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SYNTHESIS OF OXAZOLINES FROM *N*-ALLYLAMIDES USING AN ELECTROCHEMICALLY GENERATED ArS(ArSSAr)$^+$ POOL

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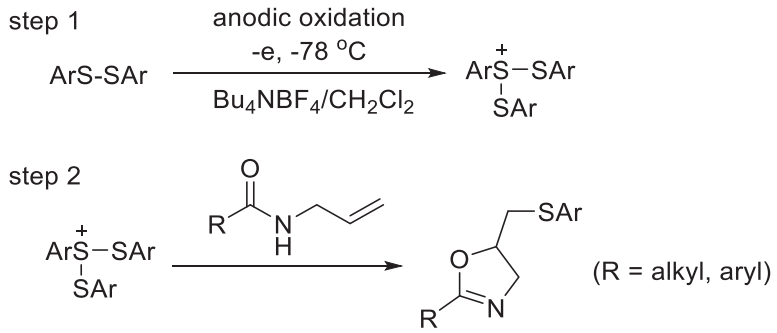
Abstract – The reaction of *N*-allylamides with ArS(ArSSAr)$^+$, which was generated and accumulated by the low-temperature anodic oxidation of ArSSAr, afforded the corresponding ArS-substituted oxazolines in moderate to good yields. *In-situ* electrochemical oxidation of ArSSAr in the presence of *N*-allylamides was also applicable. Oxazolines bearing various substituents were successfully synthesized by using the present reactions.

The synthesis of heterocyclic compounds is one of the important research topics, because heterocyclic compounds are sometimes contained in the biologically active substances, the medicinal drugs and organic materials. So far, extensive efforts have been paid for the development of synthesis of heterocycles. Among them, the cyclization[1] initiated by the electrophilic addition of a reactive species to a carbon-carbon multiple bond bearing a nucleophilic group in the same molecules serves as one of the reliable methods.

We have reported that ArS(ArSSAr)$^+$, which is generated and accumulated as a cation pool[2,3] by the low-temperature electrochemical oxidation[4,5] of diaryl disulfides (ArSSAr),[6] can be utilized as a highly reactive species of ArS$^+$ equivalent.[7-9] In this study, we have studied the reactivity of ArS(ArSSAr)$^+$ with *N*-allylamides to synthesize oxazolines bearing ArS group using the electrophilic cyclization, because the oxazoline is one of important heterocycles.[10] In the previous reports by other groups, the use of the heavy metal such as $Mn(OAc)_3$ for the reaction of ArSSAr and *N*-allylamides was developed by Mellor and co-workers.[11,12] Also, an ArS$^+$ equivalent generated by the reaction of

1-(phenylsulfanyl)pyrrolidine-2,5-dione[13a] with a catalytic amount of $BF_3 \cdot Et_2O$ reacted with *N*-allylamides to afford the ArS-substituted oxazolines.[13] However, these methods require the use of a stoichiometric amount of the heavy metal or the hazardous Lewis acid. In contrast, the electrochemistry is an easy technique to generate ArS^+ equivalent from ArSSAr in the solution.

Herein, we wish to report a two-step process consisting of the generation of $ArS(ArSSAr)^+$ pool by the electrochemical oxidation of ArSSAr (Scheme 1, step 1) followed by its reaction with *N*-allylamides (Scheme 1, step 2), which is effective in the formation of oxazolines (*ex-cell* method).[14] *Ex-cell* method can avoid unexpected oxidation of products. It was found that the *in-situ* electrochemical generation of $ArS(ArSSAr)^+$ from ArSSAr followed by the reaction with *N*-allylamides was also applicable. In addition, the use of ArSH instead of ArSSAr was also investigated.

