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In Situ Generation of Nitroso Compounds from Catalytic Hydrogen Peroxide Oxidation of Primary Aromatic Amines and Their One-Pot Use in Hetero-Diels–Alder Reactions

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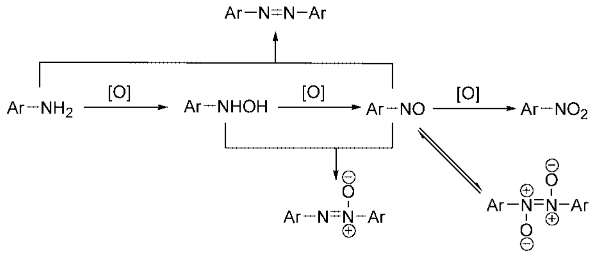
A method for in situ generation of nitroso compounds from organoselenium-catalyzed oxidation of anilines by hydrogen peroxide was developed. The generated nitroso compounds were subsequently used in hetero-Diels–Alder reactions. A variety of oxazines were synthesized in reasonable to good yields by this one-pot procedure using primary aromatic amines with different substituents and various conjugated dienes. This strategy might facilitate the current methodologies for nitroso chemistry since no isolation or purification of the nitroso compounds is required.

Introduction

Since their emergence over one century ago,[1] nitroso compounds have been used as powerful synthetic reagents in a variety of organic transformations, such as nitroso aldol reactions,[2] nitroso ene reactions,[3] Diels–Alder cycloadditions,[4] additions of Grignard reagents,[5] and couplings with amines to yield azoarenes.[6] Recently, there has been an increased use of nitroso chemistry in the area of asymmetric catalysis.[2–4] Methods for the preparation of these interesting compounds from primary amines include direct oxidation by peracids (particularly Caro's acid),[7] potassium permanganate[8] or molybdic peroxo complexes.[9] Catalytic oxidations with H_2O_2 as terminal oxidant in the presence of rhenium,[10] tungsten,[11] molybdenum[9] or selenium oxides[6d] catalysts for the oxidation of amines to nitroso compounds have been reported. However, these catalytic oxidation procedures are often slow, which might lead to the formation of dimeric byproducts such as azo or azoxy derivatives as well as to over-oxidation to the nitro compounds (Scheme 1).[12] The ultimate goal with the present work is to develop coupled oxidation systems in which PhNO is the key reagent/catalyst and where the latter is generated in situ from aniline. Herein we report an efficient and selective oxidation of primary aromatic amines to nitroso compounds with H_2O_2 catalyzed by diphenyl diselenide (PhSeSePh). Moreover, a one-pot procedure for the synthesis of oxazines (hetero-Diels–Alder adducts) from primary aromatic amines, H_2O_2 and conjugated dienes is also described.



Scheme 1. A series of oxidized products from primary aromatic amines.

Results and Discussion

Seleninic acid or seleninic anhydride has been reported to be an extremely efficient oxidant for the transformation of hydroxylamine to nitroso compounds.[13] Because diselenides can be easily oxidized by hydrogen peroxide to seleninic acid or peroxyseleninic acid,[14] we initiated a study on the direct oxidation of aniline (**1a**) by aqueous H_2O_2 (35%) in the presence of some commercially available selenium catalysts (5–10 mol-%).

The results are summarized in Table 1. In most cases, **1a** was completely oxidized to the target nitrosobenzene (**2a**) with high selectivity within 1–2 h (Entries 1–4) and only trace amounts of azobenzene byproduct could be detected, except when PhSeH was used as catalyst (Entry 5). Phenyltellurium also catalyzed this oxidation, but the reaction was much slower (Entry 6). According to the reported oxidative selenium chemistry in the literature[14] and control oxi-

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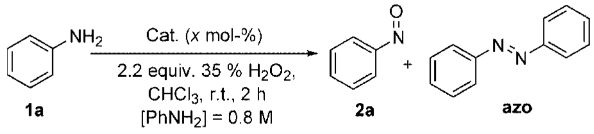
dation reaction of aniline using stoichiometric amounts of $PhSeO_2H$,[15] it was supposed that the real active oxidant in this system should be peroxyseleninic acid instead of seleninic acid.

