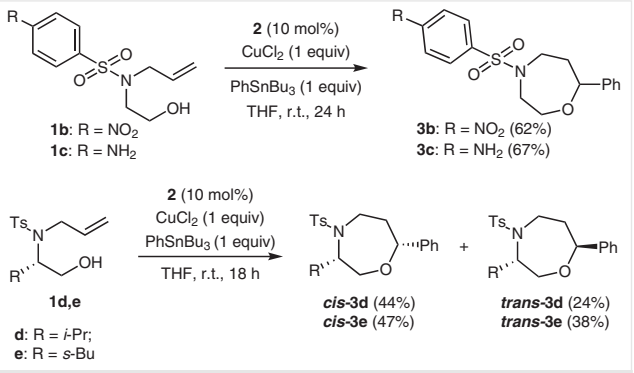


Entry	Catalyst	Oxidant	Arylating agent	Solvent	Temp (°C)	Product (%)[b]
1[c]	**2**	$CuCl_2$	Bu_3SnPh	THF	25	**3a** (75)
2	**2**	$CuCl_2$	Bu_3SnPh	THF	25	**3a** (78)
3[d]	**2**	$CuCl_2$	Bu_3SnPh	THF	25	**3a** (62)
4	–	$CuCl_2$	Bu_3SnPh	THF	25	SM
5	$Pd(OAc)_2$	$CuCl_2$	Bu_3SnPh	THF	25	**3a** (64)
6	$Pd(O_2CCF_3)_2$	$CuCl_2$	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 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 polymeric products was obtained.
[h] Reaction conditions: **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] Reaction conditions: **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.

action followed by migration of the first-formed *exo*-cyclic C–C double bond inside the ring (Table 1 entries 11 and 12). Using literature data on the Pd-catalyzed coupling of organoboron reagents and olefin in oxidative conditions as a precedent, we considered testing organoboron compounds as the aryl source.[10] Firstly, we used **2** as catalyst, $CuCl_2$ as oxidant and phenylboronic acid, and 4-tolylboronic acid as arylating agents at room temperature but, in both cases, only unreacted starting material was recovered (table 1 entries 13 and 14). Performing the reaction at reflux also failed to provide the desired oxyarylation product (Table 1 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 (Table 1 entry 16). After 18 hours, the crude mixture revealed only the arylation product **5a**, isolated in 36% yield. The same outcome was observed using **2** as catalyst instead of $Pd(OAc)_2$ (Table 1 entry 17). Finally, we tested the conditions exploited for the arylating cyclization of alkenyl amines, utilizing **2** as catalyst with $Cu(OAc)_2$, 4-tolylboronic acid, and Et_3N as additive in MeCN at reflux (Table 1 entry 18).[11] However, despite the complete conversion of the substrate, the desired product **5a** was only isolated in 44% yield from the crude mixture.

The totally 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 provide evidence for a general behavior of this catalytic system (Scheme 3).[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. As with **1a**, all the substrates gave seven-membered ring products. In this case milder conditions were found to be sufficient for cyclization because reactions were complete at room temperature in shorter reaction times (see Table 1, entry 10).



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

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, affording two diastereoisomeric seven-membered ring products (*cis*/*trans*-**3d** and *cis*/*trans*-**3e**). Thus, although the reaction was unselective from a stereochemical viewpoint, with the enantiopure chiral alkenols the 7-*endo* approach was solely operating. X-ray crystal-structure analysis of the *trans*-**3e** allowed the confirmation of the oxazepane structure with two independent molecules in the asymmetric unit as well as assignment of the *S*-configuration to the new stereocenter (Figure 1).[14] Assignment of the absolute configuration to all the products was then based on their similar ^1H NMR and ^{13}C NMR spectra.