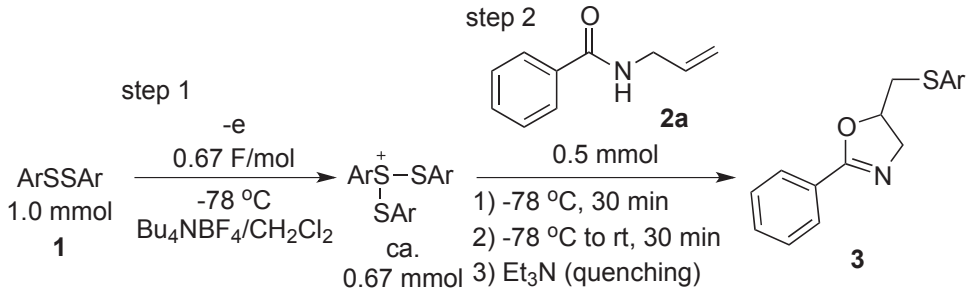


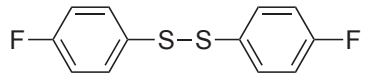
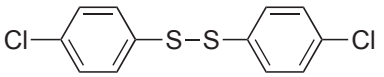
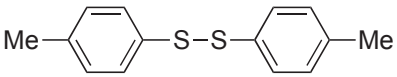
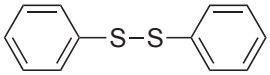
Scheme 1. Synthesis of ArS-substituted oxazolines from *N*-allylamides using electrochemically generated $ArS(ArSSAr)^+$

We first examined the reaction of *N*-allylbenzamide (**2a**) with $ArS(ArSSAr)^+$ as a model reaction. A typical procedure is as follows. The anodic oxidation of ArSSAr (**1a**, Ar = *p*-FC_6H_4, 1.0 mmol) was carried out in 0.3 M Bu_4NBF_4/CH_2Cl_2 at -78 °C using an H-type divided cell to generate and accumulate $ArS(ArSSAr)^+BF_4^-$ (ca. 0.67 mmol) in the solution, until 0.67 F/mol the electricity was consumed.[15] After the electric current was stopped, the resulting $ArS(ArSSAr)^+BF_4^-$ pool was allowed to react with *N*-allylbenzamide (**2a**) (0.50 mmol) at -78 °C for 30 min. Et_3N (1.0 mL) was then added to quench the reaction. Notably, *exo* cyclization took place exclusively to produce five-membered oxazoline **3aa** in a < 84% yield (Table 1, entry 1).[16] In addition, the reaction of $ArS(ArSSAr)^+BF_4^-$ and *N*-allylbenzamide (**2a**) at -78 °C for 30 min and additionally from -78 °C to room temperature for 30 min gave **3aa** in a 86% yield (entry 2). ArSSAr having various substituents on the aromatic ring **1b-1d** (Ar = *p*-ClC_6H_4, *p*-MeC_6H_4, and C_6H_5) could also be used, and the corresponding cyclized products **3ba-3da** were obtained in moderate to good yields (entries 3-5).

The present method was successfully applied to the synthesis of oxazolines using various *N*-allylamides as shown in Table 2.[17] The reaction of *N*-allyl-4-methylbenzamide (**2b**) with ArSSAr (Ar = *p*-FC_6H_4) in Bu_4NBF_4/CH_2Cl_2 gave **3ab** in a 64% yield (entry 1). The reactions using *N*-allyl-4-methoxybenzamide (**2c**) and *N*-allyl-4-chlorobenzamide (**2d**) afforded the desired products in good yields (entries 2 and 3). *N*-allylcyclohexanecarboxamide (**2e**) and *N*-allyloctanamide (**2f**) could be used and the corresponding products were obtained in 86% and 73% yields, respectively (entries 4 and 5). Interestingly, the reaction of *N*-allylcinnamamide (**2g**) with $ArS(ArSSAr)^+$ produced the cyclized product **3ag** in a 72% yield (entry 6). The carbon-carbon double bond between the carbonyl group and the phenyl group did not react at all.

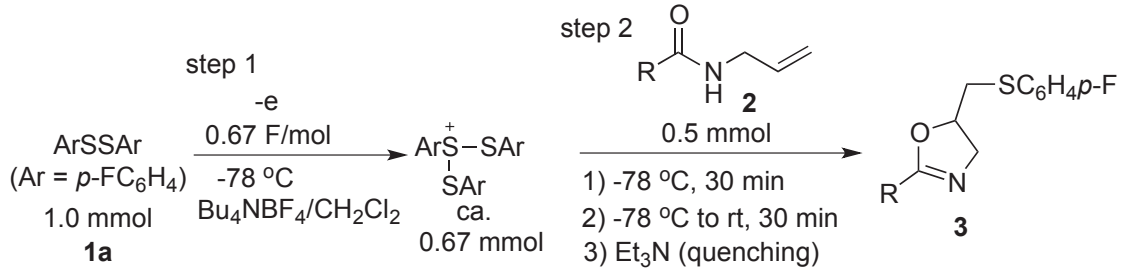
Table 1. Formation of ArS-substituted oxazolines from *N*-allylbenzamide (**2a**) using electrochemically generated $ArS(ArSSAr)^+$[a]