Table 1. Catalytic selective oxidation of aniline by aqueous hydrogen peroxide.[a]



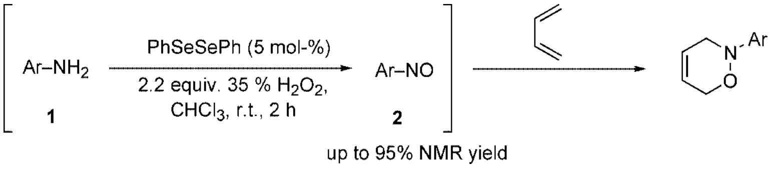
Entry	Catalyst (x mol-%)	Conversion[b] (%)	Selectivity[b] (**2a**/**azo**)
1	PhSeSePh(5)	>99	30:1
2	$PhSeO_2H$ (10)	>99	>30:1
3	$(PhSeO)_2O$ (5)	>99	30:1
4	SeO_2 (10)	>99	25:1
5	PhSeH (10)	33	1.8:1[c]
6	PhTePh (5)	13	good

[a] No side product from oxidation of the benzene ring could be detected. [b] Determined by ^1H NMR spectroscopy. [c] Azoxy byproduct was found instead of azo compound.

Organocatalytic (including proline analogs and Brønsted acid catalysts) and Lewis-acid-catalyzed asymmetric reactions of nitroso compounds have become a hot topic and gained considerable attention in recent years.[2–4] However, in almost all of these reactions, the nitrosobenzene analog (often commercially available) was used as the added reaction component. Due to the toxicity and mutagenicity of nitroso compounds, it is quite attractive to perform further transformation in one-pot after in situ generation of the nitroso compound since isolation and purification can be avoided.[4e,4h,4k] Although the impurities from the crude nitrosobenzene may cause some side reactions in the second reaction, the potential advantage of this one-pot strategy for organic synthesis is obvious. To realize the proposed tandem one-pot procedure, some modifications might be useful and necessary to minimize the negative effect of the impurities or to increase the tolerance of the second reaction. For this purpose, hetero-Diels–Alder cycloaddition reaction (HDA) of the generated nitroso compound with conjugated dienes was chosen as a test reaction (Scheme 2).[4e]

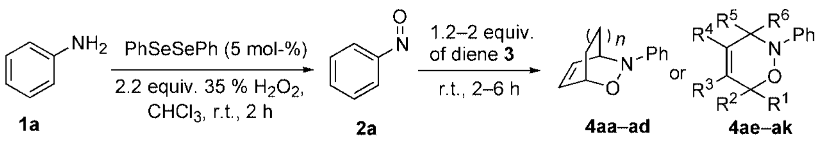
To our delight, oxazine (**4a**) formation proceeded smoothly within 2–6 h by simple addition of a series of conjugated dienes (**3**) to the in situ generated solution of nitroso compound **2a** from selenide-catalyzed oxidation of aniline by H_2O_2 (Table 2). The consecutive HDA reaction was found to be tolerant to the impurities generated from the first oxidation step, unreacted hydrogen peroxide or the water. The diene substrate scope was rather broad and both cyclic and acyclic dienes were applicable in this system to give moderate to good yields of oxazines for two steps. Both NMR yield and isolated yield are given in Table 2; in most cases the isolated yield of the product was 10–20% lower than the yield determined by ^1H NMR spectroscopy of the crude product. Reaction of **2a** with 1,3-cyclopentadiene (**3a**) afforded **4aa**. Due to the instability of HDA adduct **4aa** on the silica gel column,[16] it could not be isolated in pure form. However, the yield was determined to be 60% on the basis of ^1H NMR spectroscopy of the crude material (Entry 1). The use of 1,3-cyclohexadiene (**3b**) and 1,3-cycloheptadiene (**3c**) both produced the corresponding HDA adducts in good yields (Entries 2–3). The reaction with (*Z*,*Z*)-1,3-cyclooctadiene (**3d**) as diene was found to proceed very slowly, and the HDA adduct **4ad** could hardly be detected (Entry 4).[17] The tandem reaction involving noncyclic dienes **3e**–**k** and aniline **1a** with the present procedure also worked well and generated the desired 2-phenyl-3,6-dihydro-2*H*-[1,2]oxazines **4ae**–**ak** in fair yields. Among them, **3e** and **3f** were chosen to represent symmetric dienes and examined under the same reaction conditions (Entries 5, 6). For unsymmetrical dienes such as **3g**–**i**, usually two diastereoisomers were observed in the crude ^1H NMR spectroscopy. Unsuccessful attempts were made to separate both diastereomers from one another by chromatography in these cases (Entries 7–9). However, ^1H NMR spectroscopy allowed a satisfactory characterization of the products. Interestingly, only one isomer could be observed in the case of unsymmetrical dienes **3j** and **3k**, respectively (Entries 10, 11). To the best of our knowledge, HDA adducts **4aj**–**ak** have not been reported previously despite some existing analogs in literature.[4d] It is noteworthy that these HDA adducts can be transformed by different procedures to a variety of products, such as mitomycin and other compounds with pharmaceutical interest.[18] Jørgensen et al. have developed a one-pot procedure to prepare oxazines (HDA adducts) from primary aromatic amines, hydrogen peroxide and conjugated dienes in the presence of catalytic amount of a (peroxo)molybdenum complex.[4e] Although this molybdenum complex was a selective catalyst for the oxidation of primary aromatic amines to nitroso compounds and tolerant toward conjugated dienes, the reaction usually took 18 h to reach completion. In terms of easy availability of catalyst, reaction time and compatible outcome of target molecules, our method seems to be a competitive alternative.[19]