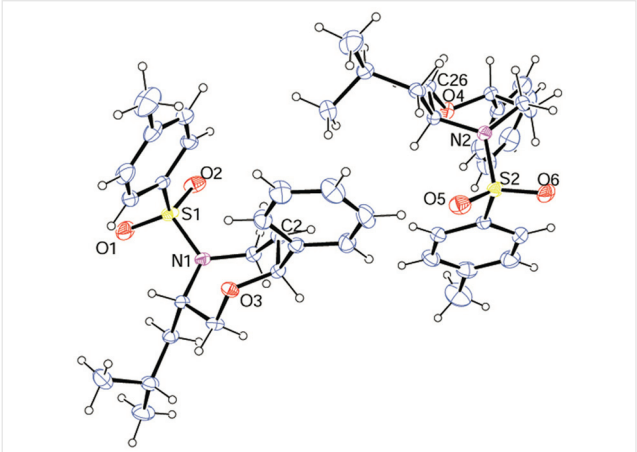
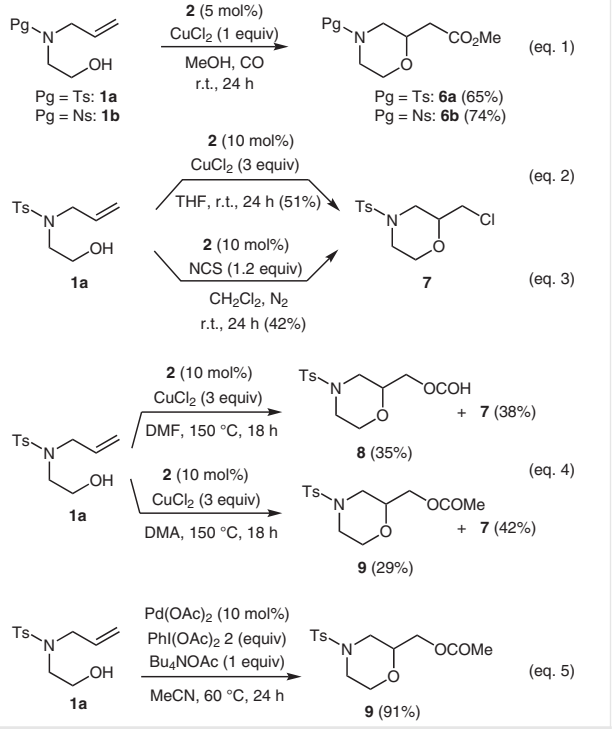


Figure 1 ORTEP drawing of compound *trans*-**3e** at 25% probability level

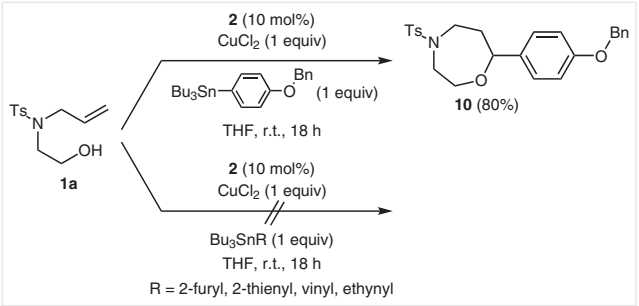
This general oxyarylation outcome affording only the 7-*endo* product with total selectivity is intriguing and, in one sense, unexpected. Wondering whether this regioselectivity depends on the substrate or on the reaction conditions, we decided to investigate other palladium-catalyzed procedures that typically occur by *exo*-cyclization. Firstly, we examined 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 hours.[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 4, eq. 1). An alkoxychlorination process was subsequently investigated under two different conditions based on the presence of **2** as catalyst (Scheme 4, eq. 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 attempted an alkoxylation/esterification sequence on substrate **1a** using analogous conditions to 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 equiv-

alents of $CuCl_2$ in DMF as well as DMA at 150 °C. These conditions furnished formic and acetic esters (**8** and **9**, respectively) as well as the chloro derivative **7** (Scheme 4, eq. 4). It is noteworthy that, despite the low selectivity, the outcome of the reaction also supplied only six-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 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 hours, selectively yielded the 5-acetoxymethylmorpholine **9** (Scheme 4, eq. 5). On the whole, all the Pd-catalyzed reactions represented in Scheme 4 resulted in the 6-*exo*-*trig* cyclization, confirming that the oxyarylation is the sole procedure that occurs with 7-*endo*-*trig* cyclization.



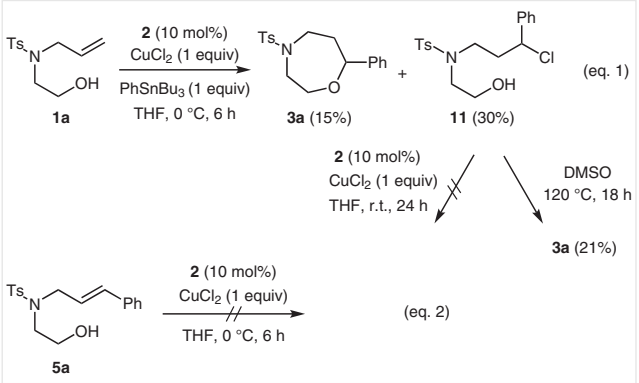
Scheme 4 Different synthetic transformation performed on alkenols **1a** and **1b**