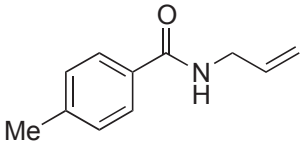
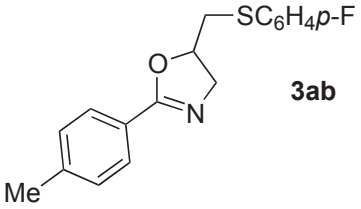
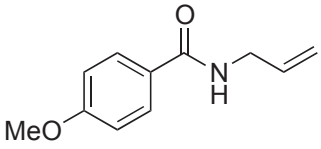
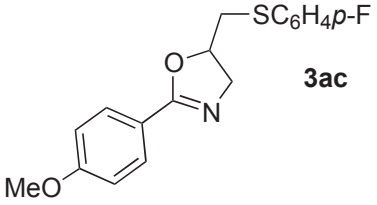
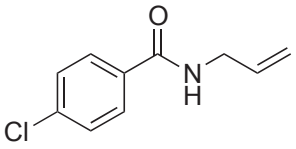
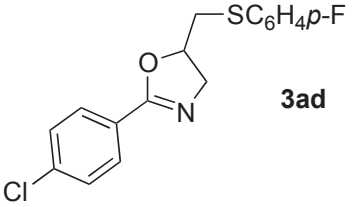
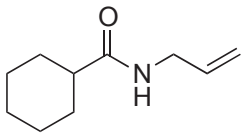
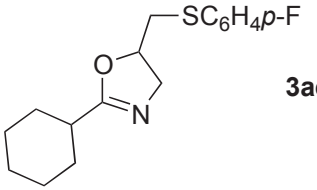
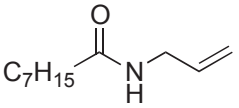
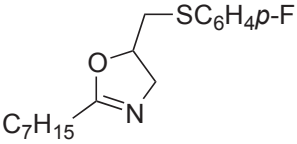
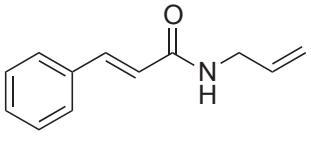
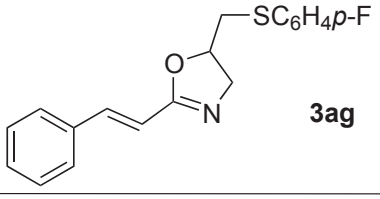


Entry	ArSSAr (**1**)		Yield (%)[b]
1		**1a**	**3aa** < 84[c,d] (86)[e,f]
2			**3aa** 86
3		**1b**	**3ba** 75
4		**1c**	**3ca** 89
5		**1d**	**3da** < 66[d] (63)[e,g]

[a] A typical procedure: ArSSAr (Ar = *p*-XC_6H_4 (X = F, Cl, Me, and H); 1.0 mmol) was electrochemically oxidized in 0.3 M Bu_4NBF_4/CH_2Cl_2 (8.0 mL) at -78 °C using 0.67 F/mol of the electricity. *N*-Allylbenzamide (**2a**) (0.5 mmol in CH_2Cl_2 (1 mL x 2)) was added to the resulting solution of $ArS(ArSSAr)^+BF_4^-$ (ca. 0.67 mmol) by the cannula transfer, and stirred at -78 °C for 30 min. Then, the temperature was gradually increased from -78 °C to rt for 30 min. Then, Et_3N (1.0 mL) was added to quench the reaction. [b] Isolated yields. [c] The resulting $ArS(ArSSAr)^+BF_4^-$ pool was allowed to react with *N*-allylbenzamide (**2a**) (0.50 mmol in CH_2Cl_2 (1 mL x 2)) at -78 °C for 30 min, and then Et_3N (1.0 mL) was added at -78 °C to quench the reaction. [d] The isolated product contained **2a** as the inpurity. [e] The yield in parentheses is based on ^1H NMR analysis after the column chromatography. [f] The purity was ca. 96% by ^1H NMR analysis. [g] The purity was ca. 79% by ^1H NMR analysis.