The synthetic aspects of the new method, shown in Scheme 2, have been clearly demonstrated by the results in

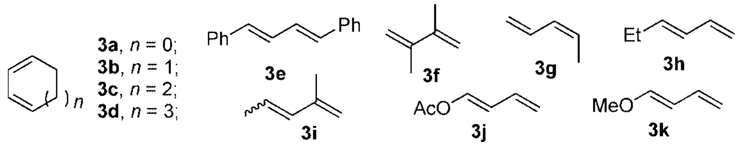


Scheme 2. One-pot procedure for further organic synthesis and catalysis based on in situ generation of nitroso compounds by catalytic oxidation with aqueous hydrogen peroxide.

Table 2. Diene substrate scope for aniline oxidation/hetero-Diels–Alder one-pot reaction.[a]



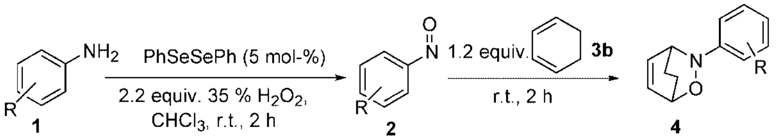
Entry	Diene	R^1	R^2	R^3	R^4	R^5	R^6	NMR yield of **4** (%)[i]	Isolated yield of **4** (%)[i]
1	**3a**	cyclopentadiene						60 (**4aa**)	[g] (**4aa**)
2	**3b**	1,3-cyclohexadiene						90 (**4ab**)	70 (**4ab**)
3	**3c**	1,3-cycloheptadiene						78 (**4ac**)	60 (**4ac**)
4	**3d**	1,3-cyclooctadiene						<5 (**4ad**)	<5 (**4ad**)
5	**3e**[b]	Ph	H	H	H	H	Ph	60 (**4ae**)	53 (**4ae**)
6	**3f**	H	H	Me	Me	H	H	90 (**4af**)	63 (**4af**)[f]
7	**3g**[b]	Me	H	H	H	H	H	68 (**4ag**)[d]	57 (**4ag**)[d,f]
8	**3h**[b]	Et	H	H	H	H	H	83 (**4ah**)[e]	70 (**4ah**)[e,f]
9	**3i**	Me	H	H	Me	H	H	53 (**4ai**)	34 (**4ai**)[h]
10	**3j**[b]	OAc	H	H	H	H	H	61 (**4aj**)[c]	45 (**4aj**)[c]
11	**3k**	OMe	H	H	H	H	H	57 (**4ak**)[c]	54 (**4ak**)[c]



[a] The HDA rection was performed using 1.2 equiv. of diene **3**, which was added subsequently after the oxidation reaction, unless otherwise noted. [b] 2 equiv. of diene was used and HDA reaction was performed for 6 h. [c] Only one isomer was obtained. [d] The isomer ratio is ca. 2:1. [e] The isomer ratio is ca. 1:1. [f] Contaminated with some azoxy byproducts. [g] Not stable on column. [h] The isomer ratio is ca. 5:2. [i] Based on the amount of aniline employed.