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 obtained results suggest that only arylstannanes are suitable substrates for domino intramolecular oxylation reactions. 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 5); 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 5 Oxidative alkoxylation reactions of 3-aza-alkenol **1a** with organotin derivatives

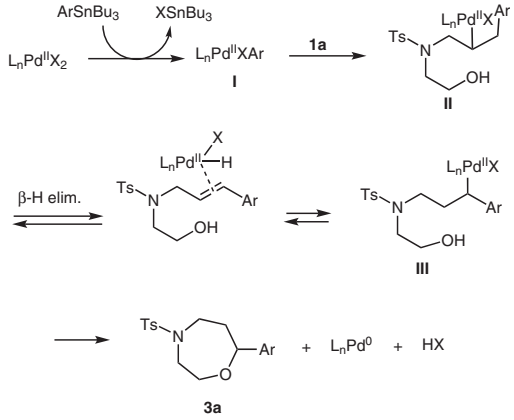
At this point, some experiments were performed in order to elucidate the mechanistic basis of the oxyarylation reaction. In order to exclude the participation of a chlorophenyl derivative as a possible first-formed intermediate, followed by cyclization,[21] we investigated the behavior of compound **11**, obtained carrying out the reaction at 0 °C (Scheme 6, eq. 1). Under the standard conditions (Table 1 entry 2) no conversion of the substrate was observed. The intramolecular displacement of the chlorine atom of **11** by the hydroxyl group, giving the desired oxazepane ring **3a**, was only achieved solely by working at 120 °C in DMSO as solvent. On the other hand, a hydroalkoxylation process on the first-formed product of olefin arylation was ruled out due to the unproductive oxidative Pd(II)-catalyzed cyclization performed on derivative **5a** (Scheme 6, eq. 2).



Scheme 6 Experimental attempts for mechanism elucidation

The results depicted in Scheme 6 suggest that the formation of the aryl-substituted seven-membered products involves a cyclization step on a palladium intermediate. The proposed mechanism to rationalize the selective 7-*endo*-*trig* reaction is outlined in Scheme 7. 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 to reversible β-hydride elimination followed by olefin insertion with opposite regiochemistry, involving the benzylic position selectively.[23] The resulting favored Pd–benzyl complex **III** is

intramolecularly intercepted by the OH group to give the final product as well as the Pd(0) species after elimination of HX. The presence of copper chloride is essential to reconvert the Pd(0) into the active Pd(II).



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

A possible alternative and competitive mechanistic pathway, based on an initial 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 non-aryl nucleophiles that afforded 1,4-oxazine derivatives through 6-*exo-trig* cyclization.

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

Funding Information

Università degli Studi dell'Insubria and Università degli Studi di Milano are acknowledged for financial support. Support through CMST COST Action, CA15106 (CHAOS) is also gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590939.

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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. Then the solvent was evaporated under reduced pressure, and water (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica 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, 1 H), 2.24–2.31 (m, 1 H), 3.27 (ddd, *J* = 13.2, 10.0, 2.8 Hz, 1 H), 3.35–3.42 (m, 1 H), 3.54–3.59 (m, 1 H), 3.67 (dt, *J* = 13.6, 2.8 Hz, 1 H), 3.73 (ddd, *J* = 12.4, 7.6, 4.4 Hz, 1 H), 4.08 (dt, *J* = 13.2, 3.2 Hz, 1 H), 4.62 (dd, *J* = 9.6, 4.4 Hz, 1 H), 7.14–7.28 (m, 5 H), 7.94 (d, *J* = 8.4, 2 H), 8.33 (d, *J*= 8.4 Hz, 2 H). ^{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.

(14) CCDC 1519865 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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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, 1 H), 2.16–2.21 (m, 1 H), 2.37 (s, 3 H), 3.15–3.19 (m, 1 H), 3.23–3.29 (m, 1 H), 3.48–3.54 (m, 1 H), 3.58–3.70 (m, 2 H), 3.99 (dt, *J* = 12.8, 2.9 Hz, 1 H), 4.54 (dd, *J* = 5.6, 9.6 Hz, 1 H), 4.97 (s, 2 H), 6.85 (d, *J* = 8.1 Hz, 2 H), 7.12 (d, *J* = 8.1 Hz, 2 H), 7.24–7.35 (m, 7 H), 7.63 (d, *J* = 8.1 Hz, 2 H). ^{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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