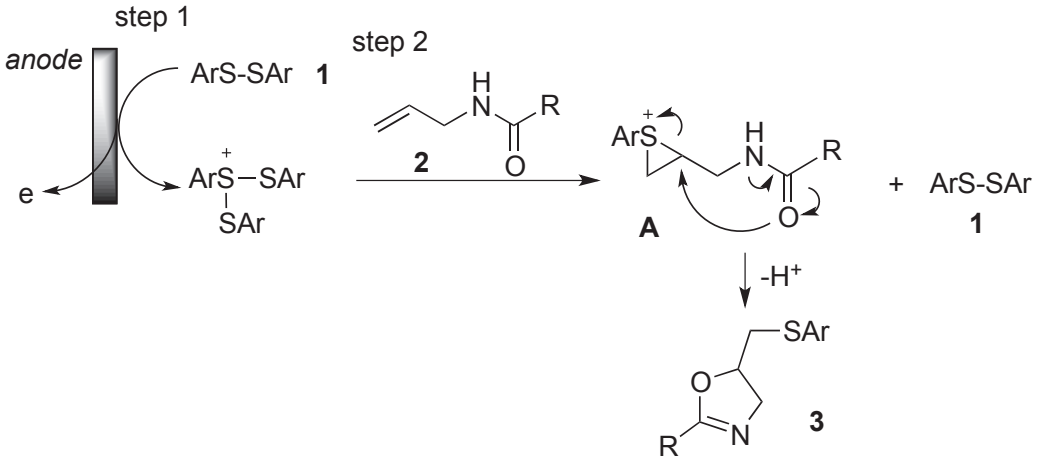
Table 2. Reactions of electro-generated $ArS(ArSSAr)^+$ pool and *N*-allylamides[a]



Entry	Amides (2)		Products		Yield (%)[b]
1		**2b**		**3ab**	64
2		**2c**		**3ac**	88
3		**2d**		**3ad**	78
4		**2e**		**3ae**	86
5		**2f**		**3af**	73[c]
6		**2g**		**3ag**	72

[a] The reaction was carried out under the same condition in Table 1. [b] Isolated yields. [c] Isolated yield after the column chromatography followed by the gel permeation chromatography (GPC).

As for the mechanism, the present reaction seems to proceed by the formation of an episulfonium ion intermediate[18,19] (Scheme 2). In the first step, the electrochemical oxidation of ArSSAr at -78 °C generates and accumulates $ArS(ArSSAr)^+$ as a cation pool. In the next step, $ArS(ArSSAr)^+$ reacts with an olefin bearing amide to give the episulfonium ion intermediate **A**, whose carbon center undergoes intramolecular nucleophilic reaction from the carbonyl group of the amide to afford the final product **3**.