Table 2. Further investigation of the synthetic utility were undertaken using different aniline substrates **1b**–**m**, 1,3-cyclohexadiene (**3b**) as a standard diene, aqueous H_2O_2 and the selenium catalyst PhSeSePh. As shown in Table 3, the tandem reaction led to a smooth formation of the HDA adducts, 3-aryl-2-oxa-3-azabicyclo[2.2.2]oct-5-enes **4ab**–**mb**. Primary aromatic amines having electron-donating (Entries 2–5, 10, 12–13) and electron-withdrawing substituents (Entries 6–9, 11) were oxidized to the corresponding nitroso compounds **2** with good to high selectivities (6:1 → 30:1)

Table 3. Organoselenium-catalyzed oxidation of aniline analogs followed by hetero-Diels–Alder reaction with 1,3-cyclohexadiene.[a]



Entry	Amine (R)	Conversion of **1** (%)	Selectivity (**2**/**azo**)	NMR yield of **2** (%)	NMR yield of **4** (%)	Isol. yield of **4** (%)
1	**1a** (H)	>99	30:1	95 (**2a**)	90 (**4ab**)	70 (**4ab**)
2	**1b** (4-Me)	>99	8:1	89 (**2b**)	89 (**4bb**)	61 (**4bb**)
3	**1c** (4-*t*Bu)	>99	>30:1	85 (**2c**)	90 (**4cb**)	45 (**4cb**)
4	**1d** (4-OMe)	>99	11:1	90 (**2d**)	90 (**4db**)	[f] (**4db**)
5	**1e** (4-OCF_3)	>99	25:1	95 (**2e**)	95 (**4eb**)	65 (**4eb**)
6	**1f** (4-Cl)	>99	8:1	85 (**2f**)	85 (**4fb**)	69 (**4fb**)
7	**1g** (4-Br)	>99	[e]	88 (**2g**)	92 **4gb**)	72 (**4gb**)
8	**1h** (4-CO_2Me)	>99[b]	6:1[c]	75 (**2h**)	85 (**4hb**)	63 (**4hb**)
9	**1i** (4-CF_3)	>99	6:1	86 (**2i**)	86 (**4ib**)	71 (**4ib**)
10	**1j** (2-Me)	>99	>30:1	75 (**2j**)	90 (**4jb**)	67 (**4jb**)
11	**1k** (2-Br)	80[d]	10:1	80 (**2k**)	70 (**4kb**)	64 (**4kb**)
12	**1l** (3-Me)	>99	>30:1	90 (**2l**)	66 (**4lb**)	41 (**4lb**)
13	**1m** (3,5-Me_2)	90[b]	>30:1	50 (**2m**)	40 (**4mb**)	40 (**4mb**)

[a] For reaction condition see Table 2. [b] 8 h. [c] Azoxy byproduct was observed instead. [d] 24 h. [e] Overlapping. [f] Full conversion but not stable on column.

within a couple of hours. Incidentally, *p*-nitroaniline could not be oxidized under current reaction condition maybe because it is too electron-deficient. All amines, except two (**1k** and **1m**), examined gave complete conversion with 2.2 equiv. of 35% aq. H_2O_2 as terminal oxidants and 5 mol-% of PhSeSePh catalyst.

The major side product observed in the first step (oxidation) was dimeric azoarenes generated from the coupling of nitroso compounds and the corresponding unreacted aniline analogs with the exception of **1h**, where the azoxy byproduct was detected instead. The HDA reaction of in situ generated nitroso compounds **2a**–**m** and 1,3-cyclohexadiene turned out to be nicely proceeding due to the compatible NMR yield of both **2** and **4** outlined in Table 3. The isolated yield of the HDA adducts **4** was still 10–20% lower than the NMR yield of the crude products. The decrease in yield of those HDA adducts by workup was attributed to the possible chromatographic, photoinduced, or thermal transformation which previously has been observed for analogs HDA adducts.[20]