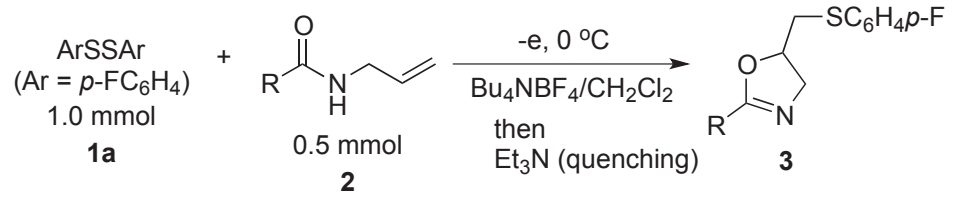


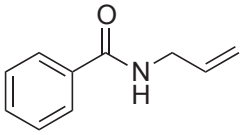
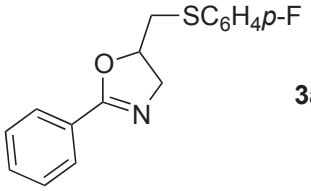
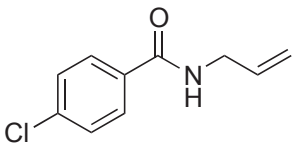
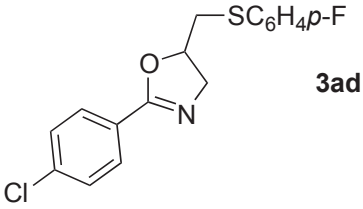
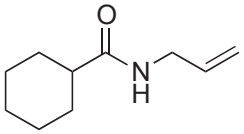
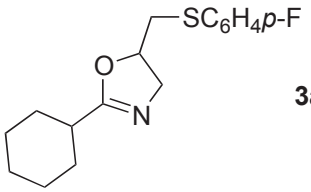
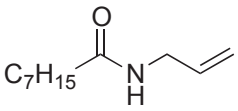
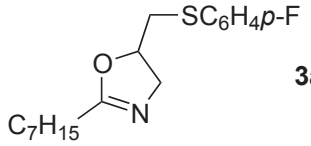
Scheme 2. Plausible reaction mechanism

The electrochemical oxidation of a mixture of ArSSAr and *N*-allylamides was also examined to obtain the desired cyclized products (Table 3). The yields in parentheses in Table 3 were determined by ^{1}H NMR analysis after the column chromatography. For example, the electrochemical oxidation of a solution of ArSSAr (1.0 mmol) and *N*-allylbenzamide (**2a**) (0.50 mmol) in Bu_4NBF_4/CH_2Cl_2 at 0 °C gave **3aa** in a < 96% yield (entry 1). This method is generally applicable to other olefinic amides such as **2d**, **2e**, and **2f**, and the corresponding cyclized products were obtained in good yields (entries 2-4).[20] In addition, ArSH can be used instead of ArSSAr. For example, the electrochemical oxidation of ArSH (**4a**, Ar = *p*-FC_6H_4, 1.0 mmol) and *N*-allylbenzamide (**2a**, 0.50 mmol) in Bu_4NBF_4/CH_2Cl_2 at 0 °C gave the cyclized oxazoline **3aa** in a 78% yield as ^{1}H NMR yield (eq 1).[20] In this reaction, it seems that ArSH is oxidized to form ArSSAr once, which is further oxidized to generate $ArS(ArSSAr)^+$. When $ArS(ArSSAr)^+$ reacts with **2a**, **3aa** is produced together with ArSSAr, which can be utilized as the substrate for the next electrochemical oxidation.

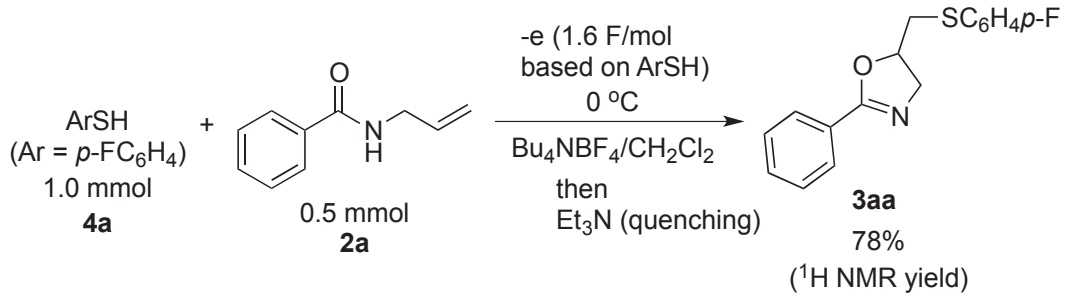
In summary, a new method for the synthesis of ArS-substituted oxazolines from *N*-allylamides was developed using $ArS(ArSSAr)^+$ pools, which were generated by the electrochemical oxidation of ArSSAr.[21,22] The ArS group can be used as a handle for further synthetic transformations thereby making the present method a useful tool for the synthesis of various compounds containing the oxazoline moiety. Further investigations of this methodology are in progress in our laboratory.

Table 3. *In-situ* electrochemical oxidation of ArSSAr (**1a**, Ar = *p*-FC_6H_4) and *N*-allylamides



Entry	Amide		Electricity (F/mol) based on ArSSAr	Product		Yield (%)[a]
1		**2a**	1.1		**3aa**	< 96 (quant)[b]
2		**2d**	1.15		**3ad**	< 90 (quant)[c]
3		**2e**	1.0		**3ae**	< 78 (85)[d]
4		**2f**	1.14		**3af**	< 71 (66)[e]

[a] Isolated yields. The isolated product contained **2** as the inpurity. The yield in parentheses is based on ^{1}H NMR analysis after the column chromatography. [b] The purity was ca. 89% by ^{1}H NMR analysis. [c] The purity was ca. 94% by ^{1}H NMR analysis. [d] The purity was ca. 95% by ^{1}H NMR analysis. [e] The purity was ca. 84% by ^{1}H NMR analysis.