Conclusions

A method for in situ generation of nitroso compounds from organoselenium-catalyzed oxidation of anilines by hydrogen peroxide was developed. This was used for a one-pot synthesis of oxazines (hetero-Diels–Alder adducts) from primary aromatic amines, H_2O_2 and conjugated dienes. The first step, the organoselenium-catalyzed oxidation of anilines by hydrogen peroxide, was highly chemoselective and efficient for the generation of nitroso compounds within a couple of hours. The consecutive HDA cycloaddition reactions were tolerant to the impurities of the nitroso compounds from the first oxidation step. A variety of different oxazines could be synthesized in reasonable yield by this procedure from primary aromatic amines with different substituents and various dienes. This new tandem procedure could serve as a convenient and environmentally friendly method for the formation of oxazine compounds since no isolation or purification of nitroso compounds is required. Moreover, this strategy based on in situ generation of nitroso compounds might facilitate the current methodologies of nitroso compounds, especially in both aldol-type and hetero-Diels–Alder reactions. We are currently investigating other procedures for the in situ generation of nitroso compounds from primary anilines and H_2O_2 with the aim of using them in coupled electron-transfer oxidations.

Experimental Section

General: All the chemicals, including selenium catalysts, aniline analogs, aqueous H_2O_2 (35%) and conjugated dienes are commercially available and were used as delivered without further purification. NMR spectra were recorded with Bruker AMX-400 and Varian Oxford AS400 instruments. Chemical shifts δ are given in ppm and coupling constants J in Hz. Mass spectra were recorded with a MicrOTOF 125 spectrometer. Infrared spectra were recorded with a Perkin–Elmer Spectrum One B v5.0 FT-IR spectrometer. Column chromatography was carried out using silica gel (Merck, 60–230 mesh). Thin-layer chromatography was performed on silica gel 60 F_{254} (Merck). All the oxazine compounds **4** were prepared in racemic form.

General Procedure for the One-Pot Tandem Reaction: The PhSeSePh catalyst (6.2 mg, 5 mol-%), anilines **1** (0.4 mmol, 1 equiv.) and 35% aqueous H_2O_2 (77 µL, 0.88 mmol, 2.2 equiv.) were mixed in 0.5 mL of $CHCl_3$ at room temp. After 1–2 h of vigorous stirring, the anilines were completely converted into the corresponding nitroso compounds **2** according to ^{1}H NMR monitoring. *tert*-Butyl methyl ether was used as an internal standard to give the NMR yields of nitroso compounds. Conjugated dienes **3** (0.48–0.80 mmol, 1.2–2.0 equiv.) were then added to the reaction mixture which was stirred for an additional 2–6 h. After evaporation of the solvent, the NMR yield was determined by ^{1}H NMR analysis of the crude products. Purification by silca gel column chromatography (eluent: AcOEt/pentane) gave the analytically pure HDA adducts **4**. The following known compounds show ^{1}H and ^{13}C NMR spectroscopic data identical to those in ref.[4e]: 3-Phenyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**4ab**), 3-*p*-tolyl-2-oxa-3-azabicyclo-[2.2.2]oct-5-ene (**4bb**), 3-(4-methoxyphenyl)-2-oxa-3-azabicyclo-[2.2.2]oct-5-ene (**4db**), 3-(4-chlorophenyl)-2-oxa-3-azabicyclo-[2.2.2]oct-5-ene (**4fb**), 3-[4-(trifluoromethyl)phenyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**4ib**). See also in the Supporting Information for other known compounds. The new compounds are characterized as follows:

3-Ethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]oxazine and 6-Ethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]oxazine (4ah): 53.5 mg, yield < 70% generated from aniline **1a** (0.4 mmol) and diene **3h** (0.8 mmol). R_f = 0.3 (pentane/EtOAc,20:1). ^{1}H NMR (400 MHz, $CDCl_3$, *italics* for major isomer): δ = 0.94 (t, J = 7.7 Hz, 3 H), *1.08* (t, J = 7.7 Hz, 3 H), *1.59–1.81* (m, 2 H), *3.70–3.78* (m, 1 H), *3.84–3.94* (m, 2 H), 4.26–4.34 (m, 1 H), 4.47–4.55 (m, 2 H), *5.87–6.09* (m, 2 H), *6.93–7.00* (m, 1 H), *7.05–7.15* (m, 2 H), *7.26–7.34* (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.0, 10.4, 23.5, 26.5, 51.6, 60.1, 67.3, 79.0, 115.3, 116.5, 121.6, 121.8, 122.9, 125.3, 127.1, 128.7, 128.8, 129.9, 148.6, 150.7 ppm. IR (liquid, CH_2Cl_2): $\tilde{\nu}$ = 2970, 2875, 1596, 1491, 1211, 751, 689 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{15}NNaO^+$ [M + Na]$^+$ 212.1046; found 212.1036.

2-Phenyl-3,6-dihydro-2*H*-[1,2]oxazin-6-yl Acetate (4aj): 39.0 mg, yield = 45% generated from aniline **1a** (0.4 mmol) and diene **3j** (0.8 mmol). R_f = 0.4 (pentane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 3.69–3.76 (m, 1 H), 4.02 (ddd, J_1 = 16.4, J_2 = 5.6, J_3 = 1.8 Hz, 1 H), 5.95–6.00 (m, 1 H), 6.31–6.37 (m, 1 H), 6.50–6.52 (m, 1 H), 7.04 (tt, J_1 = 7.3, J_2 = 1.1 Hz, 1 H), 7.09–7.13 (m, 2 H), 7.29–7.34 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 50.9, 90.7, 116.4, 123.1, 123.2, 128.8, 129.1, 149.5, 170.1 ppm. IR (liquid, CH_2Cl_2): $\tilde{\nu}$ = 3056, 2815, 1742, 1600, 1495, 1224, 1116, 957, 760 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{13}NNaO_3^+$ [M + Na]$^+$ 242.0788; found 242.0789.

6-Methoxy-2-phenyl-3,6-dihydro-2*H*-[1,2]oxazine (4ak): 103.3 mg, yield = 54% generated from aniline **1a** (1.0 mmol) and diene **3k** (1.5 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (s, 3 H), 3.67 (ddd, J_1 = 16.4, J_2 = 4.3, J_3 = 1.8 Hz, 1 H), 3.97 (ddd, J_1 = 16.4, J_2 = 5.3, J_3 = 1.4 Hz, 1 H), 5.13 (m, 1 H), 5.95 (m, 1 H), 6.17 (m, 1 H), 7.01 (t, J = 7.4 Hz, 1 H), 7.17 (d, J = 8.7 Hz, 2 H), 7.32 (dd, J_1 = 8.7, J_2 = 7.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.7, 56.1, 99.0, 116.0, 122.6, 125.0, 127.7, 128.9, 150.5 ppm. IR (liquid, CH_2Cl_2): $\tilde{\nu}$ = 3056, 2931, 2823, 1635, 1600, 1493, 1396, 1213, 1192, 1106, 1093, 755, 691 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{13}NNaO_2^+$ [M + Na]$^+$ 214.0838; found 214.0832.

3-(4-*tert*-Butylphenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (4cb): 43.7 mg, yield = 45% generated from aniline **1c** (0.4 mmol) and diene **3b** (0.48 mmol). R_f = 0.6 (pentane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 1.30–1.40 (m, 2 H), 1.50–1.61 (m, 2 H), 2.20–2.37 (m, 2 H), 4.35–4.42 (m, 1 H), 4.65–4.75 (m, 1 H), 6.15–6.20 (m, 1 H), 6.55–6.62 (m, 1 H), 6.93 (d, J = 8.6 Hz, 2 H), 7.22 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 23.9, 31.4, 34.0, 56.3, 68.9, 117.1, 125.1, 130.1, 131.5, 144.6, 149.7 ppm. IR (KBr): $\tilde{\nu}$ = 2927, 2965, 1508, 1362, 944, 835, 824 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{21}NNaO^+$ [M + Na]$^+$ 266.1515; found 266.1510.

3-[4-(Trifluoromethoxy)phenyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (4eb): 35.2 mg, yield > 65% generated from aniline **1e** (0.2 mmol) and diene **3b** (0.24 mmol). R_f = 0.2 (pentane/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31–1.43 (m, 1 H), 1.52–1.64 (m, 1 H), 2.16–2.36 (m, 2 H), 4.36–4.41 (m, 1 H), 4.68–4.73 (m, 1 H), 6.11–6.16 (m, 1 H), 6.55–6.60 (m, 1 H), 6.96–7.00 (m, 2 H), 7.03–7.07 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 23.8, 56.6, 69.3, 118.3, 121.1, 129.7, 131.6, 143.8, 150.9 ppm; the signal for OCF_3 as a q is of low intensity to observe. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –58.2 (s) ppm. IR (KBr): $\tilde{\nu}$ = 2974, 2944, 1506, 1269, 1215, 1151, 839 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{12}F_3NNaO_2^+$ [M + Na]$^+$ 294.0712; found 294.0709.