(1)

ACKNOWLEDGEMENTS

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21. General procedure for the synthesis of ArS-substituted oxazoline compounds (**3aa**) using *ex-cell* method (Table 1, entry 2): The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 320 mg, dried at 250 °C/1 mm Hg for 2 h before use) and a platinum plate cathode (20 mm x 20 mm). In the anodic chamber was placed a solution of ArSSAr (**1a**, Ar = *p*-FC_6H_4, 253.9 mg, 1.0 mmol) in 0.3 M Bu_4NBF_4/CH_2Cl_2 (8.0 mL). In the cathodic chamber were placed 0.3 M Bu_4NBF_4/CH_2Cl_2 (8.0 mL) and trifluoromethanesulfonic acid (TfOH) (60 μL, d = 1.7 g/mL, ca. 0.68 mmol). The constant current electrolysis (8 mA) was carried out at -78 °C with magnetic stirring until 0.67 F/mol of electricity was consumed. Then, *N*-allylbenzamide (**2a**, 80.6 mg, 0.50 mmol in CH_2Cl_2 (1 mL x 2)) was added to the resulting solution of $ArS(ArSSAr)^+$ (ca. 0.67 mmol) by the cannula transfer, and stirred at -78 °C for 30 min. The temperature was gradually increased from -78 °C to rt for 30 min. Then, Et_3N (1.0 mL) was added to quench the reaction. The solvent was removed under reduced pressure and the residue was quickly filtered through a short column of silica gel to remove Bu_4NBF_4. The silica gel was washed with ether, and the crude material was purified by flash chromatography (hexane/AcOEt = 3:2) to obtain the product **3aa** (123.3 mg, 86%).
22. Selected spectral data of products. 5-(((4-Fluorophenyl)thio)methyl)-2-phenyl-4,5-dihydrooxazole

(**3aa**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.24 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.88 (dd, *J* = 15.0, 6.8 Hz, 1H), 4.15 (dd, *J* = 15.0, 9.6 Hz, 1H), 4.82 (dq, *J* = 9.6, 6.8 Hz, 1H), 6.94-7.02 (m, 2H), 7.35-7.50 (m, 5H), 7.83 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.7, 59.5, 78.2, 116.2 (d, *J* = 21.9 Hz), 127.4, 128.0, 128.2, 129.8 (d, *J* = 2.9 Hz), 131.4, 133.4 (d, *J* = 7.6 Hz), 162.1 (d, *J* = 246.0 Hz), 163.6; HRMS (EI) calcd for $C_{16}H_{14}FNOS$: 287.0780, found: 278.0777.

5-(((4-Chlorophenyl)thio)methyl)-2-phenyl-4,5-dihydrooxazole (**3ba**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.25 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.88 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.15 (dd, *J* = 15.2, 9.6 Hz, 1H), 4.84 (dq, *J* = 9.6, 6.4 Hz, 1H), 7.20-7.29 (m, 2H), 7.31-7.42 (m, 4H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.7, 59.5, 78.1, 127.3, 128.0, 128.2, 129.1, 131.3, 131.7, 132.8, 133.5, 163.6; HRMS (ESI) calcd for $C_{16}H_{14}ClNNaOS$ (MNa^+): 326.0377, found: 326.0385.

2-Phenyl-5-((4-tolylthio)methyl)-4,5-dihydrooxazole (**3ca**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.02 (dd, *J* = 14.0, 7.2 Hz, 1H), 3.28 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.87 (dd, *J* = 15.2, 6.8 Hz, 1H), 4.14 (dd, *J* = 15.2, 9.6 Hz, 1H), 4.77-4.86 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.32-7.41 (m, 4H), 7.46 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 39.1, 59.5, 78.3, 127.5, 128.1, 128.2, 129.8, 131.1, 131.2, 131.3, 137.1, 163.7; HRMS (EI) calcd for $C_{17}H_{17}NOS$: 283.1031, found: 283.1028.