3-*o*-Tolyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (4jb): 53.6 mg, yield = 67% generated from aniline **1j** (0.4 mmol) and diene **3b** (0.48 mmol). R_f = 0.3 (pentane/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.46 (m, 1 H), 1.48–1.58 (m, 1 H), 2.22–2.37 (m, 5 H), 3.97–4.02 (m, 1 H), 4.70–4.75 (m, 1 H), 6.02–6.08 (m, 1 H), 6.71–6.77 (m, 1 H), 6.92–6.98 (m, 1 H), 7.02–7.11 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 22.0, 23.8, 54.7, 69.2, 120.7, 123.6, 125.5, 128.6, 129.1, 130.3, 132.4, 149.5 ppm. IR (liquid, CH_2Cl_2): $\tilde{\nu}$ = 2970, 2927, 1602, 1482, 1218, 940, 762 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{15}NNaO^+$ [M + Na]$^+$ 224.1046; found 224.1053.

3-(2-Bromophenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (4kb): 68.3 mg, yield = 64% generated from aniline **1k** (0.4 mmol) and diene **3b** (0.48 mmol). R_f = 0.6 (pentane/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.44 (m, 1 H), 1.48–1.58 (m, 1 H), 2.22–2.32 (m, 1 H), 2.33–2.42 (m, 1 H), 4.52–4.57 (m, 1 H), 4.72–4.77 (m, 1 H), 5.99–6.06 (m, 1 H), 6.68–6.76 (m, 1 H), 6.85–6.92 (m, 1 H), 7.09–7.18 (m, 2 H), 7.45 (dd, J_1 = 7.9, J_2 = 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 23.5, 54.8, 69.5, 114.5, 122.8, 125.0, 127.0, 128.9, 132.3, 132.8, 148.9 ppm. IR (liquid, CH_2Cl_2): $\tilde{\nu}$ = 3056, 2965, 2933, 1581, 1460, 1370, 1028, 938, 757 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{12}BrNNaO^+$ [M + Na]$^+$ 287.9994; found 287.9980.

3-*m*-Tolyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (4lb): 32.7 mg, yield = 41% generated from aniline **1l** (0.4 mmol) and diene **3b** (0.48 mmol). R_f = 0.5 (pentane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32–1.42 (m, 1 H), 1.52–1.64 (m, 2 H), 2.20–2.40 (m, 5 H), 4.40–4.47 (m, 1 H), 4.67–4.74 (m, 1 H), 6.16 (t, J = 6.9 Hz, 1 H), 6.58 (t, J = 6.9 Hz, 1 H), 6.75 (d, J = 7.6 Hz, 1 H), 6.79–6.86 (m, 2 H), 7.09 (t, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 21.6, 24.0, 56.4, 69.1, 114.5, 118.1, 122.8, 128.1, 129.9, 131.5, 138.1, 151.0 ppm. IR (liquid, CH_2Cl_2): $\tilde{\nu}$ = 3056, 2935, 2858, 1604, 1585, 1488, 1370, 1254, 944, 906, 781, 693 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{15}NNaO^+$ [M + Na]$^+$ 224.1046; found 224.1037.

3-(3,5-Dimethylphenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (4mb): 34.0 mg, yield = 40% generated from aniline **1m** (0.4 mmol) and diene **3b** (0.48 mmol). R_f = 0.5 (pentane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32–1.40 (m, 1 H), 1.52–1.61 (m, 1 H), 2.17–2.33 (m, 8 H), 4.39–4.45 (m, 1 H), 4.66–4.71 (m, 1 H), 6.15–6.20 (m, 1 H), 6.55–6.60 (m, 2 H), 6.61–6.65 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 21.5, 24.0, 56.3, 69.0, 115.2, 123.8, 130.0, 131.5, 137.8, 152.4 ppm. IR (liquid, CH_2Cl_2): $\tilde{\nu}$ = 2969, 2926, 1596, 1467, 1453, 1250, 1065, 938, 912, 833, 708 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{17}NNaO^+$ [M + Na]$^+$ 238.1202; found 238.1209.

Supporting Information (see footnote on the first page of this article): General procedure and characterization of some known oxazine compounds **4**.

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